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Membrane-Permeable Nucleoside Triphosphate Prodrugs of Anti-HIV Active Nucleoside Analogues: γ-(Phosphate or Phosphonate)-Modified Nucleotide Analogues

Dissertation

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von

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II Contents

III List of abbreviations and symbols

3TC	lamivudine (NRTI)
A	alkyl
AB	acyloxybenzyl
ABC	abacavir (NRTI)
Ac	acetyl
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ATP	adenosine triphosphate
AZT	3'-azido-3'-deoxythymidine, Zidovudine (NRTI)
AZU	3'-azido-2',3'-dideoxyuridine
3'-AZdd-5-ClU	3'-azido-5-chloro-2',3'-dideoxyuridine
BAB	bis(acyloxybenzyl)
Bn	benzyl
BOMCl	benzyloxychloromethyl ether
Bu	butyl
BVdU	(E)-5-(2-Bromovinyl)-2′-deoxyuridine
BIC	bictegravir
Bz	benzoyl
CA	capsid
cART	combination antiretroviral therapy
CBV	carbovir
CC50	50% cytotoxic concentration
CD4	cluster of differentiation 4
CDCl3	deuterated chloroform
CEM/0	cell line derived from human T cells
*cyclo*Sal	*cyclo*Saligenyl
d	doublet (NMR)
d4T	2′,3′-didehydro-2′,3′-dideoxythymidine (NRTI)
d4U	2',3'-Didehydro-2',3'-dideoxyuridine (NRTI)

dCK	deoxycytidine kinase
dd	doublet of doublets (NMR)
ddd	doublet of doublet of doublets (NMR)
ddC	2',3'-Dideoxycytidine, zalcitabine (NRTI)
ddI	2',3'-Dideoxyinosine, didanosine (NRTI)
ddT	2',3'-Dideoxythymidine (NRTI)
DMF	dimethylformamide
DMAP	4-(dimethylamino)pyridine
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNA Pol α	deoxyribonucleic acid polymerase α
DNA Pol β	deoxyribonucleic acid polymerase β
DNA Pol γ	mitochondrial deoxyribonucleic acid polymerase γ
DP	diphosphate
DPP	diphenyl-*H*-phosphonate
Di*PP*ro	diphosphate prodrug
dt	doublet of triplets (NMR)
dT or T	thymidine
EA	ethyl acetate
EC50	50% effective concentration
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
EFV	efavirenz (NNRTI)
eq	Equivalents
ESI	electrospray ionization
EVG	elvitegravir (INSTI)
Et	ethyl
FDA	The US Food and Drug Administration
FddClU	3'-fluoro-2',3'-dideoxy-5-chlorouridine
Fm	fluorenylmethyl
FTC	Emtricitabine (NRTI)

HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HDP	hexadecyloxypropyl
HPLC	High-performance liquid chromatography
HIV	human immunodeficiency virus
HIV-1	HIV type 1
HIV-2	HIV type 2
HMBC	heteronuclear multiple-bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation
HSV	Herpes Simplex Virus
H,H-cosy	Proton proton correlation spectroscopy
IR	infrared spectroscopy
*i*Pr	*iso*-Propyl
In	Integrase
INSTI	integrase strand transfer inhibitor
J	scalar coupling constant (NMR)
m	multiplet (NMR)
M	molar (mol·L-1)
MA	matrix protein
MAB	mono-acyloxybenzyl
MALDI	matrix-assisted laser desorption/ionization
Me	methyl
MP	monophosphate
MS	mass spectrometry
mRNA	messenger ribonucleic acid
Ms	mesyl
m/z	mass/charge ratio
NC	nucleocapsid protein

NCS	N-Chlorosuccinimide
NDP	nucleoside diphosphate
NDPK	nucleoside diphosphate kinase
Nef	negative regulatory factor
NMP	nucleoside monophosphate
NMR	nuclear magnetic resonance
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NTP	nucleoside triphosphate
Nucl. or Nu.	nucleoside
NtRTI	nucleotide reverse transcriptase inhibitor
PB	phosphate buffer
PE	petroleum ether 50-70
Ph	phenyl
PHA	phytohemagglutinin
PI	protease inhibitor
PLE	pig liver esterase
POC	*iso*-propyoxycarbonyloxymethyl
Pol	DNA polymerase (Human)
POM	pivaloyoxymethyl
ppm	parts per million
PR	protease
ProTide	nucleoside phosphoramidate prodrug
q	quartet (NMR)
rt	room temperature
RT	reverse transcriptase
RNA	ribonucleic acid
RP	reverse phase
RPMI	Roswell Park Memorial Institute medium
RPV	rilpivirine hydrochloride (NNRTI)

s	singlet (NMR)
SATE	S-acylthioethyl ester
SIV	simian immunodeficiency virus
t	triplet (NMR)
$t_{1/2}$	half life
TAF	tenofovir alafenamide (NRTI)
TBAA	tetrabutylammonium acetate
tBu	*tert-butyl*
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TDF	tenofovir disoproxil fumarate (NRTI)
TEA	triethylamine
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TK	thymidine kinase
TK^-	thymidine kinase deficient
TLC	thin layer chromatography
Tri*PPP*ro	triphosphate prodrug
TMS	trimethylsilyl
TP	triphosphate
TTP	thymidine 5'-triphosphate
UV	ultra violet
US	United States
WHO	World Health Organization

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Zusammenfassung

Nukleosidische Reverse Transkriptase-Inhibitoren (NRTIs) finden breiten Einsatz in der Therapie von Virusinfektionen und Krebs, jedoch müssen diese Substanzen zunächst durch die intrazelluläre anabolische Phosphorylierung in ihre wirksame Form, die triphosphorylierten NRTI Metabolite, überführt werden. Die Entwicklung von Prodrugsystemen für Nukleosidtriphosphate ist weiterhin sehr interessant und erstrebenswert, da diese alle Schritte der intrazellulären Phosphorylierung umgehen und somit die intrazelluläre Konzentration der letztlich wirksamen Form, der bioaktiven Nukleosidanalogatriphosphate (NTPs), maximieren können.

Die vorliegende Arbeit beschreibt die Weiterentwicklung des als Tri*PPP*ro-Konzept bekannten NTP-Freisetzungssystems zunächst am Beispiel des Nukleosidanalogons d4T. Dazu wurden kovalente Modifizierungen an der γ-Phosphatgruppe in Nukleosidtriphosphaten mit zwei unterschiedlichen, bioreversiblen Maskierungseinheiten vorgenommen, einer Alkoxycarbonyloxybenzyl(ACB)- und einer Acyloxybenzyl(AB)-Gruppe. Dieser neuartige Tri*PPP*ro-Ansatz ermöglicht die selektive, durch Enzymaktivität eingeleitete Freisetzung von d4TTP, wie diese Arbeit mittels Untersuchungen in Zellextrakten humaner $CD4^+$ T-Lymphozyten (CEM) aufzeigt. Durch die Einführung der zwei unterschiedlichen Maskierungsgruppen wurden selektiv die entsprechenden γ-(ACB)-d4TTPs durch chemische Hydrolyse und, wichtiger noch, durch die im Zellextrakt enthaltenen Enzyme freigesetzt. Der zweite Teil dieser Arbeit beschreibt die Übertragung dieser Variation des Tri*PPP*ro-Konzepts auf eine Vielzahl unterschiedlicher zugelassener sowie auch bisher inaktiver Nukleosidanaloga und demonstriert damit die generelle Anwendbarkeit und das immense Potential, das dieser neuartige Ansatz verspricht. In antiviralen Untersuchungen zeigte sich, dass einige dieser neuen Substanzen hochaktiv waren gegen HIV-1 und HIV-2, sowohl in infizierten Kulturen humaner T-Lymphoblasten (Wildtyp CEM/0-Zellen) als auch, und dies ist besonders hervorzuheben, in den entsprechenden infizierten, Thymidinkinase-defizienten Zellkulturen (CEM/TK^-). Die Stabilität, der Hydrolyseverlauf sowie die antivirale Aktivität der einzelnen Verbindungen waren dabei wie erwartet abhängig von der Länge der Acylgruppe in der Maskierungseinheit.

Der dritte Teil dieser Arbeit beschreibt die Synthese und Charakterisierung einer neuen Klasse von Nukleosidtriphosphatanaloga, in denen eine C-Alkylphosphonateinheit die γ-Phosphatgruppe ersetzt. Auch diese Verbindungen wurden mit einer bioreversiblen, lipophilen Maske versehen; dabei wurde entweder auf die beschriebene AB- oder die ACB-Modifizierung zurückgegriffen. Diese Prodrug-Gruppe

wurde sowohl durch chemische Hydrolyse, als auch, und dies ist wesentlich, durch die Enzymaktivität in Schweineleberesterase oder Zellextrakten humaner $CD4^+$ T-Lymphozyten (CEM) selektiv gespalten, sodass die entsprechenden γ-C-(Alkyl)-Nukleosidtriphosphatanaloga freigesetzt wurden. Im Gegensatz zu d4TTP erwiesen sich die γ-C-(Alkyl)-d4TTPs in Zellextrakten als sehr stabil gegenüber Dephosphorylierung. Besonders hervorzuheben ist, dass die γ-C-(Alkyl)-d4TTPs in *primer extension* Experimenten der HIV-RT als Substrate dienten, sie hingegen keine Substrate für die zellulären DNA-Polymerasen α, β und γ darstellten. In antiviralen Untersuchungen erwiesen sich die Prodrugverbindungen als hochaktiv gegenüber HIV-1 und HIV-2 in infizierten CEM/0-Zellen. Hervorzuheben ist, dass auch diese Prodrugs ihre hohe antivirale Aktivität in Thymidinkinase-defizienten CEM-Zellen (CEM/TK^-) behielten und im Vergleich zu der Ausgangssubstanz d4T die Aktivität der Verbindungen gegenüber HIV um das 1000-fache gesteigert wurde. Diese Ergebnisse verdeutlichen, dass die Prodrugverbindungen effizient in das Zellinnere gelangen und dort die Nukleosidtriphosphatanaloga freisetzen. Folglich umgehen sie alle der intrazellulären Phosphorylierungsschritte, die ausgehend vom Nukleosidanalogon d4T nötig wären, um die aktive Wirkform zu generieren.

Darüber hinaus beschreibt diese Arbeit eine neuartige Serie von γ-dialkylPhosphat-modifizierten d4TDPs und γ-dialkylPhosphonat-modifizierten d4TDPs. Diese Modifizierungen bestehen, in Abgrenzung zu den im vorigen zusammengefassten Arbeiten, beide aus nicht-spaltbaren, simplen Alkylgruppen. Der Hydrolyse dieser Verbindungen unterschied sich von dem publizierten Weg, dem die Hydrolyse der Tri*PPP*ro-Verbindungen folgt. Anstelle von d4TTP wurde die Freisetzung von d4TDP in CEM/0-Zellextrakten beobachtet; dies resultierte vermutlich aus der chemischen Hydrolyse der Phosphoanhydridbindung. Bemerkenswert war die hohe antivirale Aktivität dieser γ-(Alkyl; Alkyl-C18)-Phosphat-d4TDPs und γ-(Alkyl; Alkyl-C18)-Phosphonat-d4TDPs gegenüber HIV-1 und HIV-2 in infizierter CEM/0-Zellkultur, welche mit einer Steigerung um das 1120-fache im Vergleich mit d4T auch in CEM/TK^- Zellen erhalten wurde. Dies ist als ein deutlicher Hinweis darauf zu bewerten, dass die Verbindungen in das Zellinnere gelangen und eine phosphorylierte Form von d4T freisetzen.

Diese Arbeit beschreibt die Weiterentwicklung des Tri*PPP*ro-Prodrugkonzepts für die intrazelluläre Freisetzung modifizierter NTPs. Diese Weiterentwicklung bietet großes Potential für eine zukünftige Anwendung in der Chemotherapie zur Behandlung von viralen Infektionskrankheiten und Krebs.

Abstract

Nucleoside reverse transcriptase inhibitors (NRTIs) are extensively used as antiviral and anticancer compounds but they require intracellular anabolic phosphorylation into their antivirally active form, the triphosphorylated NRTI metabolites. The development of nucleoside triphosphate prodrugs is still highly interesting and desirable because they bypass all steps of intracellular phosphorylation and can therefore maximize the intracellular concentration of the ultimately bioactive nucleoside analogue triphosphates (NTPs).

This thesis describes the advancement of the nucleoside triphosphate delivery system (Tri*PPP*ro-concept), to a system in which the γ-phosphate is covalently modified by two different biodegradable masking units, one alkoxycarbonyloxybenzyl- (ACB) moiety and one acyloxybenzyl- (AB) group, and d4T as nucleoside analogue. This Tri*PPP*ro-approach enables the delivery of d4TTP with high selectivity and by enzyme-triggered reactions, as shown in human $CD4^+$ T-lymphocyte CEM cell extracts. The introduction of these two different groups led to the selective formation of γ-(ACB)-d4TTPs by chemical hydrolysis and, more importantly, by enzymes contained in cell extracts. The second part of this work describes the use of this variation of the Tri*PPP*ro-concept on a variety of approved, and importantly also on so-far non-active nucleoside analogues to demonstrate the general applicability and the great potential that this approach promises. In antiviral assays, some of the nucleoside triphosphate prodrugs were found to be highly active against HIV-1 and HIV-2 in cultures of infected human T-lymphoblasts (wild-type CEM/0 cells) and more importantly in thymidine kinase-deficient $CD4^+$ T-cells (CEM/TK^-) as well. The stability, hydrolysis pathway, and antiviral activity were significantly influenced by the acyl chain lengths of the prodrug moieties.

The third part of this work describes the synthesis and evaluation of a new class of nucleoside triphosphate analogues in which the γ-phosphate group has been replaced by a C-alkyl-phosphonate moiety. These compounds were converted into bioreversibly modified lipophilic prodrugs at the γ-phosphonate by covalent attachment of a prodrug group, either an AB or an ACB moiety. The prodrug group was selectively cleaved by chemical hydrolysis and, importantly, by enzyme activity present in pig liver esterase as well as human $CD4^+$ T-lymphocyte CEM cell extracts to give γ-C-(alkyl)-nucleoside triphosphate analogues. In contrast to d4TTP, γ-C-(alkyl)-d4TTPs showed a very high stability in cell extracts towards dephosphorylation. A finding of major importance was that, in primer extension assays, γ-C-(alkyl)-d4TTPs proved to be substrates for HIV-RT but not for cellular DNA-polymerases α, β and γ.

In antiviral assays, the prodrug compounds were found to be highly active against HIV-1 and HIV-2 in cultures of infected wild-type CEM/0 cells. More importantly, the high antiviral activity of the prodrugs was retained in thymidine-deficient CEM cells (TK^-) and compared to the parent nucleoside d4T, the anti-HIV activity was improved by 1000-fold. These results demonstrate that these prodrugs efficiently enter cells and deliver the nucleoside triphosphate analogues. Thus, they bypass all steps of the intracellularly needed phosphorylation.

Furthermore, this thesis describes a series of γ-dialkylphosphate-modified-d4TDPs and γ-dialkylphosphonate-modified-d4TDPs. Both γ-modifications are not identical to the previous work; in contrast, they are non-bioreversible, simple alkyl groups. The hydrolysis mechanism proceeded variously to the published cleavage pathway for Tri*PPP*ro-NTPs. The delivery of d4TDP rather than d4TTP was observed in CEM/0 cell extracts that was probably due to chemical phosphoanhydride cleavage. Interestingly, γ-(alkyl; alkyl-C18)-phosphate-d4TDPs and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs were highly active against HIV-1 and HIV-2 in cultures of infected wild-type CEM/0 cells and showed a marked improvement of antiviral activity (1120-fold more active as d4T) in CEM/TK^- cells as well, indicating that these compounds were taken-up into cells and delivered a phosphorylated form of d4T.

This thesis describes the advancement of the Tri*PPP*ro-prodrug system for intracellular delivery of NTP derivatives. This advanced prodrug offers high potential to be used in antiviral and antitumoral chemotherapies.

1 Introduction

The human immunodeficiency virus (HIV) is a retrovirus that infects cells of the body's immune system, destroying or impairing their function. Infection occurs through body fluids such as blood. Specifically, the virus infects and replicates in $CD4^+$ T cells, which make up an integral part of the immune system, ultimately destroying these cells which leads to the development of AIDS (acquired immunodeficiency syndrome).[1-8] Immunodeficiency always results in increased susceptibility to a wide range of infections and cancers, two of the leading causes of death worldwide.[9-13] Globally, approximately 38.0 million people were living with HIV at the end of 2019; 1.7 million new infections occurred in that year and 0.69 million people died from HIV-related causes,[14] according to the World Health Organization (WHO). Since the identification of AIDS in the earlier 1980s and its cause, the retrovirus HIV, the scientific progress in HIV/AIDS research has been extraordinary, especially regarding the development of antiretroviral therapy (ART) that has proven to be life-saving for millions of people.

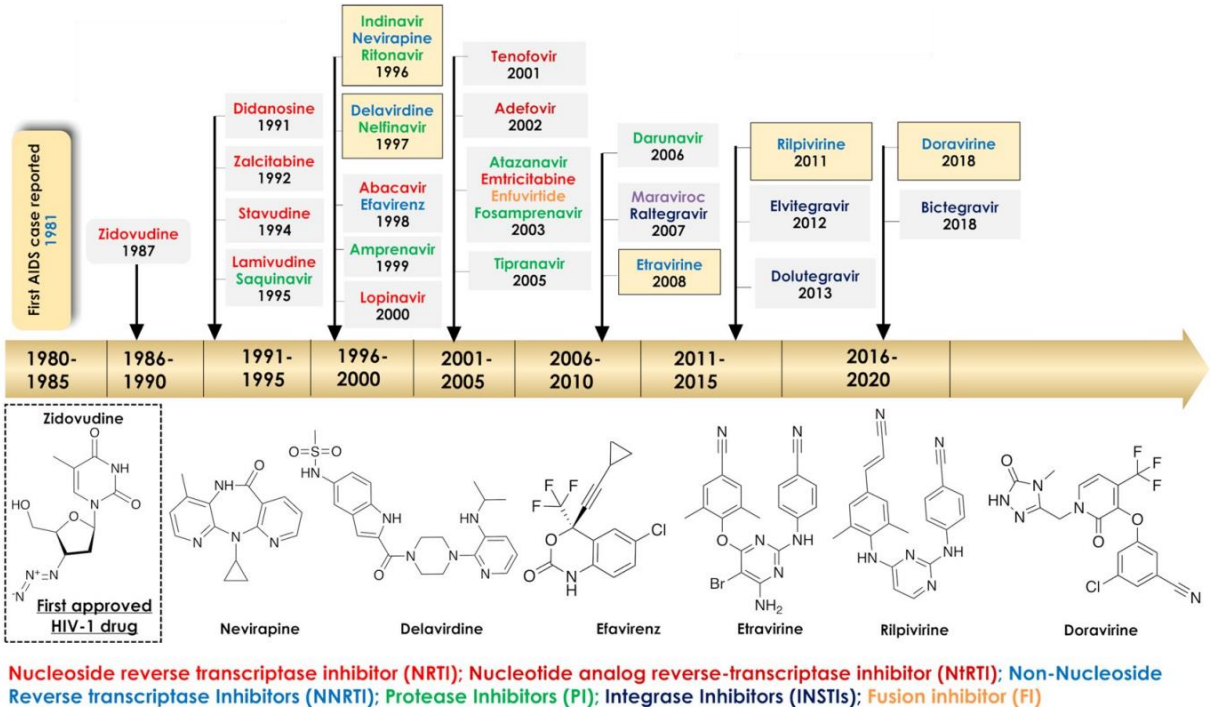


Figure 1: A brief timeline of HIV-1 drug development; the drugs that target for RT are highlighted.[15]

Although a cure for HIV-infection / AIDS does not yet exist, the introduction of highly active antiretroviral therapy (HAART), a treatment paradigm using three or more antiretroviral drugs in combination, has shown to dramatically reduce HIV-associated morbidity and mortality.[16,17] This treatment reduces the amount of HIV in the blood and increases the number of CD4-positive cells, thus strengthening the

infected individual's immune system. Approved antiretroviral (ARV) HIV medicines suppress the replication and, therefore, the spread of the virus within the body by interfering with different viral targets. These drugs can be divided into eight classes: 1. nucleoside reverse transcriptase inhibitors (NRTIs; abacavir, emtricitabine, lamivudine, zidovudine); 2. non-nucleoside reverse transcriptase inhibitors (NNRTIs; efavirenz, doravirine, etravirine, nevirapine, rilpivirine); 3. protease inhibitors (PIs; atazanavir, darunavir, fosamprenavir, saquinavir ritonavir, tipranavir); 4. fusion inhibitors (FIs; enfuvirtide); 5. CCR5 antagonists (maraviroc); 6. post-attachment inhibitors (ibalizumab-uiyk); 7. integrase strand transfer inhibitors (INSTIs; dolutegravir, raltegravir); 8. pharmacokinetic enhancers (cobicistat). Some of these drugs and their development timeline are shown in Figure 1.

Nucleotides and nucleosides are essential components of cells and they play key roles in several fundamental biological processes, including DNA and RNA synthesis, cell division, and metabolism. Nucleoside analogues play significant roles in antiviral chemotherapies and are valued for their impressive potency to treat HIV, herpes virus, hepatitis B and hepatitis C virus infections.[18-22] To date, many different nucleoside analogues have been approved as HIV reverse transcriptase (RT)[19,20] inhibitors (NRTIs)[23] and they prevent completion of the synthesis of the double-stranded viral DNA, which is an early step in the infection, thus ultimately preventing HIV from infecting new cells. The first reverse transcriptase inhibitor zidovudine (AZT) was approved by the U.S. Food and Drug Administration (FDA) for treating AIDS in 1987, and thirteen FDA-approved NRTIs are now, in 2020, commercially available.[24] The action of antiviral or antitumor active nucleoside analogues is highly dependent on the efficient intracellular conversion by host cell kinases to give, via the monophosphate (NMP) and the diphosphate (NDP), ultimately the bioactive nucleoside analogue triphosphate (NTP).[25,26] The latter are substrates for viral or cellular polymerases and are incorporated into DNA/RNA during replication or DNA excision repair synthesis, which gives rise to stalled replication forks and chain termination. However, nucleoside analogue triphosphates cannot be considered as viable drug candidates as they have poor chemical and biological stability along with high polarity, as they are negatively charged at physiological pH. This hinders them from traversing across biological barriers and reaching the targeted cells or tissues. Furthermore, former studies have shown that cellular kinases in many cases catalyse the phosphorylation of nucleoside analogues insufficiently, resulting in low or no biological activity of the given nucleoside analogue,[26-28] and metabolic bottlenecks imposed by inefficient single phosphorylation steps can lead to adverse effects.[29,30] Within the nucleoside analogue phosphorylation pathway, often the first phosphorylation step to yield the monophosphate metabolite

(NMP) catalysed by the salvage pathway enzyme thymidine kinase (TK) has been identified as the limiting step. For example, for the intracellular activation of the NRTI 3'-deoxy-2',3'-dehydrothymidine (d4T, Figure 8), the formation of its monophosphate metabolite (d4TMP, **1a**) imposes a metabolic bottleneck. This led scientists to prepare "protected" monophosphate nucleosides (pronucleotides) capable of traversing the cell membrane and of delivering the nucleoside monophosphates intracellularly. In addition, despite the availability of several nucleoside and nucleotide analogues in the clinic,[31,32] the development of prodrugs is needed to improve bioavailability after oral administration, overcome low biological half-lives or, inter-individual variability requiring dose adaptation and counter the development of resistant virus strains.[33,34] To overcome these problems, several prodrugs strategies allowing intracellular delivery of nucleotide analogues have already resulted in orally administrable forms of some antiviral nucleoside monophosphates.[35-43]

However, such NMP prodrug strategies were not in all cases successful. In the metabolism of 3'-deoxy-3'-azidothymidine (AZT, **2**, Figure 8), not the formation of the monophosphate derivative (AZTMP, **2a**) is rate limiting but the formation of the corresponding nucleoside diphosphate metabolite (AZTDP, **2b**) by the host cell enzyme thymidylate kinase (TMPK). Recently, the Meier lab has reported on a successful approach to deliver nucleoside diphosphate prodrugs (NDPs) inside cells (Di*PP*ro-approach),[44-48] proving the cell-uptake of the compounds and the intracellular delivery of the corresponding NDP. However, in both approaches, delivering the mono- or diphosphorylated forms of the nucleosides, respectively, the released NMP or NDP still need further phosphorylation into their triphosphate forms by cellular kinases in order to interact with the viral polymerases. As a consequence, a nucleoside triphosphate approach has been developed (Tri*PPP*ro) by the Meier lab which achieves to bypass all steps of phosphorylation from the nucleoside analogue into the bioactive nucleoside triphosphate form can be bypassed.[49]

Despite these obvious advantages, almost no reports on attempts to design triphosphate prodrugs had been disclosed, earlier,[50,51] and indeed, the challenges should not be underestimated: (a) a triphosphate can carry up to four negative charges requiring masking, (b) the triphosphate unit comprise two reactive, inherently labile phosphate anhydride linkages, and (c) the risk of low stability of the delivered NTP toward phosphatases leading to dephosphorylation and thus rapid clearance of the bioactive metabolite. Until recently, it had been common sense that the design of NTPs would be almost impossible: *"Direct delivery of triphosphate or diphosphate forms of nucleoside analogues would be desirable but is impractical because of their instability during synthesis."*[52]

2 Background

2.1 Human Immunodeficiency Virus (HIV)

HIV, a retrovirus, infects cells of the immune system. AIDS is the most advanced stage of HIV infection that occurs when the body's immune system is severely damaged, which can lead to life-threatening infections. HIV/AIDS continues to be a major global public health issue. Although extraordinary progress has been made in the fight against new HIV cases and AIDS deaths, the HIV pandemic continues.[14]

2.1.1 HIV transmission

HIV can be transmitted via the exchange of a variety of certain body fluids from infected people, such as blood, semen (*cum*) and pre-seminal fluid, breast milk, vaginal fluids, and rectal fluids.[59-61] Hence, HIV can be spread through specific routes: 1. having unprotected sex or sharing needles with an HIV-positive individual; 2. from mother to child during pregnancy, birth, or breastfeeding and injuries from HIV-contaminated needles or other sharp objects. In extremely rare cases, HIV has been transmitted by having oral sex, being bitten or eating food that has been pre-chewed by a person with HIV etc.[61]

2.1.2 Three stages of HIV infection

HIV infection has three distinct stages: the acute (primary), chronic (asymptomatic) and AIDS (final) stages (Figure 2),[62] and the symptoms vary depending on the stage of infection. Acute HIV infection is the earliest stage. Here, HIV multiplies rapidly and spreads throughout the body.[60] In the first few weeks after the infection event, people may experience no symptoms or influenza-like symptoms, such as fever, chills, night sweats, muscle aches, fatigue, swollen lymph nodes, mouth ulcers, headache, sore throat or rash. During chronic HIV infection, the second stage, people may not have any HIV-related symptoms because of low levels of HIV infection in the body, which is mainly detected using antibody immunoassays.[63] Without HIV treatment, the virus multiplies for approx. 10 to 15 years, while gradually destroying the immune system , ultimately leading to the progression to AIDS, which is the last stage of HIV infection.[64] The symptoms of AIDS include: 1. rapid weight loss; 2. extreme and unexplained tiredness; 3. recurring fever or profuse night sweats; 4. pneumonia; 5. memory loss, depression, and other neurologic disorders; 6. red, brown, pink, or purplish blotches on or under the skin or inside the mouth, nose, or eyelids; 7. diarrhea that lasts for more than a week; 8. prolonged swelling of the lymph glands in the armpits, groin, or neck. HIV infection can also lead to other severe illnesses like those caused by secondary infections, such as tuberculosis (TB), and also to the development of certain

cancers.[11] Once diagnosed with AIDS, people typically survive about 3 years only without HIV treatment.[64]

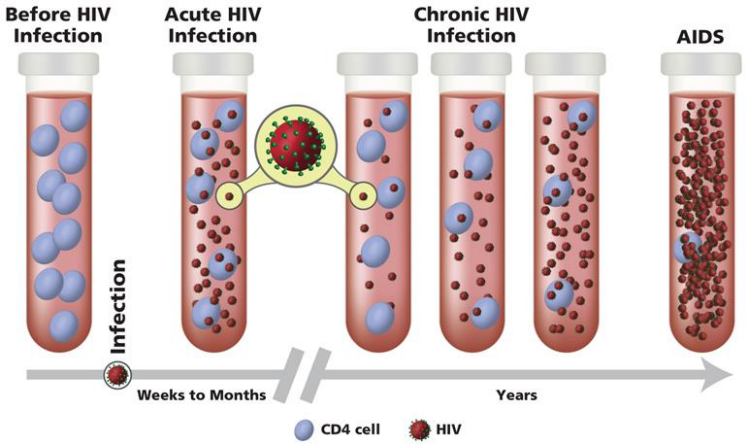


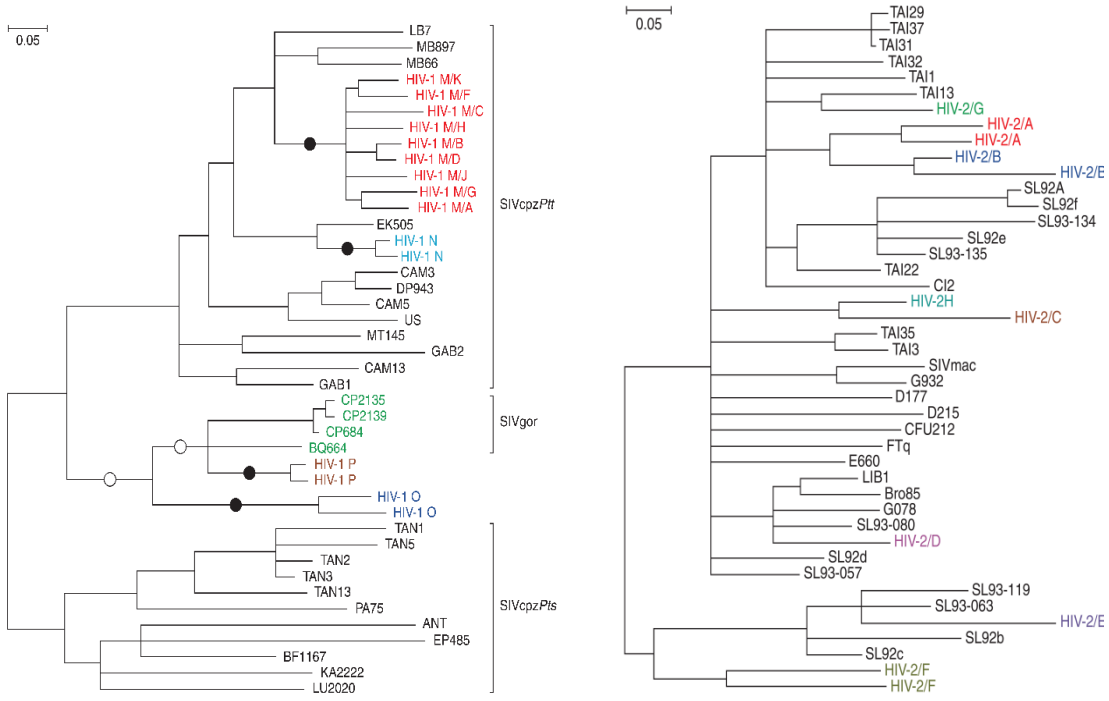
Figure 2: Three stages of HIV infection.

Researchers have recognized that viral load is a key determinant of HIV transmission in the last decades. Antiretroviral therapy stops HIV from actively replicating and thus reduces the risk of sexual transmission of the virus to an HIV-negative partner. However, since HIV is a retrovirus that integrates its genome into the DNA of the infected cell, a cure has not been achieved thus far (with the exemption of a few anecdotal cases). In order to develop a cure for HIV, scientists are also aiming to better understand how HIV persists in the body in viral reservoirs. Understanding the evolution of HIV and its replication in cells is crucial for deciphering its interaction with the immune system and developing effective control therapeutics.[82]

2.1.3 HIV structure, genome and proteome

There are two main types of HIV with slightly different genome structures: HIV-1 and HIV-2. A close relative of HIV-1 is SIV, which was isolated from the chimpanzee subspecies Pan troglodytes, whereas HIV-2 is most closely related to SIVsmm, a strain that naturally infects sooty mangabey, a different primate found in Africa.[65] HIV-1 is phylogenetically divided into four groups (Figure 3, left) — 'M', 'N', 'O' and 'P',[66-68] each of which resulted from an independent origin.[69,70] For example, HIV group M was the first to be discovered and represents the pandemic group of HIV-1. Within the M group, nine different subtypes (A-D, F-H, J, K) have been described, based on the phylogenetic clustering of viral sequences. According to the report, all HIV-1 groups M and N, O and P are very closely related to SIVcpzPtt (SIVcpz from *P. t.* troglodytes).[65] HIV-2 is closely related to SIV-2 of mangabey monkeys in West Africa (SIVsmm).[71] HIV-2 is morphologically indistinguishable from HIV-1[72] and composed of at least eight

groups (A-H), which are further divided into subtypes, for example HIV-2 group A is divided into A1 and A2 (Figure 3, right).[73,74] To test for HIV-2 specific diagnostic tools are need because of the distinct differences between HIV-1 and HIV-2 in the antigenicity of the viral proteins and the genome structure.[75] As compared to HIV-1, HIV-2 usually has a lower pathogenic potential and most people infected with HIV-2 do not progress to AIDS.[75]



HIV-1 origins HIV-2 origins

Figure 3: The phylogenetic relationships of representative SIVcpz, HIV-1, and SIVgor strains are shown for a region within the viral pol gene (left); the phylogenetic relationships of representative SIVsmm and HIV-2 strains are shown for the gag gene (right). The phylogenetic tree was built using maximum likelihood methods (Guindon and Gascuel 2003). The scale bar represents 0.05 nucleotide substitutions per site.[65]

HIV-1 has a spherical shape[76] with a diameter of about 120 nm. The virion consists of two copies of the single-stranded RNA genome, viral proteins and the viral envelope (Figure 4).[77] The viral envelope is composed of a lipid bilayer, which is derived from the host cell and contains cellular proteins, as well as the viral envelope (Env) proteins: glycoprotein 120 (gp120) and glycoprotein 41 (gp41). Gp41 is a transmembrane protein, non-covalently bound to gp120, and forming a heterotrimer of three gp41 and three gp120.[78] Gp41 is associated with the viral p17 matrix protein (which surrounds the capsid to ensure the integrity of the virion particle) and encompasses a conical capsid that consists of the viral gag protein (p24). The capsid protein contains two identical copies of the single-stranded RNA genome, enzymes (reverse transcriptase, integrase and protease), Vif (viral infectivity factor), Vpr (viral infectivity factor), Vpu (virus protein unique) and Nef (negative regulating factor) proteins as well as some cellular factors,

such as $tRNA^{lys3}$ which is used as a primer for reverse transcription. The HIV genome contains the typical retroviral genes gag (CA, MA and NC), pol (RT, PR and IN), and env (gp120 and gp41) flanked by long terminal repeats (3´-LTR and 5´-LTR), which contain the viral promoter (Figure 4, top). In addition to the structural proteins, HIV-1 has six regulatory genes, tat, rev, nef, vif, vpr, and vpu (or vpx in the case of HIV-2), that code for proteins that control the ability of HIV to infect cells and is thus considered a “complex” retrovirus (table 1).[79-81]

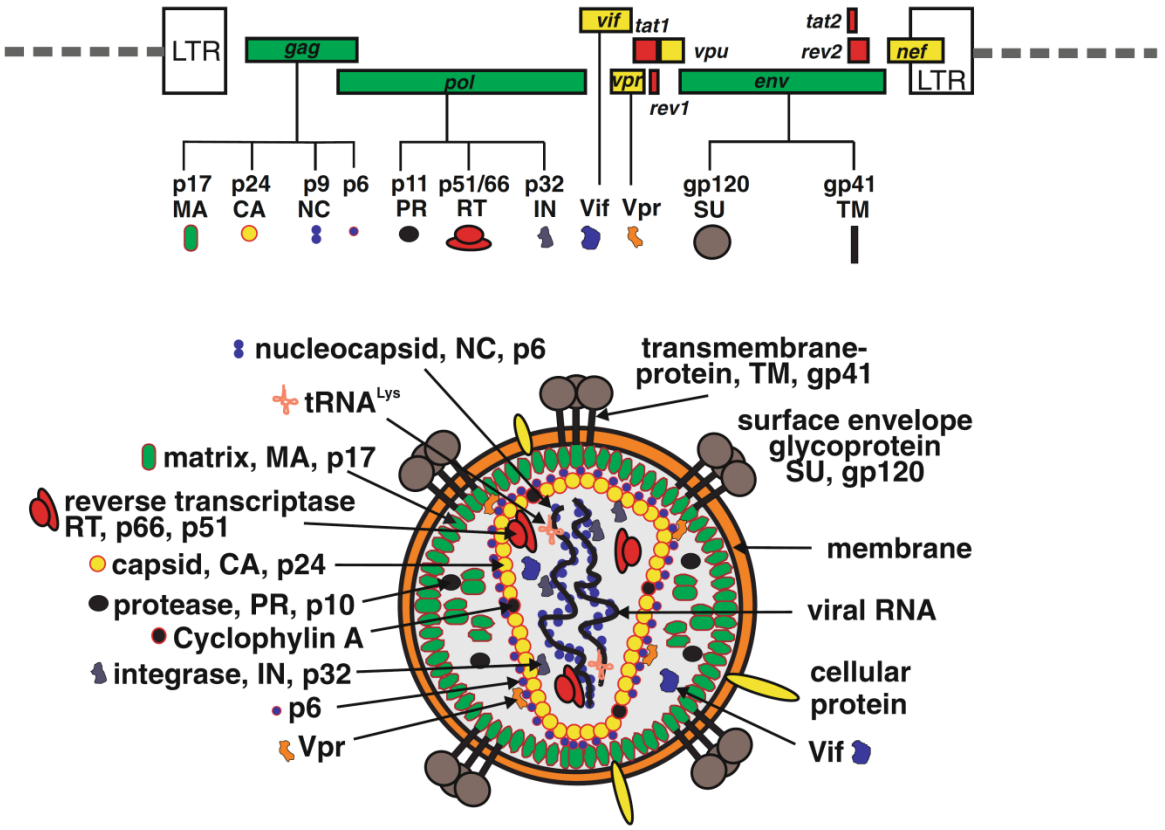


Figure 4: Schematic representation of viral genome arrangement of HIV-1 (top) and virion structure (bottom).

Table 1. Overview of HIV-1 proteins and their function

Gene	Size*	Protein	Function Role	Protein Type
gag		Pr55Gag	precursor proteins	Structural Protein
	p24	capsid protein (CA)	formation of conical capsid	
	p17	matrix protein (MA)	myristilated protein, forming the inner membrane layer	
	p7	nucleoprotein (NC)	formation of the nucleoprotein/RNA complex	
	P6		Includes Vpr into the new virions and release them from the infected cell.	

		Pr160GagPol	precursor of the viral enzymes	
	p11	protease (PR)	proteolytic cleavage of Gag (Pr55) and Gag-Pol (Pr160GagPol) precursor protein; release of structural proteins and viral enzymes	
pol	p51	reverse transcriptase (RT)	transcription of HIV RNA in proviral DNA	
	p15 (66)	RNase H	degradation of viral RNA in the viral RNA/DNA replication complex	
	p32	integrase (IN)	integration of proviral DNA into the host genome	
		PrGp160	precursor of the envelope proteins SU and TM, cleavage by cellular protease	
	gp120	surface glycoprotein (SU)	attachment of the virus to the target cell	
env				
	gp41	transmembrane protein (TM)	anchorage of gp120, fusion of viral and cell membrane	
tat	p14	transactivator protein	activator of transcription of viral genes	
rev	p19	RNA splicing regulator	regulates the export of non-spliced and partially spliced viral mRNA	Regulatory Proteins
nef	p27	negative regulating factor	myristilated protein, influence on HIV replication, enhancement of infectivity of viral particles, downregulation of CD4 on target cells and HLA on target cells.	
vif	p23	viral infectivity protein	critical for infectious virus production in vivo	
vpr	p15	virus protein r	component of virus particles, interaction with p6, facilitates virus infectivity, effect on the cell cycle	Accessory Proteins
vpu	p16	virus protein unique	efficient virus particle release, control of CD4 degradation, modulates intracellular trafficking	
vpx	p15	virus protein x	interaction with p6 in virus particles, involved in early steps of virus replication of HIV-2, component of virus particles	

*Numbers correspond to the size of the proteins (p) or glycoproteins (gp) in 1,000 Da.

2.1.4 HIV life cycle

HIV-1 infects $CD4^+$ T-cells, macrophages, and dendritic cells, causing functional defects and damage to the immune system. The HIV-1 replication cycle consists of seven steps (Figure 5): 1) binding and fusion with the membrane and entry into the cell; 2) release of single-stranded RNA into the cytoplasm; 3) reverse transcription of viral genomic RNA into proviral DNA; 4) translocation of proviral DNA to the cell nucleus and integration into the host DNA; 5) transcription of proviral DNA into mRNA coding for viral proteins; 6) translation into viral precursor proteins and HIV protease-mediated posttranslational cleavage, and 7) viral maturation and budding. In the early stages of this cycle, the virus attaches to the

surface of the host cell and releases HIV RNA and HIV enzymes (reverse transcriptase and integrase), subsequently. The late-stage starts with the initiation of proviral DNA transcription and ends with the release and maturation of fully infectious progeny virions. [83-85]

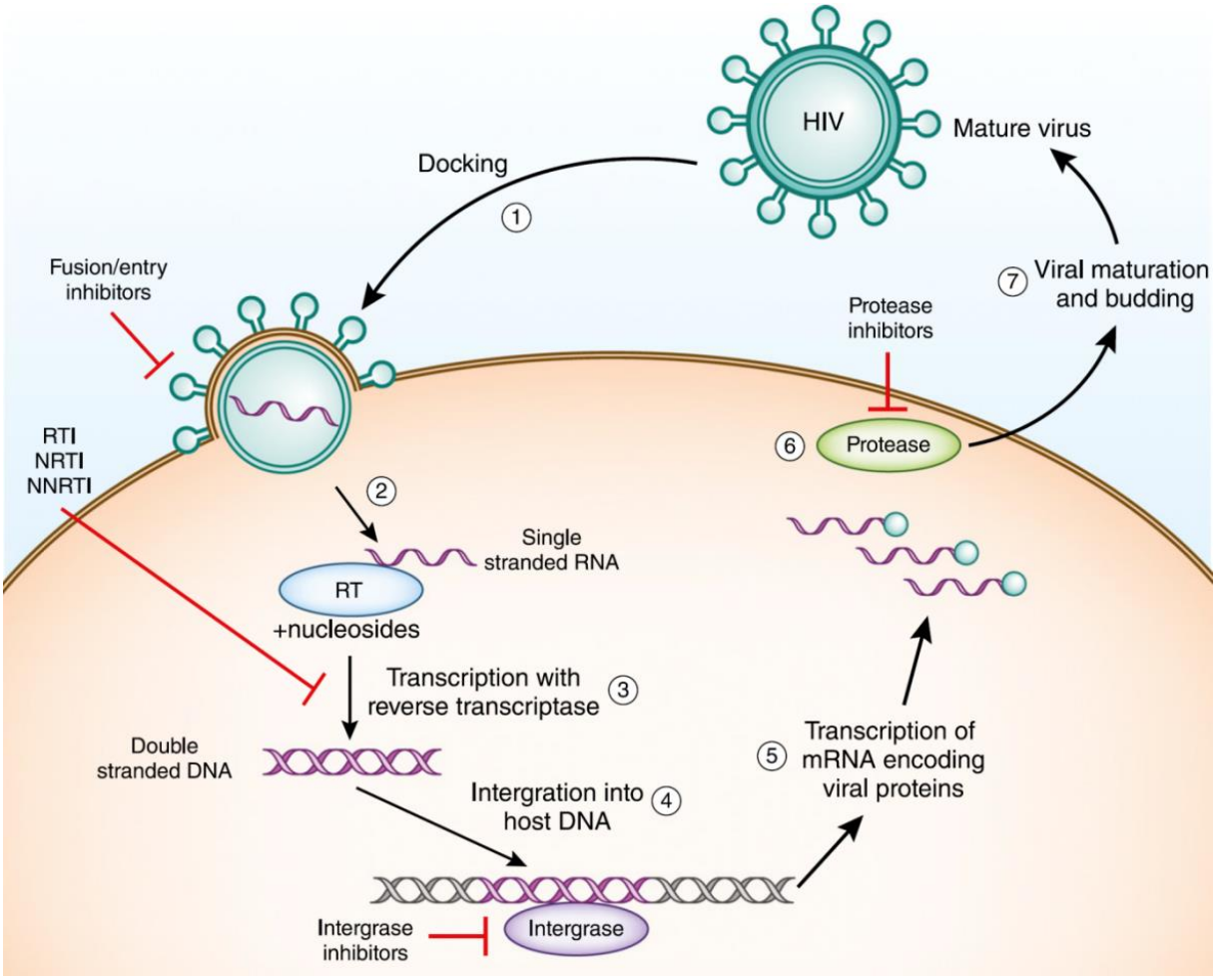


Figure 5: HIV-1 life cycle and classes of antiretroviral agents that interfere with specific steps.[82]

As is shown in Figure 5, there are four main classes of anti-HIV drugs that target different disease-relevant mechanisms, including viral attachment / cell entry (fusion/entry inhibitors), reverse transcription (RTI, NRTI, and NNRTI), integration into the host cell genome (integrase inhibitors) and viral maturation (protease inhibitors and maturation inhibitors).

2.2 Nucleosides and nucleotides

Nucleosides and their corresponding nucleotides play important roles in various intracellular processes such as signalling, metabolism, and energy regulation.[18] Natural nucleosides consist of a nucleobase and the five-carbon sugar ribose whereas nucleotides are nucleoside with one or more phosphate (or

phosphate-like) groups attached (Figure 6). Nucleobases include purines (adenine and guanine) and pyrimidines (cytosine, thymine and uracil). They are the basic building blocks of nucleic acids and hence function as the fundamental units of the genetic code. RNA is composed of a phosphate-ribose backbone and the nitrogen-containing nucleobases (A, G, C, and U), while DNA is composed of a phosphate-deoxyribose backbone and the four nitrogen-containing nucleobases (A, G, C, and T). In double-stranded DNA, a base pair is one of the pairs A-T or C-G.[86] During the transcription of DNA into RNA, A hybridizes with U and G hybridizes with C (Figure 7). These Watson-Crick base pairs form double or triple hydrogen bonds between the amine and carbonyl groups, respectively.

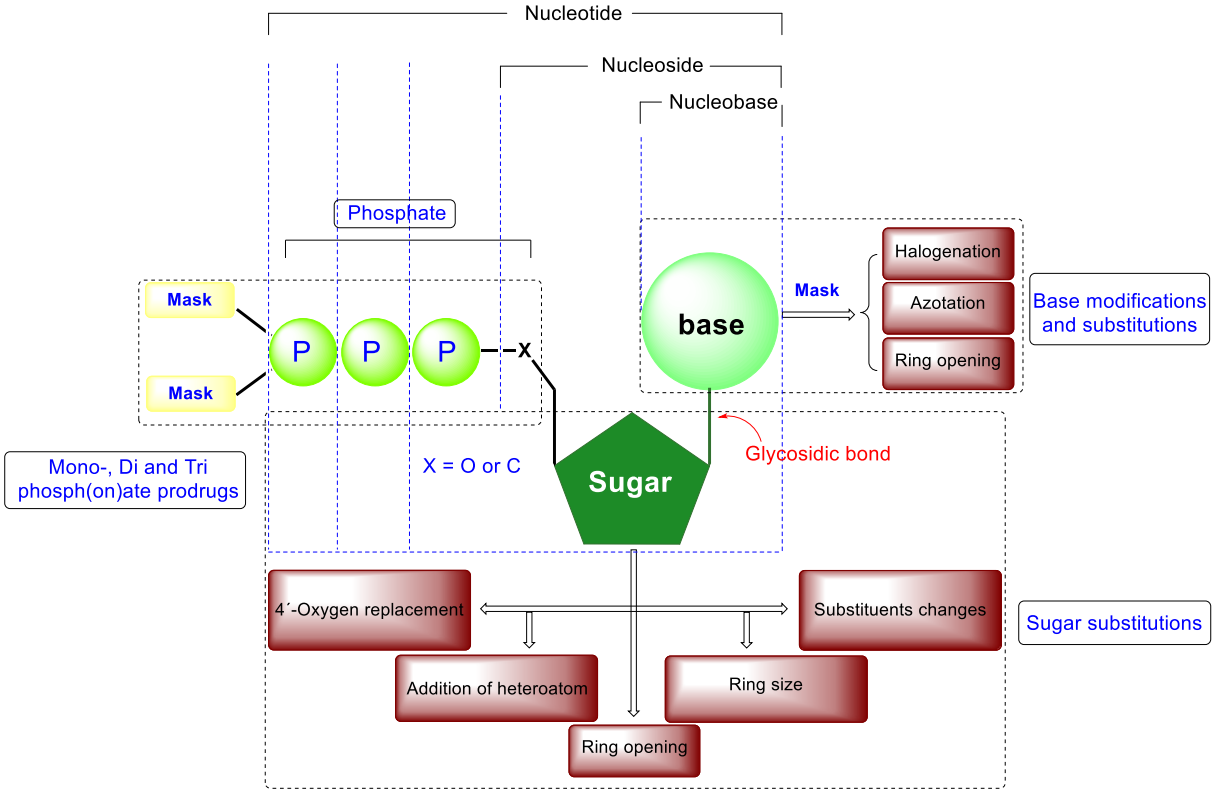


Figure 6: General structure and chemical modifications of nucleoside and nucleotide analogues.

There are numerous naturally occurring nucleosides in nature, divided into two major categories: N-nucleosides and C-nucleosides, in both of which the configuration at the anomeric centre (C-1´) is β.[87] Nucleoside analogues are derivatives of these naturally occurring ones with modifications in the sugar or nucleobase moieties, glycosidic bond and phosphate group of the nucleotide. They are developed, for example, to find new drugs with potent biological activity (Figure 6).[18,88] Chemical modifications in the nucleobase moiety of nucleosides include halogenation azotation and ring opening. The methods of substituent changes, ring opening, ring size changes, 4´-oxygen replacement, and addition of

heteroatom, can be used to modify the sugar moiety. Similar modifications can also be used at the phosphate groups in nucleotide analogues.[89-92] Therefore, a large diversity in nucleoside structure and thus biological effect can be achieved with these modifications.

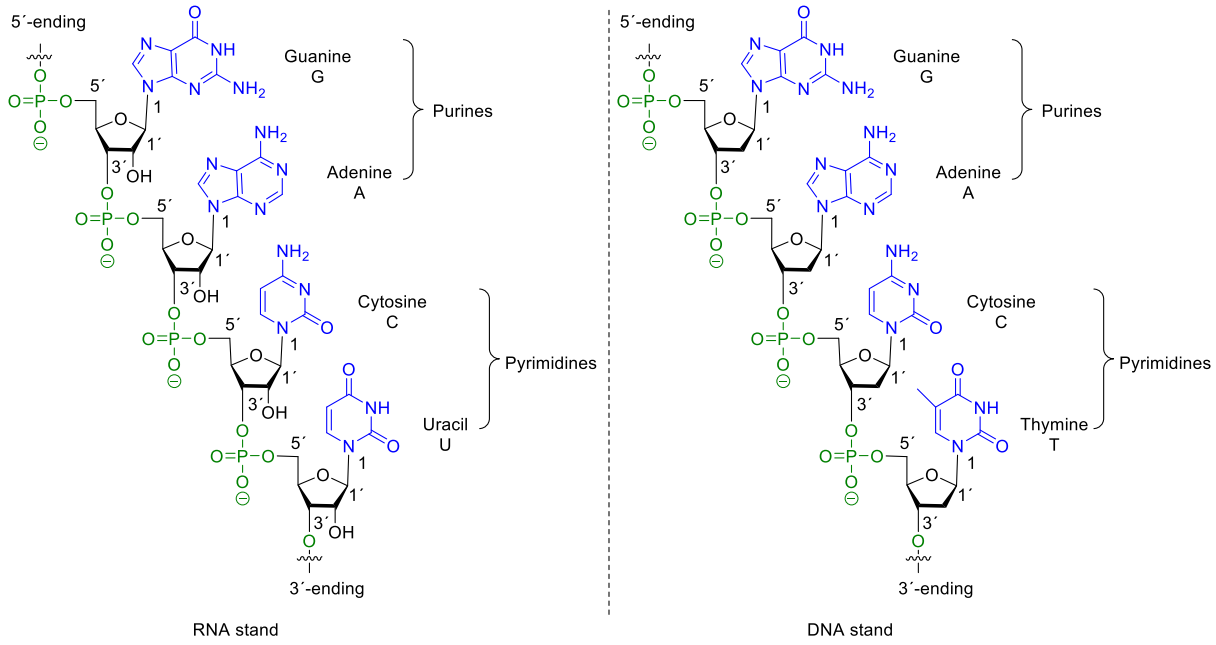


Figure 7: Primary structure of a nucleic acid fragment: RNA stand (left) and DNA strand (right).

2.2.1 Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs and NTRTIs)

When HIV infects a cell, the viral single-stranded RNA genome is first copied into double-stranded DNA by the viral enzyme reverse transcriptase (RT). Drugs from the three class of reverse transcriptase inhibitors (RTIs), namely the nucleoside RT inhibitors (NRTIs), nucleotide RT inhibitors (NTRTIs), and non-nucleoside RT inhibitors (NNRTIs), block reverse transcriptase's enzymatic function and prevent synthesis of the complete double-stranded viral DNA, thus preventing HIV from multiplying. NRTIs and NTRTIs considered as prodrugs that must undergo intracellular phosphorylation to their active forms: nucleoside 5´-triphosphate. They compete with the natural deoxyribonucleotides for incorporation into the growing proviral DNA chain.

NRTIs form the first class of antiretroviral drugs that were developed in response of the HIV pandemic starting in the 1980s. Zidovudine (AZT) is a thymidine analogue in which an azido group replace the 3´-hydroxyl group of the ribose. It was the first clinically used nucleoside HIV reverse transcriptase inhibitor and remains an important component in frequently used drug regimens, nowadays. Over the course of 40 years that followed after this seminal discovery, many nucleosides and nucleotides (Figure 8) have

been approved as an anti-HIV drug approved by the FDA for the treatment of HIV infection starting with the approval of AZT in 1987 and followed by didanosine (ddI, 1991), zalcitabine (ddC, 1992), stavudine (d4T, 1994), lamivudine (3TC, 1995), abacavir (ABC, 1998), tenofovir disoproxil fumarate (TDF, 2001) and emtricitabine (FTC, 2003).[93-101] However, zalcitabine is not used in clinical practice because of its weak antiviral activity, as well as its unfavourable pharmacokinetic and toxicity profile.

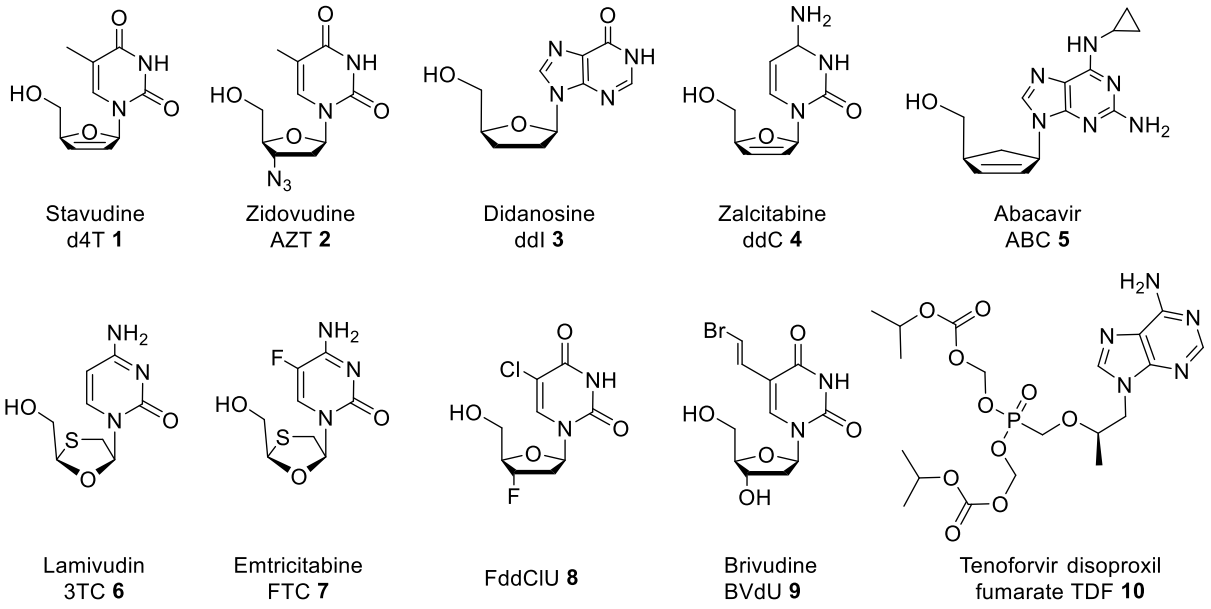


Figure 8. Representative nucleoside and nucleotide analogues.

However, viral resistance quickly developed, and so new therapy approaches were developed, which combined several nucleoside drugs and one nonnucleoside RT inhibitor or protease and integrase inhibitors (highly active antiretroviral therapy, HAART), to improve the treatment of HIV infected patients and to reduce morbidity and mortality.[102-104] In which combination HIV medicines prevent the rapid development of resistance by suppressing HIV replication in cells, thus reducing the potential pool of spontaneous resistance mutations.[105] In 1997, Combivir (AZT 300 mg plus 3TC 150 mg, GlaxoSmithKline Ltd, Brentford Middlesex, UK) became the first fixed-dose drug combination for HIV treatment. Combination therapy was not common until clinical trials showed improved virus suppression and improvement in $CD4^+$ T cell count compared to NRTI monotherapy.[98,106-110]

Approximately 20 combination of HIV drugs have been approved for treating HIV infected individuals over the last 20 years of clinical use of Combivir, and these drugs are designed to inhibit the main viral enzymes and to avoid the emergence of drug resistance. The current medicinal drug combinations, such as Kaletra (2000), Stribild (2012), Cimduo (2018), and Dovato (2019) are presented.[111]

2.2.2 Mechanisms of action of nucleoside analogues

The antiviral efficacy of nucleoside analogues is strongly dependent on their intracellular activation by virus-encoded or, in most cases, host cellular kinases to undergo stepwise addition of phosphate groups to give ultimately the bioactive nucleoside analogue triphosphates,[20,35] illustrated in Figure 9. NRTIs need three sequential phosphorylation steps to form their triphosphate active forms, while for NtRTI, already containing a phosphonate group, only one step (or two steps) is (are) required. Notably, the concentration of phosphorylated metabolites of NRTIs is dictated by the balance between enzyme-catalysed phosphorylation and dephosphorylation.[19]

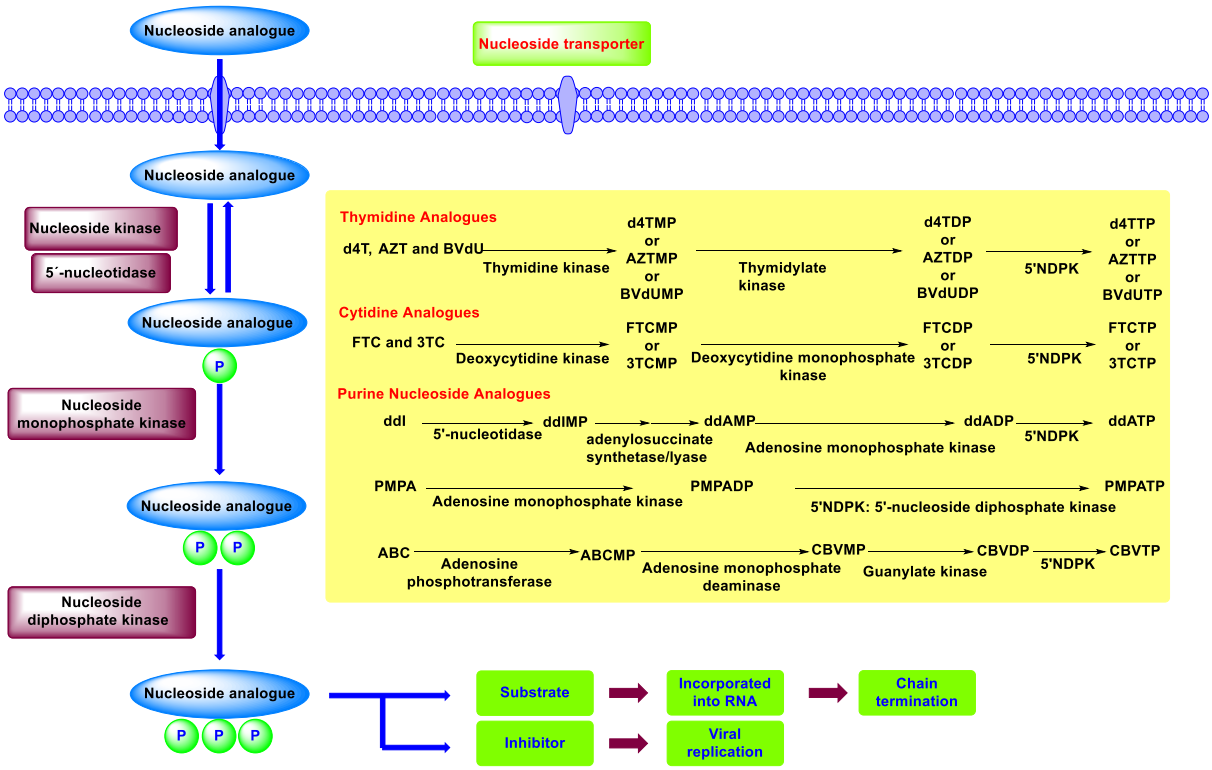


Figure 9. Host-cell-mediated sequential enzymatic phosphorylation steps required for activating the nucleoside analogue reverse-transcriptase inhibitors (NTRTIs and NRTIs) to the corresponding 5′-triphosphate. During the course of the transport or activation process, several mechanisms of resistance may impede the formation of the active metabolites.

The phosphorylation of nucleoside analogues strongly depends on their different chemical structure (Figure 10). Unlike thymidine analogues (d4T **1** and AZT **2**), the phosphorylation rate of cytidine analogues (3TC **6** and FTC **7**) by cytidine kinase does not depend on the cell-cycle.[112] Several NRTIs, such as ddA **11**, additionally undergo base modification between the phosphorylation steps. Nucleoside analogue ddA **11** is deaminated to didanosine (ddI, **3**), which is first phosphorylated to ddI-monophosphate (ddIMP, **3a**) by 5′-nucleotidase. In a second step, ddIMP **3a** is converted to ddAMP **11a**

by adenylosuccinate synthetase and adenylosuccinate lyase. Then, ddAMP **11a** is transformed by nucleoside mono- and di-phosphate kinases to the active triphosphate metabolite, 2',3'-dideoxyadenosine 5'-triphosphate (ddATP, **11c**), which completes with 2'-deoxyadenosine 5'-triphosphate (dATP) to inhibit HIV-RT-catalysed proviral DNA chain elongation.[113] The nucleoside analogue abacavir (ABC) **5** is transformed into ABCMP **5a** by adenosine phosphotransferase (APT), then converted into the guanosine analogue (CBVMP, **12a**) by adenosine monophosphate deaminase (AMPDA) followed by phosphorylation of CBVMP **12a** into the HIV-RT inhibitor CBVTP **12c** by cellular kinases (GK and 5'NDPK).[114,115] Thus, this monophosphorylation step makes abacavir an important asset in multiple NRTI combination antiretroviral therapies.

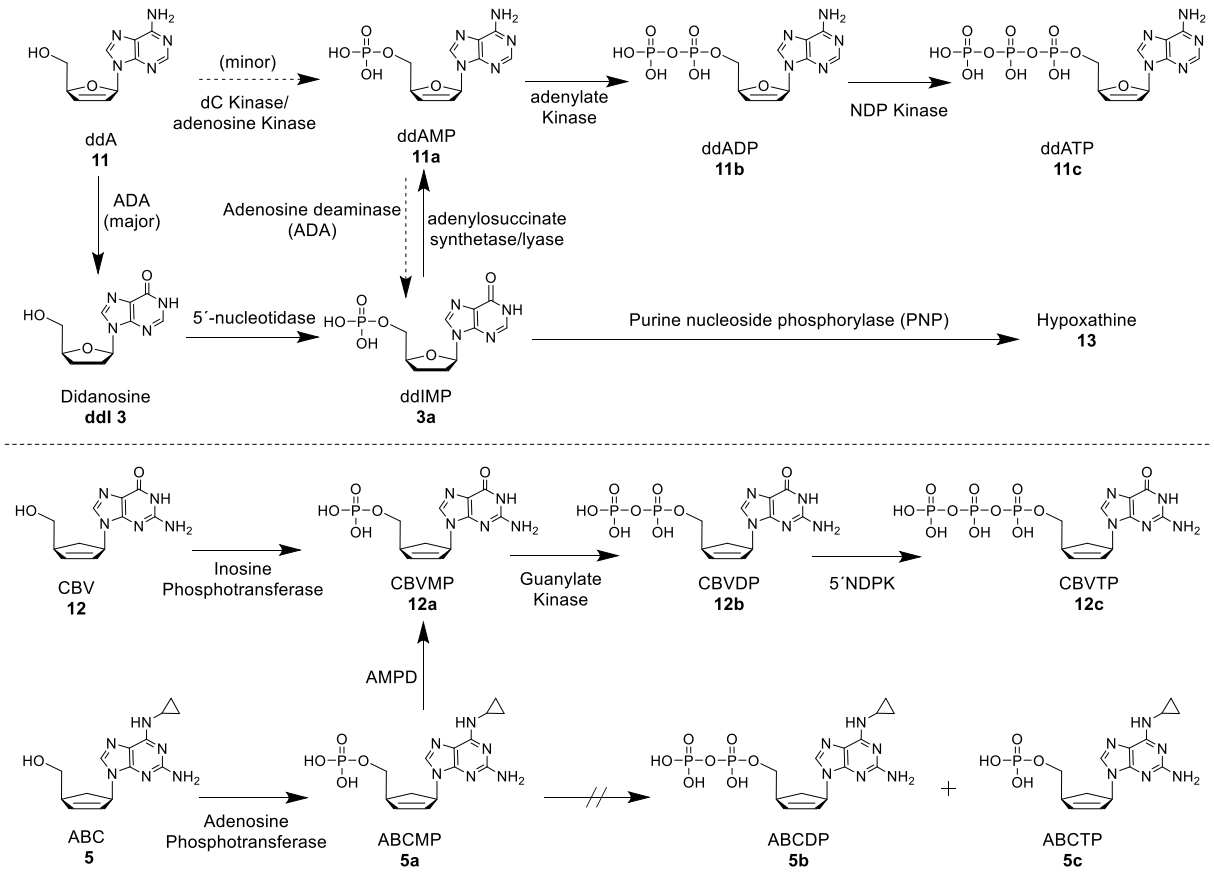


Figure 10. Activation pathway of ddI and ddA (top) and activation pathway of ABC (bottom).

2.3 Prodrug systems and Pronucleotide concept

Nucleoside and nucleotide analogues have a long history in the field of medicinal chemistry. The design of nucleoside analogues as potential anti-HIV agents focused on both nucleobase modifications and alterations in the sugar-moiety (Figure 6). Various masking groups have been introduced neutralize the

negative charges and increase the hydrophobicity of phosphate or phosphonate moieties (resulting in so-called pronucleotides) to facilitate entry of these phosphate or phosphonate nucleoside prodrugs into the cells. Several strategies, such as nucleoside monophosphate prodrugs (ProTide and *cyclo*Sal), nucleoside diphosphate prodrugs (Di*PP*ro-concept), and nucleoside triphosphate prodrugs (Tri*PPP*ro-concept), have been developed over the past decades (Figure 11). Chemically modified nucleoside prodrugs depend on the type of nucleoside as well as the masking groups: 1, symmetric compounds and non-symmetric compounds; 2, phosphoesters and phosphoramidates. Once a pronucleotide enters a cell, the masking groups of nucleoside prodrugs have to be cleaved by chemical or by enzymatic processes to release the corresponding nucleotide, which can exert its anti-viral potency after intracellular conversion to the corresponding nucleoside triphosphate.

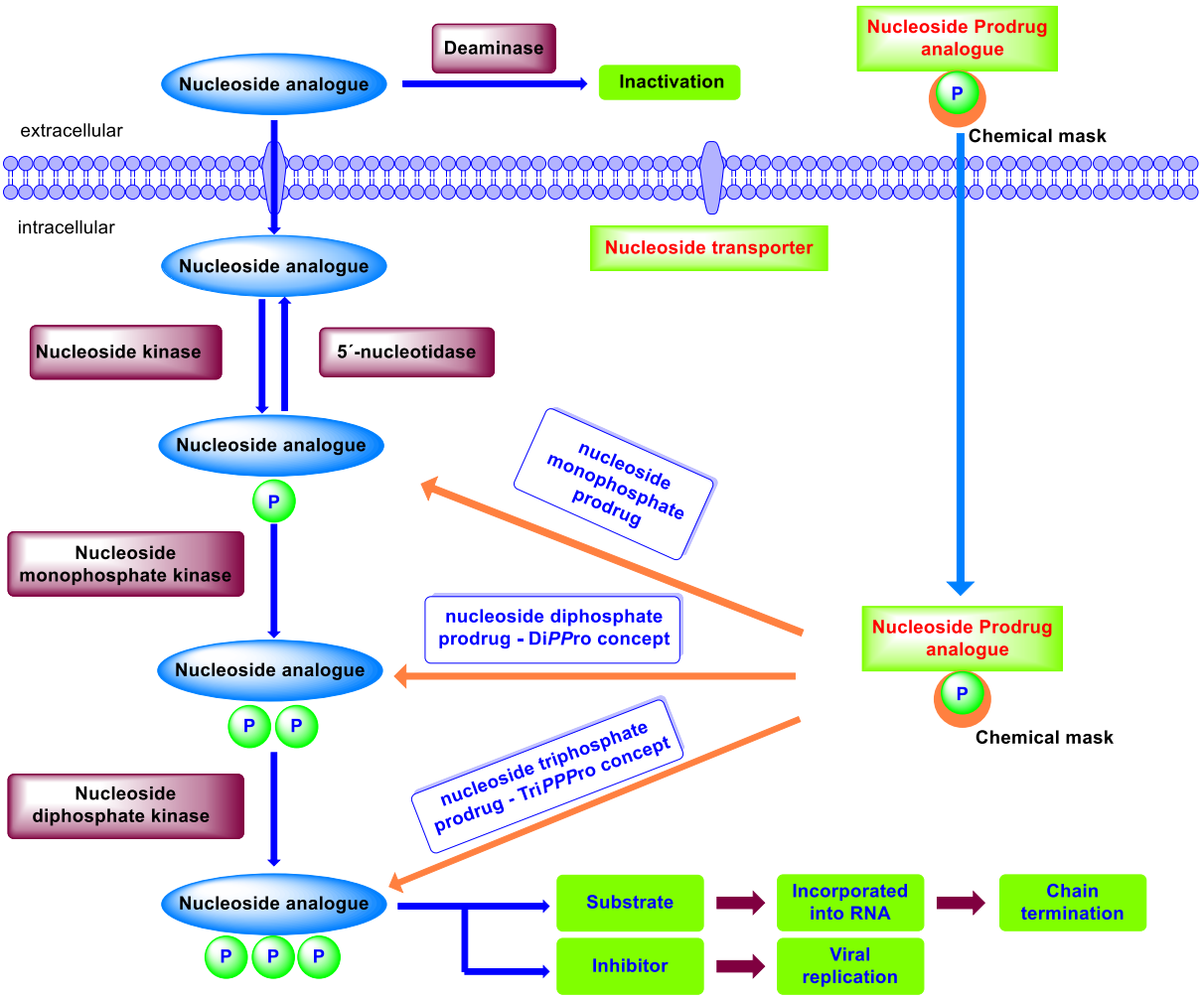


Figure 11. Metabolism of nucleoside analogues and nucleoside prodrugs.

2.3.1 Nucleoside Monophosphate Prodrugs

In an attempt to overcome one limitation, namely the inability of nucleotides and other charged organophosphate esters to traverse biological membranes, the potential of the acyloxyalkyl esters as enzyme-cleavable phosphate-protective groups have been investigated since 1983.[116] Through covalent attachment, the acyloxymethyl moieties neutralize the negative charges of the phosph(on)ate, and thus facilitate these compounds´ passive diffusion across the cell membrane.[116,117] Nucleoside analogue monophosphate prodrugs have been successfully explored in the last 37 years.[28,57,118,119] Examples of efficient NMP prodrug strategies based on the design of many different types of phosphate and phosphonate nucleoside prodrugs, such as the *cyclo*Sal-,[36-38] SATE-,[39,40] bisPOM-nucleotides[41] and nucleoside phosphoramidates,[42,43] have been introduced to overcome the first metabolic hurdles in nucleoside analogue activation (Figure 12).

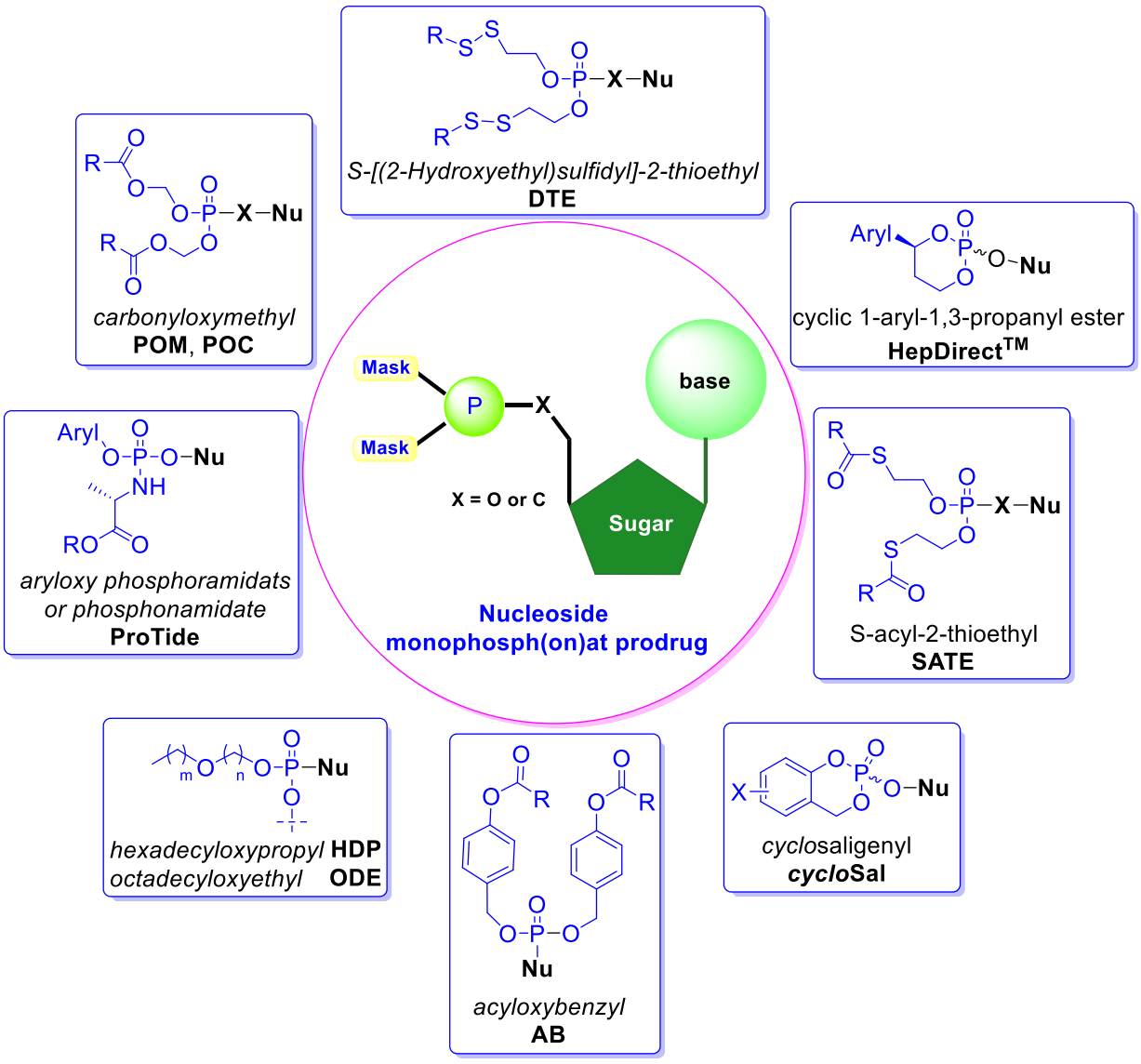


Figure 12. Prodrug technologies for nucleoside monophosph(on)ates.[119]

Farquhar *et al.* reported the synthesis of bis(carbonyloxymethyl)phosphate derivatives in different phosphate buffers[116] and developed two methods to synthesize the bis(POM)-monophosphate prodrugs, for instance 5-FdU,[41,117] 2′,3′-dideoxyuridine (ddU),[120] AZT,[121] and thymidine.[122] In 1992, Starrett *et al.* reported the first synthesis of bis(POM)-nucleoside phosphonate prodrugs of adefovir (PMEA).[123,124] The same procedure was used by Choi[125] and Tang[126] to synthesize 9-[1-phosphonomethoxy cyclopropyl)methyl]-6-deoxyguanine dipivoxil (LB80380) and several PMEA and PMPA bis(alkyloxymethyl)-carbonate prodrugs, respectively.

A similar procedure was reported by Mackman *et al*.[127-130] for the synthesis of bis(isopropyloxymethyl carbonate, POC)-5′-phosphonomethoxy prodrugs of potent nucleosides such as AZT, d4T, ddT, or ddC. In 2001, Mackman′s group disclosed the synthesis and evaluation of novel prodrugs of PMEA **15** and PMPA **17**, including Adefovir dipivoxil (bis-(POM)) prodrug **14** and Tenofovir disoproxil (bis-(POC)) prodrug **16** (Figure 13). In 2001, Shah *et al*. also reported on Tenofovir disoproxil fumarate (TDF, bis-POC-prodrug), which was approved by the FDA to combat HIV-1 and HBV infections.[132] There are eight combination HIV medicines that contain TDF.[111] Initially designed for HIV, Adefovir dipivoxil was approved by the FDA to combat infections caused by HBV in 2002.

Further investigation of tenofovir disoproxil was stopped because of its severe cytotoxicity at the dosage necessary for good antiviral response. As compared to previously studied PMEA,[123,131] the cellular uptake for the bis-(POM) prodrug Adefovir dipivoxil was found to be significantly higher by almost a factor of 100, resulting in a markedly higher antiviral efficacy. Further studies have shown that bis(POM) phosphotriesters were readily cleaved and hydrolysed in human blood serum, which limits their potential utility for intracellular drug delivery.

Both the bis-(POM) and the bis-(POC) approach have similar cleavage mechanism: The POM-prodrug **14** is cleaved to form Adefovir and pivalinic acid while the POC-prodrug **16** is cleaved to generate Tenofovir, CO_2 and formaldehyde. Once inside the cell, Adefovir **15** and Tenofovir **17** exert their therapeutic potency after host cell kinase catalysed phosphorylation to the corresponding Adefovir-DP and Tenofovir-DP, respectively (Figure 13). Both POM and POC groups increase the lipophilicity of prodrugs.[124,132]

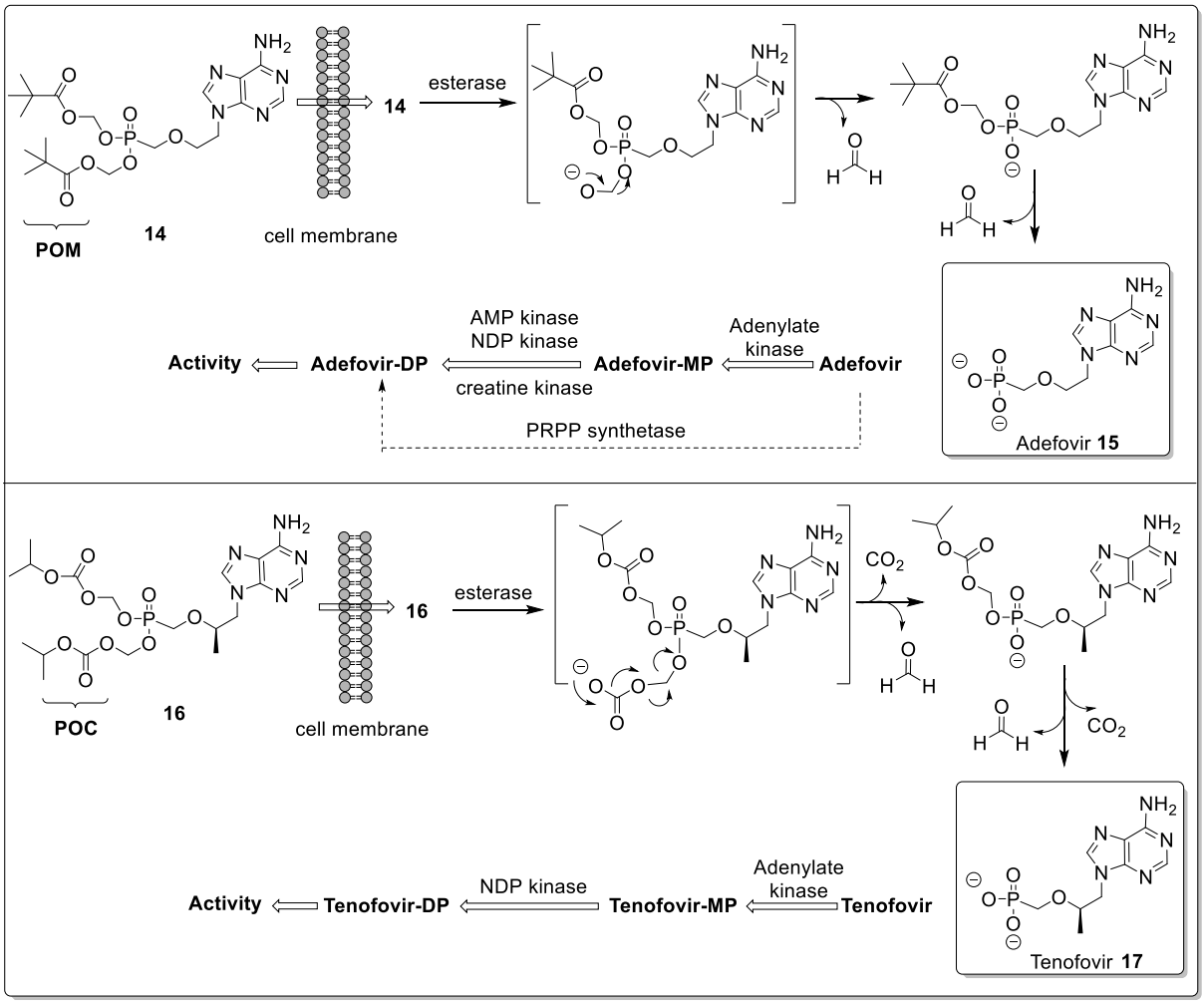


Figure 13. Metabolism of Adefovir dipivoxil and Tenofovir disoproxil.

In 1993, the Imbach group first reported on intracellular delivery of nucleoside monophosphates through a reductase-mediated activation process.[133] They showed that the S-[(2-hydroxyethyl)sulfidyl]-2-thioethyl (dithiodiethanol, DTE) prodrugs of monophosphates of different nucleoside analogues, such as AZT and ddU were able to facilitate cell entry and release the corresponding nucleoside phosph(on)ate through a reductase-mediated activation process. Later, the same group developed the bis-S-acylthioethyl ester (bis-SATE) prodrug approach, which is similar to the bis-DTE-concept.[134] As is shown in Figure 14, the SATE masking groups are cleaved by esterase to form an unstable bis(SATE)phosphotriester **18**, which rapidly undergoes an intramolecular elimination reaction to form the mono-SATE phosphate diester **19** and ethylene sulfide (byproduct, **21**). The second SATE-group is cleaved via the same mechanism to give the target 5´-O-nucleoside monophosphates **11a**.[133,134]

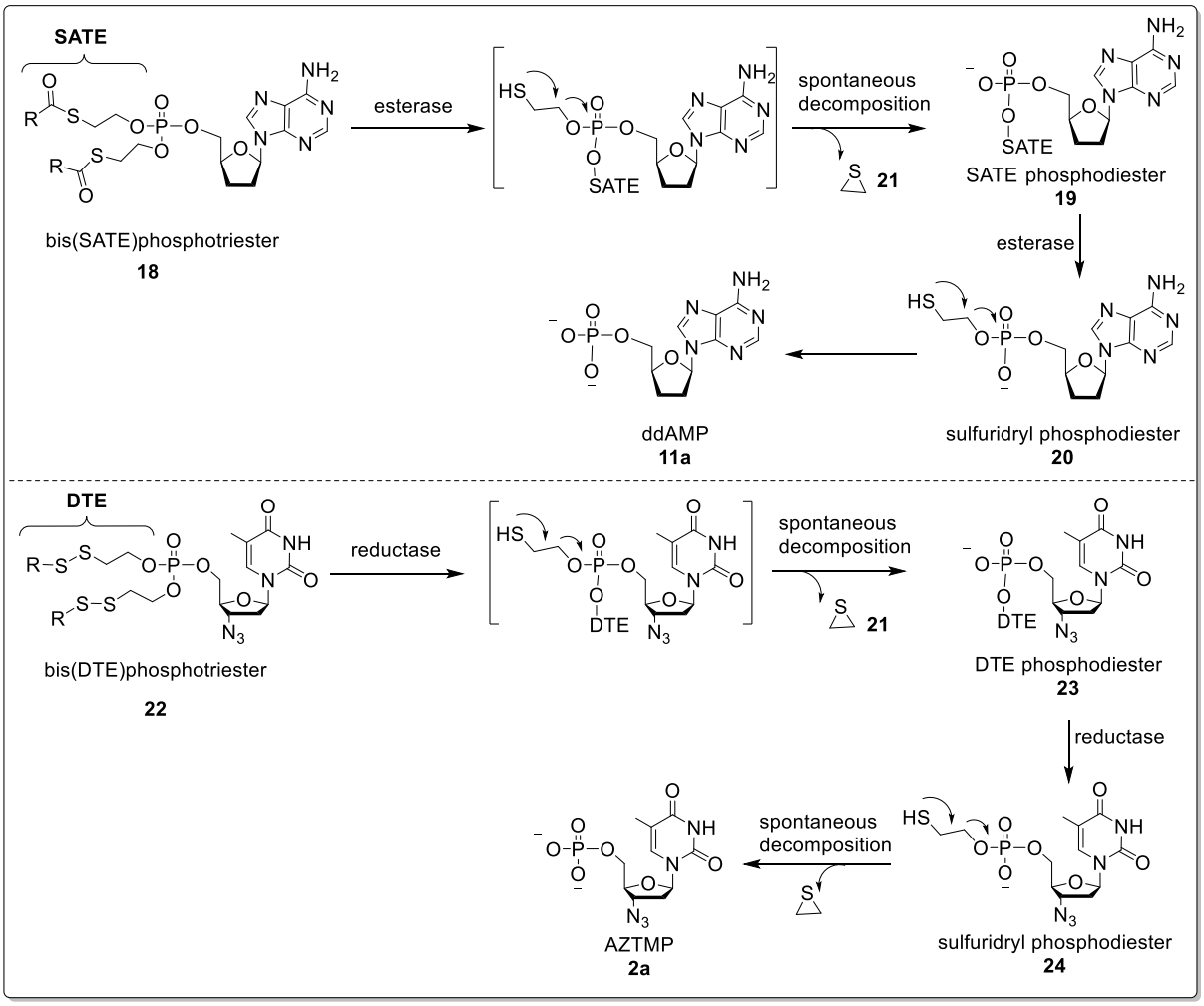


Figure 14: Metabolism of bis(SATE) phosphotriester **18** and bis(DTE) phosphotriester **22**.

In the early 2000's, Metabasis Therapeutics Inc *et al*. developed the HepDirect prodrugs system.[135-137] These HepDirect prodrugs are disclosed to improve liver-specific drug delivery, stable in blood, and intracellular enzymes activities. Once inside the cell, the HepDirect prodrugs of nucleoside monophosphate analogue **25** undergoes specific oxidation by the cytochrome P450 (CYP) isoenzyme CYP3A4 and subsequently delivers the corresponding monophosphate by spontaneous ring-opening and β-elimination (Figure 15, top).[138,139] Up to now, many reported liver-directed nucleoside prodrugs combining high plasma and tissue stabilities prodrugs exhibited a good clinical anti-HIV activity in phase 2 trials. For instance, pradefovir[136-138,142] is a 3-chlorophenyl HepDirect prodrug of Adefovir in development for hepatitis B (Figure 15, top).

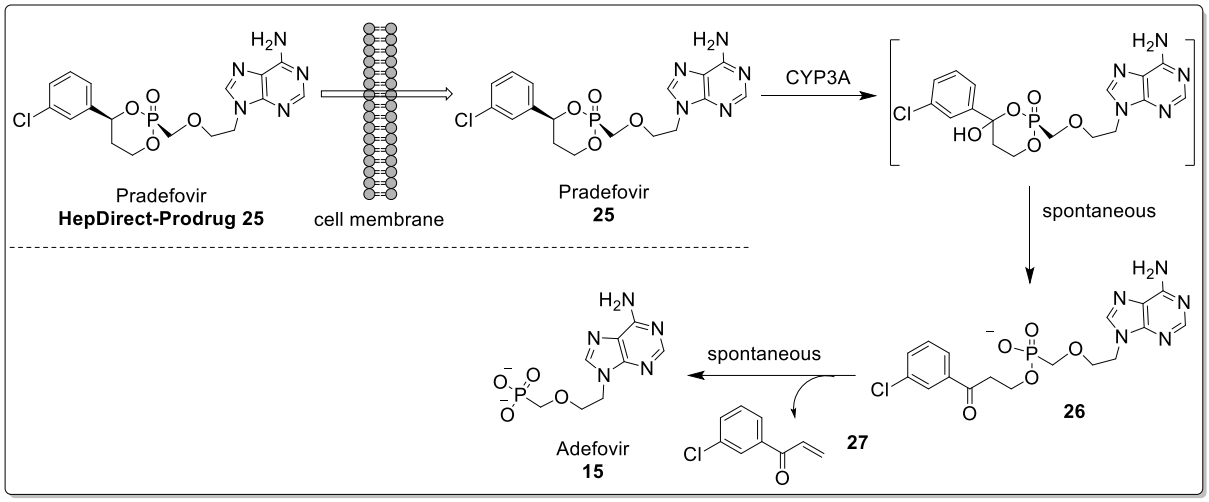


Figure 15: Metabolism of pradefovir **25** and chirality in HepDirect prodrugs.

In the mid 1990´s, Hostetler reported on 1-O-hexadecylpropanediol-3-phospho-acyclovir (HDP-P-ACV), and evaluated its antiviral activity in human hepatoma cells related prodrugs in Hepatitis B virus infection.[143] Based on this strategy, an HDP prodrug of adefovir (CMX-157, Figure 16, top) was used for treatment of HIV infection. Once delivered into the desired tissue, the HDP masking group is cleaved enzymatically by a phospholipase, releasing the nucleotide monophosph(on)ate **17**. Esterification of (*S*)-HPMPA with HDP not only increased oral bioavailability based on the resemblance to lysophosphatidylcholine, but also improved the anti-poxvirus activity.[144] Nucleoside monophosphonate prodrugs (CMX-157 and ODE-HPMPC) showed higher cell uptake rates than their unmodified counterparts, respectively.

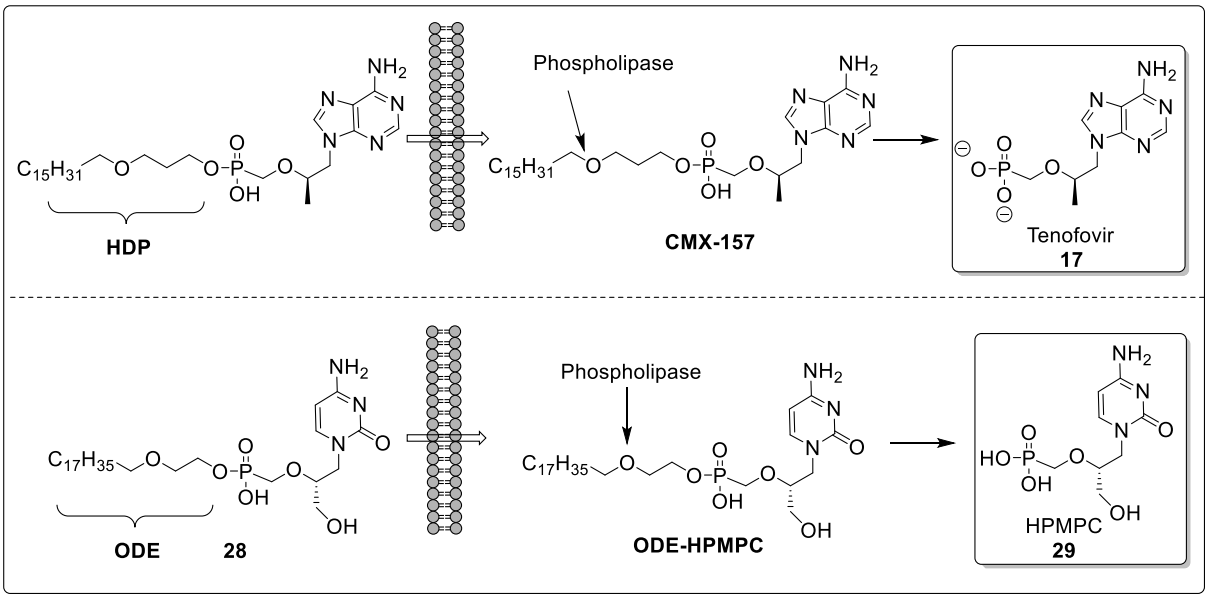


Figure 16: Metabolism of HDP-Tenofovir and ODE-HPMPC.

McGuigan *et al*. reported the aryloxyphosphoramidate prodrugs (ProTides) in the early 1990s.[145] The aryloxy amino acid amidate ProTides prodrugs contain a phosphorus atom bearing an aryloxy group and an amino acid alkyl ester. Because of their high activity and stability, several ProTides prodrugs, such as GS-7340,[146,147] GS-9131,[148-151] Sofosbuvir,[153-156] and Remdesivir,[157-160] have advanced to clinical trials for the treatment of HIV infection. The latter compounds (Sofosbuvir and Remdesivir) are also most recently candidates for the use against infections caused by SARS-CoV-2 (COVID-19).[182-185] The masking groups neutralize the negative charges and increase cell permeability that enable nucleoside analogues into target cells. After crossing the biological barriers, the GS-9131 prodrug cleaved by a carboxypeptidase or cathepsin A to generate the carboxylate **A**, followed by a spontaneous intramolecular cyclization to a five-membered ring **B**. Then, phosphoramidate diester **C** is generated by water-mediated hydrolysis of **B**. Finally, phosphoramidate diester **C** undergoes cleavage to release the nucleoside monophosphate (TFV-MP) by the histidine triad nucleotide-binding protein 1 (HINT-1) or intracellular phosphoramidase (Figure 17).

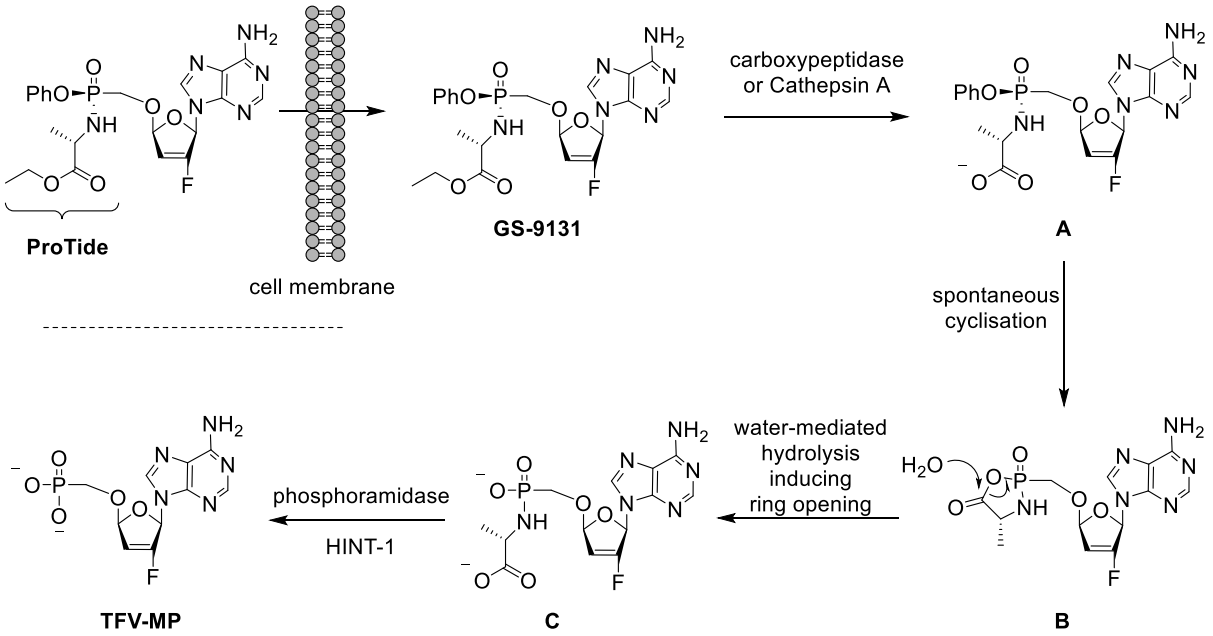


Figure 17: Mechanism of aryloxyphosphonamidates (GS-9131).

In 1996, one of the most extensively explored types of NMP prodrug strategies was originally introduced by Chris Meier, the cyclosaligenyl (*cyclo*Sal) phosph(on)ate approach.[145] This concept is based on a pH-driven chemical hydrolysis mechanism that is shown in Figure 18.[146,147] Under basic conditions (pH > 7), the phenyl ester is cleaved selectively (step a) to yield the benzyl phosphate diester **31**, followed by spontaneous cleavage of the P−O benzyl ester bond (step b) to release the nucleoside monophosphate.

In contrast, the cleavage of the benzyl ester P−O bond in *cyclo*Sal-d4TMP-prodrug **30** is undesired (step c), because it results in a phenyl phosphate diester **32** which is very stable towards hydrolysis (step d).[148-151] Meier's research demonstrated that the intracellular cleavage of *cyclo*Sal pronucleotides is based on an entirely pH-driven chemical hydrolysis mechanism and the critical point is the second hydrolysis reaction after the first cleavage of the triester to yield the diester.

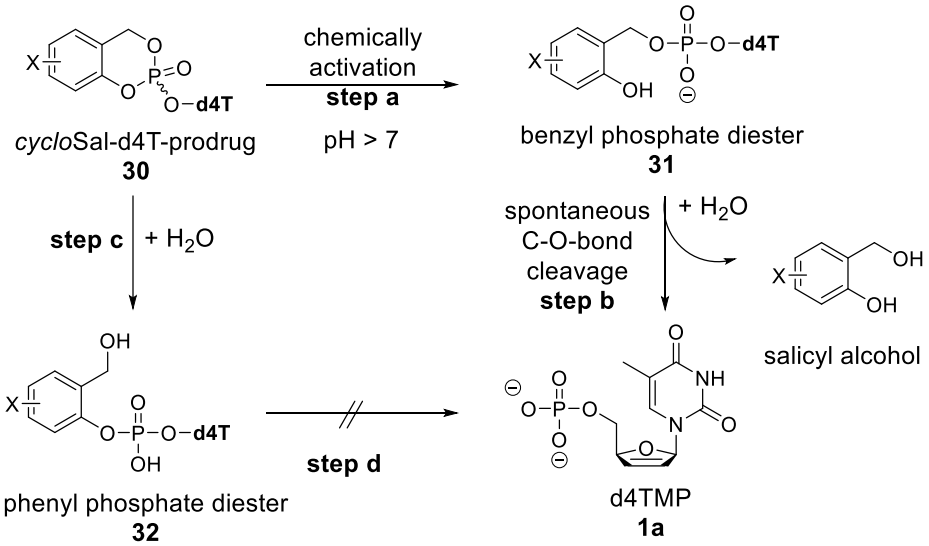


Figure 18: Hydrolysis pathways of the *cyclo*Sal-d4TMP triesters.[152]

The *cyclo*Sal-prodrug technology has been applied to many different nucleoside analogues, such as d4T, ddA, ddI, and ACV, improving their biological activities against different viruses.[36,147,161,162] Meier *et al*. developed the second generation of ''lock-in'' modified *cyclo*Sal-prodrugs **33** (Figure 19).[163] Subsequently, the third generation of *cyclo*Sal-pronucleotides bearing an esterase-cleavable geminal dicarboxylate (acylal) moiety attached to the saligenyl aromatic was reported by Meier´s group.[164] With this approach, a fast release of d4TMP was achieved because the conversion of the acylal moiety into an aldehyde group (acceptor) leads to a strong decrease in hydrolytic stability. Also, new ''lock-in'' *cyclo*Sal-prodrugs bearing enzymatically cleavable amino acid esters were developed to trap the corresponding pronucleotide inside the cell by a fast conversion of a nonpolar ester group into a charged carboxylate.[165] Recently, new generation *cyclo*Sal-prodrugs have been proven to be a highly potent dual-acting HIV inhibitor targeting both reverse transcription and virus entry.[166]

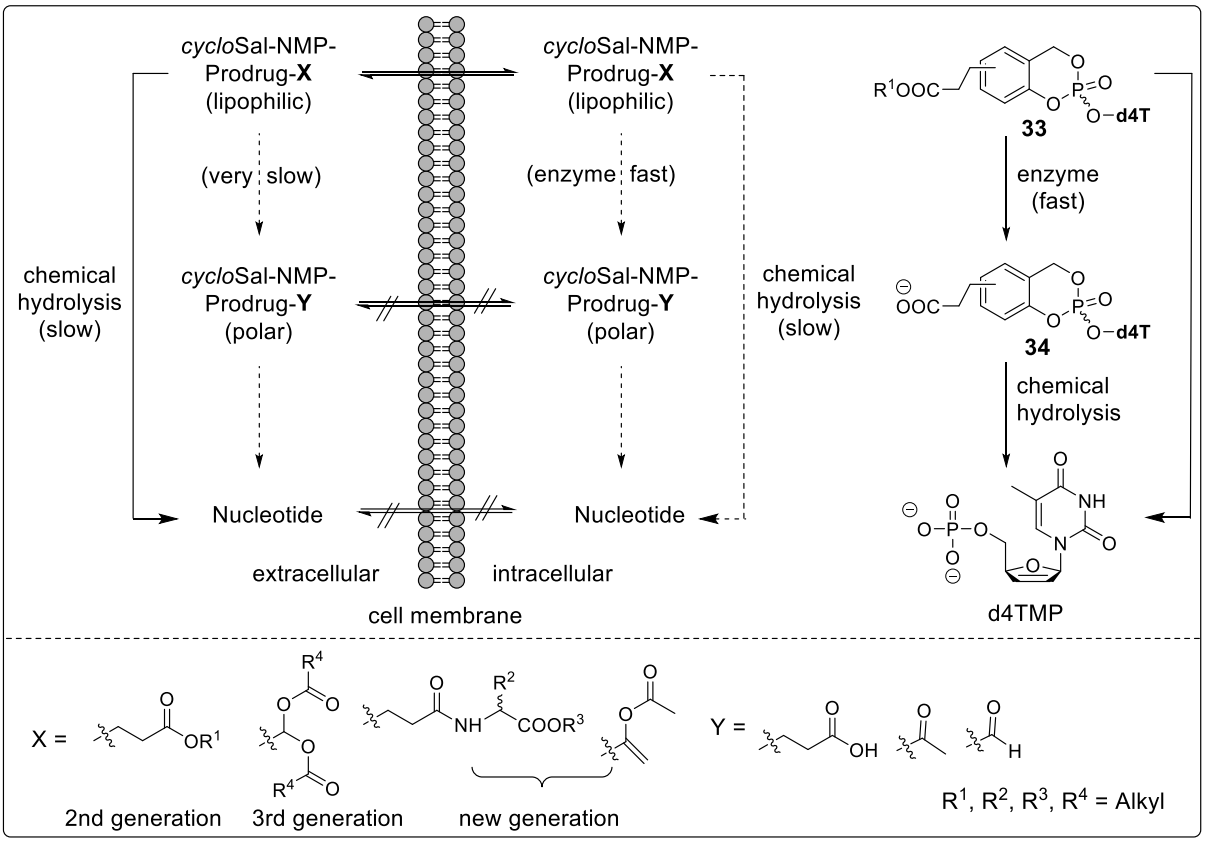


Figure 19. Mechanism of "lock-in" *cyclo*Sal pronucleotides and "lock-in" modified *cyclo*Sal-d4TMPs.

In 1993, William Thomson *et al*. developed the bis-acyloxybenzyl (BAB) concept.[170] In the case of the 5'-monophosphate of AZT prodrug (BAB-AZTMP **35**), the cleavage of the acyloxybenzyl (AB) group is initiated by ester hydrolysis and formed the mono-(4-acyloxybenzyl) ester of the 5'-monophosphate of AZT (AB-AZTMP **36**) and, subsequently, the 5'-monophosphate of AZT (AZTMP **2a**). The bis(4-acyloxybenzyl) ester prodrugs **35** (BAB-AZTMP) showed virtually similar or even slightly lower activities against HIV-1 and SIV than the parent nucleoside AZT in C8166 cells. In contrast, the AB-AZTMP **36** showed higher activity than their corresponding BAB-AZTMP **35** (Figure 20).

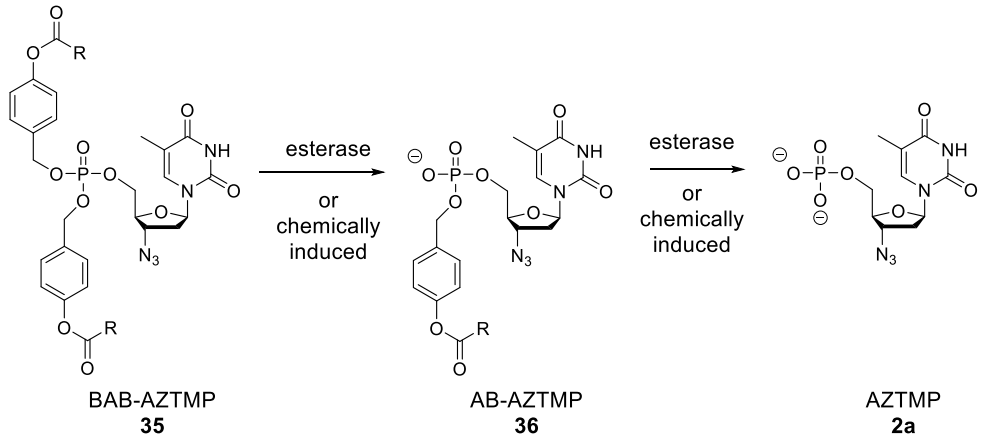


Figure 20. Activation pathway of BAB-AZTMP prodrugs.

2.3.2 Nucleoside Diphosphate Prodrugs

Di*PP*ro-strategy would be useful for antiviral nucleosides, which are poorly phosphorylated. In 1990, Hostetler *et al*. studied potential NDP prodrugs of type **37** utilizing diglycerides as masking group to achieve improved uptake into macrophages (Figure 21, left).[171–174] Nucleosides such as AZT, ddC, cidofovir, and ddT were investigated for the treatment of HIV infection. For example, the antiviral activity of the 3'-deoxythymidine diphosphate dimyristoylglycerol (3dTDP-DMG) prodrug was 14 to 37-fold higher as compared to the parent nucleoside 3dT. However, due to cleavage of the diphosphate moiety, the improved antiviral activity of the dimyristoylglycerine diphosphates of these nucleosides was attributed to the release of the corresponding NMPs instead of the originally aimed NDPs. Another approach was published by Huynh-Dinh *et al* (Figure 21, right).[50,167,168] In their approach, an acyl group was attached to the β-phosphate of the NDP, forming a mixed anhydride, such as AZTDP-derivative **38**. A too rapid, albeit selective, cleavage of the mixed anhydride was observed in chemical hydrolysis studies. Hence, AZTDP **2b** was released from this prodrug; still, in RPMI-1640 culture medium, an undefined decomposition of the compounds was detected which led to no improvement of the anti-HIV activity as compared to the parent nucleosides d4T or AZT, respectively.[168]

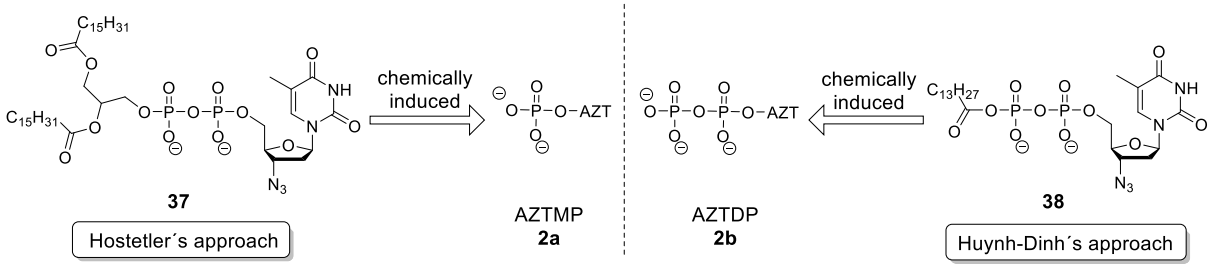


Figure 21. Hydrolysis of NDP diglyceride prodrugs.

In 2008, Meier *et al*. investigated the transfer of their *cyclo*Sal-technology to nucleoside diphosphates, as outlined in Figure 22 (top, prodrug **39**). However, the cleavage mechanism of the *cyclo*Sal-prodrugs was based on chemically induced steps. Thus, in *cyclo*Sal-NDPs the undesired hydrolytic cleavage of the pyrophosphate bond dominated, and consequently, the NDP prodrug mainly yielded the corresponding NMP and *cyclo*Sal phosphate instead of the desired NDP (Figure 22, top). Although this approach failed, the results gave helpful clues for the development of the β-modified nucleoside diphosphate prodrugs **40**,**41**, the Di*PP*ro-approach.[44-48] Unlike for the *cyclo*Sal-mask, the cleavage of the ester group of the para-acyloxybenzyl-moiety is initiated by an enzymatic reaction (Figure 22, bottom). Most of the Di*PP*ro-compounds showed good antiviral activity in HIV-infected thymidine kinase-

deficient human T-lymphocyte CEM/TK$^-$ cell cultures, thus proving the uptake of the compounds into the cells and the release of (at least) phosphorylated metabolites, most likely the corresponding nucleoside diphosphates.[45] In case of Di*PP*ro-compounds **40**, the formation of d4TMP was observed and could clearly be correlated with the stability of the Di*PP*ro-compounds in phosphate buffer solution (PB, pH 7.3), or cell extracts.[45] In contrast, a highly selective conversion of the Di*PP*ro-compounds **41** into nucleoside analogue diphosphates (e.g. d4TDP) was demonstrated in CEM cell extracts.[47] In Di*PP*ro-compounds **41**, one long ester group brings in the lipophilicity while the other, short ester group is rapidly cleaved by enzymes – this helps because it limits phosphoanhydride hydrolysis.[45,46] Finally, it was possible to tune both lipophilicity and stability of the Di*PP*ro-prodrugs by choosing the appropriate substituent R (for $R^1 = R^2$ or $R^1 \neq R^2$) in the ester unit within the masking group.

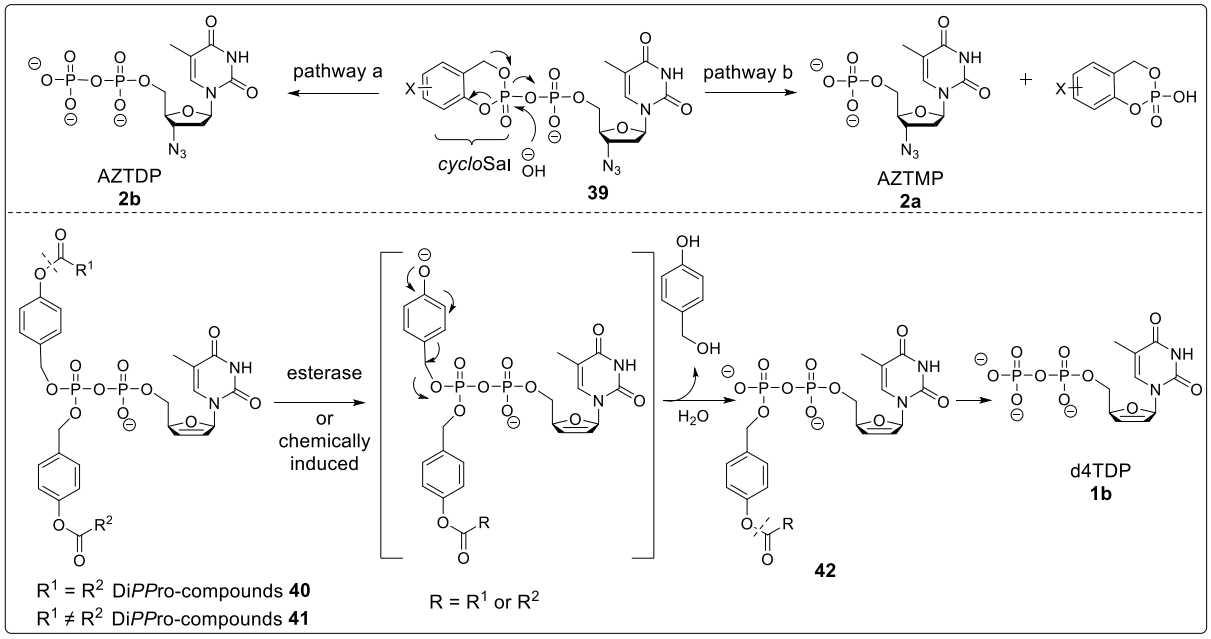


Figure 22. Hydrolysis of *cyclo*Sal-NDPs **39** and Di*PP*ro-compounds **40**,**41**.

2.3.3 Nucleoside Triphosphate Prodrugs

In the early 1980s, very few nucleoside triphosphate prodrugs have been published. These prodrugs, such as DSG-AZTTPs **45**, 13-acyl-AZTPs **47**, 13-acyl-d4TTPs **48** and 13-OMA-AZTTPs **46** (Figure 23, bottom), involved the attachment of an lipophilic alkyl or acyl moiety to the γ-phosphate unit.[50,167-170] In 1995, D. Bonnaffe *et al*. described the first synthesis of various acyl nucleoside triphosphates as candidates of nucleoside triphosphate lipophilic prodrugs (13-acyl-AZTPs **47** and 13-acyl-d4TTPs **48**).[50,167] The lipophilic acyl moiety of these compounds was designed to facilitate passive diffusion of the charged nucleotide through cell membranes, and the mixed carboxylic phosphoric anhydride was

expected to be readily hydrolysed, thus releasing the corresponding free nucleotides AZTTP **2c** and d4TTP **1c** (Figure 23, top), respectively. However, D. Bonnaffe *et al*. reported that no increase of antiretroviral activity was detected with these prodrugs as compared to their corresponding nucleoside, although the modified compounds were more lipophilic.[168] In the case of acyl NTPs, the formation of the corresponding nucleotides (such as AZTMP **2a**, AZTDP **2b**, and AZTTP **2c**) was detected in a 10 mM triethylammonium acetate (TEAA) buffer at physiological pH 7.0 (half-live 156h) and RPMI culture media ($t_{1/2}$= 1.7h). The rapid hydrolysis of these prodrugs in the RPMI medium limits their transmembrane diffusion, which explains the lack of antiretroviral activity.

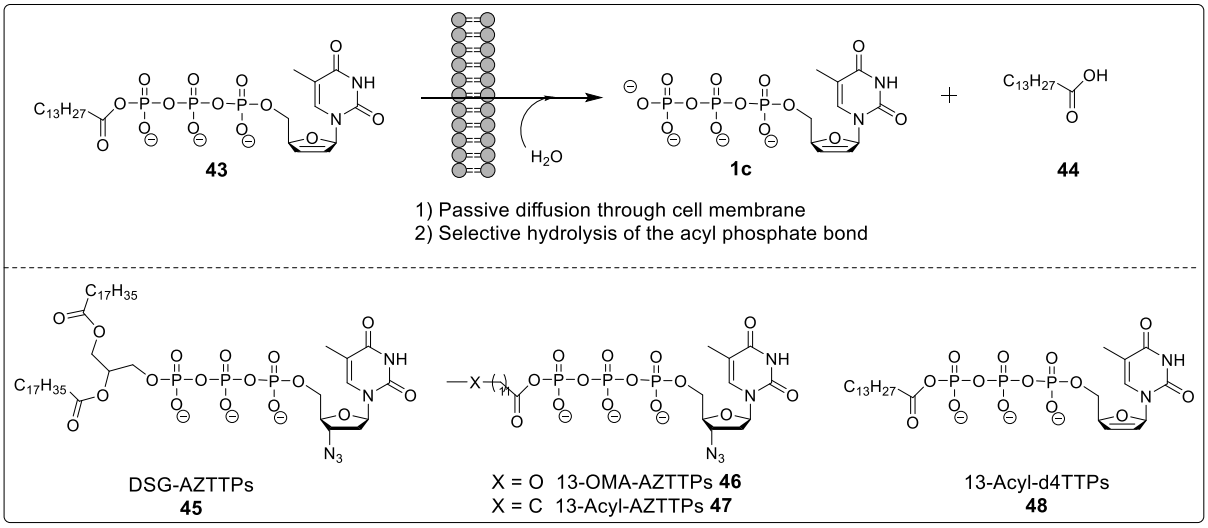


Figure 23. DS G-AZTTP and Acyl NTP prodrugs as examples.

In 1998, Kreimeyer *et al*. disclosed that ATP bearing a cholesteryl moiety at the γ-phosphate group can be across the cell membrane (Figure 24).[51] They used ^{31}P-NMR spectroscopy to investigate the transmembrane transport of such liponucleotide conjugates. This allowed them to not only monitor ATP release after internalization of cholesteryloxycarbonyl-ATP (Chol-ATP, **49**) into liposomes but also to distinguish between external and internal species in a well-compartmented system, which they achieved by using a pH gradient in a phosphate-buffered system.

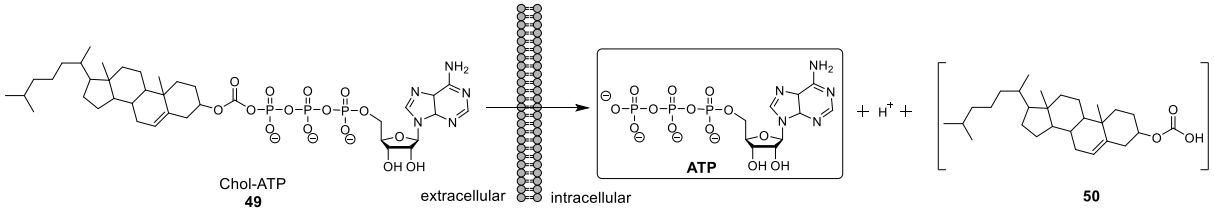


Figure 24. Chol-ATP across the membrane and release of ATP by hydrolysis.

In 2015, Meier *et al*. developed a unique pronucleotide concept for partially masking the negative charges and improving the lipophilicity of nucleoside triphosphate (NTP), namely, the Tri*PPP*ro-approach.[53] These Tri*PPP*ro-prodrugs bearing two identical lipophilic masking units at the γ-phosphate and d4T **1** as a nucleoside analogue were synthesized using the phosphoramidite method (Figure 25).[53]

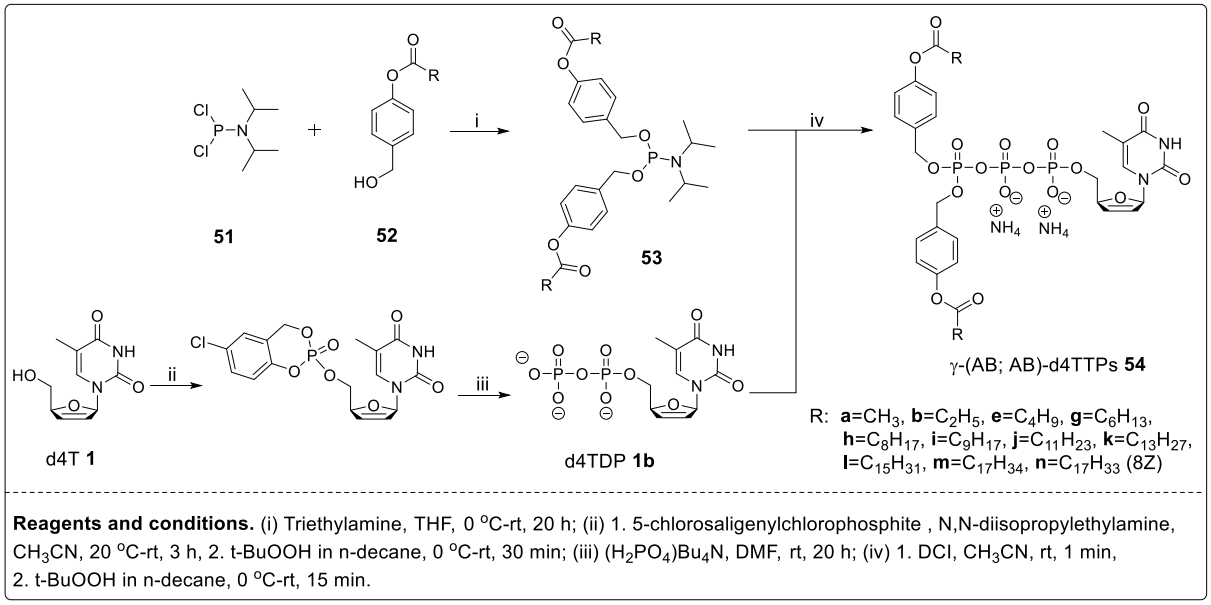


Figure 25. Synthesis of Tri*PPP*ro-prodrugs using the phosphoramidite approach.

These prodrugs were incubated in PB (pH 7.3) to study their chemical stability: the half-lives of Tri*PPP*ro-d4TTPs increased with increasing acyl chain lengths (R: C1-C13). However, the chemical stability of more lipophilic compounds (R: C15-C17) decreased, probably because of altered solubility behaviour or micelle formation. The Meier group proposed three hydrolysis pathways of Tri*PPP*ro-nucleotide prodrugs (Figure 26, bottom). Clearly, the starting material disappeared and the expected γ-(C8-AB)-d4TTP (intermediate) was formed (Figure 26, top), indicating that Tri*PPP*ro-d4TTPs **54** mainly followed pathway A[1] in their chemical hydrolysis. In all cases and to some extent, also the corresponding d4TDP **1b** and d4TMP **1a** (lower concentration) were detected. However, after complete conversion of the starting Tri*PPP*ro-compound **54h**, no further increase of d4TDP **1b** and d4TMP **1a** concentrations was detected. Therefore, it was concluded that d4TDP **1b** (pathway B) and d4TMP **1a** (pathway C) were only formed from the starting Tri*PPP*ro-d4TTPs **54** by a nucleophilic attack at the γ-phosphate or β-phosphate moiety, respectively. To support these findings, Meier´s group also prepared γ-(AB)-d4TTP (mono-masked intermediates) using the *cyclo*Sal-method and found that from these compounds exclusively d4TTP **1c** was formed in PB.

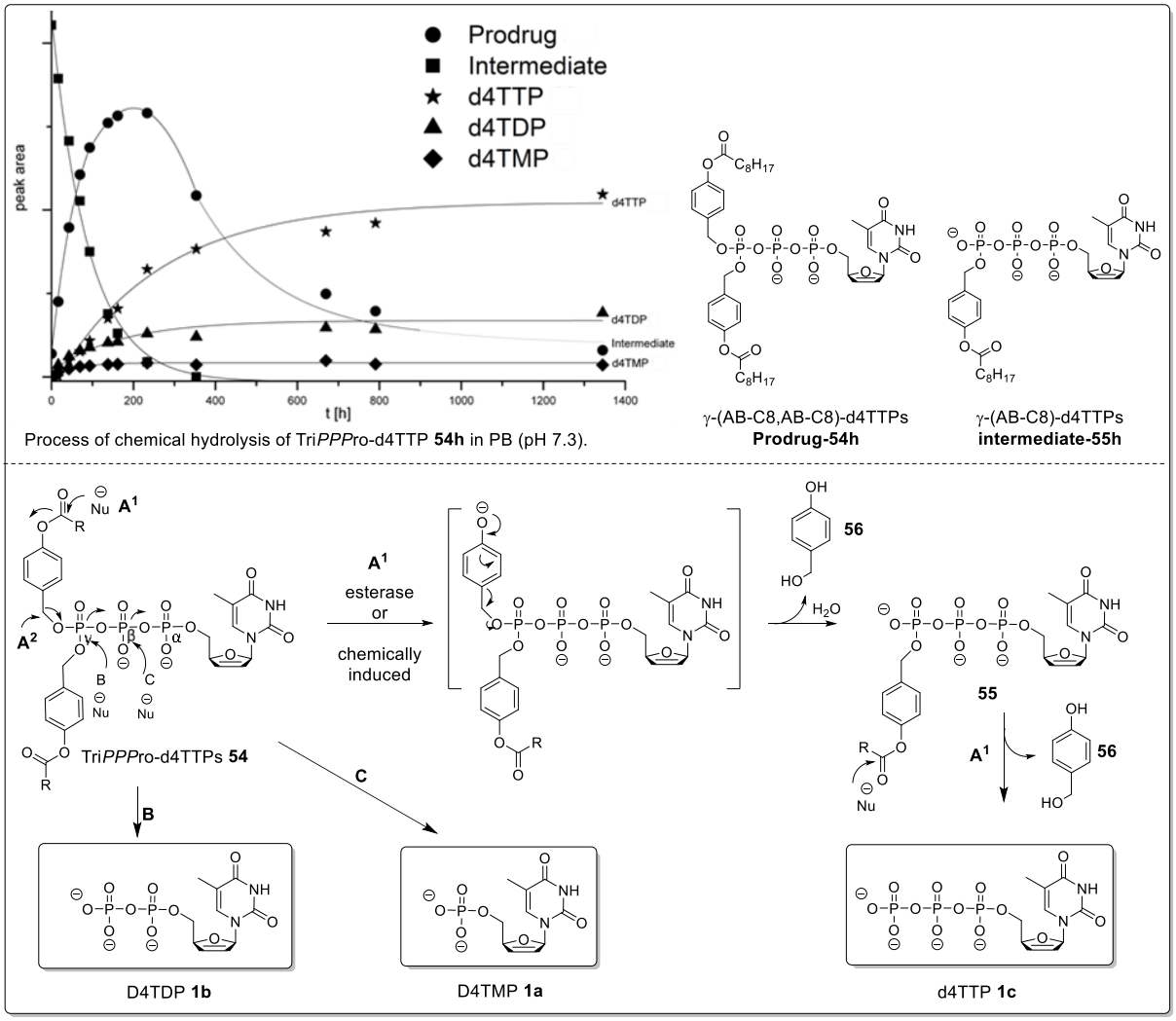
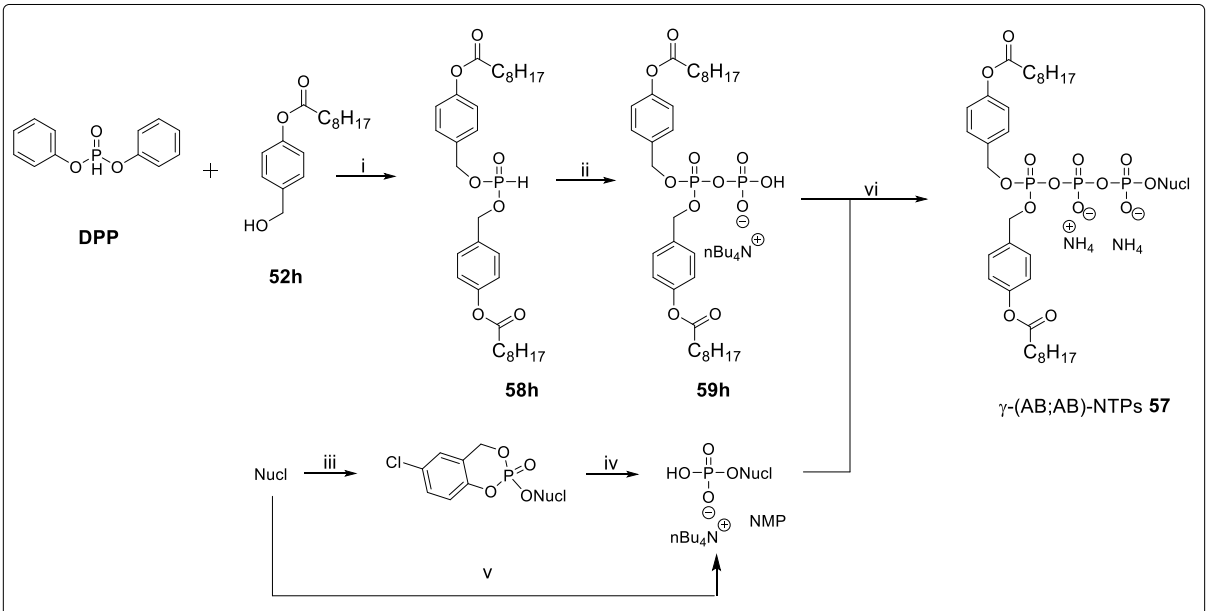


Figure 26. Process of chemical hydrolysis of Tri*PPP*ro-d4TTPs **54h** in PB (pH 7.3) and proposed hydrolysis mechanism of Tri*PPP*ro-d4TTPs **54**.[53]

Next, the prodrugs were exposed to pig liver esterase (PLE) in PB and to CEM/0 cell extracts to investigate their stability, the influence of the chain lengths on the enzymatic cleavage and the product distribution for hydrolysis in biological medium. As compared to chemical hydrolyses, all prodrug compounds were rapidly hydrolyzed and delivered the nucleoside triphosphate d4TTP **1c** much faster than in PB, demonstrating a significant contribution of the enzymatic cleavage with PLE. In contrast to hydrolysis studies with PLE, it was almost impossible to detect quantifiable amounts of d4TTP **1c** in CEM cell extracts due to its fast dephosphorylation (hydrolytic enzymes, such as phosphatases, $t_{1/2}$= 38 min) to form first d4TDP **1b** ($t_{1/2}$=59 h) and ultimately d4TMP **1a**. In antiviral assays, good antiviral activity of the prodrugs was detected in CEM/TK$^-$ cells with 100-fold improved activity as compared to the parent nucleoside d4T **1**. It was concluded from these studies that Tri*PPP*ro-d4TTPs **54** with two bioreversibly attached 4-acceptor-substituted benzyl esters efficiently enter cells and deliver d4TTP **1c**. Thereby,

compared to the parent nucleoside analogue, they bypass all steps of the intracellularly needed phosphorylation.

In 2016, Meier *et al*. developed a series of nucleoside triphosphate prodrugs to demonstrate the general applicability and potential of the strategy.[54] In order to achieve an efficient chemical synthesis of the Tri*PPP*ro-compounds **57** starting from the parent nucleoside 5'-monophosphates, the *H*-phosphonate route was developed (Figure 27). The advantage of the *H*-phosphonate route is that generally NMPs are easier to prepare than NDPs, which is the limiting step in the overall yield of the phosphoramidite method.[53] In antiviral assays, these Tri*PPP*ro-compounds were active against HIV-1 and HIV-2 in cultures of infected CEM/0 cells and, more importantly, they remained active in CEM/TK$^-$ cells as well, while their parent nucleosides were devoid of any activity. This approach was even applied to convert some inactive nucleoside analogues (such as FddClU **8**) into a highly potent Tri*PPP*ro-compounds. It was also proven that Tri*PPP*ro-ddBCNATPs deliver successfully the corresponding nucleoside triphosphate (ddBCNATP) inside cells by an uptake study using a fluorescent nucleoside analogue.

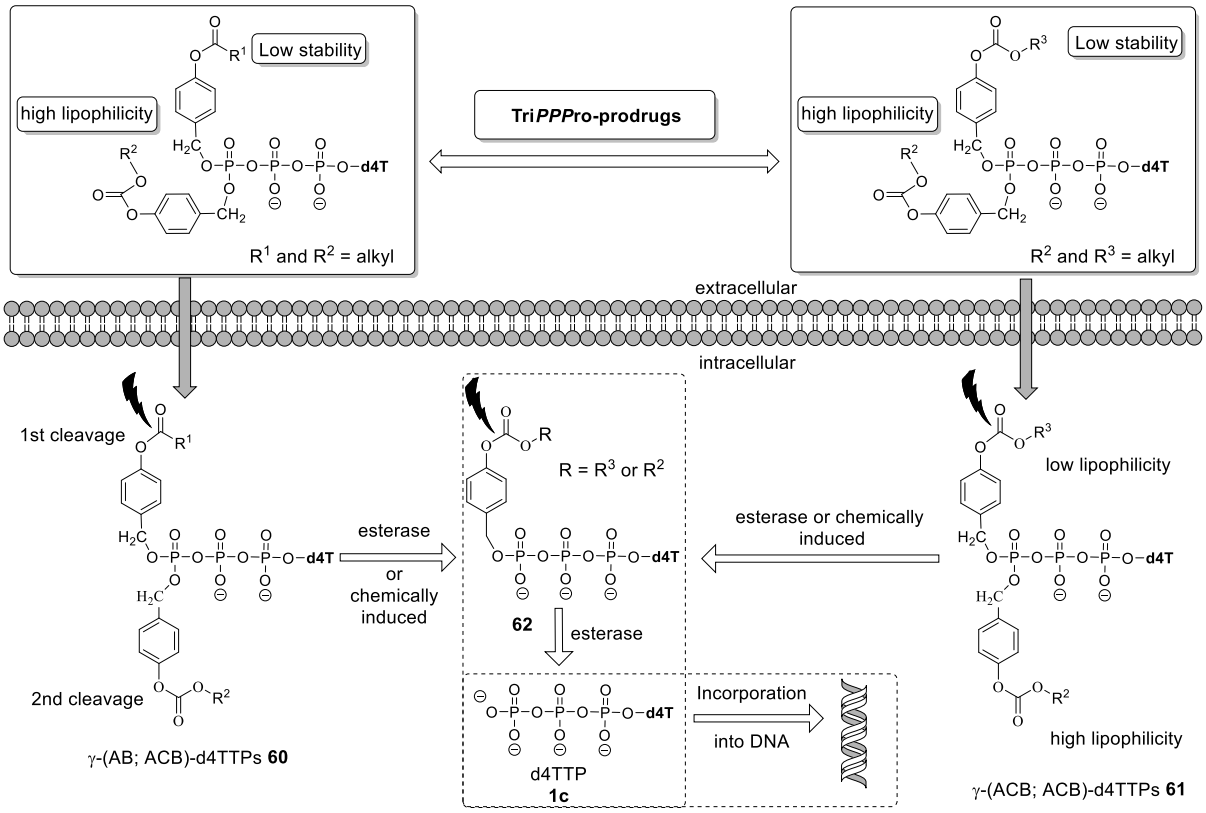


Reagents and conditions. i) pyridine, 38 °C, 2 h; ii) 1. NCS, CH_3CN, rt, 1 h, 2. $(H_2PO_4)Bu_4N$, CH_3CN, rt, 1 h; iii) 5-chlorosaligenyl chlorophosphite, N,N-diisopropylethylamine, CH_3CN, 0 °C–rt, 3 h, 2. A) oxone/water, B) t-BuOOH/n-decane, 0 °C–rt, 20 min; iv) basic hydrolysis; v) see ref. 187; vi) 1. TFAA, Et_3N, CH_3CN, 0 °C, 10 min, 2. 1-methylimidazole, Et_3N, CH_3CN, 0 °C–rt, 10 min, 3. NMP, rt, 1–3 h.

Figure 27. Synthesis of Tri*PPP*ro-prodrugs using the *H*-phosphonate route.

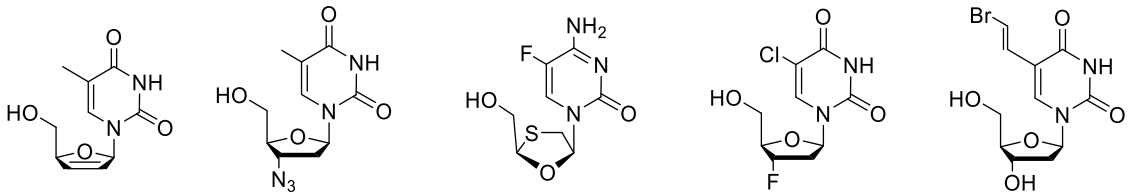
3 Motivations and Objectives

Tri*PPP*ro-prodrugs **54** allow the bypass all steps of normally needed intracellular phosphorylation steps and enable deliver the triphosphate form of nucleoside analogues as active antiviral compounds.[53] In addition to the ester functional group in the AB masking moiety, also first examples of carbonate linked compounds were studied. The chemical stability of these carbonate Tri*PPP*ro-compounds and intermediates were found to be higher than the corresponding ester Tri*PPP*ro-compounds and intermediates, respectively.[53] These observations lay the ground for this thesis, to conduct a study on a series of nucleoside analogue triphosphate derivatives bearing two different biodegradable masking units (R^1 not identical to R^2). One of the bioreversible groups is an AB or an ACB moiety while the second group is always an ACB-moiety. It was expected that such a combination would be rapidly cleaved (AB group) chemical or particularly enzymatically to form the ACB-carbonate-intermediate **62** (Scheme 1, bottom) and thereby would limit the side reaction that is responsible for the formation of the undesired d4TDP **1b** and d4TMP **1a**. The ACB-moiety comprising a long, lipophilic aliphatic chain, not only adds lipophilicity to the molecule but should also slowly be cleaved to form the triphosphate. It was expected that with these compounds a selective conversion of the Tri*PPP*ro-compounds **60**,**61** into d4TTP **1c** can be achieved.



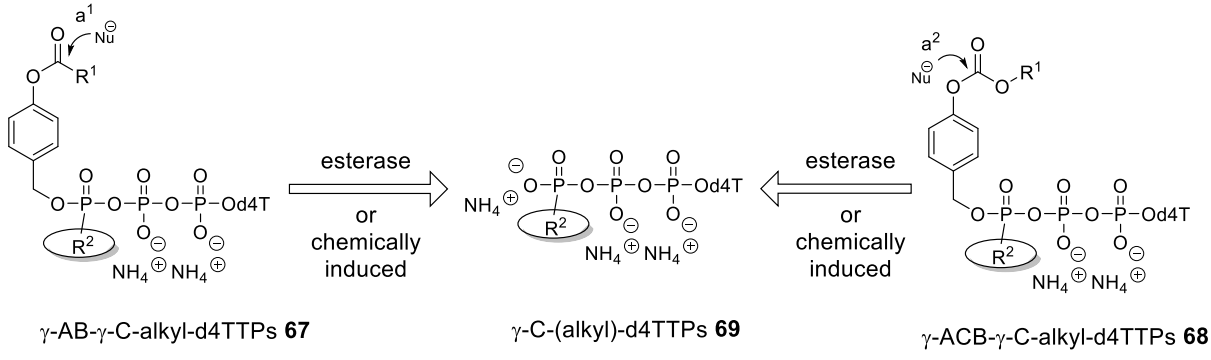
Scheme 1. Proposed hydrolysis mechanism of Tri*PPP*ro-compounds **60**,**61**.

Guided by the results from Tri*PPP*ro-compounds **60**,**61**, this thesis aimed to study the application of the Tri*PPP*ro-approach to a variety of approved, as well as so-far inactive, nucleoside analogues to demonstrate the general applicability and potential of the approach (Scheme 2). The mixed Tri*PPP*ro-nucleotides comprising an AB (C2 or C4) in combination with an ACB (OC16) moiety were expected to achieve a highly selective delivery of different NTPs in CEM cell extracts.



Scheme 2. Chemical structures of several antiviral nucleoside analogues.

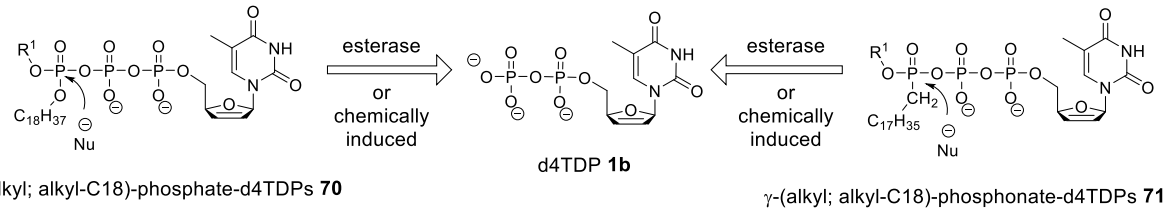
A wide variety of bioreversible masking groups for phosphonates have been applied in prodrug chemistry.[28,56-58] Those employed facilitate passive diffusion through the cell membrane by masking the negative charges. Within this thesis, a new series of γ-C-alkylphosphonate-d4TDP prodrugs **67**,**68** were prepared (Scheme 3). It was expected that such a design would allow a rapid conversion of the Tri*PPP*ro-compounds **67**,**68** into the γ-alkylated-phosphono nucleoside diphosphates, γ-C-(alkyl)-d4TTPs **69** and thereby should avoid the undesired phosphoanhydride hydrolysis from the prodrug forming d4TMP **1a** or d4TDP **1b**. Moreover, the introduction of a P-C-bond in **67**,**68** was expected to lead to chemically and enzymatically, thus metabolically resistant nucleoside triphosphate analogues.



Scheme 3. γ-AB-γ-C-alkyl-d4TTPs **67** and γ-ACB-γ-C-alkyl-d4TTPs **68** and the delivery pathways.

Generally, the concentration of phosphorylated metabolites of NRTIs is dictated by the balance between phosphorylating and dephosphorylating enzymes.[19,187] Former studies have shown that all Tri*PPP*ro-

compounds **54** were rapidly hydrolysed in cell extracts and a large amount of d4TDP **1b** and a small amount of d4TTP **1c** were observed.[53] It was speculated that d4TDP follow the intracellular activation by host cell kinases to generate d4TTP, then d4TMP is incorporated into DNA during replication or DNA excision repair synthesis, exert its antiviral activities. In addition, Meier´s group has previously demonstrated that the covalent modification of the γ-phosphate group by only *one* lipophilic, aliphatic chain can provide enough lipophilicity to enable a cellular uptake of the NTP analogues.[55] Thus, in this thesis, a series of new γ-phosphate-modified-d4TDPs **70** and γ-phosphonate-modified-d4TDPs **71** were aimed for. The γ-phosphate is esterified covalently by two different lipophilic alkyl residues (Scheme 4). It was expected that such compounds can only be slowly cleaved chemical or particularly enzymatically to form d4TDP **1b** in cells, then convert them into the ultimately bioactive d4TTP **1c** by cellular kinases. The γ-phosphate or phosphonate moiety should comprise a long, lipophilic aliphatic chain ($R^2 = C_{18}H_{37}$) to give the prodrug molecule sufficient lipophilicity to cross the biological barriers.



γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70**

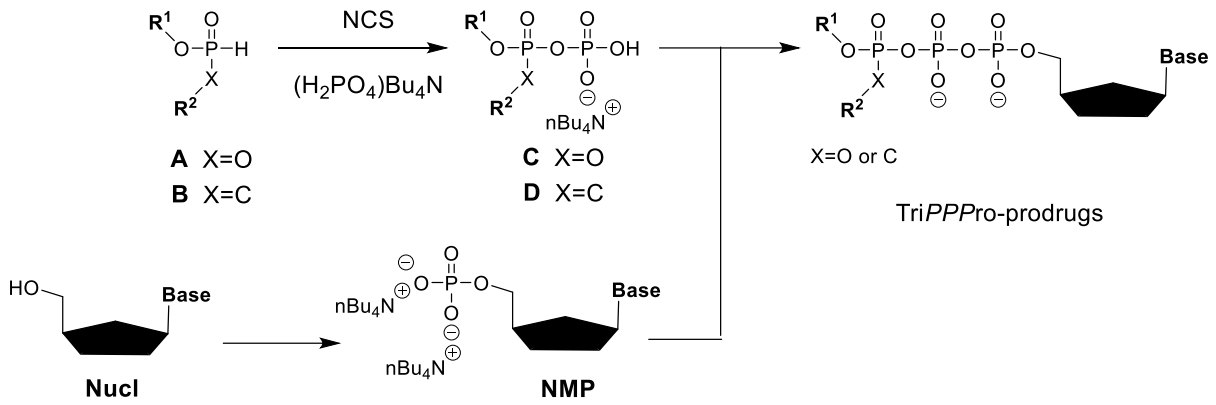
γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71**

Scheme 4. γ-(Alkyl; alkyl-C18)-phosphate-d4TDPs **70** and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** and cleavage pathways.

4 Discussion

4.1 General Synthesis Route for Tri*PPP*ro-NTPs

For the synthesis of Tri*PPP*ro-NTPs, the *H*-phosphonate route (similar to *H*-phosphinate route, Scheme 19) was used as reported previously by Gollnest (Scheme 5).[54] This approach is based on a coupling reaction of NMPs and pyrophosphates **C** or **D**. In the first step, NMPs were prepared according to the known procedure (general produce 8 and 9 in experiment section). *H*-phosphonates **A** or *H*-phosphinates **B** were converted into the corresponding phosphorochloridates and phosphonochloridates by oxidative chlorination with *N*-chlorosuccinimide (NCS)[175] followed by phosphorylation with tetra-*n*-butylammonium phosphate to yield pyrophosphates **C** or **D** in almost quantitative yields.



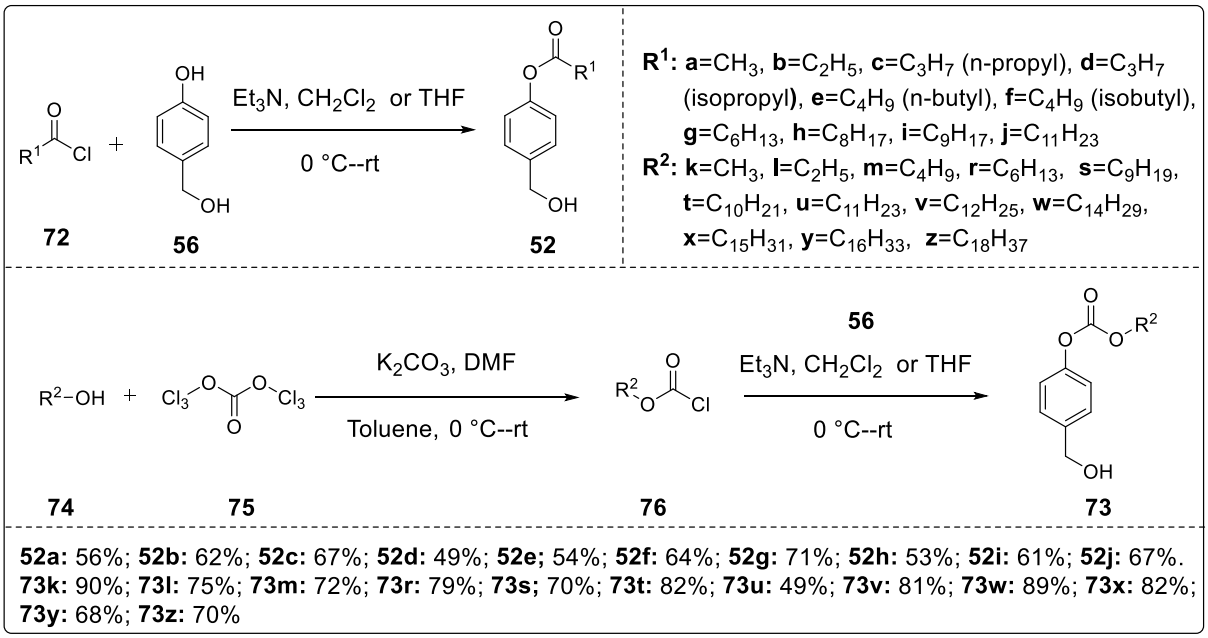
Scheme 5. *H*-Phosphonate route for the synthesis of Tri*PPP*ro-prodrugs.

4.2 Lipophilic prodrugs of nucleoside triphosphates

4.2.1 Synthesis of 4-acyloxybenzyl alcohols and 4-alkoxycarbonyloxybenzyl alcohols

In 1993, 4-acyloxybenzyl alcohols were used to improve the lipophilicity of monophosphate prodrugs.[168] In 2015, Meier´s group developed the Di*PP*ro-prodrugs containing bis(acyloxybenzyl) masking units. Following the established protocol, 4-acyloxybenzyl alcohols **52** were prepared. In this thesis, the conditions were further optimized with regard to temperature and solvent. This allowed an improvement in the yields (49%-71%, Scheme 6), for example, **52j** from 40% to 67%. With the optimized conditions, the protocol followed was this: To an ice-cold solution of 4-hydroxybenzyl alcohol **56** (1.1 equiv) and triethylamine (TEA, 1.0 equiv) in CH_2Cl_2 (HPLC grade), the acyl chlorides **72** (1.1 equiv) were added dropwise over a period of 20 min and then stirred overnight at room temperature. This method decreased the formation of di-esterified by-product.

Carbonates, closely related to the carboxylic acid esters in chemical structure, have also been used successfully in prodrug development. Tenofovir disoproxil fumarate **10** bearing carbonate ester functional groups, is one of the best-known prodrugs to combat HIV and HBV infections. In 2015, Meier´s group also prepared carbamate derivatives (Tri*PPP*ro-d4TTPs).[53] Since the alkyl chloroformates **76** needed as starting materials are quite expensive and in some cases not readily available, many compounds still needed to be synthesized. These compounds can be easily prepared from alkyl alcohols **74** with triphosgene, potassium carbonate, and DMF as a catalyst in toluene (Scheme 6). The yield of alkyl chloroformates **76** ranged from 54% to 85%. In other solvents, such as CH_2Cl_2 and pyridine, higher amounts of the alkyl chloride (by-products) were formed. Subsequently, various derivatives of 4-carbonate benzyl alcohols **73** were prepared in good yields (49%-90%) following the reaction conditions described in Scheme 6.

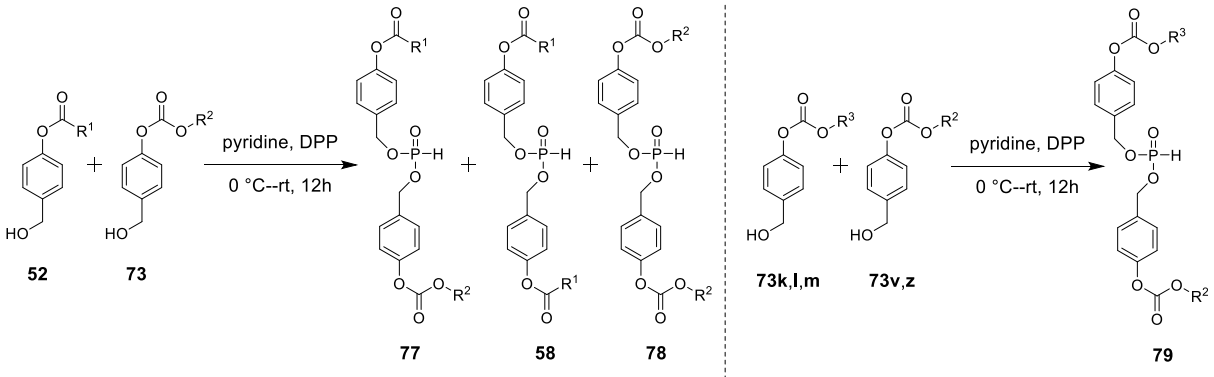


Scheme 6. Synthesis of starting materials **52** and **73**.

4.2.2 Synthesis of (AB; ACB)-*H*-phosphonates and (ACB; ACB)-*H*-phosphonates

Two versions of non-symmetric *H*-phosphonate compounds **77** were prepared. The first approach was to combine a highly lipophilic ($OC_{16}H_{33}$) 4-alkoxycarbonyloxybenzyl alcohol **73** as masking group with a series of 4-acyloxybenzyl alcohols **52** bearing different lipophilic ester group within the masking group with the aim to find a better hydrolysable group (C_nH_{2n+1}, n<9); The second approach was to combine a slightly lipophilic (C_2H_5 or C_4H_9) 4-acyloxybenzyl alcohols **52** as masking unit with a variety of 4-alkoxycarbonyloxybenzyl alcohols **73**, to find a better lipophilic protecting group (OC_nH_{2n+1}, n>9).

Therefore, *H*-phosphonates **77** were prepared from DPP, 4-acyloxybenzyl alcohols **52** and 4-alkoxycarbonyloxybenzyl alcohols **73**. The conditions were further optimized with regard to temperature, ratio of the starting reactants, and reaction time to obtain good yields. Generally, DPP was dissolved in pyridine and cooled to 0 °C. Then compounds **52** or **73** were added and stirred at 0 °C for at least 1h and then stirred at room temperature (rt) for 1h to ensure the first ester exchange step, followed by the addition of another compounds **73** or **52**, respectively. The conversion of the starting materials **52** and **73** to the *H*-phosphonates **77** gave overall yields between 24%-92% (Scheme 7). For comparison, three *H*-phosphonates **79** were synthesized as well using the same approach. These compounds have two alkoxycarbonyloxybenzyl (ACB)-moieties, but bearing different lipophilic alkyloxy residues (Scheme 7).



	R^1	R^2	Yield		R^1	R^2	Yield		R^1 or R^3	R^2	Yield
77ay	CH_3	$C_{16}H_{33}$	45%	**77bt**	C_2H_5	$C_{10}H_{21}$	47%	**77ex**	C_4H_9	$C_{15}H_{31}$	37%
77by	C_2H_5	$C_{16}H_{33}$	40%	**77bu**	C_2H_5	$C_{11}H_{23}$	43%	**77ez**	C_4H_9	$C_{18}H_{37}$	24%
77ey	n-C_4H_9	$C_{16}H_{33}$	41%	**77bv**	C_2H_5	$C_{12}H_{25}$	42%	**77is**	C_9H_{19}	C_9H_{19}	92%
77fy	*iso*-C_4H_9	$C_{16}H_{33}$	41%	**77bw**	C_2H_5	$C_{14}H_{29}$	49%	**77jr**	$C_{11}H_{23}$	C_6H_{13}	52%
77gy	C_6H_{13}	$C_{16}H_{33}$	56%	**77cv**	n-C_3H_7	$C_{12}H_{25}$	51%	**79ss**	C_9H_{19}	C_9H_{19}	55%
77hy	C_8H_{17}	$C_{16}H_{33}$	64%	**77dv**	*iso*-C_3H_7	$C_{12}H_{25}$	53%	**79lv**	C_2H_5	$C_{12}H_{25}$	47%
77iy	C_9H_{19}	$C_{16}H_{33}$	65%	**77ev**	C_4H_9	$C_{12}H_{25}$	49%	**77mv**	C_4H_9	$C_{12}H_{25}$	33%
77bs	C_2H_5	C_9H_{19}	43%	**77ew**	C_4H_9	$C_{14}H_{29}$	44%	**7mz**	C_4H_9	$C_{18}H_{37}$	41%

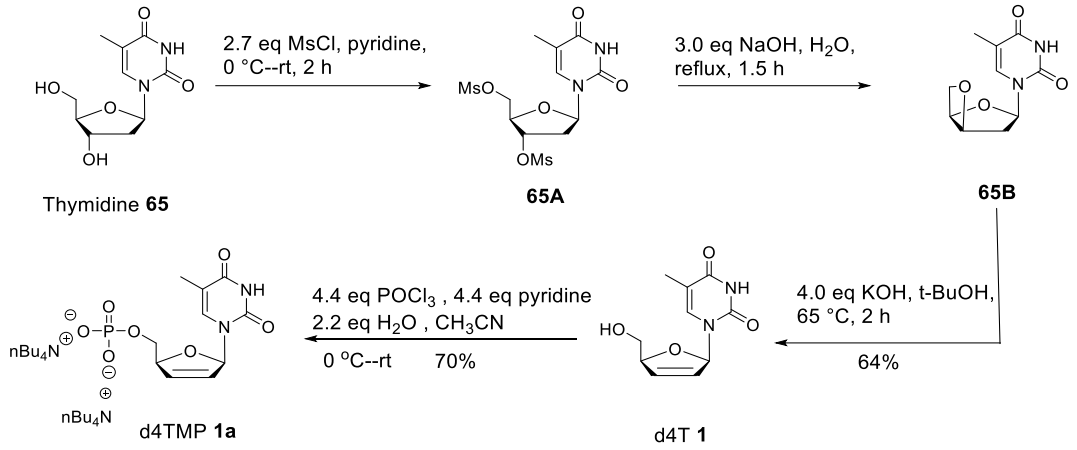
R^1: **a**=CH_3, **b**=C_2H_5, **c**=C_3H_7 (n-propyl), **d**=C_3H_7 (isopropyl), **e**=C_4H_9 (n-butyl), **f**=C_4H_9 (isobutyl), **g**=C_6H_{13}, **h**=C_8H_{17}, **i**=C_9H_{17}, **j**=$C_{11}H_{23}$

R^2 + R^3: **l**=C_2H_5, **m**=C_4H_9, **r**=C_6H_{13}, **s**=C_9H_{19}, **t**=$C_{10}H_{21}$, **u**=$C_{11}H_{23}$, **v**=$C_{12}H_{25}$, **w**=$C_{14}H_{29}$, **x**=$C_{15}H_{31}$, **y**=$C_{16}H_{33}$, **z**=$C_{18}H_{37}$

Scheme 7. Synthesis of *H*-phosphonates **77** and **79**.

4.2.3 Synthesis of 3'-deoxy-2',3'-dehydrothymidine (d4T) and d4TMP

To be able to synthesis of Tri*PPP*ro-compounds **60**,**61**, d4TMP **1a** was prepared from thymidine over four steps (procedure shown in Scheme 8). In the first step, thymidine **65** was activated by methanesulfonyl chloride (MsCl) in pyridine. In the following step, the product **65A** treated with aqueous sodium hydroxide to give compound **65B**. Afterwards, compound **65B** was reacted with potassium hydroxide in *tert*-butanol to obtain d4T **1**. Finally, d4TMP **1a** was synthesized in good overall yields according to the SOWA AND OUCHI method.[178]

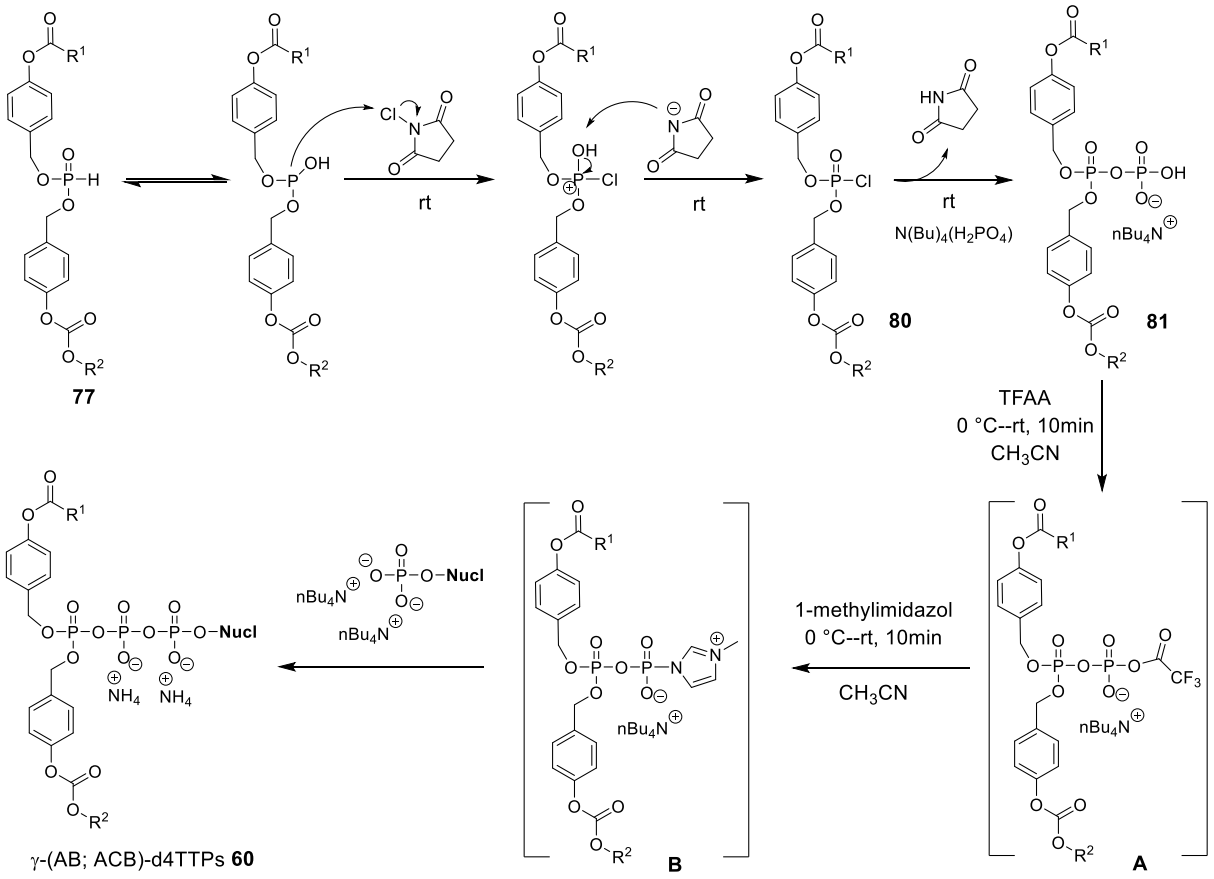


Scheme 8. Synthesis of d4TMP **1a** starting from thymidine **65**.

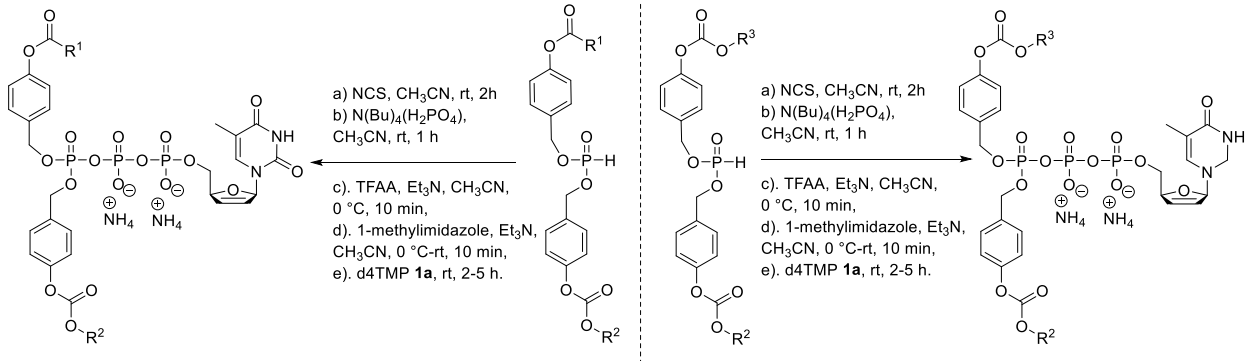
4.2.4 Synthesis of γ-(AB; ACB)-d4TTPs and γ-(ACB; ACB)-d4TTPs

Tri*PPP*ro-d4TTPs **60** were preferably synthesized using the *H*-phosphonate route. The mechanism of the *H*-phosphonate route is shown in Scheme 9. Here, *H*-phosphonates **77** reacts with NCS (oxidative chlorination) to form the corresponding phosphorochloridates **80** which was then reacted with tetra-*n*-butylammonium phosphate to generate pyrophosphates **81**. After extraction with dichloromethane (CH_2Cl_2) and an ammonium acetate solution, compounds **81** were obtained in nearly quantitatively. These compounds were immediately used in the next step due to their chemical instability. The final coupling reaction was accomplished using modified literature methods[175,176] to give γ-(AB; ACB)-d4TTPs **60** (*n*-Bu_4N^+ form). Firstly, pyrophosphates **81** reacts with trifluoroacetic acid anhydride (TFAA) and triethylamine (TEA) in CH_3CN to form intermediates **A**. Followed by addition of 1-methylimidazole and TEA in CH_3CN to generate intermediates **B**. Finally, the NMP, dissolved in CH_3CN, was added into the mixture and stirred at rt. After a reversed-phase (RP) column chromatography and a Dowex 50WX8 (NH_4^+) ion exchange, followed by a second RP-column chromatography and subsequent freeze-drying, the γ-(AB; ACB)-d4TTPs **60** (NH_4^+ form) were isolated. γ-(ACB; ACB)-d4TTPs **61** were synthesized by using the same route.

Similar to *H*-phosphonates **77**, **79**, a series of Tri*PPP*ro-compounds **60** and **61** were prepared shown in Scheme 10. The conversion of the parent nucleoside d4T **1** to the target Tri*PPP*ro-compounds **60**,**61** gave overall yields between 23%-78%. Notably, the solubility of compounds **60ey** (AB-C4; ACB-C16), **60gy** (AB-C8; ACB-C16), **60iy** (AB-C9; ACB-C16) decreased with long alkyl chains in the R^1 moiety. As a consequence, the purification of these compounds was increasingly difficult, resulting in lower overall yields. To improve the solubility, THF was added to the Tri*PPP*ro-compounds prior to column loading.



Scheme 9. The mechanism of *H*-phosphonate synthetic route.



	R^1	R^2	Yield		R^1	R^2	Yield		R^1 or R^3	R^2	Yield
60ay	CH_3	$C_{16}H_{33}$	50%	**60bt**	C_2H_5	$C_{10}H_{21}$	37%	**60ex**	C_4H_9	$C_{15}H_{31}$	74%
60by	C_2H_5	$C_{16}H_{33}$	51%	**60bu**	C_2H_5	$C_{11}H_{23}$	69%	**60ez**	C_4H_9	$C_{18}H_{37}$	39%
60ey	n-C_4H_9	$C_{16}H_{33}$	71%	**60bv**	C_2H_5	$C_{12}H_{25}$	43%	**60is**	C_9H_{19}	C_9H_{19}	78%
60fy	*iso*-C_4H_9	$C_{16}H_{33}$	73%	**60bw**	C_2H_5	$C_{14}H_{29}$	66%	**60jr**	$C_{11}H_{23}$	C_6H_{13}	54%
60gy	C_6H_{13}	$C_{16}H_{33}$	50%	**60cv**	n-C_3H_7	$C_{12}H_{25}$	52%	**61ss**	C_9H_{19}	C_9H_{19}	70%
60hy	C_8H_{17}	$C_{16}H_{33}$	46%	**60dv**	*iso*-C_3H_7	$C_{12}H_{25}$	44%	**61lv**	C_2H_5	$C_{12}H_{25}$	59%
60iy	C_9H_{19}	$C_{16}H_{33}$	23%	**60ev**	C_4H_9	$C_{12}H_{25}$	59%	**61mv**	C_4H_9	$C_{12}H_{25}$	55%
60bs	C_2H_5	C_9H_{19}	51%	**60ew**	C_4H_9	$C_{14}H_{29}$	78%	**61mz**	C_4H_9	$C_{18}H_{37}$	41%

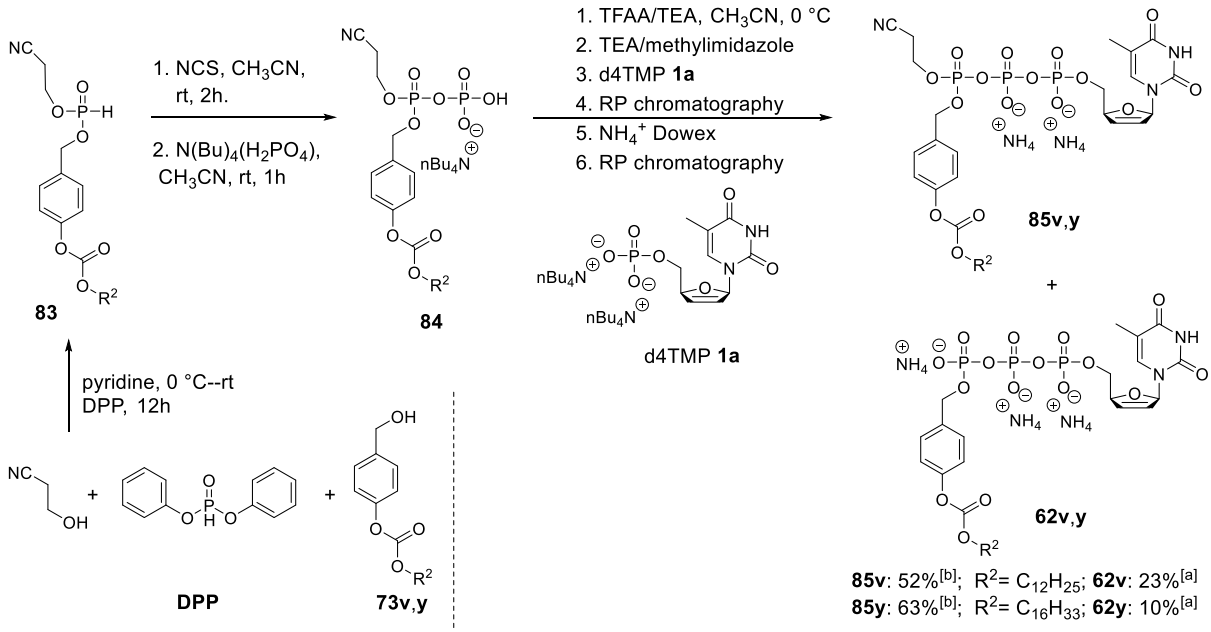
R^1: **a**=CH_3, **b**=C_2H_5, **c**=C_3H_7 (n-propyl), **d**=C_3H_7 (isopropyl), **e**=C_4H_9 (n-butyl), **f**=C_4H_9 (isobutyl), **g**=C_6H_{13}, **h**=C_8H_{17}, **i**=C_9H_{17}, **j**=$C_{11}H_{23}$

R^2 + R^3: **l**=C_2H_5, **m**=C_4H_9, **r**=C_6H_{13}, **s**=C_9H_{19}, **t**=$C_{10}H_{21}$, **u**=$C_{11}H_{23}$, **v**=$C_{12}H_{25}$, **w**=$C_{14}H_{29}$, **x**=$C_{15}H_{31}$, **y**=$C_{16}H_{33}$, **z**=$C_{18}H_{37}$

Scheme 10. Synthesis of Tri*PPP*ro-compounds **60** and **61** by *H*-phosphonate route.

4.2.5 Synthesis of γ-(ACB)-d4TTPs and γ-(ACB; β-cyanoethyl)-d4TTPs

In order to investigate the hydrolysis properties and the delivery mechanism of Tri*PPP*ro-compounds **60**,**61**, a new method for the synthesis of γ-(ACB)-d4TTPs **62** was developed. The β-cyanoethyl group was introduced as protection group for the γ-phosphate group, like Zhao´s work.[55] *H*-Phosphonates **83** were prepared from DPP, 3-hydroxypropionitrile, and 4-alkoxycarbonyloxybenzyl alcohols **73**. Compounds **83** were converted into their pyrophosphate form. After the coupling reaction of pyrophosphates **84** and d4TMP **1a**, γ-monomasked triphosphates **85** (*n*-Bu_4N^+ form) were synthesized. The crude reaction product was deprotected during the ion-exchange to yield the mixture of γ-(ACB; β-cyanoethyl)-d4TTPs **85** (NH_4^+ form) and γ-ACB-d4TTPs **62** (NH_4^+ form). Finally, γ-(ACB; β-cyanoethyl)-d4TTPs **85** (NH_4^+ form) and γ-(ACB)-d4TTPs **62** (NH_4^+ form) were obtained after RP18 column chromatography and subsequent freeze-drying (Scheme 11). It was speculated that Tri*PPP*ro-d4TTPs **85** seem to be cleaved at the β-cyanoethyl-moiety. Mechanistically this may happen by the known β-elimination leading to γ-(ACB)-d4TTPs **62**.



Scheme 11. Synthesis of compounds **62** and **85** via *H*-phosphonate route.

4.2.6 Chemical and Biological Hydrolysis

The Tri*PPP*ro-d4TTPs **60**,**61**,**85** and the γ-(ACB)-d4TTPs **62** were incubated in PB (pH 7.3) to study their chemical stability. The half-lives of Tri*PPP*ro-d4TTPs **60bs**-**60by** (AB-C2; ACB: C9-C16) ($t_{1/2}$= 25-83 h, Figure 28, left) increased with increasing alkyl chain lengths. However, chemical stabilities of

compounds **60cv**-**60dv** (AB-C3; ACB-C12) ($t_{1/2}$= 70-75 h, Figure 28, left) were in the same range as Tri*PPP*ro-d4TTP prodrugs **60ew**-**60ez** (AB-C4; ACB: C14-C18) ($t_{1/2}$= 69-74 h, Figure 28, left). For comparison, the half-lives of compounds **61lv** (ACB-C2; ACB-C12), **61mv** (AB-C4; ACB-C12), and **61mz** (AB-C4; ACB-C18) bearing different alkoxycarbonyloxybenzyl groups were found to be more stable than compounds **60bv** (AB-C2; ACB-C12), **60ev** (AB-C4; ACB-C12), and **60ez** (AB-C4; ACB-C12), respectively (Figure 28, right). The chemical stabilities of compounds **62** were significantly higher than those of compounds **60**,**61**, potentially caused by repulsive interaction between negative charges of the intermediate and the approaching nucleophile. More interestingly, the chemical stability of the carbonate intermediates γ-(ACB)-d4TTPs **62** were higher than the corresponding ester intermediates γ-(AB)-d4TTPs **55**. For example, the half-life for γ-(ACB-C16)-d4TTP **62y** ($t_{1/2}$ > 1600 h) was found to be significantly higher by almost a factor of 3 in the phosphate buffer as compared to the studies of γ-(AB-C17)-d4TTP **55n** ($t_{1/2}$ = 583 h) described before.[53]

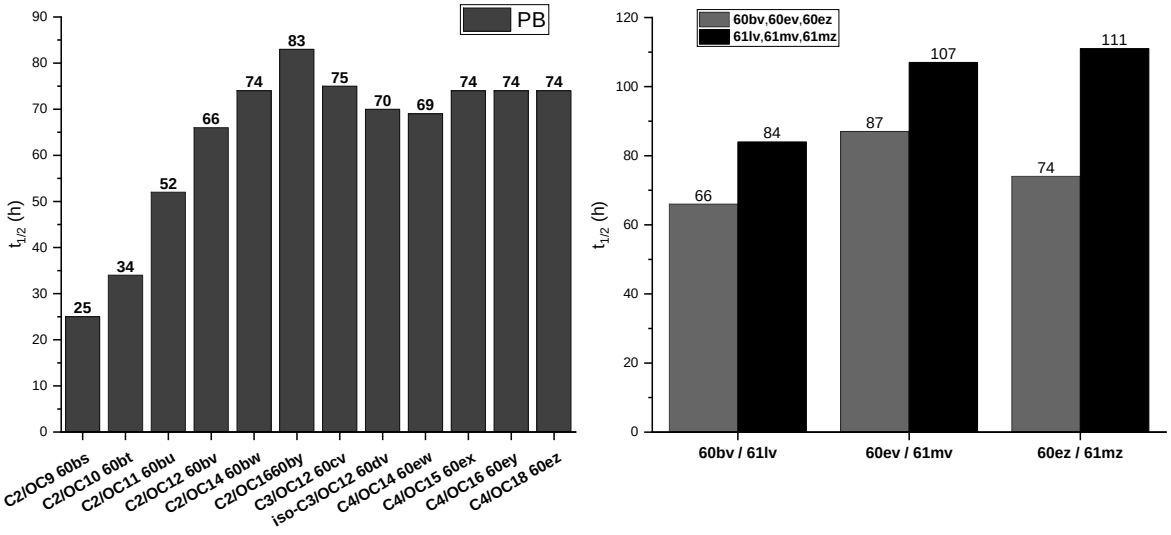
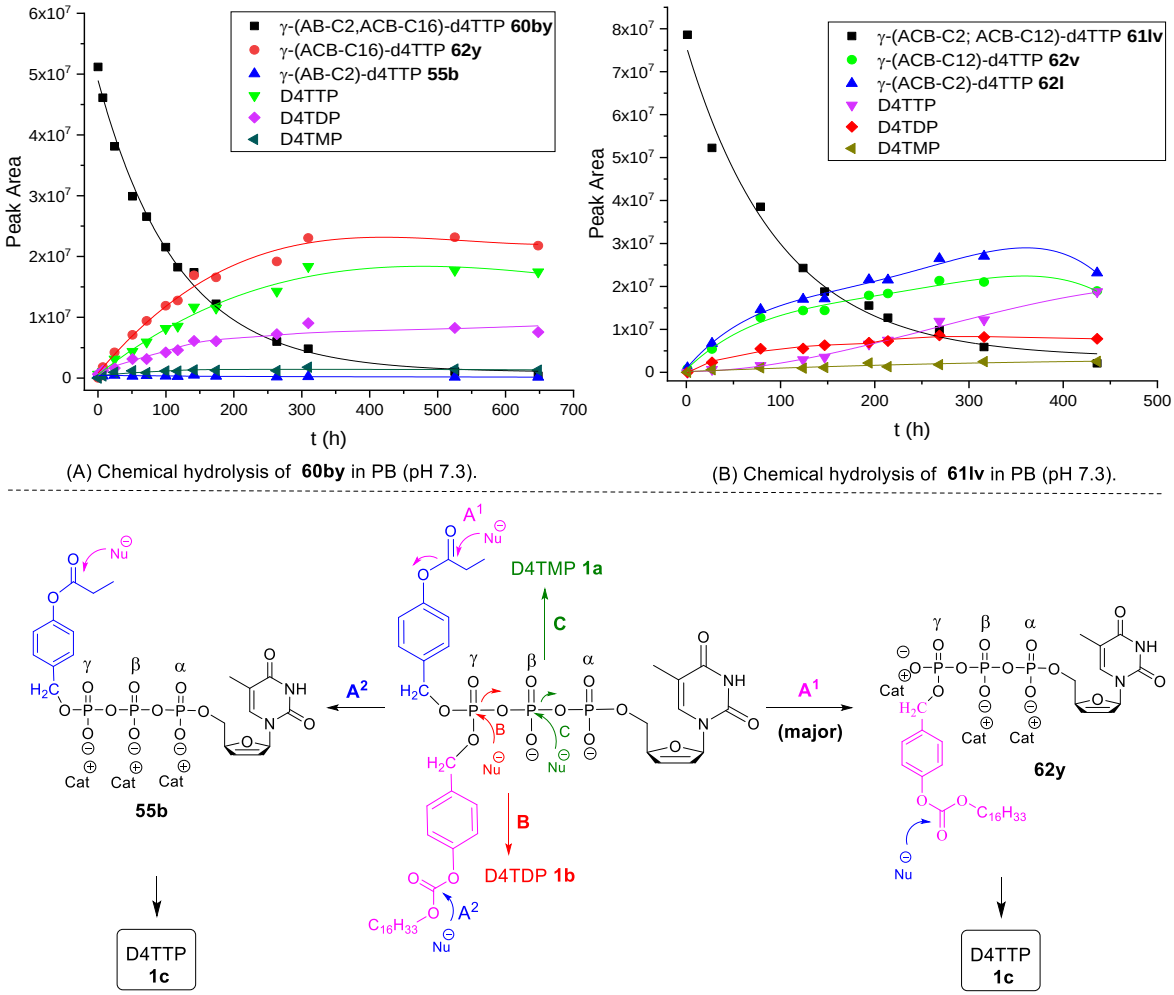


Figure 28. Half-lives of Tri*PPP*ro-d4TTP prodrugs **60**,**61** in PB (pH 7.3).

In PB, the starting material **60** disappeared and the expected γ-(ACB)-d4TTPs **62** were formed. The hydrolysis of compounds **60by** (AB-C2; ACB-C16) and **61lv** (ACB-C2; ACB-C12) are shown in Scheme 12 (top). The hydrolysis of Tri*PPP*ro-d4TTPs **60by** in PB released intermediates γ-(ACB-C16)-d4TTP **62y** and γ-(AB-C2)-d4TTP **55b**, while the hydrolysis of Tri*PPP*ro-d4TTPs **61lv** released intermediates γ-(ACB-C12)-d4TTP **62v** and γ-(ACB-C2)-d4TTP **62l**, respectively, indicating that both masking groups of Tri*PPP*ro-d4TTPs **60**,**61** were involved in the chemical hydrolysis (pathways A^1 and A^2) (Scheme 12,

bottom). As shown in Scheme 12, γ-(AB-C2; ACB-C16)-d4TTPs **60by** is mainly hydrolyzed to γ-(ACB-C16)-d4TTP **62y** with some formation of d4TTP. However, in the case of **61lv** (ACB-C2; ACB-C12), the formation of intermediate γ-(ACB-C2)-d4TTP **62l** proceeded slightly faster than γ-(ACB-C12)-d4TTP **62v** (Scheme 12, top), which were included for comparative reasons, changed due to altered chemical stability of the two carbonate residues. Therefore, the cleavage of the AB or ACB group is initiated by an ester or a carbonate hydrolysis. Additionally, some d4TDP **1b** was detected in small amounts. However, after complete consumption of the initial Tri*PPP*ro-compounds **60by**,**61lv**, no further increase of d4TDP **1b** concentrations was detected. Therefore, it was concluded that d4TDP **1b** was formed by the nucleophilic attack at the γ-phosphate moiety of the Tri*PPP*ro-compounds **60by**,**61lv**. It is noteworthy that almost no formation of d4TMP was observable in the chemical hydrolysis experiments.



Scheme 12. Diagram of chemical hydrolysis of Tri*PPP*ro-d4TTPs **60by**,**61lv** in PB (pH 7.3) and proposed hydrolysis mechanism of Tri*PPP*ro-d4TTPs **60**,**61**.

Next, Tri*PPP*ro-d4TTPs **60**,**61** were incubated in pig liver esterase (PLE) and CEM cell extracts to study their stability and to identify the formation of hydrolysis products. With PLE (half-lives: 0.17-13.8 h) and CEM/0 cell extracts (half-lives: 0.94-6.4 h), all Tri*PPP*ro-d4TTP prodrugs **60**,**61** were rapidly hydrolysed. The formation of d4TTP **1c** and d4TDP **1b** proceeded much faster compared to the hydrolysis in PB (half-lives: 74-90 h). This proves the enzymatical cleavage of the masking units (Figure 29).

As an example, the hydrolysis of compound **60ev** (AB-C4; ACB-C12) with PLE and CEM/0 cell extracts is shown in Scheme 13 (A and B, top). In case of Tri*PPP*ro-compound **60ev** ($t_{1/2}$ = 0.17 h, Figure 29) with PLE (Scheme 13, A), the highly selective cleavage of one biodegradable moiety led to the formation of γ-(ACB-C12)-d4TTP **62v**. Almost no d4TMP **1a** and no d4TDP **1b** was detected. γ-(ACB-C12)-d4TTP **62v** and γ-(AB-C4)-d4TTP **55e** first accumulated and later was cleaved as well and finally formed d4TTP **1c**. Furthermore, Tri*PPP*ro-d4TTP prodrugs **61lv** (ACB-C2; ACB-C12) ($t_{1/2}$ = 0.51 h) and **61mv** (ACB-C4; ABC-C12) ($t_{1/2}$ = 0.28 h) were also included to study whether the attachment of two different carbonate functional groups have an effect on the hydrolysis pathway or on the stability of the compounds. Interestingly, the slightly longer aliphatic chain (R^3=C_4H_9) in the ACB moiety was cleaved faster than the short chain acyl group (R^3=C_2H_5), which was similar to the hydrolysis pattern of $OC_{16}H_{33}$-bearing Tri*PPP*ro-d4TTPs **8by** (AB-C2) and **8ey** (AB-C4). Remarkably, in the case of the hydrolysis of compound **61mv** (ACB-C4; ACB-C12) with PLE, both hydrolysis intermediates bearing the long aliphatic chain (ACB-12) were formed in markedly different amounts (Scheme 13, D). However, for the chemical hydrolysis of compound **61mv**, both possible intermediates **62m** (ACB-C4) and **62v** (ACB-C12) were formed in almost identical amounts (Scheme 13, C).

The short AB-mask of Tri*PPP*ro-compound **60ev** (AB-C4; ACB-C12) ($t_{1/2}$ = 1.2 h) was cleaved readily to form intermediate γ-(ACB-C12)-d4TTP **62v** in CEM/0 cell extracts. Compared to the hydrolysis in PB and PLE, the concentration of d4TTP **1c** was very low (Scheme 13, B) due to its fast dephosphorylation by phosphorylases/kinases present in the cell extracts to the corresponding d4TDP **1b** and ultimately d4TMP **1a**. Moreover, in case of **60jr**, the ratio of γ-(ACB-C6)-d4TTP and γ-(AB-C11)-d4TTP was 10:1 after 8h incubation in CEM/0 cell extracts. This means that an almost selective cleavage process took place in cell extracts with the AB-moiety being cleaved first, which was in full agreement with the results obtained from the studies of compounds **60** in PB. Interestingly, the half-lives determined for compounds **60ev** (AB-C4; ACB-C12), **60by** (AB-C2; ACB-C16) as well as **60ey** (AB-C4; ABC-C12) and **60hy** (AB-C8; ACB-C16) increased with an increase of lipophilicity of the masking unit in CEM/0 cell extracts (Figure 29, red columns).

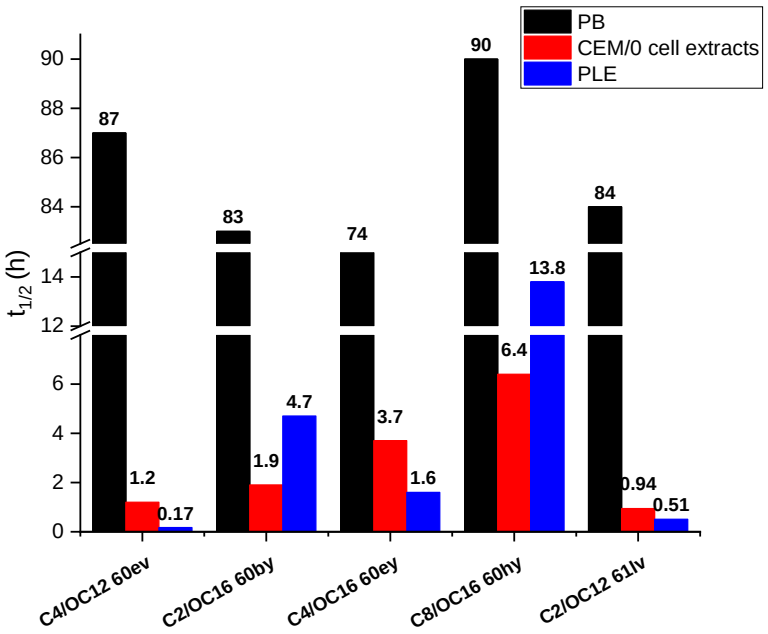
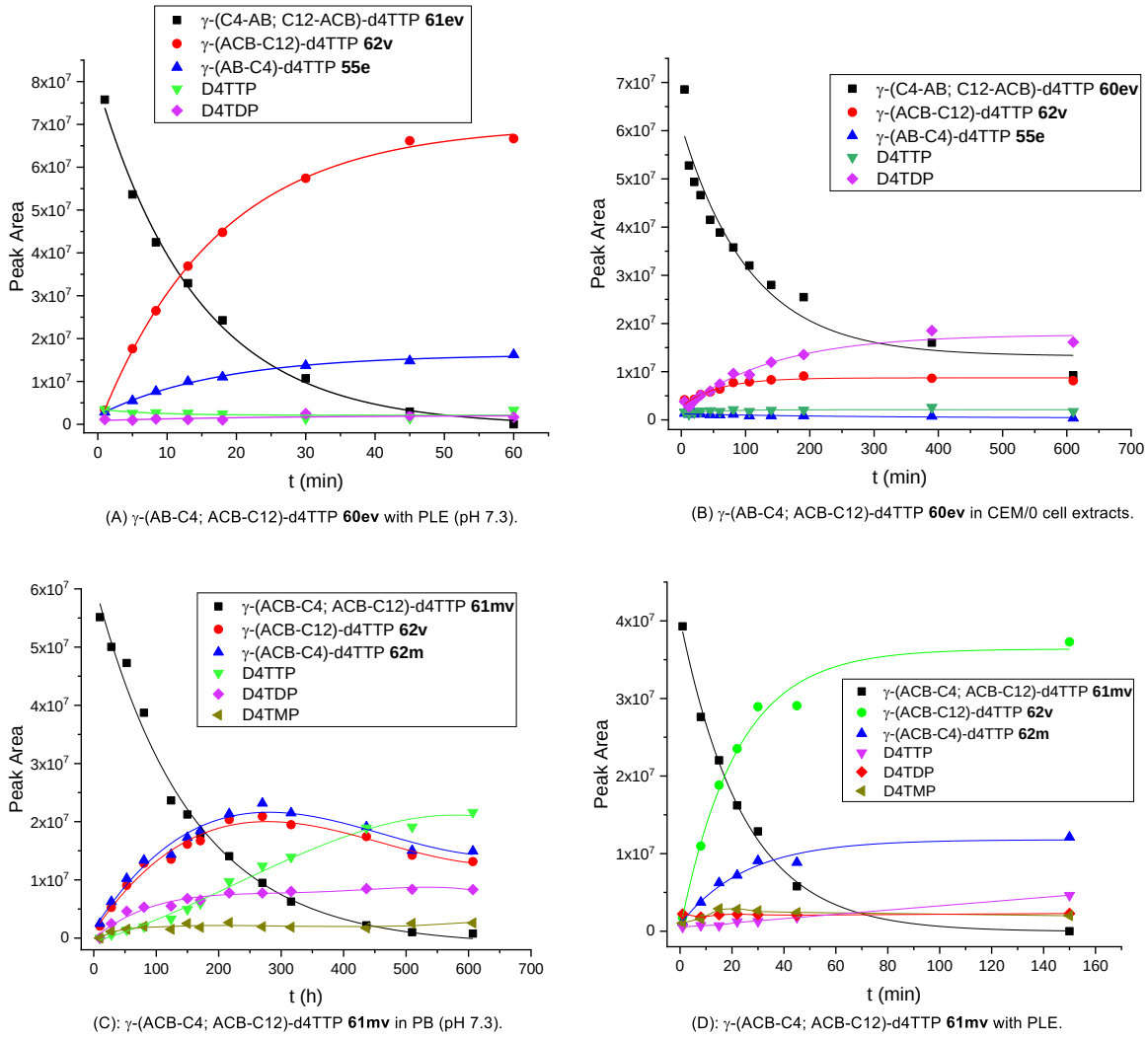


Figure 29. Half-lives of Tri*PPP*ro-d4TTPs **60**,**61** in PB (pH 7.3), PLE and CEM/0 cell extracts.



(A) γ-(AB-C4; ACB-C12)-d4TTP **60ev** with PLE (pH 7.3).

(B) γ-(AB-C4; ACB-C12)-d4TTP **60ev** in CEM/0 cell extracts.

(C): γ-(ACB-C4; ACB-C12)-d4TTP **61mv** in PB (pH 7.3).

(D): γ-(ACB-C4; ACB-C12)-d4TTP **61mv** with PLE.

Scheme 13. Diagrams of hydrolysis of prodrugs **60ev**,**61mv** in PB (pH 7.3), PLE and CEM/0 cell extracts.

4.2.7 Anti-HIV activities in CEM/0 and CEM/TK$^-$ cell cultures

Tri*PPP*ro-d4TTPs **60**,**61**,**85** and γ-(ACB)-d4TTPs **62** were evaluated for their ability to inhibit HIV replication in HIV-1- and HIV-2-infected wild-type CEM/0 cell cultures and in HIV-2-infected mutant thymidine kinase-deficient (CEM/TK$^-$) cell cultures. Table 2 summarizes the antiviral and cytotoxic data of the Tri*PPP*ro-d4TTPs **60**,**61**, γ-(β-cyanoethyl; ACB)-d4TTPs **85**, γ-(ACB)-d4TTPs **62** and the parent nucleoside analogue d4T **1** as the reference compound. The inhibition of the replication of HIV-1 and HIV-2 by prodrugs **60**,**61** was higher or similar to their parent nucleoside d4T **1** in CEM/0 cells. For the prodrug **60by** (EC_{50} = 0.0048 µM/HIV-2), the antiviral activity in this infected cell line improved by 65-fold as compared to d4T **1**. The Tri*PPP*ro-d4TTPs **60bs**-**60bv** (AB-C2; ACB: C9-C12) and **60ev**-**60ez** (AB-C4; ACB: C12-C18) bearing aliphatic carbonate functions in the ACB-units proved to be antivirally active against HIV-1 and HIV-2 in the same concentration range as compared to the parent compound d4T **1** in wild-type CEM/0 cell cultures. However, as compared to γ-(AB-C2; ACB-C16)-d4TTPs **60by**, no increased antiviral activity of prodrug **60iy** (AB-C9; ACB-C16) (EC_{50} = 0.16 µM/HIV-1; EC_{50} = 0.078 µM/HIV-2) was observed, although the compound is more lipophilic. Potentially the consequence of low solubility of Tri*PPP*ro-compound **60iy** in water, methanol, DMSO or in biological medium. Interestingly, all Tri*PPP*ro-d4TTPs **60**,**61**,**85** and γ-(ACB-C16)-d4TTP **62y** were highly potent in CEM/TK$^-$ cell cultures whereas d4T **1** lacked any relevant anti-HIV activity in this thymidine kinase-deficient cell model (EC_{50}: = 31.05 µM). The antiviral activity of β-cyanoethyl protected compounds **85** was found to be similar to that of γ-ACB-d4TTPs **62**, potentially due to the instability of the cyanoethyl-function such as in **85v** (β-cyanoethyl; ACB-C12) ($t_{1/2}$ = 23 h in PB). Consequently, it seems that even *one* long aliphatic chain in the ACB-units provides enough lipophilicity to enable a cellular uptake of the Tri*PPP*ro-d4TTPs **60**,**61**. As can be seen, Tri*PPP*ro-d4TTPs **60bv** (AB-C2; ACB-C12),**60ev** (AB-C4; ACB-C12) showed slightly better activities against HIV-1 and HIV-2 than the corresponding Tri*PPP*ro-d4TTPs **61lv** (ACB-C2; ACB-C12),**61mv** (ACB-C4; ACB-C12), respectively, in wild-type CEM/0 and CD4$^+$ T-cells thymidine kinase-deficient CEM/TK$^-$ cell cultures.

Table 2. Antiviral activity and cytotoxicity of Tri*PPP*ro-d4TTPs **60**,**61**,**85** and γ-(ACB-C16)-d4TTP **62y** in comparison with the parent nucleoside d4T **1**.

Comp.	HIV-1 (HE)	HIV-2 (ROD)	CEM/TK$^-$ HIV-2 (ROD)	Toxicity
	EC_{50}[a] [µM]	EC_{50}[a] [µM]	EC_{50}[a] [µM]	CC_{50}[b] [µM]

60by (C_2H_5/$OC_{16}H_{33}$)	0.027±0.0092	0.0048±0.0065	0.11±0.0071	34±9.3
60ey (C_4H_9/$OC_{16}H_{33}$)	0.032±0.017	0.014±0.015	0.12±0.048	21±17
60iy (C_9H_{19}/$OC_{16}H_{33}$)	0.16±0.085	0.078±0.044	0.24±0.0071	16±1.1
60bs (C_2H_5/OC_9H_{19})	0.073±0.028	0.040±0.011	1.76±0.13	84±23
60bv (C_2H_5/$OC_{12}H_{25}$)	0.061±0.027	0.13±0.072	0.64±0.12	33±21
60ev (C_4H_9/$OC_{12}H_{25}$)	0.040±0.029	0.017±0.015	0.073±0.036	27±4.9
60ez (C_4H_9/$OC_{18}H_{37}$)	0.055±0.006	0.025±0.007	0.56±0.13	58±22
60is (C_9H_{19}/OC_9H_{19})	0.11±0.021	0.09±0.011	0.15±0.02	37±2
60jr ($C_{11}H_{23}$/OC_6H_{13})	0.30±0.18	0.07±0.003	0.21±0.02	41±9
61ss (OC_9H_{19}/OC_9H_{19})	0.34±0.24	0.09±0.03	0.23±0.11	34±2
61lv (OC_2H_5/$OC_{12}H_{25}$)	0.57±0.33	0.24±0.17	1.75±0.25	64±16
61mv (OC_4H_9/$OC_{12}H_{25}$)	0.73±0.53	0.17±0.014	1.12±0.21	54±13
85y (β-cyanoethyl/$OC_{16}H_{33}$)	0.53±0.26	0.30±0.05	3.26±0.28	53±22
62y (ACB-$OC_{16}H_{33}$)	0.50±0.29	0.29±0.06	1.46±1.34	61±36
d4T	0.43±0.23	0.31±0.13	31.05±5.25	>50

[a] Antiviral activity in $CD4^+$ T-lymphocytes: 50% effective concentration; values are the mean ±SD of n=2-3 independent experiments. [b] Cytotoxicity: 50% cytostatic concentration or compound concentration required to inhibit $CD4^+$ T-cell (CEM) proliferation by 50%; values are the mean ±SD of n=2-3 independent experiments.

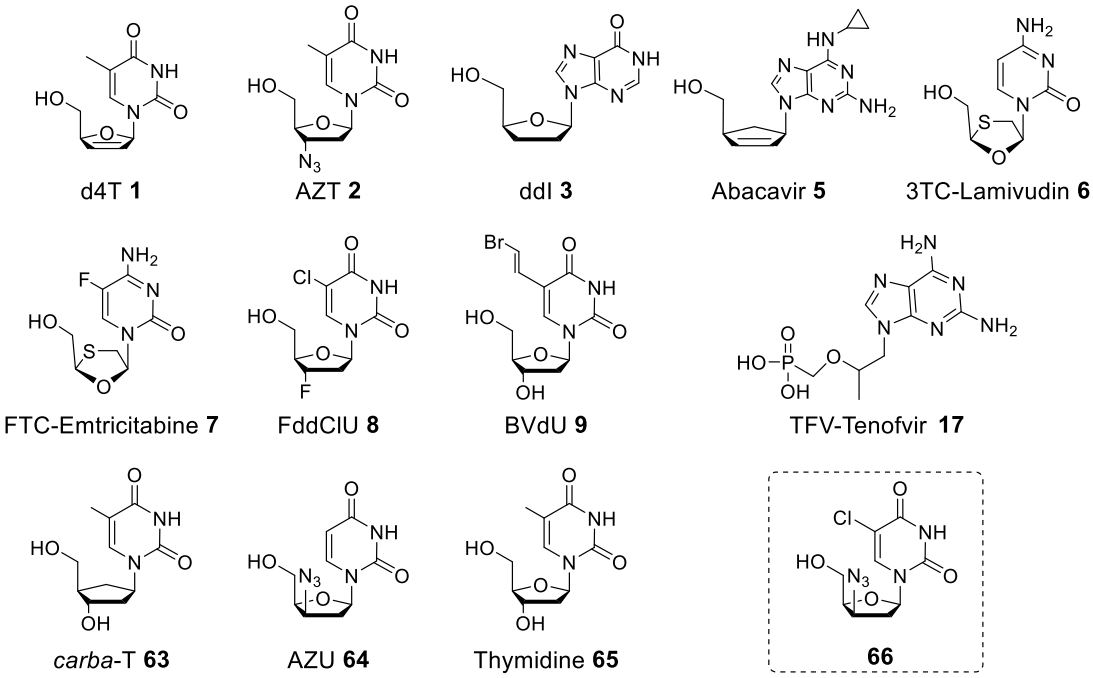
In summary, Tri*PPP*ro-d4TTPs **60**,**61** of the nucleoside analogue d4T **1** bearing two different biodegradable masking groups attached to the γ-phosphate group of the corresponding nucleoside triphosphate were synthesized using the *H*-phosphonate approach with modest to good yields (up to 78%). These compounds were selectively cleaved to form γ-(ACB-C_nH_{2n+1})-nucleoside triphosphates **62** by chemical hydrolysis (slow process) and in particular by cell extract enzymes (fast process). Furthermore, most of these prodrugs **60**,**61** were as active as or even more active than the reference compound d4T **1** against HIV-1 and HIV-2 in wild-type CEM/0 cell cultures. Significant activities were obtained depending on the lipophilicity of the Tri*PPP*ro-d4TTPs **60**,**61** against HIV-2 in mutant CEM/TK^- cell cultures. This confirms the cellular uptake of these prodrugs and the subsequent intracellular delivery of phosphorylated d4T species, most likely d4TTP. With high selectivity by an enzyme-triggered mechanism, Tri*PPP*ro-d4TTPs **60**,**61** enabled the bypass of all steps of the intracellular phosphorylation in cells. More interestingly, the inhibition of the replication of HIV-1 and HIV-2 by γ-(AB; ACB)-d4TTPs

60 was slightly higher than γ-(ACB; ACB)-d4TTPs **61**. The inhibition of the replication of HIV-1 and HIV-2 by prodrug **60by** (EC_{50} = 0.027 µM/HIV-1; EC_{50} = 0.0048 µM/HIV-2) was much higher compared to their parent nucleoside d4T **1** in wild-type CEM/0 cells. However, Tri*PPP*ro-d4TTPs **60by** (EC_{50} = 0.11 µM/HIV-2) showed a marked loss of activity in the TK-deficient cell cultures, respectively. This might be due to an insufficient lipophilicity of the compound **60by** combined with a relatively fast cleavage of the bioreversible AB- or ACB-moiety which led to the formation of γ-(ACB-C16)-d4TTP **62y** (major) and γ-(AB-C2)-d4TTP **55b**, respectively. Moreover, the γ-(ACB)**-**nucleoside triphosphates **62** were also highly potent in CEM/TK^- cell cultures (EC_{50} = 1.46 µM). Obviously, the modification at the γ-phosphate group by one lipophilic, biodegradable moiety and the 4-ACB-group gave the molecules sufficient lipophilicity to cross the biological barriers.[180]

Here, the Tri*PPP*ro-concept in which the γ-phosphate of NTPs is bioreversibly modified to deliver d4TTP with high selectivity by an enzyme-triggered mechanism which enabled the bypass of all steps of the intracellular phosphorylation was disclosed in this thesis. This concept may warrant to be applied to nucleoside analogues that show severe limitations in their activation to give the corresponding nucleoside triphosphates.

4.3 Application of the Tri*PPP*ro-concept to various nucleoside analogues

The carbonate Tri*PPP*ro-compounds **60**,**61** and γ-(ACB)-d4TTPs **62** proved to be more stable (enzymatically and chemically) than the corresponding ester γ-(AB; AB)-d4TTPs **54** and γ-(AB)-d4TTPs **55**,[53] respectively. Moreover, the monomasked γ-(ACB-C16)-d4TTP **62y** was moderately active against HIV-2 in thymidine kinase-deficient cell cultures (CEM/TK$^-$, EC_{50} = 1.46 μM), indicating a successful cellular uptake of these compounds. The γ-phosphate moiety comprises a long, lipophilic aliphatic chain (R^2 =$OC_{16}H_{33}$) providing sufficient lipophilicity to cross the cell membrane. This Tri*PPP*ro-strategy shows high potential in antiviral chemotherapies. The hydrolysis studies showed that the stability, hydrolysis, and antiviral activity were influenced by the chain lengths of the prodrug moieties. Therefore, the Tri*PPP*ro-concept applied to d4T **1** as a model, should be transferred to other nucleoside analogues to combat infections caused by HIV (Scheme 14).[181]



Scheme 14. Chemical structures of nucleoside antivirals as well as potential antiviral agents.

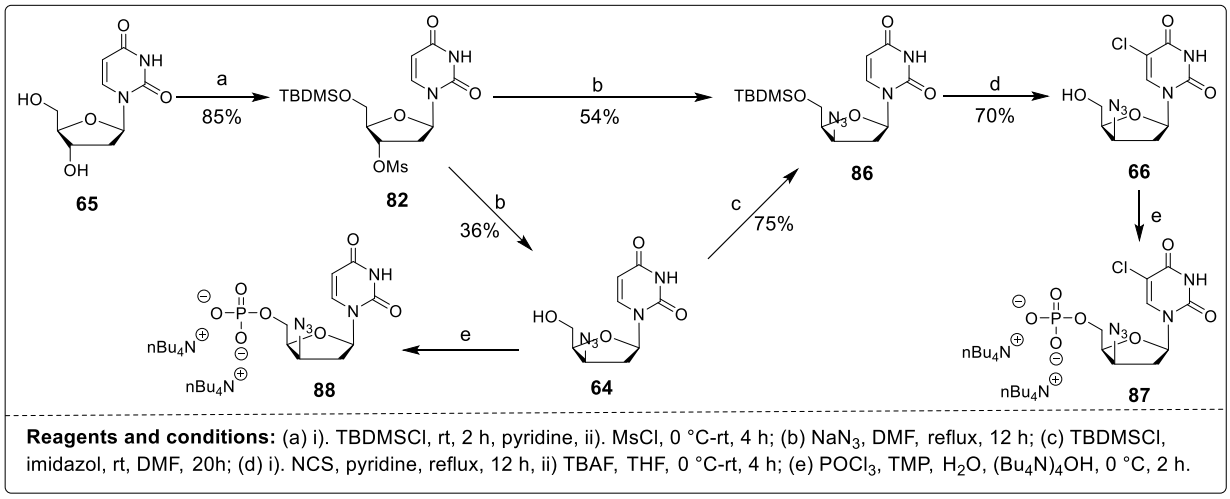
Furthermore, previous work from C. Zhao developed a second generation of lipophilic nucleoside triphosphate prodrugs.[55] γ-Acyloxybenzyl (AB)-γ-alkyl-d4TTPs **90a** comprising a non-cleavable alkyl moiety in addition to a biodegradable prodrug moiety at the γ-phosphate. Interestingly, γ-(alkyl)-d4TTPs **91** proved to be stable in cell extracts while d4TTP was rapidly dephosphorylated.[55] Moreover, γ-(AB; alkyl)-d4TTPs **90a** and γ-(alkyl-C18)-d4TTP **91a** showed marked antiviral activity against HIV-2 in

CEM/TK$^-$ cells. For example, the antiviral activity of γ-(alkyl-C18)-d4TTP **91a** improved by 430-fold (EC_{50}: 0.05 µM) compared to d4T **1**.[55] Therefore, NTP-prodrugs of a variety of other nucleoside analogues (e.g. AZT or FddClU) were synthesized and investigated.

Recently, Meier´s group showed that d4U- or ddU-diphosphate were poor substrates for cellular nucleoside diphosphate kinase (NDP-K)[46] and also the Di*PP*ro- or Tri*PPP*ro-compounds of d4U and ddU showed surprisingly only weak antiviral activity.[54] In initial hydrolysis studies, the Tri*PPP*ro-compound of ddU was rapidly hydrolysed in cell extracts and the formed ddUTP dephosphorylated quickly ($t_{1/2}$ < 1 min) to the corresponding ddUDP and ultimately ddUMP.[54] Therefore, it was speculated that the delivery of ddUTP (released from Tri*PPP*ro-ddUTPs) was not sufficient enough to exhibit antiviral activity. However, the completely inactive FddClU **8** was converted into an anti-HIV compound (γ-(AB-C8; AB-C8)-FddClUTPs).[54] These promising data lay the ground for this thesis, to develop an efficient and convergent synthesis for 3'-azido-5-chloro-2',3'-dideoxyuridine **66** (3'-AZdd-5-ClU, Scheme 14) and its corresponding nucleoside triphosphate prodrugs **89j1**.

4.3.1 Synthesis of 3'-up-azido-2',3'-dideoxyuridine and 3'-up-azido-5-chloro-2',3'-dideoxyuridine

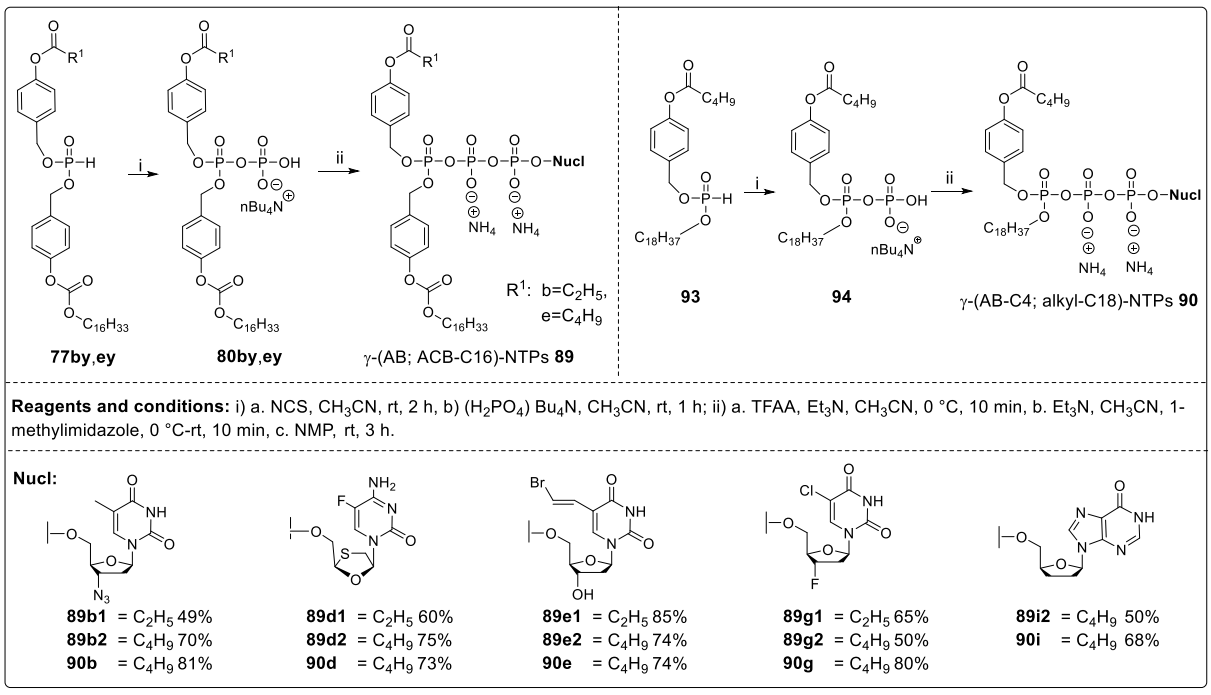
The synthesis route of the nucleoside 3'-up-AZdd-5-ClU **66** is shown in Scheme 15. 2'-Deoxyuridine **65** was the starting material and which was then reacted with *tert*-butyldimethylchlorosilane (TBDMSCl) in pyridine, followed by addition of methanesulfonyl chloride (MsCl) to form compound **82**. Then, compound **82** was reacted with NaN_3 in DMF through a conversion of the 3'-methanesulfonate group into an azido group via a S_N2 displacement. After refluxing, the target compound **86** with modest yield (54%) and deprotected nucleoside AZU **64** as by-product in 36% yield were obtained. Reaction of compound **86** with NCS in pyridine and the deprotection of TBDMS by TBAF in THF led to nucleoside 3'-up-AZdd-5-ClU **66** in 70% yield. AZUMP **88** and AZddClUMP **87** were prepared from the corresponding nucleoside monophosphate acids with tetra-*n*-butylammonium hydroxide. Nucleoside monophosphate acids were readily prepared from AZU **64** and 3'-AZdd-5-ClU **66** with $POCl_3$, trimethyl phosphate (TMP) and ice-cooled water, respectively.



Scheme 15. The synthetic pathway for compounds **64**, **66**, AZUMP **88** and AZddClUMP **87**.

4.3.2 Synthesis of γ-(AB; ACB-C16)-NTPs and γ-(AB-C4; alkyl-C18)-NTPs

Tri*PPP*ro-NTPs **89**,**90** were synthesized using the *H*-phosphonate route (Scheme 16). Therefore, the nucleoside monophosphates were synthesized. AZTMP was prepared in good overall yields according to literature procedure.[177] Other nucleoside monophosphates (NMPs) were prepared similarly to AZUMP **88** and AZddClUMP **87** (Scheme 15). Next, γ-(AB; ACB-C16)-NTPs **89** were prepared from NMPs and pyrophosphates **80by** (AB-C2; ACB-C16),**80ey** (AB-C4; ACB-C16) and the yields between 49%-85%. Similarly, the target γ-(AB-C4; alkyl-C18)-NTPs **90** was obtained in good yields (68%-81%).



Scheme 16. Synthesis of compounds **89** and **90** by *H*-phosphonate route.

The ^{1}H-NMR and ^{13}C-NMR spectra of γ-(AB-C4; ACB-C16)-AZTPs **89b2** and γ-(AB-C4; alkyl-C18)-AZTTPs **90b** are shown in Figure 30 and Figure 31, respectively

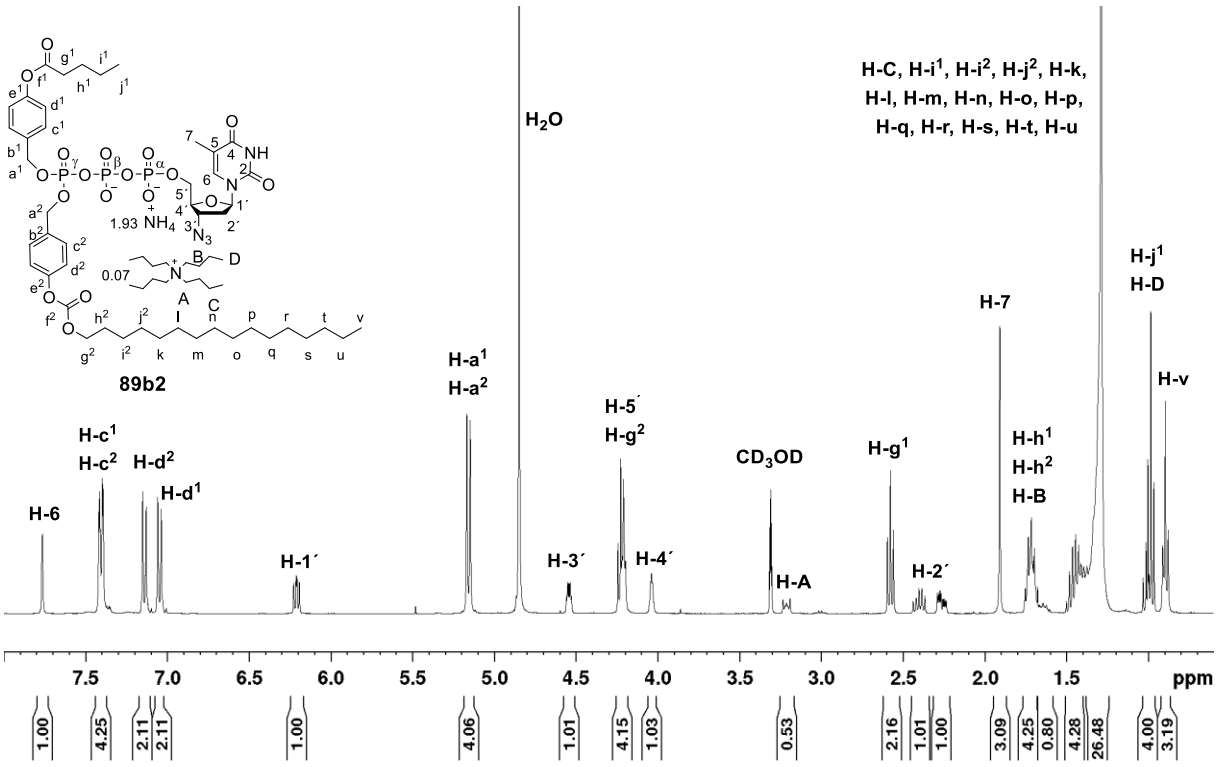


Figure 30-1: ^{1}H-NMR spectra of γ-(AB-C4; ACB-C16)-AZTPs **89b2** (CD_3OD-d_4).

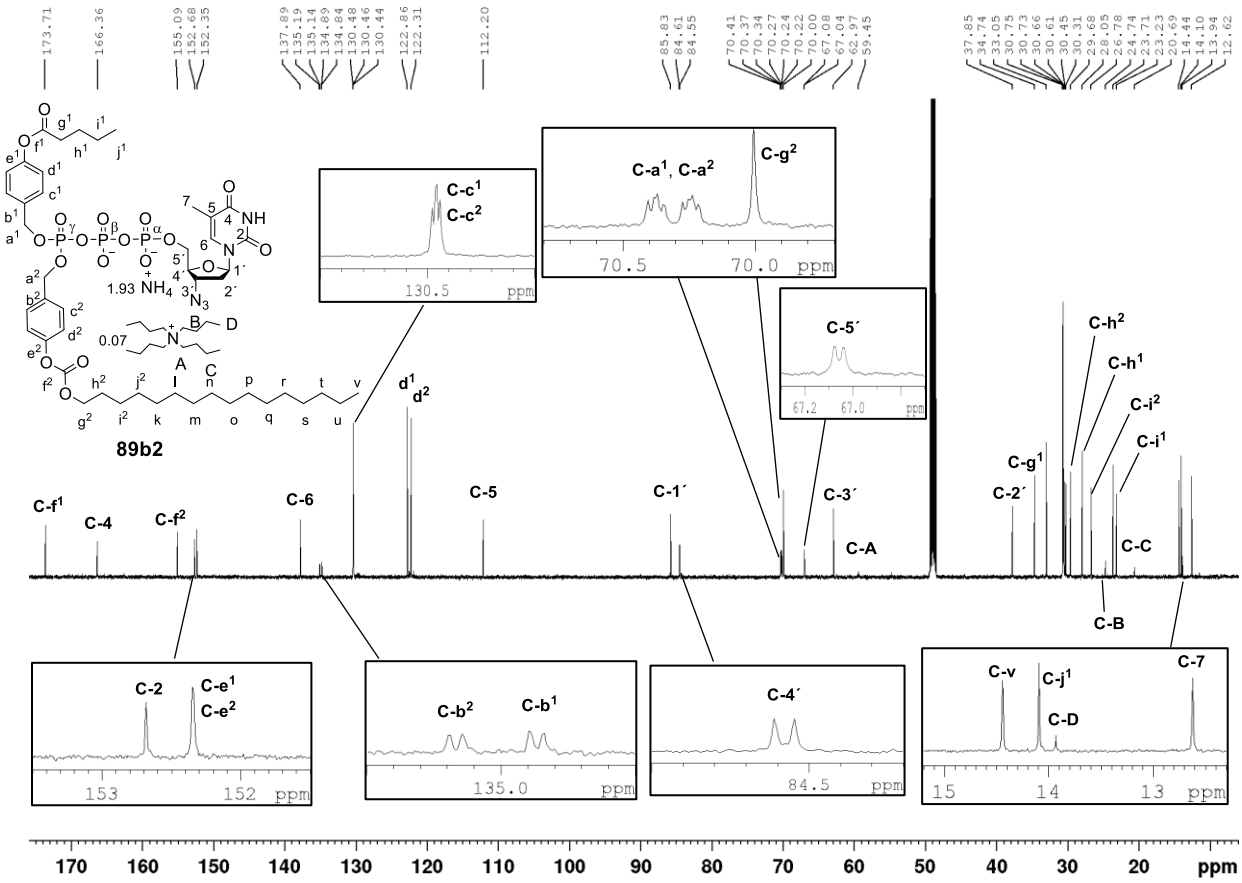


Figure 30-2: ^{13}C-NMR spectra of γ-(AB-C4; ACB-C16)-AZTPs **89b2** (CD_3OD-d_4).

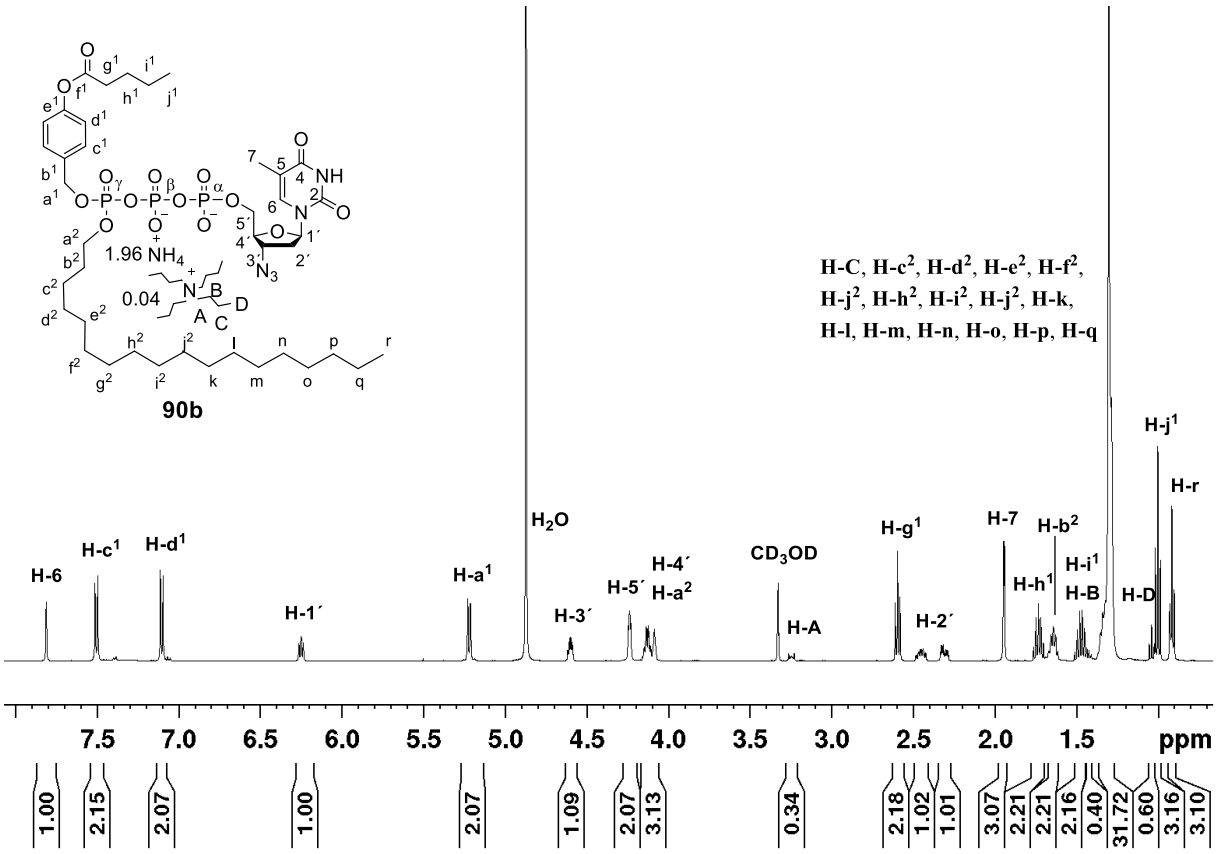


Figure 31-1: ^{1}H-NMR spectra of γ-(AB-C4; alkyl-C18)-AZTTPs **90b** (CD_3OD-d_4).

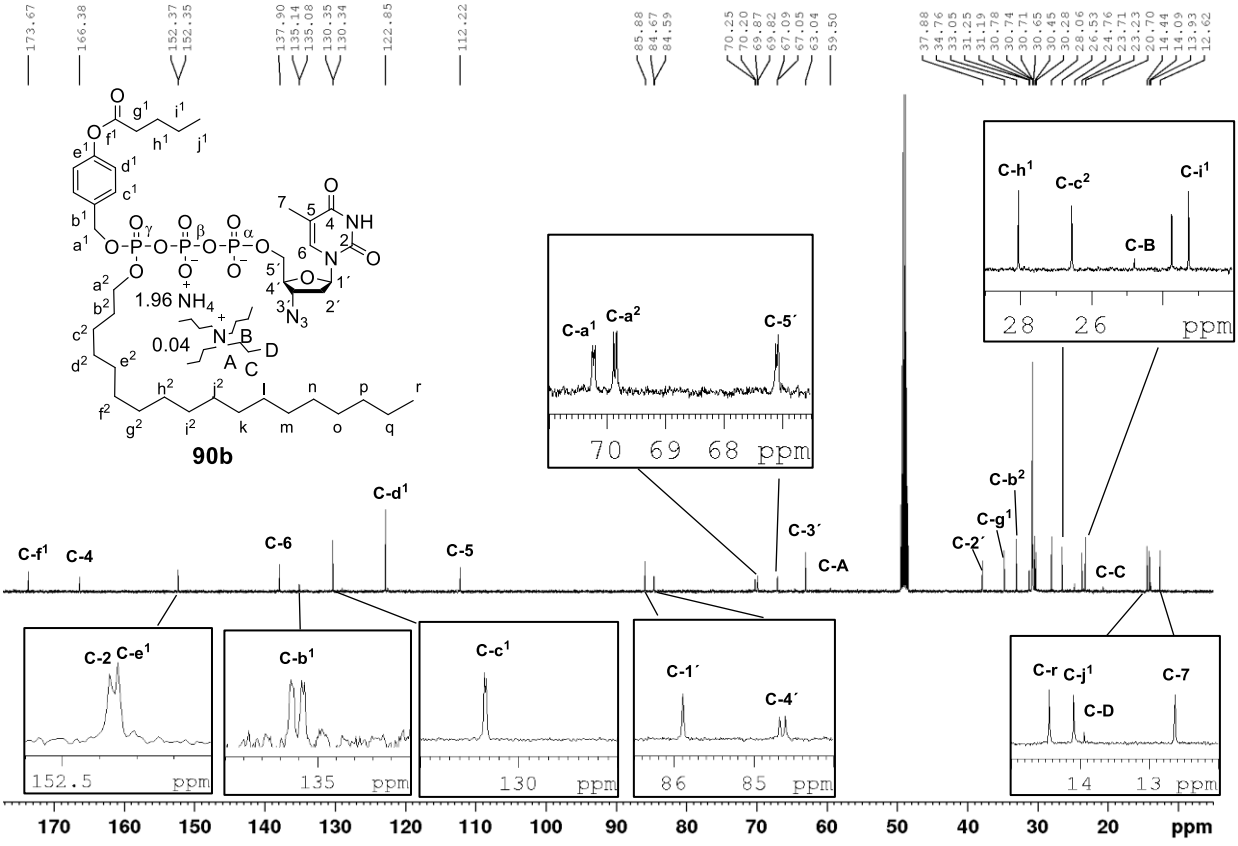


Figure 31-2: ^{13}C-NMR spectra of γ-(AB-C4; alkyl-C18)-AZTTPs **90b** (CD_3OD-d_4).

4.3.3 Chemical and Biological Hydrolysis

The hydrolysis studies disclosed how nucleotides are released from γ-(AB; ACB)-d4TTPs **60** and γ-(AB; ACB)-d4TTPs **61**. In the metabolism of γ-(AB; ACB)-d4TTPs **60**, the intracellular enzymatically-driven cleavage of both masks (AB and ACB) by an initial cleavage of the phenolic acyl ester and a subsequent spontaneous cleavage of the remaining part of the mask led to the selective release of d4TTP **1c** (Scheme 12, page 55). γ-(AB; ACB-C16)-NTPs **89** and γ-(AB-C4; alkyl-C18)-NTPs **90** were studied with regard to their stabilities and their hydrolysis products in PB (pH 7.3), PLE and CEM cell extracts. γ-(AB; ACB-C16)-NTPs **89** and γ-(AB-C4; alkyl-C18)-NTPs **90** were involved in the hydrolysis and thus proceeded similar to the previously published cleavage pathway for Tri*PPP*ro-d4TTPs **60**,**61** (Scheme 12, bottom, page 55).

As compared to γ-(AB; ACB-C16)-NTPs **89** ($t_{1/2}$ = 36-84 h), the half-lives for γ-(AB-C4; alkyl-C18)-NTPs **90** ($t_{1/2}$ = 178-600 h) were found to be significantly higher by almost a factor of 4-10 (Figure 32). In contrast, the half-lives of γ-(AB-C4; alkyl-C18)-NTPs **90** with PLE was found to be significantly lower by almost a factor of 9-23 as compared to corresponding Tri*PPP*ro-NTPs **89** (AB-C4; ACB-C16) (Figure 33). In general, half-lives as low as 0.19 h (**90g**) to 7 h (**89e2**) were determined with PLE, which points to an enzymatic cleavage. The half-lives of prodrugs **89**,**90** in CEM cell extracts were in the range of 1.3 h-5.0 h independent of the attached different nucleosides and also found to be significantly lower than the half-lives in PB, which points as in the PLE studies to an enzymatic cleavage.

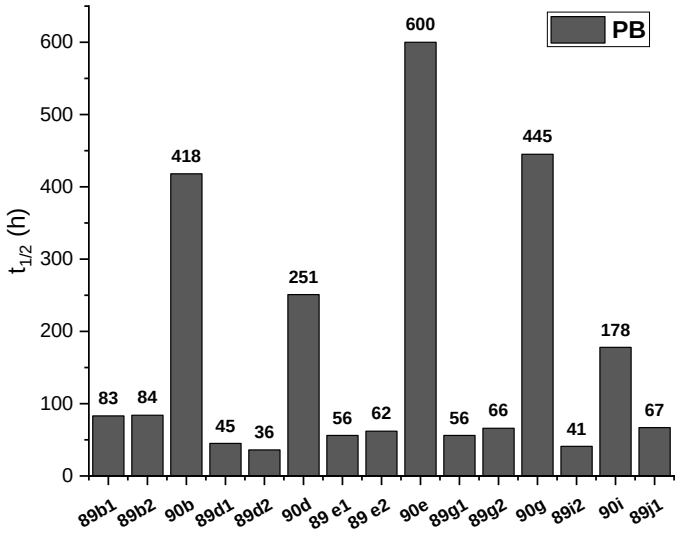


Figure 32. The hydrolysis half-lives of Tri*PPP*ro-NTPs **89**,**90** in PB (pH 7.3).

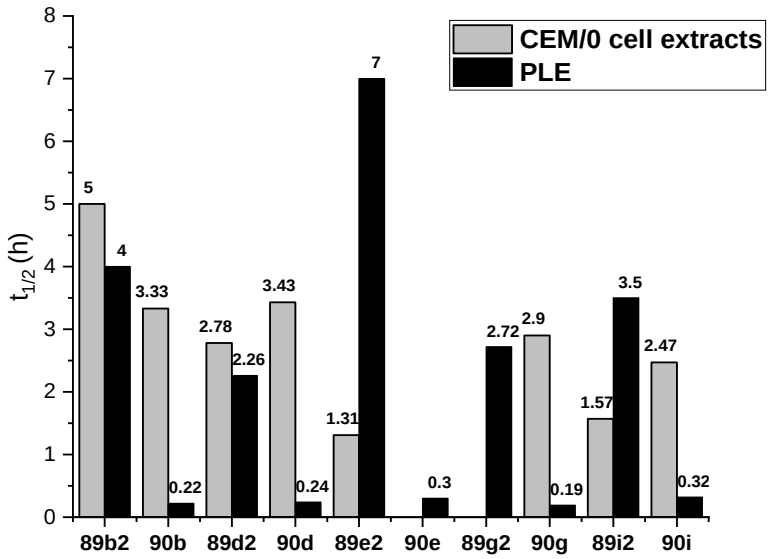
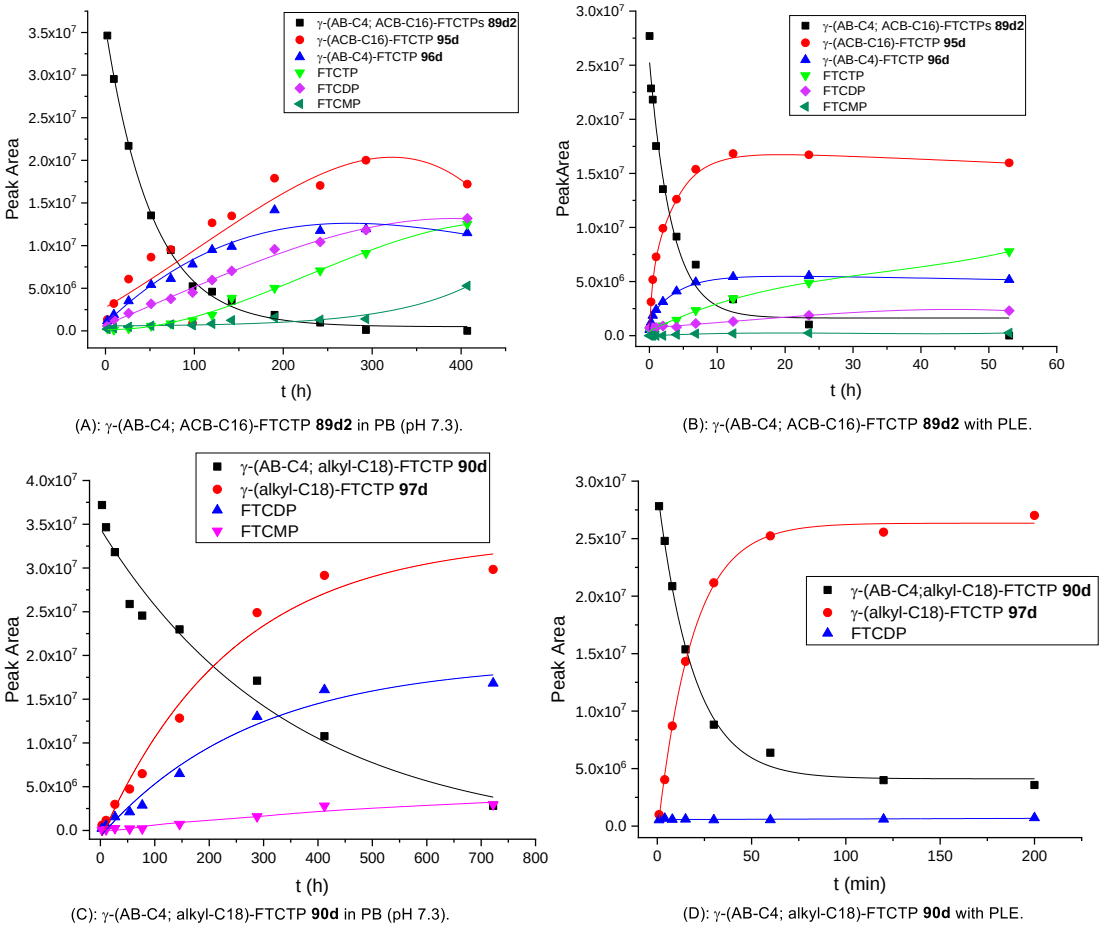
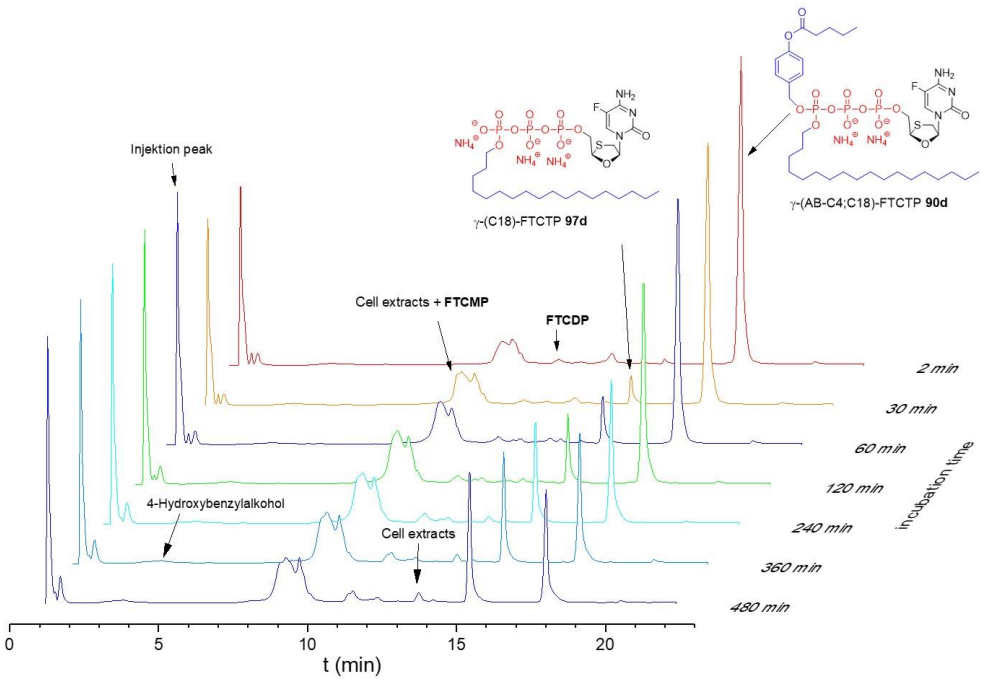


Figure 33. The hydrolysis half-lives of Tri*PPP*ro-NTPs **89**,**90** with PLE and CEM/0 cell extracts.

The hydrolysis of Tri*PPP*ro-FTCTPs **89d2**,**90d** in PB (pH 7.3) and with PLE are shown in Scheme 17. The hydrolysis of γ-(AB-C4; ACB-C16)-FTCTP **89d2** in PB released intermediates, γ-(ACB-C16)-FTCTP **95d** and γ-(AB-C4)-FTCTP **96d**, respectively. While γ-(AB-C4; ACB-C16)-FTCTP **89d2** is hydrolyzed mainly to γ-(ACB-C16)-FTCTP **95d** with some concomitant cleavage to FTCTP occurring as well. Before complete consumption of the initial γ-(AB-C4; ACB-C16)-FTCTP **89d2**, an increase in the FTCTP concentration was observed. In contrast, γ-(AB-C4; alkyl-C18)-FTCTP **90d** was only hydrolyzed to γ-(alkyl-C18)-FTCTP **97d** some cleavage to the corresponding FTCDP occurred as well. In contrast to γ-(AB; ACB-C16)-FTCTP **89d** containing a second cleavable mask, no FTCTP was detected in these studies using γ-(AB-C4; alkyl-C18)-FTCTP **90d**. Therefore, no cleavage of the alkyl residue in γ-(AB-C4; alkyl-C18)-NTPs **90** was occurred in these studies. This demonstrated the initial concept of introducing an enzyme-stable group to the γ-phosphate unit. Interestingly, a very low concentration of FTCDP was detected because of the high stability of γ-(alkyl-C18)-FTCTP **97d** in CEM cell extracts towards dephosphorylation. Furthermore, the predominant formation of γ-(alkyl-C18)-FTCTP **97d** was observed in CEM cell extracts. This supports the hypothesis that the γ-(alkyl-C18)-FTCTP **97d** in very small extend were prone to a bond breakage between the γ-phosphonate and β-phosphate (Scheme 18).



Scheme 17. Diagram of hydrolysis study of **89d2** and **90d** in PB (pH 7.3) and with PLE.



Scheme 18. HPLC profiles of **90d** after incubation in CEM/0 cell extracts.

4.3.4 Anti-HIV activities in CEM/0 and CEM/TK$^-$ cell cultures

Table 3 summarizes some antiviral and cytotoxic data of the γ-(AB-C8; AB-C8)-NTPs **57**,[54] γ-(AB; ACB-C16)-NTPs **89**, γ-(ACB-C16)-FddClUTP **95g** and the corresponding parent nucleoside analogues as reference compounds. All Tri*PPP*ro-NTPs **89** showed better activities against HIV-1 and HIV-2 than the parent nucleosides. Interestingly, the inhibition of the replication of HIV-1 and HIV-2 by prodrugs **89** was much higher, or at least similar compared to corresponding γ-(AB-C8; AB-C8)-NTPs **57**. For example, **89e2** (EC_{50} = 1.49 µM) showed higher activity than **57e** (EC_{50} > 10 µM),[54] **89g2** (EC_{50} = 2.59 µM) showed similar activity to **57g** (EC_{50} = 3.4 µM).[54] The high potential of the Tri*PPP*ro-concept was demonstrated by Tri*PPP*ro-FddClUTPs **89g2** with higher antiviral activity against HIV-2 (EC_{50} = 0.32 µM) compared to its parent nucleoside FddClU **8** (EC_{50} > 250 µM), that lacked any relevant anti-HIV activity in all cell cultures (Table 3). The antiviral studies showed that this Tri*PPP*ro-approach enables delivery and discovery of antiviral prodrugs that otherwise cannot be formed from their parent nucleosides. Unexpectedly, γ-(C2-AB; ACB-C16)-AZddClUTP **89m1** and its parent nucleoside analogue **66** showed no significant antiviral activity. It was speculated that AZddClUTP was not retained in sufficient concentrations in cells to exhibit antiviral activity or the corresponding AZddClUTP is not a substrate for RT.

Table 3. Antiviral activity and cytotoxicity of Tri*PPP*ro-NTPs **57**,**89** and γ-(ACB-C16)-FddClUTP **95g** in comparison to their parent nucleosides **7**,**8**,**9**,**66**.

Comp.	HIV-1 (HE)	HIV-2 (ROD)	CEM/TK$^-$ HIV-2 (ROD)	Toxicity
	EC_{50}[a] [µM]	EC_{50}[a] [µM]	EC_{50}[a] [µM]	CC_{50}[b] [µM]
89d2 (C4/OC16)	0.0043±0.0022	0.0087±0.0063	0.029±0.025	40.5±6.0
7 (FTC)	0.010±0.0022	0.016±0.013	0.046±0.042	>100
89e2 (C4/OC16)	1.49±0.70	1.32±0.76	>20	43± 0.2
57e[54] (C8/C8)	> 10	> 10	> 10	50 ± 10
9 (BVdU)	> 250	> 250	> 250	207 ± 60
89g2 (C4/OC16)	2.59±1.50	0.32±0.42	>20	42±4
95g (OC16)	2.5±1.0	3.6±3.7	40.2±4.8	54±13
57g[54] (C8/C8)	3.4 ± 2.5	> 10	> 10	42 ± 7

8 (FddClU)	>250	>250	>250	188±88
89m1 (C2/OC16)	>45	>45	>45	45±0
66 (AZddClU)	>100	>100	>100	>100

[a] Antiviral activity determined in $CD4^+$ T-lymphocytes: 50% effective concentration; values are the mean ±SD of n=2-3 independent experiments. [b] Cytotoxicity: 50% cytostatic concentration or compound concentration required to inhibit $CD4^+$ T-cell (CEM) proliferation by 50%; values are the mean ±SD of n=2-3 independent experiments.

In summary, a series of Tri*PPP*ro-NTPs **89**,**90** bearing different masking units at the γ-phosphate group have been synthesized in good yields. Most of the Tri*PPP*ro-NTP prodrugs **89** disclosed here showed similar or even slightly better activities against HIV-1 and HIV-2 than the parent nucleosides in wild-type (CEM/0) cell cultures.[181] In addition and more importantly, also high activities were obtained depending on the lipophilicity of the Tri*PPP*ro-NTPs **89** against HIV-2 in this thymidine kinase-deficient cell model. It was confirmed that these compounds **89** were taken-up by the cells and delivered intracellularly a phosphorylated form of parent nucleosides, most likely nucleoside triphosphates. Interestingly, γ-(ACB-C16)-FddClUTP **95g** is also active in CEM/TK^- cell cultures whereas FddClU **8** lacked any relevant anti-HIV activity in mutant CEM/TK^- cell cultures. The results show that the Tri*PPP*ro-strategy enabled the intracellular delivery of nucleoside triphosphates, such as FddClUTP, and the approach could be used to convert inactive nucleoside analogues into powerful biologically active metabolites (Table 3).The Tri*PPP*ro-approach in which the γ-phosphate of NTPs is modified by different lipophilic and biodegradable masking units which are cleaved by an enzyme-triggered mechanism enables the bypass of all steps of the intracellular phosphorylation and could therefore maximize the intracellular concentration of the ultimately bioactive NTP. The Tri*PPP*ro-approach offers high potential to be used in antiviral and maybe also in antitumoral therapies.

In contrast to γ-(AB-C2 or C4; ACB-C16)-NTPs **89** comprising two different biodegradable masking groups, γ-(AB-C4; alkyl-C18)-NTPs **90** are modified by a non-cleavable γ-alkyl-phosphate moiety in addition to a biodegradable prodrug moiety. γ-(AB-C4; alkyl-C18)-NTPs **90** are cleaved by an enzyme-triggered mechanism enables the bypass of all steps of the intracellular phosphorylation. It is worth noting that no formation of NTP was detected in all hydrolysis studies using these prodrugs **90**. Furthermore, γ-(alkyl-C18)-NTPs proved to be stable in cell extracts towards dephosphorylation. Finally, it was expected that γ-(AB-C4; alkyl-C18)-NTPs **90** have high activities against HIV in CEM/0 cell cultures and CEM/TK^- cell cultures.

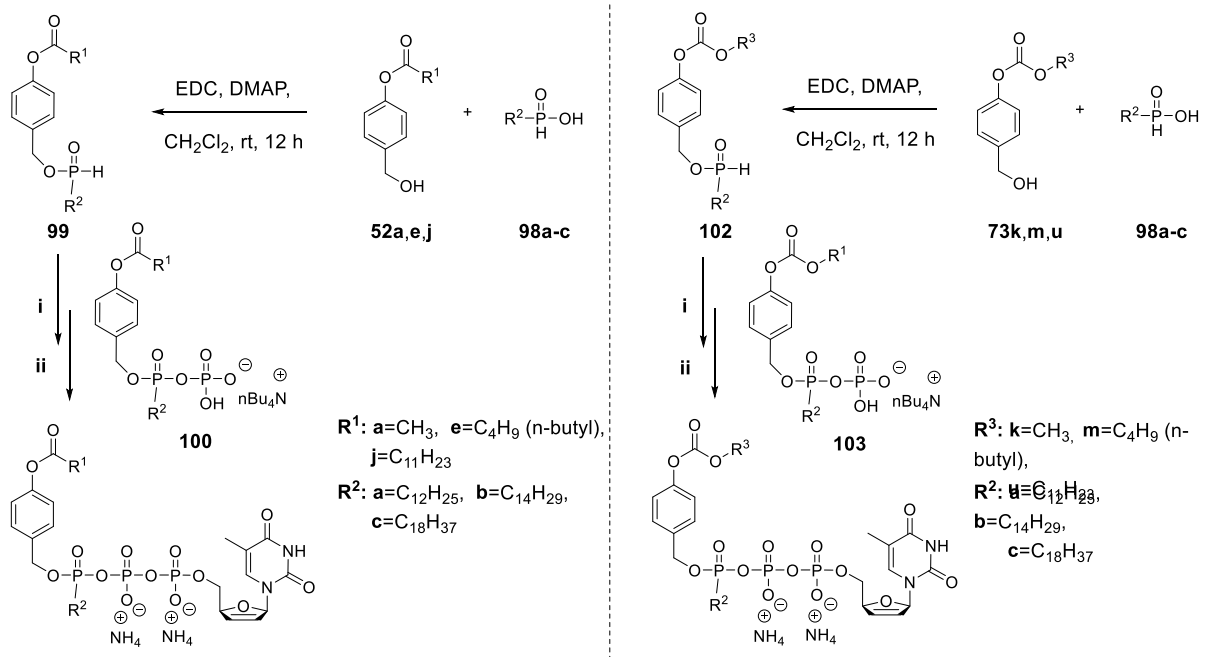
4.4 Nucleoside Diphosphate-γ-phosphonates prodrugs

The larger, more lipophilic masking units have been successfully developed in the Meier group that mask any negative charges at physiological pH. The biodegradable masking of γ-(AB; AB)-d4TTPs **54**[53] showed good antiviral activity. It was speculated that the Tri*PPP*ro-approach can: 1) enhance cell penetration; 2) avoid or minimize degradation in serum via cellular sequestration.

The study of phosphonate prodrugs has a long history, thus this Tri*PPP*ro-strategy to protect and deliver phosphonate monoesters has been of great interest. In this thesis, a new class of nucleoside triphosphate prodrugs, γ-AB-γ-C-alkyl-d4TTPs **67** and γ-ACB-γ-C-alkyl-d4TTPs **68** were developed. These Tri*PPP*ro-compounds **67**,**68** comprise a non-cleavable γ-alkyl-phosphonate moiety instead of the normal γ-phosphate group in addition to a biodegradable prodrug moiety at the γ-phosphonate unit. Here, γ-AB-γ-C-alkyl-d4TTPs **67**, γ-ACB-γ-C-alkyl-d4TTPs **68** as well as their hydrolysis intermediates γ-C-(alkyl)-d4TTPs **69** were prepared, with the aim of achieving a metabolic bypass and superior antiviral potency. Moreover, primer extension assays were also performed investigating the substrate properties of the γ-C-(alkyl)-d4TTP **69** for three different DNA-polymerases α, β and γ.[186]

4.4.1 Synthesis of γ-(AB)-γ-C-alkyl-d4TTPs and γ-(ACB)-γ-C-alkyl-d4TTPs

To prepare γ-C-alkylphosphonate-d4TDP prodrugs **67**,**68**, the *H*-phosphinate route was developed. Here, phosphinic acids **98** were readily prepared from a Grignard reagent and diethyl chlorophosphite in THF or Et_2O. *H*-phosphinates **99**,**102** were synthesized from phosphinic acids **98**, 4-dimethylaminopyridine (DMAP), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) **101** and 4-acyloxybenzyl alcohols **52** or 4-alkoxycarbonyloxybenzyl alcohols **73**, respectively. The overall yields varied between 48%-85%. They were converted into phosphonate-phosphates **100**,**103**. Using the *H*-phosphinate synthesis pathway, the linkage between the α- and the β-phosphate of the prodrug was formed and no oxidation has to be done, which was in full agreement with the *H*-phosphonate route. The overall yields obtained in the conversions of *H*-phosphinates **99**,**102** with d4TMP **1a** to γ-C-alkylphosphonate-d4TDP prodrugs **67**,**68** varied between 25%-68% (Scheme 19).



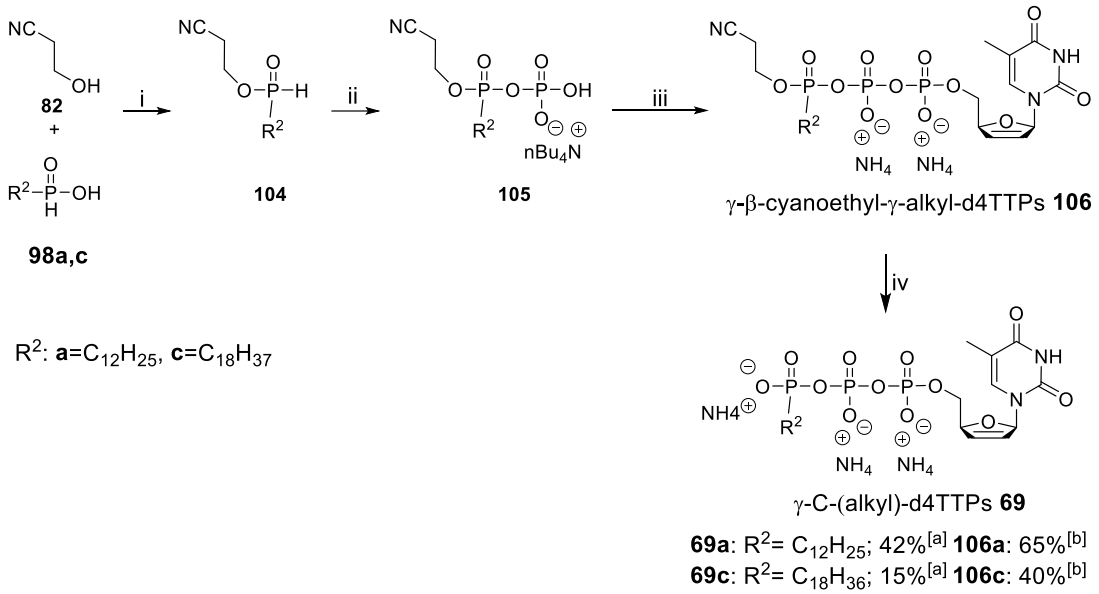
	R^1	R^2	Yield		R^1 or R^3	R^2	Yield		R^3	R^2	Yield
99aa	CH_3	$C_{12}H_{25}$	62%	**67aj**	$C_{11}H_{23}$	$C_{12}H_{25}$	33%	**102cm**	C_4H_9	$C_{18}H_{37}$	85%
99ae	C_4H_9	$C_{12}H_{25}$	53%	**67be**	C_4H_9	$C_{14}H_{29}$	57%	**68ak**	CH_3	$C_{12}H_{25}$	68%
99aj	$C_{11}H_{23}$	$C_{12}H_{25}$	59%	**67ce**	C_4H_9	$C_{18}H_{37}$	30%	**68am**	C_4H_9	$C_{12}H_{25}$	32%
99be	C_4H_9	$C_{14}H_{29}$	51%	**102ak**	CH_3	$C_{12}H_{25}$	55%	**68au**	$C_{11}H_{23}$	$C_{12}H_{25}$	25%
99ce	C_4H_9	$C_{18}H_{37}$	48%	**102am**	C_4H_9	$C_{12}H_{25}$	48%	**68bm**	C_4H_9	$C_{14}H_{29}$	52%
67aa	CH_3	$C_{12}H_{25}$	61%	**102au**	$C_{11}H_{23}$	$C_{12}H_{25}$	54%	**68cm**	C_4H_9	$C_{18}H_{37}$	51%
67ae	C_4H_9	$C_{12}H_{25}$	31%	**102bm**	C_4H_9	$C_{14}H_{29}$	53%				

Reagents and conditions: i) a. NCS, CH_3CN, rt, 2 h, b) $N(Bu)_4(H_2PO_4)$, CH_3CN, rt, 1 h ii) a. TFAA, Et_3N, CH_3CN, 0 °C, 10 min, b. 1-methylimidazole, Et_3N, CH_3CN, 0 °C-rt, 10 min, c. d4TMP, rt, 2 h.

Scheme 19. Synthesis of γ-C-alkylphosphonate-d4TDP prodrugs **67**,**68**.

4.4.2 Synthesis of γ-(β-cyanoethyl)-γ-C-alkyl-d4TTPs and γ-C-(alkyl)-d4TTPs

To investigate the hydrolysis properties of γ-C-alkylphosphonate-d4TDP prodrugs **67**,**68** and their delivery mechanism, γ-C-(alkyl)-d4TTPs **69** were prepared using the *H*-phosphinate route. The β-cyanoethyl group was introduced here as protecting group for the γ-phosphonate. After the coupling reaction of phosphonate-phosphates **105** and d4TMP **1a**, the γ-protected triphosphates **106** (*n*-Bu_4N^+ form) were formed. Tri*PPP*ro-d4TTPs **106** (NH_4^+ form) were isolated after rp-column chromatography, a Dowex 50WX8 (NH_4^+) ion exchange and freeze-drying in 40-65% yields. The crude products of γ-(β-cyanoethyl)-γ-C-alkyl-d4TTPs **106** (*n*-Bu_4N^+ form) were stirred in a mixture of tetra-*n*-butylammonium phosphate water solution and CH_3CN to obtain the target products γ-C-(alkyl)-d4TTPs **69** (NH_4^+ form) with low yields (15-42%) (Scheme 20).



R^2: **a**=$C_{12}H_{25}$, **c**=$C_{18}H_{37}$

Scheme 20. Reagents and conditions: i) EDC, DMAP, CH_2Cl_2, rt, 12 h; ii) a. NCS, CH_3CN, rt, 2 h, b) $N(Bu)_4(H_2PO_4)$, CH_3CN, rt, 1 h; iii) a. TFAA, Et_3N, CH_3CN, 0 °C, 10 min, b. 1-methylimidazole, Et_3N, CH_3CN, 0 °C--rt, 10 min, c. d4TMP **1a**, rt, 2 h. iv) *n*-$Bu_4N^+OH^-$, 8h, Dowex 50WX8 (NH_4^+ form) ion exchange. [a] yields are calculated for the conversion from **104** to **69**. [b] yields are calculated for the conversion from **104** to **106**.

The ^{1}H-NMR and ^{31}P-NMR spectra of γ-(AB-C4)-γ-C-(alkyl-C14)-d4TTP **67be** and γ-C-(alkyl-C12)-d4TTP **69a** are shown in Figure 34 and Figure 35, respectively. In ^{31}P-NMR spectra (Figure 35-1), the signal for P-γ of γ-C-(alkyl-C12)-d4TTP **69a** appears as a doublet, while in ^{31}P-NMR spectra (Figure 34-1), P-γ is the doublet of doublets due to J_{pp} coupling and the chemical shift is 25.7.

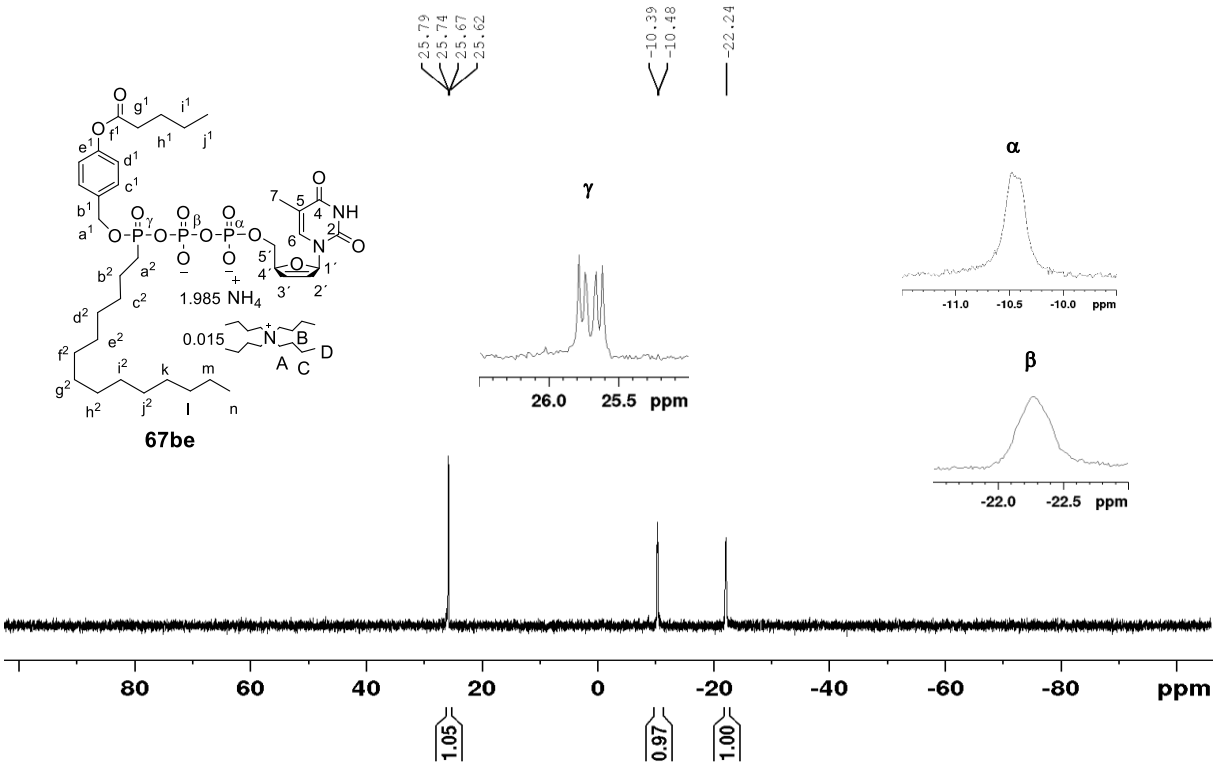


Figure 34-1: ^{31}P-NMR spectra of γ-(AB-C4)-γ-C-(alkyl-C14)-d4TTP **67be** (CD_3OD-d_4).

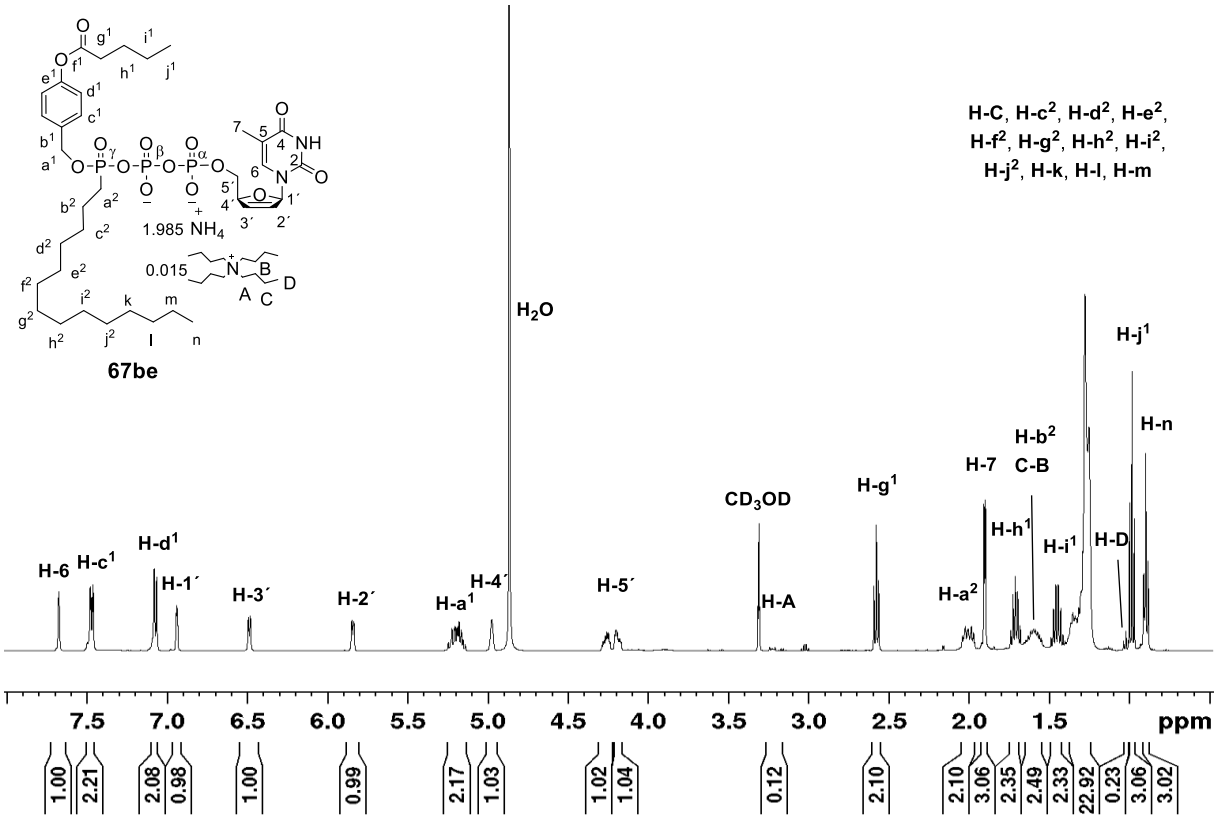


Figure 34-2: ^{1}H-NMR spectra of γ-(AB-C4)-γ-C-(alkyl-C14)-d4TTP **67be** (CD_3OD-*d*$_4$).

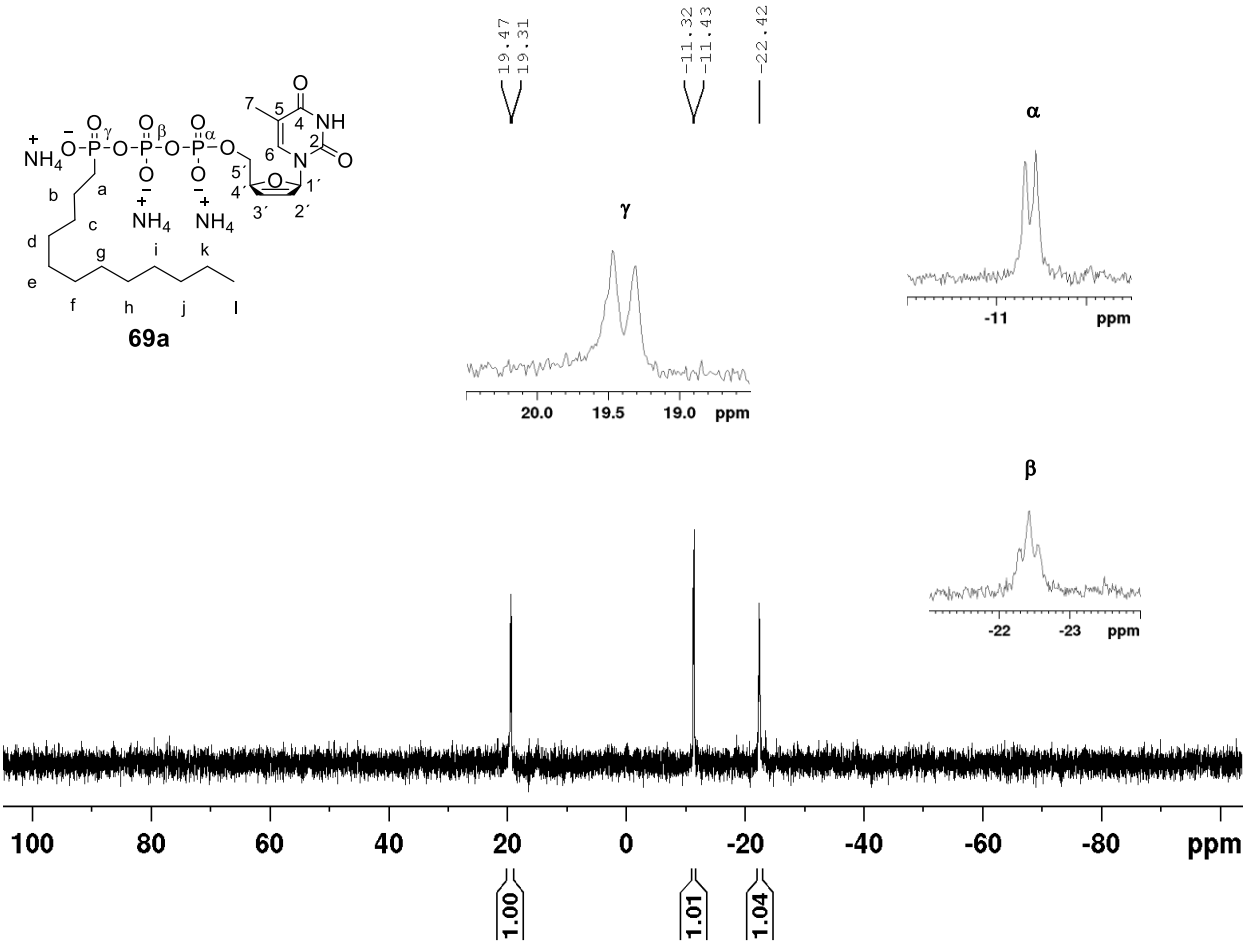


Figure 35-1: ^{31}P-NMR spectra of γ-C-(alkyl-C12)-d4TTP **69a** (CD_3OD-*d*$_4$).

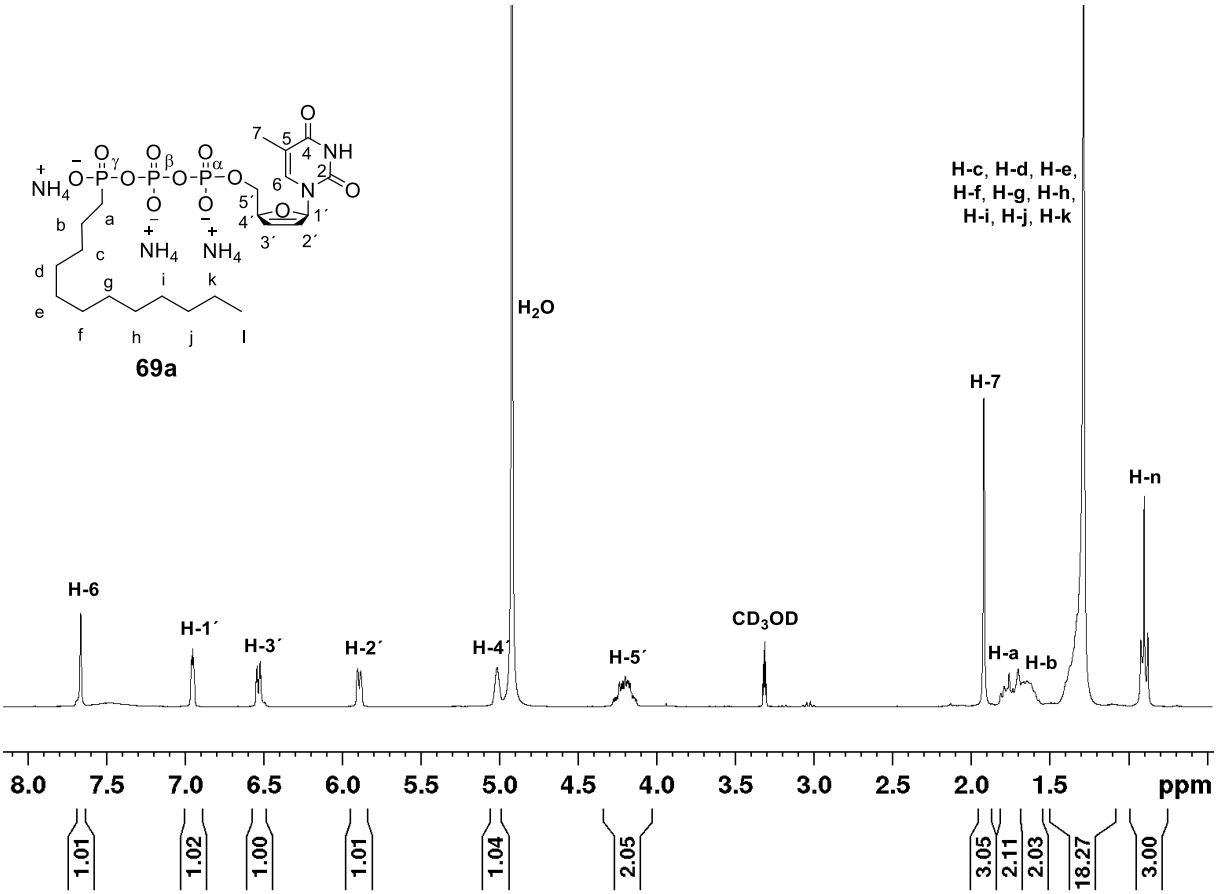


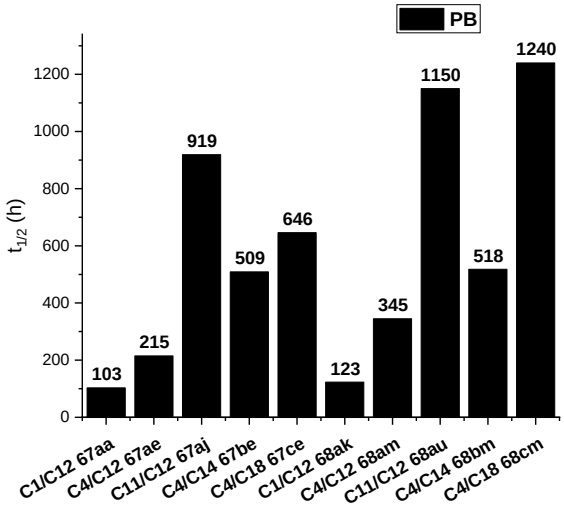
Figure 35-2: ^{1}H-NMR spectra of γ-C-(alkyl-C12)-d4TTP **69a** (CD_3OD-d_4).

4.4.3 Chemical and Biological Hydrolysis

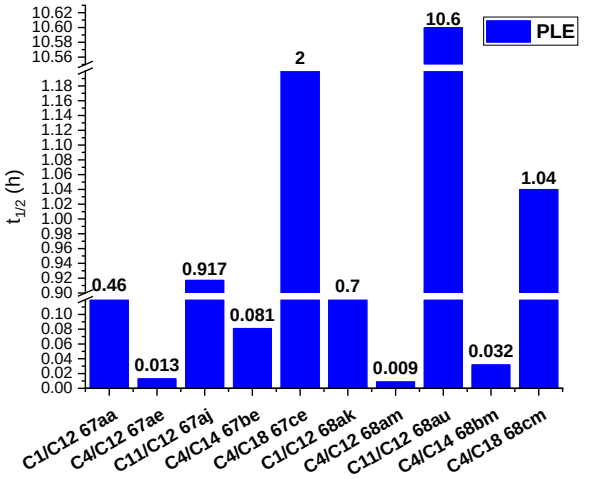
Both of Tri*PPP*ro-d4TTPs **67** ($t_{1/2}$ = 103-919 h),**68** ($t_{1/2}$ = 123-1240 h) proved to be stable in PB (Figure 36, A). As shown in Figure 36 (A), the stability of Tri*PPP*ro-d4TTPs **67aa**,**67ae**,**67aj** (AB:C1-C11; alkyl-C12), **68ak**,**68am**,**68au** (ACB:C1-C11; alkyl-C12) and Tri*PPP*ro-d4TTPs **67ae-ce** (AB:C4; alkyl: C12-C18), **68am-cm** (ACB:C4; alkyl: C12-C18) increased with the increase of alkyl chain lengths in PB. γ-ACB-γ-C-alkyl-d4TTPs **68** proved to be more stable as compared to the studies of the corresponding ester products γ-AB-γ-C-alkyl-d4TTPs **67**. For example, the half-lives for γ-(ACB-C4; alkyl-C18)-d4TTP **68cm** ($t_{1/2}$ = 1240 h) was found to be significantly higher by almost a factor of 2 than γ-(AB-C4; alkyl-C18)-d4TTP **67ce** ($t_{1/2}$ = 646 h).

With PLE, also the half-lives of Tri*PPP*ro-d4TTPs **67ae-ce** (AB-C4; alkyl: C12-C18) ($t_{1/2}$ = 0.013 h-2 h), **68am-cm** (ACB-C4; alkyl: C12-C18) ($t_{1/2}$ = 0.009 h-1.04 h), increased with increasing alkyl chain lengths (R^2) (Figure 36; B). However, Tri*PPP*ro-d4TTPs **67aa** ($t_{1/2}$ = 0.46 h), **68ak** ($t_{1/2}$ = 0.7 h) comprising shorter alkyl residues (AB or ACB: C1; alkyl-C12) in the ester or carbonate moiety (R^1) are more stable than Tri*PPP*ro-d4TTPs **67ae** (AB-C4; alkyl-C12) ($t_{1/2}$ = 0.013 h) or **68am** (ACB-C4; alkyl-C12) ($t_{1/2}$ = 0.009 h),

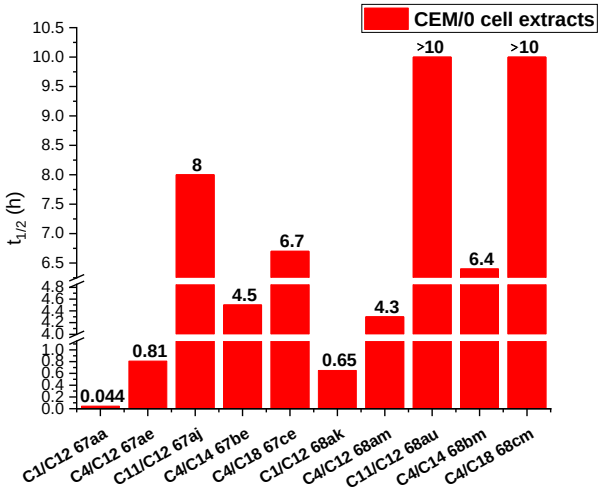
respectively. As compared to chemical hydrolyses, the half-lives of Tri*PPP*ro-d4TTPs **67**,**68** determined with PLE (Figure 36; B) are lower than the half-lives in PB. Here, half-lives as low as 0.009 h (**68am**: ACB-C4) to 10.6 h (**68au**: ACB-C11) were detected which clearly points as in the PLE studies to an enzymatic cleavage (Figure 36, B). Moreover, for prodrug **67ce** (AB-C11; alkyl-C12), **68au** (ACB-C11; alkyl-C12) containing a long alkyl chain in the AB or ACB moiety (C11), the half-life was found to be 2 h and 10.6 h, respectively. However, as compared to Tri*PPP*ro-d4TTPs **67**,**68**, the half-lives of γ-(β-cyanoethyl)-γ-C-alkyl-d4TTPs **106** ($t_{1/2}$ > 80 h) showed that the delivery of d4TDP was probably due to a pure chemical cleavage of the γ-phosphonate moiety (Figure 36, D).



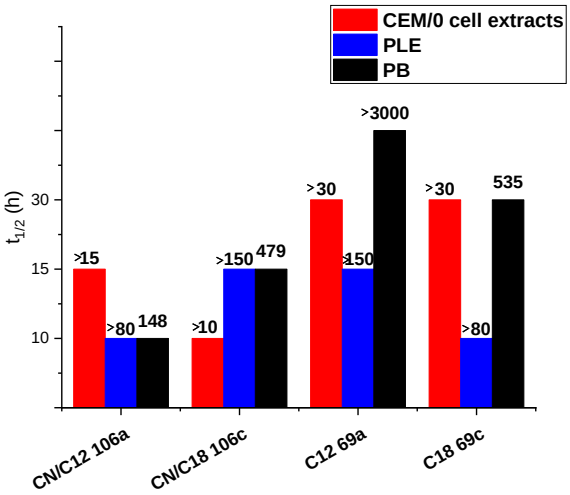
(A): Tri*PPP*ro-compounds **67**,**68** in PB (pH 7.3).



(B): Tri*PPP*ro-compounds **67**,**68** with PLE.



(C): Tri*PPP*ro-compounds **67**,**68** in CEM/0 cell extracts.



(D): Tri*PPP*ro-compounds **69**,**106** in different medium.

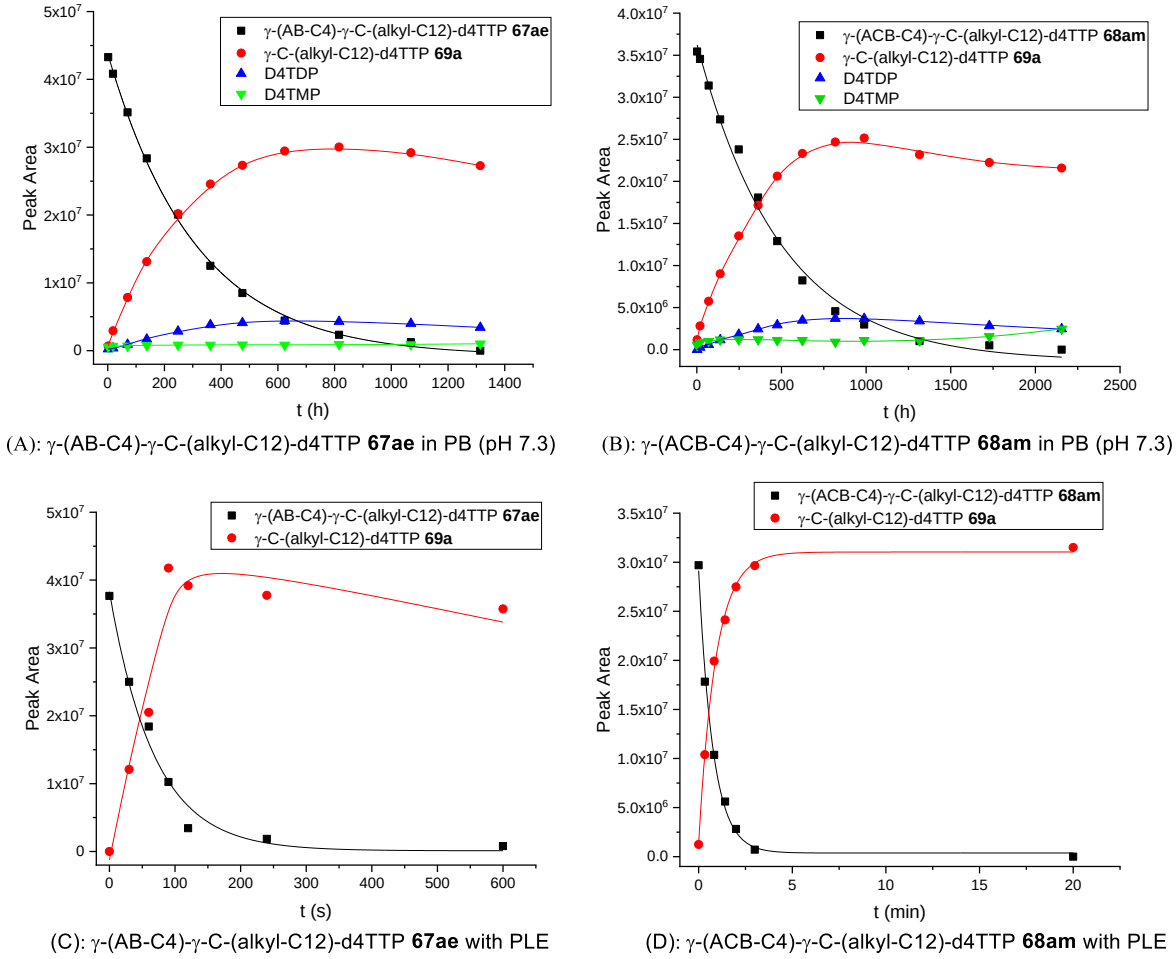
Figure 36. The hydrolysis half-lives of γ-C-alkylphosphonate-d4TDP prodrugs **67**,**68**,**106**, and γ-C-(alkyl)-d4TTPs **69** in PB (pH 7.3), PLE and CEM/0 cell extracts.

The hydrolysis of the prodrugs **67**,**68** was further investigated in human $CD4^+$ T-lymphocyte CEM cell extracts. Again, the half-lives of the prodrugs **67** ($t_{1/2}$ = 0.044 h to 8 h, Figure 36 C),**68** ($t_{1/2}$ = 0.65 h to 10 h, Figure 36 C) were found to be significantly lower than the half-lives in PB ($t_{1/2}$ = 103-1240 h, Figure 36 A), which clearly points as in the PLE studies to an enzymatic cleavage ($t_{1/2}$ = 0.009-10.6 h, Figure 36 B). The stability of Tri*PPP*ro-d4TTPs **67**,**68** correlated well with the chain lengths. The half-lives of Tri*PPP*ro-d4TTPs **67aa**-**aj** (AB: C1-C11; alkyl-C12), **68ak**-**au** (ACB: C1-C11; alkyl-C12) increased with increasing alkyl chain lengths (R^1: AB or ACB), while the stability for Tri*PPP*ro-d4TTPs **67ae-ce** (AB-C4; alkyl: C12-C18) as well as **68am-cm** (ACB-C4; alkyl: C12-C18) increased with increasing second alkyl chain lengths (R^2: alkyl). Moreover, the half-lives of prodrugs γ-AB-γ-C-alkyl-d4TTPs **67** were found to be lower than the corresponding compounds γ-ACB-γ-C-alkyl-d4TTPs **68** (Figure 36; C).

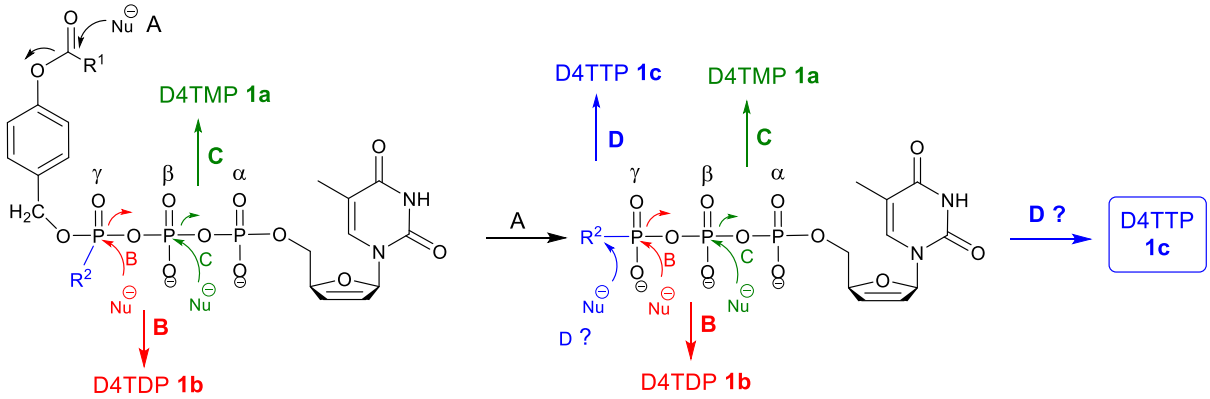
In case of γ-C-(alkyl: C12-C18)-d4TTPs **69** (alkyl-C12, $t_{1/2}$> 3000 h; alkyl-C18, $t_{1/2}$ = 535 h), the half-lives decreased with increasing alkyl chain lengths. The chemical stability of γ-C-(alkyl-C18)-d4TTP **69c** ($t_{1/2}$ = 535 h; Figure 36 D) was lower than γ-(AB-C4)-γ-C-(alkyl-C14)-d4TTP **67ce** ($t_{1/2}$ = 646 h, Figure 36 A), γ-(ACB-C4)-γ-C-(alkyl-C14)-d4TTP **68cm** ($t_{1/2}$ = 1240 h; Figure 36 A). Furthermore, γ-C-(alkyl)-d4TTPs **69** showed higher stability with PLE ($t_{1/2}$ > 80 h) and CEM/0 cell extracts ($t_{1/2}$ > 30 h, Figure 36 D).

The hydrolysis of Tri*PPP*ro-d4TTPs **67ae** (AB-C4; alkyl-C12) and **68am** (ACB-C4; alkyl-C12) in PB and with PLE is shown in Scheme 21. A predominant formation of γ-C-(alkyl-C12)-d4TTP **69a** was detected, indicating an almost selective cleavage of the AB group or the ACB group of compounds **67** or **68**, respectively (Scheme 21; A-D). Because of the very short hydrolysis time periods, only γ-C-(alkyl-C12)-d4TTP **69a** was formed with PLE (Scheme 21; C-D).

In PB, before complete consumption of the starting materials **67ae** (AB-C4; alkyl-C12) and **68am** (ACB-C4; alkyl-C12), some concomitant cleavage to d4TDP occurred as well and a very small amount of d4TMP was detected (<4%), but no d4TTP was detected (Scheme 21; A-D). The possible hydrolysis mechanism is shown in Scheme 22. Moreover, no further increase of d4TDP was detected after full conversion of the starting γ-(AB-C4)-γ-C-(alkyl-C12)-d4TTP **67ae** or γ-(ACB-C4)-γ-C-(alkyl-C12)-d4TTP **68am**.



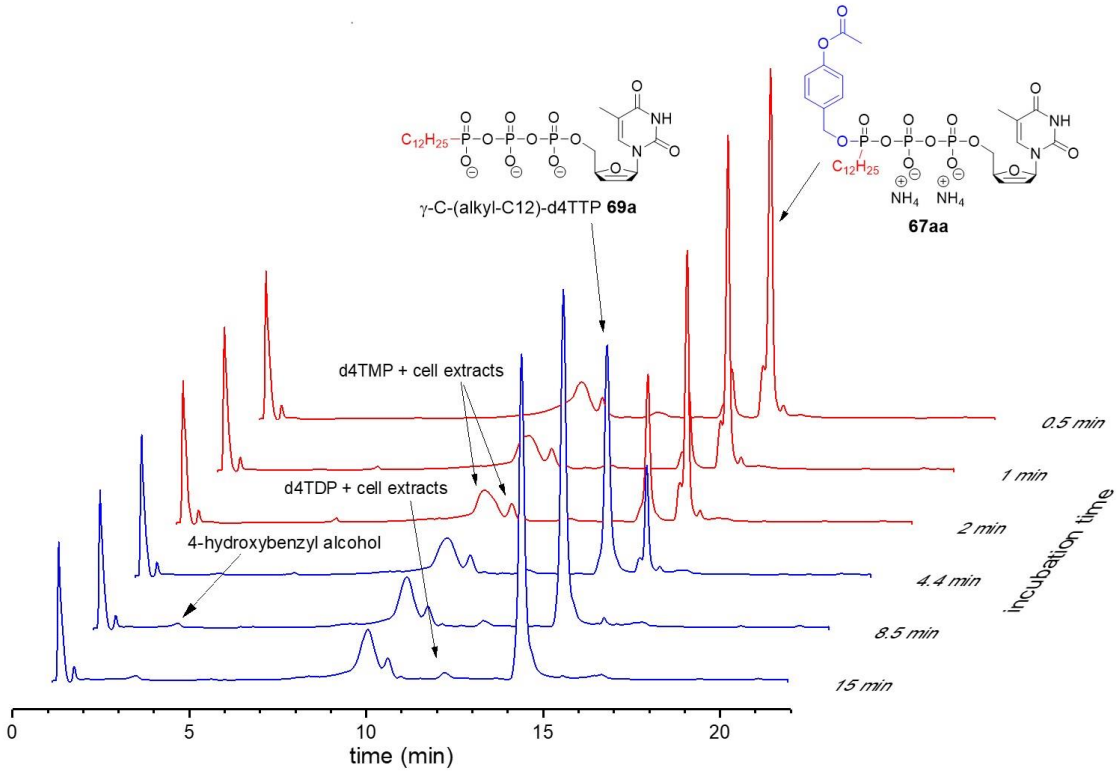
Scheme 21. Diagrams of hydrolysis of compounds **67ae** and **68am** in PB (pH 7.3) and with PLE.



Scheme 22. Hydrolysis mechanism of γ-C-alkylphosphonate-d4TDPs **67** and γ-C-(alkyl)-d4TTPs **69**.

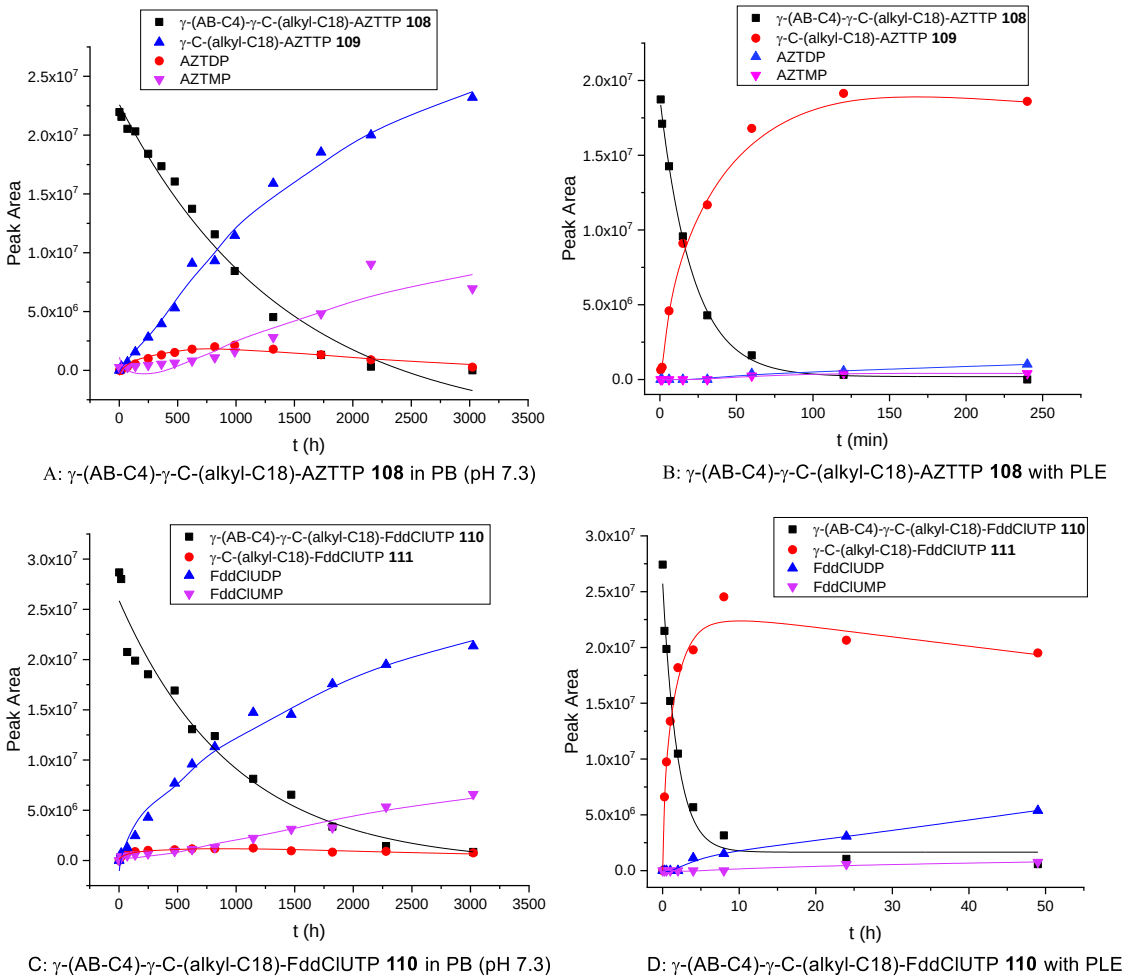
As an example, the hydrolysis of γ-(AB-C1)-γ-C-(alkyl-C12)-d4TTP **67aa** in CEM/0 cell extracts is shown in Scheme 23. After 15 min incubation, starting material **67aa** was completely consumed. An increase of γ-C-(alkyl-C12)-d4TTP **69a** concentration and a very small amount of d4TDP **1b** were observed, but no d4TTP **1c** was observed in these studies, which supports the hypothesis that the γ-C-(alkyl)-d4TTPs

69 in very small extend were prone to an anhydride bond breakage between the γ-phosphonate and β-phosphate. γ-(AB-C4)-γ-C-(alkyl-C18)-d4TTP **67ce** ($t_{1/2}$ = 6.7 h) and γ-(ACB-C4)-γ-C-(alkyl-C18)-d4TTP **68cm** ($t_{1/2}$ >10 h) showed high stability in CEM/0 cell extracts, which confirmed our initial concept of introducing an enzyme-stable group to the γ-phosphonate unit.



Scheme 23. HPLC profiles of γ-(AB-C1)-γ-C-(alkyl-C12)-d4TTP **67aa** after incubation in CEM/0 cell extracts.

As is shown in Scheme 24, the hydrolysis of γ-C-alkylphosphonate-AZTDPs **108** is similar to the hydrolysis of γ-(AB-C4)-γ-C-(alkyl-C12)-d4TTP **67ae** in PB: 1) increase of γ-C-(alkyl-C12)-AZTTP **109** concentration, 2) a very small amount of AZTDP were detected; 3) no AZTTP was formed. As compared to γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108**, in the case of γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** in PB, the concentration of γ-C-(alkyl-C18)-FddClUTP **111** was lower than FddClUDP. It was speculated that γ-C-(alkyl-C18)-FddClUTPs **111** was readily cleaved to from FddClUDP shown in Scheme 24 (C), probably due to altered chemical stability of the long alkyl chain. Moreover, the chemical stabilities of compounds **108** ($t_{1/2}$ = 984 h),**110** ($t_{1/2}$ = 670 h) were found to be stable in PB.



A: γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108** in PB (pH 7.3)

B: γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108** with PLE

C: γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** in PB (pH 7.3)

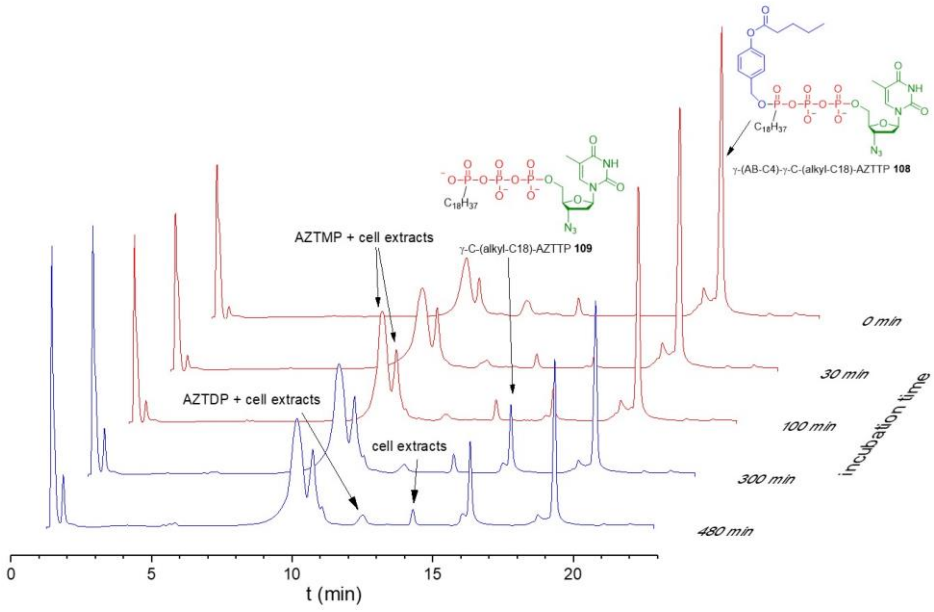
D: γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** with PLE

Scheme 24. Hydrolysis study of compounds **108** and **110** in PB (pH 7.3) and with PLE.

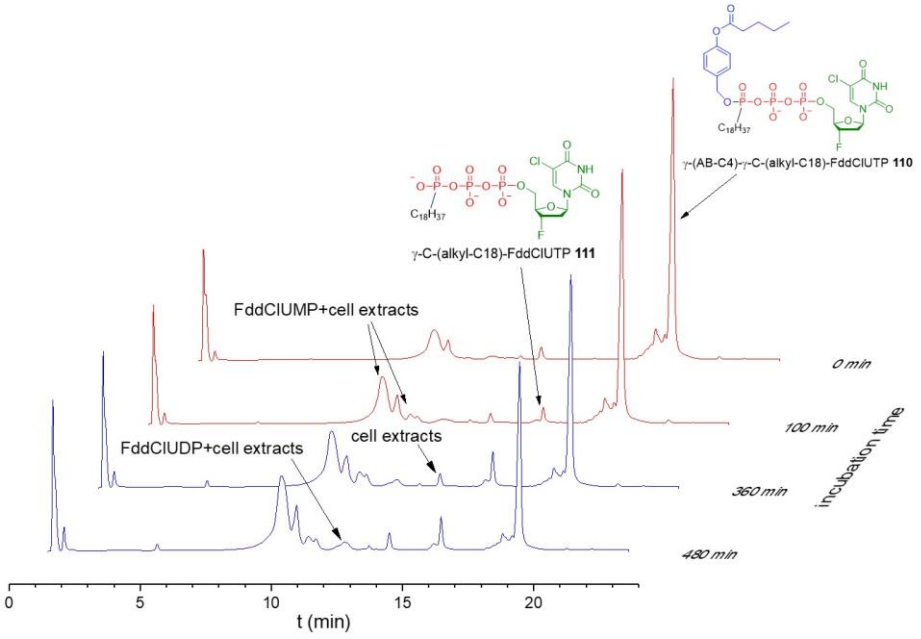
The incubation of γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108**,γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** with pig liver esterase led to a marked acceleration of the formation of γ-C-(alkyl-C18)-AZTTP **109** and γ-C-(alkyl-C18)-FddClUTP **111**, respectively. As compared to the chemical hydrolyses, Tri*PPP*ro-compounds **108** ($t_{1/2}$ = 0.25 h),**110** ($t_{1/2}$ = 1.32 h) were rapidly hydrolyzed and delivered γ-C-(alkyl-C18)-AZTTP **109** and γ-C-(alkyl-C18)-FddClUTP **111** much faster than in PB, demonstrating a significant contribution of the enzymatic cleavage (Scheme 24, B and D). As can be seen, γ-C-(alkyl-C18)-NTPs **109**,**111** proved to be stable against PLE (Scheme 24, B and D). However, the cleavage of γ-C-(alkyl-C18)-FddClUTP **111** was faster than γ-C-(alkyl-C18)-AZTTP **109**, probably due to a pure chemical cleavage of the γ-phosphonate moiety, which was in full agreement with the results obtained from the studies in PB in Scheme 24 (A and C).

The hydrolysis of the prodrugs **108**,**110** was further investigated in human $CD4^+$ T-lymphocyte CEM cell extracts. The half-lives of the prodrugs **108** ($t_{1/2}$ = 8 h),**110** ($t_{1/2}$ > 10 h) were found to be significantly

lower than the half-lives in PB buffer (up to 120-fold). The hydrolysis of compounds **108** and **110** shown in Scheme 25 and in Scheme 26. The γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108** and the γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** showed a loss of 50% and 39% of **108**,**110**, respectively, after 8 h incubation in CEM/0 cell extracts. These compounds were slowly hydrolyzed and NDP was observed in low concentration but *no* NTP formation was detected.



Scheme 25. HPLC profiles of γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108** after incubation in CEM/0 cell extracts.



Scheme 26. HPLC profiles of γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **108** after incubation in CEM/0 cell extracts.

4.4.4 Anti-HIV activities in CEM/0 and CEM/TK$^-$ cell cultures

Next, the prodrugs γ-(AB)-γ-C-(alkyl)-d4TTPs **67**, γ-(ACB)-γ-C-(alkyl)-d4TTPs **68**, γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108** and γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** were evaluated their anti-HIV ability to inhibit the replication of HIV in HIV-1- and HIV-2-infected CEM/0 cell cultures and in CEM/TK$^-$ cell cultures. Table 4 summarizes the antiviral and cytotoxic data of γ-(AB)-γ-C-(alkyl)-d4TTPs **67**, γ-(ACB)-γ-C-(alkyl)-d4TTPs **68**, γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108**, γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110**, γ-C-(alkyl)-d4TTPs **69**, γ-(AB-C4; alkyl-C18)-d4TTP **90ad**,[55] γ-(alkyl-C18)-d4TTP **91a**[55] and the parent nucleoside analogue d4T **1**, AZT **2**, FddClU **8** as the reference compounds. There are some clear trends: 1) The antiviral activity determined for Tri*PPP*ro-d4TTPs **67aa**,**67aj** (AB:C1, C11; alkyl-C12) as well as **68ak**,**68au** (ACB:C1, C11; alkyl-C12) increased with increasing alkyl chain lengths; 2) γ-C-(alkyl-C18)-d4TTP **69c** was moderately antivirally active against HIV-2 in CEM/TK$^-$ cells (EC_{50} = 1.58 μM), indicating a successful cell membrane passage of these compounds; 3) As compared to γ-C-(alkyl-C12)-d4TTP **69a** (EC_{50}: 41.1 μM), the antiviral activity of γ-(AB-C11)-γ-C-(alkyl-C12)-d4TTP **67aj** (EC_{50}: 0.066 μM) in CEM/0 cells was improved by a 622-fold, indicating that the structure-activity relationships of these potential Tri*PPP*ro-d4TTPs comprising two masking units; 4) this Tri*PPP*ro-approach applied to convert inactive nucleoside analogues into powerful biologically active metabolites. For example, with γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** (EC_{50}: 7.30 μM) the antiviral activity in this infected cell line was improved by a 34-fold as compared to parent nucleoside FddClU **8**. Therefore, the Tri*PPP*ro-approach provides a high potential to be used in antiviral chemotherapies.

As compared to **67aj** (AB-C11; alkyl-C12),**68au** (ACB-C11; alkyl-C12) bearing as R^1 a $C_{11}H_{23}$ residue in the AB- or ACB-group, Tri*PPP*ro-d4TTPs **67aa** (AB-C1; alkyl-C12), **68ak** (ACB-C1; alkyl-C12) showed a marked loss of activity in CEM/TK$^-$ cells, respectively. It was speculated that Tri*PPP*ro-d4TTPs **67aa**,**68ak** were readily cleaved to form γ-C-(alkyl-C12)-d4TTP **69a** (EC_{50} = 41.1 μM/HIV-2, Table 4). In antiviral assays, the inhibition of the replication of HIV-1 and HIV-2 by γ-(AB)-γ-C-(alkyl)-d4TTPs **67**, γ-(ACB)-γ-C-(alkyl)-d4TTPs **68**, γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108**, and γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** was much higher, e.g. **67ce** (EC_{50} = 0.0074 μM/HIV-1; EC_{50} = 0.021 μM/HIV-2), or at least similar like **68ak** (EC_{50} = 0.095 μM/HIV-1; EC_{50} = 0.35 μM/HIV-2), compared to their parent nucleosides d4T **1**, AZT **2**, FddClU **8** in CEM/0 cell cultures. More interestingly, the antiviral activity detected in CEM/0 cell cultures was completely retained in the case of γ-(AB-C4)-γ-C-(alkyl-C18)-d4TTP **67ce** (EC_{50}: 0.042 μM) and γ-(ACB-C4)-γ-C-(alkyl-C18)-d4TTP **68cm** (EC_{50}: 0.032 μM) in CEM/TK$^-$ cell

cultures. Therefore, these Tri*PPP*ro-prodrugs efficiently enter cells and deliver the corresponding nucleoside triphosphate analogues.

Table 4. Antiviral activity and cytotoxicity of γ-(AB)-γ-C-(alkyl)-d4TTPs **67**, γ-(ACB)-γ-C-(alkyl)-d4TTPs **68**, γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108** and γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** in comparison with their parent nucleosides d4T **1**, AZT **2**, FddClU **8**.

Comp.	R^1 or R^3	R^2	HIV-1 (HE)	HIV-2 (ROD)	CEM/TK$^-$ HIV-2 (ROD)	Toxicity
			$EC_{50}{}^a$ [µM]	$EC_{50}{}^a$ [µM]	$EC_{50}{}^a$ [µM]	$CC_{50}{}^b$ [µM]
67aa	CH_3	$C_{12}H_{25}$	0.023 ±0.025	0.021±0.07	26.3±0.85	>100±0
67aj	$C_{11}H_{23}$	$C_{12}H_{25}$	0.0074±0.008	0.091±0.008	0.066±0.063	37±9
67ce	C_4H_9	$C_{18}H_{37}$	0.0074±0.0014	0.021±0.006	0.042±0.002	19±8
68ak	CH_3	$C_{12}H_{25}$	0.095±0.002	0.35±0.01	36.8±4	>100±0
68au	$C_{11}H_{23}$	$C_{12}H_{25}$	0.04±0.03	0.11±0.1	0.32±0.7	39±6
68cm	C_4H_9	$C_{18}H_{37}$	0.0018±0.002	0.026±0.04	0.032±0.02	16±2
69a		$C_{12}H_{25}$	0.15±0.039	0.17±0.035	41.1±0.71	>100±0
69c		$C_{18}H_{37}$	0.046±0.021	0.11±0.064	1.58±0.75	21±9
1 (d4T)	/		0.43±0.23	0.31±0.13	31.05±5.25	>50
90ad[55]	C_4H_9	$C_{18}H_{37}$	0.18±0.09	0.16±0.10	0.17±0.00	13±1
91a[55]		$C_{18}H_{37}$	0.11±0.042	0.11±0.084	0.05±0.027	86±3
1 (d4T)[55]	/		0.43±0.25	0.22±0.05	>50	>50
108	C_4H_9	$C_{18}H_{37}$	<0.01	0.0014	0.73	28.68
2 (AZT)			0.0050± 0.0006	0.0045± 0.0018	> 100	> 100
110	C_4H_9	$C_{18}H_{37}$	0.15	1.12	7.30	32.78
8 (FddClU)			>250	>250	>250	188±88

[a] Antiviral activity determined in $CD4^+$ T-lymphocytes: 50% effective concentration; values are the mean ±SD of n=2-3 independent experiments. [b] Cytotoxicity: 50% cytostatic concentration or compound concentration required to inhibit $CD4^+$ T-cell (CEM) proliferation by 50%; values are the mean ±SD of n=2-3 independent experiments.

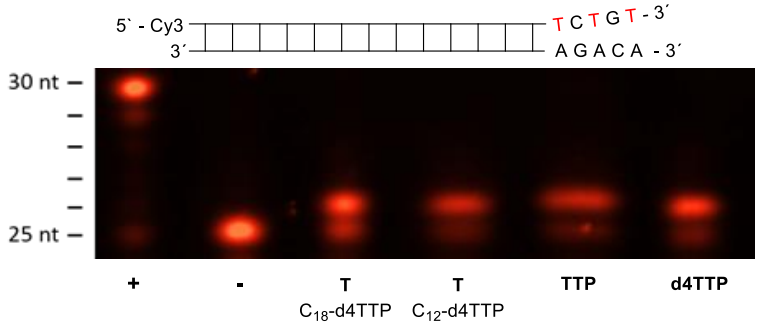
4.4.5 Primer Extension Assays

As is shown in Table 4, γ-(AB or ACB)-γ-C-(alkyl)-d4TTPs **67**,**68** are highly active against HIV-1 and HIV-2 in CEM/0 cells and more importantly in CEM/TK$^-$ cells as well. It was demonstrated that no d4TTP

was formed in all hydrolysis studies. From the results summarized above, it can be concluded that the delivered γ-C-(alkyl)-d4TTPs **69** are responsible for the inhibitory effect of these compounds. To confirm the prodrug concept, S. Weber from our group examined the γ-C-(alkyl)-d4TTPs **69** in primer extension assays and investigated their suitability as substrates for the HIV-RT in contrast to three different human DNA-polymerases. A 25nt DNA primer (5'-FITC-CGTTGGTCCTGAAGGAGGATAGGTT-3') with FITC as fluorescent label and a 30nt DNA template (5'-ACAGAAACCTATCCTCCTTCAGGACCAACG-3') was used.[172,173] For the primer extension assay, without added polymerase (negative control (- lane)) and an experiment in which all four canonical NTP were added (positive control (+ lane)) were used as controls.

Studies using γ-C-(alkyl)-d4TTPs and HIV's reverse transcriptase (RT) and cellular DNA polymerases.

Figure 37 shows the results of a primer extension assay in which the viral enzyme HIV-RT was used. In the case of a missing RT no elongation proceeded (- lane) and full extension to the 30mer occurred (+ lane) when all four canonical triphosphates were present. γ-C-(alkyl-C18)-d4TTP **69c** (lane 3) and γ-C-(alkyl-C12)-d4TTP **69a** (lane 4) were used in combination with the other three canonical triphosphates. Only the n+1 band is visible because d4TMP was incorporated and then acted as an immediate chain terminator. As a consequence, γ-C-(alkyl)-d4TTPs **69** were accepted by HIV-RT as a substrate.

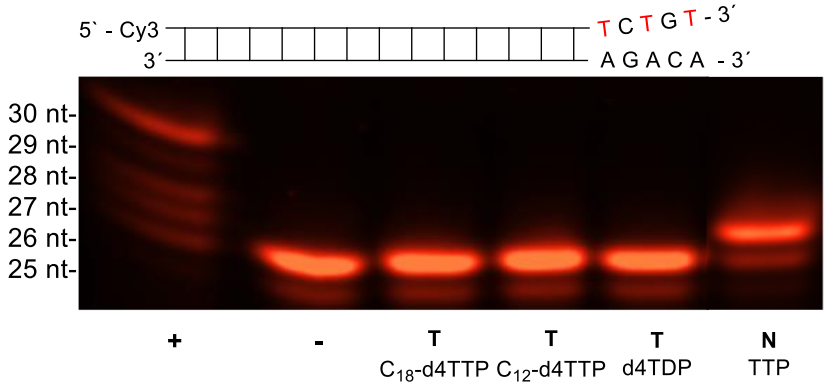


Primer extension assay using HIVRT (30min, 6U).

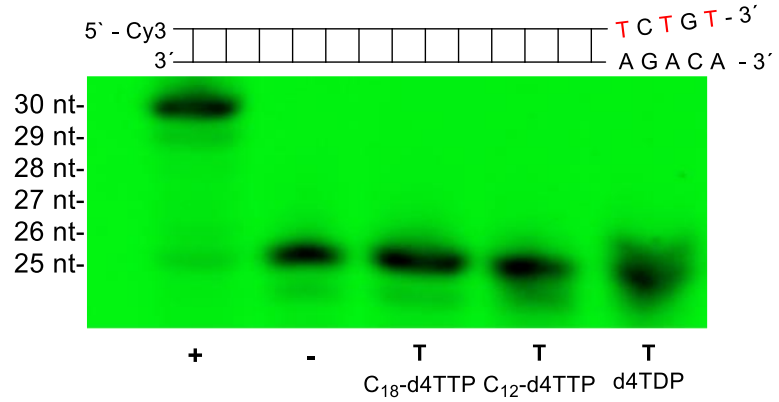
Figure 37. Primer extension assay using HIV's RT. Primer extension assay using HIV's RT. lane (+): dATP, dGTP, dCTP and TTP with HIV-RT; lane (-): dATP, dGTP, dCTP and TTP without HIV-RT; lane (C_{18}-d4TTP): γ-C-(alkyl-C18)-d4TTP **69c**; lane (C_{12}-d4TTP): γ-C-(alkyl-C12)-d4TTP **69a**; lane (TTP): TTP; lane (d4TTP): d4TTP.

Next, γ-C-(alkyl)-d4TTPs **69** were studied using human DNA polymerases α, β and γ (Figure 38). Figure 38 (A) shows the results using human DNA polymerase α and γ-C-(alkyl)-d4TTPs **69** compared to the TTP (N). Obviously, with TTP the expected the canonical incorporation of TMP was observed which led

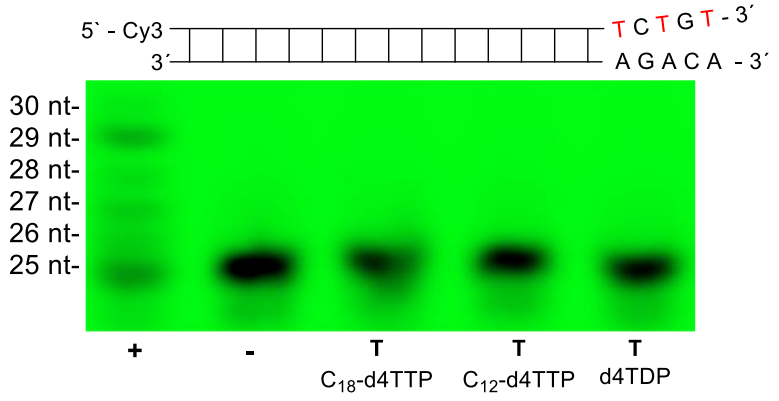
to the presence of the n + 1 band (26mer, lane-N) because TTP was accepted by DNA polymerase α as a substrate. However, when γ-C-(alkyl)-d4TTPs **69** were used, no incorporation was detectable. Therefore, it was speculated that γ-C-(alkyl)-d4TTPs **69** are not originally a substrate for DNA polymerase α. As is shown in Figure 38 (B and C), also *no* insertion was detected in the primer extension assay using γ-C-(alkyl)-d4TTPs **69**. Thus, it was concluded that human DNA polymerase α, β and γ did not recognize the γ-C-(alkyl)-d4TTPs **69** as a substrate at all.



A. Primer extension assay using DNA polymerases α (60min, 4U).



B. Primer extension assay using DNA polymerases β (4h, 6U).



C. Primer extension assay using DNA polymerases γ (60min, 4U).

Figure 38. Primer extension assay with human DNA polymerases α, β and γ. lane (+): dATP, dGTP, dCTP and TTP with DNA polymerases α (A), β (B) and γ (C), respectively; lane (-): dATP, dGTP, dCTP and TTP without DNA

polymerases α (A), β (B) and γ (C), respectively; lane (C_{18}-d4TTP): γ-C-(alkyl-C18)-d4TTP **69c**; lane (C_{12}-d4TTP): γ-C-(alkyl-C12)-d4TTP **69a**; lane: TTP; lane: d4TDP.

In summary, a new class of nucleoside triphosphate prodrugs, γ-(AB or ACB)-γ-C-alkyl-d4TTPs **67**,**68**, γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108**, and γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** were prepared by using the *H*-phosphinate route. These Tri*PPP*ro-compounds comprise a non-cleavable γ-alkyl-phosphonate moiety instead of the normal γ-phosphate group in addition to a biodegradable prodrug moiety (AB or ACB) at the γ-phosphonate unit. In addition, γ-(β-cyanoethyl)-γ-C-alkyl-d4TTPs **106** and its corresponding intermediates γ-C-alkyl-d4TTPs **69** were synthesized using the *H*-phosphinate route as well. In all cases, the hydrolysis, stability, and antiviral activity of γ-(AB or ACB)-γ-C-alkyl-d4TTPs **67**,**68** were found to be significantly influenced by two different alkyl chain lengths of the prodrug units (R^1 and R^2). The masking group in γ-(AB or ACB)-γ-C-alkyl-d4TTPs **67**,**68**, γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP **108** was selectively cleaved to form γ-C-(alkyl)-d4TTPs **69** and γ-C-(alkyl-C18)-AZTTP **109**, respectively, by chemical hydrolysis or particularly by enzymes present in cell extracts or with PLE. The predominant formation of γ-C-(alkyl)-d4TTPs **69** and γ-C-(alkyl-C18)-AZTTP **109** were detected in all hydrolysis studies using these prodrugs **67**,**68**,**108** but no d4TTP and AZTTP were formed. Moreover, γ-C-(alkyl)-d4TTPs **69** and γ-C-(alkyl-C18)-AZTTP **109** were stable in cell extracts towards dephosphorylation. As compared to γ-C-(alkyl: C12 or 18)-d4TTPs **69** and γ-C-(alkyl-C18)-AZTTP **109**, γ-C-(alkyl-C18)-FddClUTP **111** was readily hydrolyzed to give a large amount of FddClUDP in PB.

Antiviral data suggested that sufficient lipophilicity of these prodrugs exhibited higher activity against HIV-1 and HIV-2 in cultures of infected wild-type human $CD4^+$ T-lymphocyte (CEM/0) cells and more importantly in CEM/TK^- cells. γ-(ACB-C4)-γ-C-(alkyl-C18)-d4TTP **68cm** (EC_{50}: 0.032 µM) was the most active Tri*PPP*ro-d4TTPs of all the listed derivatives (1000-fold more active as d4T **1**), indicating a successful cell membrane passage of these compounds and an intracellular delivery of the nucleoside diphosphate-γ-phosphonates **69**. γ-C-(alkyl-C18)-d4TTP **69c** was very potent in CEM/TK^- cell cultures compared to d4T **1**, indicating that the modification at the γ-phosphonate group by one lipophilic and even one long aliphatic chain in the stable γ-C-alkyl-unit provides the molecule enough lipophilicity to cross the biological barriers.[186]

Interestingly, the completely inactive FddClU **8** was converted into a highly potent compound (Tri*PPP*ro-compound **110**), indicating the high potential of the Tri*PPP*ro-approach. Here, first direct proof of the successful application of an advanced prodrug concept for NTP derivatives that obviously are able to

directly deliver γ-C-alkyl-NTPs with high selectivity by an enzyme-triggered mechanism was disclosed in this thesis. This Tri*PPP*ro-concept enable the bypass of all phosphorylation steps usually needed for the activation of nucleoside analogues and can be used for the delivery of carbon-linked non-natural nucleotides as biochemical tools in Chemical Biology approaches.

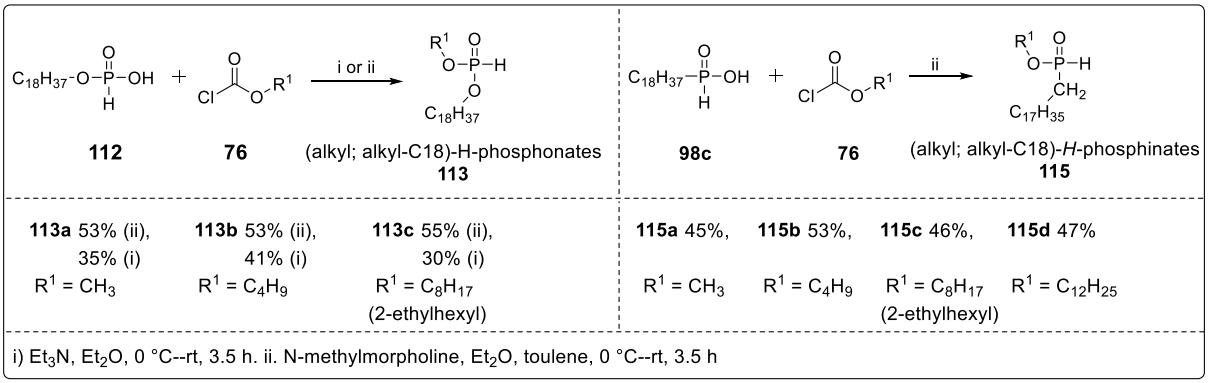
As compared to previously studied γ-(AB-C4; alkyl-C18)-d4TTP **90ad** ($t_{1/2}$ = 237 h),[55] the half-life for γ-(AB-C4)-γ-C-(alkyl-C18)-d4TTP **67ce** ($t_{1/2}$ = 646 h) was found to be significantly higher by almost a factor of 3. Moreover, the half-lives of compound γ-(AB-C4)-γ-C-(alkyl-C18)-d4TTP **67ce** ($t_{1/2}$ = 6.7 h) in CEM cell extracts was also found to be higher than the corresponding prodrug γ-(AB-C4; alkyl-C18)-d4TTP **90ad** ($t_{1/2}$ = 4.8 h).[55] Remarkably, both γ-C-(alkyl-C18)-d4TTP **69c** ($t_{1/2}$ > 30 h) and γ-(alkyl-C18)-d4TTP **91a** ($t_{1/2}$ > 30 h) proved to be stable in cell extracts towards dephosphorylation. It was demonstrated that γ-C-(alkyl-C18)-d4TTP **69c** and γ-(alkyl-C18)-d4TTP **91a**[55] were substrates for HIV-RT as shown in primer extension assays while they proved to be non-substrates for the cellular DNA-polymerases α, β and γ. In Table 4, γ-(alkyl-C18)-d4TTP **91a** (EC_{50} = 0.05 µM/HIV-2) showed better against HIV-2 than γ-C-(alkyl-C18)-d4TTP **69c** (EC_{50} = 1.58 µM/HIV-2) in CEM/TK^- cells. The results reported here maybe show that γ-(alkyl)-d4TTPs **91** are valued for their impressive potency to treat HIV infections. However, the antiviral activity determined of γ-(AB-C4)-γ-C-(alkyl-C18)-d4TTP **67ce** (EC_{50} = 0.0074 µM/HIV-1; EC_{50} = 0.021 µM/HIV-2) improved by 24-fold and 7-fold, respectively, as compared to the corresponding γ-(AB-C4; alkyl-C18)-d4TTP **90ad** (EC_{50} = 0.18 µM/HIV-1; EC_{50} = 0.16 µM/HIV-2) (Table 4).[55] More importantly, with γ-(ACB-C4)-γ-C-(alkyl-C18)-d4TTP **68cm** (EC_{50}: 0.032 µM/HIV-2) and γ-(AB-C4)-γ-C-(alkyl-C18)-d4TTP **67ce** (EC_{50}: 0.042 µM/HIV-2) the antiviral activity in CEM/TK^- cells was by a 5-fold and 4-fold, respectively, as compared to γ-(AB-C4; alkyl-C18)-d4TTP **90ad** (EC_{50} = 0.17 µM/HIV-2).[55] Therefore, γ-C-alkylphosphonate-d4TDPs **67**,**68** provide a higher potential to be used in antiviral and potentially also in antitumoral chemotherapies than γ-(AB; alkyl)-d4TTPs **90**.[55]

4.5 Stability of γ-(Phosphate or Phosphonate)-modified Nucleoside Analogues

Today a wide variety of bioreversible masking groups for phosphonates and phosphates have been applied in prodrug chemistry. Former studies have shown that the γ-phosphate or phosphonate moiety comprise a long, lipophilic aliphatic chain ($R^2 = C_{18}H_{37}$) that should give the prodrug molecule sufficient lipophilicity to cross the biological barriers. In this thesis, a series of new nucleoside analogues: γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** were prepared.

4.5.1 Synthesis of *H*-phosphonates and *H*-phosphinates

In order to give the prodrug molecule sufficient lipophilicity to cross the cell membrane, the γ-phosphate or phosphonate unit should comprise a long, lipophilic aliphatic chain ($R^2 = C_{18}H_{37}$). Then, various alkyl chains (R^1: C1-C12) were attached as well as a second masking group. Thus, (alkyl; alkyl-C18)-*H*-phosphonates **113** and (alkyl; alkyl-C18)-*H*-phosphinates **115** were prepared from alkyl chloroformates **76** and octadecyl hydrogen phosphonates **112** or octadecyl phosphinic acids **98c**, respectively. The target *H*-phosphonates **113** and *H*-phosphinates **115** were isolated varied between 30%-55% (Scheme 27).

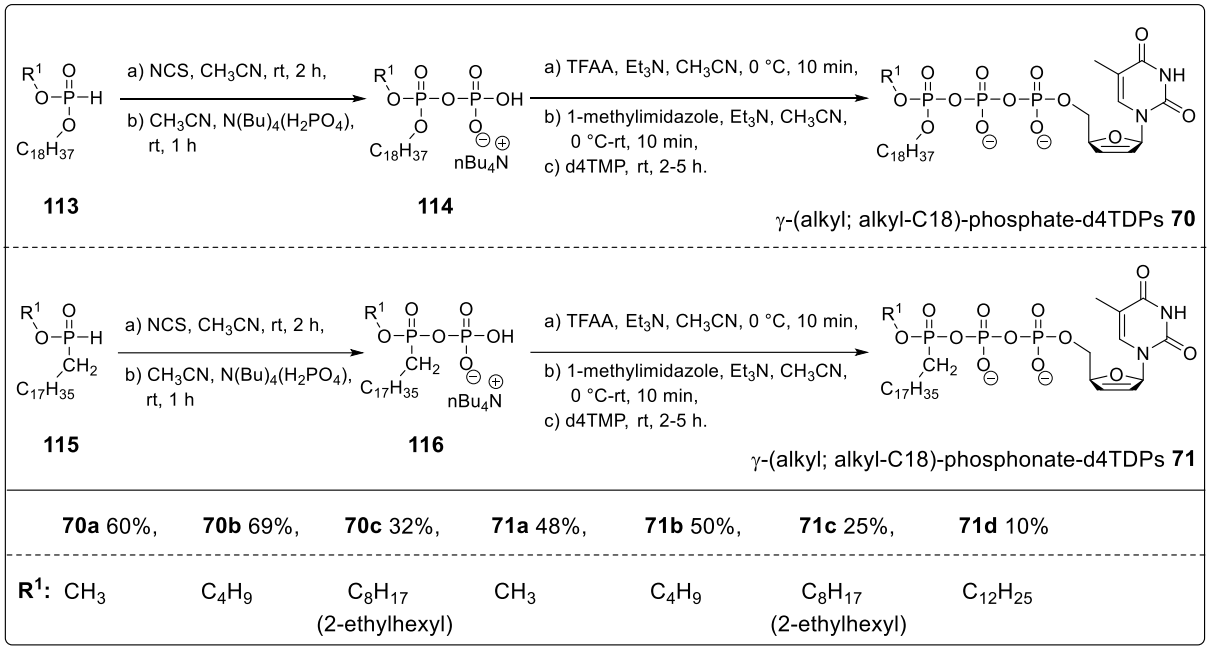


Scheme 27. Synthesis of starting materials **113** and **115**.

4.5.2 Synthesis of γ-(alkyl; alkyl-C18)-phosphate-d4TDPs and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs

γ-(Alkyl; alkyl-C18)-phosphate-d4TDPs **70** were synthesized preferably using the *H*-phosphonate route. For comparison, γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** were prepared using *H*-phosphinate route (Scheme 28). For these synthesis routes, *H*-phosphonates **113** and *H*-phosphinates **115** were reacted with NCS to form phosphorochloridates and phosphonochloridates, followed by addition of tetra-*n*-butylammonium phosphate to yield pyrophosphates **114** or phosphonates **116**, respectively. After

coupling with d4TMP **1a**, two series of compounds **70**,**71** were obtained varied between 10%-69%. It is worth noting that the solubility of compounds **71c**,**71d** decreased with long alkyl chains in the R^1 moiety. As a consequence, the target product such as γ-(alkyl-C12; alkyl-C18)-phosphonate-d4TDP **71d** was isolated in a yield of only 10%.



Scheme 28. Synthesis of γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71**.

The ^{1}H-NMR and ^{31}P-NMR spectra of γ-(alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** and γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b** are shown in Figure 39 and Figure 40, respectively. In ^{31}P-NMR spectra (Figure 39-2 and Figure 40-2), the signals for P-α and P-β of γ-(alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** are similar to the spectra of γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b**, in which the signal for P-α appears as a doublet and P-β appears as a triplet. However, in the ^{31}P-NMR spectrum (Figure 40-2), P-γ appeared as a doublet of doublets and the chemical shift is 24 as compared to γ-(alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** (doublet, δ = -10.5 ppm).

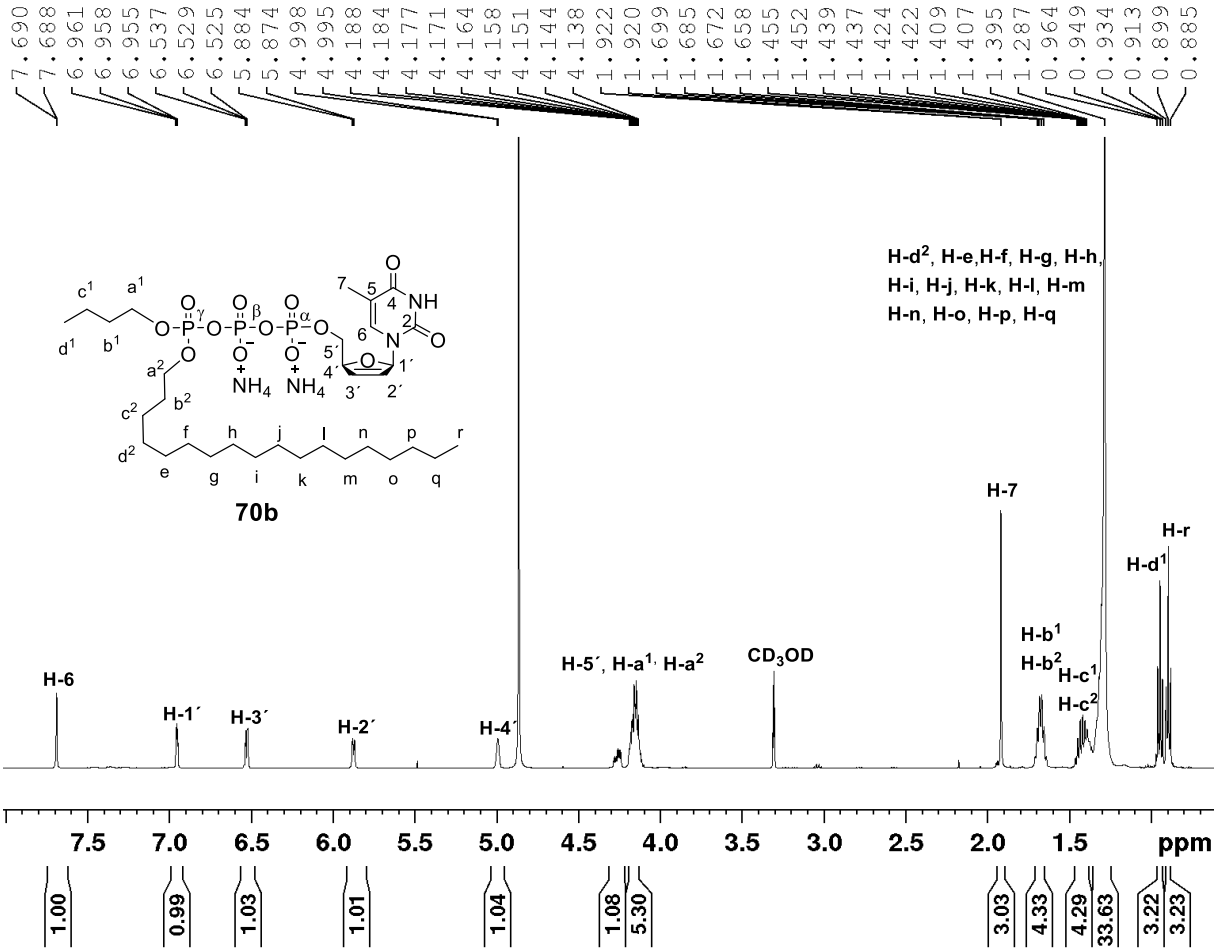


Figure 39-1: ^{1}H-NMR spectra of γ-(alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** (CD_3OD-d_4).

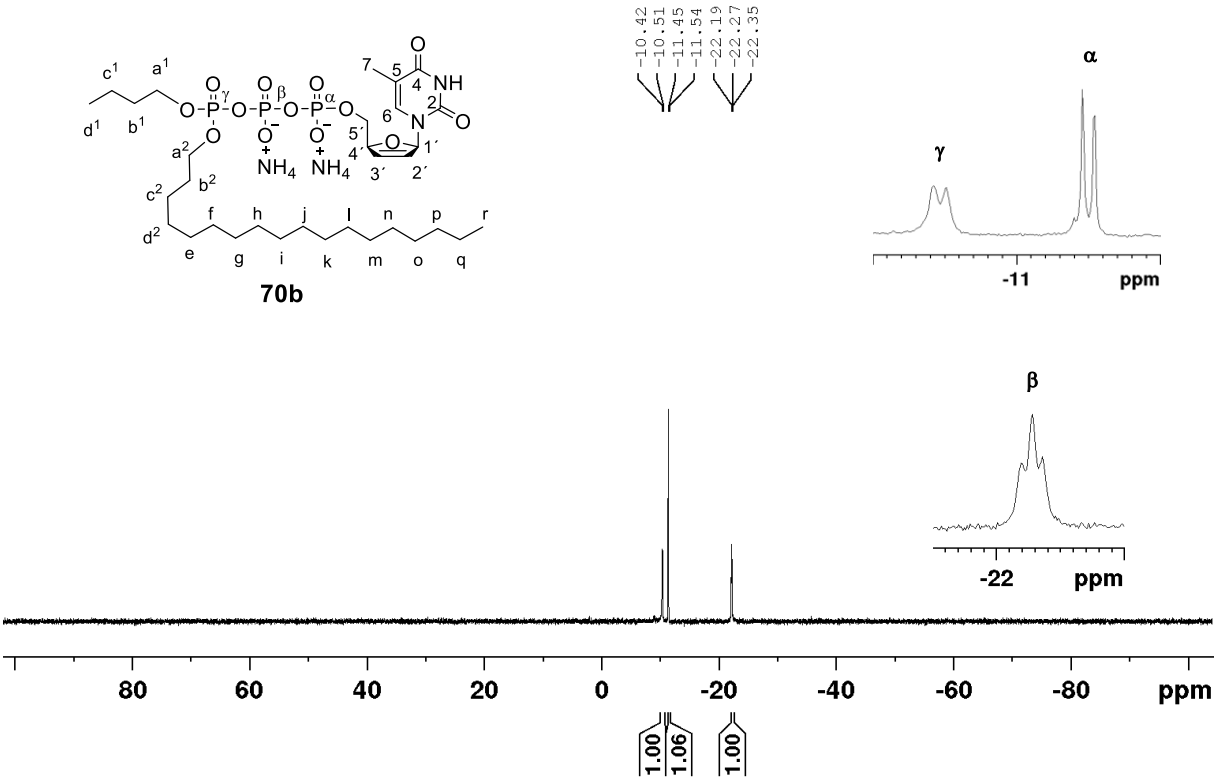


Figure 39-2: ^{31}P-NMR spectra of γ-(alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** (CD_3OD-d_4).

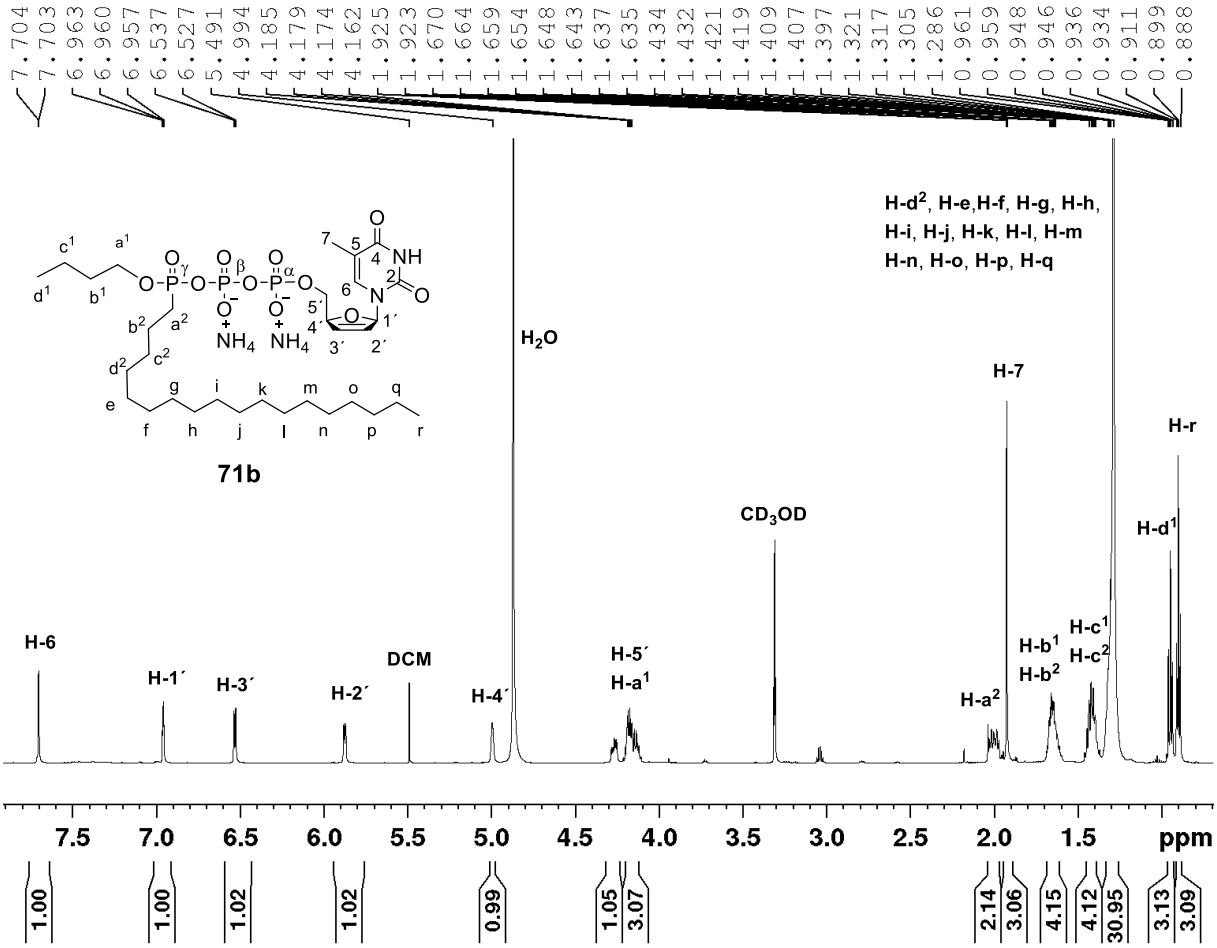


Figure 40-1: ^{1}H-NMR spectra of γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b** (CD_3OD-d_4).

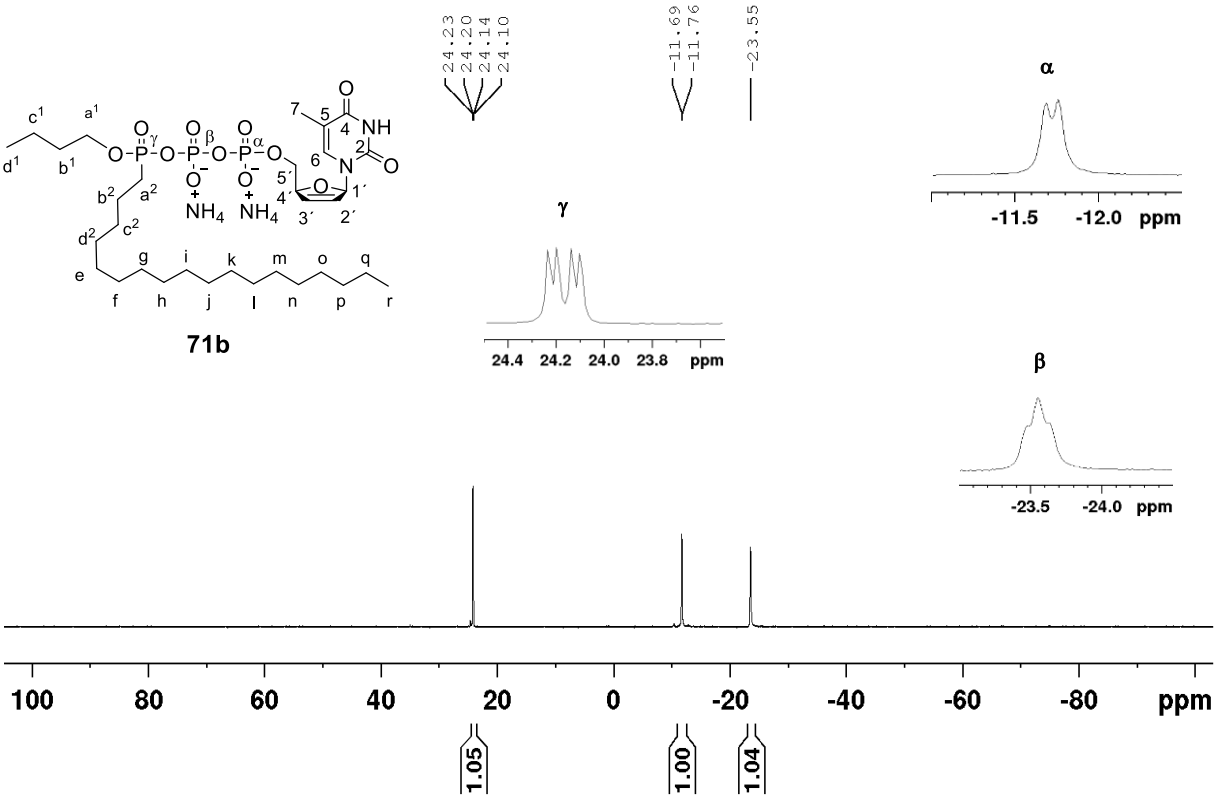
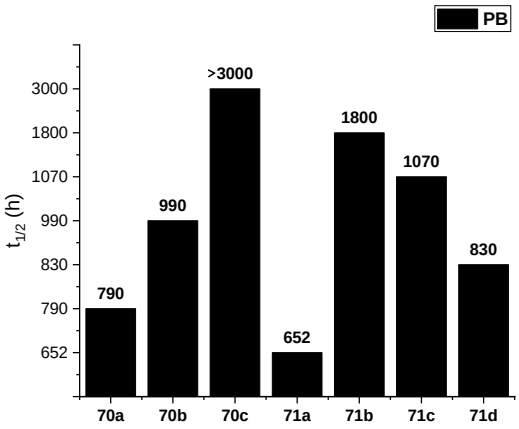


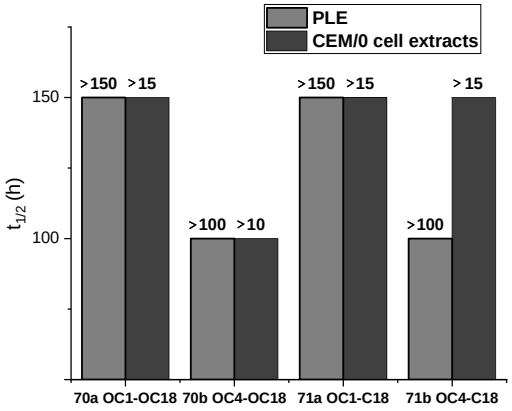
Figure 40-2: ^{31}P-NMR spectra of γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b** (CD_3OD-d_4).

4.5.3 Chemical and Biological Hydrolysis

The stability of γ-dialkylphosphate-modified-prodrugs **70a**-**c** (alkyl: C1-C8; alkyl-C18), γ-dialkylphosphonate-modified-prodrugs **71a**-**b** (alkyl: C1-C4; alkyl-C18) in PB increased with increasing alkyl chain lengths (Figure 41 A). In contrast, the half-lives of prodrugs **71b**-**d** (alkyl: C4-C12; alkyl-C18) decreased significantly (Figure 41 A). The γ-(alkyl: C1-C4; alkyl-C18)-phosphate-d4TDP prodrugs **70a**-**b** and γ-(alkyl: C1-C4; alkyl-C18)-phosphonate-d4TDP prodrugs **71a**-**b** were found to be more stable with PLE ($t_{1/2}$ > 100 h, Figure 41, B) and in cell extracts ($t_{1/2}$ > 10 h, Figure 41, B) because of the missing cleavage site. This confirmed the initial concept of introducing an enzyme-stable group to the γ-phosphate or phosphonate unit. It should be mentioned that the cleavage of the alkyl P−O or P−C bond in prodrugs **70**,**71** comprised two non-cleavable moieties at the γ-phosphate or γ-phosphonate group is impossible.



(A) Prodrugs **70**,**71** in PB (pH 7.3).



(B) Prodrugs **70**,**71** with PLE and CEM/0 cell extracts.

Figure 41. Half-lives of for γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** in PB (pH 7.3), PLE and CEM/0 cell extracts.

The hydrolysis of γ-(alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** and γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b** are shown in Scheme 29 and Scheme 30, respectively. The chemical hydrolysis was followed over a period of 155 days. In case of these prodrugs **70b**,**71b**, a predominate formation of d4TDP and a very small amount of d4TMP were observed, but no d4TTP and mono-masked nucleoside analogues were detected in these studies. This supports the hypothesis that γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** were prone to a bond breakage between the γ-phosphate or γ-phosphonate and the β-phosphate. Clearly, the starting γ-modified-prodrugs **70**,**71** disappeared and the expected d4TDP was formed.

Because of the very long hydrolysis time periods, also a cleavage of the glycosidic bond in d4T occurred as proven by the appearance of the nucleobase thymine. As is shown in Figure 42, d4T, d4TMP, and d4TDP were consumed 83%, 41% and 65%, respectively, after 32 days incubation in PB (pH 7.3). In all cases, before complete consumption of the starting materials **70**,**71**, an increase of thymine concentrations was observed. The possible hydrolysis mechanism is shown in Scheme 31.

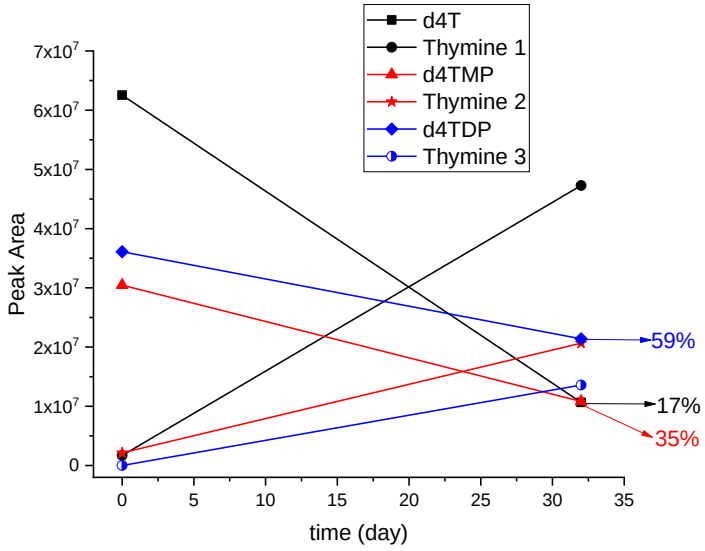
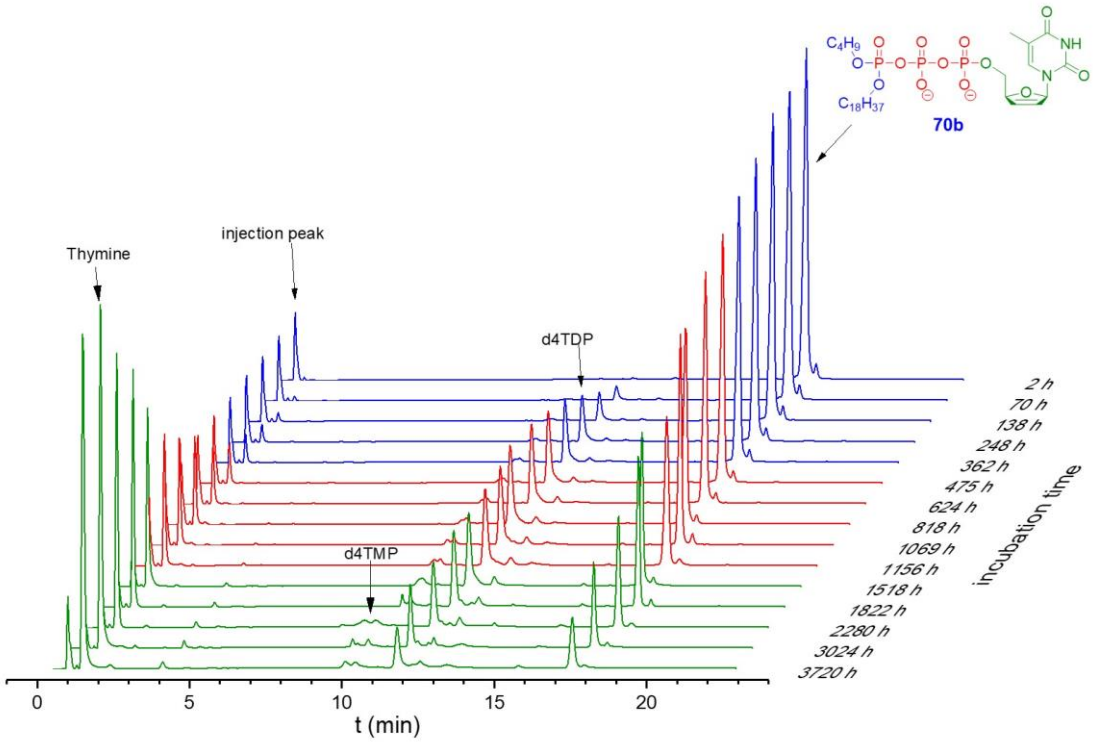
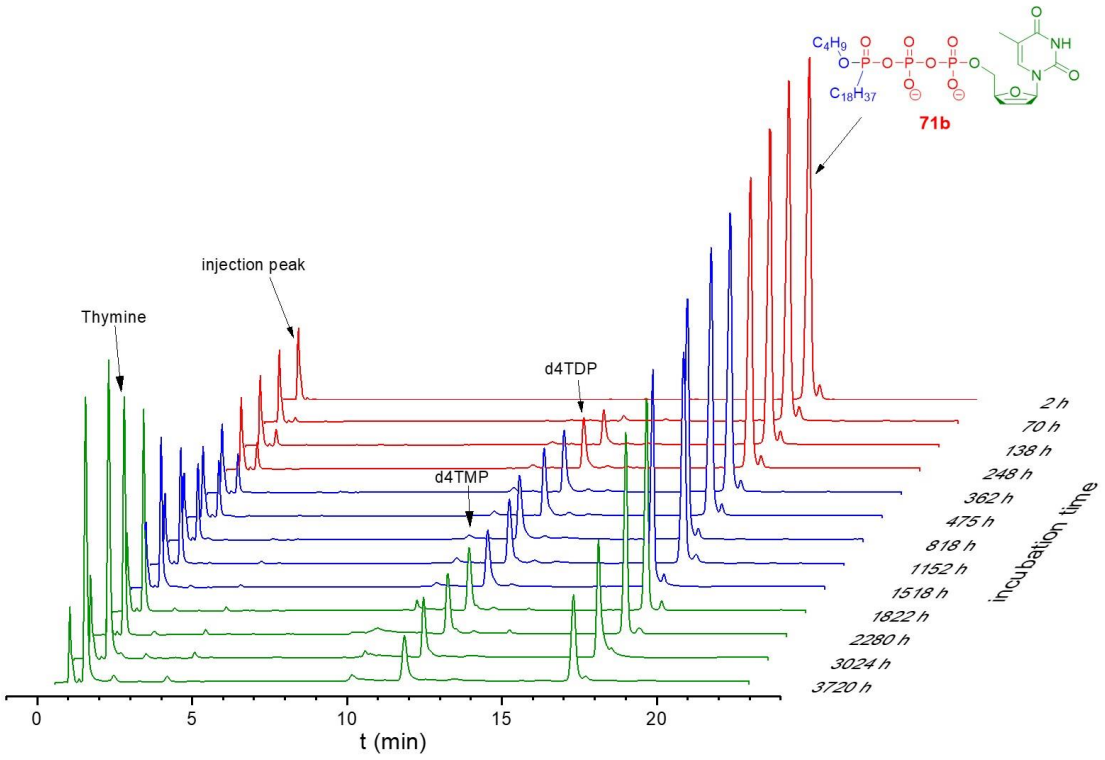


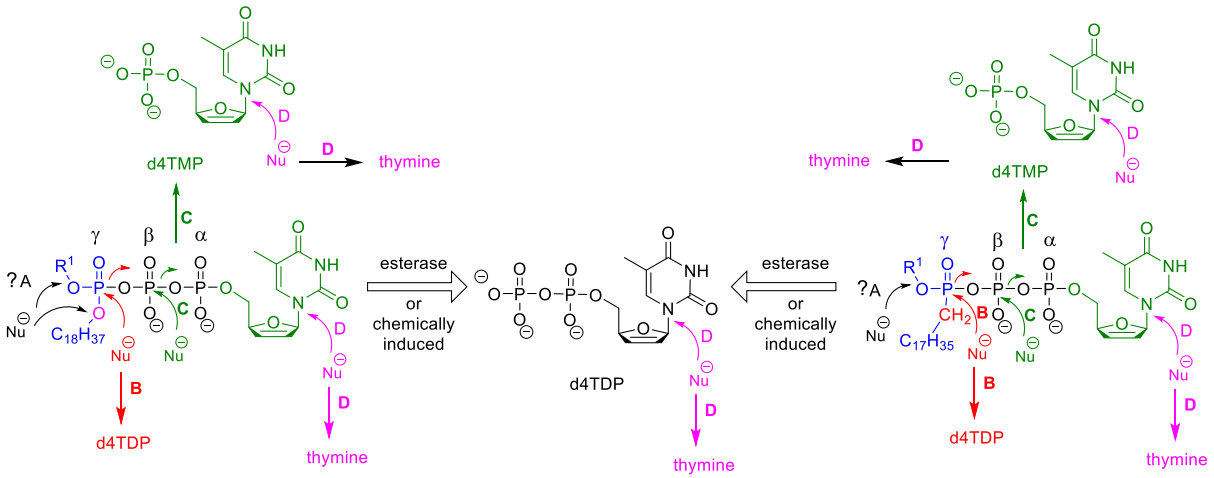
Figure 42. d4T, d4TMP, and d4TDP in PB (pH 7.3).



Scheme 29. HPLC profiles of **70b** after incubation in PB (pH 7.3).



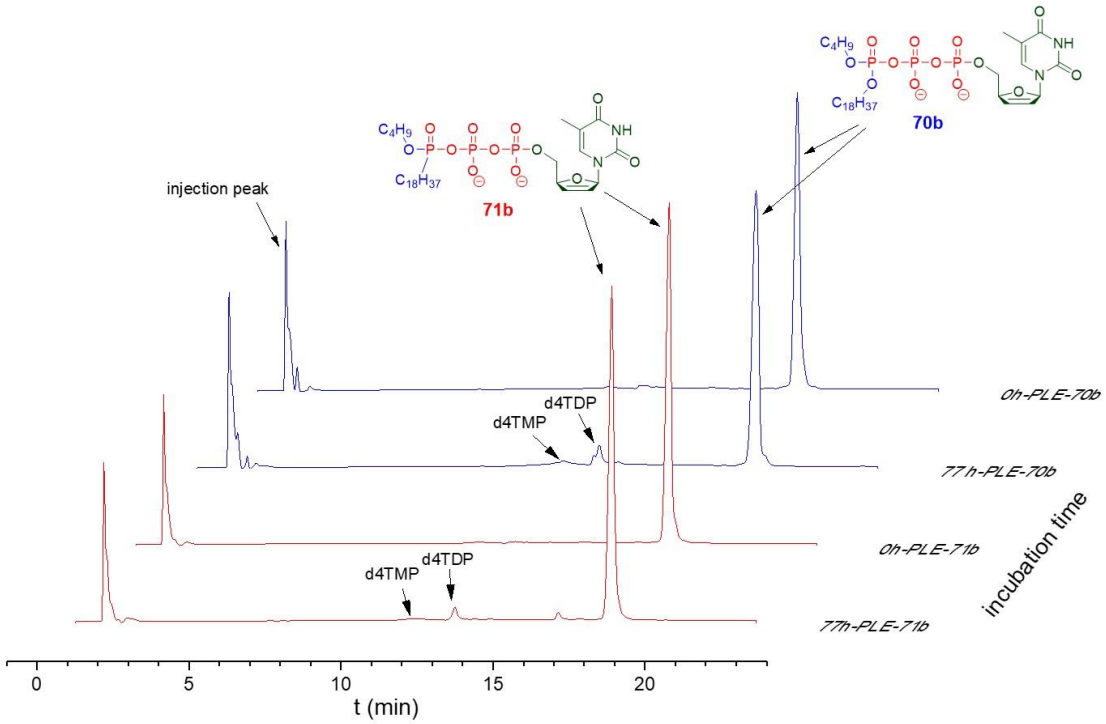
Scheme 30. HPLC profiles of **71b** after incubation in PB (pH 7.3).



Scheme 31. Hydrolysis mechanism of prodrugs **70b**,**71b**.

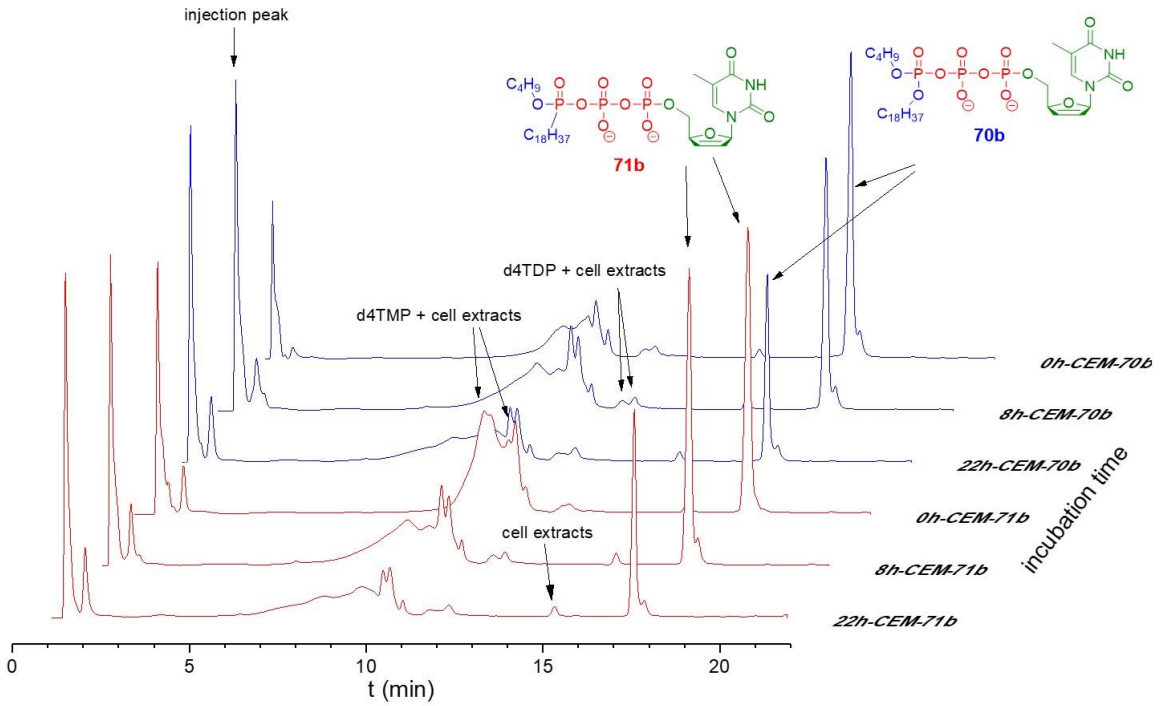
γ-(Alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** and γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b** were incubated with PLE in phosphate buffer (pH 7.3) to further investigate the influence of the chain length and to confirm the formation of d4TDP. As is shown in Scheme 32, a very small amount of the prodrugs **70b**,**71b** (< 3%) was consumed after 77h incubation, indicating that the delivery of d4TDP (trace) with PLE was probably due to a pure chemical cleavage of the γ-phosphate or γ-phosphonate

moiety. Additionally, no cleavage of the alkyl residues in prodrugs **70**,**71** to form mono-masked compounds were observed. Therefore, no d4TTP was observed because of two non-cleavable protecting groups. In addition, a very low concentration of d4TMP was detected.



Scheme 32. HPLC profiles of **70b**,**71b** after incubation with PLE.

Next, the hydrolysis of prodrugs **70**,**71** was further investigated in CEM cell extracts. Scheme 33 shows the hydrolysis of γ-(alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** and γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b**. After 8 h incubation, γ-(alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** and γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b** were consumed 11% and 7%, respectively. The γ-(alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** and the γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b** showed a loss of 54% and 50% of **70b**,**71b**, respectively, after 22 h incubation in CEM/0 cell extracts. As can be seen, these compounds were slowly hydrolyzed to give a small amount of d4TDP. It was speculated that d4TMP was also formed but in low concentrations in cell extracts (d4TMP + cell extracts, Scheme 33). In the hydrolysis of prodrugs **70**,**71** in CEM cell extracts, no formation of d4TTP was detected, which was in full agreement with the results obtained from the studies in PB and with PLE. It is worth noting that low concentration of d4TDP ($t_{1/2}$ = 59 h) was observed due the high stability of the prodrug compounds **70**,**71** ($t_{1/2}$ > 10 h) in CEM cell extracts.



Scheme 33. HPLC profiles of **70b**,**71b** after incubation in CEM/0 cell extracts.

4.5.4 Anti-HIV activities in CEM/0 and CEM/TK$^-$ cell cultures

γ-(Alkyl; alkyl-C18)-phosphate-d4TDPs **70** and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** were evaluated for their activity to inhibit the replication of HIV in HIV-1- and HIV-2-infected CEM/0 cell cultures and in HIV-2-infected CEM/TK$^-$ cell cultures. Table 5 summarizes the antiviral and cytotoxic data of the γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70**, γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** and the parent nucleoside analogue d4T **1** as the reference compound. In the antiviral test, it was observed that γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** showed virtually similar activities against HIV-1 and HIV-2 than the parent nucleoside d4T **1** in CEM/0 cell cultures. Interestingly, all γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** were also highly antivirally active against HIV-2 in mutant thymidine-deficient CEM cells (TK$^-$), indicating a successful cell membrane passage of these compounds. For example, γ-(alkyl-C8; alkyl-C18)-phosphate-d4TDP **70c** (EC_{50} = 0.005 µM/HIV-2) is the most active compounds of all the listed derivatives (1120-fold more active as d4T **1**, which showed a 150-fold loss inactivity in the TK-deficient cell cultures; EC_{50} = 5.6 µM/HIV-2) (Figure 43). Generally, the concentration of phosphorylated metabolites of NRTIs is dictated by the balance between phosphorylating and

dephosphorylating enzymes.[19,187] Additionally, it was demonstrated that γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** are gradually hydrolyzed into d4TDP **1b** and no d4TTP **1c** was formed in cell extracts. Thus, it was speculated that γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** have good antiviral activities due to their high stability. Once inside the cell, low concentrations of d4TDP **1b** were formed which maybe led to form d4TTP **1c**. Then d4TTP **1c** is used by polymerase and incorporated into DNA during replication, which gives rise to stalled replication forks and chain termination. Moreover, it was also speculated that the whole molecule is a substrate for HIV-RT. For example, the antiviral activity determined of γ-(alkyl-C8; alkyl-C18)-phosphate-d4TDP **70c** (EC_{50} = 0.005 μM/HIV-2) in the CEM/TK^- cell cultures improved by 7-fold as compared to the antiviral activity observed in wild-type CEM/0 cell cultures (EC_{50} = 0.036 μM/HIV-2). Otherwise, we also speculated that d4TDP is a substrate for HIV-RT. Because some results prove that HIV-RT can utilize a deoxynucleoside diphosphate (dNDP) in the polymerization reaction.[188] To confirm the mechanism, γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** and d4TDP would be further examined in primer extension assays and investigated their suitability as substrates for the HIV-RT.

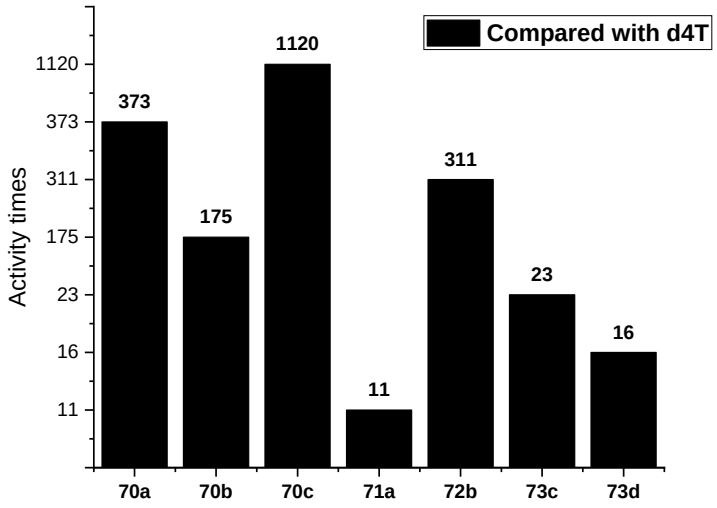


Figure 43. The improved activity as compared to the parent nucleoside d4T.

However, the inhibition of the replication of HIV-1 and HIV-2 by γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** was similar such as **71b** (EC_{50} = 0.031 μM/HIV-1; EC_{50} = 0.035 μM/HIV-2), or lower like **71c** (EC_{50} = 0.09 μM/HIV-1; EC_{50} = 0.14 μM/HIV-2), compared to their parent nucleoside d4T **1** (EC_{50} = 0.073 μM/HIV-1; EC_{50} = 0.037 μM/HIV-2) in CEM/0 cells. The antiviral activity determined for γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71b-d** (alkyl: C4-C12) decreased with increasing alkyl chain lengths. It was

speculated that γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** showed a marked loss of activity in the TK-deficient cell cultures because of the low solubility and high metabolic stability, such as **71d** (EC_{50} = 0.13 µM/HIV-1; EC_{50} = 0.21 µM/HIV-2). Moreover, γ-(alkyl-C1; alkyl-C18)-phosphonate-d4TDP **71a** showed lower antiviral activity than γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b** for some unknown reasons. However, it cannot be excluded that the initial cleavage under biological conditions proceeded at least in part also by an attack at the P-C position, implicating the existence of enzymes capable of C-P bond cleavage.

Table 5. Antiviral activity and cytotoxicity of prodrug compounds γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** in comparison with the parent nucleoside d4T **1**.

Comp.	HIV-1 (HE)	HIV-2 (ROD)	CEM/TK$^-$ HIV-2 (ROD)	Toxicity
	EC_{50}[a] [µM]	EC_{50}[a] [µM]	EC_{50}[a] [µM]	CC_{50}[b] [µM]
70a	0.077±0.017	0.025±0.019	0.015±0.014	34±6
70b	0.070±0.039	0.041±0.043	0.032±0.031	30±8
70c[c]	0.075±0.044	0.036±0.025	0.005±0.0069	34±7
71a	0.051±0.042	0.080±0.067	0.48±0.10	40±3
71b	0.031±0.017	0.035±0.021	0.018±0.006	33±8
71c[c]	0.090±0.072	0.14±0.12	0.24±0.17	42±1
71d	0.13±0.08	0.21±0.13	0.35±0.28	50±6
d4T	0.073±0.019	0.037±0.028	5.6±3.3	>100

Antiviral activity determined in $CD4^+$ T-lymphocytes: 50% effective concentration; values are the mean ±SD of n=2-3 independent experiments. [b] Cytotoxicity: 50% cytostatic concentration or compound concentration required to inhibit $CD4^+$ T-cell (CEM) proliferation by 50%; values are the mean ±SD of n=2-3 independent experiments. [c] R^1= 2-ethylhexyl.

In summary, a potential new generation of γ-dialkylphosphate-modified-d4TDPs **70** was discovered, in that they comprised two non-cleavable moieties at the γ-phosphate group. For comparison, γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** were synthesized as well using the *H*-phosphinate route (Scheme 28). In all cases, the γ-phosphate or γ-phosphonate masking unit was cleaved to form d4TDP **1b** by chemical hydrolysis or maybe by enzymes present in cell extracts. In these studies, no d4TTP **1c** and mono-masked nucleoside analogues were obtained starting from compounds **70**,**71**. Because of the

very long hydrolysis periods, a cleavage of the glycosidic bond in compounds **70**,**71** resulted in the appearance of the nucleobase thymine. In contrast, the formation of thymine was not detected from compounds **70**,**71** in cell extracts. Interestingly, all γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** retained similar or even better activities against HIV-1 and HIV-2 than the parent nucleoside d4T **1** in CEM/0 cells and more importantly retained very good activities against HIV-2 in CEM/TK$^-$ cells, such as γ-(alkyl-C8; alkyl-C18)-phosphate-d4TDP **70c** (EC_{50} = 0.005 µM/HIV-2). The results reported here maybe show that this strategy enabled the intracellular delivery of nucleoside diphosphates or γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** are substrates for HIV-RT and the play key roles in antiviral chemotherapies. Work along this line in currently underway in laboratories. Using these insights, γ-phosphate or phosphonate-modified NTP-prodrugs of other nucleoside analogues such as AZT or ddU will be synthesized and investigated.

It was expected that this approach may be used to convert inactive nucleoside analogues into powerful biologically active metabolites. The advantage of the strategy used here is that γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** proved to be more stable in PB, PLE and CEM cell extracts. However, the antiviral activity determined of γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71b**-**d** (alkyl: C4-C11) decreased as compared to the corresponding γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70**. It was speculated if their correlates with lower concentration of γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** in cells.

5 Summary and conclusion

In summary, several types of nucleoside triphosphate prodrugs (Scheme 34) have been developed in this thesis: 1) γ-(AB; ACB)-d4TTPs **60**, γ-(ACB; ACB)-d4TTPs **61**, and γ-(AB; ACB)-NTPs **89** bearing two different biodegradable masking units (AB or ACB) attached to the γ-phosphate group; 2) γ-(AB-C4; alkyl-C18)-NTPs **90** comprising a non-cleavable moiety in addition to a biodegradable prodrug moiety at the γ-phosphate group; 3) γ-AB-γ-C-alkyl-d4TTPs **67** and γ-ACB-γ-C-alkyl-d4TTPs **68** bearing a non-cleavable γ-alkyl-phosphonate moiety instead of the normal γ-phosphate group in addition to a biodegradable prodrug moiety (AB or ACB) at the γ-phosphonate unit; 4) γ-dialkylphosphate-modified-d4TDPs **70** and γ-dialkylphosphonate-modified-d4TDPs **71** bearing different non-cleavable alkyl moieties at the γ-phosphate or γ-phosphonate group, respectively.

All prodrugs were incubated in PB (pH 7.3), pig liver esterase (PLE), and CEM cell extracts to study their chemical and biological stability, respectively.

The half-lives of Tri*PPP*ro-d4TTPs **60**,**61** increased with increasing alkyl chain lengths (Figure 28, page 54). γ-(ACB; ACB)-d4TTPs **61** ($t_{1/2}$ = 84-111 h, Figure 28, page 54) proved to be more stable (chemically) than the corresponding γ-(AB; ACB)-d4TTPs **60** ($t_{1/2}$ = 66-87 h, Figure 28, page 54). The chemical stability of the carbonate intermediates γ-(ACB)-d4TTPs **62** (ACB-C12, $t_{1/2}$ = 625 h; ACB-C16, $t_{1/2}$> 1600 h) were found to be significantly higher than the corresponding ester intermediates γ-(AB)-d4TTPs **55** ($t_{1/2}$ < 583 h).[53] In PB, before complete consumption of the starting material **60**, an increase of γ-(ACB)-d4TTPs **62** and d4TTP concentrations were observed and a small amount of γ-(AB)-d4TTPs **55** was detected. As compared to chemical hydrolyses, all Tri*PPP*ro-d4TTPs **60**,**61** were rapidly hydrolyzed and delivered the nucleoside triphosphates d4TTP **1c** much faster than in PB, demonstrating a significant contribution of the enzymatic cleavage with PLE (Figure 29, blue, page 57). There is a highly selective cleavage of one biodegradable moiety (AB) which led to the formation of γ-(ACB)-d4TTPs **62**. γ-(ACB)-d4TTPs **62** first accumulated and later is cleaved as well and finally formed d4TTP **1c**. γ-(AB or ACB; ACB)-d4TTPs **60**,**61** were selectively cleaved to form γ-(ACB)-d4TTPs **62** by chemical hydrolysis (slow process) and in particular by cell extract enzymes (fast process). The half-lives of the prodrugs **60**,**61** in CEM cell extracts also correlated well with the chain lengths and were found to be significantly lower than the half-lives in PB (Figure 29, red, page 57). These prodrugs **60**,**61** comprising a short AB-group in the prodrug moiety were found to be more readily cleaved to form intermediate γ-(ACB)-d4TTPs **62**.[180]

In contrast to hydrolysis studies with PB and PLE, it was almost impossible to detect significant concentrations of d4TTP **1c** due to its fast dephosphorylation to form first d4TDP **1b** (mainly concentration) and ultimately d4TMP **1a**.[180]

In the second part of this work the Tri*PPP*ro-approach applied to d4T **1** as a model, was transferred to other nucleoside analogues to combat HIV infections. The half-lives of γ-(AB: C2 or C4; ACB-C16)-NTPs **89** comprising the same nucleotide were almost identical (Figure 32, page 66). In the hydrolysis of γ-(AB: C2 or C4; ACB-C16)-NTPs **89** in PB, both intermediates γ-(C16-ACB)-NTPs and γ-(AB: C2 or C4)-NTPs, respectively, were formed (Scheme 17, A, page 68), indicating that both masking units of γ-(AB; ACB-C16)-NTPs **89** were involved in the hydrolysis and thus proceeded similar to the previously published cleavage pathway for Tri*PPP*ro-d4TTPs **60**,**61** (Scheme 12, page 55). Before complete consumption of the starting material **89**, an increase of NTP concentrations were observed and NDP was detected in some amounts (Scheme 17, A, page 68). Moreover, the chemical stability of the intermediates γ-(ACB-C16)-NTPs were also found to be higher than the corresponding intermediates γ-(AB-C4)-NTPs. All compounds **89** were rapidly hydrolyzed with PLE and delivered NTPs much faster compared to the chemical hydrolysis, which was in full agreement with the results as γ-(AB or ACB; ACB)-d4TTPs **60**,**61**. With PLE, a large amount of γ-(C16-ACB)-NTPs, an increase of NTP concentrations and almost no NDP were detected. In contrast, a very small amount of NTP and a large amount of NDP were observed due to the fast dephosphorylation of the NTP by phosphorylases/kinases present in the cell extracts.[181]

The chemical stability of γ-(AB-C4; alkyl-C18)-NTPs **90** ($t_{1/2}$ = 178-600 h, Figure 32, page 66) was higher than Tri*PPP*ro-NTPs **89** ($t_{1/2}$ = 36-84 h, Figure 32, page 66). In contrast, Tri*PPP*ro-NTPs **89** ($t_{1/2}$ = 0.19-0.32 h, Figure 33, page 67) proved to be more stable as compared to the studies of the corresponding products γ-(AB-C4; alkyl-C18)-NTPs **90** ($t_{1/2}$ = 1.57 h to 5.0 h, Figure 32, page 66) with PLE. In all case, γ-(AB-C4; alkyl-C18)-NTPs **90** were only hydrolyzed to γ-(alkyl-C18)-NTPs some cleavage to the corresponding NDP occurred as well. In contrast to γ-(AB; ACB-C16)-NTPs **89**, no cleavage of the alkyl residue in γ-(AB-C4; alkyl-C18)-NTPs **90** was occurred in these studies. Therefore, no NTPs were detected in these studies using γ-(AB-C4; alkyl-C18)-NTPs **90** in PB, PLE and CEM cell extracts. A large amount of γ-(alkyl-C18)-FTCP **97d** and a very low concentration of FTCDP were detected in CEM cell extracts (Scheme 18, page 68). This supports that γ-(alkyl-C18)-NTPs showed a very high stability in cell extracts towards dephosphorylation.

The third part of this work describes the first direct proof of the successful application of an advanced prodrug concept for NTP derivatives that obviously are able to efficiently enter the cells and to directly deliver γ-C-alkyl-NTPs with high selectivity by an enzyme-triggered mechanism. In PB, the stability of Tri*PPP*ro-d4TTPs **67**,**68** increased with increasing alkyl chain lengths (R^1 and R^2). The chemical stability of these prodrugs **67**,**68** was higher such as **67ce** ($t_{1/2}$ = 646 h, Figure 44), as compared to the corresponding ester products γ-(AB-C4; ACB-C16)-d4TTP **60ey** ($t_{1/2}$ = 74 h, Figure 44).The half-lives for the ester products γ-AB-γ-C-alkyl-d4TTPs **67** ($t_{1/2}$ = 103-919 h, Figure 36, A, page 76) was found to be lower than the corresponding carbonate compounds γ-ACB-γ-C-alkyl-d4TTPs **68** ($t_{1/2}$ = 123-1240 h, Figure 36, A, page 76). In the hydrolysis of Tri*PPP*ro-d4TTPs **67**,**68** in PB, the cleavage of the AB group or the ACB group was initiated by an ester or carbonate hydrolysis (Scheme 22, page 78) and thus proceeded similar to the cleavage pathway for Tri*PPP*ro-d4TTPs **60**,**61** (Scheme 12, page 55). As hydrolysis products starting from the Tri*PPP*ro-d4TTPs **67**,**68** a predominant formation of γ-C-(alkyl)-d4TTPs **69** and small amount of d4TDP was observed. It is worth noting that no concentration of d4TTP was observed after full conversion of the starting γ-(AB or ACB)-γ-C-(alkyl)-d4TTPs **67**,**68** which led to the conclusion that γ-(AB or ACB)-γ-C-(alkyl)-d4TTPs **67**,**68** were prone to a bond breakage between the γ-phosphonate and β-phosphate. As compared to the chemical hydrolyses, γ-(AB or ACB)-γ-C-(alkyl)-d4TTPs **67**,**68** were rapidly hydrolyzed with PLE ($t_{1/2}$ = 0.009 h to 10.6 h, Figure 36, B, page 76) and delivered γ-C-alkyl-d4TTP derivatives **69** much faster than in PB, demonstrating a significant contribution of the enzymatic cleavage. The hydrolysis and stability of γ-(AB or ACB)-γ-C-alkyl-d4TTPs **67**,**68** were found to be significantly influenced by two different alkyl chain lengths of the prodrug groups (R^1 and R^2). With PLE, the half-lives of γ-(β-cyanoethyl)-γ-C-alkyl-d4TTPs **106** ($t_{1/2}$ > 80 h, Figure 36, D, page 76) and γ-C-alkyl-d4TTPs **69** ($t_{1/2}$ > 80 h, Figure 36, D, page 76) showed that the delivery of d4TDP was probably due to a pure chemical cleavage of the γ-phosphonate moiety as well (Figure 36, D, page 76). Because there is no esterase cleavage site. In CEM cell extracts, the half-lives of Tri*PPP*ro-d4TTPs **67**,**68** correlated well with the chain lengths (R^1 and R^2) and were also found to be significantly lower than the half-lives in PB (up to 2300-fold, Figure 36, page 76). In the hydrolysis of γ-(AB or ACB)-γ-C-alkyl-d4TTPs **67**,**68** in CEM cell extracts, before complete consumption of the starting materials **67**,**68**, an increase of γ-C-(alkyl)-d4TTPs **69** concentrations and a very low concentration of d4TDP (<4%) were detected. In addition, the half-lives of prodrugs γ-ACB-γ-C-alkyl-d4TTPs **68** ($t_{1/2}$ = 0.044-8 h, Figure 36, C, page 76) were found to be higher than the corresponding γ-AB-γ-C-alkyl-d4TTPs **67** ($t_{1/2}$ = 0.65-10 h,

Figure 36, C, page 76). In all case, the hydrolysis, stability, and antiviral activity of γ-(AB or ACB)-γ-C-alkyl-d4TTPs **67**,**68** were found to be significantly influenced by two different alkyl chain lengths of the prodrug units (R^1 and R^2). More importantly, the predominant formation of γ-C-(alkyl)-d4TTPs **69** was detected in all hydrolysis studies using these prodrugs **67**,**68**, but no d4TTP was formed.[186]

The last part of this work describes a series of γ-dialkylphosphate-modified-d4TDPs **70** and γ-dialkylphosphonate-modified-d4TDPs **71**. As compared to γ-(AB or ACB; ACB)-d4TTPs **60**,**61** and γ-(AB or ACB)-γ-C-(alkyl)-d4TTPs **67**,**68**, both γ-modifications in these compounds **70**,**71** are not bioreversible because they are simple alkyl groups. Therefore, the chemical and biological stabilities of compounds **70**,**71** were found to be significantly higher than γ-(AB or ACB; ACB)-d4TTPs **60**,**61** and γ-(AB or ACB)-γ-C-(alkyl)-d4TTPs **67**,**68**, such as γ-(alkyl-C4; alkyl-C18)-phosphate-d4TDP **70b** ($t_{1/2}$ = 990 h, Figure 44). In the hydrolysis of compounds **70**,**71** in PB, a predominate formation of d4TDP and a very small amount of d4TMP were observed, but no d4TTP and mono-alkylated nucleotide analogues were detected in these studies. In addition, the delivery of d4TDP rather than d4TTP was also proven in human cell extracts and PLE, which was in full agreement with the results obtained from the studies in PB. This confirms the hypothesis that γ-modified-prodrugs **70**,**71** were prone to a bond breakage between the γ-phosphate or γ-phosphonate and the β-phosphate. In addition, an increase of thymine concentrations was observed after long incubation times due to a cleavage of the glycosidic bond in d4T. More importantly, a very small amount of d4TDP was observed in CEM cell extracts probably due to its dephosphorylation by phosphorylases/kinases as well as the high biological stability of the compounds **70**,**71** in CEM cell extracts.

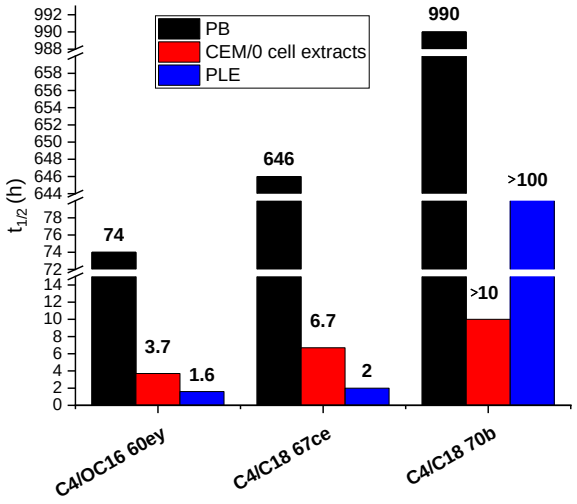
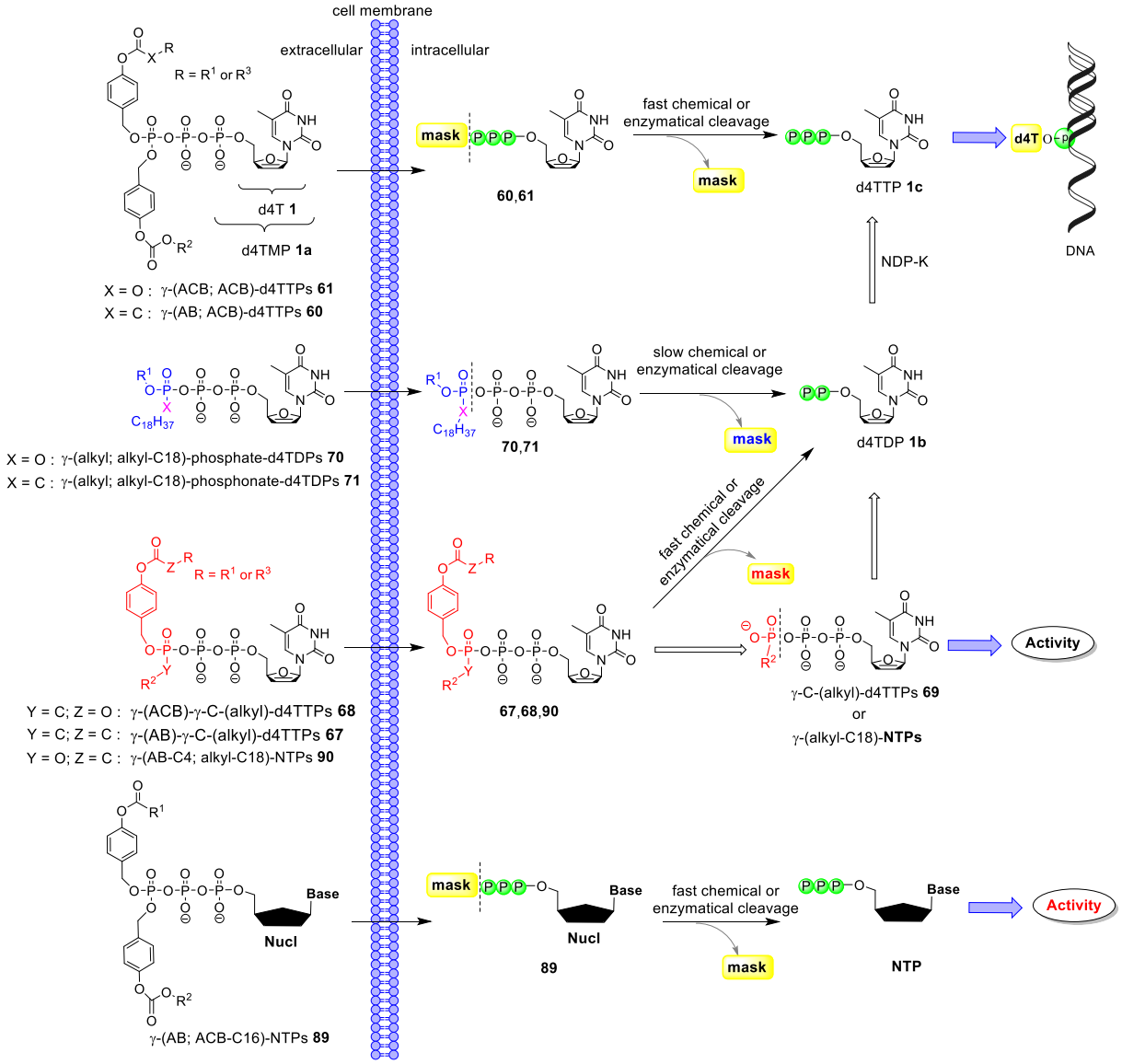


Figure 44. Half-lives of **60ey**,**67ce** and **70b** in PB (pH 7.3), PLE and CEM/0 cell extracts.



Scheme 34. Metabolism of nucleoside analogues and the corresponding nucleotide prodrugs.

All prodrugs were evaluated for their activity to inhibit the HIV replication in HIV-1- and HIV-2-infected CEM/0 cell cultures and in HIV-2-infected mutant thymidine kinase-deficient CEM/TK$^-$ cell cultures.

In the first part of this work, most of the Tri*PPP*ro-d4TTPs **60**,**61** showed virtually similar or even slightly better activities against HIV-1 and HIV-2 than the parent nucleoside d4T **1** in wild-type CEM/0 cells. In addition and more importantly, all Tri*PPP*ro-d4TTP prodrugs **60**,**61** were also highly potent in CEM/TK$^-$ cell cultures whereas d4T **1** lacked any relevant anti-HIV activity in this thymidine kinase-deficient cell model. However, all Tri*PPP*ro-d4TTPs **60**,**61** showed a marked loss of activity in the TK$^-$ deficient cell cultures, such as **60by** (EC_{50} = 0.11 µM/HIV-2). It was speculated that all Tri*PPP*ro-compounds **60**,**61** were rapidly hydrolysed in cell extracts and d4TTP was not retained in sufficient concentrations (fast dephosphorylation, $t_{1/2}$ = 0.6 h) in cells to exhibit antiviral activity. Interestingly, γ-(ACB-C16)-d4TTP **62y**

(EC_{50} = 1.46 µM/HIV-2) is also potent in CEM/TK^- cell cultures whereas d4T **1** (EC_{50} = 31.05 µM/HIV-2) lacked any relevant anti-HIV activity in mutant CEM/TK^- cell cultures. Consequently, it seems that even *one* long aliphatic chain in the ACB-units provides enough lipophilicity to enable a cellular uptake of the aliphatic Tri*PPP*ro-d4TTPs **60**,**61**, which is in full agreement with the results as γ-(ACB-C16)-FddClUTP **95g** (Table 6). Moreover, Tri*PPP*ro-FddClUTPs **89g2** (EC_{50} > 20 µM/HIV-2) was also potent in CEM/TK^- cell cultures whereas FddClU **1h** (EC_{50} > 250 µM/HIV-2) lacked any relevant anti-HIV activity in this thymidine kinase-deficient cell model. It was confirmed that these compounds **60**,**61**,**89** were taken-up by the cells and delivered intracellularly a phosphorylated form of parent nucleosides, most likely nucleoside triphosphates. The results reported here clearly show that the Tri*PPP*ro-strategy enabled the intracellular delivery of nucleoside triphosphates, and the approach could be used to convert inactive nucleoside analogues into powerful biologically active metabolites. The Tri*PPP*ro-concept in which the γ-phosphate of NTPs is modified by different lipophilic and biodegradable masking groups which are cleaved by an enzyme-triggered mechanism enables the bypass of all steps of the intracellular phosphorylation. Thus, the Tri*PPP*ro-approach offers high potential to be used in antiviral and potentially also in antitumoral therapies.

In the third part of this work the antiviral activity determined for Tri*PPP*ro-prodrugs **67**,**68** increased with increasing alkyl chain lengths (R^1 and R^2).The inhibition of the replication of HIV-1 and HIV-2 by prodrugs **67**,**68** was much higher such as **67ce** (EC_{50} = 0.0074 µM/HIV-1; EC_{50} = 0.021 µM/HIV-2), or at least similar like, compared to their parent nucleoside **1** (EC_{50} = 0.43 µM/HIV-1; EC_{50} = 0.31 µM/HIV-2) in wild-type CEM/0 cells. More interestingly, the antiviral activity observed in the wild-type CEM/0 cell cultures was completely retained in the case of the lipophilic γ-(ACB-C4)-γ-C-(alkyl-C18)-d4TTP **68cm** (EC_{50} = 0.032 µM) in CEM/TK^- cell cultures. With γ-(ACB-C4)-γ-C-(alkyl-C18)-d4TTP **68cm** the antiviral activity in this infected cell line was by a 4-fold as compared to γ-(AB-C4; ACB-C16)-d4TTPs **60ey** (EC_{50} = 0.12 µM/HIV-2). γ-(ACB-C4)-γ-C-(alkyl-C18)-d4TTP **68cm** showed a marked antiviral activity against HIV-2 in CEM/TK^- cells (1000-fold more active as d4T **1**), indicating a successful cell membrane passage of these compounds and an intracellular delivery of the nucleoside diphosphate-γ-phosphonates. This maybe due the sufficient lipophilicity of the compound **68cm** combined with a relatively slow cleavage of the bioreversible ACB-moiety which led to the formation of γ-C-(alkyl-C18)-d4TTP **69c**, which also proved to be active in this assay (EC_{50} = 1.58 µM/HIV-2). Consequently, the γ-phosphonate moiety comprise a long, lipophilic aliphatic chain ($R^2 = C_{18}H_{37}$) that should give the prodrug molecule sufficient

lipophilicity to cross the biological barriers. This is in full agreement with the results as γ-(ACB-C16)-d4TTP **62y** and γ-(ACB-C16)-FddClUTP **95g**. In addition, the antiviral activity of γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** (EC_{50}: 7.30 µM) improved by 3-fold compared to γ-(AB-C4; ACB-C16)-FddClUTPs **89g2** (EC_{50} > 20µM/HIV-2, Table 6). With γ-(AB-C4)-γ-C-(alkyl-C18)-d4TTP **67ce** (EC_{50}: 0.042 µM) and γ-(ACB-C4)-γ-C-(alkyl-C18)-d4TTP **68cm** (EC_{50} = 0.032 µM) the antiviral activity in this infected cell line was improved by a 3-fold and 4-fold, respectively, as compared to γ-(AB-C4; ACB-C16)-d4TTP **60ey** (EC_{50}: 0.12 µM, Table 6). Therefore, Tri*PPP*ro-prodrugs **67**,**68** provide a higher potential to be used in antiviral and potentially also in antitumoral chemotherapies than Tri*PPP*ro-prodrugs **60**,**61**. It was convinced that this Tri*PPP*ro-strategy is not limited to HIV treatment but can also be used for other viral targets and can also be used as a delivery for carbon-linked non-natural nucleotides as biochemical tools in Chemical Biology approaches.

In the last part of this work, the inhibition of the replication of HIV-1 and HIV-2 by γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** was similar compared to their parent nucleosides d4T **1** in the wild-type CEM/0 cell cultures. In addition and more importantly, γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** were also highly antivirally active against HIV-2 in in CEM/TK^- cell cultures. γ-(Alkyl-C8; alkyl-C18)-phosphate-d4TDP **70c** (EC_{50} = 0.005 µM/HIV-2, Table 6) is the most active compounds of all the listed derivatives (1120-fold more active as d4T **1**). It was speculated that γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** can only be cleaved by chemical means to form d4TDP (slow process) in cells due to their high stability, then convert them into the ultimately bioactive d4TTP by cellular kinases. The antiviral activity determined for prodrugs **70** (alkyl: C1-C8; alkyl-C18) increased with increasing alkyl chain lengths (R^1), indicating a successful cell membrane passage of these compounds, probably due to the increasing lipophilicity to cross the cell membrane. In contrast, decreased antiviral activity of γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71b**-**d** (alkyl: C4-C12) was observed, although the compound is more lipophilic but maybe also too low in solubility. The results reported here maybe show that this Tri*PPP*ro-approach enabled the intracellular delivery of nucleoside diphosphates. Moreover, it was also speculated that γ-(alkyl; alkyl-C18)-phosphate-d4TDPs **70** and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs **71** are substrates for HIV-RT and the play key roles in antiviral chemotherapies. This Tri*PPP*ro-concept seems to be very interesting for application with nucleoside analogues that show severe limitations in their activation to give the corresponding nucleoside diphosphates. It was expected that this strategy may be used to convert inactive nucleoside analogues into powerful biologically active metabolites.

Table 6. Antiviral activity and cytotoxicity of γ-(AB-C2; ACB-C16)-d4TTP **60by**, γ-(ACB-C16)-d4TTP **62y**, γ-(AB-C4)-γ-C-(alkyl-C18)-d4TTP **67ce**, γ-(alkyl-C8; alkyl-C18)-phosphate-d4TDP **70c**, γ-(alkyl-C4; alkyl-C18)-phosphonate-d4TDP **71b**, γ-(AB-C4; ACB-C16)-FddClUTP **89g2**, γ-(ACB-C16)-FddClUTP **95**, and γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP **110** in comparison with the parent nucleoside d4T **1**, FddClU **8**.

Comp.	HIV-1 (HE) EC_{50}[a] [μM]	HIV-2 (ROD) EC_{50}[a] [μM]	CEM/TK$^-$ HIV-2 (ROD) EC_{50}[a] [μM]	Toxicity CC_{50}[b] [μM]
60by (C_2H_5/$OC_{16}H_{33}$)	0.027±0.0092	0.0048±0.0065	0.11±0.0071	34±9.3
60ey (C_4H_9/$OC_{16}H_{33}$)	0,032±0,017	0,014±0,015	0,12±0,048	21±17
62y (ACB-$OC_{16}H_{33}$)	0.50±0.29	0.29±0.06	1.46±1.34	61±36
67ce (AB-C_4H_9; alkyl-$C_{18}H_{37}$)	0.0074±0.0014	0.021±0.006	0.042±0.002	19±8
68cm (AB-C_4H_9; alkyl-$C_{18}H_{37}$)	0.0018±0.002	0.026±0.04	0.032±0.02	16±2
69c (alkyl-$C_{18}H_{37}$)	0.046±0.021	0.11±0.064	1.58±0.75	21±9
d4T	0.43±0.23	0.31±0.13	31.05±5.25	>50
70b (alkyl-C_4H_9; alkyl-$C_{18}H_{37}$)	0.070±0.039	0.041±0.043	0.032±0.031	30±8
70c (alkyl-C_8H_{17}; alkyl-$C_{18}H_{37}$)	0.075±0.044	0.036±0.025	0.005±0.0069	34±7
71b (alkyl-C_4H_9; alkyl-$C_{18}H_{37}$)	0.031±0.017	0.035±0.021	0.018±0.006	33±8
d4T	0.073±0.019	0.037±0.028	5.6±3.3	>100
89g2 (AB-C4; ACB-OC16)	2.59±1.50	0.32±0.42	>20	42±4
95g (ACB-OC16)	2.5±1.0	3.6±3.7	40.2±4.8	54±13
110 (AB-C_4H_9; alkyl-$C_{18}H_{37}$)	0.15	1.12	7.30	32.78
8 (FddClU)	>250	>250	>250	188±88

Antiviral activity determined in $CD4^+$ T-lymphocytes: 50% effective concentration; values are the mean ±SD of n=2-3 independent experiments. [b] Cytotoxicity: 50% cytostatic concentration or compound concentration required to inhibit $CD4^+$ T-cell (CEM) proliferation by 50%; values are the mean ±SD of n=2-3 independent experiments. [c] R^1= 2-ethylhexyl.

In summary, the design of anti-HIV prodrugs that undergo selective tissue biodistribution and uptake in target HIV-infected cells to a therapeutic concentration has presented a significant challenge to medicinal chemists. These nucleoside triphosphate prodrugs are designed to efficiently cross the biological barrier. Once inside the cell or tissues, the two different masking groups are then degraded

chemically and/or enzymatically, leading to the formation of NDP, NTP, respectively. This Tri*PPP*ro-approach has been shown that the stability, hydrolysis, and antiviral activity were significantly influenced by the chain lengths of the prodrug masking moieties.

All prodrugs showed virtually similar or even slightly better activities against HIV-1 and HIV-2 than the parent nucleoside d4T **1** in all cell cultures. However, Tri*PPP*ro-d4TTPs **60**,**61** showed a marked loss of activity in CEM/TK$^-$ cell cultures. The antiviral activity observed in the wild-type CEM/0 cell cultures was completely retained in the case of the lipophilic Tri*PPP*ro-prodrugs **67ce**,**68cm** in mutant thymidine-deficient CEM cells (TK$^-$). More interestingly, the inhibition of the replication of HIV-2 by prodrugs **70**,**71** was higher, or at least similar, compared to the corresponding Tri*PPP*ro-prodrugs **67ce**,**68cm** in CEM/TK$^-$ cell cultures. It was convincingly shown that the Tri*PPP*ro-strategy offers high potential in antiviral and antitumoral chemotherapies. Highly active Tri*PPP*ro-prodrugs may be used in the future as commercial drugs. However, many development steps still have to be achieved, e.g. toxicity assay, testing phases and the development of reaction routes that allow the production of industrial size quantities of the compounds.

6 Experiment Section

General: Without further noticed, all manipulations involving water-sensitive reagents were carried out under nitrogen (N_2) atmosphere and dry conditions using the Schlenk technology.

6.1 Solvents and Reagents

Solvents：

Anhydrous solvents:

Acetonitrile C_2H_3N; drying via MBraun solvent purification system (MBSPS-800), stored over molecular sieve (4 Å).

Dichlormethane CH_2Cl_2; drying via MBraun solvent purification system (MBSPS-800), stored over molecular sieve (4 Å).

Diethyl ether $C_4H_{10}O$; drying via MBraun solvent purification system (MBSPS-800), stored over molecular sieve (4 Å).

Pyridine C_5H_5N; drying via MBraun solvent purification system (MBSPS-800), stored over molecular sieve (4 Å).

Tetrahydrofuran C_4H_8O; drying via MBraun solvent purification system (MBSPS-800), stored over molecular sieve (4 Å).

NMR solvents chloroform-d_1 ($CDCl_3$-d_1), dimethyl sulfoxide-d_6 (DMSO-d_6), deuterium oxide (D_2O), methanol-d_4 (MeOD-d_4), and tetrahydrofuran-d_8 (THF-d_8) were purchased form Euriso-Top.

Other dry solvents such as *N,N*-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO), methanol (MeOH), and toulene were purchased from Acros Organics (extra dry over molecular sieves).

Non-anhydrous solvents:

Dichloromethane (CH_2Cl_2), ethyl acetate (EA), methanol (MeOH), and petroleum ether (PE, 50-70), and were distilled prior to use. Acetonitrile, acetone, chloroform, *n*-hexane, *iso*-propanol and tetrahydrofuran are HPLC grade. Water (H_2O): ultrapure water (Milli-Q).

Regents:

Triethylamine (Et_3N) was refluxed over CaH_2 for three days and distilled under nitrogen. Trifluoroacetic anhydride (TFAA) was dried over phosphorus pentoxide for one hour and distilled under nitrogen. 1-Methylimidazole was dried over sodium and distilled under nitrogen. All further reagents were purchased from Alfa Aesar, Acros Organics, Sigma Aldrich, TCI and Carbosynth and used as received.

Column chromatography: Normal phase column chromatography were performed by using Macherey-Nagel silica gel 60 M (0.040-0.063 mm).

Automated flash chromatography: The purification was performed on an Interchim Purflash 430 or Büchi system using cartridges filled with silica gel MN 60 M (0.04-0.063 mm) from Macherey Nagel or RP silica gel (MN RS16 C_{18}ec, RS 40 C_{18}ec and RS 120 C_{18}ec) columns.

Analytical thin-layer chromatography (TLC): For thin layer chromatography Macherey-Nagel precoated aluminium plates Alugram® Xtra SIL G/UV_{254} and UV lamp (wavelength: 254 nm) were used. Additionally, some compounds were visualized by using the following staining reagents and heating.

Basic potassium permanganate reagent: 3.0 g $KMnO_4$, 20 g Potassium carbonate, and 2.5 mL 10% NaOH in 400 mL water.

Phosphomolybdic Acid (PMA) reagent: 20g phosphomolybdic acid in 200 mL of ethanol.

High Performance Liquid Chromatography (HPLC): HPLC was required for analytical studies and monitoring reactions. A VWR-Hitachi LaChromElite HPLC system (L-2130, L-2200, L-2455), EzChromElite software and equipped with a Nucleodur 100-5 C_{18}ec (Macherey-Nagel) was available. CH_3CN for HPLC was obtained from VWR (HPLC grade) and ultrapure water was produced by a Sartorius Aurium® pro (Sartopore 0.2 µm, UV). Method for nucleotides, Tri*PPP*ro-compounds and mono-masked nucleoside analogues: Nucleodur 100-5 C18ec; 0-20 min: TBAA buffer/CH_3CN gradient (5-80%); 20-30 min: buffer/CH_3CN (80%); 30-33 min: buffer/CH_3CN (80-5%); 33-38 min: buffer/CH_3CN (5%); flow: 1 mL/min.

Nuclear magnetic resonance spectroscopy (NMR): All NMR spectra were measured in the institute of inorganic chemistry and in the institute of organic chemistry at the University of Hamburg. NMR spectra were recorded at room temperature in automation mode with a Varian Gemini 2000BB, Bruker Fourier 300, Bruker AMX 400, Bruker DRX 500 or Bruker AVIII 600. All ^{1}H- and ^{13}C-NMR chemical shifts (δ) were quoted in parts per million (ppm) downfield from tetramethylsilane (TMS) and calibrated on solvent signal. The ^{31}P-NMR chemical shifts (proton decoupled) are also quoted in ppm using phosphoric acid as the external standard. For an exact substance identification also two-dimensional experiments like H,H-COSY, HSQC and HMBC were performed. All chemical shifts are calibrated on the used solvent signals: 1, MeOD-d_4 3.31 ppm (^{1}H), 49.00 ppm (^{13}C); 2, $CDCl_3$-d_1 7.26 ppm (^{1}H), 77.16 ppm (^{13}C); 3, D_2O 4.79 ppm (^{1}H); 4, DMSO-d_6 2.50 ppm (^{1}H), 39.5 ppm (^{13}C); 5, THF-d_8 3.58 ppm (^{1}H), 67.57 ppm (^{13}C).

Mass Spectrometry (MS): All HRMS (ESI) mass spectra were acquired with an Agilent 6224 EIS-TOF spectrometer. ALl prodrug compounds were test using a Bruker UltrafleXtreme spectrometer: MALDI measurements (matrix: 9-aminoacridine [9-AA] or 2,5-dihydroxybenzoic acid [DHB]).

Infrared spectroscopy (IR): IR spectra were recorded on a Bruker Alpha IR-spectrometer at room temperature in the range of 400-4000 cm^{-1}.

Other instruments: Polarimeter (A. Krüss Optonic GmbH P8000 polarimeter), Freeze dryer (Alpha 2-4 LD Plus freeze dryer from Christ Co), pH meter (ProLab 300 from Schott Co) Ultrasonic cleaning device (Sonorex RK512H from Bandelin Co), Centrifuges (Heraeus Biofuge Pico and Biofuge Pimo R).

6.2 General Synthetic Procedures

General Procedure 1: Preparation of 4-acyloxybenzyl alcohols 52.

4-Hydroxybenzylalcohol **56** (1.1 eq.) and triethylamine (TEA, 1.0 eq.) in THF or CH_2Cl_2 were cooled down to 0 °C. The corresponding acyl chloride **72** in THF or CH_2Cl_2 was added dropwise and the mixture was stirred overnight at room temperature. The precipitate was filtered, and the solvent was removed in vacuum. The residue was diluted with CH_2Cl_2 and washed once with water. The organic layer was dried with Magnesium sulphate and the solvent was removed in vaccum. The crude was purified using column chromatography to give 4-acyloxybenzyl alcohols **52**.

General Procedure 2: Preparation of 4-(hydroxymethyl)phenylalkylcarbonate 73.

The reactions carried out under nitrogen (N_2) atmosphere under dry conditions. a) A mixture of triphosgene (1.0 equiv.), Potassium carbonate (2.0 equiv.) and DMF (0.72 equiv.) as a catalyst in toluene stirred for 30 min and cooled to 0 °C. A solution of alkyl alcohol ($C_nH_{2n+1}OH$) **74** in toluene was added dropwise to the mixture (n>10, added dropwise to the mixture at room temperature in case of solidification). The mixture was warmed to room temperature and stirred for 12 h. The solvent was removed in vaccum and the residue was purified using column chromatography (petroleum ether/ethyl acetate 97:3 v/v) to give alkyl chloroformates **76**. b) 4-Hydroxybenzyl alcohol **56** (1.1 equiv.) and TEA (1.0 equiv.) in CH_2Cl_2 or THF were cooled to 0 °C. The corresponding alkyl chloroformate in CH_2Cl_2 or THF was added dropwise to the mixture and stirred overnight. The solvent was removed in vaccum and the residue was washed once with saturated sodium bicarbonate solution and twice with water. The organic layer was dried with Magnesium sulphate and the solvent was removed in vaccum. The crude material was purified using column chromatography to give compound 4-(hydroxymethyl)phenylalkylcarbonate **73**.

General Procedure 3: Preparation of *H*-phosphonates 77 and 79.

General Procedure 3a: Under dry conditions, diphenyl *H*-phosphonate (DPP, 1.0 equiv.) was dissolved pyridine and cooled to 0 °C. 4-Acyloxybenzyl alcohols **52** (1.05 equiv.) was added and stirred at 0 °C for 1h and then stirred at room temperature (rt) for 1h. Following, 4-(hydroxymethyl)phenylalkyl carbonate 73 (1.0 equiv.) was added and the mixture was stirred for 12 h. Then the solvent was removed in vacuum. The residue was purified by flash column chromatography (silica) with ethyl acetate/petroleum ether/0.5% acetic acid as eluent.

General Procedure 3b: Under dry conditions, DPP (1.0 equiv.) was dissolved in pyridine and cooled to 0 °C. 4-(Hydroxymethyl)phenylalkylcarbonate **73** (1.0 equiv.) was added and stirred at 0 °C for 1 h and then stirred at room temperature (rt) for 1 h. Following, 4-acyloxybenzyl alcohols **52** (1.05 equiv.) was added and the mixture was stirred for 12 h. Then the solvent was removed in vacuum. The residue was purified by column chromatography with ethyl acetate/petroleum ether/0.5% acetic acid as eluent.

General Procedure 4: Preparation of non-symmetric *H*-phosphonate 93.

Under dry conditions, diphenyl phosphonate (1.2 equiv.) was dissolved in 3 mL pyridine and cooled to 0 °C. Aliphatic alcohol **92** (1.0 equiv.) was added and stirred at 0 °C for 30 min and then stirred at room temperature (rt) for 1h. Following, 4-(hydroxymethyl)phenyl pentanoate **52e** (1.4 equiv.) was added and the mixture was stirred for 3 h. Then the solvent was removed in vacuum. The crude product was purified by flash column chromatography (silica) with ethyl acetate/petroleum ether/0.5% acetic acid as eluent.

General Procedure 5: Preparation of *H*-phosphinates 99 and 102.

The reactions carried out under nitrogen (N_2) atmosphere under dry conditions. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (EDC; 1.2 equiv.) was added to a solution of 4-acyloxybenzyl alcohols **52** (2.0 equiv.) or 4-alkoxycarbonyloxybenzyl alcohols **73** (2.0 equiv.), phosphinic acid **98** (1.0 equiv.) and 4-dimethylaminopyridine (DMAP; 0.2 equiv.) in dry CH_2Cl_2. The reaction mixture was stirred for 12 h at room temperature (rt). The solvent was removed in vaccum and the residue was purified using column chromatography to give compounds *H*-phosphinates **99** and **102**, respectively.

General Procedure 6: Preparation of *H*-phosphonate 113.

The reactions carried out under nitrogen (N_2) atmosphere under dry conditions. N-methylmorpholine (1.1 equiv.) was added to a solution of hydrogen phosphonate **112** (1.0 equiv.) and alkyl chloroformates 76 (1 M solution in toluene) in dry diethyl ether. The reaction mixture was stirred for 30 min and cooled to 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The solvent was removed in vaccum and the residue was purified using column chromatography to give compound non-symmetric *H*-phosphonate **113**.

General Procedure 7: Preparation of *H*-phosphinate 115.

The reactions carried out under nitrogen (N_2) atmosphere under dry conditions. N-methylmorpholine (1.1 equiv.) was added to a solution of phosphonic acid **98c** (1.0 equiv.) and alkyl chloroformates **76** (1.1 equiv; 1 M solution in toluene) in dry diethyl ether. The reaction mixture was stirred for 30 min and cooled to 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The solvent was removed in vaccum and the residue was purified using column chromatography to give compound non-symmetric *H*-phosphinates **115**.

General Procedure 8: Preparation of nucleoside monophosphates 2 (option 1).

According to the protocol reported by SOWA AND OUCHI activated Phosphorus oxychloride was used as phosphorylating agent. Under dry conditions phosphoryl chloride (4.4 eq.) was dissolved in CH_3CN. To this solution pyridine (4.4 eq.) and water (2.2 eq.) were added slowly at 0 °C. The solution was kept at the same temperature for 5 min. The corresponding nucleoside was added and the mixture was stirred for 4-5 h at rt. Next, the solution was poured into ice water and stirred for 1 h. After hydrolysis the neutralization was performed with tetra-n-butylammonium hydroxide (40%) in water. The solution was freeze-dried and the crude product was purified by automatic RP18 flash chromatography (water/CH_3CN gradient; 5-100%, 0-70 min, flow 1 mL/min).

General procedure 9: Preparation of nucleoside monophosphates (option 2).

Under dry conditions the corresponding nucleosides (1.25 mmol, 1.0 eq.) and 0.93 mL phosphorous oxychloride (12.5 mmol, 10.0 eq.) were suspended in 5 mL trimethyl phosphate (TMP). The mixture was cooled down to 0 °C and stirred for 1h. Next, the solution was poured into ice water and stirred for 1 h. The solution was freeze-dried and the crude product was purified by automatic RP18 flash chromatography (water: 100%, 30 min, flow 1 mL/min; water/CH_3CN gradient; 50%/50%, 40 min, flow 1 mL/min). The crude product was adjusted to pH 7.0 using *tetra*-n-butylammonium hydroxide (40%) in water. The corresponding nucleoside monophosphate (*n*-Bu_4N^+ form) was purified by automatic RP18 flash chromatography (CH_3CN: 100%, 20 min, flow 1 mL/min; water/CH_3CN gradient; 50%/50%, 40 min, flow 1 mL/min) and freeze-drying.

General Procedure 10: Preparation of Tri*PPP*ro-derivatives 60,61.

The reactions were performed in a nitrogen (N_2) atmosphere and dry conditions. a) *H*-phosphonates 77 or 79 (0.15 mmol, 1.0 equiv.) were dissolved in 3 mL CH_3CN and *N*-chlorosuccinimide (NCS, 0.30 mmol, 2.0 equiv.) was added. After stirring for 2 h at room temperature, tetrabutylammonium phosphate solution (0.4 M in CH_3CN, 0.45 mmol, 3.0 equiv.) was added quickly. The mixture was stirred for 1 h

and the solvent was removed in vacuum. The residue was extracted with CH_2Cl_2/H_2O. The organic phase was dried over sodium sulfate and the solvent was removed by evaporation to afford pyrophosphate in almost quantitative yield. b) The corresponding pyrophosphate was dissolved in 3 mL CH_3CN and cooled down to 0 °C. A mixture of trifluoroacetic anhydride (TFAA, 0.75 mmol, 5.0 equiv.) and Et_3N (1.20 mmol, 8.0 equiv.) in 3 mL CH_3CN was cooled to 0 °C and added to the mixture. After stirring for 10 min, all volatile components were removed in vacuum. The residue was subsequently dissolved in 3 mL CH_3CN at 0 °C. 1-Methylimidazole (0.45 mmol, 3.0 equiv.) and Et_3N (TEA, 0.75 mmol, 5.0 equiv.) was added. The mixture was warmed to room temperature and stirred for 10 min. The resulting activated imidazolidate formed and NMP (0.6-0.85 equiv.) in 4 mL CH_3CN was added. The reaction was stirred at rt for 2-5 h and dried in vacuum. The crude product was purified by automatic RP18 flash chromatography, and then followed by ion-exchange to the ammonium form with Dowex 50WX8 cation-exchange resin and a second RP18 chromatography purification step. Product-containing fractions were collected and the organic solvent evaporated. The remaining aqueous solutions were freeze-dried and the desired product were obtained as white solids.

General Procedure 11: Preparation of Tri*PPP*ro-NTPs 89 and γ-(AB-C4; alkyl-C18)-NTPs 90:

The reactions were performed in a nitrogen (N_2) atmosphere and dry conditions. a) *H*-phosphonate 77by, 77ey or 93 (0.225 mmol, 1.0 equiv.) was dissolved in 4 mL CH_3CN and NCS (0.45 mmol, 2.0 equiv.) was added. After stirring for 2 h at room temperature, tetrabutylammonium phosphate solution (0.4 M in CH_3CN, 0.675 mmol, 3.0 equiv.) was added quickly. The mixture was stirred for 1 h and the solvent was removed in vacuum. The residue was extracted with CH_2Cl_2/H_2O. The organic phase was dried over sodium sulfate and the solvent was removed by evaporation to afford pyrophosphate in almost quantitative yield. b) The corresponding pyrophosphate was dissolved in 4 mL CH_3CN and cooled down to 0 °C. A mixture of TFAA (1.125 mmol, 5.0 equiv.) and Et_3N (1.80 mmol, 8.0 equiv.) in 4 mL CH_3CN was cooled to 0 °C and added to the mixture. After stirring for 10 min, all volatile components were removed in vacuum. The residue was subsequently dissolved in 4 mL CH_3CN at 0 °C. 1-Methylimidazole (0.675 mmol, 3.0 equiv.) and Et_3N (1.125 mmol, 5.0 equiv.) was added. The mixture was warmed to room temperature and stirred for 10 min. The resulting activated imidazolidate formed and NMP (0.6-0.85 equiv.) in 6 mL CH_3CN was added. The reaction was stirred at rt for 5 h and dried in vacuum. The crude product was purified by automatic RP18 flash chromatography, and then followed by ion-exchange to the ammonium form with Dowex 50WX8 cation-exchange resin and a second RP18 chromatography purification step. Product-containing fractions were collected and the organic solvent

evaporated. The remaining aqueous solutions were freeze-dried and the desired product were obtained as white solids.

General Procedure 12: Preparation of γ-AB-γ-C-alkyl-d4TTPs 67, γ-ACB-γ-C-alkyl-d4TTPs 68, γ-(alkyl; alkyl-C18)-phosphate-d4TDPs 70 and γ-(alkyl; alkyl-C18)-phosphonate-d4TDPs 71:

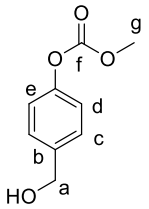
The reactions were performed in a nitrogen (N_2) atmosphere and dry conditions. a) *H*-phosphonates **113** or *H*-phosphinates **99**,**102**,**115** (0.30 mmol, 1.0 equiv.) were dissolved in 6 mL CH_3CN and 80 mg NCS (0.60 mmol, 2.0 equiv.) was added. After stirring for 2 h at room temperature, tetrabutylammonium phosphate solution (0.4 M in CH_3CN) (0.90 mmol, 3.0 equiv.) was added quickly. The mixture was stirred for 1 h and the solvent was removed in vacuum. The residue was extracted with CH_2Cl_2/H_2O. The organic phase was dried over sodium sulfate and the solvent was removed by evaporation to afford pyrophosphate in almost quantitative yield. b) The corresponding pyrophosphate was dissolved in 4 mL CH_3CN and cooled down to 0 °C. A mixture of TFAA (1.50 mmol, 5.0 equiv.) and Et_3N (2.40 mmol, 8.0 equiv.) in 4 mL CH_3CN was cooled to 0 °C and added to the mixture. After stirring for 10 min, all volatile components were removed in vacuum. The residue was subsequently dissolved in 6 mL CH_3CN at 0 °C. 1-Methylimidazole (0.90 mmol, 3.0 equiv.) and Et_3N (1.5 mmol, 5.0 equiv.) was added. The mixture was warmed to room temperature and stirred for 10 min. The resulting activated imidazolidate formed and the corresponding NMP (0.5-0.7 equiv.) in 6 mL CH_3CN was added. The reaction was stirred at rt for 2-5 h and dried in vacuum. The crude product was purified by automatic RP18 flash chromatography, and then followed by ion-exchange to the ammonium form with Dowex 50WX8 cation-exchange resin and a second RP18 chromatography purification step. Product-containing fractions were collected and the organic solvent evaporated. The remaining aqueous solutions were freeze-dried and the desired product were obtained as white solids.

6.3 Experiment Data of the Compounds

4-(Hydroxymethyl)phenyl methyl carbonate 73k.

According to general procedure 2 with 4.1 g 4-hydroxybenzyl alcohol **56** (33 mmol, 1.1 equiv.) and 4.2 mL triethylamine (30 mmol, 1.0 equiv.) in 40 mL CH_2Cl_2 at 0 °C and dropwise addition of 2.32 mL methyl carbonochloridate (30 mmol, 1.0 equiv.) in 10 mL CH_2Cl_2. Reaction time was 12 h at room temperature. Column chromatography (petroleum ether/ethyl acetate 7:3 v/v).

Yield: 4.91 g (27 mmol, 90%) colourless oil.



Chemical Formula: $C_9H_{10}O_4$.

Molecular weight: 182.06 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 205.0471; found 205.0347.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.33-7.28 (m, 2H, H-c), 7.14-7.09 (m, 2H, H-d), 4.58 (s, 2H, H-a), 3.87 (s, 3H, H-g).

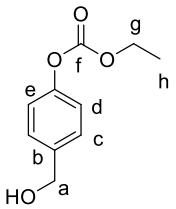
^{13}C-NMR (400 MHz, $CDCl_3$): δ [ppm] = 154.3 (C-f), 150.4 (C-e), 138.7 (C-b), 128.0 (C-c),121.1 (C-d), 64.5 (C-a), 55.4 (C-g).

IR: ν [cm^{-1}] = 3361, 2959, 2874, 1757, 1596, 1508, 1439, 1254, 1210, 1167, 1103, 1059, 1013, 947, 930, 848, 821, 778, 724, 697, 634, 605, 506.

Ethyl (4-(hydroxymethyl)phenyl) carbonate 73l.

According to general procedure 2 with 4.1 g 4-hydroxybenzyl alcohol **56** (33 mmol, 1.1 equiv.) and 4.2 mL triethylamine (30 mmol, 1.0 equiv.) in 40 mL CH_2Cl_2 at 0 °C and dropwise addition of 2.3 mL methyl carbonochloridate (30 mmol, 1.0 equiv.) in 10 mL CH_2Cl_2. Reaction time was 12 h at room temperature. Column chromatography (petroleum ether/ethyl acetate 7:3 v/v).

Yield: 4.43 g (25 mmol, 75%) colourless oil.



Chemical Formula: $C_{10}H_{12}O_4$.

Molecular weight: 196.07 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 219.0628; found 219.0553.

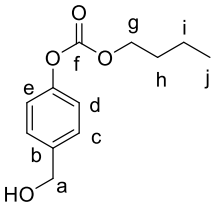
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.37-7.32 (m, 2H, H-c), 7.17-7.12 (m, 2H, H-d), 4.63 (s, 2H, H-a), 4.30 (q, $^3J_{HH}$= 7.10 Hz, 2H, H-g), 2.14 (s, 1H, OH), 0.88 (t, $^3J_{HH}$= 7.09 Hz, 3H, H-h).

^{13}C-NMR (400 MHz, $CDCl_3$): δ [ppm] = 153.6 (C-f), 150.3 (C-e), 138.7 (C-b), 127.9 (C-c), 121.0 (C-d), 64.8 (C-g), 64.3 (C-a), 14.1 (C-h).

IR: ν [cm^{-1}] = 3375, 2986, 2938, 2876, 1755, 1607, 1508, 1466, 1394, 1369, 1246, 1206, 1096, 1055, 1013, 996, 899, 822, 778, 735, 634, 593, 507, 459.

Butyl (4-(hydroxymethyl)phenyl) carbonate 73m.

According to general procedure 2 with 4.7 g 4-hydroxybenzyl alcohol **56** (36 mmol, 1.0 equiv.) and 5.0 mL triethylamine (36 mmol, 1.0 equiv.) in 40 mL CH_2Cl_2 at 0 °C and dropwise addition of 4.6 mL methyl carbonochloridate (36 mmol, 1.0 equiv.) in 10 mL CH_2Cl_2. Reaction time was 12 h at room temperature. Column chromatography (petroleum ether/ethyl acetate 7:3 v/v).



Yield: 5.83 g (26 mmol, 72%) colourless oil.

Chemical Formula: $C_{12}H_{16}O_4$.

Molecular weight: 224.26 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 247.0941; found 247.0901.

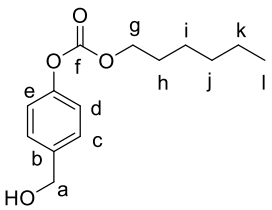
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.36-7.32 (m, 2H, H-c), 7.16-7.12 (m, 2H, H-d), 4.63 (s, 2H, H-a), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g), 2.05 (s, 1H, OH), 1.76-1.68 (m, 2H, H-h), 1.50-1.40 (m, 2H, H-i), 0.97 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.7 (C-f), 150.3 (C-e), 138.7 (C-b), 127.9 (C-c), 121.0 (C-d), 68.6 (C-g), 64.8 (C-a), 30.4 (C-h), 18.8 (C-i), 13.5 (C-j).

IR: v [cm^{-1}] = 3380, 2961, 2934, 2874, 1756, 1607, 1508, 1460, 1391, 1247, 1207, 1118, 1103, 960, 924, 868, 820, 778, 740, 602, 507, 435.

Hexyl (4-(hydroxymethyl)phenyl) carbonate 73r.

According to general procedure 2 with 1.48 g triphosgene (5.0 mmol, 1.0 equiv.), 1.38 g Potassium carbonate (10.0 mmol, 2.0 equiv.), 0.29 mL DMF (3.6 mmol, 0.72 equiv.) in 10 mL toluene at 0 °C and dropwise addition of 1.02 g 1-hexanol (10.0 mmol, 2.0 equiv) in 10 mL toluene. Yield: 1.24 g (8.3 mmol, 83%) colorless oil. b) 1.13 g 4-Hydroxybenzyl alcohol **56** (9.1 mmol, 1.1 equiv.) and 1.15 mL TEA (8.3 mmol 1.0 equiv.) in 10 mL CH_2Cl_2 were cooled to 0 °C followed by a dropwise addition of hexyl chloroformate (8.3 mmol, 1.0 equiv.) in 10 mL CH_2Cl_2. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v).



Yield: 1.60 g (6.4 mmol, 77%) white solid.

Chemical Formula: $C_{14}H_{20}O_4$.

Molecular weight: 252.31 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 275.1254; found 275.1234.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.34-7.29 (m, 2H, H-c), 7.15-7.10 (m, 2H, H-d), 4.59 (s, 2H, H-a), 4.23 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g), 2.55 (s, 1H, OH), 1.73 (quint, $^3J_{HH}$= 6.8 Hz, 2H, H-h), 1.46-1.37 (m, 2H, H-i), 1.36-1.20 (m, 4H, H-j, H-k), 0.90 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-l).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.8 (C-f), 150.3 (C-e), 138.6 (C-b), 127.9 (C-c), 121.0 (C-d), 69.0 (C-g), 64.3 (C-a), 28.4 (C-h), 25.2 (C-i), 31.2, 22.4 (C-j, C-k), 13.9 (C-l).

IR: v [cm^{-1}] = 3387, 2957, 2929, 2871, 2157, 1757, 1607, 1508, 1466, 1392, 1247, 1209, 1046, 1014, 920, 848, 779, 603, 504.

4-(Hydroxymethyl)phenyl nonyl carbonate 73s.

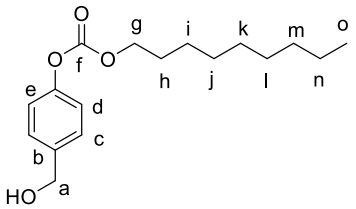
According to general procedure 2 with 2.97 g triphosgene (10.0 mmol, 1.0 equiv), 2.76 g Potassium carbonate (20.0 mmol, 2.0 equiv), 0.58 mL DMF (7.2 mmol, 0.72 equiv) in 20 mL toluene at 0 °C and dropwise addition of 3.5 mL 1-nonanol (20.0 mmol, 2.0 equiv) in 20 mL toluene. Yield: 1.10 g (5.3 mmol, 27%) colorless oil. b) 0.73 g 4-Hydroxybenzyl alcohol **56** (5.9 mmol, 1.1 equiv.) and 0.74 mL TEA (5.3 mmol 1.0 equiv.) in 10 mL CH_2Cl_2 were cooled to 0 °C followed by a dropwise addition of nonyl chloroformate (5.3 mmol, 1.0 equiv.) in 10 mL CH_2Cl_2. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v).

Yield: 1.10 g (10.5 mmol, 70%) white solid.

Chemical Formula: $C_{17}H_{26}O_4$.

Molecular weight: 294.39 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 317.1723; found 317.1701.



^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.31-7.27 (m, 2H, H-c), 7.13-7.08 (m, 2H, H-d), 4.54 (s, 2H, H-a), 4.21 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g), 2.85(s, 1H, OH), 1.72 (quint, $^3J_{HH}$= 7.4 Hz, 2H, H-h), 1.45-1.37 (m, 2H, H-i), 1.36-1.20 (m, 10H, H-j, H-k, H-l, H-m, H-n), 0.88 (t, $^3J_{HH}$= 6.90 Hz, 3H, H-o).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 153.8 (C-f), 150.3 (C-e), 138.7 (C-b), 127.9 (C-c), 121.0 (C-d), 69.0 (C-g), 64.3 (C-a), 28.5 (C-h), 25.6 (C-i), 31.7, 29.3, 29.1, 22.6 (C-j, C-k, C-l, C-m, C-n), 14.0 (C-o).

IR: v [cm^{-1}] = 3311, 2954, 2922, 2855, 2778, 1750, 1508, 1469, 1456, 1420, 1239, 1211, 1036, 1012, 955, 820, 782, 746, 722, 519, 496, 463.

Decyl (4-(hydroxymethyl)phenyl) carbonate 73t.

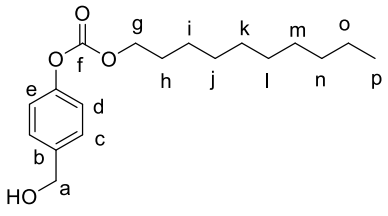
According to general procedure 2 with 4.45 g triphosgene (15.0 mmol, 1.0 equiv.), 4.15 g Potassium carbonate (30.0 mmol, 2.0 equiv.), 0.87 mL DMF (10.8 mmol, 0.72 equiv.) in 45 mL toluene at 0 °C and dropwise addition of 5.73 mL decyl alcohol (30.0 mmol, 2.0 equiv) in 15 mL toluene. Yield: 4.27 g (19.5 mmol, 65%) colorless oil. b) 2.60 g 4-Hydroxybenzyl alcohol **56** (21.5 mmol, 1.1 equiv.) and 2.72 mL TEA (19.5 mmol 1.0 equiv.) in 20 mL CH_2Cl_2 were cooled to 0 °C followed by a dropwise addition of decyl chloroformate (19.5 mmol, 1.0 equiv.) in 20 mL CH_2Cl_2. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v).

Yield: 4.89 g (6.4 mmol, 81.5%) yellow solid.

Chemical Formula: $C_{18}H_{28}O_4$.

Molecular weight: 308.42 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 331.1880; found 331.1872.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.37-7.32 (m, 2H, H-c), 7.17-7.12 (m, 2H, H-d), 4.64 (s, 2H, H-a), 4.23 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g), 2.13 (s, 1H, OH), 1.74 (quint, $^3J_{HH}$= 7.3 Hz, 2H, H-h), 1.46-1.37 (m, 2H, H-i), 1.36-1.20 (m, 12H, H-j, H-k, H-l, H-m, H-n, H-o), 0.88 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-p).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.8 (C-f), 150.4 (C-e), 138.6 (d, $^4J_{CP}$= 1.4 Hz, C-b), 128.0 (C-c), 121.1 (C-d), 69.0 (C-g), 64.5 (C-a), 28.5 (C-h), 25.6 (C-i), 31.8, 29.45, 29.42, 29.2, 29.1, 22.6 (C-j, C-k, C-l, C-m, C-n, C-o), 14.1 (C-p).

IR: ν [cm^{-1}] = 3290, 2955, 2918, 2850, 1750, 1608, 1505, 1468, 1417, 1398, 1366, 1250, 1212, 956, 887, 821, 777, 721, 519, 493, 427.

4-(Hydroxymethyl)phenyl undecyl carbonate 73u.

According to general procedure 2 with 5.10 g triphosgene (17.1 mmol, 1.0 equiv), 4.56 g Potassium carbonate (34.2 mmol, 2.0 equiv), 0.96 mL DMF (12.3 mmol, 0.72 equiv) in 30 mL toluene at 0 °C and dropwise addition of 5.89 g undecan-1-ol (34.2 mmol, 2.0 equiv) in 30 mL toluene. Yield: 6.60 g (28.1 mmol, 85%) colorless oil. b) 4-Hydroxybenzyl alcohol **56** (30.9 mmol, 1.1 equiv.) and TEA (28.1 mmol 1.0 equiv.) in 30 mL CH_2Cl_2 were cooled to 0 °C. Dropwise addition of undecyl chloroformate (28.1 mmol, 1.0 equiv.) in 30 mL CH_2Cl_2. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v).

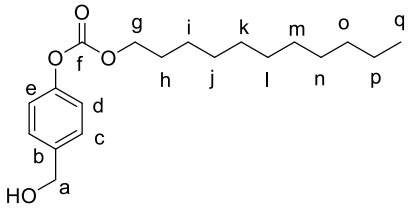
Yield: 4.80 g (13.8 mmol, 49%) white solid.

Chemical Formula: $C_{19}H_{30}O_4$.

Molecular weight: 322.44 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 345.2036; found 345.1980.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.35 (m, 2H, H-c), 7.18-7.14 (m, 2H, H-d), 4.67 (s, 2H, H-a), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g), 1.88 (s, 1H, OH), 1.73 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h), 1.46-1.37 (m, 2H, H-i), 1.36-1.23 (m, 14H, H-j, H-k, H-l, H-m, H-n, H-o, H-p), 0.88 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-q).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.8 (C-f), 150.4 (C-e), 138.6 (C-b), 128.0 (C-c), 121.1 (C-d), 69.0 (C-g), 64.5 (C-a), 28.5 (C-h), 25.6 (C-i), 31.9, 29.55, 29.51, 29.44, 29.3, 29.2, 22.6 (C-j, C-k, C-l, C-m, C-n, C-o, C-p), 14.1 (C-q).

IR: v [cm^{-1}] = 3274, 2955, 2916, 2848, 1750, 1506, 1464, 1397, 1255, 1214, 1041, 1013, 955, 820, 776, 720, 521, 472.

Dodecyl (4-(hydroxymethyl)phenyl) carbonate 73v.

According to general procedure 2 with 4.1 g 4-hydroxybenzyl alcohol **56** (33 mmol, 1.1 equiv.) and 4.2 mL triethylamine (30 mmol, 1.0 equiv.) in 40 mL CH_2Cl_2 at 0 °C and dropwise addition of 7.46g dodecyl carbonochloridate (30 mmol, 1.0 equiv.) in 10 mL CH_2Cl_2. Reaction time was 12 h at room temperature. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v).

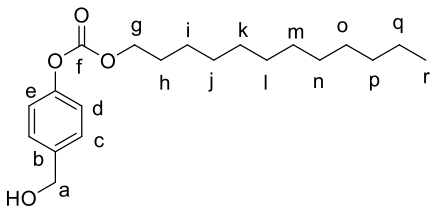
Yield: 6.34 g (24.3 mmol, 81%) white solid.

Chemical Formula: $C_{20}H_{32}O_4$.

Molecular weight: 336.47 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 359.2193; found 359.2159.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.40-7.35 (m, 2H, H-c), 7.18-7.14 (m, 2H, H-d), 4.67 (s, 2H, H-a), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g), 1.77-1.70 (m, 3H, H-h, OH), 1.46-1.37 (m, 2H, H-i), 1.36-1.20 (m, 16H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.88 (t, $^3J_{HH}$= 6.80 Hz, 3H, H-r).

^{13}C-NMR (400 MHz, $CDCl_3$): δ [ppm] = 153.7 (C-f), 150.4 (C-e), 138.6 (C-b), 127.9 (C-c), 121.0 (C-d), 68.9 (C-g), 64.4 (C-a), 28.5 (C-h), 25.6 (C-i), 31.8, 29.55, 29.54, 29.47, 29.40, 29.2, 29.1, 22.6 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 14.0 (C-r).

IR: ν [cm^{-1}] =3311, 2954, 2920, 2894, 2853, 2772, 1750, 1607, 1505, 1467, 1455, 1398, 1373, 1291, 1265, 1209, 1102, 1068, 1052, 980, 956, 842, 798, 764, 732, 695, 602, 521, 501, 474

4-(Hydroxymethyl)phenyl tetradecyl carbonate 73w.

According to general procedure 2 with 4.45 g triphosgene (15.0 mmol, 1.0 equiv), 4.15 g Potassium carbonate (30.0 mmol, 2.0 equiv), 0.87 mL DMF (10.8 mmol, 0.72 equiv) in 30 mL toluene at 0 °C and dropwise addition of 6.43 g 1-tetradecanol (30.0 mmol, 2.0 equiv.) in 30 mL toluene. Yield: 4.50 g (16.3 mmol, 54%) colorless oil. b) 2.17 g 4-Hydroxybenzyl alcohol **56** (17.9 mmol, 1.1 equiv.) and 2.3 mL TEA (16.3 mmol 1.0 equiv.) in 20 mL CH_2Cl_2 were cooled to 0 °C. Dropwise addition of tetradecyl chloroformate (16.3 mmol, 1.0 equiv.) in 20 mL CH_2Cl_2. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v).

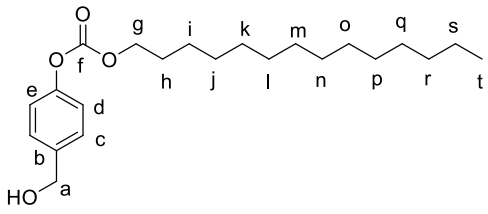
Yield: 5.30 g (14.5 mmol, 89%) white solid.

Chemical Formula: $C_{22}H_{36}O_4$.

Molecular weight: 364.53 g/mol.

HRMS (ESI^+, m/z):

$[M+Na]^+$ 387.2506; found 387.2398.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.37-7.32 (m, 2H, H-c), 7.18-7.12 (m, 2H, H-d), 4.65 (s, 2H, H-a), 4.23 (t, $^3J_{HH}$= 6.8 Hz, 2H, H-g), 2.02 (s, 1H, OH), 1.73 (quint, $^3J_{HH}$= 6.8 Hz, 2H, H-h), 1.46-1.37 (m, 2H, H-i), 1.36-1.20 (m, 20H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s), 0.88 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-t).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.8 (C-f), 150.4 (C-e), 138.6 (C-b), 128.0 (C-c), 121.1 (C-d), 69.0 (C-g), 64.6 (C-a), 28.5 (C-h), 25.6 (C-i), 31.9, 29.65, 29.62, 29.60, 29.5, 29.4, 29.3, 29.2, 22.6 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s), 14.1 (C-t).

IR: ν [cm^{-1}] = 3281, 2955, 2916, 2848, 1749, 1608, 1506, 1465, 1418, 1357, 1341, 1256, 1214, 1107, 1013, 983, 956, 846, 822, 779, 747, 630, 503, 482, 450.

4-(Hydroxymethyl)phenyl pentadecyl carbonate 73x.

According to general procedure 2 with 1.61 g triphosgene (5.4 mmol, 1.0 equiv.), 1.49 g Potassium carbonate (10.8 mmol, 2.0 equiv.), 0.31 mL DMF (3.9 mmol, 0.72 equiv.) in 15 mL toluene at 0 °C and dropwise addition of 2.48 g 1-pentadecanol (10.8 mmol, 2.0 equiv) in 15 mL toluene. Yield: 2.21 g (8.2 mmol, 76%) colorless oil. b) 1.12 g 4-Hydroxybenzyl alcohol **56** (9.0 mmol, 1.1 equiv.) and 1.18 mL TEA (8.2 mmol 1.0 equiv.) in 10 mL CH_2Cl_2 were cooled to 0 °C. Dropwise addition of pentadecyl chloroformate (8.2 mmol, 1.0 equiv.) in 10 mL CH_2Cl_2. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v).

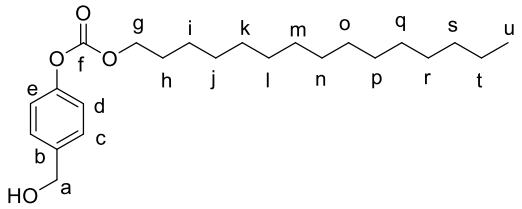
Yield: 2.54 g (6.7 mmol, 82%) white solid.

Chemical Formula: $C_{23}H_{38}O_4$.

Molecular weight: 378.55 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 401.2662; found 401.2557.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.38-7.32 (m, 2H, H-c), 7.18-7.12 (m, 2H, H-d), 4.65 (s, 2H, H-a), 4.23 (t, $^3J_{HH}$= 6.8 Hz, 2H, H-g), 1.98(s, 1H, OH), 1.74 (quint, $^3J_{HH}$= 7.3 Hz, 2H, H-h), 1.46-1.37 (m, 2H, H-i), 1.36-1.20 (m, 22H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t), 0.88 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-u).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.8 (C-f), 150.4 (C-e), 138.6 (C-b), 128.0 (C-c), 121.1 (C-d), 69.0 (C-g), 64.6 (C-a), 31.9, 29.65, 29.64, 29.62, 29.60, 29.5, 29.4, 29.3, 29.2, 22.6 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t), 28.5 (C-h), 25.6 (C-i), 14.1 (C-u).

IR: ν [cm^{-1}] = 3265, 2955, 2916, 2870, 2848, 1750, 1505, 1471, 1414, 1302, 1214, 1199, 1043, 1013, 975, 847, 776, 743, 505, 484, 464.

Hexadecyl (4-(hydroxymethyl)phenyl) carbonate 73y.

According to general procedure 2 with 2.97 g triphosgene (10 mmol, 1.0 equiv), 2.76 g Potassium carbonate (20 mmol, 2.0 equiv), 0.58 mL DMF (7.2 mmol, 0.72 equiv) in 30 mL toluene at 0 °C and dropwise addition of 4.85 g 1-octadecanol (20 mmol, 2.0 equiv) in 20 mL toluene. Yield: 4.5 g (14.8 mmol, 74%) colorless oil. b) 1.84 g 4-Hydroxybenzyl alcohol **56** (14.9 mmol, 1.1 equiv.) and 1.88 mL TEA (13.5 mmol 1.0 equiv.) in 30 mL CH_2Cl_2 were cooled to 0 °C. Dropwise addition of hexadecyl

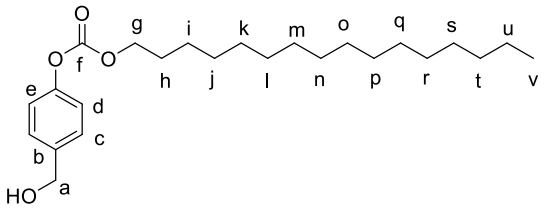
chloroformate (13.5 mmol, 1.0 equiv.) in 20 mL CH_2Cl_2. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v).

Yield: 3.60 g (9.2 mmol, 68%) white solid.

Chemical Formula: $C_{24}H_{40}O_4$.

Molecular weight: 392.58 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 415.2819; found 415.2831.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.37-7.32 (m, 2H, H-c), 7.17-7.12 (m, 2H, H-d), 4.63 (s, 2H, H-a), 4.23 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g), 2.22(s, 1H, OH), 1.73 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h), 1.46-1.37 (m, 2H, H-i), 1.36-1.20 (m, 24H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.88 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-v).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.8 (C-f), 150.4 (C-e), 138.6 (C-b), 128.0 (C-c), 121.1 (C-d), 69.0 (C-g), 64.4 (d, $^4J_{CP}$= 1.5 Hz, C-a), 31.9, 29.65, 29.62, 29.61, 29.59, 29.51, 29.49, 29.44, 29.3, 29.2, 22.6 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 28.5 (C-h), 25.6 (C-i), 14.1 (C-v).

IR: ν [cm^{-1}] = 3290, 2955, 2916, 2848, 1750, 1608, 1505, 1464, 1418, 1397, 1367, 1322, 1282, 1252, 1214, 1110, 1012, 980, 887, 846, 821, 778, 719, 630, 523, 505, 484.

4-(Hydroxymethyl)phenyl octadecyl carbonate 73z.

According to general procedure 2, with 2.97 g triphosgene (10 mmol, 1.0 equiv), 2.76 g Potassium carbonate (20 mmol, 2.0 equiv), 0.58 mL DMF (7.2mmol, 0.72 equiv) in 20 mL toluene at 0 °C and dropwise addition of 5.41 g 1-octadecanol (20 mmol, 2.0 equiv) in 20 mL toluene. Yield: 5.80 g (28 mmol, 75%) colorless oil. b) 2.23 g 4-hydroxybenzyl alcohol **56** (18 mmol, 1.2 equiv.) and 2.1 mL TEA (15 mmol 1.0 equiv.) in 30 mL CH_2Cl_2 were cooled to 0 °C. Dropwise addition of octadecyl chloroformate (15 mmol, 1.0 equiv.) in 20 mL CH_2Cl_2. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v).

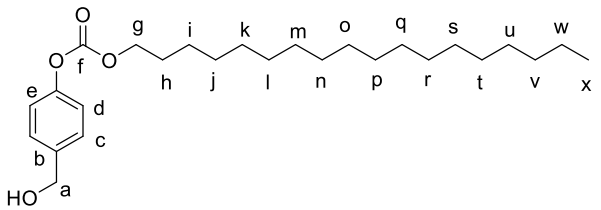
Yield: 4.00 g (10.5 mmol, 70%) white solid.

Chemical Formula: $C_{26}H_{44}O_4$.

Molecular weight: 420.63 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 443.3132; found 443.3102.



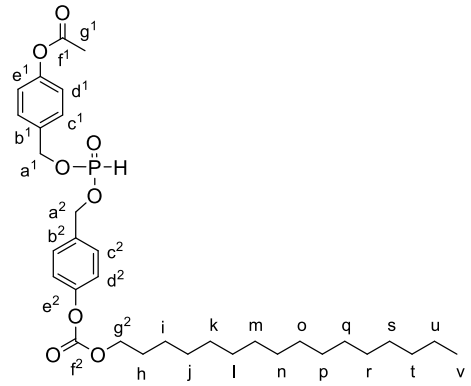
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.33 (m, 2H, H-c), 7.18-7.13 (m, 2H, H-d), 4.66 (s, 2H, H-a), 4.24 (t, $^{3}J_{HH}$= 6.8 Hz, 2H, H-g), 1.93 (s, 1H, OH), 1.74 (quint, $^{3}J_{HH}$= 6.9 Hz, 2H, H-h), 1.46-1.37 (m, 2H, H-i), 1.36-1.20 (m, 28H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u, H-v, H-w), 0.88 (t, $^{3}J_{HH}$= 6.8 Hz, 3H, H-x).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.8 (C-f), 150.5 (C-e), 138.6 (C-b), 128.0 (C-c), 121.1 (C-d), 69.0 (C-g), 64.6 (d, $^{4}J_{CP}$= 1.5 Hz, C-a), 31.9, 29.66, 29.63, 29.62, 29.60, 29.5, 29.4, 29.3, 29.2, 22.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u, C-v, C-w), 28.5 (C-h), 25.6 (C-i), 14.1 (C-x).

IR: v [cm^{-1}] = 3272, 2955, 2915, 2848, 1750, 1608, 1505, 1463, 1415, 1371, 1302, 1288, 1255, 1214, 1114, 1086, 1057, 1043, 972, 955, 889, 847, 821, 779, 719, 630, 606, 524, 508, 489, 434.

(AB-C1; ACB-C16)-*H*-phosphonate 77ay.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.27 g 4-(hydroxymethyl)phenyl acetate **52a** (1.65 mmol, 1.05 equiv.) was added and following with 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **73y** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.43 g (0.71 mmol, 45%) white solid.

Chemical Formula: $C_{33}H_{49}O_8P$.

Molecular weight: 604.72 g/mol.

HRMS (ESI^{+}, m/z):

$[M+Na]^{+}$ 627.3057; found 627.3078.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.34 (m, 4H, H-c^1, H-c^2), 7.21-7.16 (m, 2H, H-d^2), 7.11-7.06 (m, 2H, H-d^1), 6.93 (d, $^{1}J_{HP}$= 709.7 Hz, 1H, P-H), 5.10-4.96 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^{3}J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.30 (s, 3H, H-g^1), 1.74 (quint, $^{3}J_{HH}$= 7.3 Hz, 2H, H-h), 1.45-1.37 (m, 2H, H-i), 1.35-1.20 (m, 24H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.88 (t, $^{3}J_{HH}$= 6.8 Hz, 3H, H-v).

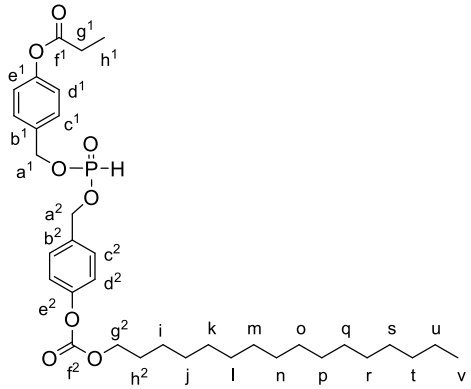
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 169.2(C-f^1), 153.5 (C-f^2), 151.3 (C-e^2), 150.8 (C-e^1), 133.2, 133.1 (2 × d, $^{3}J_{CP}$= 5.8 Hz, $^{3}J_{CP}$= 6.6 Hz, C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.9 (C-d^1), 121.4 (C-d^2), 69.1 (C-g^2), 66.6, 66.5 (2 × d, $^{3}J_{CP}$= 5.1 Hz, $^{3}J_{CP}$= 5.8 Hz, C-a^1, C-a^2), 28.5 (C-h), 25.6 (C-i), 31.9, 29.64, 29.61, 29.59, 29.51, 29.4, 29.3, 29.2, 22.6 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 21.1 (C-g^1), 14.1 (C-v).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.74.

IR: ν [cm^{-1}] = 2955, 2915, 2849, 1752, 1606, 1508, 1465, 1367, 1322, 1284, 1229, 1061, 961, 915, 853, 803, 748, 652, 525, 505, 472, 423.

(AB-C2; ACB-C16)-*H*-phosphonate 77by.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **52b** (1.65 mmol, 1.05 equiv.) was added and following with 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **73y** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.39 g (0.63 mmol, 40%) white solid.

Chemical Formula: $C_{34}H_{51}O_8P$.

Molecular weight: 618.75 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 641.3214; found 641.3149.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.37-7.31 (m, 4H, H-c^1, H-c^2), 7.18-7.13 (m, 2H, H-d^2), 7.09-7.04 (m, 2H, H-d^1), 6.91 (d, $^1J_{HP}$= 709.6 Hz, 1H, P-H), 5.10-4.95 (m, 4H, H-a^1, H-a^2), 4.22 (t, $^3J_{HH}$= 6.8 Hz, 2H, H-g^2), 2.56 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.74 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.44-1.36 (m, 2H, H-i), 1.35-1.20 (m, 27H, H-h^1, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.86 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-v).

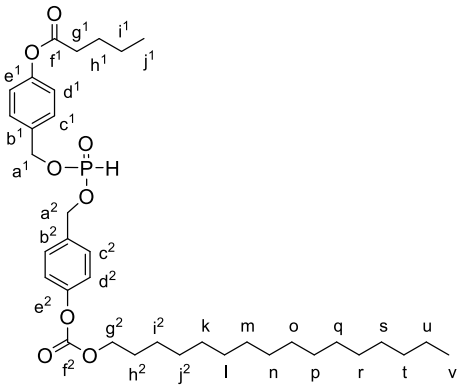
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.5 (C-f^1), 153.3 (C-f^2), 151.1 (C-e^2), 150.8 (C-e^1), 133.1, 132.8 (2 × d, $^3J_{CP}$= 5.9 Hz, $^3J_{CP}$= 6.6 Hz, C-b^1, C-b^2), 129.1 (C-c^1, C-c^2), 121.7 (C-d^1), 121.2 (C-d^2), 68.9 (C-g^2), 66.5, 66.3 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 28.4 (C-h^2), 27.5 (C-g^1), 25.5 (C-i), 31.7, 29.51, 29.49, 29.48, 29.46, 29.38, 29.31, 29.2, 29.0, 22.5 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 13.9 (C-v), 8.8 (C-h^1).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.77.

IR: ν [cm^{-1}] = 2924, 2853, 1758, 1711, 1610, 1509, 1463, 1390, 1359, 1249, 1218, 1143, 958, 892, 780, 606, 504, 479, 451.

(AB-C4; ACB-C16)-*H*-phosphonate 77ey.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.34 g 4-(hydroxymethyl)phenyl pentanoate **52e** (1.65 mmol, 1.05 equiv.) was added and following with 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **73y** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.42 g (0.64 mmol, 41%) white solid.

Chemical Formula: $C_{36}H_{55}O_8P$.

Molecular weight: 646.80 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 669.3530; found 669.3506.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.38-7.32 (m, 4H, H-c^1, H-c^2), 7.20-7.15 (m, 2H, H-d^2), 7.10-7.04 (m, 2H, H-d^1), 6.93 (d, $^1J_{HP}$= 709.1 Hz, 1H, P-H), 5.10-4.95 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^3J_{HH}$= 6.70 Hz, 2H, H-g^2), 2.55 (t, $^3J_{HH}$= 7.60 Hz, 2H, H-g^1), 1.73 (quint, $^3J_{HH}$= 7.40 Hz, 4H, H-h^1, H-h^2), 1.49-1.37 (m, 4H, H-i^1, H-i^2), 1.35-1.20 (m, 24H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.96 (t, $^3J_{HH}$= 7.45 Hz, 3H, H-j^1), 0.87 (t, $^3J_{HH}$= 6.70 Hz, 3H, H-v).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.0 (C-f^1), 153.4 (C-f^2), 151.2 (C-e^2), 150.9 (C-e^1), 133.1, 132.8 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 5.9 Hz, C-b^1, C-b^2), 129.1 (C-c^1, C-c^2), 121.8 (C-d^1), 121.3 (C-d^2), 69.0 (C-g^2), 66.6, 66.4 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 33.9 (C-g^1), 31.8, 29.57, 29.54, 29.52, 29.44, 29.36, 29.2, 29.1, 22.6 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 28.5 (C-h^2), 26.8 (C-h^1), 25.6 (C-i^2), 22.1 (C-i^1), 14.0 (C-v), 13.6 (C-j^1).

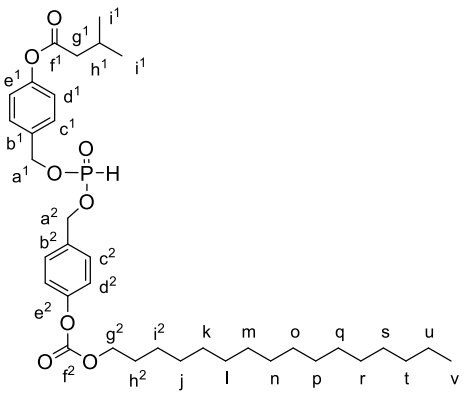
^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.74.

IR: ν [cm^{-1}] = 2956, 2915, 2872, 2849, 1753, 1607, 1509, 1465, 1382, 1285, 1218, 1168, 1056, 996, 961, 835, 786, 719, 506, 452.

(AB-C4; ACB-C16)-*H*-phosphonate 77fy.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.34 g 4-(hydroxymethyl)phenyl 3-methylbutanoate **52f** (1.65 mmol, 1.05 equiv.) was added and following with 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **73y** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

Yield: 0.42 g (0.64 mmol, 41%) white solid.



Chemical Formula: $C_{36}H_{55}O_8P$.

Molecular weight: 646.80 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 669.3530; found 669.3484.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.38-7.34 (m, 4H, H-c^1, H-c^2), 7.20-7.16 (m, 2H, H-d^2), 7.10-7.06 (m, 2H, H-d^1), 6.93 (d, $^1J_{HP}$= 708.4 Hz, 1H, P-H), 5.10-4.97 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^3J_{HH}$= 6.8 Hz, 2H, H-g^2), 2.43 (d, $^3J_{HH}$= 7.1 Hz, 2H, H-g^1), 2.24 (hept, $^3J_{HH}$= 6.8 Hz, 1H, H-h^1), 1.74 (quint, $^3J_{HH}$= 7.1 Hz, 2H, H-h^2), 1.45-1.37 (m, 2H, H-i^2), 1.36-1.20 (m, 24H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.05 (d, $^3J_{HH}$= 6.8 Hz, 6H, H-i^1), 0.88 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-v).

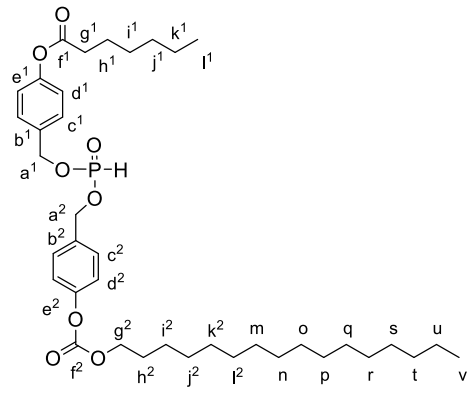
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 171.4 (C-f^1), 153.5 (C-f^2), 151.3 (C-e^2), 150.9 (C-e^1), 133.2, 132.9 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 6.4 Hz, C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 122.0 (C-d^1), 121.4 (C-d^2), 69.1 (C-g^2), 66.7, 66.5 (2 × d, $^3J_{CP}$= 5.1 Hz, $^3J_{CP}$= 5.2 Hz, C-a^1, C-a^2), 43.3 (C-g^1), 31.9, 29.66, 29.64, 29.61, 29.53, 29.46, 29.3, 29.2, 22.7, 22.6 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 28.5 (C-h^2), 25.8 (C-h^1), 25.7 (C-i^2), 22.4 (C-i^1), 14.1 (C-v).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 8.95.

IR: ν [cm^{-1}] = 2955, 2916, 2849, 1756, 1606, 1558, 1540, 1469, 1368, 1249, 1220, 1165, 997, 961, 890, 832, 782, 718, 527, 505, 452, 424.

(AB-C6; ACB-C16)-*H*-phosphonate 77gy.

According to general procedure 3b, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **73y** (1.57 mmol, 1.0 equiv.) was added and following with 0.39 g 4-(hydroxymethyl)phenyl heptanoate **52g** (1.65 mmol, 1.05 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 7:3:0.005 v/v/v).



Yield: 0.59 g (0.88 mmol, 56%) white solid.

Chemical Formula: $C_{38}H_{59}O_8P$.

Molecular weight: 674.86 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 697.3840; found 697.3855.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.34 (m, 4H, H-c^1, H-c^2), 7.20-7.16 (m, 2H, H-d^2), 7.10-7.06 (m, 2H, H-d^1), 6.94 (d, $^1J_{HP}$= 708.9 Hz, 1H, P-H), 5.10-4.97 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.55 (t, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.79-1.70 (m, 4H, H-h^1, H-h^2), 1.45-1.37 (m, 4H, H-i^1, H-i^2), 1.35-1.24 (m, 28H, H-j^1, H-j^2, H-k^1, H-k^2, H-l^2, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.94-0.85 (m, 6H, H-l^1, H-v).

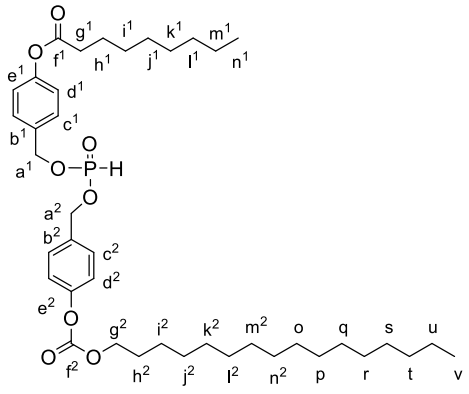
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.1 (C-f^1), 153.5 (C-f^2), 151.3 (C-e^2), 151.0 (C-e^1), 133.2, 132.9 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 6.4 Hz, C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.9 (C-d^1), 121.4 (C-d^2), 69.1 (C-g^2), 66.7, 66.5 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 34.4 (C-g^1), 31.9, 31.4, 29.66, 29.64, 29.61, 29.53, 29.46, 29.3, 29.2, 22.7, 22.4 (C-j^1, C-j^2, C-k^1, C-k^2, C-l^2, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 28.7 (C-i^1), 28.5 (C-h^2), 25.7 (C-i^2), 24.8 (C-h^1), 14.09, 13.98 (C-l^1, C-v).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.76.

IR: ν [cm^{-1}] = 2956, 2915, 2849, 1753, 1607, 1509, 1464, 1382, 1286, 1250, 1219, 1057, 961, 835, 747, 720, 608, 509, 448.

(AB-C8; ACB-C16)-*H*-phosphonate 77hy

According to general procedure 3b, with 0.30 mL DPP (1.57mmol, 1.0 equiv.) at 0 °C. 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **73y** (1.57 mmol, 1.0 equiv.) was added and following with 0.44 g 4-(hydroxymethyl)phenyl nonanoate **52h** (1.65 mmol, 1.05 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 7:3:0.005 v/v/v).



Yield: 0.70 g (1.0 mmol, 64%) white solid.

Chemical Formula: $C_{40}H_{63}O_8P$.

Molecular weight: 702.91 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 725.4153; found 725.4235.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.38-7.33 (m, 4H, H-c^1, H-c^2), 7.20-7.16 (m, 2H, H-d^2), 7.10-7.05 (m, 2H, H-d^1), 6.93 (d, $^1J_{HP}$= 709.4 Hz, 1H, P-H), 5.10-4.96 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^3J_{HH}$= 6.80 Hz, 2H, H-g^2), 2.55 (t, $^3J_{HH}$= 7.55 Hz, 2H, H-g^1), 1.79-1.69 (m, 4H, H-h^1, H-h^2), 1.45-1.37 (m, 4H, H-i^1, H-i^2),

1.36-1.20 (m, 32H, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-l^2, H-m^1, H-m^2, H-n^2, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.91-0.85 (m, 6H, H-n^1, H-v).

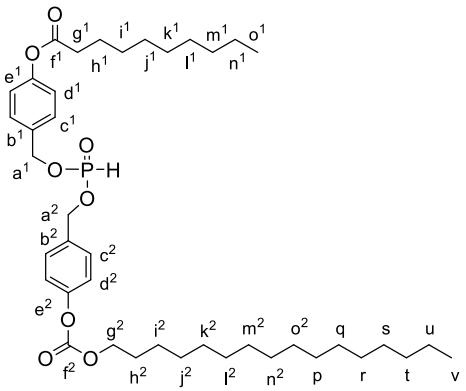
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.1 (C-f^1), 153.5 (C-f^2), 151.3 ($^4J_{CP}$= 1.5 Hz, C-e^2), 151.0 ($^4J_{CP}$= 1.5 Hz, C-e^1), 133.23, 133.17, 133.15, 132.95, 132.92, 132.87 (C-b^1, C-b^2), 129.22, 129.20 (C-c^1, C-c^2), 121.9 (C-d^1), 121.4 (C-d^2), 69.1 (C-g^2), 66.7, 66.5 (2 × dd, $^3J_{CP}$= 3.6 Hz, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 3.6 Hz, $^3J_{CP}$= 5.8 Hz, C-a^1, C-a^2), 34.3 (C-g^1), 31.9, 31.7, 29.63, 29.61, 29.60, 29.58, 29.50, 29.4, 29.3, 29.2, 29.06, 29.04, 22.64, 22.59 (C-i^1, C-j^1, C-j^2, C-k^1, C-k^2, C-l^1, C-l^2, C-m^1, C-m^2, C-n^2, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 28.5 (C-h^2), 25.6 (C-i^2), 24.9 (C-h^1), 14.06, 14.04 (C-n^1, C-v).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 8.98.

IR: ν [cm^{-1}] = 2955, 2916, 2849, 1753, 1607, 1509, 1466, 1381, 1250, 1220, 1167, 1057, 997, 878, 786, 748, 513, 479, 447, 423.

(AB-C9; ACB-C16)-*H*-phosphonate 77iy

According to general procedure 3b, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **73y** (1.57 mmol, 1.0 equiv.) was added and following with 0.46 g 4-(hydroxymethyl)phenyl decanoate **52i** (1.65 mmol, 1.05 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 7:3:0.005 v/v/v).



Yield: 0.73 g (1.02 mmol, 65%) white solid.

Chemical Formula: $C_{41}H_{65}O_8P$.

Molecular weight: 716.94 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 739.4309; found 739.3924.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.34 (m, 4H, H-c^1, H-c^2), 7.21-7.16 (m, 2H, H-d^2), 7.10-7.05 (m, 2H, H-d^1), 6.94 (d, $^1J_{HP}$= 709.4 Hz, 1H, P-H), 5.11-4.97 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.55 (t, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.79-1.70 (m, 4H, H-h^1, H-h^2), 1.45-1.37 (m, 4H, H-i^1, H-i^2), 1.36-1.20 (m, 34H, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-l^2, H-m^1, H-m^2, H-n^1, H-n^2, H-o^2, H-p, H-q, H-r, H-s, H-t, H-u), 0.91-0.85 (m, 6H, H-o^1, H-v).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.1 (C-f^1), 153.5 (C-f^2), 151.3 (C-e^2), 151.0 (C-e^1), 133.2, 132.9 (2 × dd, $^3J_{CP}$= 2.7 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 2.7 Hz, $^3J_{CP}$= 6.4 Hz, C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.9

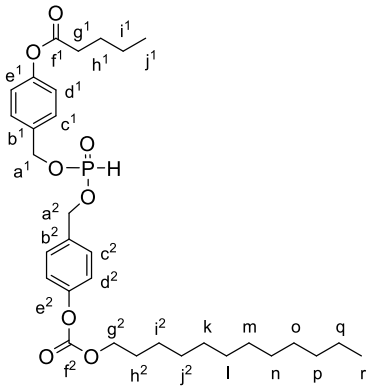
(C-d^1), 121.4 (C-d^2), 69.1 (C-g^2), 66.7, 66.6 (C-a^1, C-a^2), 34.4 (C-g^1), 31.9, 31.8, 29.66, 29.64, 29.61, 29.53, 29.46, 29.38, 29.33, 29.22, 29.19, 29.08, 22.66, 22.64 (C-i^1, C-j^1, C-j^2, C-k^1,C-k^2, C-l^1, C-l^2, C-m^1, C-m^2, C-n^1, C-n^2, C-o^2, C-p, C-q, C-r, C-s, C-t, C-u), 28.6 (C-h^2), 25.7 (C-i^2), 24.9 (C-h^1), 14.08, 14.07 (C-o^1, C-v).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 8.99.

IR: ν [cm^{-1}] = 2956, 2917, 2849, 1750, 1606, 1558, 1509, 1466, 1412, 1250, 1220, 1106, 1059, 997, 924, 786, 770, 720, 581, 540.

(AB-C4; ACB-C12)-*H*-phosphonate 77ev.

According to general procedure 3b, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **73v** (1.57 mmol, 1.0 equiv.) was added and following with 0.34 g 4-(hydroxymethyl)phenyl pentanoate **52e** (1.65 mmol, 1.05 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.45 g (0.77 mmol, 49%) white solid.

Chemical Formula: $C_{32}H_{47}O_8P$.

Molecular weight: 590.69 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 613.2901; found 613.2841.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.33 (m, 4H, H-c^1, H-c^2), 7.21-7.15 (m, 2H, H-d^2), 7.10-7.05 (m, 2H, H-d^1), 6.93 (d, $^1J_{HP}$= 708.8 Hz, 1H, P-H), 5.10-4.97 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.56 (t, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.74 (quint, $^3J_{HH}$= 7.5 Hz, 4H, H-h^1, H-h^2), 1.49-1.37 (m, 4H, H-i^1, H-i^2), 1.36-1.24 (m, 16H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.97 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.88 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-r).

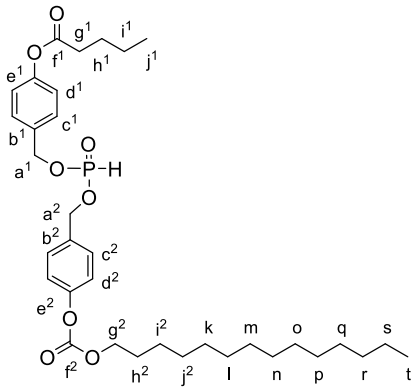
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.0 (C-f^1), 153.5 (C-f^2), 151.3 (C-e^2), 151.0 (C-e^1), 133.2, 132.9 (2 × d, $^3J_{CP}$= 6.4 Hz, $^3J_{CP}$= 6.4 Hz, C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.9 (C-d^1), 121.4 (d, $^4J_{CP}$= 1.8 Hz, C-d^2), 69.1 (C-g^2), 66.7, 66.5 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.6 Hz, C-a^1, C-a^2), 34.0 (C-g^1), 31.9, 29.57, 29.56, 29.49, 29.42, 29.3, 29.1, 22.6 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 28.5 (C-h^2), 26.9 (C-h^1), 25.6 (C-i^2), 22.2 (C-i^1), 14.1 (C-r), 13.7 (C-j^1).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 8.94.

IR: v [cm^{-1}] = 2956, 2917, 2871, 2850, 1752, 1607, 1509, 1466, 1416, 1382, 1251, 1218, 1154, 1104, 1060, 961, 896, 786, 774, 721, 609, 541, 468, 432.

(AB-C4; ACB-C14)-*H*-phosphonate 77ew.

According to general procedure 3b, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.57 g 4-(hydroxymethyl)phenyl tetradecyl carbonate **73w** (1.57 mmol, 1.0 equiv.) was added and following with 0.34 g 4-(hydroxymethyl)phenyl pentanoate **52e** (1.65 mmol, 1.05 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.43 g (0.69 mmol, 44%) white solid.

Chemical Formula: $C_{34}H_{51}O_8P$.

Molecular weight: 618.75 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 641.3214; found 641.3201.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.32 (m, 4H, H-c^1, H-c^2), 7.21-7.15 (m, 2H, H-d^2), 7.10-7.05 (m, 2H, H-d^1), 6.93 (d, $^1J_{HP}$= 708.8 Hz, 1H, P-H), 5.10-4.96 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^3J_{HH}$= 6.70 Hz, 2H, H-g^2), 2.56 (t, $^3J_{HH}$= 7.55 Hz, 2H, H-g^1), 1.74 (quint, $^3J_{HH}$= 7.50 Hz, 4H, H-h^1, H-h^2), 1.49-1.37 (m, 4H, H-i^1, H-i^2), 1.36-1.20 (m, 20H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s), 0.97 (t, $^3J_{HH}$= 7.40 Hz, 3H, H-j^1), 0.88 (t, $^3J_{HH}$= 6.80 Hz, 3H, H-t).

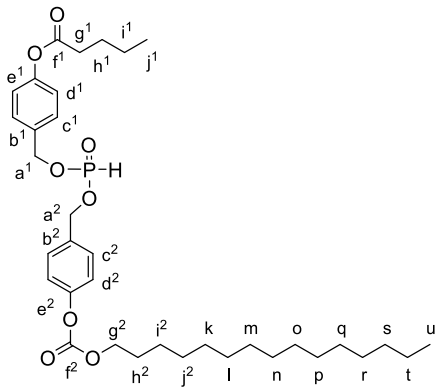
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.1 (C-f^1), 153.5 (C-f^2), 151.3 (C-e^2), 151.0 (C-e^1), 133.2, 132.9 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 5.9 Hz, C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.9 (C-d^1), 121.4 (C-d^2), 69.1 (C-g^2), 66.7, 66.5 (2 × d, $^3J_{CP}$= 5.1 Hz, $^3J_{CP}$= 5.9 Hz, C-a^1, C-a^2), 34.0 (C-g^1), 31.9, 29.63, 29.61, 29.59, 29.51, 29.4, 29.3, 29.2, 22.6 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s), 28.5 (C-h^2), 26.9 (C-h^1), 25.6 (C-i^2), 22.2 (C-i^1), 14.1 (C-t), 13.7 (C-j^1).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.73.

IR: v [cm^{-1}] = 2956, 2916, 2872, 2849, 1753, 1607, 1558, 1509, 1465, 1382, 1281, 1250, 1218, 1167, 1105, 1057, 996, 961, 835, 786, 748, 560, 509, 454.

(AB-C4; ACB-C15)-*H*-phosphonate 77ex.

According to general procedure 3b, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.59 g 4-(hydroxymethyl)phenyl pentadecyl carbonate **73x** (1.57 mmol, 1.0 equiv.) was added and following with 0.34 g 4-(hydroxymethyl)phenyl pentanoate **52e** (1.65 mmol, 1.05 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.37 g (0.58 mmol, 37%) white solid.

Chemical Formula: $C_{35}H_{53}O_8P$.

Molecular weight: 632.77 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 655.3370; found 655.3357.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.32 (m, 4H, H-c^1, H-c^2), 7.21-7.15 (m, 2H, H-d^2), 7.10-7.05 (m, 2H, H-d^1), 6.93 (d, $^1J_{HP}$= 708.7 Hz, 1H, P-H), 5.10-4.95 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^3J_{HH}$= 6.8 Hz, 2H, H-g^2), 2.56 (t, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.74 (quint, $^3J_{HH}$= 7.5 Hz, 4H, H-h^1, H-h^2), 1.50-1.39 (m, 4H, H-i^1, H-i^2), 1.36-1.20 (m, 22H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t), 0.97 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.88 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-u).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.1 (C-f^1), 153.5 (C-f^2), 151.3 (C-e^2), 151.0 (C-e^1), 133.2, 132.9 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 6.6 Hz, C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.9 (C-d^1), 121.4 (C-d^2), 69.1 (C-g^2), 66.7, 66.5 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 5.8 Hz, C-a^1, C-a^2), 34.0 (C-g^1), 31.9, 29.63, 29.62, 29.60, 29.58, 29.51, 29.4, 29.3, 29.2, 22.6 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t), 28.5 (C-h^2), 26.9 (C-h^1), 25.6 (C-i^2), 22.2 (C-i^1), 14.1 (C-u), 13.7 (C-j^1).

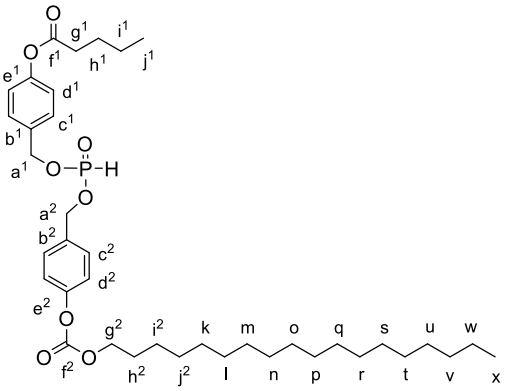
^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.73.

IR: ν [cm^{-1}] = 2955, 2915, 2871, 2849, 1753, 1607, 1509, 1465, 1382, 1251, 1218, 1155, 996, 895, 787, 719, 559, 451, 421.

(AB-C4; ACB-C18)-*H*-phosphonate 77ez

According to general procedure 3b, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.66 g 4-(hydroxymethyl)phenyl octadecyl carbonate **73z** (1.57 mmol, 1.0 equiv.) was added and following with 0.34 g 4-(hydroxymethyl)phenyl pentanoate **52e** (1.65 mmol, 1.05 equiv.). Column chromatography(SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

Yield: 0.25 g (0.69 mmol, 24%) white solid.



Chemical Formula: $C_{38}H_{59}O_8P$

Molecular weight: 674.86 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 697.3840; found 697.3795.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.32 (m, 4H, H-c^1, H-c^2), 7.21-7.16 (m, 2H, H-d^2), 7.10-7.05 (m, 2H, H-d^1), 6.93 (d, $^1J_{HP}$= 709.2 Hz, 1H, P-H), 5.10-4.96 (m, 4H, H-a^1, H-a^2), 4.26 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.55 (t, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.74 (quint, $^3J_{HH}$= 7.5 Hz, 4H, H-h^1, H-h^2), 1.50-1.37 (m, 4H, H-i^1, H-i^2), 1.36-1.20 (m, 28H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u, H-v, H-w), 0.97 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.88 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-x).

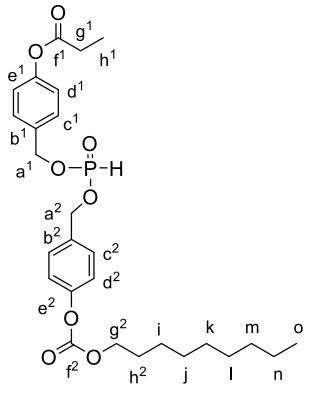
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.0 (C-f^1), 153.5 (C-f^2), 151.3 (C-e^2), 151.0 (C-e^1), 133.2, 132.9 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 6.5 Hz, C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.9 (C-d^1), 121.4 (C-d^2), 69.1 (C-g^2), 66.7, 66.5 (2 × d, $^3J_{CP}$= 5.1 Hz, $^3J_{CP}$= 5.8 Hz, C-a^1, C-a^2), 34.0 (C-g^1), 31.9, 29.64, 29.61, 29.58, 29.51, 29.4, 29.3, 29.2, 22.6 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u, C-v, C-w), 28.5 (C-h^2), 26.9 (C-h^1), 25.6 (C-i^2), 22.2 (C-i^1),14.1 (C-x), 13.7 (C-j^1).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.73.

IR: ν [cm^{-1}] = 2955, 2915, 2872, 2848, 1754, 1607, 1509, 1464, 1382, 1281, 1265, 1218, 1168, 1105, 997, 961, 896, 836, 784, 719, 634, 508, 456, 423.

(AB-C2; ACB-C9)-*H*-phosphonate 77bs

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **52b** (1.65 mmol, 1.05 equiv.) was added and following with 0.46 g 4-(hydroxymethyl)phenyl nonyl carbonate **73s** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.35 g (0.68 mmol, 43%) white solid.

Chemical Formula: $C_{27}H_{37}O_8P$.

Molecular weight: 520.56 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 543.2118; found 543.2095.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.35-7.29 (m, 4H, H-c^1, H-c^2), 7.17-7.13 (m, 2H, H-d^2), 7.07-7.03 (m, 2H, H-d^1), 6.89 (d, $^1J_{HP}$= 710.2 Hz, 1H, P-H), 5.05-4.94 (m, 4H, H-a^1, H-a^2), 4.21 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.55 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.70 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.42-1.35 (m, 2H, H-i), 1.34-1.20 (m, 10H, H-j, H-k, H-l, H-m, H-n), 1.22 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-h^1), 0.86 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-o).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 172.5 (C-f^1), 153.3 (C-f^2), 151.1 (C-e^2), 150.8 (C-e^1), 133.1, 132.7 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 6.4 Hz, C-b^1, C-b^2), 129.05, 129.04 (C-c^1, C-c^2), 121.7 (C-d^1), 121.2 (C-d^2), 68.9 (C-g^2), 66.5, 66.3 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 28.4 (C-h^2), 27.5 (C-g^1), 25.5 (C-i), 31.6, 29.2, 29.0, 22.4 (C-j, C-k, C-l, C-m, C-n), 13.9 (C-o), 8.8 (C-h^1).

^{31}P-NMR (202 MHz, $CDCl_3$): δ [ppm] = 7.82.

IR: ν [cm^{-1}] = 2925, 2855, 1757, 1608, 1509, 1462, 1421, 1380, 1250, 1216, 1204, 1166, 1139, 1056, 949, 892, 850, 817, 777, 723, 600, 503, 446, 424.

(AB-C2; ACB-C10)-*H*-phosphonate 77bt.

According to general procedure 3b, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **52b** (1.65 mmol, 1.05 equiv.) was added and following with 0.48 g decyl (4-(hydroxymethyl)phenyl) carbonate **73t** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

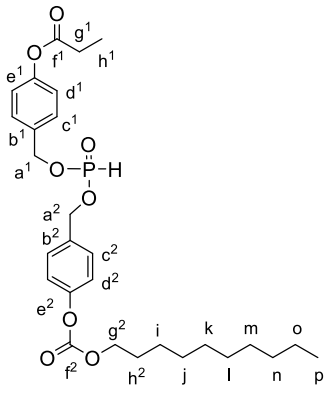
Yield: 0.40 g (0.74 mmol, 47%) white solid.

Chemical Formula: $C_{28}H_{39}O_8P$.

Molecular weight: 534.59 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 557.2275; found 557.2295.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.32 (m, 4H, H-c^1, H-c^2), 7.20-7.13 (m, 2H, H-d^2), 7.10-7.05 (m, 2H, H-d^1), 6.92 (d, $^1J_{HP}$= 709.2 Hz, 1H, P-H), 5.10-4.96 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.58 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.73 (quint, $^3J_{HH}$= 7.0 Hz, 2H, H-h^2), 1.45-1.37 (m, 2H, H-i), 1.36-1.22 (m, 15H, H-h^1, H-j, H-k, H-l, H-m, H-n, H-o), 0.88 (t, $^3J_{HH}$= 6.75 Hz, 3H, H-p).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.7 (C-f^1), 153.5 (C-f^2), 151.2 (C-e^2), 150.9 (C-e^1), 133.1, 132.8 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 5.8 Hz, C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.8 (C-d^1), 121.3 (C-d^2), 69.0 (C-g^2), 66.6, 66.5 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 5.8 Hz, C-a^1, C-a^2), 28.5 (C-h^2), 27.6 (C-g^1), 25.6 (C-i), 31.8, 29.41, 29.38, 29.2, 29.1, 22.6 (C-j, C-k, C-l, C-m, C-n, C-o), 14.0 (C-p), 8.9 (C-h^1).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.72.

IR: ν [cm^{-1}] = 2924, 2854, 1758, 1610, 1509, 1462, 1421, 1380, 1354, 1248, 1204, 1166, 1142, 1058, 958, 892, 821, 778, 722, 602, 503, 436.

(AB-C2; ACB-C11)-*H*-phosphonate 77bu.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **52b** (1.65 mmol, 1.05 equiv.) was added and following with 0.51 g 4-(hydroxymethyl)phenyl undecyl carbonate **73u** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

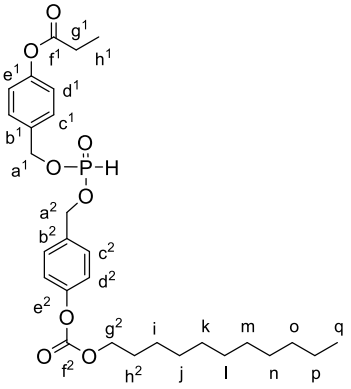
Yield: 0.37 g (0.68 mmol, 43%) white solid.

Chemical Formula: $C_{29}H_{41}O_8P$.

Molecular weight: 548.61 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 571.2431; found 571.2386.



^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.32-7.27 (m, 4H, H-c^1, H-c^2), 7.15-7.09 (m, 2H, H-d^2), 7.06-6.99 (m, 2H, H-d^1), 6.85 (d, $^1J_{HP}$= 709.5 Hz, 1H, P-H), 5.05-4.88 (m, 4H, H-a^1, H-a^2), 4.18 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.51 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.67 (quint, $^3J_{HH}$= 6.8 Hz, 2H, H-h^2), 1.38-1.32 (m, 2H, H-i), 1.31-1.15 (m, 14H, H-j, H-k, H-l, H-m, H-n, H-o, H-p), 1.18 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-h^1), 0.85 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-q).

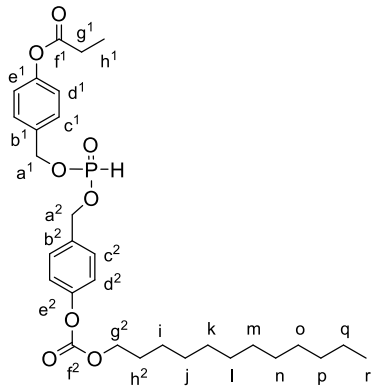
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 172.3 (C-f^1), 153.2 (C-f^2), 151.0 (C-e^2), 150.7 (C-e^1), 133.0, 132.7 (2 × d, $^3J_{CP}$= 6.4 Hz, $^3J_{CP}$= 6.4 Hz, C-b^1, C-b^2), 128.91, 128.89 (C-c^1, C-c^2), 121.6 (C-d^1), 121.0 (C-d^2), 68.7 (C-g^2), 66.3, 66.1 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 28.2 (C-h^2), 27.3 (C-g^1), 25.3 (C-i), 31.6, 29.25, 29.22, 29.1, 29.0, 28.9, 22.3 (C-j, C-k, C-l, C-m, C-n, C-o, C-p), 13.8 (C-q), 8.7 (C-h^1).

^{31}P-NMR (202 MHz, $CDCl_3$): δ [ppm] = 7.81.

IR: v [cm^{-1}] = 2954, 2918, 2850, 1755, 1607, 1509, 1462, 1421, 1388, 1357, 1250, 1218, 1167, 1103, 995, 961, 894, 827, 748, 721, 633, 608, 540, 509, 445, 423.

(AB-C2; ACB-C12)-*H*-phosphonate 77bv.

According to general procedure 3a, with 0.30 mL DPP (1.57mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **52b** (1.65 mmol, 1.05 equiv.) was added and following with 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **73v** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.37 g (0.66 mmol, 42%) white solid.

Chemical Formula: $C_{30}H_{43}O_8P$.

Molecular weight: 562.64 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 585.2588; found 585.2572.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.34-7.27 (m, 4H, H-c^1, H-c^2), 7.16-7.10 (m, 2H, H-d^2), 7.07-7.00 (m, 2H, H-d^1), 6.88 (d, $^1J_{HP}$= 710.1 Hz, 1H, P-H), 5.05-4.90 (m, 4H, H-a^1, H-a^2), 4.19 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.52 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.69 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.42-1.33 (m, 2H, H-i), 1.32-1.18 (m, 19H, H-h^1, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.85 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-r).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.4 (C-f^1), 153.2 (C-f^2), 151.1 (C-e^2), 150.8 (C-e^1), 133.0, 132.7 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 5.8 Hz, C-b^1, C-b^2), 129.0 (C-c^1, C-c^2), 121.6 (C-d^1), 121.1 (C-d^2), 68.8 (C-g^2), 66.4, 66.3 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 5.8 Hz, C-a^1, C-a^2), 28.3 (C-h^2), 27.4 (C-g^1), 25.4 (C-i), 31.6, 29.4, 29.28, 29.21, 29.1, 28.9, 22.4 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 13.8 (C-r), 8.7 (C-h^1).

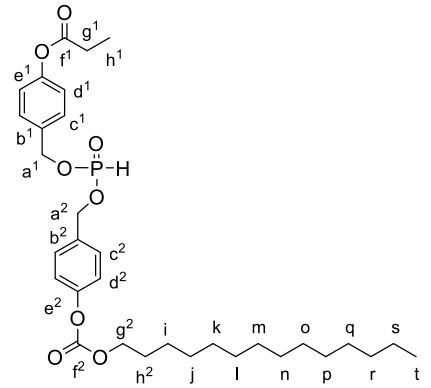
^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.81.

IR: v [cm^{-1}] = 2918, 2850, 1756, 1608, 1509, 1463, 1421, 1380, 1250, 1218, 1167, 1059, 994, 958, 893, 827, 806, 777, 721, 607, 520, 505, 466.

(AB-C2; ACB-C14)-*H*-phosphonate 77bw.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **52b** (1.65 mmol, 1.05 equiv.) was added and following with 0.57 g 4-

(hydroxymethyl)phenyl tetradecyl carbonate **73w** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.46 g (0.77 mmol, 49%) white solid.

Chemical Formula: $C_{32}H_{47}O_8P$.

Molecular weight: 590.69 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 613.2901; found 613.2845.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.33-7.27 (m, 4H, H-c^1, H-c^2), 7.16-7.09 (m, 2H, H-d^2), 7.06-7.00 (m, 2H, H-d^1), 6.86 (d, $^1J_{HP}$= 709.5 Hz, 1H, P-H), 5.05-4.90 (m, 4H, H-a^1, H-a^2), 4.19 (t, $^3J_{HH}$= 6.8 Hz, 2H, H-g^2), 2.52 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.69 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.44-1.33 (m, 2H, H-i), 1.35-1.20 (m, 23H, H-h^1, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s), 0.84 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-t).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.3 (C-f^1), 153.2 (C-f^2), 151.0 (C-e^2), 150.7 (C-e^1), 133.0, 132.7 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 5.8 Hz, C-b^1, C-b^2), 128.9 (C-c^1, C-c^2), 121.6 (C-d^1), 121.1 (C-d^2), 68.7 (C-g^2), 66.4, 66.2 (2 × d, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 5.8 Hz, C-a^1, C-a^2), 28.3 (C-h^2), 27.4 (C-g^1), 25.4 (C-i), 31.6, 29.39, 29.37, 29.36, 29.35, 29.26, 29.19, 29.06, 28.9, 22.4 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s), 13.8 (C-t), 8.7 (C-h^1).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.81.

IR: ν [cm^{-1}] = 2917, 2850, 1757, 1607, 1509, 1463, 1421, 1380, 1357, 1249, 1219, 1167, 1057, 960, 894, 825, 777, 747, 720, 609, 502, 452.

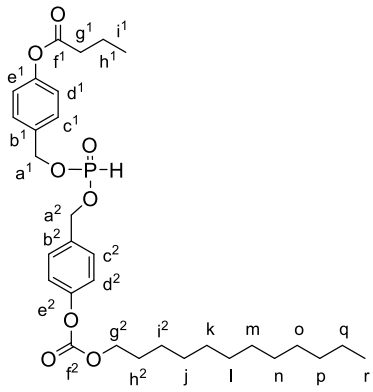
(AB-C3; ACB-C12)-*H*-phosphonate 77cv.

According to general procedure 3a, with 0.30 mL DPP (1.57mmol, 1.0 equiv.) at 0 °C. 0.32 g 4-(hydroxymethyl)phenyl butyrate **52c** (1.65 mmol, 1.05 equiv.) was added and following with 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **73v** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

Yield: 0.46 g (0.80 mmol, 51%) white solid.

Chemical Formula: $C_{31}H_{45}O_8P$.

Molecular weight: 576.67 g/mol.



HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 599.2744; found 599.2692.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.34-7.27 (m, 4H, H-c^1, H-c^2), 7.15-7.08 (m, 2H, H-d^2), 7.05-6.99 (m, 2H, H-d^1), 6.88 (d, $^1J_{HP}$= 710.0 Hz, 1H, P-H), 5.03-4.89 (m, 4H, H-a^1, H-a^2), 4.18 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.47 (q, $^3J_{HH}$= 7.3 Hz, 2H, H-g^1), 1.78-1.64 (m, 4H, H-h^1, H-h^2), 1.42-1.32 (m, 2H, H-i^2), 1.31-1.18 (m, 16H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.98 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-i^1), 0.84 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-r).

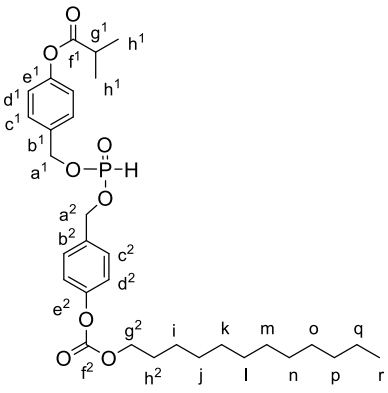
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 171.5 (C-f^1), 153.2 (C-f^2), 151.0 (C-e^2), 150.7 (C-e^1), 133.0, 132.7 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.5 Hz, C-b^1, C-b^2), 128.9 (C-c^1, C-c^2), 121.6 (C-d^1), 121.0 (C-d^2), 68.7 (C-g^2), 66.3, 66.2 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 35.8 (C-g^1), 28.3 (C-h^2), 25.4 (C-i^2), 31.6, 29.32, 29.31, 29.24, 29.17, 29.0, 28.9, 22.4 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 18.1 (C-h^1), 13.8 (C-r), 13.3 (C-i^1).

^{31}P-NMR (202 MHz, $CDCl_3$): δ [ppm] = 7.82.

IR: ν [cm^{-1}] = 2955, 2917, 2870, 2850, 1753, 1607, 1510, 1469, 1422, 1250, 1220, 1166, 1148, 1061, 996, 877, 837, 775, 719, 604, 556, 539, 503, 467, 450, 432.

(AB-C3; ACB-C12)-*H*-phosphonate 77dv.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.32 g 4-(hydroxymethyl)phenyl isobutyrate **52d** (1.65 mmol, 1.05 equiv.) was added and following with 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **73v** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.48 g (0.83 mmol, 53%) white solid.

Chemical Formula: $C_{31}H_{45}O_8P$.

Molecular weight: 576.67 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 599.2744; found 599.2742.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.34-7.27 (m, 4H, H-c^1, H-c^2), 7.16-7.11 (m, 2H, H-d^2), 7.08-7.00 (m, 2H, H-d^1), 6.88 (d, $^{1}J_{HP}$= 709.4 Hz, 1H, P-H), 5.04-4.93 (m, 4H, H-a^1, H-a^2), 4.20 (t, $^{3}J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.75 (hept, $^{3}J_{HH}$= 7.0 Hz, 2H, H-g^1), 1.69 (quint, $^{3}J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.42-1.34 (m, 2H, H-i), 1.33-1.20 (m, 16H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 1.27 (d, $^{3}J_{HH}$= 7.2 Hz, 6H, H-h^1), 0.85 (t, $^{3}J_{HH}$= 7.0 Hz, 3H, H-r).

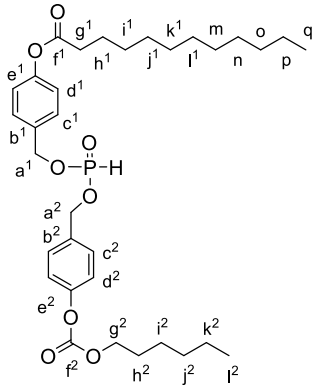
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 175.0 (C-f^1), 153.3 (C-f^2), 151.0 (C-e^2), 150.9 (C-e^1), 133.0, 132.7 (2 × d, $^{3}J_{CP}$= 6.4 Hz, $^{3}J_{CP}$= 6.4 Hz, C-b^1, C-b^2), 128.99, 128.98 (C-c^1, C-c^2), 121.6 (C-d^1), 121.1 (C-d^2), 68.8 (C-g^2), 66.4, 66.2 (2 × d, $^{3}J_{CP}$= 5.5 Hz, $^{3}J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 33.9 (C-g^1), 28.3 (C-h^2), 25.4 (C-i), 31.7, 29.38, 29.37, 29.29, 29.23, 29.1, 28.9, 22.4 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 18.6 (C-h^1), 13.9 (C-r).

^{31}P-NMR (202 MHz, $CDCl_3$): δ [ppm] = 7.77.

IR: ν [cm^{-1}] = 2955, 2917, 2872, 2850, 1753, 1607, 1509, 1467, 1422, 1382, 1350, 1278, 1217, 1251, 1185, 1165, 1105, 994, 962, 868, 847, 786, 773, 720, 634, 634, 581, 542, 515, 467, 448, 434.

(AB-C11; ACB-C6)-*H*-phosphonate 77jr.

According to general procedure 3b, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.40 g hexyl (4-(hydroxymethyl)phenyl) carbonate **73r** (1.57 mmol, 1.0 equiv.) was added and following with 0.51 g 4-(hydroxymethyl)phenyl dodecanoate **52j** (1.65 mmol, 1.05 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.49 g (0.82 mmol, 52%) white solid.

Chemical Formula: $C_{33}H_{49}O_8P$.

Molecular weight: 604.72 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 627.3057; found 627.2886.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.38-7.33 (m, 4H, H-c^1, H-c^2), 7.21-7.16 (m, 2H, H-d^2), 7.10-7.05 (m, 2H, H-d^1), 6.93 (d, $^{1}J_{HP}$= 708.8 Hz, 1H, P-H), 5.10-4.96 (m, 4H, H-a^1, H-a^2), 4.25 (t, $^{3}J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.55 (t, $^{3}J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.78-1.70 (m, 4H, H-h^1, H-h^2), 1.45-1.37 (m, 4H, H-i^1, H-i^2), 1.36-1.24 (m, 18H, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-m, H-n, H-o, H-p), 0.93-0.85 (m, 6H, H-l^2, H-q).

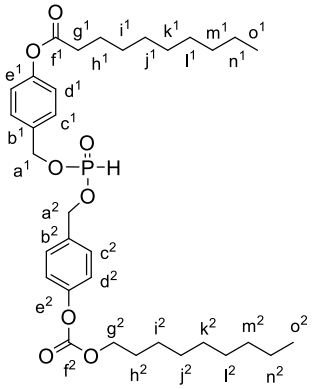
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 172.1 (C-f^1), 153.5 (C-f^2), 151.3 (C-e^2), 151.0 (C-e^1), 133.2, 132.9 (2 × d, $^3J_{CP}$= 6.4 Hz, $^3J_{CP}$= 6.4 Hz, C-b^1, C-b^2), 129.25, 129.2 (C-c^1, C-c^2), 121.9 (C-d^1), 121.4 (C-d^2), 69.1 (C-g^2), 66.7, 66.6 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 34.3 (C-g^1), 31.9, 31.4, 29.6, 29.4, 29.3, 29.2, 29.1, 22.6, 22.5 (C-j^1, C-j^2, C-k^1, C-k^2, C-l^1, C-m, C-n, C-o, C-p), 29.1 (C-i^1), 28.5 (C-h^2), 25.3 (C-i^2), 24.9 (C-h^1), 14.1, 14.0 (C-l^2, C-q).

^{31}P-NMR (202 MHz, $CDCl_3$): δ [ppm] = 7.75.

IR: ν [cm^{-1}] = 2956, 2917, 2849, 1750, 1607, 1510, 1467, 1385, 1286, 1252, 1221, 1167, 1104, 1063, 1011, 997, 924, 836, 784, 772, 726, 583, 542, 516, 448, 421.

(AB-C9; ACB-C9)-*H*-phosphonate 77is

According to general procedure 3b, with 0.15 mL DPP (0.79 mmol, 1.0 equiv.) at 0 °C. 0.23 g 4-(hydroxymethyl)phenyl nonyl carbonate **73s** (0.79 mmol, 1.0 equiv.) was added and following with 0.21 g 4-(hydroxymethyl)phenyl decanoate **52i** (0.79 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.44 g (0.72 mmol, 92%) white solid.

Chemical Formula: $C_{34}H_{51}O_8P$.

Molecular weight: 618.75 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 641.3214; found 641.3203.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.31 (m, 4H, H-c^1, H-c^2), 7.22-7.14 (m, 2H, H-d^2), 7.10-7.03 (m, 2H, H-d^1), 6.90 (d, $^1J_{HP}$= 711.5 Hz, 1H, P-H), 5.11-4.95 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.54 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.79-1.67 (m, 4H, H-h^1, H-h^2), 1.45-1.37 (m, 4H, H-i^1, H-i^2), 1.36-1.20 (m, 20H, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-l^2, H-m^1, H-m^2, H-n^1, H-n^2), 0.88 (t, $^3J_{HH}$= 6.8 Hz, 6H, H-o^1, H-o^2).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.0 (C-f^1), 153.5 (C-f^2), 151.2 (d, $^3J_{CP}$= 2.2 Hz, C-e^2), 150.9 (C-e^1), 133.1, 132.8 (2 × dd, $^3J_{CP}$= 2.2 Hz, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 2.3 Hz, $^3J_{CP}$= 3.3 Hz, C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.9 (C-d^1), 121.3 (C-d^2), 69.0 (C-g^2), 66.6, 66.5 (2 × t, $^3J_{CP}$= 5.4 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 34.3 (C-g^1), 31.77, 31.76, 29.35, 29.33, 29.17, 29.12, 29.0, 22.6 (C-i^1, C-j^1, C-j^2, C-k^1, C-k^2, C-l^1, C-l^2, C-m^1, C-m^2, C-n^1, C-n^2), 28.5 (C-h^2), 25.6 (C-i^2), 24.8 (C-h^1), 14.0, (C-o^1, C-o^2).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.71.

IR: ν [cm^{-1}] = 2956, 2918, 2871, 2850, 1751, 1652, 1605, 1558, 1509, 1466, 1382, 1250, 1220, 1167, 1143, 1057, 997, 965, 924, 891, 836, 773, 749, 721, 605, 583, 513, 470, 455, 431, 419.

(ACB-C2; ACB-C12)-*H*-phosphonate 79lv.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.32 g ethyl (4-(hydroxymethyl)phenyl) carbonate **73l** (1.65 mmol, 1.05 equiv.) was added and following with 0.48 g decyl (4-(hydroxymethyl)phenyl) carbonate **73v** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

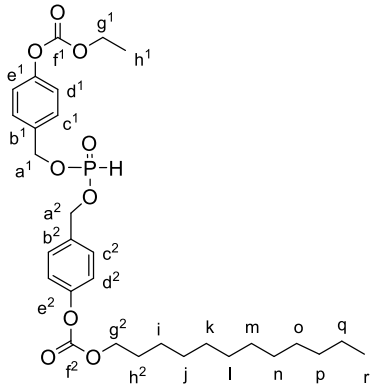
Yield: 0.40 g (0.74 mmol, 47%) white solid.

Chemical Formula: $C_{30}H_{43}O_9P$.

Molecular weight: 578.64 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 601.2537; found 601.2485.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.32-7.24 (m, 4H, H-c^1, H-c^2), 7.14-7.07 (m, 4H, H-d^1, H-d^2), 6.85 (d, $^1J_{HP}$= 708.9 Hz, 1H, P-H), 5.02-4.86 (m, 4H, H-a^1, H-a^2), 4.22 (q, $^3J_{HH}$= 7.1 Hz, 2H, H-g^1), 4.17 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 1.67 (quint, $^3J_{HH}$= 7.0 Hz, 2H, H-h^2), 1.39-1.32 (m, 2H, H-i), 1.29 (t, $^3J_{HH}$= 7.1 Hz, 3H, H-h^1), 1.27-1.16 (m, 16H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.83 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-r).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.12, 152.99 (C-f^1, C-f^2), 150.98, 150.95 (C-e^1, C-e^2), 133.0, 132.9 (2 × d, $^4J_{CP}$= 1.4 Hz, $^4J_{CP}$= 1.5 Hz, C-b^1, C-b^2), 128.9 (C-c^1, C-c^2), 121.0 (C-d^1, C-d^2), 68.7 (C-g^2), 66.17, 66.12 (C-a^1, C-a^2), 64.5 (C-g^1), 31.5, 29.3, 29.19, 29.12, 29.0, 28.8, 22.3 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 28.2 (C-h^2), 25.3 (C-i), 13.79, 13.74 (C-h^1, C-r).

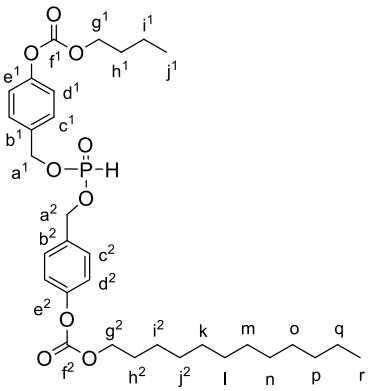
^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.78.

IR: ν [cm^{-1}] = 2924, 2853, 1757, 1610, 1509, 1465, 1421, 1369, 1247, 1217, 1169, 1058, 954, 900, 825, 778, 722, 633, 599, 509, 408.

(ACB-C4; ACB-C12)-*H*-phosphonate 79mv.

According to general procedure 3b, with 0.30 mL DPP (1.57mmol, 1.0 equiv.) at 0 °C. 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **73v** (1.57 mmol, 1.0 equiv.) was added and following with 0.35 g

butyl (4-(hydroxymethyl)phenyl) carbonate **73m** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.32 g (0.52 mmol, 33%) white solid.

Chemical Formula: $C_{32}H_{47}O_9P$.

Molecular weight: 606.69 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 629.2850; found 629.2876.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.38-7.33 (m, 4H, H-c^1, H-c^2), 7.20-7.14 (m, 4H, H-d^1, H-d^2), 6.93 (d, $^1J_{HP}$= 710.0 Hz, 1H, P-H), 5.10-4.96 (m, 4H, H-a^1, H-a^2), 4.28-4.21 (m, 4H, H-g^1, H-g^2), 1.78-1.66 (m, 4H, H-h^1, H-h^2), 1.50-1.36 (m, 4H, H-i^1, H-i^2), 1.36-1.23 (m, 16H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.96 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.87 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-r).

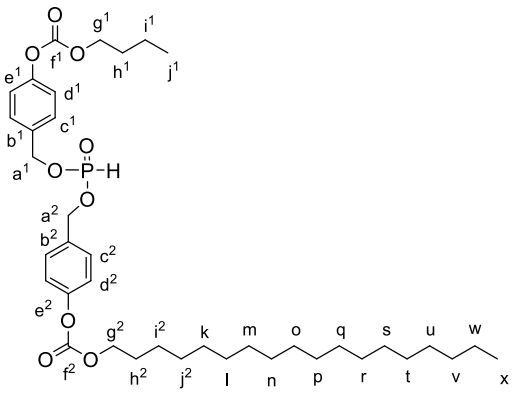
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.5 (C-f^1, C-f^2), 151.3 (C-e^1, C-e^2), 133.22, 133.15, (C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.4 (C-d^1, C-d^2), 69.1, 68.8 (C-g^1, C-g^2), 66.56, 66.50 (C-a^1, C-a^2), 31.8, 29.57, 29.56, 29.49, 29.42, 29.3, 29.1, 22.6, (C-g^1, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 30.5 (C-h^1), 28.5 (C-h^2), 25.6 (C-i^2), 18.9 (C-i^1), 14.1 (C-r), 13.6 (C-j^1).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.78.

IR: ν [cm^{-1}] = 2957, 2923, 2853, 1757, 1609, 1509, 1464, 1390, 1246, 1204, 1170, 1064, 949, 820, 777, 725, 633, 601, 510, 424.

(ACB-C4; ACB-C18)-*H*-phosphonate 79mz.

According to general procedure 3b, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.66 g 4-(hydroxymethyl)phenyl octadecyl carbonate **73z** (1.57 mmol, 1.0 equiv.) was added and following with 0.34 g butyl (4-(hydroxymethyl)phenyl) carbonate **73m** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.44 g (0.64 mmol, 41%) white solid.

Chemical Formula: $C_{38}H_{59}O_9P$.

Molecular weight: 690.85 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 713.3789; found 713.3738.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39-7.33 (m, 4H, H-c^1, H-c^2), 7.20-7.15 (m, 4H, H-d^1, H-d^2), 6.94 (d, $^1J_{HP}$= 709.2 Hz, 1H, P-H), 5.10-4.96 (m, 4H, H-a^1, H-a^2), 4.29-4.21 (m, 4H, H-g^1, H-g^2), 1.78-1.67 (m, 4H, H-h^1, H-h^2),1.51-1.37 (m, 4H, H-i^1, H-i^2), 1.36-1.20 (m, 28H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u, H-v, H-w), 0.97 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.88 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-x).

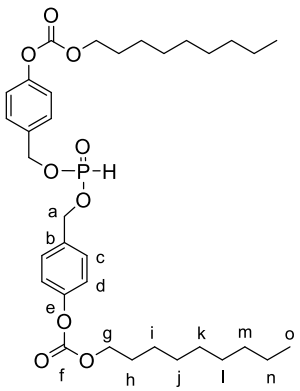
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.5 (C-f^1, C-f^2), 151.3 (C-e^1, C-e^2), 133.22, 133.16, (C-b^1, C-b^2), 129.2 (C-c^1, C-c^2), 121.4 (C-d^1, C-d^2), 69.1, 68.8 (C-g^1, C-g^2), 66.58, 66.53 (C-a^1, C-a^2), 31.9, 29.65, 29.62, 29.59, 29.52, 29.4, 29.3, 29.2, 22.6, (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u, C-v, C-w), 30.5 (C-h^1), 28.5 (C-h^2), 25.6 (C-i^2), 18.9 (C-i^1), 14.1 (C-x), 13.6 (C-j^1).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.75.

IR: ν [cm^{-1}] = 2957, 2915, 2849, 1753, 1606, 1509, 1464, 1400, 1381, 1324, 1243, 1169, 1065, 992, 961, 897, 852, 834, 804, 778, 746, 727, 719, 632, 608, 526, 510, 457, 429.

(ACB-C9; ACB-C9)-*H*-phosphonate 79ss.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.97 g 4-(hydroxymethyl)phenyl nonyl carbonate **73s** (3.30 mmol, 2.1 equiv.) was added. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.53 g (0.83 mmol, 53%) white solid.

Chemical Formula: $C_{34}H_{51}O_9P$.

Molecular weight: 634.75 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 657.3163; found 657.3159.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.38-7.31 (m, 4H, H-c), 7.20-7.14 (m, 4H, H-d), 6.92 (d, $^1J_{HP}$= 709.4 Hz, 1H, P-H), 5.10-4.96 (m, 4H, H-a), 4.23 (t, $^3J_{HH}$= 6.7 Hz, 4H, H-g), 1.72 (quint, $^3J_{HH}$= 6.9 Hz, 4H, H-h), 1.44-1.36 (m, 4H, H-i), 1.35-1.22 (m, 20H, H-j, H-k, H-l, H-m, H-n), 0.87 (t, $^3J_{HH}$= 6.80 Hz, 6H, H-o).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 153.4 (C-f), 151.2 (C-e), 133.1 (d, $^3J_{CP}$= 5.5 Hz, C-b), 129.1 (C-c), 121.3 (C-d), 69.0 (C-g), 66.44 (d, $^3J_{CP}$= 6.4 Hz, C-a), 31.7, 29.3, 29.1, 22.5 (C-j, C-k, C-l, C-m, C-n), 28.4 (C-h), 25.5 (C-i), 14.0 (C-o).

^{31}P-NMR (202 MHz, $CDCl_3$): δ [ppm] = 7.74.

IR: v [cm^{-1}] = 2954, 2921, 2853, 1752, 1607, 1509, 1466, 1421, 1381, 1329, 1246, 1205, 1170, 1052, 1015, 990, 995, 838, 806, 778, 722, 609, 541, 523, 484, 460, 412.

(β-cyanoethyl; ACB-C12)-*H*-phosphonate 83v.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.12 g 3-hydroxypropionitrile **82** (1.65 mmol, 1.05 equiv.) was added and following with 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **73v** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 4:6:0.005 v/v/v).

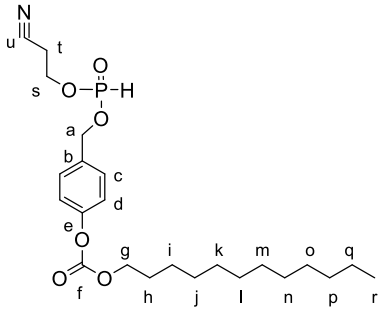
Yield: 0.31 g (0.66 mmol, 42%) white solid.

Chemical Formula: $C_{23}H_{36}NO_5P$.

Molecular weight: 453.52 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 476.2172; found 476.2179.



^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.45-7.38 (m, 2H, H-c), 7.22-7.16 (m, 2H, H-d), 6.91 (d, $^1J_{HP}$= 718.6 Hz, 1H, P-H), 5.18-5.07 (m, 2H, H-a), 4.21 (t, $^3J_{HH}$= 6.70 Hz, 2H, H-g), 4.20-4.05 (m, 2H, H-s), 2.64 (dt, $^3J_{HH}$= 2.0 Hz, $^3J_{HH}$= 6.1 Hz, 2H, H-t), 1.72 (quint, $^3J_{HH}$= 7.1 Hz, 2H, H-h), 1.44-1.35 (m, 2H, H-i), 1.34-1.22 (m, 16H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.86 (t, $^3J_{HH}$= 6.80 Hz, 3H, H-r).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 153.4 (C-f), 151.4 (C-e), 132.90 (d, $^3J_{CP}$= 5.5 Hz, C-b), 129.4 (C-c), 121.5 (C-d), 116.3 (C-u), 69.1 (C-g), 66.96 (d, $^3J_{CP}$= 5.5 Hz, C-a), 59.8 (d, $^3J_{CP}$= 5.5 Hz, C-s), 28.4 (C-h), 25.5 (C-i), 31.8, 29.49, 29.48, 29.41, 29.3, 29.2, 29.1, 22.5 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 19.7 (d, $^3J_{CP}$= 7.3 Hz, C-t), 14.0 (C-r).

^{31}P-NMR (202 MHz, $CDCl_3$): δ [ppm] = 7.65.

IR: v [cm^{-1}] = 2923, 2853, 1757, 1720, 1608, 1509, 1466, 1391, 1248, 1217, 1052, 959, 823, 777, 722, 685, 606, 511.

(β-cyanoethyl; ACB-C16)-*H*-phosphonate 83y.

According to general procedure 3a, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.12 g 3-hydroxypropionitrile **82** (1.65 mmol, 1.05 equiv.) was added and following with 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **73v** (1.57 mmol, 1.0 equiv.). Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 4:6:0.005 v/v/v).

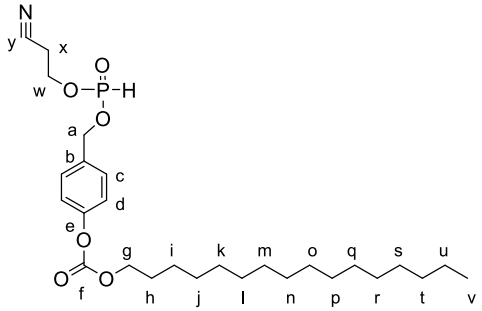
Yield: 0.35 g (0.68 mmol, 43%) white solid.

Chemical Formula: $C_{27}H_{44}NO_5P$.

Molecular weight: 509.62 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 532.2798; found 532.2791.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.46-7.40 (m, 2H, H-c), 7.23-7.18 (m, 2H, H-d), 6.93 (d, $^1J_{HP}$= 719.3 Hz, 1H, P-H), 5.20-5.07 (m, 2H, H-a), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g), 4.22-4.08 (m, 2H, H-w), 2.67 (dt, $^3J_{HH}$= 2.3 Hz, $^3J_{HH}$= 6.1 Hz, 2H, H-x), 1.73 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h), 1.45-1.37 (m, 2H, H-i), 1.36-1.22 (m, 24H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.88 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-v).

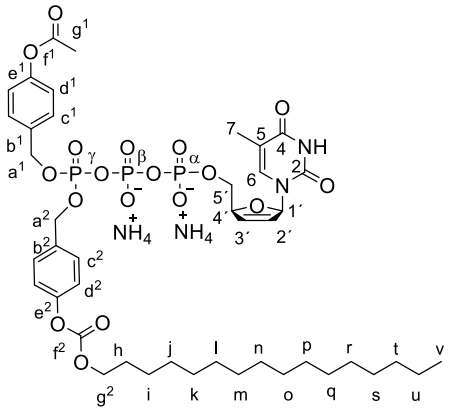
^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 153.5 (C-f), 151.4 (C-e), 132.9 (d, $^3J_{CP}$= 5.8 Hz, C-b), 129.5 (C-c), 121.5 (C-d), 116.3 (C-y), 69.1 (C-g), 67.1 (d, $^3J_{CP}$= 5.8 Hz, C-a), 59.8 (d, $^3J_{CP}$= 5.8 Hz, C-w), 28.5 (C-h), 25.6 (C-i), 31.9, 29.62, 29.60, 29.59, 29.57, 29.50, 29.4, 29.1, 22.6 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 19.8 (d, $^3J_{CP}$= 5.1 Hz, C-x), 14.1 (C-v).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.66.

IR: ν [cm^{-1}] = 2956, 2916, 2849, 1758, 1608, 1509, 1467, 1395, 1246, 1220, 1170, 1051, 959, 819, 777, 720, 605, 526, 476, 453, 421.

γ-(AB-C1; ACB-C16)-d4TTP 60ay.

According to general procedure 10 with 91 mg *H*-phosphonate **77ay** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 5 h.



Yield: 65 mg (0.064 mmol, 50%) white solid.

Chemical Formula: $C_{43}H_{68}N_4O_{18}P_3$.

Molecular weight: 1020.37 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 985.306; found, 985.110.

^{1}H NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.66 (d, $^4J_{HH}$= 1.1 Hz, 1H, H-6), 7.43-7.38 (m, 4H, H-c^1, H-c^2), 7.16-7.12 (m, 2H, H-d^2), 7.09-7.05 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.5 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.46 (dt, $^3J_{HH}$= 5.9 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.4 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.0 Hz, 4H, H-a^1, H-a^2), 4.96-4.91 (m, 1H, H-4´), 4.31-4.16 (m, 2H, H-5´), 4.23 (dt, $^3J_{HH}$= 6.7 Hz, $^4J_{HH}$=1.0 Hz, 2H, H-g^2), 2.26 (d, $^4J_{HH}$= 1.1 Hz, 3H, H- g^1), 1.89 (d, $^4J_{HH}$= 1.1 Hz, 3H, H-7), 1.73 (quint, $^3J_{HH}$= 6.8 Hz, 2H, H-h), 1.46-1.40 (m, 2H, H-i), 1.39-1.27 (m, 24H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-t).

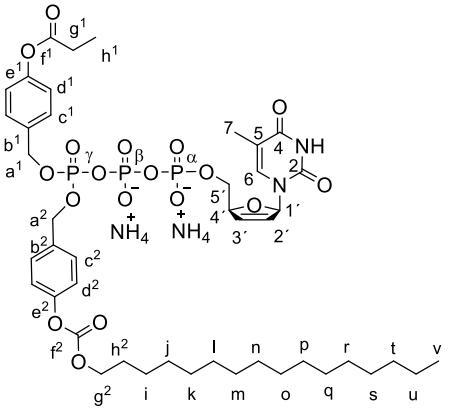
^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 171.0 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.76 (C-2), 152.69 (C-e^2), 152.3 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.2 (d, $^3J_{CP}$= 7.7 Hz, C-b^2), 134.9 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.5, 130.4 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.5 Hz, C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.8 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 33.0, 30.76, 30.75, 30.73, 30.72, 30.66, 30.61, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h), 26.8 (C-i), 20.9 (C-g^1), 14.4 (C-v), 12.5 (C-7).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = -11.81 (d, $^2J_{pp}$= 18.6 Hz, P-α), -13.20 (d, $^2J_{pp}$= 17.7 Hz, P-γ), -23.77 (t, $^2J_{pp}$= 18.2 Hz, P-β).

IR: ν [cm^{-1}] = 3188, 2969, 2921, 2852, 1759, 1689, 1509, 1463, 1394, 1370, 1246, 1219, 1168, 1127, 1113, 1078, 1026, 906, 836, 781, 721, 696, 645, 485.

γ-(AB-C2; ACB-C16)-d4TTP 60by.

According to general procedure 10 with 93 mg *H*-phosphonate **77by** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 5 h.



Yield: 67 mg (0.065 mmol, 51%) white solid.

Chemical Formula: $C_{44}H_{69}N_4O_{18}P_3$.

Molecular weight: 1034.38 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 999.322; found, 999.318.

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.66 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.44-7.38 (m, 4H, H-c^1, H-c^2), 7.16-7.12 (m, 2H, H-d^2), 7.08-7.04 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.5 Hz, $^4J_{HH}$=1.9 Hz, 1H, H-1´), 6.46 (dt, $^3J_{HH}$= 6.1 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 2.4 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.0 Hz, 4H, H-a^1, H-a^2), 4.96-4.92 (m, 1H, H-4´), 4.31-4.16 (m, 2H, H-5´), 4.23 (dt, $^3J_{HH}$= 6.6 Hz, $^4J_{HH}$=1.1 Hz, 2H, H-g^2), 2.60 (qd, $^3J_{HH}$= 6.6 Hz, $^4J_{HH}$= 1.3 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 1.1 Hz, 3H, H-7), 1.73 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.46-1.39 (m, 2H, H-i), 1.38-1.25 (m, 24H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.22 (td, $^3J_{HH}$= 7.5 Hz, $^4J_{HH}$=0.9 Hz, 3H, H-h^1), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-v).

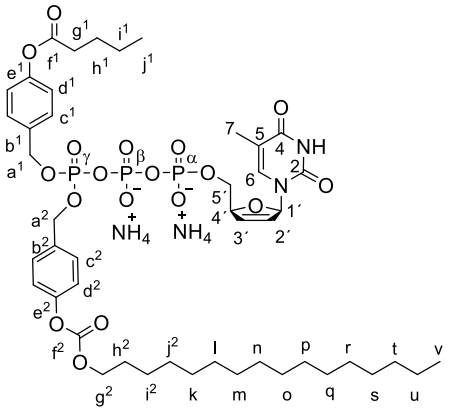
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 174.5 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.76 (C-2), 152.69 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.2 (d, $^3J_{CP}$= 7.5 Hz, C-b^2), 134.9 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.5, 130.49, 130.45 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.8 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 3.4 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.4 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 4.2 Hz, C-5´), 33.0, 30.75, 30.73, 30.66, 30.61, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.4 (C-g^1), 26.8 (C-i), 14.4 (C-v), 12.5 (C-7), 9.3 (C-h^1).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -11.77 (d, $^2J_{pp}$= 19.9 Hz, P-α), -13.22 (d, $^2J_{pp}$= 16.7 Hz, P-γ), -23.67 (t, $^2J_{pp}$= 22.4 Hz, P-β).

IR: ν [cm^{-1}] = 3191, 2987, 2971, 2921, 2854, 1759, 1688, 1508, 1454, 1408, 1394, 1248, 1221, 1168, 1127, 1076, 1066, 1048, 1027, 901, 837, 781, 721, 577, 517, 488, 401.

γ-(AB-C4; ACB-C16)-d4TTP 60ey.

According to general procedure 10 with 97 mg *H*-phosphonate **77ey** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 5 h.



Yield: 97 mg (0.091 mmol, 71%) white solid.

Chemical Formula: $C_{46}H_{73}N_4O_{18}P_3$.

Molecular weight: 1062.41 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1027.353; found, 1027.153.

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.64 (d, $^4J_{HH}$= 1.1 Hz, 1H, H-6), 7.44-7.37 (m, 4H, H-c^1, H-c^2), 7.16-7.12 (m, 2H, H-d^2), 7.08-7.03 (m, 2H, H-d^1), 6.94-6.90 (m, 1H, H-1´), 6.46-6.42 (m, 1H, H-3´), 5.85-5.78 (m, 1H, H-2´), 5.14 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.96-4.92 (m, 1H, H-4´), 4.31-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.58 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.89 (s, 3H, H-7), 1.76-1.68 (m, 4H, H-h^1, H-h^2), 1.49-1.39 (m, 4H, H-i^1, H-i^2), 1.39-1.25 (m, 24H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-v).

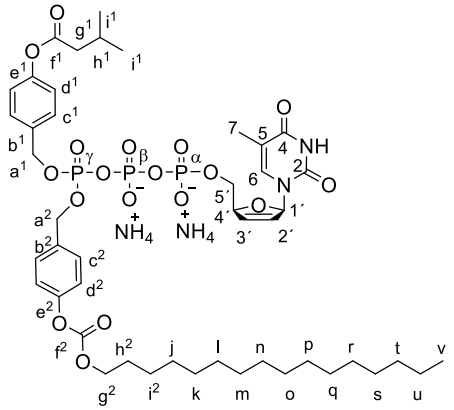
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.76 (C-2), 152.69 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.1 (d, $^3J_{CP}$= 7.6 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 6.6 Hz, C-b^1), 130.52, 130.49, 130.46 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^4J_{CP}$= 1.9 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.1 Hz, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.3 (C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 34.7 (C-g^1), 33.1, 30.76, 30.67, 30.62, 30.5, 30.3, 23.7 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.0 (C-h^1), 26.8 (C-i^2), 23.2 (C-i^1), 14.5 (C-v), 14.1 (C-j^1), 12.5 (C-7).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -10.27 (d, $^2J_{pp}$= 18.9 Hz, P-α), -11.82 (d, $^2J_{pp}$= 15.7 Hz, P-γ), -22.17 (t, $^2J_{pp}$= 22.4 Hz, P-β).

IR: v [cm^{-1}] = 3065, 2921, 2851, 1757, 1688, 1659, 1452, 1206, 1126, 1062, 1040, 993, 867, 835, 781, 735, 479, 421.

γ-(AB-C4; ACB-C16)-d4TTP 60fy.

According to general procedure 10 with 97 mg *H*-phosphonate **77fy** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 4 h.



Yield: 114 mg (0.077 mmol, 73%) white solid.

Chemical Formula: $C_{46}H_{73}N_4O_{18}P_3$.

Molecular weight: 1062.41 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1027.353; found, 1027.246.

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.62 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 7.42-7.36 (m, 4H, H-c^1, H-c^2), 7.15-7.11 (m, 2H, H-d^2), 7.06-7.01 (m, 2H, H-d^1), 6.92-6.89 (m, 1H, H-1´), 6.46-6.40 (m, 1H, H-3´), 5.80-5.76 (m, 1H, H-2´), 5.13 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.96-4.91 (m, 1H, H-4´), 4.25-4.12 (m, 2H, H-5´), 4.21 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.42 (d, $^3J_{HH}$= 7.1 Hz, 2H, H-g^1), 2.19 (hept, $^3J_{HH}$= 6.8 Hz, 1H, H-h^1), 1.88 (s, 3H, H-7), 1.71 (quint, $^3J_{HH}$= 7.0 Hz, 2H, H-h^2), 1.44-1.38 (m, 2H, H-i^2), 1.37-1.25 (m, 24H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.05 (d, $^3J_{HH}$= 6.6 Hz, 6H, H-i^1), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-v).

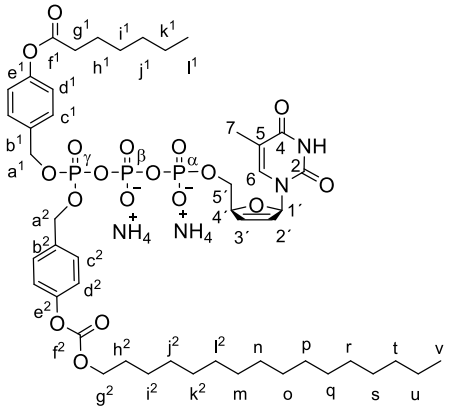
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 172.9 (C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.73 (C-2), 152.66 (C-e^2), 152.3 (C-e^1), 138.6 (C-6), 135.6 (C-3´), 135.1 (d, $^3J_{CP}$= 7.7 Hz, C-b^2), 134.9 (d, $^3J_{CP}$= 5.5 Hz, C-b^1), 130.49, 130.47 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (C-d^1), 122.3 (C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.7 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 4.3 Hz, $^3J_{CP}$= 6.5 Hz, $^3J_{CP}$= 3.4 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.8 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 44.0 (C-g^1), 33.0, 30.75, 30.66, 30.62, 30.5, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 26.9 (C-h^1), 26.8 (C-i^2), 22.7 (C-i^1), 14.5 (C-v), 12.5 (C-7).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -13.14 (d, $^2J_{pp}$= 16.9 Hz, P-α), -14.58 (d, $^2J_{pp}$= 17.7 Hz, P-γ), -24.90 (t, $^2J_{pp}$= 18.8 Hz, P-β). MALDI-MS (m/z): calculated for $C_{46}H_{66}N_2O_{18}P_3$ $[M-H]^-$ 1027.353; found, 1027.246.

IR: ν [cm^{-1}] = 3189, 2987, 2970, 2921, 2854, 1758, 1690, 1509, 1453, 1408, 1393, 1248, 1222, 1127, 1077, 1027, 904, 837, 781, 721, 643, 515, 489.

γ-(AB-C6; ACB-C16)-d4TTP 60gy.

According to general procedure 10 with 101 mg *H*-phosphonate **77gy** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 5 h.



Yield: 69 mg (0.064 mmol, 50%) white solid.

Chemical Formula: $C_{48}H_{77}N_4O_{18}P_3$.

Molecular weight: 1090.44 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1055.384; found, 1055.231.

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.63 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 7.42-7.36 (m, 4H, H-c^1, H-c^2), 7.15-7.10 (m, 2H, H-d^2), 7.06-7.01 (m, 2H, H-d^1), 6.93-6.90 (m, 1H, H-1´), 6.46-6.40 (m, 1H, H-3´), 5.81-5.76 (m, 1H, H-2´), 5.14 (d, $^3J_{HH}$= 7.8 Hz, 4H, H-a^1, H-a^2), 4.96-4.91 (m, 1H, H-4´), 4.30-4.12 (m, 2H, H-5´), 4.22 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.56 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.88 (s, 3H, H-7), 1.76-1.68 (m, 4H, H-h^1, H-h^2), 1.46-1.38 (m, 4H, H-i^1, H-i^2), 1.38-1.25 (m, 28H, H-j^1, H-j^2, H-k^1, H-k^2, H-l^2, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.92 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-l^1), 0.88 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-v).

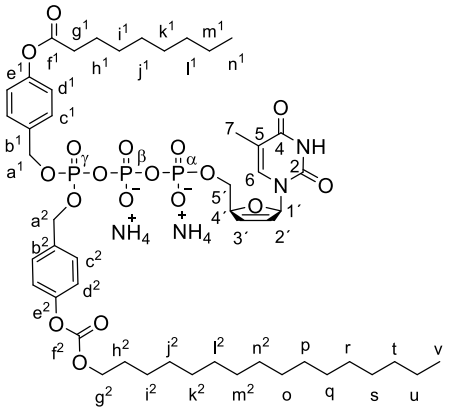
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.74 (C-2), 152.67 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.1 (d, $^3J_{CP}$= 7.6 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 6.6 Hz, C-b^1), 130.52, 130.49, 130.47 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.0 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.1 Hz, C-d^2), 112.0 (C-5), 90.8 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.3 (C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 35 (C-g^1), 33.0, 32,6, 30.76, 30.73, 30.67,30.62, 30.4, 30.3, 23.7 (C-j^1, C-j^2, C-k^1, C-k^2, C-l^2, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.8 (C-i^1), 29.7 (C-h^2), 26.8 (C-i^2), 25.9 (C-h^1), 14.46, 14.41 (C-v, C-l^1), 12.5 (C-7).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -11.77 (d, $^2J_{pp}$= 18.3 Hz, P-α), -13.20 (d, $^2J_{pp}$= 15.8 Hz, P-γ), -23.72 (t, $^2J_{pp}$= 22.4 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1758, 1685, 1653, 1507, 1452, 1406, 1393, 1382, 1250, 1228, 1167, 1075, 1028, 897, 840, 782, 506, 485, 436.

γ-(AB-C8; ACB-C16)-d4TTP 60hy.

According to general procedure 10 with 105 mg *H*-phosphonate **77hy** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 5 h.



Yield: 65 mg (0.059 mmol, 46%) white solid.

Chemical Formula: $C_{50}H_{81}N_4O_{18}P_3$.

Molecular weight: 1118.48 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1083.416; found, 1083.272.

^{1}H NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.65 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 7.43-7.36 (m, 4H, H-c^1, H-c^2), 7.16-7.10 (m, 2H, H-d^2), 7.08-7.01 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.5 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.46 (dt, $^3J_{HH}$= 5.9 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.1 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.96-4.91 (m, 1H, H-4´), 4.30-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.57 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.88 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.79-1.67 (m, 4H, H-h^1, H-h^2), 1.46-1.25 (m, 36H, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-l^2, H-m^1, H-m^2, H-n^2, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.94-0.86 (m, 6H, H-n^1, H-v).

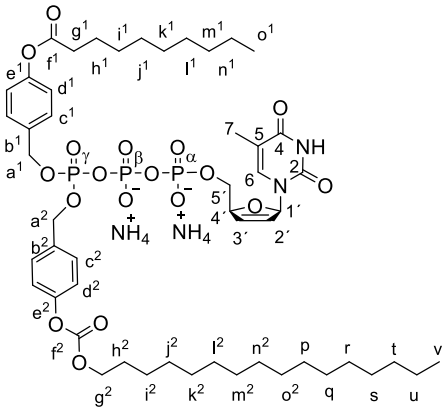
^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.78 (C-2), 152.70 (C-e^2), 152.4 (C-e^1), 138.7 (C-6), 135.7 (C-3´), 135.2 (d, $^3J_{CP}$= 7.6 Hz, C-b^2), 134.9 (d, $^3J_{CP}$= 7.6 Hz, C-b^1), 130.53, 130.51, 130.49 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^4J_{CP}$= 1.9 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.3 (C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.6 Hz, C-5´), 35.0 (C-g^1), 33.07, 30.00, 32.7, 30.78, 30.75, 30.67, 30.63, 30.46, 30.39, 30.33, 30.30, 30.2, 23.7, 23.6 (C-j^1, C-j^2, C-k^1, C-k^2, C-l^1, C-l^2, C-m^1, C-m^2, C-n^2, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.9 (C-i^1), 29.7 (C-h^2), 26.8 (C-i^2), 25.9 (C-h^1), 14.44, 14.39 (C-n^1, C-v), 12.5 (C-7).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = -11.77 (d, $^2J_{pp}$= 17.6 Hz, P-α), -13.20 (d, $^2J_{pp}$= 17.6 Hz, P-γ), -23.72 (t, $^2J_{pp}$= 16.8 Hz, P-β).

IR: ν [cm^{-1}] = 2997, 2986, 2971, 2922, 2901, 1654, 1636, 1449, 1408, 1383, 1026, 927, 867, 829, 780, 717, 638, 586, 505, 486, 445, 429.

γ-(AB-C9; ACB-C16)-d4TTP 60iy.

According to general procedure 10 with 105 mg *H*-phosphonate **77iy** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 5 h.



Yield: 33 mg (0.029 mmol, 23%) white solid.

Chemical Formula: $C_{51}H_{83}N_4O_{18}P_3$.

Molecular weight: 1132.49 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1083.416; found, 1083.272.

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.65 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.43-7.36 (m, 4H, H-c^1, H-c^2), 7.16-7.10 (m, 2H, H-d^2), 7.06-7.01 (m, 2H, H-d^1), 6.91 (dt, $^3J_{HH}$= 3.5 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-1´), 6.46 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 5.9 Hz, $^3J_{HH}$= 2.0 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.14 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.96-4.91 (m, 1H, H-4´), 4.30-4.15 (m, 2H, H-5´), 4.22 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.56 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.88 (d, $^4J_{HH}$= 1.1 Hz, 3H, H-7), 1.76-1.68 (m, 4H, H-h^1, H-h^2), 1.46-1.25 (m, 38H, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-l^2, H-m^1, H-m^2, H-n^1, H-n^2, H-o^2, H-p, H-q, H-r, H-s, H-t, H-u), 0.91-0.87 (m, 6H, H-o^1, H-v).

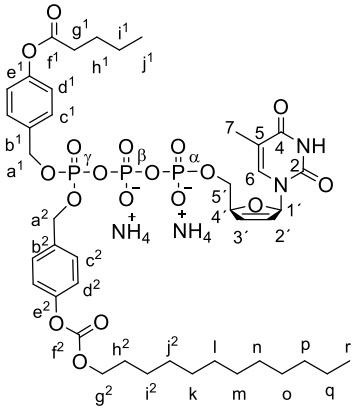
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 173.8 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.78 (C-2), 152.69 (C-e^2), 152.4 (C-e^1), 138.7 (C-6), 135.8 (C-3´), 135.2 (C-b^2), 134.9 (C-b^1), 130.54, 130.52, 130.49 (C-c^1, C-c^2), 127.1 (C-2´), 122.9 (d, $^3J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.8 (C-1´), 87.2 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.3 (C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 35.0 (C-g^1), 33.07, 33.05, 30.77, 30.75, 30.68, 30.63, 30.59, 30.46, 30.43, 30.3, 24.8, 23.7 (C-j^1, C-j^2, C-k^1, C-k^2, C-l^2, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 30.2 (C-i^1), 29.7 (C-h^2), 26.8 (C-i^2), 25.9 (C-h^1), 14.4, 13.9 (C-o^1, C-v), 12.5 (C-7).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -11.85 (d, $^2J_{pp}$= 19.6 Hz, P-α), -13.25 (d, $^2J_{pp}$= 17.6 Hz, P-γ), -23.89 (t, $^2J_{pp}$= 18.8 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1759, 1723, 1711, 1692, 1463, 1450, 1407, 1393, 1381, 1250, 1229, 1075, 1066, 893, 879, 445, 425.

γ-(AB-C4; ACB-C12)-d4TTP 60ev.

According to general procedure 10 with 91 mg *H*-phosphonate **77ev** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 5 h.



Yield: 73 mg (0.075 mmol, 59%) white solid.

Chemical Formula: $C_{42}H_{65}N_4O_{18}P_3$.

Molecular weight: 1006.35 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 971.290; found, 971.135.

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.67 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 7.43-7.38 (m, 4H, H-c^1, H-c^2), 7.16-7.11 (m, 2H, H-d^2), 7.08-7.02 (m, 2H, H-d^1), 6.94-6.91 (m, 1H, H-1´), 6.50-6.44 (m, 1H, H-3´), 5.82-5.77 (m, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.96-4.92 (m, 1H, H-4´), 4.31-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.58 (dt, $^3J_{HH}$= 7.6 Hz, $^4J_{HH}$= 0.8 Hz, 2H, H-g^1), 1.89 (s, 3H, H-7), 1.76-1.68 (m, 4H, H-h^1, H-h^2), 1.49-1.40 (m, 4H, H-i^1, H-i^2), 1.39-1.25 (m, 16H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.99 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-r).

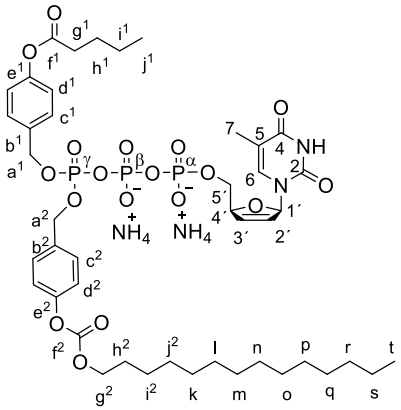
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.77 (C-2), 152.70 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.2 (d, $^3J_{CP}$= 7.7 Hz, C-b^2), 134.9 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.53, 130.51, 130.47 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.3 (2 × dd, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 34.8 (C-g^1), 33.1, 30.75, 30.68, 30.62, 30.5, 30.3, 23.7 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.7 (C-h^2), 28.1 (C-h^1), 26.8 (C-i^2), 23.2 (C-i^1), 14.4 (C-r), 14.1 (C-j^1), 12.5 (C-7).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -11.79 (d, $^2J_{pp}$= 15.9 Hz, P-α), -13.22 (d, $^2J_{pp}$= 15.7 Hz, P-γ), -23.57 (t, $^2J_{pp}$= 19.4 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1747, 1729, 1451, 1406, 1393, 1381, 1250, 1229, 1075, 1066, 1055, 892, 431.

γ-(AB-C4; ACB-C14)-d4TTP 60ew.

According to general procedure 10 with 93 mg *H*-phosphonate **77ew** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 4 h.



Yield: 85 mg (0.082 mmol, 78%) white solid.

Chemical Formula: $C_{44}H_{69}N_4O_{18}P_3$.

Molecular weight: 1034.38 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 999.322; found, 999.191.

^{1}H NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.63 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.43-7.36 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 2H, H-d^2), 7.08-7.02 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-1´), 6.44 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$= 1.7 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$= 1.3 Hz, 1H, H-2´), 5.14 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.96-4.91 (m, 1H, H-4´), 4.31-4.12 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.5 Hz, 2H, H-g^2), 2.58 (dt, $^3J_{HH}$= 7.4 Hz, $^4J_{HH}$= 0.5 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.76-1.66 (m, 4H, H-h^1, H-h^2), 1.50-1.37 (m, 4H, H-i^1, H-i^2), 1.38-1.25 (m, 20H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-t).

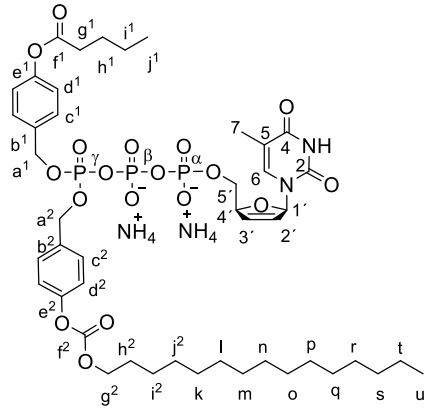
^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.75 (C-2), 152.70 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.6 (C-3´), 135.2 (d, $^3J_{CP}$= 7.7 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.52, 130.50, 130.47 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.3 (2 × dd, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 34.7 (C-g^1), 33.0, 30.77, 30.76, 30.73, 30.66, 30.61, 30.4, 30.3, 23.7 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s), 29.7 (C-h^2), 28.1 (C-h^1), 26.8 (C-i^2), 23.2 (C-i^1), 14.4 (C-t), 14.1 (C-j^1), 12.5 (C-7).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = -11.72 (d, $^2J_{pp}$= 16.2 Hz, P-α), -13.18 (d, $^2J_{pp}$= 15.9 Hz, P-γ), -23.58 (t, $^2J_{pp}$= 18.4 Hz, P-β).

IR: ν [cm^{-1}] = 3189, 3040, 2956, 2922, 2852, 1758, 1689, 1509, 1462, 1245, 1220, 1167, 1127, 1080, 1008, 905, 837, 781, 722, 644, 576, 514, 490, 426.

γ-(AB-C4; ACB-C15)-d4TTP 60ex.

According to general procedure 11 with 142 mg *H*-phosphonate **77ex** (0.225 mmol, 1.0 equiv.) and 124 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.16 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 122 mg (0.17 mmol, 74%) white solid.

Chemical Formula: $C_{45}H_{71}N_4O_{18}P_3$.

Molecular weight: 1048.40g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1013.337; found, 1013.202.

^{1}H NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.62 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 7.41-7.36 (m, 4H, H-c^1, H-c^2), 7.16-7.12 (m, 2H, H-d^2), 7.07-7.02 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.3 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-1´), 6.44 (dt, $^3J_{HH}$= 6.1 Hz, $^4J_{HH}$= 1.5 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$= 1.5 Hz, 1H, H-2´), 5.14 (d, $^3J_{HH}$= 8.1 Hz, 4H, H-a^1, H-a^2), 4.97-4.92 (m, 1H, H-4´), 4.30-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.5 Hz, 2H, H-g^2), 2.58 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 1.2 Hz, 3H, H-7), 1.77-1.67 (m, 4H, H-h^1, H-h^2), 1.51-1.39 (m, 4H, H-i^1, H-i^2), 1.38-1.25 (m, 22H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t), 0.98 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.80 Hz, 3H, H-u).

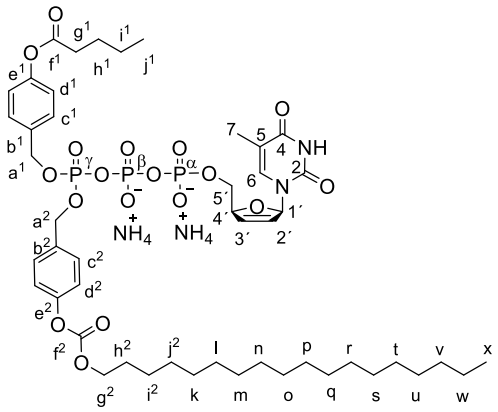
^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 173.7 (C-f^1), 166.4 (C-4), 155.1 (C-f^2), 152.71 (C-2), 152.65 (C-e^2), 152.3 (C-e^1), 138.5 (C-6), 135.6 (C-3´), 135.0 (d, $^3J_{CP}$= 7.5 Hz, C-b^2), 134.7 (d, $^3J_{CP}$= 7.6 Hz, C-b^1), 130.49, 130.47, 130.44 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.1 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 3.2 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 34.7 (C-g^1), 33.0, 30.76, 30.73, 30.66, 30.61, 30.4, 30.3, 23.7 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t), 29.7 (C-h^2), 28.0 (C-h^1), 26.8 (C-i^2), 23.2 (C-i^1), 14.5 (C-u), 14.1 (C-j^1), 12.5 (C-7).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = -11.68 (d, $^2J_{pp}$= 17.9 Hz, P-α), -13.12 (d, $^2J_{pp}$= 17.7 Hz, P-γ), -23.50 (t, $^2J_{pp}$= 18.9 Hz, P-β).

IR: ν [cm^{-1}] = 3190, 2958, 2922, 2852, 1758, 1690, 1509, 1463, 1247, 1220, 1168, 1078, 1010, 907, 837, 781, 722, 644, 577, 489, 425.

γ-(AB-C4; ACB-C18)-d4TTP 60ez.

According to general procedure 10 with 101 mg *H*-phosphonate **77ez** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 4 h.



Yield: 54 mg (0.041 mmol, 39%) white solid.

Chemical Formula: $C_{48}H_{77}N_4O_{18}P_3$.

Molecular weight: 1090.44 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1055.384; found, 1055.282.

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.64 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.44-7.36 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 2H, H-d^2), 7.08-7.02 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.3 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.44 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$= 1.5 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$= 1.3 Hz, 1H, H-2´), 5.14 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.96-4.92 (m, 1H, H-4´), 4.31-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.58 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 0.8 Hz, 3H, H-7), 1.76-1.67 (m, 4H, H-h^1, H-h^2), 1.51-1.40 (m, 4H, H-i^1, H-i^2), 1.39-1.25 (m, 28H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u, H-v, H-w), 0.98 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-x).

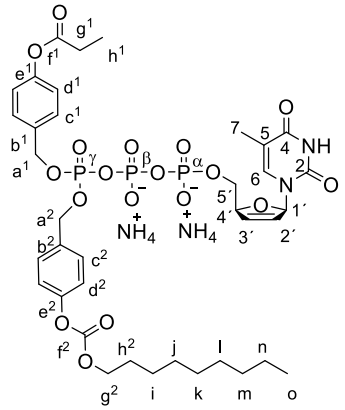
^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.75 (C-2), 152.69 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.1 (d, $^3J_{CP}$= 7.7 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 6.6 Hz, C-b^1), 130.52, 130.49, 130.47 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 3.3 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.9 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 4.3 Hz, $^3J_{CP}$= 6.6 Hz, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 34.8 (C-g^1), 33.1, 30.75, 30.67, 30.62, 30.5, 30.3, 23.7 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u, C-v, C-w), 29.7 (C-h^2), 28.0 (C-h^1), 26.8 (C-i^2), 23.2 (C-i^1), 14.5 (C-x), 14.1 (C-j^1), 12.5 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.77 (d, $^2J_{pp}$= 19.6 Hz, P-α), -13.22 (d, $^2J_{pp}$= 17.7 Hz, P-γ), -23.65 (t, $^2J_{pp}$= 17.8 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1759, 1691, 1451, 1406, 1393, 1382, 1250, 1229, 1075, 1055, 892, 427.

γ-(AB-C2; ACB-C9)-d4TTP 60bs.

According to general procedure 11 with 117 mg *H*-phosphonate **77bs** (0.225 mmol, 1.0 equiv.) and 124 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.16 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 75 mg (0.080mmol, 51%) white solid.

Chemical Formula: $C_{37}H_{55}N_4O_{18}P_3$.

Molecular weight: 936.27 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 901.212; found, 901.135.

^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.66 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.44-7.38 (m, 4H, H-c^1, H-c^2), 7.16-7.12 (m, 2H, H-d^2), 7.09-7.03 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.3 Hz, $^4J_{HH}$=1.9 Hz, 1H, H-1´), 6.45 (dt, $^3J_{HH}$= 6.1 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-3´), 5.82 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 2.3 Hz, $^4J_{HH}$= 1.3 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.1 Hz, 4H, H-a^1, H-a^2), 4.96-4.92 (m, 1H, H-4´), 4.30-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.60 (qd, $^3J_{HH}$= 7.6 Hz, $^4J_{HH}$= 0.8 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 1.2 Hz, 3H, H-7), 1.73 (quint, $^3J_{HH}$= 6.7 Hz, 2H, H-h^2), 1.47-1.39 (m, 2H, H-i), 1.38-1.27 (m, 10H, H-j, H-k, H-l, H-m, H-n), 1.22 (td, $^3J_{HH}$= 7.6 Hz, $^4J_{HH}$=0.5 Hz, 3H, H-h^1), 0.90 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-o).

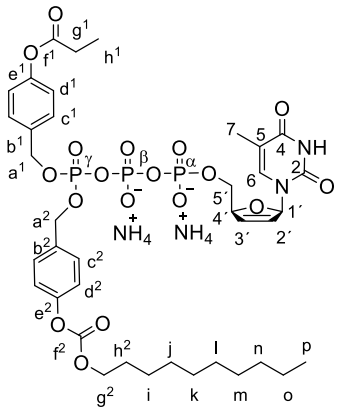
^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 174.5 (d, $^4J_{CP}$= 1.5 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.74 (C-2), 152.68 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.14 (d, $^3J_{CP}$= 7.3 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.3 Hz, C-b^1), 130.53, 130.49, 130.45 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^4J_{CP}$= 1.5 Hz, C-d^1), 122.3 (d, $^4J_{CP}$= 1.4 Hz, C-d^2), 112.0 (C-5), 90.8 (C-1´), 87.1 (d, $^3J_{CP}$= 8.7 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 2.2 Hz, $^3J_{CP}$= 5.9 Hz, $^3J_{CP}$= 2.3 Hz, $^3J_{CP}$= 5.2 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.8 (d, $^3J_{CP}$= 5.2 Hz, C-5´), 33.0, 30.6, 30.34, 30.31, 23.7 (C-j, C-k, C-l, C-m, C-n), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 14.4 (C-o), 12.5 (C-7), 9.3 (C-h^1).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = -11.72 (d, $^2J_{pp}$= 19.8 Hz, P-α), -13.18 (d, $^2J_{pp}$= 15.9 Hz, P-γ), -23.60 (t, $^2J_{pp}$= 17.8 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1758, 1684, 1507, 1453, 1406, 1393, 1383, 1249, 1224, 1075, 1055, 1027, 897, 836, 781, 730, 486.

γ-(AB-C2; ACB-C10)-d4TTP 60bt.

According to general procedure 10 with 80 mg *H*-phosphonate **77bt** (0.15 mmol, 1.0 equiv.) and 83 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.11 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 56 mg (0.039 mmol, 37%) white solid.

Chemical Formula: $C_{38}H_{57}N_4O_{18}P_3$.

Molecular weight: 950.29 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 915.228; found, 915.153.

^{1}H NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.66 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 7.45-7.37 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 2H, H-d^2), 7.09-7.03 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.5 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-1´), 6.46 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 2.3 Hz, $^4J_{HH}$= 1.2 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.1 Hz, 4H, H-a^1, H-a^2), 4.96-4.92 (m, 1H, H-4´), 4.31-4.14 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.60 (qd, $^3J_{HH}$= 7.6 Hz, $^4J_{HH}$= 0.7 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.73 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.47-1.27 (m, 14H, H-i, H-j, H-k, H-l, H-m, H-n, H-o), 1.22 (td, $^3J_{HH}$= 7.5 Hz, $^4J_{HH}$=0.5 Hz, 3H, H-h^1), 0.90 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-p).

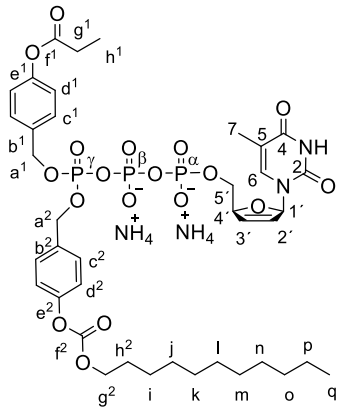
^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 174.5 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.75 (C-2), 152.69 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.1 (d, $^3J_{CP}$= 7.7 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.52, 130.48, 130.44 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 7.7 Hz, C-4´), 70.4, 70.3 (2 × dd, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 33.0, 30.62, 30.61, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 14.4 (C-p), 12.5 (C-7), 9.3 (C-h^1).

^{31}P NMR (243 M, CD$_3$OD): δ [ppm] = -11.73 (d, $^2J_{pp}$= 19.7 Hz, P-α), -13.17 (d, $^2J_{pp}$= 17.6 Hz, P-γ), -23.58 (t, $^2J_{pp}$= 17.9 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1758, 1687, 1508, 1451, 1406, 1393, 1832, 1249, 1225, 1075, 1055, 1027, 897, 836, 781, 724, 485.

γ-(AB-C2; ACB-C11)-d4TTP 60bu.

According to general procedure 11 with 123 mg *H*-phosphonate **77bu** (0.225 mmol, 1.0 equiv.) and 124 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.16 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 105 mg (0.11 mmol, 69%) white solid.

Chemical Formula: $C_{39}H_{59}N_4O_{18}P_3$.

Molecular weight: 964.30 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 929.243; found, 929.182.

^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.65 (d, $^4J_{HH}$= 1.3 Hz, 1H, H-6), 7.45-7.37 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 2H, H-d^2), 7.09-7.03 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.5 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.45 (dt, $^3J_{HH}$= 6.1 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 2.4 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.1 Hz, 4H, H-a^1, H-a^2), 4.96-4.92 (m, 1H, H-4´), 4.31-4.14 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.60 (qd, $^3J_{HH}$= 7.6 Hz, $^4J_{HH}$= 1.0 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 1.3 Hz, 3H, H-7), 1.73 (quint, $^3J_{HH}$= 6.7 Hz, 2H, H-h^2), 1.47-1.40 (m, 2H, H-i), 1.39-1.27 (m, 14H, H-j, H-k, H-l, H-m, H-n, H-o, H-p), 1.22 (td, $^3J_{HH}$= 7.6 Hz, $^4J_{HH}$=0.5 Hz, 3H, H-h^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-q).

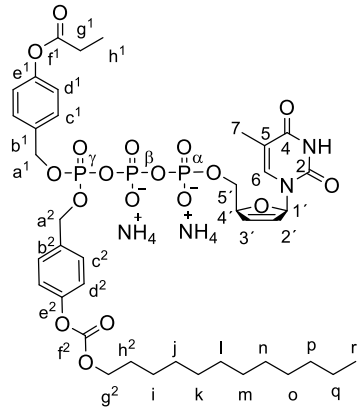
^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 174.4 (d, $^4J_{CP}$= 1.5 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.72 (C-2), 152.66 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.6 (C-3´), 135.1 (d, $^3J_{CP}$= 7.4 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.3 Hz, C-b^1), 130.51, 130.48, 130.45 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^4J_{CP}$= 1.5 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.8 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 2.2 Hz, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 2.2 Hz, $^3J_{CP}$= 5.9 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.2 Hz, C-5´), 33.0, 30.69, 30.67, 30.60, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 14.5 (C-q), 12.5 (C-7), 9.3 (C-h^1).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = -11.72 (d, $^2J_{pp}$= 19.6 Hz, P-α), -13.17 (d, $^2J_{pp}$= 16.9 Hz, P-γ), -23.58 (t, $^2J_{pp}$= 18.1 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1758, 1685, 1508, 1454, 1407, 1393, 1242, 1221, 1167, 1127, 1076, 1066, 1027, 899, 836, 805, 778, 724, 695, 517, 484, 427.

γ-(AB-C2; ACB-C12)-d4TTP 60bv.

According to general procedure 12 with 169 mg *H*-phosphonate **77bv** (0.30 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt **1a** (0.21 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 66 mg (0.091 mmol, 43%) white solid.

Chemical Formula: $C_{40}H_{61}N_4O_{18}P_3$.

Molecular weight: 978.32 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 943.259; found, 943.185.

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.66 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.45-7.37 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 2H, H-d^2), 7.10-7.02 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.3 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-1´), 6.46 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 2.5 Hz, $^4J_{HH}$= 1.5 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.1 Hz, 4H, H-a^1, H-a^2), 4.96-4.92 (m, 1H, H-4´), 4.31-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.60 (qd, $^3J_{HH}$= 7.6 Hz, $^4J_{HH}$= 0.8 Hz, 2H, H-g^1), 1.88 (d, $^4J_{HH}$= 1.2 Hz, 3H, H-7), 1.73 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.47-1.26 (m, 18H, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 1.22 (td, $^3J_{HH}$= 7.6 Hz, $^4J_{HH}$=0.8 Hz, 3H, H-h^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-r).

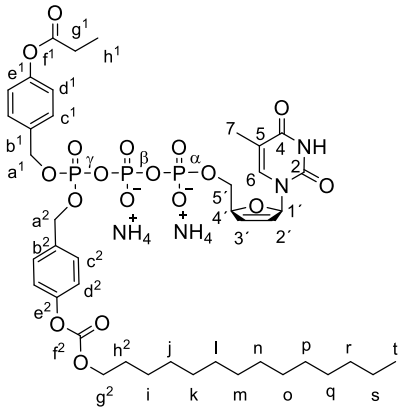
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 174.5 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.76 (C-2), 152.69 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.2 (d, $^3J_{CP}$= 6.6 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.51, 130.46 (2 × d, $^3J_{CP}$= 4.4 Hz, $^3J_{CP}$= 4.4 Hz, C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.4 Hz, C-5´), 33.1, 30.74, 30.73, 30.66, 30.61, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 14.4 (C-r), 12.5 (C-7), 9.3 (C-h^1).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -11.79 (d, $^2J_{pp}$= 19.7 Hz, P-α), -13.20 (d, $^2J_{pp}$= 15.8 Hz, P-γ), -23.65 (t, $^2J_{pp}$= 17.9 Hz, P-β).

IR: ν [cm^{-1}] = 3186, 2987, 2971, 2901, 1758, 1685, 1508, 1453, 1407, 1393, 1249, 1222, 1168, 1075, 1055, 1027, 1012, 899, 836, 781, 729, 486, 425.

γ-(AB-C2; ACB-C14)-d4TTP 60bw.

According to general procedure 11 with 133 mg *H*-phosphonate **77bw** (0.225 mmol, 1.0 equiv.) and 124 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.16 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 104 mg (0.11 mmol, 66%) white solid.

Chemical Formula: $C_{42}H_{65}N_4O_{18}P_3$.

Molecular weight: 1006.35 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 971.290; found, 971.204.

^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.62 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.44-7.36 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 2H, H-d^2), 7.10-7.02 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-1´), 6.44 (dt, $^3J_{HH}$= 6.1 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 2.4 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.1 Hz, 4H, H-a^1, H-a^2), 4.96-4.92 (m, 1H, H-4´), 4.31-4.12 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.5 Hz, 2H, H-g^2), 2.60 (qd, $^3J_{HH}$= 7.5 Hz, $^4J_{HH}$= 0.8 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.72 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.47-1.25 (m, 22H, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s), 1.22 (td, $^3J_{HH}$= 7.5 Hz, $^4J_{HH}$=0.5 Hz, 3H, H-h^1), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-t).

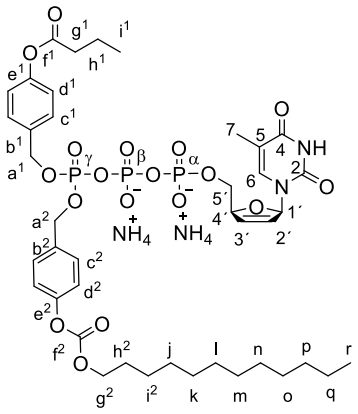
^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 174.4 (d, $^4J_{CP}$= 1.5 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.72 (C-2), 152.65 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.6 (C-3´), 135.1 (d, $^3J_{CP}$= 7.4 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.3 Hz, C-b^1), 130.5, 130.47, 130.44 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^4J_{CP}$= 1.5 Hz, C-d^1), 122.3 (d, $^4J_{CP}$= 1.5 Hz, C-d^2), 112.0 (C-5), 90.8 (C-1´), 87.1 (d, $^3J_{CP}$= 8.1 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 2.2 Hz, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 2.2 Hz, $^3J_{CP}$= 5.1 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 3.7 Hz, C-5´), 33.0, 30.77, 30.75, 30.73,30.66, 30.61, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 14.5 (C-t), 12.5 (C-7), 9.3 (C-h^1).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = -11.79 (d, $^2J_{pp}$= 17.7 Hz, P-α), -13.20 (d, $^2J_{pp}$= 17.8 Hz, P-γ), -23.62 (t, $^2J_{pp}$= 17.9 Hz, P-β).

IR: ν [cm^{-1}] = 3186, 2987, 2970, 2921, 2853, 1758, 1689, 1508, 1453, 1408, 1394, 1241, 1222, 1066, 1055, 1013, 903, 837, 782, 729, 734, 489.

γ-(AB-C3; ACB-C12)-d4TTP 60cv.

According to general procedure 11 with 130 mg *H*-phosphonate **77cv** (0.225 mmol, 1.0 equiv.) and 124 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.16 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 81 mg (0.082 mmol, 52%) white solid.

Chemical Formula: $C_{41}H_{63}N_4O_{18}P_3$.

Molecular weight: 992.34 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 957.275; found, 957.186.

^{1}H NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.65 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.44-7.37 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 2H, H-d^2), 7.08-7.02 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-1´), 6.45 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 2.4 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.1 Hz, 4H, H-a^1, H-a^2), 4.97-4.91 (m, 1H, H-4´), 4.31-4.15 (m, 2H, H-5´), 4.23 (dt, $^3J_{HH}$= 6.6 Hz, $^4J_{HH}$=0.6 Hz, 2H, H-g^2), 2.60 (dt, $^3J_{HH}$= 7.4 Hz, $^4J_{HH}$= 0.7 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 1.1 Hz, 3H, H-7), 1.82-1.68 (m, 4H, H-h^1, H-h^2), 1.45-1.25 (m, 18H, H-i^2, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 1.04 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-i^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-r).

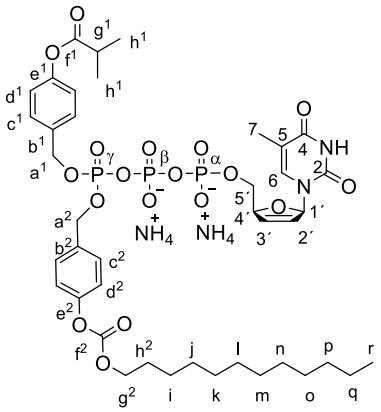
^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 173.6 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.73 (C-2), 152.67 (C-e^2), 152.3 (C-e^1), 138.6 (C-6), 135.6 (C-3´), 135.1 (d, $^3J_{CP}$= 7.6 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.5, 130.48, 130.44 (C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 36.9 (C-g^1), 33.0, 30.72, 30.71, 30.64, 30.59, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.7 (C-h^2), 26.8 (C-i^2), 19.3 (C-h^1), 14.4 (C-r), 13.9 (C-i^1), 12.5 (C-7).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = -11.65 (d, $^2J_{pp}$= 15.7 Hz, P-α), -13.10 (d, $^2J_{pp}$= 15.7 Hz, P-γ), -23.49 (t, $^2J_{pp}$= 17.3 Hz, P-β).

IR: ν [cm^{-1}] = 3177, 2987, 2970, 2921, 2901, 1758, 1691, 1509, 1452, 1408, 1393, 1382, 1248, 1222, 1127, 1076, 1050, 1027, 900, 836, 781, 727, 573, 488, 425.

γ-(AB-C3; ACB-C12)-d4TTP 60dv.

According to general procedure 11 with 130 mg *H*-phosphonate **77dv** (0.225 mmol, 1.0 equiv.) and 124 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.16 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 69 mg (0.069 mmol, 44%) white solid.

Chemical Formula: $C_{41}H_{63}N_4O_{18}P_3$.

Molecular weight: 992.34 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 957.275; found, 957.194.

^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.64 (d, $^4J_{HH}$= 1.1 Hz, 1H, H-6), 7.44-7.38 (m, 4H, H-c^1, H-c^2), 7.17-7.12 (m, 2H, H-d^2), 7.08-7.02 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-1´), 6.44 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 5.9 Hz, $^3J_{HH}$= 2.1 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.1 Hz, 4H, H-a^1, H-a^2), 4.97-4.91 (m, 1H, H-4´), 4.31-4.12 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.81 (hept, $^3J_{HH}$= 7.0 Hz, 1H, H-g^1), 1.88 (d, $^4J_{HH}$= 0.8 Hz, 3H, H-7), 1.72 (quint, $^3J_{HH}$= 6.6 Hz, 2H, H-h^2), 1.46-1.39 (m, 2H, H-i), 1.38-1.25 (m, 22H, H-h^1, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-r).

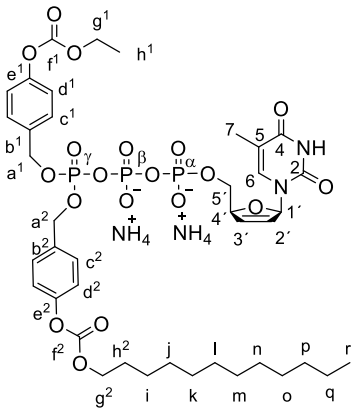
^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 177.0 (d, $^4J_{CP}$= 1.4 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.74 (C-2), 152.67 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.1 (d, $^3J_{CP}$= 8.0 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.3 Hz, C-b^1), 130.51, 130.49, 130.47 (C-c^1, C-c^2), 127.2 (C-2´), 122.8 (d, $^4J_{CP}$= 1.5 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.8 (C-1´), 87.2 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 2.2 Hz, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 2.2 Hz, $^3J_{CP}$= 6.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 3.0 Hz, C-5´), 35.2 (C-g^1), 33.0, 30.73, 30.66, 30.61, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.7 (C-h^2), 26.8 (C-i), 19.2 (C-h^1), 14.4 (C-r), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = -11.75 (d, $^2J_{pp}$= 19.6 Hz, P-α), -13.20 (d, $^2J_{pp}$= 17.5 Hz, P-γ), -23.60 (t, $^2J_{pp}$= 17.9 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2922, 2901, 1756, 1691, 1510, 1463, 1451, 1408, 1393, 1242, 1222, 1167, 1076, 1048, 1027, 1012, 902, 838, 781, 724, 579, 484.

γ-(ACB-C2; ACB-C12)-d4TTP 61lv.

According to general procedure 11 with 130 mg *H*-phosphonate **79lv** (0.225 mmol, 1.0 equiv.) and 124 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.16 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 93 mg (0.093 mmol, 59%) white solid.

Chemical Formula: $C_{40}H_{61}N_4O_{19}P_3$.

Molecular weight: 994.31 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 959.254; found, 959.197.

^{1}H NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.64 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.45-7.38 (m, 4H, H-c^1, H-c^2), 7.17-7.12 (m, 4H, H-d^1, H-d^2), 6.92 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.4 Hz, 1H, H-1´), 6.44 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.3 Hz, $^4J_{HH}$= 1.5 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 7.8 Hz, 4H, H-a^1, H-a^2), 4.96-4.92 (m, 1H, H-4´), 4.29 (dt, $^3J_{HH}$= 7.1 Hz, $^4J_{HH}$= 1.1 Hz, 2H, H-g^1), 4.28-4.15 (m, 2H, H-5´), 4.23 (dt, $^3J_{HH}$= 6.6 Hz, $^4J_{HH}$= 0.9 Hz, 2H, H-g^2), 1.89 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.73 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.45-1.39 (m, 2H, H-i,), 1.38-1.26 (m, 16H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 1.34 (td, $^3J_{HH}$= 7.1 Hz, $^4J_{HH}$=0.7 Hz, 3H, H-h^1), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-r).

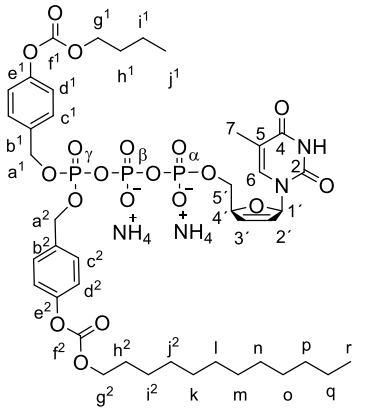
^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 166.5 (C-4), 155.1, 155.0 (C-f^1, C-f^2), 152.75 (C-2), 152.69, 152.68 (C-e^1, C-e^2), 138.6 (C-6), 135.7 (C-3´), 135.17, 135.12 (C-b^1, C-b^2), 130.52, 130.49 (C-c^1, C-c^2), 127.2 (C-2´), 122.34, 122.32 (C-d^1, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 7.8 Hz, C-4´), 70.32, 70.29, 70.26 (C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 4.4 Hz, C-5´), 65.9 (C-g^1), 33.0, 30.72, 30.65, 30.59, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.7 (C-h^2), 26.8 (C-i), 14.5, 14.4 (C-h^1, C-r), 12.5 (C-7).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = -11.72 (d, $^2J_{pp}$= 18.8 Hz, P-α), -13.20 (d, $^2J_{pp}$= 17.8 Hz, P-γ), -23.62 (t, $^2J_{pp}$= 18.8 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1758, 1688, 1451, 1406, 1393, 1249, 1221, 1126, 1075, 1055, 1027, 1012, 899, 835, 778, 722, 486.

γ-(ACB-C4; ACB-C12)-d4TTP 61mv.

According to general procedure 11 with 137 mg *H*-phosphonate **79mv** (0.225 mmol, 1.0 equiv.) and 124 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.16 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 88 mg (0.087 mmol, 55%) white solid.

Chemical Formula: $C_{42}H_{65}N_4O_{19}P_3$.

Molecular weight: 1022.35 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 987.285; found, 987.189.

^{1}H NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.66 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.44-7.38 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 4H, H-d^1, H-d^2), 6.92 (dt, $^3J_{HH}$= 3.3 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-1´), 6.45 (dt, $^3J_{HH}$= 6.1 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.3 Hz, $^4J_{HH}$= 1.3 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.97-4.91 (m, 1H, H-4´), 4.32-4.15 (m, 6H, H-5´, H-g^1, H-g^2), 1.89 (d, $^4J_{HH}$= 1.2 Hz, 3H, H-7), 1.78-1.66 (m, 4H, H-h^1, H-h^2), 1.51-1.39 (m, 4H, H-i^1, H-i^2), 1.38-1.26 (m, 16H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-r).

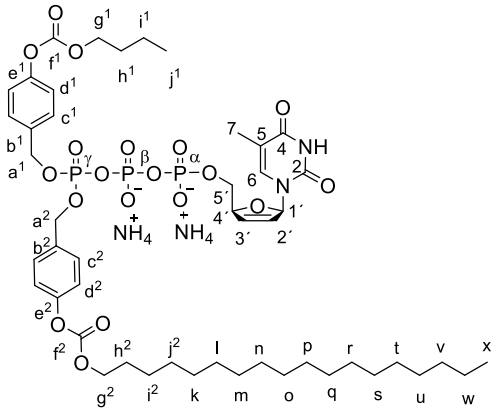
^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 166.5 (C-4), 155.1 (C-f^1, C-f^2), 152.73 (C-2), 152.68 (C-e^1, C-e^2), 138.6 (C-6), 135.6 (C-3´), 135.13, 135.08 (C-b^1, C-b^2), 130.52, 130.49 (C-c^1, C-c^2), 127.2 (C-2´), 122.3 (C-d^1, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 7.9 Hz, C-4´), 70.31, 70.29 (C-a^1, C-a^2), 70.0, 69.7 (C-g^1, C-g^2), 67.9 (d, $^3J_{CP}$= 3.2 Hz, C-5´), 33.0, 31.7, 30.73, 30.72, 30.66, 30.60, 30.4, 30.3, 23.7 (C-h^1, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.7 (C-h^2), 26.8 (C-i^2), 19.9 (C-i^1), 14.5 (C-r), 14.0 (C-j^1), 12.5 (C-7).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = -11.73 (d, $^2J_{pp}$= 17.8 Hz, P-α), -13.20 (d, $^2J_{pp}$= 15.8 Hz, P-γ), -23.59 (t, $^2J_{pp}$= 19.3 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1758, 1688, 1509, 1453, 1406, 1393, 1249, 1222, 1127, 1075, 1066, 1055, 1027, 1013, 900, 837, 779, 723, 488, 427.

γ-(ACB-C4; ACB-C18)-d4TTP 61mz.

According to general procedure 10 with 104 mg *H*-phosphonate **79mz** (0.15 mmol, 1.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt **1a** (0.13 mmol, 0.85 equiv.). Reaction time was 5 h.



Yield: 72 mg (0.066 mmol, 52%) white solid.

Chemical Formula: $C_{48}H_{77}N_4O_{19}P_3$.

Molecular weight: 1106.44 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1071.379; found, 1071.243.

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.66 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.44-7.38 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 4H, H-d^1, H-d^2), 6.92 (dt, $^3J_{HH}$= 3.6 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-1´), 6.45 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.3 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.1 Hz, 4H, H-a^1, H-a^2), 4.97-4.91 (m, 1H, H-4´), 4.32-4.15 (m, 6H, H-5´, H-g^1, H-g^2), 1.89 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.78-1.66 (m, 4H, H-h^1, H-h^2), 1.51-1.40 (m, 4H, H-i^1, H-i^2), 1.38-1.26 (m, 28H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u, H-v, H-w), 0.98 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-x).

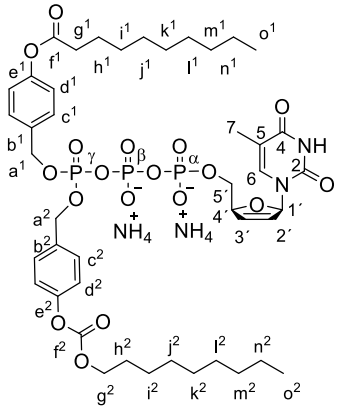
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 166.5 (C-4), 155.1 (C-f^1, C-f^2), 152.77 (C-2), 152.71 (C-e^1, C-e^2), 138.6 (C-6), 135.7 (C-3´), 135.23, 135.19 (C-b^1, C-b^2), 130.54, 130.51 (C-c^1, C-c^2), 127.2 (C-2´), 122.3 (C-d^1, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 8.7 Hz, C-4´), 70.29 (C-a^1, C-a^2), 70.0, 69.7 (C-g^1, C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 33.1, 31.8, 30.78, 30.76, 30.73, 30.67, 30.62, 30.5, 30.3, 23.7 (C-h^1, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u, C-v, C-w), 29.7 (C-h^2), 26.8 (C-i^2), 19.9 (C-i^1), 14.5 (C-r), 14.0 (C-j^1), 12.5 (C-7).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -11.76 (d, $^2J_{pp}$= 19.8 Hz, P-α), -13.19 (d, $^2J_{pp}$= 16.8 Hz, P-γ), -23.64 (t, $^2J_{pp}$= 18.3 Hz, P-β).

IR: ν [cm^{-1}] = 2986, 2968, 2923, 1749, 1684, 1507, 1453, 1405, 1393, 1222, 1066, 899, 833, 777, 725, 549, 492, 450.

γ-(AB-C9; ACB-C9)-d4TTP 8is.

According to general procedure 10 with 91 mg *H*-phosphonate **77is** (0.15 mmol, 1.0 equiv.) and 83 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.09 mmol, 0.60 equiv.). Reaction time was 5 h.



Yield: 94 mg (0.070 mmol, 78%) white solid.

Chemical Formula: $C_{44}H_{69}N_4O_{18}P_3$.

Molecular weight: 1034.38 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 999.322; found, 999.245.

^{1}H NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.64 (d, $^4J_{HH}$= 1.1 Hz, 1H, H-6), 7.42-7.36 (m, 4H, H-c^1, H-c^2), 7.16-7.10 (m, 2H, H-d^2), 7.07-7.01 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-1´), 6.44 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.14 (d, $^3J_{HH}$= 7.6 Hz, 4H, H-a^1, H-a^2), 4.97-4.91 (m, 1H, H-4´), 4.30-4.14 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.57 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 0.9 Hz, 3H, H-7), 1.78-1.68 (m, 4H, H-h^1, H-h^2), 1.46-1.24 (m, 24H, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-l^2, H-m^1, H-m^2, H-n^1, H-n^2), 0.91-0.87 (t, $^3J_{HH}$= 6.7 Hz, 6H, H-o^1, H-o^2).

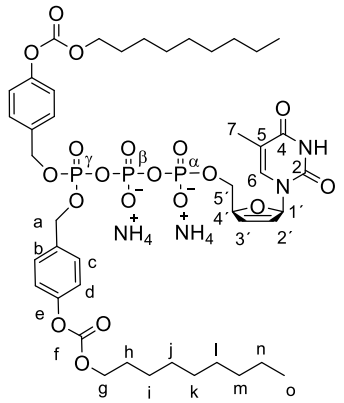
^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.2 Hz, C-f^1), 166.5 (C-4), 155.1 (C-f^2), 152.76 (C-2), 152.69 (C-e^2), 152.4 (C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.1 (d, $^3J_{CP}$= 7.7 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.50, 130.48 (2 × d, $^3J_{CP}$= 2.2 Hz, $^3J_{CP}$= 3.3 Hz, C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.1 Hz, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.2 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 35.0 (C-g^1), 33.02, 33.01, 30.59, 30.57, 30.41, 30.39, 30.35, 30.32, 30.2, 23.7 (C-i^1, C-j^1, C-j^2, C-k^1, C-k^2, C-l^1, C-l^2, H-m^1, H-m^2, H-n^1, H-n^2), 29.7 (C-h^2), 26.8 (C-i^2), 25.9 (C-h^1), 14.4 (C-o^1, C-o^2), 12.5 (C-7).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = -11.67 (d, $^2J_{pp}$= 16.6 Hz, P-α), -13.09 (d, $^2J_{pp}$= 15.6 Hz, P-γ), -24.43 (t, $^2J_{pp}$= 16.8 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1758, 1694, 1508, 1452, 1406, 1393, 1382, 1250, 1228, 1168, 1075, 1055, 899, 782, 491, 438.

γ-(ACB-C9; ACB-C9)-d4TTP 61ss.

According to general procedure 10 with 95 mg *H*-phosphonate **79ss** (0.15 mmol, 1.0 equiv.) and 83 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.11 mmol, 0.70 equiv.). Reaction time was 5 h.



Yield: 77 mg (0.074 mmol, 70%) white solid.

Chemical Formula: $C_{44}H_{69}N_4O_{19}P_3$.

Molecular weight: 1050.38 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1015.317; found, 1015.231.

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.65 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 7.44-7.36 (m, 4H, H-c), 7.18-7.11 (m, 4H, H-d), 6.92 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.46 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 3.5 Hz, $^4J_{HH}$= 1.5 Hz, 1H, H-2´), 5.15 (d, $^3J_{HH}$= 8.1 Hz, 4H, H-a), 4.98-4.91 (m, 1H, H-4´), 4.30-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 4H, H-g), 1.89 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.73 (quint, $^3J_{HH}$= 6.7 Hz, 4H, H-h), 1.46-1.25 (m, 24H, H-i, H-j, H-k, H-l, H-m, H-n), 0.90 (t, $^3J_{HH}$= 6.8 Hz, 6H, H-o).

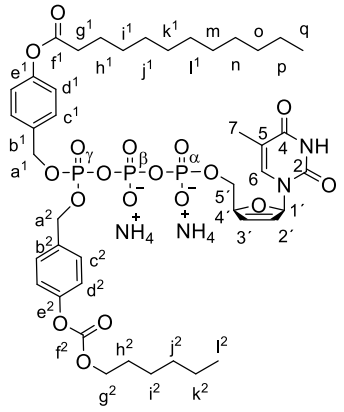
^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.5 (C-4), 155.1 (C-f), 152.76 (C-2), 152.69 (C-e), 138.6 (C-6), 135.7 (C-3´), 135.1 (d, $^3J_{CP}$= 7.3 Hz, C-b), 130.5 (d, $^3J_{CP}$= 3.6 Hz, C-c), 127.1 (C-2´), 122.3 (d, $^4J_{CP}$= 1.4 Hz, C-d), 112.0 (C-5), 90.8 (C-1´), 87.2 (d, $^3J_{CP}$= 8.6 Hz, C-4´), 70.3 (dd, $^3J_{CP}$= 2.1 Hz, $^3J_{CP}$= 5.9 Hz, C-a), 70.0 (C-g), 67.9 (d, $^3J_{CP}$= 5.0 Hz, C-5´), 33.0, 30.6, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n), 29.7 (C-h), 26.8 (C-i), 14.4 (C-o), 12.5 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.75 (d, $^2J_{pp}$= 19.6 Hz, P-α), -13.21 (d, $^2J_{pp}$= 15.8 Hz, P-γ), -23.66 (t, $^2J_{pp}$= 18.0 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1759, 1690, 1509, 1453, 1406, 1393, 1249, 1222, 1127, 1075, 1055, 1027, 901, 837, 782, 779, 517, 486.

γ-(AB-C11; ACB-C6)-d4TTP 8jr.

According to general procedure 11 with 136 mg *H*-phosphonate **77jr** (0.225 mmol, 1.0 equiv.) and 106 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.14 mmol, 0.60 equiv.). Reaction time was 5 h.



Yield: 72 mg (0.073 mmol, 54%) white solid.

Chemical Formula: $C_{43}H_{67}N_4O_{18}P_3$.

Molecular weight: 1020.37 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 985.306; found, 985.230.

^{1}H NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.64 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.43-7.36 (m, 4H, H-c^1, H-c^2), 7.18-7.10 (m, 2H, H-d^2), 7.08-7.02 (m, 2H, H-d^1), 6.92 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-1´), 6.44 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 3.2 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.14 (d, $^3J_{HH}$= 7.6 Hz, 4H, H-a^1, H-a^2), 4.97-4.92 (m, 1H, H-4´), 4.31-4.14 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.57 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.89 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.78-1.68 (m, 4H, H-h^1, H-h^2), 1.48-1.25 (m, 22H, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-m, H-n, H-o, H-p), 0.97-0.86 (m, 6H, H-l^2, H-q).

^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 173.6 (C-f^1), 166.4 (C-4), 155.0 (C-f^2), 152.69 (C-2), 152.62 (C-e^2), 152.3 (C-e^1), 138.5 (C-6), 135.5 (C-3´), 135.0 (d, $^3J_{CP}$= 6.7 Hz, C-b^2), 134.7 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.47, 130.45, 130.44, 129.6 (C-c^1, C-c^2), 127.2 (C-2´), 122.8 (d, $^3J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 Hz, C-d^2), 112.0 (C-5), 90.8 (C-1´), 87.0 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 6.5 Hz, $^3J_{CP}$= 2.3 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.6 Hz, C-5´), 35.0 (C-g^1), 33.0, 32.5, 30.69, 30.57, 30.42, 30.37, 23.7, 23.5 (C-j^1, C-j^2, C-k^1, C-k^2, C-l^1, H-m, H-n, H-o, H-p), 30.1 (C-i^1), 29.6 (C-h^2), 26.4 (C-i^2), 25.9 (C-h^1), 14.5, 14.4 (C-l^2, C-q), 12.5 (C-7).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = -11.75 (d, $^2J_{pp}$= 18.3 Hz, P-α), -13.16 (d, $^2J_{pp}$= 17.8 Hz, P-γ), -23.62 (t, $^2J_{pp}$= 17.8 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2901, 1758, 1692, 1508, 1452, 1406, 1393, 1381, 1249, 1226, 1168, 1075, 1055, 1027, 900, 838, 782, 727, 486, 432.

γ-(β-cyanoethyl; ACB-C12)-d4TTP 85v.

According to general procedure 12 with 136 mg *H*-phosphonate **83v** (0.30 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.21 mmol, 0.70 equiv.). Reaction time was 5 h.

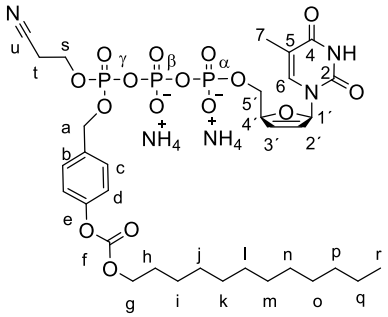
Yield: 98 mg (0.11 mmol, 52%) white solid.

Chemical Formula: $C_{33}H_{54}N_5O_{16}P_3$.

Molecular weight: 869.28 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 834.218; found, 834.179.



^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.65 (d, $^4J_{HH}$= 1.1 Hz, 1H, H-6), 7.55-7.49 (m, 2H, H-c), 7.22-7.16 (m, 2H, H-d), 6.97-6.91 (m, 1H, H-1´), 6.52-6.45 (m, 1H, H-3´), 5.88-5.82 (m, 1H, H-2´), 5.23 (d, $^3J_{HH}$= 8.0 Hz, 2H, H-a), 5.01-4.95 (m, 1H, H-4´), 4.33 (q, $^3J_{HH}$= 6.1 Hz, 2H, H-s), 4.27-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g), 2.87 (t, $^3J_{HH}$= 6.0 Hz, 2H, H-t), 1.90 (s, 3H, H-7), 1.73 (q, $^3J_{HH}$= 6.7 Hz, 2H, H-h), 1.46-1.25 (m,18H, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.89 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 166.5 (C-4), 155.1 (C-f), 152.8 (C-2), 152.76 (C-e), 138.6 (C-6), 135.6 (C-3´), 135.1, 134.98, 134.96 (C-b), 130.63 (d, $^4J_{CP}$= 1.5 Hz, C-c), 127.2 (C-2´), 122.4 (C-d), 118.6 (C-u), 112.0 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 8.7 Hz, C-4´), 70.5 (d, $^3J_{CP}$= 5.2 Hz, C-a), 70.0 (C-g), 67.9 (d, $^3J_{CP}$= 5.8 Hz, C-5´), 64.3 (d, $^3J_{CP}$= 5.1 Hz, C-s), 33.0, 30.73, 30.66, 30.61, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.7 (C-h), 26.8 (C-i), 19.9 (d, $^3J_{CP}$= 8.1 Hz, C-t), 14.5 (C-r), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = -11.67 (d, $^2J_{pp}$= 18.5 Hz, P-α), -13.65 (d, $^2J_{pp}$= 15.9 Hz, P-γ), -23.47 (t, $^2J_{pp}$= 16.7 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2963, 1752, 1692, 1507, 1452, 1408, 1375, 1249, 1127, 1066, 1046, 902, 837, 781, 718, 608, 505, 486, 437.

γ-(ACB-C12)-d4TTP 62v.

According to general procedure 12 with 136 mg *H*-phosphonate **83v** (0.30 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt **1a** (0.21 mmol, 0.70 equiv.). Reaction time was 5 h.

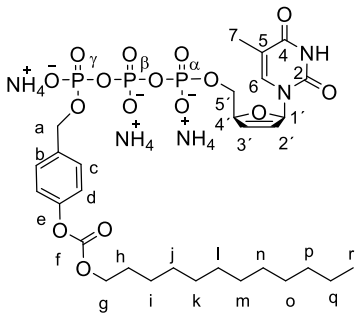
Yield: 41 mg (0.048 mmol, 23%) white solid.

Chemical Formula: $C_{30}H_{54}N_5O_{16}P_3$.

Molecular weight: 833.28 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 781.191; found, 781.162.



^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.65 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.52-7.44 (m, 2H, H-c), 7.16-7.09 (m, 2H, H-d), 6.92 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-1´), 6.48 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.7 Hz, 1H, H-3´), 5.82 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 3.2 Hz, $^4J_{HH}$= 1.3 Hz, 1H, H-2´), 5.05 (d, $^3J_{HH}$= 6.3 Hz, 2H, H-a), 5.01-4.95 (m, 1H, H-4´), 4.27-4.10 (m, 2H, H-5´), 4.22 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g), 1.90 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.73 (q, $^3J_{HH}$= 6.6 Hz, 2H, H-h), 1.46-1.25 (m, 18H, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.6 (C-4), 155.3 (C-f), 152.8 (C-2), 152.0 (C-e), 138.6 (C-6), 137.5 (d, $^3J_{CP}$= 8.9 Hz, C-b), 135.8 (C-3´), 129.8 (C-c), 127.1 (C-2´), 122.0 (C-d), 112.0 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 8.7 Hz, C-4´), 69.9 (C-g), 68.2 (d, $^3J_{CP}$= 5.1 Hz, C-a), 67.8 (d, $^3J_{CP}$= 5.9 Hz, C-5´), 33.1, 30.75, 30.68, 30.63, 30.5, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.7 (C-h), 26.8 (C-i), 14.5 (C-r), 12.5 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -10.96 (d, $^2J_{pp}$= 19.6 Hz, P-α), -11.28 (d, $^2J_{pp}$= 17.9 Hz, P-γ), -21.97 (t, $^2J_{pp}$= 17.9 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2963, 1699, 1652, 1521, 1507, 1456, 1247, 1231, 1066, 1047, 1027, 668, 548, 471, 436.

γ-(β-cyanoethyl; ACB-C16)-d4TTP 85y.

According to general procedure 12 with 153 mg *H*-phosphonate **83y** (0.30 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt **1a** (0.21 mmol, 0.70 equiv.). Reaction time was 5 h.

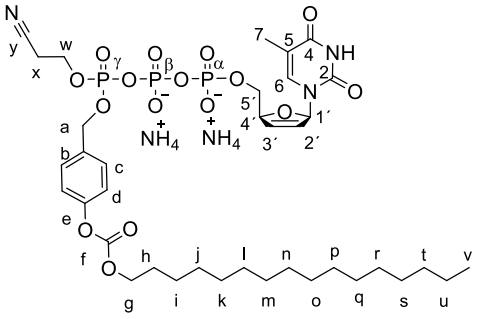
Yield: 123 mg (0.13 mmol, 63%) white solid.

Chemical Formula: $C_{37}H_{62}N_5O_{16}P_3$.

Molecular weight: 925.34 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 890.280; found, 890.226.



^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.65 (s, 1H, H-6), 7.55-7.49 (m, 2H, H-c), 7.22-7.16 (m, 2H, H-d), 6.97-6.91 (m, 1H, H-1´), 6.52-6.45 (m, 1H, H-3´), 5.88-5.82 (m, 1H, H-2´), 5.23 (d, $^3J_{HH}$= 8.0 Hz, 2H, H-a), 5.01-4.95 (m, 1H, H-4´), 4.33 (q, $^3J_{HH}$= 6.9, 2H, H-w), 4.27-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g), 2.87 (t, $^3J_{HH}$= 6.0 Hz, 2H, H-x), 1.90 (s, 3H, H-7), 1.73 (q, $^3J_{HH}$= 6.8 Hz, 2H, H-h), 1.46-1.25 (m, 26H, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.89 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-v).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.6 (C-4), 155.1 (C-f), 152.8 (C-2), 152.77 (C-e), 138.7 (C-6), 135.7 (C-3´), 135.1, 134.99, 134.98 (C-b), 130.6 (d, $^3J_{CP}$= 2.2 Hz, C-c), 127.2 (C-2´), 122.4, 122.0 (C-d), 118.6 (C-y), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.7 Hz, C-4´), 70.5 (d, $^3J_{CP}$= 5.8 Hz, C-a), 70.0 (C-g), 67.9 (d, $^3J_{CP}$= 5.8 Hz, C-5´), 64.1 (d, $^3J_{CP}$= 5.8 Hz, C-w), 33.1, 30.78, 30.77, 30.74, 30.68, 30.63, 30.5, 30.3 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h), 26.8 (C-i), 19.9 (d, $^3J_{CP}$= 8.1 Hz, C-x), 14.5 (C-v), 12.5 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.67 (d, $^2J_{pp}$= 17.6 Hz, P-α), -13.65 (d, $^2J_{pp}$= 15.9 Hz, P-γ), -23.53 (t, $^2J_{pp}$= 16.8 Hz, P-β).

IR: ν [cm^{-1}] = 3190, 2969, 2921, 2852, 1759, 1689, 1662, 1510, 1464, 1394, 1248, 1221, 1128, 1077, 1027, 906, 836, 780, 721, 695, 577, 513, 489, 427.

γ-(ACB-C16)-d4TTP 62y.

According to general procedure 12 with 153 mg *H*-phosphonate **83y** (0.30 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt **1a** (0.21 mmol, 0.70 equiv.). Reaction time was 5 h.

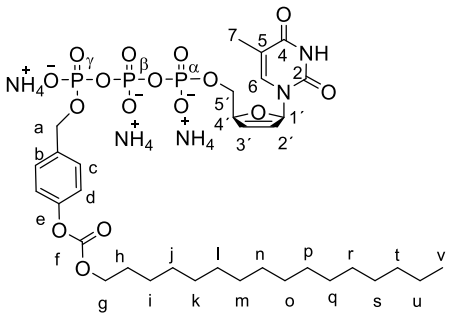
Yield: 19 mg (0.021 mmol, 10%) white solid.

Chemical Formula: $C_{34}H_{62}N_5O_{16}P_3$.

Molecular weight: 889.34 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 837.254; found, 837.128.



^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.68 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.52-7.46 (m, 2H, H-c), 7.15-7.09 (m, 2H, H-d), 6.95-6.91 (m, 1H, H-1´), 6.54-6.49 (m, 1H, H-3´), 5.85-5.78 (m, 1H, H-2´), 5.05 (d, $^3J_{HH}$= 5.4 Hz, 2H, H-a), 5.01-4.94 (m, 1H, H-4´), 4.31-4.15 (m, 2H, H-5´), 4.22 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g), 1.90 (d, $^4J_{HH}$= 1.2 Hz, 3H, H-7), 1.72 (q, $^3J_{HH}$= 6.7 Hz, 2H, H-h), 1.46-1.25 (m, 26H, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-v).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.6 (C-4), 155.3 (C-f), 152.8 (C-2), 152.0 (C-e), 138.7 (C-6), 137.6 (C-b), 135.9 (C-3´), 129.8 (C-c), 127.0 (C-2´), 121.9 (C-d), 112.0 (C-5), 90.9 (C-1´), 87.1 (C-4´), 69.9 (C-g), 68.1 (C-a), 67.9 (C-5´), 33.1, 30.78, 30.6, 30.5, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h), 26.8 (C-i), 14.4 (C-v), 12.5 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.15 (d, $^2J_{pp}$= 17.6 Hz, P-α), -11.35 (d, $^2J_{pp}$= 19.9 Hz, P-γ), -22.28 (t, $^2J_{pp}$= 18.9 Hz, P-β).

IR: ν [cm^{-1}] = 2987, 2971, 2917, 2850, 1758, 1688, 1508, 1453, 1394, 1220, 1127, 1066, 1014, 904, 869, 836, 782, 644, 491, 427.

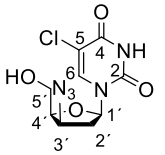
3'-Azido-5-chloro-2',3'-dideoxyuridine (3'-AZdd-5-ClU, 66).

Under dry conditions the corresponding nucleoside **87** (0.73 g, 1.0 eq.) and NCS (0.80 g, 3.0 eq.) were dissolved in pyridine and heated to reflux for 12 h. Then the solvent was removed in vacuum. The residue was added 4 mL of a 0.5 M solution of TBAF in dry THF. After 4h, THF was removed in vacuum and the residue was purified by flash column chromatography (silica) with CH_2Cl_2/MeOH (15:1) as eluent.

Yield: 0.4 g (1.4 mmol, 70%) yellow solid.

Chemical Formula: $C_9H_{10}ClN_5O_4$.

Molecular weight: 287.66 g/mol.



HRMS (ESI$^+$, m/z): $[M+Na]^+$ 310.0313; found 310.0564.

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm]= 8.06 (s, 1H, H-6), 6.08 (dd, $^{3}J_{HH}$= 7.5 Hz, $^{3}J_{HH}$= 2.6 Hz, 1H, H-1´), 4.46-4.38 (m, 1H, H-3´), 4.20-4.12 (m, 1H, H-4´), 3.93-3.86 (m, 2H, H-5´), 2.85-2.72 (m, 1H, H-2´a), 2.33-2.24 (m, 2H, H-2´b).

^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 161.5 (C-4), 151.3 (C-2), 139.0 (C-6), 109.0 (C-5), 86.6 (C-1´), 84.8 (C-4´), 62.3 (C-3´), 61.2 (C-5´), 39.4 (C-2´).

IR: ν [cm^{-1}] = 3342, 2973, 2810, 2105, 1686, 1625, 1452, 1391, 1333, 1265, 1127, 1088, 1048, 1023, 1000, 915, 864, 821, 794, 755, 731, 699, 664, 636, 607, 544, 443.

3'-Azido-5-chloro-2',3'-dideoxyuridine monophosphate 66a (AZddClUMP).

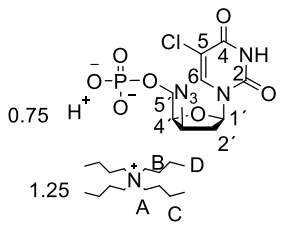
According to general procedure 9, with 0.36 g 3'-AZdd-5-ClU **66** (1.25 mmol, 1.0 equiv.) and 0.93 mL $POCl_3$ (12.5 mmol, 10.0 equiv.) in 5.0 mL TMP at 0 °C and stirred for 1h. Next, the solution was poured into ice water and stirred for 1 h.

Yield: 0.37 g (0.56 mmol, 45%) white solid.

Chemical Formula: $C_9H_9ClN_5O_7P_2^-$.

Molecular weight: 364.99 g/mol.

MALDI-MS (m/z): $[M-H]^-$ 366.001; found, 365.964.



^{1}H-NMR (400 MHz, CD_3OD): δ [ppm]= 8.05 (s, 1H, H-6), 6.09 (dd, $^{3}J_{HH}$= 7.6 Hz, $^{3}J_{HH}$= 2.7 Hz, 1H, H-1´), 4.44-4.40 (m, 1H, H-3´), 4.20-4.14 (m, 1H, H-4´), 3.92-3.88 (m, 2H, H-5´), 3.38-3.20 (m, 10H, H-A), 2.82-2.75 (m, 1H, H-2´a), 2.62-2.47 (m, 2H, H-2´b), 1.76-1.58 (m, 10H, H-B), 1.48-1.34 (m, 10H, H-C), 1.00 (t, $^{3}J_{HH}$=7.3 Hz, 15H, H-D).

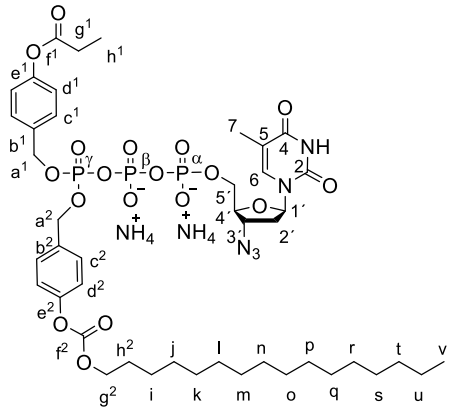
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 161.2 (C-4), 151.1 (C-2), 138.7 (C-6), 109.1 (C-5), 86.6 (C-1´), 83.2 (d, $^{3}J_{CP}$= 8.1 Hz, C-4´), 65.0 (d, $^{3}J_{CP}$= 5.1 Hz, C-5´), 62.3 (C-3´), 59.4 (t, $^{3}J_{CP}$= 2.9 Hz, C-A), 39.3 (C-2´), 24.7 (C-B), 20.7 (t, $^{4}J_{CP}$= 1.5 Hz, C-C), 14.0 (C-D).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 0.43.

IR: ν [cm^{-1}] = 2960, 2874, 2773, 2106, 1690, 1626, 1452, 1383, 1331, 1262, 1223, 1177, 1127, 1054, 1001, 938, 877, 793, 752, 662, 634, 539, 510, 443.

γ-(AB-C2; ACB-C16)-AZTTP 89b1.

According to general procedure 11 with 140 mg *H*-phosphonate **77by** (0.225 mmol, 1.0 equiv.) and 131 mg (n-$Bu_4N)_2$·AZTMP salt **2a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 85 mg (0.079 mmol, 49%) white solid.

Chemical Formula: $C_{44}H_{70}N_7O_{18}P_3$.

Molecular weight: 1077.39 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1042.339; found, 1042.289.

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.75 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 7.44-7.38 (m, 4H, H-c^1, H-c^2), 7.15-7.12 (m, 2H, H-d^2), 7.08-7.04 (m, 2H, H-d^1), 6.20 (dd, $^3J_{HH}$= 7.9 Hz, $^3J_{HH}$=6.5 Hz, 1H, H-1´), 5.16 (d, $^3J_{HH}$= 8.0 Hz, 4H, H-a^1, H-a^2), 4.53 (dd, $^3J_{HH}$= 6.6 Hz, $^3J_{HH}$=2.8 Hz, 1H, H-3´), 4.26-4.18 (m, 4H, H-5´, H-g^2), 4.06-4.01 (m, 1H, H-4´), 2.60 (q, $^3J_{HH}$= 7.6 Hz, 2H, H-g^1), 2.45-2.35 (m, 1H, H-2´a), 2.30-2.23 (m, 1H, H-2´b), 1.90 (d, $^4J_{HH}$= 0.8 Hz, 3H, H-7), 1.72 (quint, $^3J_{HH}$= 6.7 Hz, 2H, H-h^2), 1.46-1.39 (m, 2H, H-i), 1.38-1.26 (m, 24H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.22 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-h^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-v).

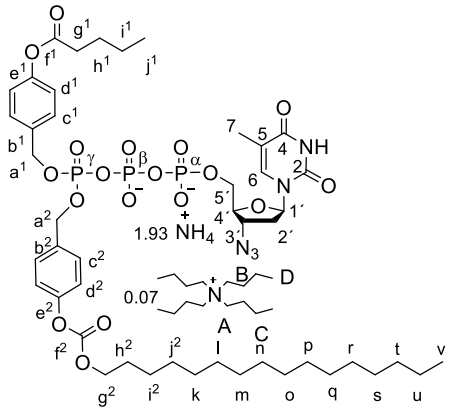
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 174.4 (C-f^1), 166.3 (C-4), 155.1 (C-f^2), 152.7 (C-2), 152.4 (C-e^2), 152.3 (C-e^1), 137.9 (C-6), 135.1 (d, $^3J_{CP}$= 7.9 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.5 Hz, C-b^1), 130.5 (C-c^1, C-c^2), 122.8 (d, $^3J_{CP}$= 5.1 Hz, C-d^1), 122.3 (d, $^3J_{CP}$= 2.9 Hz, C-d^2), 112.2 (C-5), 85.9 (C-1´), 84.5 (C-4´), 70.4, 70.3, 70.2 (C-a^1, C-a^2), 70.0 (C-g^2), 67.0 (d, $^3J_{CP}$= 5.0 Hz, C-5´), 62.9 (d, $^3J_{CP}$= 3.8 Hz, C-3´), 37.8 (C-2´), 33.0, 30.8, 30.6, 30.5, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 14.5 (C-v), 12.6 (C-7), 9.4 (C-h^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.79 (d, $^2J_{pp}$= 17.7 Hz, P-α), -12.99 (d, $^2J_{pp}$= 15.9 Hz, P-γ), -23.47 (t, $^2J_{pp}$= 17.1 Hz, P-β).

IR: ν [cm^{-1}] = 2969, 2922, 2852, 2104, 1754, 1714, 1509, 1462, 1365, 1217, 1167, 1127, 1056, 1004, 916, 854, 826, 779, 720, 515, 484, 414.

γ-(AB-C4; ACB-C16)-AZTTP 89b2.

According to general procedure 11 with 146 mg *H*-phosphonate **77ey** (0.225 mmol, 1.0 equiv.) and 131 mg (n-$Bu_4N)_2$·AZTMP salt **2a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 124 mg (0.110 mmol, 70%) white solid.

Chemical Formula: $C_{46}H_{66}N_5O_{18}P_3^{2-}$.

Molecular weight: 1069.36 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1070.370; found, 1070.355.

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.76 (d, $^4J_{HH}$= 1.1 Hz, 1H, H-6), 7.44-7.37 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 2H, H-d^2), 7.08-7.02 (m, 2H, H-d^1), 6.20 (dd, $^3J_{HH}$= 7.9 Hz, $^3J_{HH}$=5.9 Hz, 1H, H-1´), 5.16 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.58-4.52 (m, 1H, H-3´), 4.26-4.18 (m, 4H, H-5´, H-g^2), 4.06-4.01 (m, 1H, H-4´), 3.26-3.18 (m, 0.56H, H-A), 2.58 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 2.45-2.35 (m, 1H, H-2´a), 2.30-2.23 (m, 1H, H-2´b), 1.90 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.77-1.60 (m, 4.56H, H-B, H-h^1, H-h^2), 1.49-1.26 (m, 28.56H, H-C, H-i^1, H-i^2 , H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.01 (t, $^3J_{HH}$= 7.2 Hz, 0.84H, H-D), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-v).

^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 173.7 (C-f^1), 166.4 (C-4), 155.1 (C-f^2), 152.7 (C-2), 152.4 (C-e^1, C-e^2), 137.9 (C-6), 135.1 (d, $^3J_{CP}$= 7.6 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.48, 130.46, 130.44 (C-c^1, C-c^2), 122.9 (C-d^1), 122.3 (C-d^2), 112.2 (C-5), 85.8 (C-1´), 84.5 (d, $^3J_{CP}$= 9.9 Hz, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.0 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 62.9 (C-3´), 59.5 (C-A), 37.8 (C-2´), 34.7 (C-g^1), 33.0, 30.75, 30.73, 30.66, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.0 (C-h^1), 26.8 (C-i^2), 24.7 (C-B), 23.2 (C-i^1), 20.7 (C-C), 14.4 (C-v), 14.1 (C-j^1), 13.9 (C-D), 12.6 (C-7).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -11.88 (d, $^2J_{pp}$=19.3 Hz, P-α), -13.14 (d, $^2J_{pp}$=17.7 Hz, P-γ), -23.53 (t, $^2J_{pp}$= 17.5 Hz, P-β).

IR: ν [cm^{-1}] = 3015, 2969, 2922, 2852, 2104, 1754, 1714, 1509, 1455, 1366, 1217, 1167, 1128, 1083, 1005, 916, 853, 827, 780, 720, 515, 486, 414.

γ-(AB-C4; alkyl-C18)-AZTTP 90b.

According to general procedure 11 with 118 mg *H*-phosphonate **93** (0.225 mmol, 1.0 equiv.) and 131 mg (n-$Bu_4N)_2$·AZTMP salt **2a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.

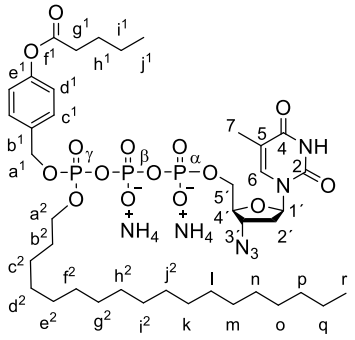
Yield: 125.5 mg (0.128 mmol, 81%) white solid.

Chemical Formula: $C_{40}H_{72}N_7O_{15}P_3$.

Molecular weight: 983.46 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 948.370; found, 948.340.



^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.79 (s, 1H, H-6), 7.52-7.46 (m, 2H, H-c^1), 7.12-7.06 (m, 2H, H-d^1), 6.23 (dd, $^3J_{HH}$= 7.9 Hz, $^3J_{HH}$=6.1 Hz, 1H, H-1´), 5.16 (d, $^3J_{HH}$= 8.3 Hz, 4H, H-a^1), 4.62-4.55 (m, 1H, H-3´), 4.26-4.18 (m, 2H, H-5´), 4.16-4.05 (m, 3H, H-4´, H-a^2), 2.58 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 2.48-2.36 (m, 1H, H-2´a), 2.33-2.23 (m, 1H, H-2´b), 1.92 (d, $^3J_{HH}$= 2.5 Hz, 3H, H-7), 1.73 (quint, $^3J_{HH}$= 7.4 Hz, 2H, H-h^1), 1.62 (quint, $^3J_{HH}$= 6.7 Hz, 2H, H-b^2), 1.46 (sext, $^3J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.36-1.26 (m, 30H, H-c^2, H-d^2, H-e^2, H-f^2, H-j^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.98 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-r).

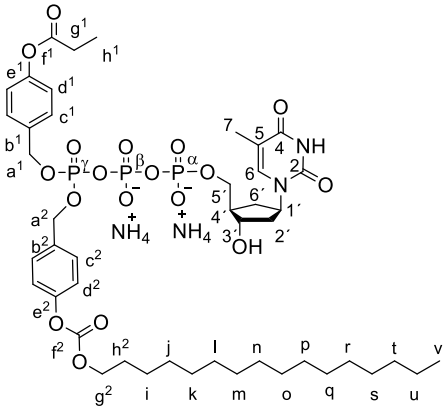
^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 173.6 (C-f^1), 163.7 (C-4), 152.4 (C-2), 152.3 (C-e^1), 137.9 (C-6), 135.1 (d, $^3J_{CP}$= 7.3 Hz, C-b^1), 130.3 (d, $^3J_{CP}$= 1.8 Hz, C-c^1), 122.8 (C-d^1), 112.2 (C-5), 85.9 (C-1´), 84.6 (d, $^3J_{CP}$= 9.6 Hz, C-4´), 70.2 (dd, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 2.7 Hz, C-a^1), 69.8 (d, $^3J_{CP}$= 6.6 Hz, C-a^2), 67.0 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 63.0 (C-3´), 37.9 (C-2´), 34.8 (C-g^1), 31.2 (d, $^3J_{CP}$= 7.5 Hz, C-b^2), 33.0, 30.78, 30.73, 30.71, 30.65, 30.4, 30.3, 23.7 (C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 28.0 (C-h^1), 26.5 (C-c^2), 23.2 (C-i^1), 14.5 (C-r), 14.1 (C-j^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -10.30 (d, $^2J_{pp}$=18.1 Hz, P-α), -13.05 (d, $^2J_{pp}$=16.1 Hz, $^3J_{pp}$=5.8 Hz, P-γ), -22.22 (t, $^2J_{pp}$= 16.8 Hz, P-β).

IR: ν [cm^{-1}] = 3015, 2926, 2922, 2852, 2105, 1738, 1508, 1436, 1366, 1229, 1216, 1167, 1127, 1084, 1009, 914, 719, 527, 515, 414.

γ-(AB-C2; ACB-C16)-*carba*-TTP 89c1.

According to general procedure 11 with 140 mg *H*-phosphonate **77by** (0.225 mmol, 1.0 equiv.) and 108 mg (*n*-$Bu_4N)_2$·*carba*-TMP salt **63a** (0.135 mmol, 0.6 equiv.). Reaction time was 3h.



Yield: 92 mg (0.088 mmol, 65%) white solid.

Chemical Formula: $C_{45}H_{73}N_4O_{18}P_3$.

Molecular weight: 1050.41 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1015.353; found, 1015.219.

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.52 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 7.44-7.38 (m, 4H, H-c^1, H-c^2), 7.18-7.12 (m, 2H, H-d^2), 7.09-7.03 (m, 2H, H-d^1), 5.17 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 5.11-4.97 (m, 1H, H-3´), 4.34-4.26 (m, 1H, H-1´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 4.17-3.98 (m, 2H, H-5´), 2.60 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 2.25-2.09 (m, 2H, H-2´a, H-4´), 2.09-2.01 (m, 1H, H-6´a), 1.99-1.91 (m, 1H, H-6´b), 1.88 (d, $^4J_{HH}$= 0.9 Hz, 3H, H-7), 1.78-1.58 (m, 3H, H-h^2, H-2´b), 1.45-1.25 (m, 26 H, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.22 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-h^1), 0.89 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-v).

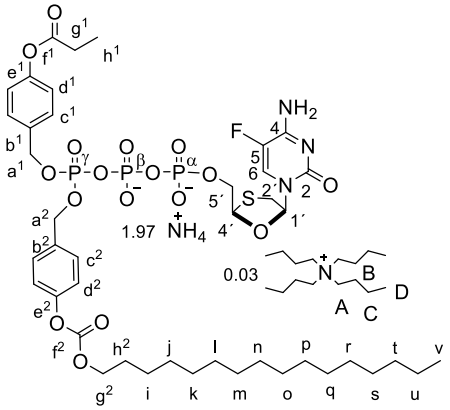
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 174.4 (C-f^1), 166.4 (C-4), 155.1 (C-f^2), 152.9 (C-2), 152.7 (C-e^2), 152.4 (C-e^1), 139.9 (C-6), 135.1 (d, $^3J_{CP}$= 7.8 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.8 Hz, C-b^1), 130.47, 130.43 (C-c^1, C-c^2), 122.9 (C-d^1), 122.3 (C-d^2), 111.5 (C-5), 73.3 (C-1´), 70.4, 70.3 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.6 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 6.6 Hz, C-5´), 55.5 (C-3´), 48.7(C-4´), 39.7 (C-6´), 33.04, 33.01, 30.76, 30.73, 30.67, 30.61, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 14.5 (C-v), 12.4 (C-7), 9.3 (C-h^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -10.97 (d, $^2J_{pp}$=19.5 Hz, P-α), -13.14 (d, $^2J_{pp}$=17.6 Hz, P-γ), -23.58 (t, $^2J_{pp}$= 17.6 Hz, P-β).

IR: ν [cm^{-1}] = 3184, 3016, 2969, 2922, 2852, 1753, 1683, 1508, 1456, 1365, 1216, 1167, 1127, 1077, 1005, 920, 845, 779, 720, 597, 513, 484, 420.

γ-(AB-C2; ACB-C16)-FTCTP 89d1.

According to general procedure 11 with 140 mg *H*-phosphonate **77by** (0.225 mmol, 1.0 equiv.) and 112 mg FTCMP 1.6×nBu_4N^+ salt **7a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 103 mg (0.095 mmol, 60%) white solid.

Chemical Formula: $C_{42}H_{59}FN_3O_{17}P_3S_2^-$.

Molecular weight: 1021.28 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1022.285; found, 1022.178.

^{1}H-NMR (600 MHz, CD_3OD): δ [ppm]= 8.14 (d, $^3J_{HH}$= 6.5 Hz, 1H, H-6), 7.42-7.38 (m, 4H, H-c^1, H-c^2), 7.17-7.12 (m, 2H, H-d^2), 7.07-7.03 (m, 2H, H-d^1), 6.18 (dt, $^3J_{HH}$= 4.9 Hz, $^3J_{HH}$= 1.3 Hz, 1H, H-1´), 5.37 (t, $^3J_{HH}$= 4.2 Hz, 1H, H-4´), 5.15 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.41-4.35 (m, 1H, H-5´$_a$), 4.34-4.28 (m, 1H, H-5´$_b$), 4.22 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 3.44 (dd, $^2J_{HH}$= 12.1 Hz, $^3J_{HH}$= 5.5 Hz, 1H, H-2´$_a$), 3.23-3.17 (m, 0.24H, H-A), 3.11 (dd, $^3J_{HH}$= 11.8 Hz, $^3J_{HH}$= 4.3 Hz, 1H, H-2´$_b$), 2.59 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.71 (quint, $^3J_{HH}$= 6.8 Hz, 2H, H-h^2), 1.67-1.58 (m, 0.24H, H-B), 1.44-1.25 (m, 26.24H, H-C, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.21 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-h^1), 1.00 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-D), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-v).

^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 174.4 (C-f^1), 158.7 (d, $^2J_{CP}$= 15.5 Hz, C-4), 155.0 (C-f^2), 154.7 (C-2), 152.6 (C-e^2), 152.3 (C-e^1), 138.6, 137.0 (C-5), 135.1 (d, $^3J_{CP}$= 7.5 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.46, 130.42 (C-c^1, C-c^2), 127.5, 127.3 (C-6), 122.8 (C-d^1), 122.3 (C-d^2), 89.0 (C-1´), 85.8 (d, $^3J_{CP}$= 9.2 Hz, C-4´), 70.4, 70.2 (2 × d, $^3J_{CP}$= 6.5 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 59.4 (C-A), 37.9 (C-2´), 33.0, 30.77, 30.74, 30.68, 30.62, 30.5, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.4 (C-g^1), 26.8 (C-i), 24.7 (C-B), 20.7 (C-C), 14.5 (C-v), 14.0 (C-D), 9.4 (C-h^1).

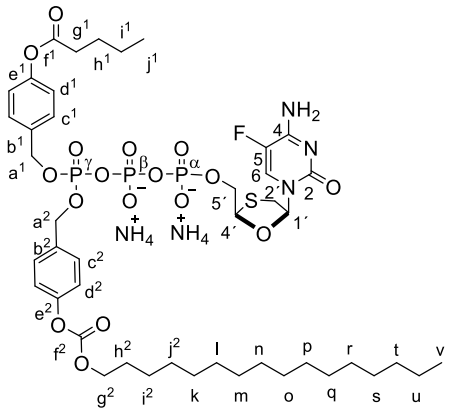
^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -11.82 (d, $^2J_{pp}$=20.4 Hz, P-α), -13.14 (d, $^2J_{pp}$=14.7 Hz, P-γ), -23.44 (t, $^2J_{pp}$= 17.7 Hz, P-β).

^{19}F-NMR (188 MHz, CD_3OD): δ [ppm]= -167.5- -167.2.

IR: ν [cm^{-1}] = 3015, 2970, 2921, 2851, 1738, 1683, 1606, 1508, 1455, 1365, 1228, 1216, 1166, 1079, 1003, 924, 774, 719, 526, 514, 412.

γ-(AB-C4; ACB-C16)-FTCTP 89d2.

According to general procedure 11 with 146 mg *H*-phosphonate **77ey** (0.225 mmol, 1.0 equiv.) and 112 mg FTCMP 1.6×nBu_4N^+ salt **7a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 129 mg (0.118 mmol, 75%) white solid.

Chemical Formula: $C_{44}H_{73}N_5O_{17}P_3FS$.

Molecular weight: 1096.36 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1050.316; found, 1050.284.

^{1}H-NMR (600 MHz, CD_3OD): δ [ppm]= 8.14 (d, $^3J_{HH}$= 6.5 Hz, 1H, H-6), 7.45-7.38 (m, 4H, H-c^1, H-c^2), 7.17-7.11 (m, 2H, H-d^2), 7.07-7.02 (m, 2H, H-d^1), 6.18 (dt, $^3J_{HH}$= 4.9 Hz, $^3J_{HH}$= 1.6 Hz, 1H, H-1´), 5.37 (t, $^3J_{HH}$= 4.2 Hz, 1H, H-4´), 5.15 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.42-4.27 (m, 2H, H-5´), 4.22 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 3.44 (dd, $^3J_{HH}$= 12.1 Hz, $^3J_{HH}$= 5.5 Hz, 1H, H-2´$_a$), 3.11 (dd, $^3J_{HH}$= 11.9 Hz, $^3J_{HH}$= 4.7 Hz, 1H, H-2´$_b$). 2.57 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.75-1.67 (m, 4H, H-h^1, H-h^2), 1.50-1.40 (m, 4H, H-i^1, H-i^2), 1.39-1.26 (m, 24H, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-v).

^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 173.7 (C-f^1), 158.9 (d, $^2J_{CP}$= 15.5 Hz, C-4), 155.1 (C-f^2), 154.8 (C-2), 152.7 (C-e^2), 152.3 (C-e^1), 139.0, 136.7 (C-5), 135.2 (d, $^3J_{CP}$= 7.3 Hz, C-b^2), 134.9 (d, $^3J_{CP}$= 7.3 Hz, C-b^1), 130.5 (C-c^1, C-c^2), 127.7, 127.3 (C-6), 122.9 (C-d^1), 122.3 (C-d^2), 89.1 (C-1´), 85.8 (C-4´), 70.4, 70.3 (2 × d, $^3J_{CP}$= 5.9 Hz, $^3J_{CP}$= 5.7 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.9 Hz, C-5´), 37.9 (C-2´), 34.7 (C-g^1), 33.0, 30.8, 30.5, 30.3, 23.7 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 29.7 (C-h^2), 28.0 (C-h^1), 26.8 (C-i^2), 23.2 (C-i^1), 14.4 (C-v), 14.1 (C-j^1)).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -11.93 (d, $^2J_{pp}$=20.0 Hz, P-α), -13.27 (d, $^2J_{pp}$=17.7 Hz, P-γ), -23.60 (t, $^2J_{pp}$= 18.7 Hz, P-β).

^{19}F-NMR (188 MHz, CD_3OD): δ [ppm]= -167.3- -167.8.

IR: v [cm^{-1}] = 3015, 2969, 2922, 2852, 1739, 1682, 1606, 1508, 1455, 1366, 1228, 1217, 1166, 1129, 1082, 1004, 924, 775, 718, 514.

γ-(AB-C4; alkyl-C18)-FTCTP 90d.

According to general procedure 11 with 118 mg *H*-phosphonate **93** (0.225 mmol, 1.0 equiv.) and 127.6 mg (n-$Bu_4N)_2$·FTCMP **7a** (0.1575 mmol, 0.7 equiv.). Reaction time was 3 h.

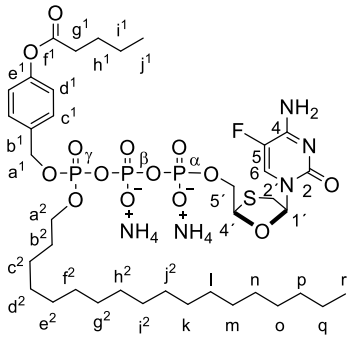
Yield: 110.8 mg (0.115 mmol, 73%) white solid.

Chemical Formula: $C_{38}H_{71}N_5O_{14}P_3FS$.

Molecular weight: 965.39 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 928.315; found, 928.275.



^{1}H-NMR (600 MHz, CD_3OD): δ [ppm]= 8.16 (d, $^3J_{HH}$= 6.5 Hz, 1H, H-6), 7.50-7.47 (m, 2H, H-c^1), 7.10-7.07 (m, 2H, H-d^1), 6.21 (dt, $^3J_{HH}$= 5.1 Hz, $^3J_{HH}$= 1.5 Hz, 1H, H-1´), 5.40 (t, $^3J_{HH}$= 4.2 Hz, 1H, H-4´), 5.21 (d, $^3J_{HH}$= 8.2 Hz, 2H, H-a^1), 4.42-4.28 (m, 2H, H-5´), 4.16-4.07 (m, 2H, H-a^2), 3.47 (dd, $^3J_{HH}$= 12.1 Hz, $^3J_{HH}$= 5.2 Hz, 1H, H-2´$_a$), 3.15 (dd, $^3J_{HH}$= 12.1 Hz, $^3J_{HH}$= 4.7 Hz, 1H, H-2´$_b$). 2.57 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.73 (quint, $^3J_{HH}$= 7.4 Hz, 2H, H-h^1), 1.62 (quint, $^3J_{HH}$= 6.8 Hz, 2H, H-b^2), 1.45 (sext, $^3J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.35-1.26 (m, 30H, H-c^2, H-d^2, H-e^2, H-f^2, H-j^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-v).

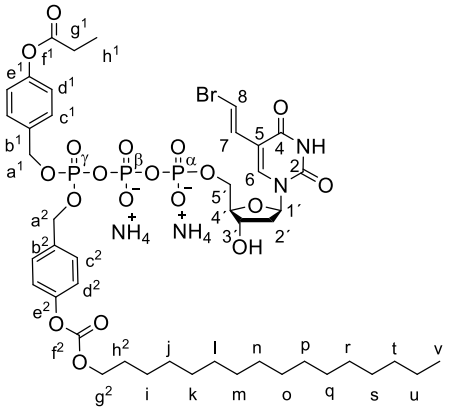
^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 173.6 (C-f^1), 158.8 (d, $^2J_{CP}$= 15.5 Hz, C-4), 154.7 (C-2), 152.3 (C-e^1), 138.7, 137.1 (C-5), 135.1 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.4 (C-c^1), 128.9 (C-6), 122.8 (C-d^1), 89.1 (C-1´), 85.8 (C-4´), 70.3 (d, $^3J_{CP}$= 5.5 Hz, C-a^1), 69.9 (d, $^3J_{CP}$= 6.5 Hz, C-a^2), 67.9 (d, $^3J_{CP}$= 5.3 Hz, C-5´), 37.9 (C-2´), 34.8 (C-g^1), 31.2 (d, $^3J_{CP}$= 6.8 Hz, C-b^2), 33.0, 30.80, 30.79, 30.74, 30.68, 30.5, 30.3, 23.7 (C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 28.0 (C-h^1), 26.5 (C-c^2), 23.2 (C-i^1), 14.5 (C-r), 14.1 (C-j^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.85 (d, $^2J_{pp}$=17.3 Hz, P-α), -13.01 (d, $^2J_{pp}$=17.1 Hz, $^3J_{pp}$=5.8 Hz, P-γ), -23.52 (t, $^2J_{pp}$= 16.2 Hz, P-β).

IR: ν [cm-1] = 3015, 2969, 2922, 2852, 1738, 1683, 1606, 1539, 1508, 1455, 1366, 1229, 1216, 1166, 1129, 1082, 1004, 921, 773, 718, 526, 513.

γ-(AB-C2; ACB-C16)-BVdUTP 89e1.

According to general procedure 11 with 140 mg *H*-phosphonate **77by** (0.225 mmol, 1.0 equiv.) and 122 mg BVdUMP 1.5×nBu_4N^+ **9a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 152 mg (0.133 mmol, 85%) white solid.

Chemical Formula: $C_{45}H_{70}N_4O_{19}BrP_3$.

Molecular weight: 1142.3030 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1107.243; found, 1107.174.

^{1}H-NMR (600 MHz, CD_3OD): δ [ppm]= 7.95 (s, 1H, H-6), 7.43-7.38 (m, 5H, H-8, H-c^1, H-c^2), 7.15-7.12 (m, 2H, H-d^2), 7.08-7.03 (m, 2H, H-d^1), 7.01 (d, $^2J_{HH}$= 13.6 Hz, 1H, H-7), 6.28 (t, $^3J_{HH}$= 6.7 Hz, 1H, H-1´), 5.17 (d, $^3J_{HH}$= 8.0 Hz, 4H, H-a^1, H-a^2), 4.57-4.53 (m, 1H, H-3´), 4.27-4.18 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 4.05-4.01 (m, 1H, H-4´), 2.60 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 2.25-2.20 (m, 2H, H-2´), 1.73 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.45-1.39 (m, 2H, H-i), 1.38-1.25 (m, 24H, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.22 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-h^1), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-v).

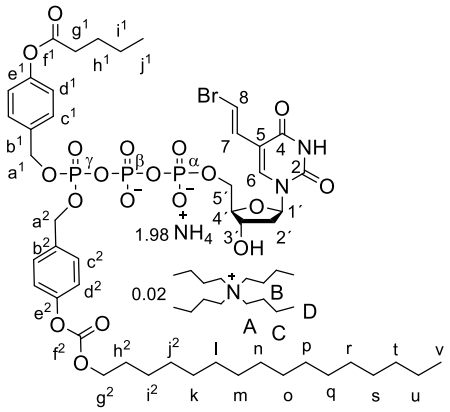
^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 174.5 (C-f^1), 163.7 (C-4), 155.1 (C-f^2), 152.7 (C-2), 152.4 (C-e^2), 151.2 (C-e^1), 140.3 (C-6), 135.2 (d, $^3J_{CP}$= 7.7 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.7 (C-7), 130.51, 130.46, 130.42 (C-c^1, C-c^2), 122.8 (C-d^1), 122.3 (C-d^2), 112.4 (C-5), 109.2 (C-8), 87.4 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 86.4 (C-1´), 72.2 (C-3´), 70.46, 70.43, 70.40, 70.30, 70.27 (C-a^1, C-a^2), 70.0 (C-g^2), 67.7 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 40.8 (C-2´), 33.1, 30.75, 30.73,30.66, 30.61, 30.5, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.4 (C-g^1), 26.8 (C-i), 14.4 (C-v), 9.3 (C-h^1).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = -11.55 (d, $^2J_{pp}$= 18.7 Hz, P-α), -13.19 (d, $^2J_{pp}$= 18.0 Hz, P-γ), -23.56 (t, $^2J_{pp}$= 17.9 Hz, P-β).

IR: ν [cm^{-1}] = 3015, 2970, 2943, 1738, 1547, 1512, 1441, 1366, 1228, 1216, 1091, 899, 786, 538, 527, 516.

γ-(AB-C4; ACB-C16)-BVdUTP 89e2.

According to general procedure 11 with 146 mg *H*-phosphonate **77ey** (0.225 mmol, 1.0 equiv.) and 122 mg BVdUMP 1.5×nBu_4N^+ **9a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 137 mg (0.117 mmol, 74%) white solid.

Chemical Formula: $C_{47}H_{66}N_2O_{19}BrP_3^{2-}$.

Molecular weight: 1134.27 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1135.274; found, 1135.252.

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm]= 7.94 (s, 1H, H-6), 7.43-7.38 (m, 5H, H-8, H-c^1, H-c^2), 7.15-7.11 (m, 2H, H-d^2), 7.08-6.97 (m, 3H, H-d^1, H-7), 6.27 (t, $^3J_{HH}$= 6.7 Hz, 1H, H-1´), 5.16 (d, $^3J_{HH}$= 8.3 Hz, 4H, H-a^1, H-a^2), 4.57-4.52 (m, 1H, H-3´), 4.27-4.17 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 4.05-4.01 (m, 1H, H-4´), 3.24-3.18 (m, 0.16H, H-A), 2.58 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 2.25-2.20 (m, 2H, H-2´), 1.77-1.67 (m, 4.16H, H-B, H-h^1, H-h^2), 1.49-1.25 (m, 28.16H, H-C, H-i^1, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.01 (t, $^3J_{HH}$= 7.2 Hz, 0.24H, H-D), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-v).

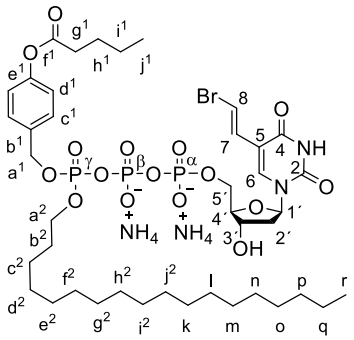
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 173.6 (C-f^1), 163.6 (C-4), 155.0 (C-f^2), 152.6 (C-2), 152.3 (C-e^2), 151.1 (C-e^1), 140.2 (C-6), 135.0 (d, $^3J_{CP}$= 7.4 Hz, C-b^2), 134.7 (d, $^3J_{CP}$= 7.4 Hz, C-b^1), 130.6 (C-7), 130.44, 130.42, 130.39 (C-c^1, C-c^2), 122.8 (C-d^1), 122.2 (C-d^2), 112.3 (C-5), 109.2 (C-8), 87.2 (d, $^3J_{CP}$= 8.3 Hz, C-4´), 86.5 (C-1´), 72.1 (C-3´), 70.4, 70.3 (2 × dd, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 2.8 Hz, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 2.8 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.7 (d, $^3J_{CP}$= 5.6 Hz, C-5´), 59.4 (C-A), 40.7 (C-2´), 34.7 (C-g^1), 33.0, 30.74, 30.71, 30.64, 30.59, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.0 (C-h^1), 26.8 (C-i^2), 24.7 (C-B), 23.2 (C-i^1), 20.6 (C-C), 14.5 (C-v), 14.1 (C-j^1), 14.0 (C-D).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.53 (d, $^2J_{pp}$= 19.4 Hz, P-α), -13.18 (d, $^2J_{pp}$= 17.6 Hz, P-γ), -23.53 (t, $^2J_{pp}$= 17.9 Hz, P-β).

IR: ν [cm^{-1}] = 3197, 3015, 2969, 2922, 2852, 1739, 1508, 1456, 1365, 1227, 1216, 1168, 1007, 921, 818, 720, 526, 514, 425.

γ-(AB-C4; alkyl-C18)-BVdUTP 90e.

According to general procedure 11 with 118 mg *H*-phosphonate **93** (0.225 mmol, 1.0 equiv.) and 122 mg BVdUMP 1.5×nBu_4N^+ **9a** (0.158 mmol, 0.7 equiv.). Reaction time was 5 h.



Yield: 119.6 mg (0.117 mmol, 74%) white solid.

Chemical Formula: $C_{41}H_{72}N_4O_{16}BrP_3$.

Molecular weight: 1048.33 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1013.274; found, 1013.233.

^{1}H-NMR (500 MHz, CD_3OD): δ [ppm]= 7.97 (s, 1H, H-6), 7.52-7.46 (m, 2H, H-c^1), 7.42 (dd, $^2J_{HH}$= 13.5 Hz, $^4J_{HH}$= 1.9 Hz, 1H, H-8), 7.12-7.07 (m, 2H, H-d^1), 7.03 (dd, $^2J_{HH}$= 13.6 Hz, $^4J_{HH}$= 1.2 Hz, 1H, H-7), 6.30 (t, $^3J_{HH}$= 6.7 Hz, 1H, H-1´), 5.24-5.16 (m, 2H, H-a^1), 4.60-4.54 (m, 1H, H-3´), 4.30-4.18 (m, 2H, H-5´), 4.17-4.10 (m, 2H, H-a^2), 4.09-4.04 (m, 1H, H-4´), 2.59 (t, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 2.32-2.24 (m, 2H, H-2´), 1.74 (quint, $^3J_{HH}$= 7.5 Hz, 2H, H-h^1), 1.62 (quint, $^3J_{HH}$= 6.1 Hz, 2H, H-b^2), 1.46 (sext, $^3J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.34-1.26 (m, 30H, H-c^2, H-d^2, H-e^2, H-f^2, H-j^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 1.0 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-r).

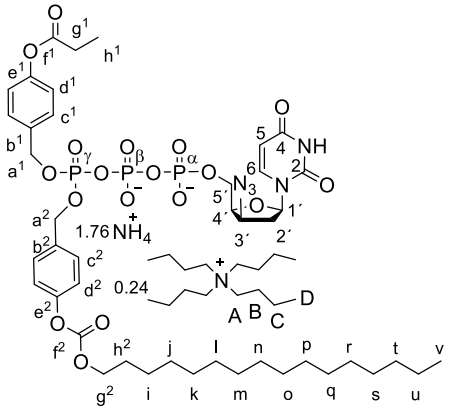
^{13}C-NMR (126 MHz, CD_3OD): δ [ppm] = 173.6 (C-f^1), 163.7 (C-4), 152.3 (C-2), 151.1 (C-e^1), 140.2 (C-6), 135.0 (d, $^3J_{CP}$= 7.4 Hz, C-b^1), 130.7 (C-7), 130.3 (d, $^3J_{CP}$= 4.6 Hz, C-c^1), 122.8 (C-d^1), 112.4 (C-5), 109.2 (C-8), 87.3 (d, $^3J_{CP}$= 8.3 Hz, C-4´), 86.5 (C-1´), 72.1 (d, $^3J_{CP}$= 2.8 Hz, C-3´), 70.3 (dd, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 2.7 Hz, C-a^1), 69.9 (d, $^3J_{CP}$= 6.6 Hz, C-a^2), 66.7 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 40.7 (C-2´), 34.7 (C-g^1), 33.0, 30.78, 30.73, 30.71, 30.6, 30.4, 30.3, 23.7 (C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 31.2 (d, $^3J_{CP}$= 7.6 Hz, C-b^2), 28.0 (C-h^1), 26.5 (C-c^2), 23.2 (C-i^1), 14.5 (C-r), 14.1 (C-j^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -10.30 (d, $^2J_{pp}$= 18.2 Hz, P-α), -11.70 (d, $^2J_{pp}$= 16.1 Hz, P-γ), -23.55 (t, $^2J_{pp}$= 16.0 Hz, P-β).

IR: ν [cm-1] = 3204, 3015, 2969, 2923, 2852, 1737, 1595, 1558, 1540, 1455, 1366, 1228, 1216, 1204, 1167, 1128, 1081, 1012, 923, 800, 720, 527, 515, 427.

γ-(AB-C2; ACB-C16)-AZUTP 89f1.

According to general procedure 11 with 140 mg *H*-phosphonate **77by** (0.225 mmol, 1.0 equiv.) and 129 mg (n-$Bu_4N)_2$·AZUMP salt **64a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 119 mg (0.104mmol, 66%) white solid.

Chemical Formula: $C_{43}H_{60}N_5O_{18}P_3^{2-}$.

Molecular weight: 1027.32 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1028.323; found, 1028.225.

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm]= 7.82 (d, $^3J_{HH}$= 8.2 Hz, 1H, H-6), 7.47-7.39 (m, 4H, H-c^1, H-c^2), 7.18-7.11 (m, 2H, H-d^2), 7.10-7.05 (m, 2H, H-d^1), 6.00 (dd, $^3J_{HH}$= 7.6 Hz, $^3J_{HH}$= 2.4 Hz, 1H, H-1´), 5.70 (d, $^3J_{HH}$= 8.1 Hz, 1H, H-5), 5.17 (d, $^3J_{HH}$= 8.0 Hz, 4H, H-a^1, H-a^2), 4.37-4.27 (m, 4H, H-3´, H-4´, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 3.25-3.17 (m, 1.92H, H-A), 2.76-2.65 (m, 1H, H-2´a), 2.59 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 2.24-2.14 (m, 1H, H-2´b), 1.72 (quint, $^3J_{HH}$= 7.1 Hz, 2H, H-h^2), 1.68-1.59 (m, 1.92H, H-B), 1.48-1.25 (m, 27.92H, H-C, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.22 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-h^1), 1.00 (t, $^3J_{HH}$=7.3 Hz, 2.88H, H-D), 0.89 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-v).

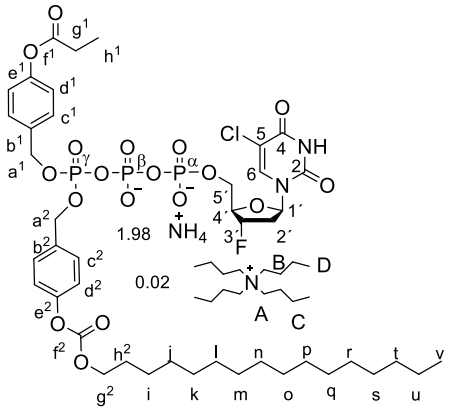
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 174.4 (C-f^1), 166.2 (C-4), 155.1 (C-f^2), 152.7 (C-2), 152.4 (C-e^2), 152.1 (C-e^1), 142.2 (C-6), 135.2 (d, $^3J_{CP}$= 7.7 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.4 Hz, C-b^1), 130.49, 130.45 (C-c^1, C-c^2), 122.8 (C-d^1), 122.3 (C-d^2), 102.2 (d, $^3J_{CP}$= 9.1 Hz, C-5), 86.3 (C-1´), 83.1 (C-4´), 70.42, 70.37, 70.29, 70.24 (C-a^1, C-a^2), 70.0 (C-g^2), 65.4 (d, $^3J_{CP}$= 5.8 Hz, C-5´), 62.2 (d, $^3J_{CP}$= 8.8 Hz, C-3´), 59.4 (C-A), 39.3 (C-2´), 33.0, 30.8, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 24.7 (C-B), 20.7 (C-C),14.5 (C-v), 13.9 (C-D), 9.4 (C-h^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.29 (d, $^2J_{pp}$= 18.7 Hz, P-α), -13.08 (d, $^2J_{pp}$= 18.0 Hz, P-γ), -23.44 (t, $^2J_{pp}$= 17.9 Hz, P-β).

IR: ν [cm^{-1}] =3028, 2969, 2922, 2852, 2108, 1756, 1685, 1508, 1457, 1420, 1376, 1217, 1167, 1129, 1057, 1004, 923, 810, 778, 720, 514, 418.

γ-(AB-C2; ACB-C16)-FddClUTP 89g1.

According to general procedure 11 with 140 mg *H*-phosphonate **77by** (0.225 mmol, 1.0 equiv.) and 98 mg FddClUMP 1.15×nBu$_4$N$^+$ **8a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 130 mg (0.117 mmol, 74%) white solid.

Chemical Formula: $C_{43}H_{59}N_2O_{18}FClP_3^{2-}$.

Molecular weight: 1038.27 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1039.273; found, 1039.138.

^{1}H-NMR (400 MHz, CD$_3$OD): δ [ppm]= 8.12 (s, 1H, H-6), 7.45-7.39 (m, 4H, H-c^1, H-c^2), 7.17-7.12 (m, 2H, H-d^2), 7.09-7.04 (m, 2H, H-d^1), 6.28 (dd, $^3J_{HH}$= 9.5 Hz, $^3J_{HH}$= 5.3 Hz, 1H, H-1´), 5.48 (dd, $^2J_{HH}$= 53.2 Hz, $^3J_{HH}$= 4.5 Hz, 1H, H-3´), 5.17 (d, $^3J_{HH}$= 8.3 Hz, 4H, H-a^1, H-a^2), 4.40-4.12 (m, 3H, H-4´, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 3.26-3.18 (m, 0.16H, H-A), 2.59 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 2.52-2.26 (m, 2H, H-2´), 1.72 (quint, $^3J_{HH}$= 6.8 Hz, 2H, H-h^2), 1.68-1.62 (m, 0.16H, H-B), 1.45-1.39 (m, 2H, H-i), 1.38-1.25 (m, 24.16H, H-C, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.22 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-h^1), 1.07 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-D), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-v).

^{13}C-NMR (101 MHz, CD$_3$OD): δ [ppm] = 174.4 (C-f^1), 161.4 (C-4), 155.0 (C-f^2), 152.6 (C-e^2), 152.3 (C-e^1), 151.2 (C-2), 138.9 (C-6), 135.0 (d, $^3J_{CP}$= 7.5 Hz, C-b^2), 134.6 (d, $^3J_{CP}$= 7.5 Hz, C-b^1), 130.4, 129.8 (C-c^1, C-c^2), 122.8 (C-d^1), 122.3 (C-d^2), 110.0 (C-5), 96.7 (dd, $^1J_{CF}$= 177.5 Hz, $^2J_{CF}$= 11.8 Hz, C-3´), 86.8 (C-1´), 85.2 (d, $^3J_{CF}$= 25.6 Hz, C-4´), 70.3, 70.2 (2 × dd, $^3J_{CP}$= 5.2 Hz, $^3J_{CP}$= 2.2 Hz, $^3J_{CP}$= 5.2 Hz, $^3J_{CP}$= 2.2 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 66.6 (C-5´), 59.4 (C-A), 38.8 (d, $^2J_{CF}$= 21.1 Hz, C-2´), 33.0, 30.8, 30.6, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 24.7 (C-B), 20.6 (C-C), 14.5 (C-v), 14.0 (C-D), 9.3 (C-h^1).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = -11.95 (d, $^2J_{pp}$=18.2 Hz, P-α), -13.16 (d, $^2J_{pp}$=18.2 Hz, P-γ), -23.60 (t, $^2J_{pp}$= 18.1 Hz, P-β).

^{19}F-NMR (188 MHz, CD3OD): δ [ppm]= -175.3- -176.2.

IR: ν [cm^{-1}] = 3003, 2969, 2922, 2852, 1754, 1719, 1509, 1456, 1365, 1217, 1168, 1129, 1073, 1025, 1008, 919, 822, 779, 752, 720, 515.

γ-(ACB-C16)-FddClUTP 117.

According to general procedure 11 with 140 mg *H*-phosphonate **77by** (0.225 mmol, 1.0 equiv.) and 98 mg FddClUMP 1.15×nBu$_4$N$^+$ **8a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.

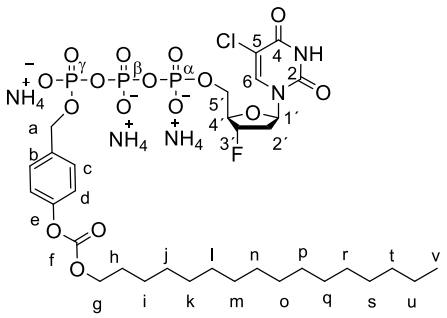
Yield: 15 mg (0.016 mmol, 10%) white solid.

Chemical Formula: $C_{33}H_{60}N_5O_{16}P_3FCl$.

Molecular weight: 929.28 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 877.205; found, 877.115.



^{1}H-NMR (400 MHz, CD$_3$OD): δ [ppm]= 8.17 (s, 1H, H-6), 7.52 (d, $^3J_{HH}$= 8.4 Hz, 2H, H-c), 7.13 (d, $^3J_{HH}$= 8.3 Hz, 2H, H-d), 6.30 (dd, $^3J_{HH}$= 9.3 Hz, $^3J_{HH}$= 5.3 Hz, 1H, H-1´), 5.46 (dd, $^2J_{HH}$= 53.3 Hz, $^3J_{HH}$= 3.8 Hz, 1H, H-3´), 5.09 (s, 2H, H-a), 4.45-4.10 (m, 3H, H-4´, H-5´), 4.24 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g), 2.62-2.24 (m, 2H, H-2´), 1.72 (quint, $^3J_{HH}$= 6.8 Hz, 2H, H-h), 1.45-1.25 (m, 26H, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 0.92 (t, $^3J_{HH}$= 6.6 Hz, 3H, H-v).

^{13}C-NMR (101 MHz, CD$_3$OD): δ [ppm] = 161.5 (C-4), 155.3 (C-f), 152.0 (C-e), 151.4 (C-2), 139.1 (C-6), 137.8 (C-b), 129.8 (C-c), 122.0 (C-d), 110.0 (C-5), 96.2 (C-3´), 97.0 (dd, $^1J_{CF}$= 170.2 Hz, $^2J_{CF}$= 10.3 Hz, C-3´), 86.9 (C-1´), 85.8 (C-4´), 69.9 (C-g), 68.1 (C-a), 66.5 (C-5´), 42.0 (C-2´), 33.0, 30.8, 30.5, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h), 26.8 (C-i), 14.4 (C-v).

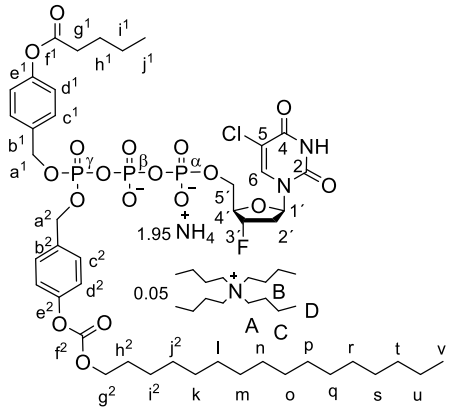
^{19}F-NMR (188 MHz, CD3OD): δ [ppm]= -175.0- -176.4.

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = -11.05 (d, $^2J_{pp}$=18.2 Hz, P-α), -11.56 (d, $^2J_{pp}$=18.2 Hz, P-γ), -22.17 (t, $^2J_{pp}$= 18.1 Hz, P-β).

IR: ν [cm^{-1}] = 2922, 2852, 1757, 1716, 1508, 1456, 1365, 1217, 1168, 1129, 1059, 1005, 917, 820, 779, 752, 720, 698, 606, 516, 419.

γ-(AB-C4; ACB-C16)-FddClUTP 89g2.

According to general procedure 11 with 146 mg *H*-phosphonate **77ey** (0.225 mmol, 1.0 equiv.) and 98 mg FddClUMP 1.15×nBu$_4$N$^+$ **8a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 88 mg (0.079 mmol, 50%) white solid.

Chemical Formula: $C_{45}H_{63}N_2O_{18}FClP_3^{2-}$.

Molecular weight: 1066.30 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1067.305; found, 1067.259.

^{1}H-NMR (400 MHz, CD$_3$OD): δ [ppm]= 8.11 (s, 1H, H-6), 7.45-7.38 (m, 4H, H-c^1, H-c^2), 7.17-7.12 (m, 2H, H-d^2), 7.09-7.02 (m, 2H, H-d^1), 6.27 (dd, $^3J_{HH}$= 9.5 Hz, $^3J_{HH}$= 5.3 Hz, 1H, H-1´), 5.48 (dd, $^2J_{HH}$= 53.2 Hz, $^3J_{HH}$= 4.4 Hz, 1H, H-3´), 5.17 (d, $^3J_{HH}$= 8.3 Hz, 4H, H-a^1, H-a^2), 4.42-4.12 (m, 3H, H-4´, H-5´), 4.23 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 3.26-3.17 (m, 0.4H, H-A), 2.58 (t, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 2.53-2.24 (m, 2H, H-2´), 1.77-1.61 (m, 4.4H, H-B, H-h^1, H-h^2), 1.45-1.26 (m, 28.4H, H-C, H-i^1, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.01 (t, $^3J_{HH}$= 7.3 Hz, 0.6H, H-D), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-v).

^{13}C-NMR (101 MHz, CD$_3$OD): δ [ppm] = 173.7 (C-f^1), 161.4 (C-4), 155.1 (C-f^2), 152.7 (C-e^2), 152.3 (C-e^1), 151.3 (C-2), 138.9 (d, $^3J_{CP}$= 5.1 Hz, C-6), 135.2 (d, $^3J_{CP}$= 7.5 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.3 Hz, C-b^1), 130.5 (C-c^1, C-c^2), 122.8 (C-d^1), 122.3 (C-d^2), 110.0 (C-5), 96.9 (dd, $^1J_{CF}$= 176.1 Hz, $^2J_{CF}$= 11.2 Hz, C-3´), 86.8 (C-1´), 85.7 (C-4´), 70.4, 70.3, 70.2 (C-a^1, C-a^2), 70.0 (C-g^2), 66.5 (C-5´), 59.5 (C-A), 38.9 (d, $^2J_{CF}$= 20.8 Hz, C-2´), 34.7 (C-g^1), 33.0, 30.8, 30.4, 30.3, 23.7 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.0 (C-h^1), 26.8 (C-i^2), 24.7 (C-B), 23.2 (C-i^1), 20.7 (C-C), 14.4 (C-v), 14.1 (C-j^1), 13.6 (C-D).

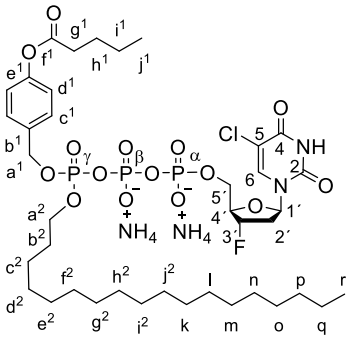
^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = -11.97 (d, $^2J_{pp}$=17.7 Hz, P-α), -13.16 (d, $^2J_{pp}$=17.2 Hz, P-γ), -23.54 (t, $^2J_{pp}$= 17.7 Hz, P-β).

^{19}F-NMR (188 MHz, CD$_3$OD): δ [ppm] = -175.4- -176.2.

IR: ν [cm^{-1}] = 3015, 2969, 2922, 2852, 1754, 1718, 1508, 1457, 1365, 1217, 1168, 1128, 1006, 923, 850, 818, 778, 720, 526, 420.

γ-(AB-C4; alkyl-C18)-FddClUTP 90g.

According to general procedure 11 with 118 mg *H*-phosphonate **93** (0.225 mmol, 1.0 equiv.) and 98 mg FddClUMP 1.15×nBu$_4$N$^+$ **8a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 123.5 mg (0.126 mmol, 80%) white solid.

Chemical Formula: $C_{39}H_{69}N_4O_{15}P_3FCl$.

Molecular weight: 980.36 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 945.304; found, 945.253.

^{1}H-NMR (600 MHz, CD$_3$OD): δ [ppm]= 8.13 (s, 1H, H-6), 7.51-7.47 (m, 2H, H-c^1), 7.11-7.07 (m, 2H, H-d^1), 6.28 (dd, $^3J_{HH}$= 9.5 Hz, $^3J_{HH}$= 5.3 Hz, 1H, H-1´), 5.48 (dd, $^2J_{HH}$= 53.1 Hz, $^3J_{HH}$= 2.9 Hz, 1H, H-3´), 5.17 (dd, $^3J_{HH}$= 8.0 Hz, ^3JHH= 1.8 Hz, 2H, H-a^1), 4.45-4.33 (m, 1H, H-4´), 4.32-4.24 (m, 1H, H-5´$_a$), 4.19-4.13 (m, 1H, H-5´$_b$), 4.13-4.08 (m, 2H, H-a^2), 2.57 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 2.55-2.30 (m, 2H, H-2´), 1.73 (quint, $^3J_{HH}$= 7.4 Hz, 2H, H-h^1), 1.6 2 (quint, $^3J_{HH}$= 6.7 Hz, 2H, H-b^2), 1.44 (sext, $^3J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.34-1.26 (m, 30H, H-c^2, H-d^2, H-e^2, H-f^2, H-j^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-r).

^{13}C-NMR (151 MHz, CD$_3$OD): δ [ppm] = 173.6 (C-f^1), 161.4 (C-4), 152.3 (C-e^1), 151.3 (C-2), 138.9 (C-6), 135.0 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.3 (d, $^3J_{CP}$= 3.3 Hz, C-c^1), 122.8 (C-d^1), 110.0 (C-5), 96.0 (d,$^1J_{CF}$= 175.7 Hz, C-3´), 86.8 (C-1´), 85.6 (dd, $^3J_{CP}$= 25.9 Hz, $^3J_{CP}$= 9.9 Hz, C-4´), 70.2 (dd, $^3J_{CP}$= 5.6 Hz, $^3J_{CP}$= 3.3 Hz, C-a^1), 69.8 (d, $^3J_{CP}$= 6.6 Hz, C-a^2), 66.5 (dd, $^2J_{CP}$= 11.9 Hz, $^3J_{CP}$= 5.4 Hz, C-5´), 38.9 (d, $^2J_{CF}$= 21.0 Hz, C-2´), 34.7 (C-g^1), 31.2 (d, $^3J_{CP}$= 7.6 Hz, C-b^2), 33.0, 30.80, 30.79, 30.74, 30.72 30.66, 30.5, 30.3, 23.7 (C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 28.0 (C-h^1), 26.5 (C-c^2), 23.2 (C-i^1), 14.5 (C-r), 14.1 (C-j^1).

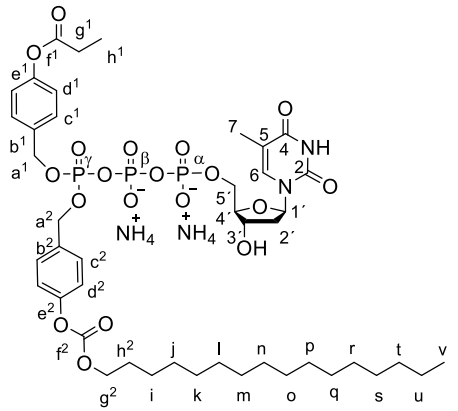
^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = -11.97 (d, $^2J_{pp}$=17.4 Hz, P-α), -12.91 (dd, $^2J_{pp}$=17.6 Hz, $^3J_{pp}$=5.8 Hz, P-γ), -23.53 (t, $^2J_{pp}$= 16.5 Hz, P-β).

^{19}F-NMR (188 MHz (gekoppelt), CD$_3$OD): δ [ppm] = -175.3- -176.2.

IR: ν [cm-1] = 3015, 2969, 2922, 2852, 1738, 1508, 1439, 1366, 1229, 1216, 1204, 1166, 1129, 1075, 1007, 916, 822, 752, 720, 699, 527, 515.

γ-(AB-C2; ACB-C16)-TTP 89h1.

According to general procedure 11 with 140 mg *H*-phosphonate **77by** (0.225 mmol, 1.0 equiv.) and 109 mg (n-$Bu_4N)_2$·TMP salt **65a** (0.135 mmol, 0.6 equiv.). Reaction time was 3 h.



Yield: 93 mg (0.088 mmol, 65%) white solid.

Chemical Formula: $C_{45}H_{63}N_2O_{18}FClP_3^{2-}$.

Molecular weight: 1066.30 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1017.332; found, 1017.200.

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.77 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 7.44-7.36 (m, 4H, H-c^1, H-c^2), 7.18-7.11 (m, 2H, H-d^2), 7.09-7.03 (m, 2H, H-d^1), 6.34-6.26 (m, 1H, H-1´), 5.15 (d, $^3J_{HH}$= 8.2 Hz, 4H, H-a^1, H-a^2), 4.59-4.52 (m, 1H, H-3´), 4.28-4.16 (m, 4H, H-g^2, H-5´), 4.05-3.98 (m, 1H, H-4´), 2.60 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 2.31-2.09 (m, 2H, H-2´), 1.90 (d, $^4J_{HH}$= 0.9 Hz, 3H, H-7), 1.72 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-h^2), 1.45-1.23 (m, 26 H, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.22 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-h^1), 0.89 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-v).

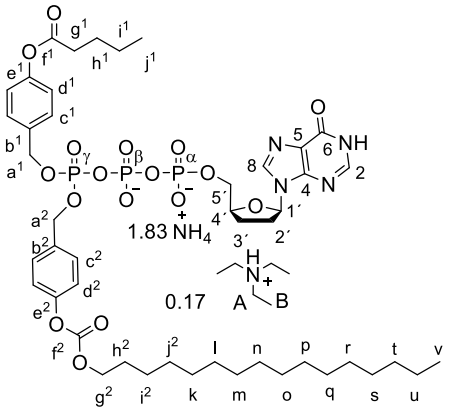
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 174.4 (C-f^1), 166.3 (C-4), 155.0 (C-f^2), 152.6 (C-2), 152.32 (C-e^2), 152.29 (C-e^1), 138.0 (C-6), 135.0 (d, $^3J_{CP}$= 7.4 Hz, C-b^2), 134.7 (d, $^3J_{CP}$= 7.4 Hz, C-b^1), 130.44, 130.39 (C-c^1, C-c^2), 122.8 (C-d^1), 122.3 (C-d^2), 111.9 (C-5), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 86.0 (C-1´), 72.3 (C-3´), 70.4, 70.2 (2 × d, $^3J_{CP}$= 5.9 Hz, $^3J_{CP}$= 5.3 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 66.9 (d, $^3J_{CP}$= 5.8 Hz, C-5´), 40.5 (C-2´), 33.0, 30.76, 30.73, 30.67, 30.61, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 14.5 (C-v), 12.6 (C-7), 9.3 (C-h^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.50 (d, $^2J_{pp}$=17.6 Hz, P-α), -13.04 (d, $^2J_{pp}$=15.6 Hz, P-γ), -23.44 (t, $^2J_{pp}$= 17.6 Hz, P-β).

IR: ν [cm^{-1}] = 3016, 2969, 2922, 2852, 1757, 1691, 1509, 1462, 1365, 1217, 1168, 1127, 1077, 1006, 925, 823, 781, 721, 515, 495, 421.

γ-(AB-C4; ACB-C16)-ddITP 89i2.

According to general procedure 11 with 146 mg *H*-phosphonate **77ey** (0.225 mmol, 1.0 equiv.) and 144 mg (n-$Bu_4N)_2$·ddIMP salt **3a** (0.18 mmol, 0.8 equiv.). Reaction time was 3 h.



Yield: 140 mg (0.13 mmol, 72%) white solid.

Chemical Formula: $C_{46}H_{65}N_4O_{17}P_3^{2-}$.

Molecular weight: 1038.36 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1041.380; found, 1041.319.

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm]= 8.48 (s, 1H, H-8), 8.00 (s, 1H, H-2), 7.40-7.34 (m, 4H, H-c^1, H-c^2), 7.14-7.07 (m, 2H, H-d^2), 7.04-6.98 (m, 2H, H-d^1), 6.23 (dd, $^3J_{HH}$= 6.6 Hz, $^3J_{HH}$= 3.3 Hz, 1H, H-1´), 5.15 (d, $^3J_{HH}$= 8.3 Hz, 4H, H-a^1, H-a^2), 4.39-4.26 (m, 2H, H-4´, H-5´$_a$), 4.22 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 4.19-4.13 (m, 1H, H-5´$_b$), 3.22 (q, $^3J_{HH}$= 7.6 Hz, 1H, H-A), 2.58 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 2.53-2.35 (m, 2H, H-2´), 2.26-2.05 (m, 2H, H-3´), 1.76-1.68 (m, 4H, H-h^1, H-h^2), 1.48-1.26 (m, 29.5H, H-B, H-i^1, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.00 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.6 Hz, 3H, H-v).

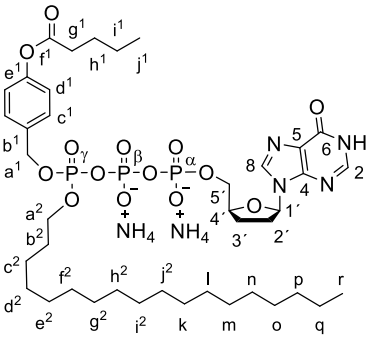
^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 173.7 (C-f^1), 159.0 (C-4), 155.1 (C-f^2), 152.6 (C-e^2), 152.3 (C-e^1), 146.7 (C-2), 140.6 (C-8), 135.1 (d, $^3J_{CP}$= 7.8 Hz, C-b^2), 134.9 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 130.46, 130.44 (C-c^1, C-c^2), 125.2 (C-5), 122.8 (C-d^1), 122.3 (C-d^2), 86.9 (C-1´), 82.1 (d, $^3J_{CP}$= 8.9 Hz, C-4´), 70.3, 70.2 (2 x dd, $^3J_{CP}$= 5.9 Hz, $^4J_{CP}$= 1.4 Hz, $^3J_{CP}$= 5.9 Hz, $^4J_{CP}$= 1.4 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 68.1 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 43.1 (C-A), 34.7 (C-g^1), 33.9 (C-2´), 33.1, 30.78, 30.75, 30.68, 30.63, 30.5, 30.3, 23.7 (C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.1 (C-h^1), 26.8 (C-i^2), 26.7 (C-3´), 23.2 (C-i^1), 14.5 (C-v), 14.1 (C-j^1), 11.6 (C-B).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.42 (d, $^2J_{pp}$=19.4 Hz, P-α), -13.07 (d, $^2J_{pp}$=17.6 Hz, P-γ), -23.46 (t, $^2J_{pp}$= 17.3 Hz, P-β).

IR: ν [cm^{-1}] = 3408, 3001, 2917, 2162, 1759, 1658, 1436, 1406, 1313, 1257, 1015, 951, 702, 669, 516.

γ-(AB-C4; alkyl-C18)-ddITP 90i.

According to general procedure 11 with 118 mg *H*-phosphonate **93** (0.225 mmol, 1.0 equiv.) and 126 mg (n-$Bu_4N)_2$·ddIMP salt **3a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 102.2 mg (0.107 mmol, 68%) white solid.

Chemical Formula: $C_{40}H_{71}N_6O_{14}P_3$.

Molecular weight: 952.42 g/mol.

MALDI-MS (m/z):

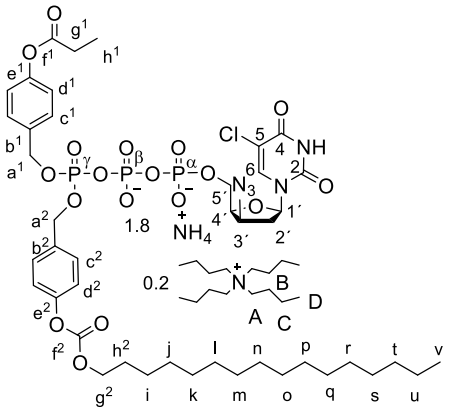
$[M-H]^-$ 917.364; found, 917.324.

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm]= 8.56 (s, 1H, H-8), 8.03 (s, 1H, H-2), 7.50-7.45 (m, 2H, H-c^1), 7.10-7.04 (m, 2H, H-d^1), 6.28 (dd, $^3J_{HH}$= 6.6 Hz, $^3J_{HH}$= 3.1 Hz, 1H, H-1´), 5.25-5.16 (m, 2H, H-a^1), 4.45-4.30 (m, 2H, H-4´, H-5´$_a$), 4.22-4.05 (m, 3H, H-5´$_b$, H-a^2), 2.59 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 2.55-2.35 (m, 2H, H-2´), 2.29-2.05 (m, 2H, H-3´), 1.73 (quint, $^3J_{HH}$= 7.3 Hz, 2H, H-h^1), 1.61 (quint, $^3J_{HH}$= 6.9 Hz, 2H, H-b^2), 1.46 (sext, $^3J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.34-1.26 (m, 30H, H-c^2, H-d^2, H-e^2, H-f^2, H-j^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.99 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.91 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-r).

IR: ν [cm-1] = 3016, 2969, 2921, 2852, 1738, 1588, 1546, 1508, 1455, 1366, 1228, 1216, 1166, 1129, 1083, 1002, 919, 808, 791, 718, 688, 648, 607, 514.

γ-(AB-C2; ACB-C16)-AzddClUTP 89j1.

According to general procedure 11 with 140 mg *H*-phosphonate **77by** (0.225 mmol, 1.0 equiv.) and 106 mg AZddClUMP 1.25×nBu_4N^+ salt **87a** (0.158 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 137 mg (0.124 mmol, 79%) white solid.

Chemical Formula: $C_{43}H_{59}ClN_5O_{18}P_3^{2-}$.

Molecular weight: 1061.28 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1062.284; found, 1062.142.

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm]= 7.91 (s, 1H, H-6), 7.46-7.39 (m, 4H, H-c^1, H-c^2), 7.18-7.12 (m, 2H, H-d^2), 7.10-7.04 (m, 2H, H-d^1), 6.00 (dd, $^3J_{HH}$= 7.6 Hz, $^3J_{HH}$= 2.1 Hz, 1H, H-1´), 5.18 (d, $^3J_{HH}$= 8.1

Hz, 4H, H-a^1, H-a^2), 4.36-4.28 (m, 4H, H-3´, H-4´, H-5´), 4.22 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^2), 3.25-3.17 (m, 1.6H, H-A), 2.73-2.63 (m, 1H, H-2´a), 2.59 (q, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 2.21-2.13 (m, 2H, H-2´b), 1.72 (quint, $^3J_{HH}$= 6.6 Hz, 2H, H-h^2), 1.67-1.58 (m, 1.6H, H-B), 1.48-1.25 (m, 27.6H, H-C, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.22 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-h^1), 1.00 (t, $^3J_{HH}$=7.3 Hz, 2.4H, H-D), 0.89 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-v).

^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 174.4 (C-f^1), 161.4 (C-4), 155.1 (C-f^2), 152.7 (C-2), 152.4 (C-e^2), 151.1 (C-e^1), 138.8 (C-6), 135.1 (d, $^3J_{CP}$= 7.6 Hz, C-b^2), 134.8 (d, $^3J_{CP}$= 7.6 Hz, C-b^1), 130.49, 130.44 (C-c^1, C-c^2), 122.9 (C-d^1), 122.3 (C-d^2), 109.1 (C-5), 86.5 (C-1´), 83.2 (d, $^3J_{CP}$= 7.6 Hz, C-4´), 70.4, 70.3 (2 × d, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 65.3 (d, $^3J_{CP}$= 5.6 Hz, C-5´), 62.3 (C-3´), 59.4 (C-A), 39.3 (C-2´), 33.0, 30.75, 30.72, 30.66, 30.61, 30.4, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.3 (C-g^1), 26.8 (C-i), 24.7 (C-B), 20.7 (C-C),14.5 (C-v), 14.0 (C-D), 9.3 (C-h^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.51 (d, $^2J_{pp}$=17.7 Hz, P-α), -13.16 (d, $^2J_{pp}$=17.6 Hz, P-γ), -23.50 (t, $^2J_{pp}$= 17.1 Hz, P-β).

IR: ν [cm^{-1}] = 3190, 2922, 2852, 2109, 1758, 1697, 1633, 1509, 1455, 1247, 1219, 1167, 1128, 1058, 1004, 821, 846, 779, 754, 721, 497.

γ-(AB-C4; ACB-C16)-FTVDP 89l2.

According to general procedure 11 with 145.9 mg *H*-phosphonate **77by** (0.225 mmol, 1.0 equiv.) and 138.6 mg (*n*-$Bu_4N)_2$·TFV salt **17a** (0.180 mmol, 0.8 equiv.). Reaction time was 3 h.

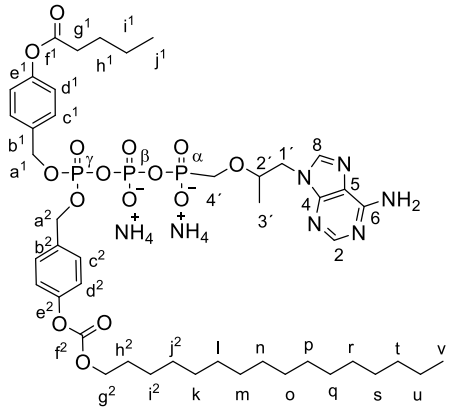
Yield: 114.4 mg (0.079 mmol, 60%) white solid.

Chemical Formula: $C_{45}H_{66}N_5O_{15}P_3^{2-}$.

Molecular weight: 1009.38 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 1010.385; found, 1010.269.



^{1}H NMR (600 MHz, CD_3OD): δ [ppm]= 8.40 (s, 1H, H-8), 8.18 (s, 1H, H-2), 7.41-7.36 (m, 4H, H-c^1, H-c^2), 7.13-7.07 (m, 2H, H-d^2), 7.04-6.99 (m, 2H, H-d^1), 5.15 (d, $^3J_{HH}$= 8.02 Hz, 4H, H-a^1, H-a^2), 4.40 (dd, $^3J_{HH}$= 14.5 Hz, $^3J_{HH}$= 3.1 Hz, 1H, H-1´$_a$), 4.22 (t, $^3J_{HH}$= 6.6 Hz, $^4J_{HH}$=1.1 Hz, 2H, H-g^2), 4.25-4.15 (m, 1H, H-1´$_b$), 3.96-3.78 (m, 3H, H-2´, H-4´), 3.26-3.18 (m, 0.56H, H-A), 2.57 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.77-

1.64 (m, 4.56H, H-B, H-h^1, H-h$^{2´}$),1.49-1.26 (m, 28.56H, H-C, H-i^1, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q, H-r, H-s, H-t, H-u), 1.02 (t, $^3J_{HH}$= 7.2 Hz, 0.84H, H-D), 1.01-0.95 (m, 6H, H-3´, H-j^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-v).

^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 173.7 (C-f^1), 155.1 (C-f^2), 154.2 (C-6), 152.6 (C-e^2), 152.3 (C-e^1), 151.4 (C-4), 148.2 (C-2), 145.6 (C-8), 135.2 (C-b^2), 135.1 (C-b^1), 130.4 (C-c^1, C-c^2), 122.8 (d, $^4J_{CP}$= 2.2 Hz, C-d^1), 122.3 (d, $^4J_{CP}$= 2.2 Hz, C-d^2), 117.6 (C-5), 70.3 (C-a^1, C-a^2), 70.0 (C-g^2), 65.5 (C-4´$_a$), 64.0 (C-4´$_b$), 58.0 (C-A), 47.6 (C-1´), 34.7 (C-g^1), 33.0, 30.8, 30.3, 23.7 (C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q, C-r, C-s, C-t, C-u), 29.7 (C-h^2), 28.0 (C-h^1), 26.8 (C-i^2), 24.7 (C-B), 23.2 (C-i^1), 20.7 (C-C), 19.0 (C-3´), 14.5 (C-v), 14.1 (C-j^1), 13.9 (C-D).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = 7.81 (d, $^2J_{pp}$=25.4 Hz, P-α), -13.18 (d, $^2J_{pp}$=17.7 Hz, P-γ), -23.67 (dd, $^2J_{pp}$= 17.7 Hz, $^2J_{pp}$= 15.7 Hz, P-β).

IR: v [cm-1] = 3029, 2957, 2922, 2852, 2163, 1755, 1717, 1653, 1576, 1508, 1457, 1419, 1217, 1167, 1123, 1059, 921, 875, 784, 719, 641, 517, 437.

(AB-C1; alkyl-C12)-*H*-phosphinate 99aa.

According to general procedure 5, with 0.23 g dodecylphosphinic acid **98a** (1.0 mmol, 1.0 equiv.), 0.33 g 4-(hydroxymethyl)phenyl acetate **52a** (2.0 mmol, 2.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

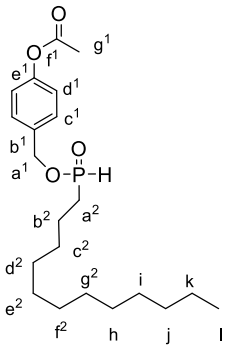
Yield: 0.24 g (0.62 mmol, 62%) white solid.

Chemical Formula: $C_{21}H_{35}O_4P$.

Molecular weight: 382.23 g/mol.

HRMS (ESI$^+$, m/z):

[M+Na]$^+$ 405.2165; found, 405.2455.



^{1}H-NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.43-7.38 (m, 2H, H-c^1), 7.14-7.10 (m, 2H, H-d^1), 7.12 (dt, $^1J_{HH}$= 530.7 Hz, $^4J_{HH}$= 1.9 Hz, 1H, P-H), 5.16-4.95 (m, 2H, H-a^1), 2.31 (s, 3H, H-g^1), 1.83-1.75 (m, 2H, H-a^2), 1.64-1.55 (m, 2H, H-b^2), 1.42-1.36 (m, 2H, H-c^2), 1.32-1.24 (m, 16H, H-d^2, H-e^2, H-f^2, H-g^2, H-h, H-i, H-j, H-k), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-l).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 169.3 (C-f^1), 150.8 (C-e^1), 133.4 (d, $^3J_{CP}$= 6.0 Hz, C-b^1), 129.5 (C-c^1), 121.9 (C-d^1), 67.8 (d, $^3J_{CP}$= 6.6 Hz, C-a^1), 31.9, 31.5, 30.3, 29.57, 29.51, 29.34, 29.30, 29.28, 22.6 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h, C-i, C-j, C-k), 29.0, 28.1 (C-a^2), 21.1 (C-g^1), 20.6 (d, $^3J_{CP}$= 3.0 Hz, C-b^2), 14.1 (C-l).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 39.6.

IR: ν [cm^{-1}] = 3674, 2987, 2957, 2848, 1754, 1509, 1465, 1407, 1393, 1369, 1228, 1202, 1188, 1165, 1057, 1044, 985, 945, 919, 863, 825, 810, 765, 719, 645, 633, 592, 547, 516, 505, 464, 445.

(AB-C4; alkyl-C12)-H-phosphinate 99ae.

According to general procedure 5, with 0.23 g dodecylphosphinic acid **98a** (1.0 mmol, 1.0 equiv.), 0.42 g 4-(hydroxymethyl)phenyl pentanoate **52e** (2.0 mmol, 2.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

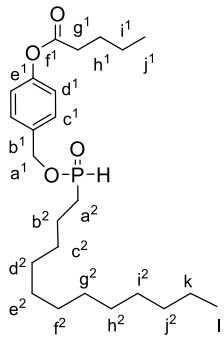
Yield: 0.22 g (0.53 mmol, 53%) white solid.

Chemical Formula: $C_{24}H_{41}O_4P$.

Molecular weight: 424.27 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 447.2634; found, 447.2975.



^{1}H-NMR (400 MHz, CD_3OD): δ [ppm] = 7.42-7.37 (m, 2H, H-c^1), 7.12-7.06 (m, 2H, H-d^1), 7.13 (dt, $^1J_{HH}$= 529.9 Hz, $^4J_{HH}$= 1.9 Hz, 1H, P-H), 5.15-4.96 (m, 2H, H-a^1), 2.55 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.83-1.68 (m, 4H, H-a^2, H-h^1), 1.64-1.50 (m, 2H, H-b^2), 1.44 (sext, $^3J_{HH}$= 7.4 Hz, 2H, H-i^1), 1.40-1.32 (m, 2H, H-c^2), 1.30-1.24 (m, 16H, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k), 0.95 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.87 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-l).

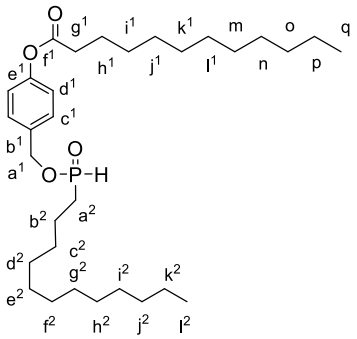
^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 172.1 (C-f^1), 150.9 (C-e^1), 133.2 (d, $^3J_{CP}$= 6.0 Hz, C-b^1), 129.2 (C-c^1), 121.9 (C-d^1), 66.7 (d, $^3J_{CP}$= 6.6 Hz, C-a^1), 34.0 (C-g^1), 31.8, 30.4, 30.3, 29.54, 29.48, 29.27, 29.25, 29.22, 29.0, 28.3, 22.6 (C-a^2, C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^2, C-j^2, C-k), 26.9 (C-h^1), 22.2 (C-i^1), 20.6 (d, $^3J_{CP}$= 3.0 Hz, C-b^2), 14.1 (C-l), 13.4 (C-j^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 39.4.

IR: v [cm^{-1}] = 2955, 2916, 2872, 2848, 1752, 1606, 1510, 1466, 1415, 1381, 1347, 1268, 1220, 1189, 1158, 1085, 1042, 987, 923, 897, 872, 826, 801, 767, 720, 692, 559, 525, 502, 498, 445.

(AB-C11; alkyl-C12)-*H*-phosphinate 99aj.

According to general procedure 5, with 0.23 g dodecylphosphinic acid **98a** (1.0 mmol, 1.0 equiv.), 0.61 g 4-(hydroxymethyl)phenyl dodecanoate **52j** (2.0 mmol, 2.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 7:3:0.005 v/v/v).



Yield: 0.35 g (0.59 mmol, 59%) white solid.

Chemical Formula: $C_{31}H_{55}O_4P$.

Molecular weight: 522.38 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 545.3730; found, 545.3571.

^{1}H-NMR (500 MHz, CD_3OD): δ [ppm] = 7.42-7.37 (m, 2H, H-c^1), 7.12-7.07 (m, 2H, H-d^1), 7.11 (dt, $^1J_{HH}$= 530.1 Hz, $^4J_{HH}$= 1.9 Hz, 1H, P-H), 5.15-4.98 (m, 2H, H-a^1), 2.55 (t, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.82-1.72 (m, 4H, H-a^2, H-h^1), 1.63-1.53 (m, 2H, H-b^2), 1.43-1.23 (m, 34H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-m, H-n, H-o, H-p), 0.92-0.85 (m, 6H, H-l^2, H-q).

^{13}C NMR (126 MHz, CD_3OD): δ [ppm] = 172.2 (C-f^1), 150.9 (C-e^1), 133.2 (d, $^3J_{CP}$= 5.9 Hz, C-b^1), 129.3 (C-c^1), 121.9 (C-d^1), 66.8 (d, $^3J_{CP}$= 6.7 Hz, C-a^1), 34.4 (C-g^1), 31.9, 30.5, 30.3, 29.58, 29.52, 29.43, 29.37, 29.31, 29.2, 29.1, 28.1, 22.7 (C-a^2, C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^1, C-i^2, C-j^1, C-j^2, C-k^1, C-k^2, C-l^1, C-m, C-n, C-o, C-p), 24.9 (C-h^1), 20.6 (d, $^3J_{CP}$= 3.0 Hz, C-b^2), 14.1 (C-l^2, C-q).

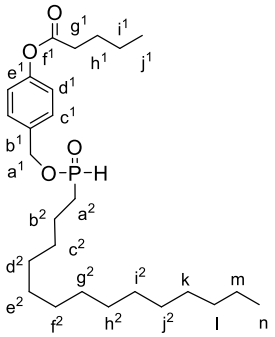
^{31}P NMR (202 MHz, CD_3OD): δ [ppm] = 40.7.

IR: v [cm^{-1}] = 3662, 2987, 2957, 2915, 2848, 1752, 1606, 1511, 1465, 1409, 1406, 1382, 1328, 1297, 1266, 1222, 1202, 1167, 1152, 1065, 1056, 1006, 925, 891, 871, 829, 793, 773, 719, 692, 577, 564, 530, 502, 462, 445.

(AB-C4; alkyl-C14)-*H*-phosphinate 99be.

According to general procedure 5, with 0.26 g tetradecylphosphinic acid **98b** (1.0 mmol, 1.0 equiv.), 0.42 g 4-(hydroxymethyl)phenyl pentanoate **52e** (2.0 mmol, 2.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

Yield: 0.23 g (0.51 mmol, 51%) white solid.



Chemical Formula: $C_{26}H_{45}O_4P$.

Molecular weight: 452.31 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 475.2947; found, 475.3245.

^{1}H-NMR (600 MHz, CD_3OD): δ [ppm] = 7.39-7.35 (m, 2H, H-c^1), 7.10-7.05 (m, 2H, H-d^1), 7.14 (dt, $^1J_{HH}$= 530.1 Hz, $^4J_{HH}$= 1.9 Hz, 1H, P-H), 5.15-4.96 (m, 2H, H-a^1), 2.53 (t, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.83-1.68 (m, 4H, H-a^2, H-h^1), 1.60-1.54 (m, 2H, H-b^2), 1.43 (sext, $^3J_{HH}$= 7.4 Hz, 2H, H-i^1), 1.40-1.32 (m, 2H, H-c^2), 1.30-1.24 (m, 20H, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m), 0.94 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.85 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-n).

^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 172.2 (C-f^1), 150.9 (C-e^1), 133.2 (d, $^3J_{CP}$= 6.0 Hz, C-b^1), 129.3 (C-c^1), 121.9 (C-d^1), 66.8 (d, $^3J_{CP}$= 6.6 Hz, C-a^1), 34.1 (C-g^1), 31.9, 30.5, 30.3, 29.65, 29.62, 29.58, 29.52, 29.32, 29.28, 22.7 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m), 29.0, 28.1 (C-a^2), 26.9 (C-h^1), 22.2 (C-i^1), 20.6 (d, $^3J_{CP}$= 3.0 Hz, C-b^2), 14.1 (C-n), 13.7 (C-j^1).

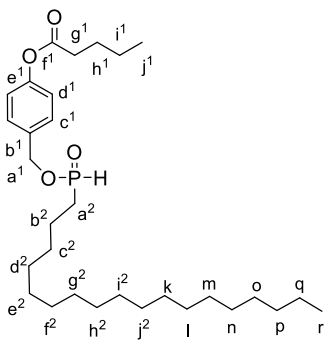
^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = 39.4.

IR: v [cm^{-1}] =2954, 2915, 2848, 1753, 1509, 1465, 1382, 1347, 1267, 1220, 1105, 1062, 985, 859, 821, 768, 720, 692, 633, 560, 525, 505, 477.

(AB-C4; alkyl-C18)-*H*-phosphinate 99ce.

According to general procedure 5, with 0.32 g octadecylphosphinic acid **98c** (1.0 mmol, 1.0 equiv.), 0.42 g 4-(hydroxymethyl)phenyl pentanoate **52e** (2.0 mmol, 2.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 7:3:0.005 v/v/v).

Yield: 0.25 g (0.48 mmol, 48%) white solid.



Chemical Formula: $C_{30}H_{53}O_4P$.

Molecular weight: 508.37 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 531.3573; found, 531.3517.

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm] = 7.42-7.36 (m, 2H, H-c^1), 7.12-7.06 (m, 2H, H-d^1), 7.11 (dt, $^{1}J_{HH}$= 530.0 Hz, $^{4}J_{HH}$= 1.8 Hz, 1H, P-H), 5.15-4.96 (m, 2H, H-a^1), 2.56 (t, $^{3}J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.85-1.68 (m, 4H, H-a^2, H-h^1), 1.65-1.54 (m, 2H, H-b^2), 1.52-1.41 (m, 2H, H-i^1), 1.40-1.32 (m, 2H, H-c^2), 1.37-1.24 (m, 30H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.96 (t, $^{3}J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.87 (t, $^{3}J_{HH}$= 6.6 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 172.1 (C-f^1), 150.9 (C-e^1), 133.2 (d, $^{3}J_{CP}$= 6.0 Hz, C-b^1), 129.3 (C-c^1), 121.9 (C-d^1), 66.8 (d, $^{3}J_{CP}$= 6.6 Hz, C-a^1), 34.1 (C-g^1), 31.9, 30.5, 30.3, 29.66, 29.63, 29.58, 29.52, 29.36, 29.33, 29.29, 22.7 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.0, 28.1 (C-a^2), 26.9 (C-h^1), 22.2 (C-i^1), 20.6 (d, $^{3}J_{CP}$= 3.0 Hz, C-b^2), 14.1 (C-n), 13.7 (C-j^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 39.4.

IR: ν [cm^{-1}] = 3191, 3039, 2955, 2921, 2851, 1759, 1691, 1508, 1463, 1226, 1201, 1166, 1123, 1080, 1041, 994, 903, 838, 806, 783, 768, 719, 691, 644, 514.

(ACB-C1; alkyl-C12)-*H*-phosphinate 102ak.

According to general procedure 5, with 0.23 g dodecylphosphinic acid **98a** (1.0 mmol, 1.0 equiv.), 0.36 g 4-(hydroxymethyl)phenyl methyl carbonate **73k** (2.0 mmol, 2.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

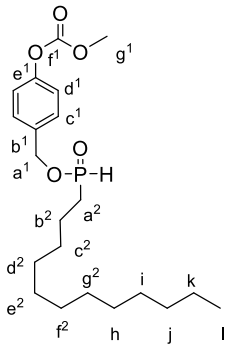
Yield: 0.22 g (0.55 mmol, 55%) white solid.

Chemical Formula: $C_{21}H_{35}O_5P$.

Molecular weight: 398.22 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 421.2114; found, 421.2207.



^{1}H-NMR (400 MHz, CD_3OD): δ [ppm] = 7.42-7.36 (m, 2H, H-c^1), 7.18-7.13 (m, 2H, H-d^1), 7.13 (dt, $^{1}J_{HH}$= 530.3 Hz, $^{4}J_{HH}$= 1.9 Hz, 1H, P-H), 5.16-4.94 (m, 2H, H-a^1), 3.86 (s, 3H, H-g^1), 1.80-1.70 (m, 2H, H-a^2), 1.62-1.48 (m, 2H, H-b^2), 1.38-1.30 (m, 2H, H-c^2), 1.26-1.18 (m, 16H, H-d^2, H-e^2, H-f^2, H-g^2, H-h, H-i, H-j, H-k), 0.84 (t, $^{3}J_{HH}$= 6.8 Hz, 3H, H-l).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 154.0 (C-f^1), 151.1 (C-e^1), 133.6 (d, $^{3}J_{CP}$= 6.0 Hz, C-b^1), 129.2 (C-c^1), 121.3 (C-d^1), 66.6 (d, $^{3}J_{CP}$= 6.6 Hz, C-a^1), 55.4 (C-g^1), 31.8, 30.4, 30.3, 29.54, 29.47, 29.33,

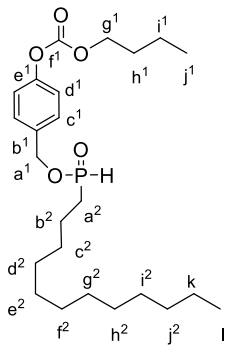
29.26, 29.24, 22.6 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h, C-i, C-j, C-k), 29.0, 28.1 (C-a^2), 20.6 (d, $^3J_{CP}$= 3.0 Hz, C-b^2), 14.0 (C-l).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 39.6.

IR: ν [cm^{-1}] = 3662, 2987, 2970, 2922, 2854, 1762, 1509, 1439, 1406, 1393, 1380, 1255, 1219, 1065, 1056, 1016, 959, 932, 892, 862, 820, 779, 723, 597, 508, 439.

(ACB-C4; alkyl-C12)-*H*-phosphinate 102am.

According to general procedure 5, with 0.23 g dodecylphosphinic acid **98a** (1.0 mmol, 1.0 equiv.), 0.45 g butyl (4-(hydroxymethyl)phenyl) carbonate **73m** (2.0 mmol, 2.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.21 g (0.48 mmol, 48%) white solid.

Chemical Formula: $C_{24}H_{41}O_5P$.

Molecular weight: 440.27 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 463.2584; found, 463.2699.

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm] = 7.42-7.36 (m, 2H, H-c^1), 7.21-7.14 (m, 2H, H-d^1), 7.10 (dt, $^1J_{HH}$= 530.5 Hz, $^4J_{HH}$= 1.9 Hz, 1H, P-H), 5.16-4.94 (m, 2H, H-a^1), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^1), 1.84-1.66 (m, 4H, H-a^2, H-h^1) 1.64-1.50 (m, 2H, H-b^2), 1.48-1.28 (m, 2H, H-i^1), 1.38-1.20 (m, 18H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k), 0.95 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.86 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-l).

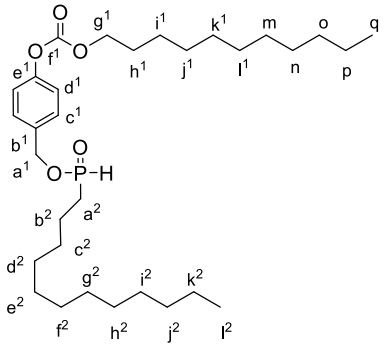
^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 153.5 (C-f^1), 151.1 (C-e^1), 133.4 (d, $^3J_{CP}$= 6.0 Hz, C-b^1), 129.2 (C-c^1), 121.3 (C-d^1), 68.7 (C-g^1), 66.7 (d, $^3J_{CP}$= 6.6 Hz, C-a^1), 31.8, 30.5, 30.4, 30.2, 29.51, 29.45, 29.28, 29.24, 29.22, 29.0, 22.6 (C-a^2, C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^1, C-h^2, C-i^2, C-j^2, C-k), 20.6 (d, $^3J_{CP}$= 3.0 Hz, C-b^2), 18.8(C-i^1), 14.0 (C-l), 13.6 (C-j^1).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 39.4.

IR: ν [cm^{-1}] = 3662, 2987, 2968, 2920, 2853, 1759, 1609, 11509, 1466, 1404, 1393, 1382, 1326, 1248, 1217, 1066, 1056, 1015, 990, 962, 899, 869, 822, 780, 719, 507, 459, 437.

(ACB-C11; alkyl-C12)-*H*-phosphinate 102au.

According to general procedure 5, with 0.23 g dodecylphosphinic acid **98a** (1.0 mmol, 1.0 equiv.), 0.64 g 4-(hydroxymethyl)phenyl undecyl carbonate **73u** (2.0 mmol, 2.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).



Yield: 0.29 g (0.54 mmol, 54%) white solid.

Chemical Formula: $C_{31}H_{55}O_5P$.

Molecular weight: 538.38 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 561.3679; found, 561.3762.

^{1}H-NMR (400 MHz, CD_3OD): δ [ppm] = 7.44-7.38 (m, 2H, H-c^1), 7.22-7.18 (m, 2H, H-d^1), 7.11 (dt, $^1J_{HH}$= 529.8 Hz, $^4J_{HH}$= 1.9 Hz, 1H, P-H), 5.16-4.96 (m, 2H, H-a^1), 4.24 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^1), 1.84-1.70 (m, 4H, H-a^2, H-h^1) 1.64-1.56 (m, 2H, H-b^2), 1.44-1.22 (m, 34H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-m, H-n, H-o, H-p), 0.90-0.84 (m, 6H, H-l^2, H-q).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 153.6 (C-f^1), 151.2 (C-e^1), 133.5 (d, $^3J_{CP}$= 6.6 Hz, C-b^1), 129.3 (C-c^1), 121.4 (C-d^1), 69.1 (C-g^1), 66.7 (d, $^3J_{CP}$= 6.6 Hz, C-a^1), 31.9, 30.5, 30.3, 29.8, 29.58, 29.56, 29.52, 29.45, 29.29, 29.23, 29.17, 29.0, 28.5, 28.3, 25.6, 22.6 (C-a^2, C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^1, C-h^2, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-m, H-n, H-o, H-p), 20.6 (d, $^3J_{CP}$= 3.0 Hz, C-b^2), 14.1 (C-l^2, C-q).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 39.5.

IR: ν [cm^{-1}] = 3674, 2987, 2970, 2922, 2854, 1759, 1606, 1508, 1465, 1406, 1393, 1382, 1248, 1215, 1065, 1055, 1015, 960, 892, 879, 866, 820, 779, 720, 604, 507, 432.

(ACB-C4; alkyl-C14)-*H*-phosphinate 102bm.

According to general procedure 5, with 0.26 g tetradecylphosphinic acid **98b** (1.0 mmol, 1.0 equiv.), 0.45 g butyl (4-(hydroxymethyl)phenyl) carbonate **73m** (2.0 mmol, 2.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

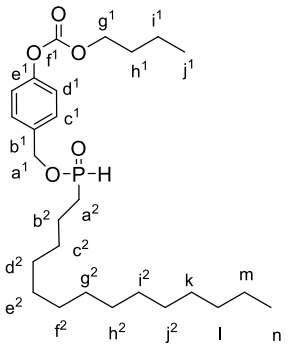
Yield: 0.25 g (0.53 mmol, 53%) white solid.

Chemical Formula: $C_{26}H_{45}O_5P$.

Molecular weight: 468.30 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 491.2897; found, 491.2910.



^{1}H-NMR (500 MHz, CD_3OD): δ [ppm] = 7.44-7.36 (m, 2H, H-c^1), 7.23-7.16 (m, 2H, H-d^1), 7.11 (dt, $^1J_{HH}$= 529.7 Hz, $^4J_{HH}$= 1.8 Hz, 1H, P-H), 5.17-4.95 (m, 2H, H-a^1), 4.26 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^1), 1.84-1.68 (m, 4H, H-a^2, H-h^1) 1.64-1.53 (m, 2H, H-b^2), 1.52-1.42 (m, 2H, H-i^1), 1.40-1.20 (m, 22H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m), 0.97 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.87 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-n).

^{13}C NMR (126 MHz, CD_3OD): δ [ppm] = 153.6 (C-f^1), 151.2 (C-e^1), 133.5 (d, $^3J_{CP}$= 6.0 Hz, C-b^1), 129.3 (C-c^1), 121.4 (C-d^1), 68.8 (C-g^1), 66.7 (d, $^3J_{CP}$= 6.6 Hz, C-a^1), 31.8, 30.55, 30.49, 30.3, 29.65, 29.62, 29.58, 29.52, 29.33, 29.29, 29.1, 28.1, 22.7 (C-a^2, C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^1, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m), 20.6 (d, $^3J_{CP}$= 3.0 Hz, C-b^2), 18.9 (C-i^1), 14.1 (C-n), 13.6 (C-j^1).

^{31}P NMR (202 MHz, CD_3OD): δ [ppm] = 41.0.

IR: ν [cm^{-1}] = 3662, 2987, 2968, 2916, 2850, 1759, 1609, 1509, 1466, 1405, 1393, 1381, 1249, 1215, 1168, 1066, 1056, 1014, 971, 900, 869, 819, 781, 719, 512, 475, 432.

(ACB-C4; alkyl-C18)-*H*-phosphinate 102cm.

According to general procedure 2, with 0.32 g octadecylphosphinic acid **98c** (1.0 mmol, 1.0 equiv.), 0.45 g butyl (4-(hydroxymethyl)phenyl) carbonate **73m** (2.0 mmol, 2.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 6:4:0.005 v/v/v).

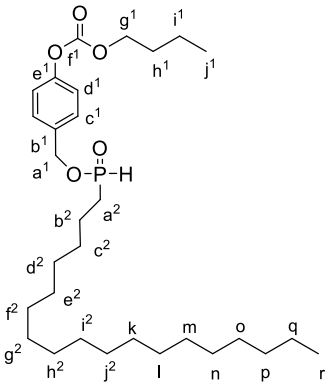
Yield: 0.45 g (0.85 mmol, 85%) white solid.

Chemical Formula: $C_{30}H_{53}O_5P$.

Molecular weight: 524.36 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 547.3523; found, 547.3518.



^{1}H-NMR (600 MHz, CD_3OD): δ [ppm] = 7.39-7.35 (m, 2H, H-c^1), 7.18-7.14 (m, 2H, H-d^1), 7.13 (dt, $^{1}J_{HH}$= 530.0 Hz, $^{4}J_{HH}$= 1.8 Hz, 1H, P-H), 5.12-4.95 (m, 2H, H-a^1), 4.22 (t, $^{3}J_{HH}$= 6.7 Hz, 2H, H-g^1), 1.78-1.66 (m, 4H, H-a^2, H-h^1) 1.64-1.51 (m, 2H, H-b^2), 1.42 (sext, $^{3}J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.36-1.31 (m, 2H, H-c^2), 1.40-1.20 (m, 28H, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.93 (t, $^{3}J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.84 (t, $^{3}J_{HH}$= 7.0 Hz, 3H, H-r).

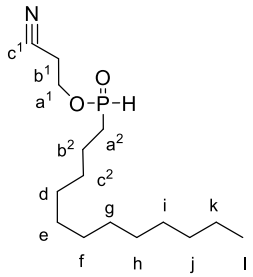
^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 153.6 (C-f^1), 151.2 (C-e^1), 133.5 (d, $^{3}J_{CP}$= 6.0 Hz, C-b^1), 129.3 (C-c^1), 121.4 (C-d^1), 68.8 (C-g^1), 66.7 (d, $^{3}J_{CP}$= 6.6 Hz, C-a^1), 31.8, 30.55, 30.49, 30.3, 29.67, 29.63, 29.59, 29.53, 29.33, 29.30, 29.1, 28.1, 22.7 (C-a^2, C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^1, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 20.6 (d, $^{3}J_{CP}$= 3.0 Hz, C-b^2), 18.9 (C-i^1), 14.1 (C-r), 13.6 (C-j^1).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = 39.5.

IR: ν [cm^{-1}] = 3662, 2987, 2969, 2915, 2848, 1759, 1607, 1509, 1464, 1405, 1393, 1382, 1250, 1220, 1065, 1056, 1027, 1015, 969, 898, 819, 779, 719, 603, 529, 507, 459, 436.

(β-cyanoethyl; alkyl-C12)-*H*-phosphinate 104a

According to general procedure 5, with 0.23 g dodecylphosphinic acid **98a** (1.0 mmol, 1.0 equiv.), 0.14 g 3-hydroxypropionitrile **82** (2.0 mmol, 1.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 4:6:0.005 v/v/v).



Yield: 0.12 g (0.42 mmol, 42%) white solid.

Chemical Formula: $C_{15}H_{30}NO_2P$.

Molecular weight: 287.20 g/mol.

HRMS (ESI$^+$, m/z): $[M+Na]^+$ 310.1906; found, 310.2115.

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.11 (dt, $^{1}J_{HH}$= 535.2 Hz, $^{4}J_{HH}$= 1.9 Hz, 1H, P-H), 4.32-4.10 (m, 2H, H-a^1), 2.82-2.62 (m, 2H, H-b^1), 1.84-1.70 (m, 2H, H-a^2), 1.62-1.48 (m, 2H, H-b^2), 1.38-1.30 (m, 2H, H-c^2), 1.27-1.16 (m, 16H, H-d, H-e, H-f, H-g, H-h, H-i, H-j, H-k), 0.81 (t, $^{3}J_{HH}$= 6.7 Hz, 3H, H-l).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 118.8 (C-c^1), 60.2 (d, $^{3}J_{CP}$= 6.4 Hz, C-a^1), 31.8, 31.4, 30.2, 29.54, 29.48, 29.31, 29.27, 29.25, 22.6 (C-c^2, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k), 29.0, 28.1 (C-a^2), 20.4 (d, $^{3}J_{CP}$= 3.0 Hz, C-b^2), 20.0 (d, $^{3}J_{CP}$= 6.3 Hz, C-b^1), 14.1 (C-l).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 41.9.

IR: ν [cm^{-1}] = 3662, 3382, 2987, 2969, 2921, 2853, 2355, 2252, 1465, 1406, 1393, 1380, 1224, 1065, 1055, 961, 832, 778, 720, 443.

(β-cyanoethyl; alkyl-C18)-*H*-phosphinate 104c.

According to general procedure 5, with 0.32 g octadecylphosphinic acid **98c** (1.0 mmol, 1.0 equiv.), 0.14 g 3-hydroxypropionitrile **82** (2.0 mmol, 1.0 equiv.), 0.19 g EDC (1.2 mmol, 1.2 equiv.), 24 mg DMAP (0.2 mmol, 0.2 equiv.) dissolved in 5 mL CH_2Cl_2. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 4:6:0.005 v/v/v).

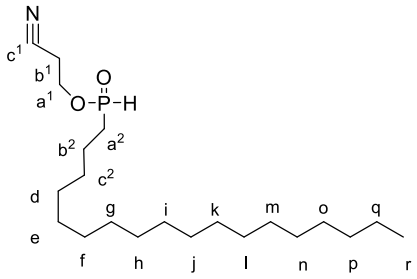
Yield: 0.19 g (0.51 mmol, 51%) white solid.

Chemical Formula: $C_{21}H_{42}NO_2P$.

Molecular weight: 371.30 g/mol.

HRMS (ESI^+, m/z):

$[M+Na]^+$ 394.2845; found, 394.3081.



^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.16 (dt, $^1J_{HH}$= 534.7 Hz, $^4J_{HH}$= 1.9 Hz, 1H, P-H), 4.38-4.12 (m, 2H, H-a^1), 2.86-2.66 (m, 2H, H-b^1), 1.88-1.75 (m, 2H, H-a^2), 1.67-1.52 (m, 2H, H-b^2), 1.43-1.34 (m, 2H, H-c^2), 1.33-1.20 (m, 28H, H-d, H-e, H-f, H-g, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.86 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-l).

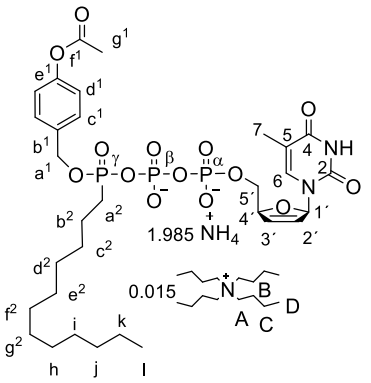
^{13}C NMR (101 MHz, CD_3OD): ν [ppm] = 116.5 (C-c^1), 60.3 (d, $^3J_{CP}$= 6.6 Hz, C-a^1), 31.9, 31.4, 30.3, 29.63, 29.60, 29.55, 29.49, 29.30, 29.25, 28.4, 22.6 (C-c^2, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.0, 28.1 (C-a^2), 20.4 (d, $^3J_{CP}$= 3.3 Hz, C-b^2), 20.0 (d, $^3J_{CP}$= 6.6 Hz, C-b^1), 14.1 (C-r).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 42.0.

IR: ν [cm^{-1}] = 3662, 3413, 2987, 2970, 2915, 2848, 2362, 2251, 1472, 1462, 1407, 1393, 1331, 1240, 1223, 1209, 1196, 1183, 1054, 1026, 993, 971, 959, 939, 879, 814, 793, 755, 729, 577, 481, 460, 434.

γ-(AB-C1)-γ-C-(alkyl-C12)-d4TTP 67aa.

According to general procedure 12 with 115 mg *H*-phosphinate **99aa** (0.3 mmol, 1.0 equiv) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.21 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 103 mg (0.13 mmol, 61%) white solid.

Chemical Formula: $C_{31}H_{45}N_2O_{14}P_3^{2-}$.

Molecular weight: 762.21 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 763.217; found, 763.207.

^{1}H-NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.69 (dd, $^3J_{HH}$= 3.1 Hz, $^4J_{HH}$=1.3 Hz, 1H, H-6), 7.52-7.44 (m, 2H, H-c^1), 7.12-7.06 (m, 2H, H-d^1), 6.94 (dt, $^3J_{HH}$= 3.5 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.49 (dt, $^3J_{HH}$= 5.9 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-3´), 5.84 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$= 1.8 Hz, 1H, H-2´), 5.30-5.10 (m, 2H, H-a^1), 5.00-4.94 (m, 1H, H-4´), 4.31-4.15 (m, 2H, H-5´), 3.28-3.17 (m, 0.12H, H-A), 2.27 (s, 3H, H-g^1), 2.08-1.96 (m, 2H, H-a^2), 1.90 (dd, $^3J_{HH}$= 4.9 Hz, $^4J_{HH}$= 1.1 Hz, 3H, H-7), 1.70-1.55 (m, 4.24H, H-B, H-C, H-b^2, H-c^2), 1.42-1.20 (m, 16H, H-d^2, H-e^2, H-f^2, H-g^2, H-h, H-i, H-j, H-k), 1.01 (t, $^3J_{HH}$= 7.3 Hz, 0.18H, H-D), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-l).

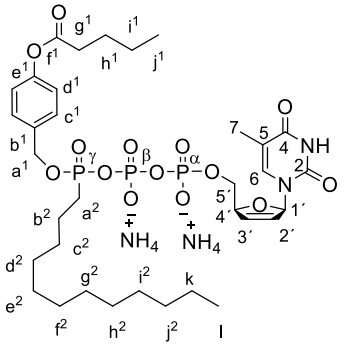
^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 171.1 (C-f^1), 166.5 (d, $^3J_{CP}$= 2.8 Hz, C-4), 152.8 (C-2), 152.2 (d, $^4J_{CP}$= 1.8 Hz, C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.56 (dd, $^3J_{CP}$= 7.4 Hz, $^3J_{CP}$= 3.8 Hz, C-b^1), 130.30 (d, $^3J_{CP}$= 8.3 Hz, C-c^1), 127.2 (C-2´), 122.9 (C-d^1), 112.1 (C-5), 90.8 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 67.96, 67.88, 67.81 (C-a^1, C-5´), 59.5 (C-A), 39.6, 33.0, 31.6, 31.4, 30.74, 30.72, 30.68, 30.5, 30.4, 30.2, 23.7 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h, C-i, C-j, C-k), 27.9, 26.1 (C-a^2), 24.7 (C-B), 23.2 (d, $^3J_{CP}$= 5.4 Hz, C-b^2), 20.7 (C-C), 20.9 (C-g^1), 14.4 (C-l), 13.9 (C-D), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 24.42 (dd, $^2J_{pp}$= 23.6, $^2J_{pp}$= 11.8 Hz, P-γ), -11.68 (d, $^2J_{pp}$= 19.2 Hz, P-α), -23.53 (t, $^2J_{pp}$= 26.5 Hz, P-β).

IR: ν [cm^{-1}] = 3198, 2923, 2853, 1763, 1687, 1663, 1508, 1455, 1369, 1217, 1195, 1166, 1122, 1077, 1041, 994, 902, 837, 806, 783, 767, 722, 692, 646, 508, 492, 423.

γ-(AB-C4)-γ-C-(alkyl-C12)-d4TTP 67ae.

According to general procedure 12 with 127 mg *H*-phosphinate **99ae** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.21 mmol, 0.7 equiv.). Reaction time was 2 h.



Yield: 52 mg (0.065 mmol, 31%) white solid.

Chemical Formula: $C_{34}H_{59}N_4O_{14}P_3$.

Molecular weight: 840.32 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 805.264; found, 805.227.

^{1}H-NMR (400 MHz, CD$_3$OD-d$_4$): δ [ppm] = 7.68 (dd, $^3J_{HH}$= 2.9 Hz, $^4J_{HH}$=1.3 Hz, 1H, H-6), 7.50-7.45 (m, 2H, H-c^1), 7.10-7.05 (m, 2H, H-d^1), 6.94 (dt, $^3J_{HH}$= 3.3 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.49 (dt, $^3J_{HH}$= 5.9 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-3´), 5.84 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$= 1.8 Hz, 1H, H-2´), 5.26-5.13 (m, 2H, H-a^1), 5.00-4.94 (m, 1H, H-4´), 4.30-4.15 (m, 2H, H-5´), 2.58 (t, 2H, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 2.06-1.96 (m, 2H, H-a^2), 1.90 (dd, $^3J_{HH}$= 4.6 Hz, $^4J_{HH}$= 1.1 Hz, 3H, H-7), 1.71 (quint, $^3J_{HH}$= 7.3 Hz, 2H, H-h^1), 1.64-1.54 (m, 2H, H-b^2), 1.44 (sext, $^3J_{HH}$= 7.7 Hz, 2H, H-i^1), 1.38-1.24 (m, 18H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k), 0.99 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-l).

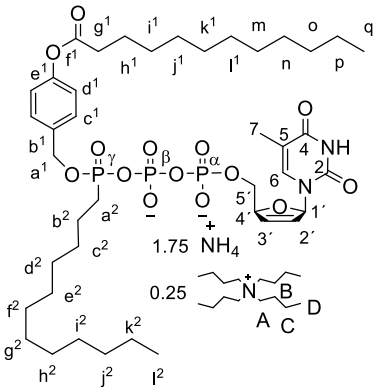
^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 173.8 (C-f^1), 166.5 (d, $^3J_{CP}$= 2.7 Hz, C-4), 152.8 (C-2), 152.2 (d, $^4J_{CP}$= 1.7 Hz, C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.50 (dd, $^3J_{CP}$= 7.2 Hz, $^3J_{CP}$= 3.9 Hz, C-b^1), 130.34 (d, $^3J_{CP}$= 7.7 Hz, C-c^1), 127.2 (C-2´), 122.8 (d, $^4J_{CP}$= 1.1 Hz, C-d^1), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 9.1 Hz, C-4´), 67.99, 67.89, 67.80 (C-a^1, C-5´), 34.7 (C-g^1), 27.97, 26.1 (C-a^2), 28.03 (C-h^1), 33.0, 31.6, 31.4, 30.76, 30.73, 30.69, 30.51, 30.45, 30.2, 23.7 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^1, C-i^2, C-j^2, C-k), 23.2 (d, $^3J_{CP}$= 5.2 Hz, C-b^2), 14.5 (C-l), 14.1 (C-j^1), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 24.44 (dd, $^2J_{pp}$= 23.6, $^2J_{pp}$= 11.8 Hz, P-γ), -11.68 (d, $^2J_{pp}$= 17.8 Hz, P-α), -23.49 (t, $^2J_{pp}$= 26.5 Hz, P-β).

IR: ν [cm^{-1}] = 3385, 2987, 2970, 2923, 2901, 1758, 1659, 1452, 1407, 1394, 1382, 1250, 1229, 1167, 1123, 1077, 1066, 1048, 1014, 907, 493, 448, 433.

γ-(AB-C11)-γ-C-(alkyl-C12)-d4TTP 67aj.

According to general procedure 12 with 157 mg *H*-phosphinate **99aj** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.21 mmol, 0.7 equiv.). Reaction time was 4 h.



Yield: 65 mg (0.069 mmol, 33%) white solid.

Chemical Formula: $C_{41}H_{65}N_2O_{14}P_3^{2-}$.

Molecular weight: 902.37 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 903.373; found, 903.340.

^{1}H-NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.67 (dd, $^3J_{HH}$= 2.3 Hz, $^4J_{HH}$=1.1 Hz, 1H, H-6), 7.52-7.45 (m, 2H, H-c^1), 7.15-7.05 (m, 2H, H-d^1), 6.94 (dt, $^3J_{HH}$= 3.3 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.49 (dt, $^3J_{HH}$= 5.9 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-3´), 5.84 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 3.3 Hz, $^4J_{HH}$= 1.5 Hz, 1H, H-2´), 5.25-5.15 (m, 2H, H-a^1), 5.05-4.97 (m, 1H, H-4´), 4.30-4.15 (m, 2H, H-5´), 3.27-3.17 (m, 2H, H-A), 2.57 (t, 2H, $^3J_{HH}$= 7.4 Hz, H-g^1), 2.05-1.95 (m, 2H, H-a^2), 1.90 (dd, $^3J_{HH}$= 3.7 Hz, $^4J_{HH}$= 1.5 Hz, 3H, H-7), 1.80-1.55 (m, 8H, H-B, H-C, H-b^2, H-h^1), 1.45-1.24 (m, 34H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-m, H-n, H-o, H-p), 1.01 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-D), 0.89 (t, $^3J_{HH}$= 6.6 Hz, 6H, H-l^2, H-q).

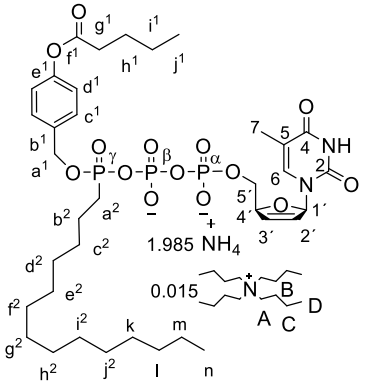
^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 173.7 (C-f^1), 166.5 (d, $^3J_{CP}$= 2.7 Hz, C-4), 152.8 (C-2), 152.2 (d, $^4J_{CP}$= 1.6 Hz, C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.50 (dd, $^3J_{CP}$= 7.2 Hz, $^3J_{CP}$= 3.9 Hz, C-b^1), 130.35 (d, $^3J_{CP}$= 7.7 Hz, C-c^1), 127.2 (C-2´), 122.8 (C-d^1), 112.0 (C-5), 90.8 (C-1´), 87.1 (d, $^3J_{CP}$= 9.1 Hz, C-4´), 67.98, 67.88, 67.78 (C-a^1, C-5´), 59.5 (C-A), 35.0 (C-g^1), 39.6, 33.06, 33.04, 31.6, 31.4, 30.76, 30.74, 30.70, 30.57, 30.51, 30.47, 30.44, 30.37, 30.2, 30.1, 23.72, 23.71 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^1, C-i^2, C-j^1, C-j^2, C-k^1, C-k^2, C-l^1, C-m, C-n, C-o, C-p), 27.9, 26.1 (C-a^2), 25.9 (C-h^1), 24.8 (C-B), 23.2 (d, $^3J_{CP}$= 4.8 Hz, C-b^2), 20.7 (C-C), 14.5 (C-l^2, C-q), 13.9 (C-D), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 25.75 (dd, $^2J_{pp}$= 23.6, $^3J_{pp}$= 9.5 Hz, P-γ), -10.48 (d, $^2J_{pp}$= 16.4 Hz, P-α), -22.26 (t, $^2J_{pp}$= 18.5 Hz, P-β).

IR: ν [cm^{-1}] = 3197, 2922, 2852, 1760, 1691, 1508, 1458, 1377, 1245, 1222, 1199, 1166, 1123, 1078, 1040, 994, 903, 838, 806, 783, 768, 720, 691, 646, 514.

γ-(AB-C4)-γ-C-(alkyl-C14)-d4TTP 67be.

According to general procedure 12 with 136 mg *H*-phosphinate **99be** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.21 mmol, 0.7 equiv.). Reaction time was 4 h.



Yield: 104 mg (0.12 mmol, 57%) white solid.

Chemical Formula: $C_{36}H_{55}N_2O_{14}P_3^{2-}$.

Molecular weight: 832.29 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 833.295; found, 833.260.

^{1}H-NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.68 (dd, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$=1.2 Hz, 1H, H-6), 7.50-7.45 (m, 2H, H-c^1), 7.11-7.06 (m, 2H, H-d^1), 6.94 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.49 (dt, $^3J_{HH}$= 5.9 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-3´), 5.84 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 3.7 Hz, $^4J_{HH}$= 1.6 Hz, 1H, H-2´), 5.26-5.14 (m, 2H, H-a^1), 5.00-4.95 (m, 1H, H-4´), 4.30-4.16 (m, 2H, H-5´), 3.28-3.20 (m, 0.12H, H-A), 2.58 (t, $^3J_{HH}$= 7.5 Hz, 2H, H-g^1), 2.06-1.96 (m, 2H, H-a^2), 1.90 (dd, $^3J_{HH}$= 3.8 Hz, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.71 (quint, $^3J_{HH}$= 7.5 Hz, 2H, H-h^1), 1.66-1.54 (m, 2.12H, H-B, H-b^2), 1.46 (sext, $^3J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.40-1.24 (m, 22.12H, H-C, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m), 1.02 (t, $^3J_{HH}$= 7.2 Hz, 0.18H, H-D), 0.98 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-n).

^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 173.8 (C-f^1), 166.6 (d, $^3J_{CP}$= 4.5 Hz, C-4), 152.8 (C-2), 152.2 (d, $^4J_{CP}$= 2.7 Hz, C-e^1), 138.7 (C-6), 135.8 (C-3´), 135.6, 135.1 (C-b^1), 130.3 (d, $^2J_{CP}$= 13.8 Hz, C-c^1), 127.2 (C-2´), 122.8 (d, $^4J_{CP}$= 1.1 Hz, C-d^1), 112.1 (C-5), 90.9 (d, $^4J_{CP}$= 1.8 Hz, C-1´), 87.2 (d, $^3J_{CP}$= 9.2 Hz, C-4´), 67.9, 67.8 (2 x d, $^3J_{CP}$= 6.2 Hz, $^3J_{CP}$= 5.6 Hz, C-a^1, C-5´), 59.5 (t, $^3J_{CP}$= 2.8 Hz, C-A), 34.8 (C-g^1), 28.1 (C-h^1), 27.6, 26.5 (C-a^2), 33.1, 31.6, 31.4, 30.79, 30.77, 30.75, 30.69, 30.52, 30.46, 30.2, 23.7 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^1, C-i^2, C-j^2, C-k, C-l, C-m), 24.8 (C-B), 23.2 (d, $^3J_{CP}$= 5.4 Hz, C-b^2), 20.7 (C-C), 14.3 (C-n), 14.1 (C-j^1), 13.9 (C-D), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 25.74 (dd, $^2J_{pp}$= 25.2, $^3J_{pp}$= 9.2 Hz, P-γ), -10.47 (d, $^2J_{pp}$= 18.3 Hz, P-α), -22.24 (t, $^2J_{pp}$= 16.5 Hz, P-β).

IR: ν [cm^{-1}] = 3185, 3034, 2923, 2852, 1759, 1690, 1508, 1457, 1224, 1166, 1123, 1078, 993, 900, 838, 806, 783, 768, 722, 692, 576, 510, 491.

γ-(AB-C4)-γ-C-(alkyl-C18)-d4TTP 67ce.

According to general procedure 12 with 153 mg *H*-phosphinate **99ce** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.21 mmol, 0.7 equiv.). Reaction time was 5 h.

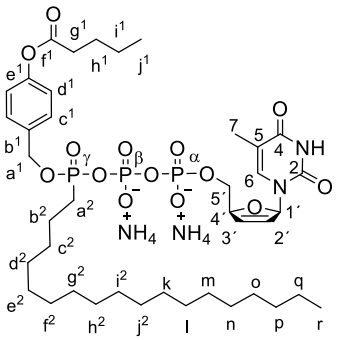
Yield: 58 mg (0.063 mmol, 30%) white solid.

Chemical Formula: $C_{40}H_{71}N_4O_{14}P_3$.

Molecular weight: 924.42 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 889.358; found, 889.334.



^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.68 (dd, $^3J_{HH}$= 2.8 Hz, $^4J_{HH}$= 1.3 Hz, 1H, H-6), 7.50-7.45 (m, 2H, H-c^1), 7.11-7.05 (m, 2H, H-d^1), 6.94 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.49 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.4 Hz, 1H, H-3´), 5.84 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.28-5.12 (m, 2H, H-a^1), 5.02-4.96 (m, 1H, H-4´), 4.30-4.22 (m, 1H, H-5´$_a$), 4.20-4.15 (m, 1H, H-5´$_b$), 2.58 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 2.07-1.95 (m, 2H, H-a^2), 1.90 (dd, $^3J_{HH}$=2.8 Hz, $^4J_{HH}$=1.0 Hz, 3H, H-7), 1.71 (quint, $^3J_{HH}$= 7.4 Hz, 2H, H-h^1), 1.66-1.54 (m, 2H, H-b^2), 1.46 (sext, $^3J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.37-1.25 (m, 30H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.98 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.1 Hz, C-f^1), 166.5 (d, $^3J_{CP}$= 3.5 Hz, C-4), 152.8 (C-2), 152.2 (d, $^3J_{CP}$= 2.2 H$_v$, C-e^1), 138.6 (C-6), 135.7 (C-3´), 135.5 (dd, $^3J_{CP}$= 6.6 Hz, $^3J_{CP}$= 5.1 Hz, C-b^1), 130.3 (d, $^2J_{CP}$= 10.3 Hz, C-c^1), 127.2 (C-2´), 122.8 (d, $^4J_{CP}$= 1.4 Hz, C-d^1),112.0 (C-5), 90.8 (d, $^3J_{CP}$= 2.2 Hz, C-1´), 87.2 (d, $^3J_{CP}$= 9.0 Hz, C-4´), 67.96, 67.88, 67.80 (C-a^1, C-5´), 34.7 (C-g^1), 43.1, 33.1, 31.6, 31.4, 30.80, 30.75, 30.72, 30.54, 30.47, 30.2, 23.7, 11.6 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 28.0 (C-h^1), 27.7, 26.3 (C-a^2), 23.28, 23.24 (C-b^2, C-i^1), 14.4 (C-r), 14.1 (C-j^1), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 24.55 (dd, $^2J_{pp}$=23.8 Hz, $^3J_{pp}$=8.0 Hz, P-γ), -11.56 (d, $^2J_{pp}$=17.5 Hz, P-α), -23.39 (t, $^2J_{pp}$= 20.5 Hz, P-β).

IR: ν [cm^{-1}] =3191, 3039, 2955, 2921, 2851, 1759, 1691, 1508, 1463, 1226, 1201, 1166, 1123, 1080, 1041, 994, 903, 838, 806, 783, 768, 719, 691, 644, 514.

γ-(ACB-C1)-γ-C-(alkyl-C12)-d4TTP 68ak.

According to general procedure 12 with 119 mg *H*-phosphinate **102ak** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.21 mmol, 0.7 equiv.). Reaction time was 3 h.

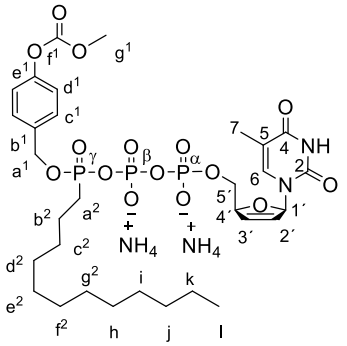
Yield: 119 mg (0.14 mmol, 68%) white solid.

Chemical Formula: $C_{31}H_{53}N_4O_{15}P_3$.

Molecular weight: 814.27 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 779.212; found, 779.215.



^{1}H-NMR (600 MHz, CD$_3$OD): δ [ppm] = 7.67 (dd, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$=1.2 Hz, 1H, H-6), 7.52-7.46 (m, 2H, H-c^1), 7.20-7.15 (m, 2H, H-d^1), 6.94 (dt, $^3J_{HH}$= 3.2 Hz, $^4J_{HH}$=1.3 Hz, 1H, H-1´), 6.49 (dt, $^3J_{HH}$= 6.2 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-3´), 5.84 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 3.7 Hz, $^4J_{HH}$= 1.6 Hz, 1H, H-2´), 5.27-5.14 (m, 2H, H-a^1), 5.00-4.95 (m, 1H, H-4´), 4.30-4.22 (m, 1H, H-5´$_a$), 4.20-4.15 (m, 1H, H-5´$_b$), 3.87 (s, 3H, H-g^1), 2.06-1.96 (m, 2H, H-a^2), 1.90 (dd, $^3J_{HH}$= 3.8 Hz, $^4J_{HH}$= 1.2 Hz, 3H, H-7), 1.70-1.55 (m, 2H, H-b^2), 1.40-1.34 (m, 2H, H-c^2), 1.33-1.24 (m, 16H, H-d^2, H-e^2, H-f^2, H-g^2, H-h, H-i, H-j, H-k), 0.89 (t, $^3J_{HH}$= 7.5 Hz, 3H, H-l).

^{13}C NMR (151 MHz, CD$_3$OD): δ [ppm] = 166.5 (d, $^3J_{CP}$= 2.7 Hz, C-4), 155.6 (C-f^1), 152.8 (C-2), 152.5 (d, $^4J_{CP}$= 1.4 Hz, C-e^1), 138.5 (C-6), 135.80 (dd, $^3J_{CP}$= 7.2 Hz, $^3J_{CP}$= 3.8 Hz, C-b^1), 135.6 (C-3´), 130.42 (d, $^3J_{CP}$= 8.0 Hz, C-c^1), 127.2 (C-2´), 122.2 (d, $^4J_{CP}$= 1.1 Hz, C-d^1), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.9 Hz, C-4´), 67.88, 67.78 (C-a^1, C-5´), 56.0 (C-g^1), 27.9, 26.1 (C-a^2), 33.0, 31.6, 31.3, 30.72, 30.70, 30.66, 30.5, 30.4, 30.2, 23.7 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h, C-i, C-j, C-k), 23.2 (d, $^3J_{CP}$= 5.5 Hz, C-b^2), 14.5 (C-l), 12.5 (C-7).

^{31}P NMR (243 MHz, CD$_3$OD): δ [ppm] = 25.74 (dd, $^2J_{pp}$= 23.5, $^2J_{pp}$= 11.5 Hz, P-γ), -10.46 (d, $^2J_{pp}$= 18.6 Hz, P-α), -22.20 (dt, $^2J_{pp}$= 27.5 Hz, $^3J_{pp}$= 8.9 Hz, P-β).

IR: ν [cm^{-1}] = 3186, 2923, 2853, 1764, 1688, 1663, 1509, 1439, 1248, 1220, 1122, 1077, 1041, 993, 900, 836, 806, 781, 722, 693, 644, 576, 513.

γ-(ACB-C4)-γ-C-(alkyl-C12)-d4TTP 68am.

According to general procedure 12 with 132 mg *H*-phosphinate **102am** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt **1a** (0.21 mmol, 0.7 equiv.). Reaction time was 2 h.

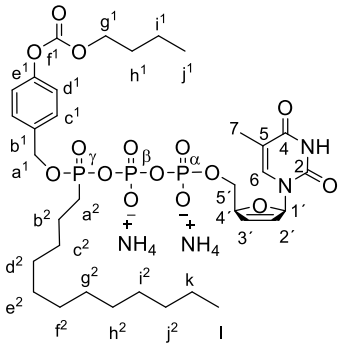
Yield: 57 mg (0.067 mmol, 32%) white solid.

Chemical Formula: $C_{34}H_{59}N_4O_{15}P_3$.

Molecular weight: 856.32 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 821.259; found, 821.230.



^{1}H-NMR (600 MHz, CD_3OD): δ [ppm] = 7.69 (dd, $^3J_{HH}$= 3.1 Hz, $^4J_{HH}$=1.3 Hz, 1H, H-6), 7.52-7.46 (m, 2H, H-c^1), 7.20-7.15 (m, 2H, H-d^1), 6.94 (dt, $^3J_{HH}$= 3.1 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.49 (dt, $^3J_{HH}$= 5.9 Hz, $^4J_{HH}$=1.8 Hz, 1H, H-3´), 5.84 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$= 1.8 Hz, 1H, H-2´), 5.26-5.14 (m, 2H, H-a^1), 5.00-4.95 (m, 1H, H-4´), 4.30-4.15 (m, 2H, H-5´), 4.24 (t, $^3J_{HH}$= 6.5 Hz, 2H, H-g^1), 2.06-1.98 (m, 2H, H-a^2), 1.91 (dd, $^3J_{HH}$= 4.9 Hz, $^4J_{HH}$= 1.1 Hz, 3H, H-7), 1.71 (quint, $^3J_{HH}$= 6.8 Hz, 2H, H-h^1), 1.65-1.56 (m, 2H, H-b^2), 1.45 (sext, $^3J_{HH}$= 7.6 Hz, 2H, H-i^1), 1.37-1.25 (m, 18H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-l).

^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 166.5 (d, $^3J_{CP}$= 2.8 Hz, C-4), 155.1 (C-f^1), 152.8 (C-2), 152.6 (d, $^4J_{CP}$= 1.6 Hz, C-e^1), 138.6 (C-6), 135.8 (dd, $^3J_{CP}$= 7.2 Hz, $^3J_{CP}$= 3.9 Hz, C-b^1), 135.7 (C-3´), 130.47 (d, $^3J_{CP}$= 8.2 Hz, C-c^1), 127.2 (C-2´), 122.3 (d, $^4J_{CP}$= 1.1 Hz, C-d^1), 112.1 (C-5), 90.9 (d, $^4J_{CP}$= 1.4 Hz, C-1´), 87.1 (d, $^3J_{CP}$= 9.1 Hz, C-4´), 69.7 (C-g^1), 67.88, 67.80 (C-a^1, C-5´), 33.1, 32.2, 31.8, 31.6, 31.4, 30.77, 30.74, 30.70, 30.52, 30.49, 30.46, 30.2, 23.7 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^1, C-h^2, C-i^2, C-j^2, C-k), 28.0, 26.1 (C-a^2), 23.2 (d, $^3J_{CP}$= 5.5 Hz, C-b^2), 20.0 (C-i^1), 14.4 (C-l), 14.0 (C-j^1), 12.5 (C-7).

^{31}P NMR (243 MHz, CD_3OD): δ [ppm] = 24.35 (dd, $^2J_{pp}$= 23.6, $^2J_{pp}$= 11.7 Hz, P-γ), -11.87 (d, $^2J_{pp}$= 20.2 Hz, P-α), -23.60 (dt, $^2J_{pp}$= 26.5 Hz, $^2J_{pp}$= 11.5 Hz, P-β).

IR: ν [cm^{-1}] = 3188, 2958, 2922, 2852, 1761, 1691, 1509, 1455, 1244, 1219, 1121, 1076, 1042, 994, 901, 837, 805, 781, 720, 690, 646, 576, 514.

γ-(ACB-C11)-γ-C-(alkyl-C12)-d4TTP 68au.

According to general procedure 3 with 161 mg *H*-phosphinate **102au** (0.3 mmol, 1.0 equiv.) and 118 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.15 mmol, 0.5 equiv.). Reaction time was 5 h.

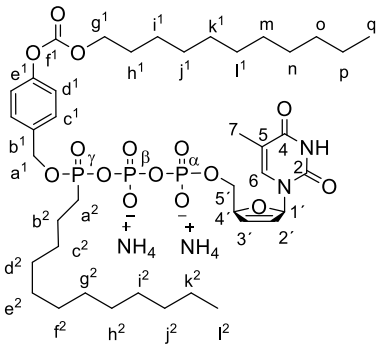
Yield: 36 mg (0.038 mmol, 25%) white solid.

Chemical Formula: $C_{41}H_{73}N_4O_{15}P_3$.

Molecular weight: 954.43 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 919.368; found, 919.342.



^{1}H-NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.68 (dd, $^3J_{HH}$= 2.0 Hz, $^4J_{HH}$=1.2 Hz, 1H, H-6), 7.52-7.46 (m, 2H, H-c^1), 7.20-7.15 (m, 2H, H-d^1), 6.94 (dt, $^3J_{HH}$= 3.3 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.49 (dt, $^3J_{HH}$= 5.9 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-3´), 5.84 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 3.7 Hz, $^4J_{HH}$= 1.5 Hz, 1H, H-2´), 5.27-5.13 (m, 2H, H-a^1), 5.02-4.95 (m, 1H, H-4´), 4.30-4.15 (m, 2H, H-5´), 4.23 (t, $^3J_{HH}$= 6.5 Hz, 2H, H-g^1), 2.07-1.95 (m, 2H, H-a^2), 1.90 (dd, $^3J_{HH}$= 3.2 Hz, $^4J_{HH}$= 1.1 Hz, 3H, H-7), 1.72 (quint, $^3J_{HH}$= 6.8 Hz, 2H, H-h^1), 1.64-1.55 (m, 2H, H-b^2), 1.45-1.20 (m, 34H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^1, H-m, H-n, H-o, H-p), 0.94-0.87 (m, 6H, H-l^2, H-q).

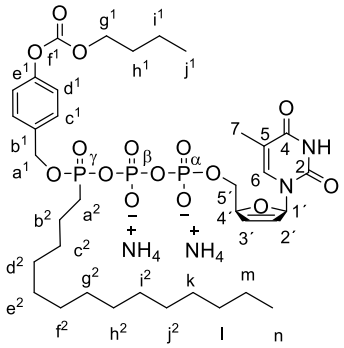
^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 166.5 (d, $^3J_{CP}$= 2.7 Hz, C-4), 155.1 (C-f^1), 152.8 (C-2), 152.6 (d, $^4J_{CP}$= 1.4 Hz, C-e^1), 138.6 (C-6), 135.8 (dd, $^3J_{CP}$= 7.2 Hz, $^3J_{CP}$= 3.9 Hz, C-b^1), 135.7 (C-3´), 130.4 (d, $^3J_{CP}$= 7.7 Hz, C-c^1), 127.2 (C-2´), 122.3 (d, $^4J_{CP}$= 1.1 Hz, C-d^1), 112.0 (C-5), 90.9 (d, $^4J_{CP}$= 1.4 Hz, C-1´), 87.1 (d, $^3J_{CP}$= 9.1 Hz, C-4´), 70.0 (C-g^1), 67.88, 67.80 (C-a^1, C-5´), 33.06, 33.04, 31.6, 31.4, 30.77, 30.75, 30.70, 30.67, 30.61, 30.52, 30.47, 30.44, 30.3, 30.2, 26.8, 23.7 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^1, C-i^2, C-j^1, C-j^2, C-k^1, C-k^2, C-l^1, C-m, C-n, C-o, C-p), 29.7 (C-h^1), 28.0, 26.1 (C-a^2), 23.2 (d, $^3J_{CP}$= 5.9 Hz, C-b^2), 14.5 (C-l^2, C-q), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 24.48 (dd, $^2J_{pp}$= 25.2, $^3J_{pp}$= 7.8 Hz, P-γ), -11.77 (d, $^2J_{pp}$= 19.4 Hz, P-α), -23.58 (t, $^2J_{pp}$= 22.5 Hz, P-β).

IR: ν [cm^{-1}] = 3187, 2957, 2922, 2853, 1760, 1689, 1509, 1455, 1394, 1243, 1220, 1123, 1076, 1043, 1010, 994, 901, 837, 805, 781, 721, 692, 646, 576, 514.

γ-(ACB-C4)-γ-C-(alkyl-C14)-d4TTP 68bm.

According to general procedure 12 with 140 mg *H*-phosphinate **102bm** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.21 mmol, 0.7 equiv.). Reaction time was 2 h.



Yield: 97 mg (0.11 mmol, 52%) white solid.

Chemical Formula: $C_{36}H_{63}N_4O_{15}P_3$.

Molecular weight: 884.35 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 849.290; found, 849.247.

^{1}H-NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.69 (dd, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$=1.2 Hz, 1H, H-6), 7.53-7.46 (m, 2H, H-c^1), 7.21-7.15 (m, 2H, H-d^1), 6.94 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.49 (dt, $^3J_{HH}$= 5.9 Hz, $^4J_{HH}$=1.4 Hz, 1H, H-3´), 5.84 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$= 1.5 Hz, 1H, H-2´), 5.26-5.14 (m, 2H, H-a^1), 5.00-4.94 (m, 1H, H-4´), 4.32-4.15 (m, 2H, H-5´), 4.24 (t, $^3J_{HH}$= 6.6 Hz, 2H, H-g^1), 2.06-1.96 (m, 2H, H-a^2), 1.91 (d, $^3J_{HH}$= 2.2 Hz, 3H, H-7), 1.72 (quint, $^3J_{HH}$= 6.7 Hz, 2H, H-h^1), 1.66-1.55 (m, 2H, H-b^2), 1.44 (sext, $^3J_{HH}$= 7.6 Hz, 2H, H-i^1), 1.38-1.24 (m, 22H, H-c^2, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m), 0.98 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-n).

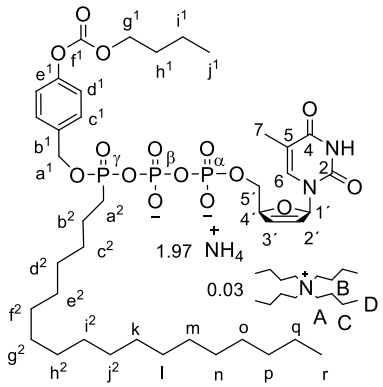
^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 166.5 (d, $^3J_{CP}$= 2.8 Hz, C-4), 155.1 (C-f^1), 152.8 (C-2), 152.6 (d, $^4J_{CP}$= 1.3 Hz, C-e^1), 138.6 (C-6), 135.83 (dd, $^3J_{CP}$= 7.2 Hz, $^3J_{CP}$= 3.8 Hz, C-b^1), 135.68 (C-3´), 130.4 (d, $^3J_{CP}$= 7.8 Hz, C-c^1), 127.2 (C-2´), 122.3 (d, $^4J_{CP}$= 1.1 Hz, C-d^1), 112.0 (C-5), 90.9 (d, $^4J_{CP}$= 1.3 Hz, C-1´), 87.2 (d, $^3J_{CP}$= 8.9 Hz, C-4´), 69.7 (C-g^1), 67.88, 67.80 (C-a^1, C-5´), 33.0, 31.7, 31.6, 31.4, 30.77, 30.75, 30.69, 30.61, 30.51, 30.45, 30.2, 23.7 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^1, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m), 28.0, 26.1 (C-a^2), 23.2 (d, $^3J_{CP}$= 5.6 Hz, C-b^2), 20.0 (C-i^1), 14.5 (C-n), 14.0 (C-j^1), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 24.58 (dd, $^2J_{pp}$= 25.2, $^3J_{pp}$= 7.8 Hz, P-γ), -11.71 (d, $^2J_{pp}$= 19.7 Hz, P-α), -22.24 (dt, $^2J_{pp}$= 25.1 Hz, $^3J_{pp}$= 5.9 Hz, P-β).

IR: ν [cm^{-1}] = 3392, 3154, 2958, 2923, 2853, 1760, 1691, 1509, 1465, 1407, 1248, 1221, 1127, 1078, 1045, 1012, 902, 837, 781, 720, 671, 517, 491, 447.

γ-(ACB-C4)-γ-C-(alkyl-C18)-d4TTP 68cm.

According to general procedure 12 with 157 mg *H*-phosphinate **102cm** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt **1a** (0.21 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 101 mg (0.11 mmol, 51%) white solid.

Chemical Formula: $C_{40}H_{63}N_2O_{15}P_3^{2-}$.

Molecular weight: 904.35 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 905.353; found, 905.308.

^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.67 (dd, $^3J_{HH}$= 2.5 Hz, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 7.50-7.45 (m, 2H, H-c^1), 7.20-7.15 (m, 2H, H-d^1), 6.94 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.49 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.4 Hz, 1H, H-3´), 5.84 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.9 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.28-5.14 (m, 2H, H-a^1), 5.00-4.96 (m, 1H, H-4´), 4.30-4.16 (m, 2H, H-5´), 4.24 (t, $^3J_{HH}$= 6.5 Hz, 2H, H-g^1), 3.26-3.20 (m, 0.24H, H-A), 2.05-1.95 (m, 2H, H-a^2), 1.91 (dd, $^3J_{HH}$=4.5 Hz, $^4J_{HH}$=1.1 Hz, 3H, H-7), 1.71 (quint, $^3J_{HH}$= 6.7 Hz, 2H, H-h^1), 1.66-1.54 (m, 2.24H, H-b^2, H-B), 1.46 (sext, $^3J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.37-1.25 (m, 30.24H, H-c^2, H-C, H-d^2, H-e^2, H-f^2, H-g^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 1.01 (t, $^3J_{HH}$= 7.4 Hz, 0.36H, H-D), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 166.5 (d, $^3J_{CP}$= 5.5 Hz, C-4), 155.1 (C-f^1), 152.8 (d, $^3J_{CP}$= 2.1 Hz, C-2), 152.6 (d, $^3J_{CP}$= 2.4 Hz, C-e^1), 138.6 (C-6), 135.8 (dd, $^3J_{CP}$= 7.5 Hz, $^3J_{CP}$= 3.8 Hz, C-b^1), 135.7 (d, $^3J_{CP}$= 2.1 Hz, C-3´), 130.3 (d, $^2J_{CP}$= 16.4 Hz, C-c^1), 127.2 (C-2´), 122.3 (d, $^3J_{CP}$= 3.2 Hz, C-d^1), 112.0 (C-5), 90.8 (d, $^3J_{CP}$= 3.2 Hz, C-1´), 87.2 (d, $^3J_{CP}$= 8.8 Hz, C-4´), 69.7 (C-g^1), 67.85, 67.81 (C-a^1, C-5´), 59.5 (C-A), 33.1, 31,7, 31.5, 31.4, 30.79, 30.75, 30.71, 30.53, 30.46, 30.2, 23.7 (C-c^2, C-d^2, C-e^2, C-f^2, C-g^2, C-h^1, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 27.5, 26.6 (C-a^2), 24.7 (C-B), 23.2 (d, $^3J_{CP}$= 5.4 Hz, C-b^2), 20.7 (C-C), 20.0 (C-i^1), 14.5 (C-r), 14.03 (C-j^1), 13.96 (C-D), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 24.54 (dd, $^2J_{pp}$=23.5 Hz, $^3J_{pp}$=11.8 Hz, P-γ), -11.60 (d, $^2J_{pp}$=17.8 Hz, P-α), -23.40 (t, $^2J_{pp}$= 20.5 Hz, P-β).

IR: ν [cm^{-1}] =3187, 2958, 2921, 2852, 1761, 1690, 1509, 1457, 1219, 1122, 1076, 1041, 993, 901, 838, 781, 720, 690, 645, 575, 514.

γ-(β-cyanoethyl)-γ-(alkyl-C12)-d4TTP 106a.

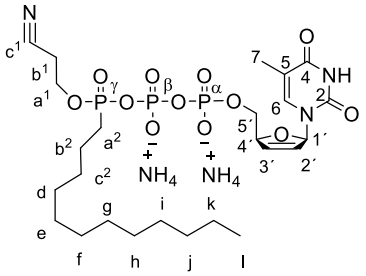
According to general procedure 12 with 86 mg *H*-phosphinate **104a** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt **1a** (0.21 mmol, 0.7 equiv.). Reaction time was 2 h.

Yield: 96 mg (0.14 mmol, 65%) white solid.

Chemical Formula: $C_{25}H_{48}N_5O_{12}P_3$.

Molecular weight: 703.25 g/mol.

MALDI-MS (m/z): $[M-H]^-$ 668.191; found, 668.200.



^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.69 (dd, $^4J_{HH}$= 1.2 Hz, $^4J_{HH}$= 0.7 Hz, 1H, H-6), 6.96 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.52 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.88 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.02-4.96 (m, 1H, H-4´), 4.42-4.32 (m, 2H, H-a^1), 4.30-4.21 (m, 1H, H-5´$_a$), 4.21-4.15 (m, 1H, H-5´$_b$), 2.95-2.85 (m, 2H, H-b^1), 2.10-1.97 (m, 2H, H-a^2), 1.92 (d, $^4J_{HH}$=1.1 Hz, 3H, H-7), 1.74-1.60 (m, 2H, H-b^2), 1.46-1.38 (m, 2H, H-c^2), 1.37-1.25 (m, 16H, H-d, H-e, H-f, H-g, H-h, H-i, H-j, H-k), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-l).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.7 (C-4), 152.9 (C-2), 138.7 (C-6), 135.8 (C-3´), 127.2 (C-2´), 118.8 (C-c^1), 112.1 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 9.0 Hz, C-4´), 67.8 (d, $^3J_{CP}$= 5.7 Hz, C-5´), 62.0 (d, $^3J_{CP}$= 7.0 Hz, C-a^1), 33.1, 31.7, 31.5, 30.8, 30.6, 30.5, 30.4, 30.3, 23.7 (C-c^2, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k), 27.8, 26.0 (C-a^2), 23.2 (d, $^3J_{CP}$= 5.3 Hz, C-b^2), 20.2 (d, $^3J_{CP}$= 7.1 Hz, C-b^1), 14.4 (C-r), 12.5 (C-7).

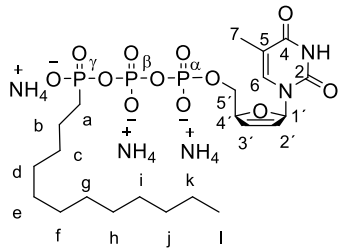
^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 24.39 (dd, $^2J_{pp}$= 25.5 Hz, $^3J_{pp}$= 4.0 Hz, P-γ), -11.64 (d, $^2J_{pp}$=19.5 Hz, P-α), -23.65 (dd, $^2J_{pp}$= 25.3 Hz, $^2J_{pp}$= 19.5 Hz, P-β).

IR: ν [cm^{-1}] = 3186, 2987, 2970, 2923, 1695, 1453, 1407, 1394, 1250, 1124, 1077, 1065, 1050, 908, 839, 806, 784, 524, 441.

γ-C-(alkyl-C12)-d4TTP 69a.

According to general procedure 12 with 86 mg *H*-phosphinate **104a** (0.3 mmol, 1.0 equiv.), 80 mg NCS (0.6 mmol, 2.0 equiv.), 2.3 mL tetrabutylammonium phosphate (0.9 mmol, 3.0 equiv.), 165 mg d4TMP 2×nBu_4N^+ salt **1a** (0.21 mmol, 0.7 equiv.) and 0.97 mL 40% $nBu_4N^+OH^-$ in H_2O (1.50 mmol, 5 equiv.) and then stirred for 8 h at room temperature. The counterion was exchanged to the ammonium-form

with Dowex 50WX8 ion-exchange resin and then purified with rp18 chromatography. Product-containing fractions were collected and the organic solvent evaporated. The remaining aqueous solutions were freeze-dried and the desired product obtained.



Yield: 60 mg (0.088 mmol, 42%) white solid.

Chemical Formula: $C_{22}H_{48}N_5O_{12}P_3$.

Molecular weight: 667.25 g/mol.

MALDI-MS (m/z): $[M-H]^-$ 615.164; found, 615.198.

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.66 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 6.95 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.53 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.89 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.3 Hz, $^4J_{HH}$= 1.3 Hz, 1H, H-2´), 5.04-4.98 (m, 1H, H-4´), 4.28-4.10 (m, 2H, H-5´), 1.91 (d, $^4J_{HH}$=1.0 Hz, 3H, H-7), 1.80-1.68 (m, 2H, H-a), 1.68-1.56 (m, 2H, H-b), 1.46-1.25 (m, 18H, H-c, H-d, H-e, H-f, H-g, H-h, H-i, H-j, H-k), 0.89 (t, $^3J_{HH}$= 6.6 Hz, 3H, H-l).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.6 (C-4), 152.9 (C-2), 138.6 (C-6), 135.8 (C-3´), 127.2 (C-2´), 112.0 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 9.0 Hz, C-4´), 67.8 (d, $^3J_{CP}$= 5.6 Hz, C-5´), 33.1, 30.81, 30.79, 30.77, 30.73, 30.48, 23.7 (C-a, C-b, C-c, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 32.4, 32.2 (C-c), 30.53, 28.9 (C-a), 24.6 (d, $^3J_{CP}$= 4.7 Hz, C-b),14.5 (C-l), 12.5 (C-7).

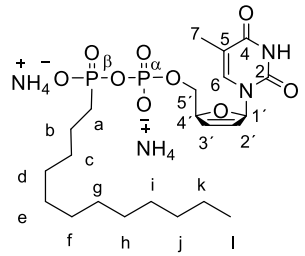
^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 19.47 (d, $^2J_{pp}$=25.4 Hz, P-γ), -11.43 (d, $^2J_{pp}$=19.5 Hz, P-α), -22.42 (t, $^2J_{pp}$= 21.8 Hz, P-β).

IR: v [cm^{-1}] = 3173, 3035, 2921, 2850, 1688, 1659, 1429, 1219, 1178, 1118, 1085, 1049, 987, 897, 836, 803, 783, 767, 736, 691, 575, 520, 462, 427.

γ-C-(alkyl-C12)-d4TDP 107a.

According to general procedure 12 with 86 mg *H*-phosphinate **104a** (0.3 mmol, 1.0 equiv.), 80 mg NCS (0.6 mmol, 2.0 equiv.), 2.3 mL tetrabutylammonium phosphate (0.9 mmol, 3.0 equiv.), 165 mg d4TMP 2×nBu_4N^+ salt **1a** (0.21 mmol, 0.7 equiv.) and 0.97 mL 40% $nBu_4N^+OH^-$ in H_2O (1.50 mmol, 5 equiv.) and then stirred for 8 h at room temperature. The counterion was exchanged to the ammonium-form with Dowex 50WX8 ion-exchange resin and then purified with rp18 chromatography. Product-containing

fractions were collected and the organic solvent evaporated. The remaining aqueous solutions were freeze-dried and the desired product obtained.



Yield: 33 mg (0.057 mmol, 27%) white solid.

Chemical Formula: $C_{22}H_{44}N_4O_9P_2$.

Molecular weight: 570.26 g/mol.

MALDI-MS (m/z): $[M-H]^-$ 535.198; found, 535.259.

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.69 (d, $^4J_{HH}$= 1.2 Hz, 1H, H-6), 6.95 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.50 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.87 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.3 Hz, $^4J_{HH}$= 1.3 Hz, 1H, H-2´), 5.02-4.96 (m, 1H, H-4´), 4.24-4.10 (m, 2H, H-5´), 1.92 (d, $^4J_{HH}$=1.1 Hz, 3H, H-7), 1.80-1.69 (m, 2H, H-a), 1.68-1.56 (m, 2H, H-b,), 1.36-1.25 (m, 18H, H-c, H-d, H-e, H-f, H-g, H-h, H-i, H-j, H-k), 0.89 (t, $^3J_{HH}$= 6.7 Hz, 3H, H-l).

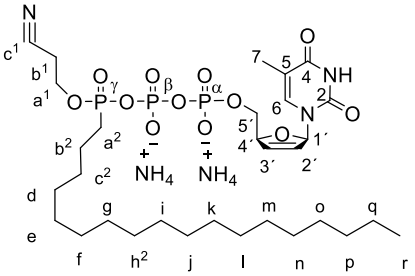
^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.6 (C-4), 152.9 (C-2), 138.7 (C-6), 135.8 (C-3´), 127.2 (C-2´), 112.1 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 9.6 Hz, C-4´), 67.5 (d, $^3J_{CP}$= 5.6 Hz, C-5´), 33.1, 32.4, 32.3, 30.81, 30.79, 30.76, 30.70, 30.63, 30.48, 23.7 (C-c, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 30.53, 29.1 (C-a), 24.6 (d, $^3J_{CP}$= 4.3 Hz, C-b), 14.4 (C-l), 12.5 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 18.85 (d, $^2J_{pp}$=26.9 Hz, P-β), -11.33 (d, $^2J_{pp}$=25.5 Hz, P-α).

IR: ν [cm-1] = 3185, 2987, 2969, 2921, 2852, 1678, 1660, 1452, 1430, 1220, 1174, 1103, 1084, 1044, 999, 906, 836, 802, 781, 765, 738, 690, 643, 578, 474, 423, 401.

γ-(β-cyanoethyl)-γ-(alkyl-C18)-d4TTP 106c.

According to general procedure 3 with 111 mg *H*-phosphinate **104c** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt (0.21 mmol, 0.7 equiv.). Reaction time was 2 h.



Yield: 66 mg (0.084 mmol, 40%) white solid.

Chemical Formula: $C_{31}H_{60}N_5O_{12}P_3$.

Molecular weight: 787.35 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 752.285; found, 752.285.

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.69 (dd, $^{4}J_{HH}$= 1.2 Hz, $^{4}J_{HH}$= 0.6 Hz, 1H, H-6), 6.96 (dt, $^{3}J_{HH}$= 3.4 Hz, $^{4}J_{HH}$=1.6 Hz, 1H, H-1´), 6.52 (dt, $^{3}J_{HH}$= 6.0 Hz, $^{4}J_{HH}$=1.6 Hz, 1H, H-3´), 5.88 (ddd, $^{3}J_{HH}$= 6.0 Hz, $^{3}J_{HH}$= 2.2 Hz, $^{4}J_{HH}$= 1.4 Hz, 1H, H-2´), 5.02-4.96 (m, 1H, H-4´), 4.40-4.32 (m, 2H, H-a^1), 4.30-4.21 (m, 1H, H-5´$_a$), 4.21-4.15 (m, 1H, H-5´$_b$), 2.95-2.85 (m, 2H, H-b^1), 2.10-1.97 (m, 2H, H-a^2), 1.92 (d, $^{4}J_{HH}$=1.1 Hz, 3H, H-7), 1.74-1.64 (m, 2H, H-b^2), 1.46-1.39 (m, 2H, H-c^2), 1.37-1.25 (m, 28H, H-d, H-e, H-f, H-g, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.89 (t, $^{3}J_{HH}$= 6.8 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.6 (C-4), 152.8 (C-2), 138.5 (C-6), 135.7 (C-3´), 127.2 (C-2´), 118.7 (C-c^1), 112.0 (C-5), 90.9 (C-1´), 87.2 (d, $^{3}J_{CP}$= 9.0 Hz, C-4´), 67.8 (d, $^{3}J_{CP}$= 5.5 Hz, C-5´), 62.0 (d, $^{3}J_{CP}$= 7.0 Hz, C-a^1), 39.7, 33.0, 31.7, 31.4, 30.77, 30.73, 30.6, 30.5, 30.4, 30.2, 27.5, 23.7 (C-c^2, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 27.8, 25.9 (C-a^2), 23.2 (d, $^{3}J_{CP}$= 5.4 Hz, C-b^2), 20.2 (d, $^{3}J_{CP}$= 7.1 Hz, C-b^1), 14.5 (C-r), 12.5 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 24.43 (dd, $^{2}J_{pp}$=25.4 Hz, $^{3}J_{pp}$=4.0 Hz, P-γ), -11.64 (d, $^{2}J_{pp}$=19.5 Hz, P-α), -23.39 (dd, $^{2}J_{pp}$= 25.3 Hz, $^{2}J_{pp}$= 19.6 Hz, P-β).

IR: ν [cm^{-1}] = 3186, 2987, 2970, 2921, 2852, 1689, 1453, 1225, 1120, 1077, 1048, 993, 899, 837, 805, 783, 767, 720, 692, 645, 576, 515, 488.

γ-C-(alkyl-C18)-d4TTP 69c.

According to general procedure 12 with 111 mg *H*-phosphinate **104c** (0.3 mmol, 1.0 equiv.), 80 mg NCS (0.6 mmol, 2.0 equiv.), 2.3 mL tetrabutylammonium phosphate (0.9 mmol, 3.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt **1a** (0.21 mmol, 0.7 equiv.) and 0.97 mL 40% $nBu_4N^+OH^-$ in H_2O (1.50 mmol, 5 equiv.) and then stirred for 8 h at room temperature. The counterion was exchanged to the ammonium-form with Dowex 50WX8 ion-exchange resin and then purified with rp18 chromatography. Product-containing fractions were collected and the organic solvent evaporated. The remaining aqueous solutions were freeze-dried and the desired product obtained.

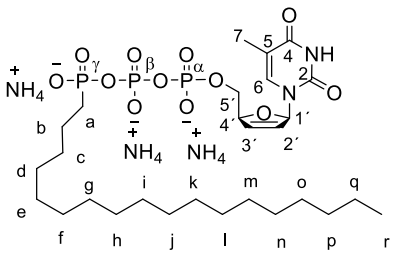
Yield: 24 mg (0.031 mmol, 15%) white solid.

Chemical Formula: $C_{28}H_{60}N_5O_{12}P_3$.

Molecular weight: 751.35 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 699.258; found, 699.256.



^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.69 (d, $^{4}J_{HH}$= 1.2 Hz, 1H, H-6), 6.95 (dt, $^{3}J_{HH}$= 3.4 Hz, $^{4}J_{HH}$=1.6 Hz, 1H, H-1´), 6.54 (dt, $^{3}J_{HH}$= 6.0 Hz, $^{4}J_{HH}$=1.6 Hz, 1H, H-3´), 5.88 (ddd, $^{3}J_{HH}$= 6.0 Hz, $^{3}J_{HH}$= 2.3 Hz, $^{4}J_{HH}$= 1.3 Hz, 1H, H-2´), 5.05-4.96 (m, 1H, H-4´), 4.30-4.21 (m, 1H, H-5´$_a$), 4.21-4.15 (m, 1H, H-5´$_b$), 1.92 (d, $^{4}J_{HH}$=1.0 Hz, 3H, H-7), 1.84-1.75 (m, 2H, H-a), 1.74-1.56 (m, 4H, H-b, H-c), 1.37-1.25 (m, 28H, H-d, H-e, H-f, H-g, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.89 (t, $^{3}J_{HH}$= 6.8 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.7 (C-4), 152.9 (C-2), 138.7 (C-6), 135.9 (C-3´), 127.1 (C-2´), 112.0 (C-5), 90.9 (C-1´), 87.2 (d, $^{3}J_{CP}$= 9.0 Hz, C-4´), 67.8 (C-5´), 39.7, 33.1, 32.5, 30.78, 30.74, 30.53, 30.45, 24.6, 23.7 (C-c, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.0, 27.6 (C-a^2), 23.2 (C-b), 14.4 (C-r), 12.5 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 19.60 (d, $^{2}J_{pp}$=25.4 Hz, P-γ), -11.23 (d, $^{2}J_{pp}$=19.5 Hz, P-α), -22.30 (dd, $^{2}J_{pp}$= 25.3 Hz, $^{2}J_{pp}$= 19.6 Hz, P-β).

IR: ν [cm^{-1}] = 3186, 2987, 2918, 2850, 1689, 1453, 1224, 1114, 1078, 1055, 989, 838, 803, 784, 719, 645, 520, 489.

γ-(AB-C4)-γ-C-(alkyl-C18)-AZTTP 108.

According to general procedure 12 with 153 mg *H*-phosphinate **99ce** (0.3 mmol, 1.0 equiv.) and 131 mg (*n*-$Bu_4N)_2$·AZTMP **2a** (0.21 mmol, 0.7 equiv.). Reaction time was 3 h.

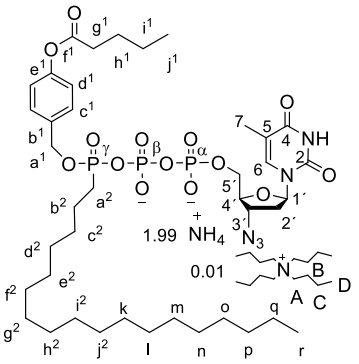
Yield: 82 mg (0.031 mmol, 40%) white solid.

Chemical Formula: $C_{40}H_{64}N_5O_{14}P_3^{2-}$.

Molecular weight: 931.37 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 932.375; found, 932.327.



^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.80 (d, $^{4}J_{HH}$= 1.2 Hz, 1H, H-6), 7.52-7.47 (m, 2H, H-c^1), 7.12-7.05 (m, 2H, H-d^1), 6.23 (dd, $^{3}J_{HH}$= 7.3 Hz, $^{3}J_{HH}$=5.9 Hz, 1H, H-1´), 5.28- 5.15 (m, 2H, H-a^1), 4.62-4.55 (m, 1H, H-3´), 4.28-4.18 (m, 2H, H-5´), 4.10-4.04 (m, 1H, H-4´),3.28-3.18 (m, 0.08H, H-A), 2 .58 (t, $^{3}J_{HH}$= 7.4 Hz, 2H, H-g^1), 2.50-2.36 (m, 1H, H-2´a), 2.35-2.25 (m, 1H, H-2´b), 2.08-1.96 (m, 2H, H-a^2), 1.92 (dd, $^{3}J_{HH}$= 2.0 Hz, $^{4}J_{HH}$= 1.3 Hz, 3H, H-7), 1.73 (quint, $^{3}J_{HH}$= 7.4 Hz, 2H, H-h^1), 1.64-1.54 (m, 2.08H, H-B, H-b^2), 1.49 (sext, $^{3}J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.42-1.24 (m, 30.08H, H-C, H-c^2, H-d^2, H-e^2, H-f^2, H-j^2, H-h^2, H-

i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 1.02 (t, $^3J_{HH}$= 7.3 Hz, 0.12H, H-D), 0.98 (t, $^3J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-r).

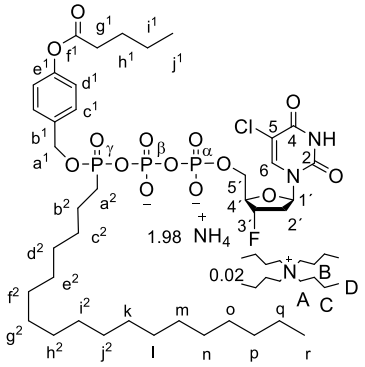
^{13}C-NMR (151 MHz, CD_3OD): δ [ppm] = 173.7 (C-f^1), 166.4 (C-4), 152.4 (C-2), 152.2 (d, $^4J_{CP}$= 0.8 Hz, C-e^1), 137.9 (C-6), 135.5 (dd, $^3J_{CP}$= 7.2 Hz, $^4J_{CP}$= 1.4 Hz, C-b^1), 130.3 (d, $^3J_{CP}$= 3.6 Hz, C-c^1), 122.8 (C-d^1), 112.2 (C-5), 85.9 (C-1´), 84.6 (d, $^3J_{CP}$= 9.2 Hz, C-4´), 67.9 (dd, $^3J_{CP}$= 7.0 Hz, $^3J_{CP}$= 2.7 Hz, C-a^1), 67.0 (d, $^3J_{CP}$= 5.6 Hz, C-5´), 63.0 (C-3´), 59.5 (C-A), 37.9 (C-2´), 34.8 (C-g^1), 33.1, 31.6, 31.4, 30.79, 30.74, 30.70, 30.6, 30.53, 30.46, 30.2, 23.7, 9.1 (C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 28.1 (C-h^1), 28.0, 26.1 (C-a^2), 24.8 (C-B), 23.31, 23.23 (C-b^2, C-i^1), 20.7 (C-C), 14.4 (C-r), 14.1 (C-j^1). 13.9 (C-D), 12.6 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 24.54 (d, $^2J_{pp}$=25.4 Hz, P-γ), -11.84 (d, $^2J_{pp}$=19.5 Hz, P-α), -23.44 (t, $^2J_{pp}$= 21.5 Hz, P-β).

IR: v [cm-1] = 3202, 2987, 2970, 2922, 2853, 2105, 1759, 1696, 1508, 1453, 1409, 1394, 1381, 1249, 1201, 1166, 1123, 1102, 1077, 1055, 1013, 908, 832, 764, 720, 680, 514.

γ-(AB-C4)-γ-C-(alkyl-C18)-FddClUTP 110.

According to general procedure 12 with 153 mg *H*-phosphinate **99ce** (0.3 mmol, 1.0 equiv.) and 131 mg FddClUMP 1.15×nBu_4N^+ **8a** (0.21 mmol, 0.7 equiv.). Reaction time was 3 h.



Yield: 82 mg (0.031 mmol, 45%) white solid.

Chemical Formula: $C_{39}H_{61}ClFN_2O_{14}P_3^{2-}$.

Molecular weight: 928.30 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 929.309; found, 929.270.

^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 8.15 (d, $^3J_{HH}$= 2.1 Hz, 1H, H-6), 7.52-7.47 (m, 2H, H-c^1), 7.12-7.05 (m, 2H, H-d^1), 6.32-6.27 (m, 1H, H-1´), 5.54 (dt, $^2J_{HH}$= 53.2 Hz, $^3J_{HH}$= 4.1 Hz, 1H, H-3´), 5.27-5.17 (m, 2H, H-a^1), 4.42-4.12 (m, 3H, H-4´, H-5´), 3.26-3.20 (m, 0.16H, H-A), 2.58 (t, $^3J_{HH}$= 7.4 Hz, 2H, H-g^1), 2.55-2.36 (m, 1H, H-2´), 2.06-1.98 (m, 2H, H-a^2), 1.71 (quint, $^3J_{HH}$= 7.5 Hz, 2H, H-h^1), 1.67-1.56 (m, 2.16H, H-B, H-b^2), 1.46 (sext, $^3J_{HH}$= 7.5 Hz, 2H, H-i^1), 1.40-1.24 (m, 30.16H, H-C, H-c^2, H-d^2, H-e^2, H-f^2,

H-g^2, H-h^2, H-i^2, H-j^2, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 1.02 (t, $^3J_{HH}$= 7.4 Hz, 0.24H, H-D), 0.98 (t, $^3J_{HH}$= 7.4 Hz, 3H, H-j^1), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-r).

^{13}C-NMR (101 MHz, CD_3OD): δ [ppm] = 173.7 (C-f^1), 161.5 (C-4), 152.2 (C-e^1), 151.3 (C-2), 139.0 (C-6), 135.6 (dd, $^3J_{CP}$= 7.2 Hz, $^4J_{CP}$= 1.4 Hz, C-b^1), 130.4 (d, $^3J_{CP}$= 3.3 Hz, C-c^1), 122.8 (C-d^1), 110.1 (C-5), 97.2 (dd, $^1J_{CF}$= 176.1 Hz, $^2J_{CF}$= 10.4 Hz, C-3´), 86.8 (C-1´), 85.5 (C-4´), 67.9 (dd, $^3J_{CP}$= 6.4 Hz, $^4J_{CP}$= 1.3 Hz, C-a^1), 66.63, 66.55, 66.47 (C-5´), 59.5 (C-A), 39.1 (d, $^2J_{CF}$= 20.6 Hz, C-2´), 34.8 (C-g^1), 33.1, 31.6, 31.4, 30.80, 30.76, 30.72, 30.55, 30.47, 30.2, 23.7 C-d^2, C-e^2, C-f^2, C-g^2, C-h^2, C-i^2, C-j^2, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 39.7, 28.1 (C-h^1), 28.0, 26.1 (C-a^2), 24.8 (C-B), 23.3, 23.2 (C-b^2, C-i^1), 20.7 (C-C), 14.5 (C-r), 14.10 (C-j^1), 13.95 (C-D).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 24.55 (d, $^2J_{pp}$=23.5 Hz, P-γ), -11.85 (d, $^2J_{pp}$=16.8 Hz, P-α), -23.40 (t, $^2J_{pp}$= 20.8 Hz, P-β).

^{19}F-NMR (188 MHz (gekoppelt), CD_3OD): δ [ppm] = -175.6- -176.2.

IR: ν [cm-1] = 3194, 2922, 2852, 2112, 1758, 1702, 1508, 1457, 1379, 1320, 1244, 1200, 1166, 1125, 1075, 1056, 994, 910, 823, 752, 719, 698, 645, 609, 513, 451.

(Alkyl-C1; alkyl-C18)-*H*-phosphonate 113a.

According to general procedure 6, with 0.78 g hydrogen phosphonate **112** (2.33 mmol, 1.0 equiv.), 0.28 g N-methylmorpholine (2.8 mmol, 1.2 equiv.) and 0.26 g methyl chloroformate **76k** (2.8 mmol, 1.2 equiv.) in 15 mL Et_2O and 2.8 mL toluene at 0 °C. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 5:1:0.005 v/v/v).

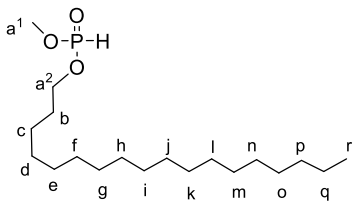
Yield: 0.43 g (1.23 mmol, 53%) colorless oil.

Chemical Formula: $C_{19}H_{41}O_3P$.

Molecular weight: 348.28 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 371.2685; found 371.2643.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 6.75 (d, $^1J_{HH}$= 696.2 Hz, 1H, P-H), 4.08-4.02 (m, 2H, H-a^2), 3.75 (d, $^2J_{HH}$= 11.9 Hz, 3H, H-a^1), 1.66 (quint, $^2J_{HH}$= 6.7 Hz, 2H, H-b), 1.38-1.20 (m, 30H, H-c, H-d, H-e, H-f, H-j, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.85 (t, $^3J_{HH}$= 6.80 Hz, 3H, H-r).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 65.9 (d, $^3J_{CP}$= 5.90 Hz, C-a^2), 51.8 (dd, $^3J_{CP}$= 8.20 Hz, $^3J_{CP}$= 5.20 Hz, C-a^1), 31.8, 30.37, 30.31, 29.6, 29.5, 29.4, 29.3, 29.0, 22.6 (C-b, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 25.4 (C-c), 14.0 (C-r).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 9.09.

IR: ν [cm^{-1}] = 2955, 2917, 2850, 1761, 1467, 1255, 1049, 977, 721.

(Alkyl-C4; alkyl-C18)-*H*-phosphonate 113b.

According to general procedure 6, with 0.78 g hydrogen phosphonate **112** (2.33 mmol, 1.0 equiv.), 0.28 g N-methylmorpholine (2.8 mmol, 1.2 equiv.) and 0.38 g butyl chloroformate **76m** (2.8 mmol, 1.2 equiv.) in 15 mL Et_2O and 2.8 mL toluene at 0 °C. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 85:15:0.005 v/v/v).

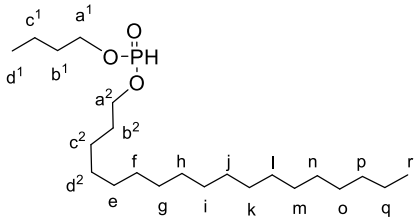
Yield: 0.49 g (1.26 mmol, 53%) colorless oil.

Chemical Formula: $C_{22}H_{47}O_3P$.

Molecular weight: 348.28 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 413.3155; found 413.3148.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 6.72 (d, $^1J_{HH}$= 692.0 Hz, 1H, P-H), 4.05-3.94 (m, 4H, H-a^1, H-a^2) 1.65-1.55 (m, 4H, H-b^1, H-b^2), 1.38-1.26 (m, 4H, H-c^1, H-c^2), 1.30-1.20 (m, 28H, H-d^2, H-e, H-f, H-j, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.86 (t, $^3J_{HH}$= 7.40 Hz, 3H, H-d^1), 0.80 (t, $^3J_{HH}$= 6.70 Hz, 3H, H-r).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 66.5, 65.2 (2 x d, $^3J_{CP}$= 5.90 Hz, $^3J_{CP}$= 5.80 Hz, C-a^1, C-a^2), 32.24, 32.18, 30.25, 30.19, 29.51, 29.48, 29.44, 29.36, 29.30, 29.2, 28.9, 22.5 (C-b^1, C-b^2, C-d^2, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 25.3 (C-c^2), 18.5 (C-c^1), 13.9, 13.3 (C-d^1, C-r).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.63.

IR: ν [cm^{-1}] =3662, 2987, 2969, 2917, 2850, 1466, 1406, 1393, 1381, 1253, 1065, 969, 892, 792, 720, 552, 431.

(Alkyl-C8; alkyl-C18)-*H*-phosphonate 113c.

According to general procedure 6, with 0.78 g hydrogen phosphonate **112** (2.33 mmol, 1.0 equiv.), 0.28 g N-methylmorpholine (2.8 mmol, 1.2 equiv.) and 0.54 g 2-ethylhexyl chloroformate **76q** (2.8 mmol, 1.2 equiv.) in 25 mL Et_2O and 5 mL toluene at 0 °C. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 10:1:0.005 v/v/v).

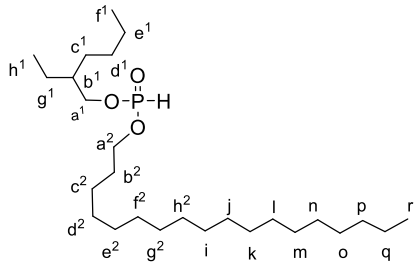
Yield: 0.57 g (1.28 mmol, 55%) colorless oil.

Chemical Formula: $C_{26}H_{55}O_3P$.

Molecular weight: 446.39 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 469.3781; found 469.3887.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 6.75 (d, $^1J_{HH}$= 691.8 Hz, 1H, P-H), 4.07-3.98 (m, 2H, H-a^2), 3.97-3.87 (m, 2H, H-a^1), 1.64 (quint, $^3J_{HH}$= 6.70 Hz, 2H, H-b^2), 1.58-1.48 (m, 1H, H-b^1), 1.40-1.20 (m, 38H, H-c^1, H-c^2, H-d^1, H-d^2, H-e^1, H-e^2, H-f^2, H-g^1, H-g^2, H-h^2, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.88-0.82 (m, 9H, H-f^1, H-h^1, H-r).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 67.5 (d, $^3J_{CP}$= 6.30 Hz, C-a^1), 65.6 (d, $^3J_{CP}$= 6.05 Hz, C-a^2), 40.0 (d, $^3J_{CP}$= 6.60 Hz, C-b^1), 31.8, 30.4, 30.3, 29.80, 29.78, 29.61, 29.57, 29.54, 29.46, 29.41, 29.3, 29.0, 28.7, 23.2, 22.8, 22.6 (C-b^2, C-c^1, C-d^1, C-d^2, C-e^1, C-e^2, C-f^2, C-g^1, C-g^2, C-h^2, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 25.4 (C-c^2), 14.0, 13.9, 10.8 (C-h^1, C-f^1, C-r).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.91.

IR: ν [cm^{-1}] = 3662, 2987, 2969, 2916, 2849, 1468, 1406, 1393, 1381, 1240, 1077, 1065, 1051, 1027, 968, 892, 858, 718, 550.

(Alkyl-C1; alkyl-C18)-*H*-phosphinate 115a.

According to general procedure 7, with 0.32 g octadecylphosphinic acid **98c** (1.0 mmol, 1.0 equiv.), 0.12g N-methylmorpholine (1.2 mmol, 1.2 equiv.) and 0.11 g methyl chloroformate **76k** (1.2 mmol, 1.2 equiv.) in 8 mL Et_2O and 1.2 mL toluene at 0 °C. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 5:1:0.005 v/v/v).

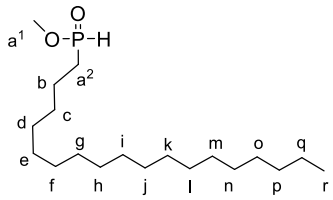
Yield: 0.15 g (0.45 mmol, 45%) white solid.

Chemical Formula: $C_{19}H_{41}O_2P$.

Molecular weight: 332.28 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 355.2736; found 355.2940.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.00 (dt, $^1J_{HH}$= 529.2 Hz, $^3J_{HH}$= 1.90 Hz, 1H, P-H), 3.74 (d, $^2J_{HH}$= 11.75 Hz, 3H, H-a^1), 1.78-1.68 (m, 2H, H-a^2), 1.62-1.48 (m, 2H, H-b), 1.40-1.32 (m, 2H, H-c), 1.28-1.20 (m, 28H, H-d, H-e, H-f, H-j, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.84 (t, $^3J_{HH}$= 6.70 Hz, 3H, H-r).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 52.6 (t, $^3J_{CP}$= 8.30 Hz, C-a^1), 31.8, 30.4, 30.3, 29.6, 29.5, 29.3, 29.2, 29.0, 28.9, 22.6, 20.57, 20.54 7 (C-a^2, C-c, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 20.5 (t, $^3J_{CP}$= 2.95 Hz, C-b), 14.0 (C-r).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 42.11 (d, $^2J_{pp}$=15.5 Hz).

IR: ν [cm^{-1}] = 2954, 2914, 2848, 1469, 1400, 1258, 1239, 1222, 1208, 1196, 1182, 1047, 1020, 1005, 991, 970, 958, 935, 909, 877, 845, 812, 784, 771, 718, 710, 436.

(Alkyl-C4; alkyl-C18)-*H*-phosphinate 115b.

According to general procedure 7, with 0.74 g octadecylphosphinic acid **98c** (2.33 mmol, 1.0 equiv.), 0.28 g N-methylmorpholine (2.8 mmol, 1.2 equiv.) and 0.38 g butyl chloroformate **76m** (2.8 mmol, 1.2 equiv.) in 15 mL Et_2O and 2.8 mL toluene at 0 °C. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 85:15:0.005 v/v/v).

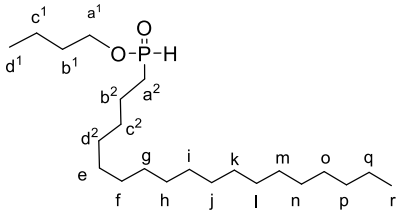
Yield: 0.46 g (1.23 mmol, 53%) white soild.

Chemical Formula: $C_{22}H_{47}O_2P$.

Molecular weight: 374.33 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 397.3206; found 397.3235.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.04 (dt, $^1J_{HH}$= 525.9 Hz, $^3J_{HH}$= 1.90 Hz, 1H, P-H), 4.15-3.90 (m, 2H, H-a^1), 1.78-1.64 (m, 4H, H-a^2, H-b^1), 1.62-1.52 (m, 2H, H-b^2), 1.44-1.34 (m, 4H, H-c^1, H-c^2), 1.30-

1.20 (m, 28H, H-d^2, H-e, H-f, H-j, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.92 (t, $^3J_{HH}$= 7.40 Hz, 3H, H-d^1), 0.85 (t, $^3J_{HH}$= 6.80 Hz, 3H, H-r).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 66.0 (t, $^3J_{CP}$= 7.30 Hz, C-a^1), 32.4 (d, $^3J_{CP}$= 6.40 Hz, C-b^1), 31.9, 30.5, 30.3, 29.63, 29.60, 29.56, 29.50, 29.30, 29.27, 29.0, 25.5, 22.6 (C-c^2, C-d^2, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 29.0, 28.1 (C-a^2), 20.7 (t, $^3J_{CP}$= 3.65 Hz, C-b^2), 18.7 (C-c^1), 14.1 (C-r), 13.5 (C-d^1).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 39.5.

IR: ν [cm^{-1}] = 2954, 2916, 2870, 2848, 2437, 1769, 1395, 1377, 1240, 1189, 1162, 1111, 1086, 1051, 1038, 1026, 1011, 986, 971, 890, 857, 757, 718, 550, 519, 491, 443.

(Alkyl-C8; alkyl-C18)-*H*-phosphinate 115c.

According to general procedure 7, with 0.32 g octadecylphosphinic acid **98c** (1.0 mmol, 1.0 equiv.), 0.12g N-methylmorpholine (1.2 mmol, 1.2 equiv.) and 0.23 g 2-ethylhexyl chloroformate **76q** (1.2 mmol, 1.2 equiv.) in 8 mL Et_2O and 1.2 mL toluene at 0 °C. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 10:1:0.005 v/v/v).

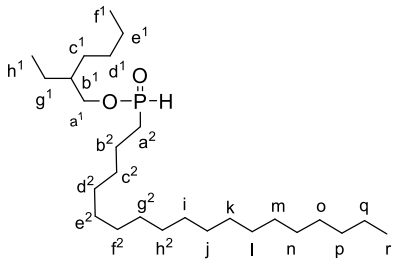
Yield: 0.20 g (0.46 mmol, 46%) colorless oil.

Chemical Formula: $C_{26}H_{55}O_2P$.

Molecular weight: 430.39 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 453.3832; found 453.4214.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.04 (dt, $^1J_{HH}$= 525.3 Hz, $^3J_{HH}$= 1.90 Hz, 1H, P-H), 4.05-3.80 (m, 2H, H-a^1), 1.79-1.70 (m, 2H, H-a^2), 1.62-1.52 (m, 3H, H-b^1, H-b^2), 1.40-1.24 (m, 38H, H-c^1, H-c^2, H-d^1, H-d^2, H-e^1, H-e^2, H-f^2, H-g^1, H-g^2, H-h^2, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.92-0.84 (m, 9H, H-f^1, H-h^1, H-r).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 68.3 (t, $^3J_{CP}$= 7.30 Hz, C-a^1), 40.1 (d, $^3J_{CP}$= 6.60 Hz, C-b^1), 31.9, 30.4, 30.3, 29.9, 29.64, 29.61, 29.57, 29.52, 29.31, 29.28, 29.16, 29.07, 28.83, 28.80, 28.2, 23.3, 22.90, 22.6 (C-a^2, C-c^1, C-c^2, C-d^1, C-d^2, C-e^1, C-e^2, C-f^2, C-g^1, C-g^2, C-h^2, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 20.7 (t, $^3J_{CP}$= 2.95 Hz, C-b^2), 14.05, 13.96, 10.88, 10.85 (C-h^1, C-f^1, C-r).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 39.9 (d, $^3J_{pp}$=5.85 Hz).

IR: v [cm^{-1}] = 2956, 2921, 2852, 2332, 1463, 1378, 1231, 1036, 967, 853, 773, 720, 530, 445.

(Alkyl-C12; alkyl-C18)-*H*-phosphinate 115d.

According to general procedure 7, with 0.74 g octadecylphosphinic acid **98c** (2.33 mmol, 1.0 equiv.), 0.28 g N-methylmorpholine (2.8 mmol, 1.2 equiv.) and 0.70 g lauryl chloroformate **76v** (2.8 mmol, 1.2 equiv.) in 15 mL Et_2O and 2.8 mL toluene at 0 °C. Column chromatography (SiO_2, petrol ether/ethyl acetate/CH_3COOH 10:1:0.005 v/v/v).

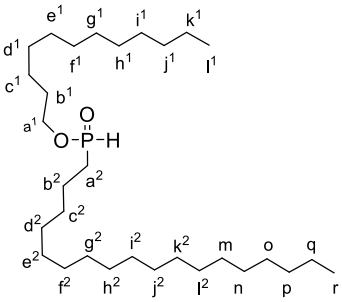
Yield: 0.53 g (1.1 mmol, 47%) white soild.

Chemical Formula: $C_{30}H_{63}O_2P$.

Molecular weight: 486.46 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 509.4458; found 509.4420.



^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.06 (dt, $^1J_{HH}$= 525.3 Hz, $^3J_{HH}$= 1.90 Hz, 1H, P-H), 4.12-3.90 (m, 2H, H-a^1), 1.80-1.65 (m, 4H, H-a^2, H-b^1) 1.64-1.52 (m, 2H, H-b^2), 1.40-1.24 (m, 48H, H-c^1, H-c^2, H-d^1, H-d^2, H-e^1, H-e^2, H-f^1, H-f^2, H-g^1, H-g^2, H-h^1, H-h^2, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^2, H-m, H-n, H-o, H-p, H-q), 0.87 (t, $^3J_{HH}$= 6.80 Hz, H-i^1, H-r).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 66.3 (t, $^3J_{CP}$= 7.30 Hz, C-a^1), 31.89, 31.88, 30.48, 30.43, 30.37, 30.33, 29.66, 29.63, 29.59, 29.54, 29.52, 29.47, 29.32, 29.31, 29.2, 29.11, 29.09, 28.3, 25.5, 22.6 (C-a^2, C-b^1, C-b^2, C-c^1, C-c^2, C-d^1, C-d^2, C-e^1, C-e^2, C-f^1, C-f^2, C-g^1, C-g^2, C-h^1, C-h^2, C-i^1, C-i^2, C-j^1, C-j^2, C-k^1, C-k^2, C-l^2, C-m, C-n, C-o, C-p, C-q), 20.7 (t, $^3J_{CP}$= 2.95 Hz, C-b^2), 14.1 (C-l^1, C-r).

^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 39.4.

IR: v [cm^{-1}] = 2953, 2913, 2872, 2847, 1469, 1390, 1276, 1257, 1239, 1223, 1205, 1189, 1181, 1082, 1066, 1026, 995, 985, 945, 926, 912, 891, 877, 844, 826, 813, 794, 776, 718, 546, 455, 435.

γ-(Alkyl-C1; alkyl-C18)-phosphate-d4TDP 70a.

According to general procedure 12 with 104 mg *H*-phosphonate **113a** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt (0.21 mmol, 0.7 equiv.). Reaction time was 3 h.

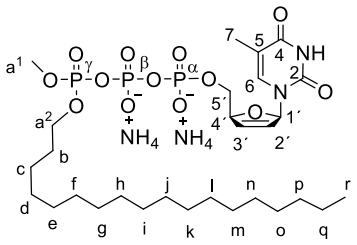
Yield: 97 mg (0.13 mmol, 60%) white solid.

Chemical Formula: $C_{29}H_{59}N_4O_{13}P_3$.

Molecular weight: 764.33 g/mol.

HRMS (ESI$^+$, m/z):

$[M+Na]^+$ 729.269; found, 729.224.



^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.69 (d, $^4J_{HH}$= 0.8 Hz, 1H, H-6), 6.96 (dt, $^3J_{HH}$= 3.3 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.53 (dt, $^3J_{HH}$= 6.1 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.89 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.4 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.03-4.97 (m, 1H, H-4´), 4.30-4.10 (m, 4H, H-a^2, H-5´), 3.83 (dd, $^2J_{HH}$= 11.5 Hz, $^4J_{HH}$= 1.0 Hz, 3H, H-a^1), 1.92 (d, $^4J_{HH}$= 1.0 Hz, 3H, H-7), 1.80-1.55 (m, 4H, H-b, H-c), 1.45-1.25 (m, 28H, H-d, H-e, H-f, H-j, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.89 (t, $^3J_{HH}$= 6.8 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.6 (C-4), 152.9 (C-2), 138.7 (C-6), 135.8 (C-3´),127.2 (C-2´), 112.1 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 8.9 Hz, C-4´), 69.7 (d, $^3J_{CP}$= 5.9 Hz, C-a^2), 67.8 (d, $^3J_{CP}$= 5.9 Hz, C-5´), 55.5 (d, $^3J_{CP}$= 5.9 Hz, C-a^1), 39.7, 33.1, 31.33, 31.25, 30.78, 30.75, 30.72, 30.68, 30.5, 30.3, 23.7 (C-b, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 26.5 (C-c), 14.5 (C-r), 12.5 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.4 - -12.0 (m, 2P, P-γ, P-α), -23.55 (t, $^2J_{pp}$= 16.8 Hz, P-β).

IR: ν [cm^{-1}] = 3200, 2921, 2852, 1689, 1664, 1455, 1247, 1127, 1079, 1015, 908, 837, 806, 783, 768, 720, 695, 644, 519, 490.

γ-(Alkyl-C4; alkyl-C18)-phosphate-d4TDP 70b.

According to general procedure 12 with 117 mg *H*-phosphonate **113b** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt (0.21 mmol, 0.7 equiv.). Reaction time was 3 h.

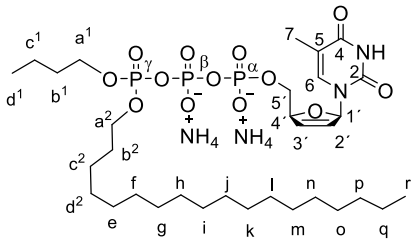
Yield: 117 mg (0.14 mmol, 69%) white solid.

Chemical Formula: $C_{32}H_{65}N_4O_{13}P_3$.

Molecular weight: 806.38 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 771.316; found, 771.283.



^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.69 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 6.96 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.5 Hz, 1H, H-1´), 6.53 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.88 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.02-4.98 (m, 1H, H-4´), 4.30-4.10 (m, 6H, H-a^1, H-a^2, H-5´), 1.92 (d, $^4J_{HH}$= 1.2 Hz, 3H, H-7), 1.72-1.64 (m, 4H, H-b^1, H-b^2), 1.45-1.38 (m, 4H, H-c^1, H-c^2), 1.32-1.26 (m, 28H, H-d^2, H-e, H-f, H-j, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.94 (t, $^3J_{HH}$= 7.3 Hz, $^4J_{HH}$= 1.3 Hz, 3H, H-d^1), 0.89 (t, $^3J_{HH}$= 6.9 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.6 (C-4), 152.8 (C-2), 138.6 (C-6), 135.8 (C-3´), 127.2 (C-2´), 112.1 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 9.2 Hz, C-4´), 69.7, 69.3 (2 × d, $^3J_{CP}$= 6.4 Hz, $^3J_{CP}$= 6.4 Hz, C-a^1, C-a^2), 67.8 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 33.37, 33.31, 33.10, 31.32, 31.27, 30.76, 30.73, 30.70, 30.67, 30.4, 30.3, 23.7 (C-b^1, C-b^2, C-d^2, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 26.6 (C-c^2), 19.7 (C-c^1), 14.4 (C-r), 14.0 (C-d^1), 12.5 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -10.5 (d, $^2J_{pp}$=18.6 Hz, P-γ), -11.5 (d, $^2J_{pp}$=16.6 Hz, P-α), -22.27 (t, $^2J_{pp}$= 17.2 Hz, P-β).

IR: ν [cm^{-1}] = 3393, 2958, 2922, 2852, 2506, 1690, 1662, 1465, 1249, 1127, 1080, 1023, 932, 911, 837, 772, 719, 695, 492.

γ-(Alkyl-C8; alkyl-C18)-phosphate-d4TDP 70c.

According to general procedure 12 with 134 mg *H*-phosphonate **113c** (0.3 mmol, 1.0 equiv) and 118 mg d4TMP 2×nBu$_4$N$^+$ salt (0.15 mmol, 0.5 equiv.). Reaction time was 5 h.

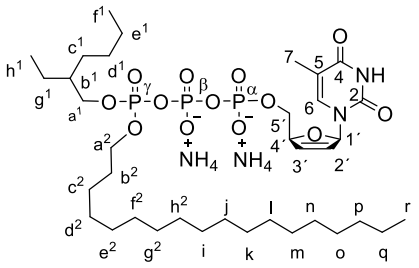
Yield: 42 mg (0.05 mmol, 32%) white solid.

Chemical Formula: $C_{36}H_{73}N_4O_{13}P_3$.

Molecular weight: 862.44 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 827.378; found, 827.354.



^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.69 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 6.96 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.53 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.88 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 2.2 Hz, $^4J_{HH}$= 1.6 Hz, 1H, H-2´), 5.02-4.96 (m, 1H, H-4´), 4.32-4.12 (m, 4H, H-5´, H-a^2), 4.11-4.04 (m, 2H, H-a^1), 1.92 (d, $^4J_{HH}$=1.0 Hz, 3H, H-7), 1.75-1.62 (m, 2H, H-b^2), 1.62-1.52(m, 1H, H-b^1), 1.45-1.25 (m, 38H, H-c^1, H-c^2, H-d^1, H-d^2, H-e^1, H-e^2, H-f^2, H-g^2, H-h^2, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.96-0.86 (m, 9H, H-f^1, H-h^1, H-r).

^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 166.6 (C-4), 152.8 (C-2), 138.7 (C-6), 135.8 (C-3´),127.2 (C-2´), 112.1 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 9.1 Hz, C-4´), 71.5 (d, $^3J_{CP}$= 6.6 Hz, C-a^1), 69.7 (d, $^3J_{CP}$= 6.1 Hz, C-a^2), 67.8 (d, $^3J_{CP}$= 6.1 Hz, C-5´), 41.4 (d, $^3J_{CP}$= 7.7 Hz, C-b^1), 33.1, 31.35, 31.30, 31.0, 30.77, 30.75, 30.69, 30.5, 30.3, 30.04, 30.02, 24.31, 24.28, 24.1, 23.7 (C-b^2, C-c^1, C-d^1, C-d^2, C-e^1, C-e^2, C-f^2, C-g^1, C-g^2, C-h^2, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 26.7 (C-c^2), 14.5 (C-f^1, C-r), 12.5 (C-7), 11.4 (C-h^1).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = -11.70 (d, $^2J_{pp}$=17.6 Hz, P-γ), -12.60 (d, $^2J_{pp}$=17.5 Hz, P-α), -23.46 (t, $^2J_{pp}$= 16.2 Hz, P-β).

IR: ν [cm^{-1}] = 3674, 2959, 2928, 2873, 2298, 1689, 1664, 1461, 1332, 1247, 1126, 1078, 1013, 904, 837, 805, 782, 769, 727, 698, 643, 575, 513, 485.

γ-(Alkyl-C1; alkyl-C18)-phosphonate-d4TDP 71a.

According to general procedure 12 with 100 mg *H*-phosphinate **115a** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt (0.21 mmol, 0.7 equiv.). Reaction time was 2 h.

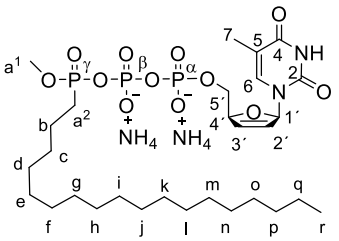
Yield: 75 mg (0.10 mmol, 48%) white solid.

Chemical Formula: $C_{29}H_{59}N_4O_{12}P_3$.

Molecular weight: 748.33 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 713.274; found, 713.228.



^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.69 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 6.96 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.53 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.89 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 2.4 Hz, $^4J_{HH}$= 1.4 Hz, 1H, H-2´), 5.04-4.96 (m, 1H, H-4´), 4.32-4.12 (m, 2H, H-5´), 3.80 (dd, $^2J_{HH}$= 11.5 Hz, $^4J_{HH}$= 1.1 Hz, 3H, H-a^1), 2.07-1.94 (m, 2H, H-a^2), 1.92 (s, 3H, H-7), 1.80-1.56 (m, 6H, H-b, H-c, H-d), 1.55-1.20 (m, 26H, H-e, H-f, H-j, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.89 (t, $^3J_{HH}$= 6.70 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 166.6 (C-4), 152.8 (C-2), 138.7 (C-6), 135.8 (C-3´),127.2 (C-2´), 112.1 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 9.9 Hz, C-4´), 67.9 (d, $^3J_{CP}$= 5.2 Hz, C-5´), 53.2 (d, $^3J_{CP}$= 7.2 Hz, C-a^1), 39.7, 33.1, 31.7, 31.5, 30.78, 30.74, 30.62, 30.57, 30.46, 30.3, 27.55, 27.48, 25.6, 23.7 (C-a^2, C-c, C-d, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 23.2 (d, $^3J_{CP}$= 5.3 Hz, C-b), 14.4 (C-r), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 25.60 (dd, $^2J_{pp}$=23.5 Hz, $^3J_{pp}$=5.7 Hz, P-γ), -11.75 (d, $^2J_{pp}$=17.8 Hz, P-α), -23.56 (t, $^2J_{pp}$= 20.3 Hz, P-β).

IR: ν [cm^{-1}] = 3662, 3182, 2922, 2852, 1689, 1664, 1454, 1228, 1122, 1077, 1044, 1010, 995, 904, 837, 806, 783, 767, 721, 691, 646, 515, 492.

γ-(Alkyl-C4; alkyl-C18)-phosphonate-d4TDP 71b.

According to general procedure 12 with 112 mg *H*-phosphinate **115b** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt (0.21 mmol, 0.7 equiv.). Reaction time was 2 h.

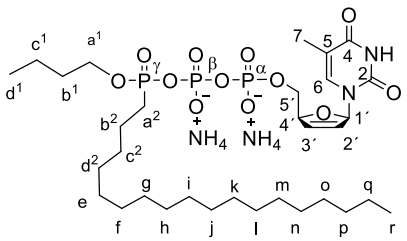
Yield: 83 mg (0.15 mmol, 50%) white solid.

Chemical Formula: $C_{32}H_{65}N_4O_{12}P_3$.

Molecular weight: 790.38 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 755.321; found, 755.267.



^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.70 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 6.96 (dt, $^3J_{HH}$= 3.5 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.53 (dt, $^3J_{HH}$= 6.1 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.89 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$= 1.8 Hz, 1H, H-2´), 5.02-4.98 (m, 1H, H-4´), 4.32-4.10 (m, 4H, H-5´, H-a^1), 2.05-1.95 (m, 2H, H-a^2), 1.92 (d, $^4J_{HH}$=1.1 Hz, 3H, H-7), 1.70-1.60 (m, 4H, H-b^1, H-b^2), 1.45-1.38 (m, 4H, H-c^1, H-c^2), 1.34-1.27 (m, 28H, H-d^2, H-e, H-f, H-j, H-h, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.94 (dt, $^3J_{HH}$= 7.4 Hz, $^4J_{HH}$= 1.3 Hz, 3H, H-d^1), 0.89 (t, $^3J_{HH}$= 7.0 Hz, 3H, H-r).

^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 166.6 (C-4), 152.8 (C-2), 138.7 (C-6), 135.8 (C-3´),127.2 (C-2´), 112.1 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 8.9 Hz, C-4´), 67.8 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 66.9 (d, $^3J_{CP}$= 7.2 Hz, C-a^1), 43,1, 33.1, 31.6, 31.5, 30.78, 30.75, 30.72, 30.6, 30.5, 30.3, 23.7, 11.5 (C-c^2, C-d^2, C-e, C-f, C-g, C-h, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 33.5 (d, $^3J_{CP}$= 6.5 Hz, C-b^1), 27.3, 26.4 (C-a^2), 23.3 (d, $^3J_{CP}$= 5.5 Hz, C-b^2), 19.9 (C-c^1), 14.4 (C-r), 14.0 (C-d^1), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 24.15 (dd, $^2J_{pp}$=23.5 Hz, $^3J_{pp}$=8.7 Hz, P-γ), -11.70 (d, $^2J_{pp}$=17.6 Hz, P-α), -23.55 (t, $^2J_{pp}$= 20.5 Hz, P-β).

IR: ν [cm^{-1}] = 3198, 3034, 2956, 2921, 2852, 1689, 1664, 1463, 1227, 1121, 1077, 993, 837, 806, 783, 768, 720, 692, 512, 492.

γ-(Alkyl-C8; alkyl-C18)-phosphonate-d4TDP 71c.

According to general procedure 12 with 129 mg *H*-phosphinate **115c** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt (0.21 mmol, 0.7 equiv.). Reaction time was 5 h.

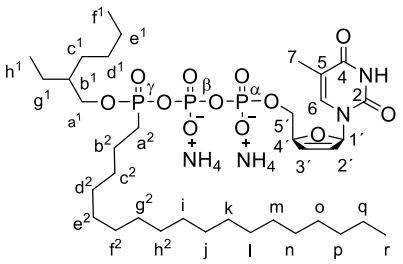
Yield: 45 mg (0.05 mmol, 25%) white solid.

Chemical Formula: $C_{36}H_{73}N_4O_{12}P_3$.

Molecular weight: 846.44 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 811.383; found, 811.345.



^{1}H NMR (400 MHz, CD$_3$OD): δ [ppm] = 7.71 (d, $^4J_{HH}$= 1.0 Hz, 1H, H-6), 6.96 (dt, $^3J_{HH}$= 3.5 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.53 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.89 (ddd, $^3J_{HH}$= 6.1 Hz, $^3J_{HH}$= 3.2 Hz, $^4J_{HH}$= 1.6 Hz, 1H, H-2´), 5.02-4.97 (m, 1H, H-4´), 4.32-3.98 (m, 4H, H-5´, H-a^1), 2.10-1.97 (m, 2H, H-a^2), 1.92 (d, $^4J_{HH}$=1.0 Hz, 3H, H-7), 1.80-1.44 (m, 9H, H-b^1, H-b^2, H-c^1, H-c^2, H-g^1) 1.45-1.25 (m, 32H, H-d^1, H-d^2, H-e^1, H-e^2, H-f^2, H-g^2, H-h^2, H-i, H-j, H-k, H-l, H-m, H-n, H-o, H-p, H-q), 0.97-0.85 (m, 9H, H-h^1, H-f^1, H-r).

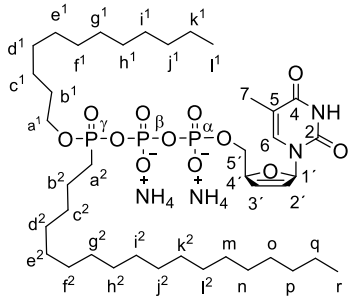
^{13}C NMR (101 MHz, CD$_3$OD): δ [ppm] = 166.6 (C-4), 152.8 (C-2), 138.7 (C-6), 135.9 (C-3´),127.2 (C-2´), 112.1 (C-5), 90.9 (C-1´), 87.3 (d, $^3J_{CP}$= 8.9 Hz, C-4´), 69.0 (C-a^1), 67.8 (C-5´), 41.5 (C-b^1), 33.1, 31.4, 31.1, 30.8, 30.52, 30.47, 30.3, 30.1, 30.0, 27.8, 25.9, 24.44, 24.37, 24.1, 23.7 (C-c^1, C-c^2, C-d^1, C-d^2, C-e^1, C-e^2, C-f^2, C-g^1, C-g^2, C-h^2, C-i, C-j, C-k, C-l, C-m, C-n, C-o, C-p, C-q), 27.8, 25.9 (C-a^2), 23.4 (C-b^2), 14.4, 11.44, 11.39 (C-h^1, C-f^1, C-r), 12.5 (C-7).

^{31}P NMR (162 MHz, CD$_3$OD): δ [ppm] = 24.10 (dd, $^2J_{pp}$=23.5 Hz, $^3J_{pp}$=8.7 Hz, P-γ), -11.70 (d, $^2J_{pp}$=20.5 Hz, P-α), -23.58 (t, $^2J_{pp}$= 23.4 Hz, P-β).

IR: ν [cm^{-1}] = 3662, 3200, 2958, 2924, 2854, 1694, 1464, 1408, 1394, 1250, 1123, 1077, 1066, 1045, 908, 839, 784, 721, 523, 446.

γ-(Alkyl-C12; alkyl-C18)-phosphonate-d4TDP 71d.

According to general procedure 12 with 146 mg *H*-phosphinate **115d** (0.3 mmol, 1.0 equiv.) and 165 mg d4TMP 2×nBu$_4$N$^+$ salt (0.21 mmol, 0.7 equiv.). Reaction time was 5 h.



Yield: 19 mg (0.02 mmol, 10%) white solid.

Chemical Formula: $C_{40}H_{81}N_4O_{12}P_3$.

Molecular weight: 902.51 g/mol.

MALDI-MS (m/z):

$[M-H]^-$ 867.446; found, 867.407.

^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.72 (d, $^4J_{HH}$= 0.6 Hz, 1H, H-6), 6.96 (dt, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-1´), 6.53 (dt, $^3J_{HH}$= 6.0 Hz, $^4J_{HH}$=1.6 Hz, 1H, H-3´), 5.79 (ddd, $^3J_{HH}$= 6.0 Hz, $^3J_{HH}$= 3.4 Hz, $^4J_{HH}$= 1.8 Hz, 1H, H-2´), 5.02-4.98 (m, 1H, H-4´), 4.32-4.08 (m, 4H, H-5´, H-a^1), 2.10-1.95 (m, 2H, H-a^2), 1.92 (d, $^4J_{HH}$=1.0 Hz, 3H, H-7), 1.72-1.64 (m, 4H, H-b^1, H-b^2), 1.45-1.38 (m, 4H, H-c^1, H-c^2), 1.35-1.26 (m, 44H, H-d^1, H-d^2, H-e^1, H-e^2, H-f^1, H-f^2, H-g^1, H-g^2, H-h^1, H-h^2, H-i^1, H-i^2, H-j^1, H-j^2, H-k^1, H-k^2, H-l^2, H-m, H-n, H-o, H-p, H-q), 0.90 (t, $^3J_{HH}$= 6.8 Hz, 6H, H-l^1, H-r).

^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 166.6 (C-4), 152.8 (C-2), 138.7 (C-6), 135.9 (C-3´),127.1 (C-2´), 112.1 (C-5), 90.9 (C-1´), 87.3 (d, $^3J_{CP}$= 8.9 Hz, C-4´), 67.8 (d, $^3J_{CP}$= 5.5 Hz, C-5´), 67.1 (d, $^3J_{CP}$= 7.7 Hz, C-a^1), 33.10, 33.07, 31.57, 31.50, 31.46, 30.83, 30.79, 30.74, 30.55, 30.50, 30.46, 30.4, 30.3, 23.74 (C-b^1, C-c^2, C-d^1, C-d^2, C-e^1, C-e^2, C-f^1, C-f^2, C-g^1, C-g^2, C-h^1, C-h^2, C-i^1, C-i^2, C-j^1, C-j^2, C-k^1, C-k^2, C-l^2, C-m, C-n, C-o, C-p, C-q), 27.3, 26.4 (C-a^2), 26.8 (C-c^1), 23.4 (d, $^3J_{CP}$= 4.8 Hz, C-b^2), 14.45,14.43 (C-i^1, C-r), 12.6 (C-7).

^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = 24.10 (dd, $^2J_{pp}$=23.5 Hz, $^3J_{pp}$=8.7 Hz, P-γ), -11.70 (d, $^2J_{pp}$=20.5 Hz, P-α), -23.58 (t, $^2J_{pp}$= 23.4 Hz, P-β).

IR: ν [cm^{-1}] = 3661, 2956, 2921, 2852, 2302, 1692, 1665, 1229, 1122, 1077, 1043, 994, 904, 837, 806, 782, 769, 720, 689, 518.

6.4 Preparation of different medium

6.4.1 Preparation of phosphate buffer (PB, pH 7.3)

1.55 g Potassium dihydrogen phosphate and 5.47 g disodium hydrogen phosphate were dissolved in 1L ultrapure water. Then diluted phosphoric acid was added to adjust the pH 7.3. All prodrugs were incubated in this buffer to study their chemical stability.

6.4.2 Preparation of 2 mM tetra-*n*-butylammonium acetate solution (pH 6.3)

2.7 mL *tetra*-n-butylammonium hydroxide (40% in water) was diluted with 2 L ultrapure water. Then glacial acetic acid was added to adjust the pH 6.3. This solution was used as eluent for ion-exchange (RP-HPLC).

6.4.3 Preparation of cell extracts

Human $CD4^+$ T-lymphocyte CEM cells were grown in RPMI-1640-based cell culture medium to a final density of ~$3 \cdot 10^6$ cells/mL. Then, cells were centrifuged for 10 min at 1,250 rpm at 4 °C, washed twice with cold PB, and the pellet was re-suspended at 10^8 cells/mL and sonicated (Hielscher Ultrasound Techn., 100% amplitude, 3·times for 10 sec) to destroy cell integrity. The resulting cell suspension was then centrifuged at 10,000 rpm to remove cell debris, and the supernatant divided in aliquots before being frozen at -80 C and used.

6.5 Hydrolysis studies

6.5.1 Chemical Hydrolysis in PB.

Stock solutions (50mM in DMSO) of compounds **60**,**61**,**62**,**67**,**68**,**69**,**70**,**71**,**89**,**90**,**106**,**108**,**110** were prepared. After dilution of 22 µL stock solution with 200 µL DMSO and 378 µL milliQ water to 1.9 mM hydrolysis solutions the reaction was started by addition of 600 µL phosphate buffer saline (PB, 50mM, pH 7.3). The solution was incubated at 37 °C in a thermomixer. An initial aliquot (25 µL) was taken directly and analyzed by analytical HPLC at 250-285 nm. Further aliquots were taken for monitoring the kinetic hydrolysis. The exponential decay curves (pseudo-first order) based on absolute integral values were calculated with commercially available software (OriginPro 9.0G) and yielded the half-lives ($t_{1/2}$) of the prodrugs via one determination.

6.5.2 Enzymatic hydrolysis of prodrug compounds with *pig liver esterase* (PLE)

To a mixture of 105 µL 6 mM prodrugs **60**,**61**,**67**,**68**,**69**,**70**,**71**,**89**,**90**,**106**,**108**,**110** solution (DMSO/H_2O 1:1), 157.5 µL and 1050 µL PB buffer (pH 7.3) were added. 2. Prepare of PLE solution (100 U/mL, PB, pH 7.3) and added 78.8 µL PLE solution to prodrug solution. The mixture was incubated with 800 rpm at 37 °C in a thermomixer. 3. At different times, 75 µl aliquots were taken and the reaction was stopped

by addition to 79.5 mL MeOH. Then, the samples were tested directly using HPLC (injection volume 80 µL).

6.5.3 Enzyme-catalyzed hydrolysis of prodrugs in CEM cell extracts

21 µL of the appropriate 50 mM DMSO stock solution was diluted to 6.0 mM hydrolysis solution by addition of 154 µL DMSO. Different samples including 10 µL water and 10 µL hydrolysis solution were prepared in 2 mL Eppendorf® vials. The reaction was started by addition of 50 µL human CEM cell extract and the mixture was incubated at 37 °C for different time periods. The resulting suspension was kept on ice for 5 min, followed by defrosting, ultrasonication for 10 min and by centrifugation for 5 min (13,000 rpm). The supernatant (80 µL) were directly injected to HPLC. The calculation of $t_{1/2}$ was performed analogously to that for the chemical hydrolysis studies.

6.6 Anti-HIV activity assay

Inhibition of HIV-1(III_B)- and HIV-2(ROD)-induced cytopathogenicity in wild-type CEM/0 CEM $CD4^+$ T-cells and thymidine kinase-deficient CEM/TK^- cell cultures was measured in microtiter 96-well plates containing ~$3 \cdot 10^5$ CEM cells/mL infected with 100 $CCID_{50}$ of HIV per milliliter and containing appropriate dilutions of the test compounds. After 4−5 days of incubation at 37 °C in a CO_2-controlled humidified atmosphere, virus-induced cellular effects and syncytia cell formation was examined microscopically. The EC_{50} (50% effective concentration) was defined as the compound concentration required to inhibit HIV-induced giant cell formation by 50%.

6.7 Primer-extension reactions

HIV-RT and human DNA polymerase β and γ were obtained from Roboklon, human DNA polymerase α was obtained from Chimerx. The primers and templates were purchased from Life Technologies and Microsynth. The fluorescent labeled primer was purchased from Metabion and Microsynth. The gels were prepared with the size of 450mm×200mm×0.4mm according to the electrophoresis apparatus.

Sequence of Primer and Template

5'-FITC and 5'-Cy3 labeled Primer-sequence:

5´-FITC-CGTTG GTCCT GAAGG AGGAT AGGTT-3´

5´-Cy3-CGTTG GTCCT GAAGG AGGAT AGGTT-3´

Template-sequence:

3´-GCAAC CAGGA CTTCC TCCTA TCCAA AGACA-5´

The primer extension assays were performed under the following conditions:

FITC and Cy3 labeled primer extension assay:

1) Hybridization: After 5 min incubation at 95 °C in 20 mM Tris-HCl (pH 7.6) and 50 mM NaCl, the hybridization/annealing of the primer to the template strand was achieved by a cooling phase from 95 °C to -20 °C lasted more than 2 hours.

2) For HIV- RT assay: The final assay solution (10 µL) consists of 50 mM Tris-HCl (pH 8.6 at 22 °C), 10 mM $MgCl_2$, 40mM KCl, dNTPs 66 µM, HIV RT 6 U, Hybrid 0.32 µM in a reaction volume of 10 µL, incubated 37 °C for 15 min, 80 °C for 3 min; 50 mA, 45w for 4 h. The assays were separated using a denaturating PAGE (15%). The result was visualized by fluorescence imaging.

3) For human DNA pol β assay: The final assay solution (10 µL) consists of 50 mM Tris-HCl (pH 8.7), 10 mM $MgCl_2$, 100mM KCl, 1.0 mM dithiothreitol, 0.4 mg/mL of bovine serum albumin, 15% glycerol, dNTPs 66 µM, DNA Polymerase Beta 6 U, Hybrid 0.32 µM in a reaction volume of 10 µL, incubated 37 °C for 60 min, 80 °C for 3 min; 50 mA, 45w for 4 h. The assays were separated using a denaturating PAGE (15%). The result was visualized by fluorescence imaging.

4) For human DNA pol α assay: The final assay solution (25 µL) consists of 60 mM Tris-HCl (pH 8), 5 mM MgOAc, 100mM KCl, 1.0 mM dithiothreitol, 0.01% (w/v) of bovine serum albumin, dNTPs 250 µM, DNA Polymerase alpha 4U, Hybrid 0.20 µM in a reaction volume of 25 µL, incubated 37 °C for 5 min without dNTPs, then incubated 60 min at 37°C, 80 °C for 3 min; 50 mA, 45w for 3 h. The assays were separated using a denaturating PAGE (15%). The result was visualized by fluorescence imaging.

5) For human DNA pol γ assay: The final assay solution (25 µL) consists of 60 mM Tris-HCl (pH 8), 5 mM MgOAc, 100mM KCl, 1.0 mM dithiothreitol, 0.01% (w/v) of bovine serum albumin, dNTPs 250 µM, DNA Polymerase gamma 4U, Hybrid 0.20 µM in a reaction volume of 25 µL, incubated 37 °C for 5 min without dNTPs, then incubated 60 min at 37°C, 80 °C for 3 min; 50 mA, 45w for 3 h. The assays were separated using a denaturating PAGE (15%). The result was visualized by fluorescent imaging.

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8 Attachment

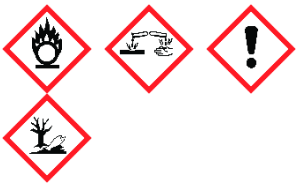
8.1 Hazards

The hazard and precautionary statements of the used compounds and solvents were listed below.[179]

Compound	Pictograms	Hazard statements	Precautionary statements
Acetic acid glacial		226, 290, 314	210, 260, 280, 370+378, 303+361+353 305+351+338
Acetic anhydride		226, 302, 314, 333	210, 280, 301+330+331, 303+361+353, 304+340+311, 305+351+338+310
Acetone		225, 319, 336	210, 305+351+338
Acetonitrile		225, 319, 302+312+332	210, 280, 301+312+330, 302+352+312, 304+340+312, 305+351+338
Acetyl chloride		225, 314	210, 280, 301+330+331, 303+361+353, 305+351+338+310
Ammonia 25%		219, 314, 335, 400	173, 280, 301+330+331, 305+351+338, 308+310
Ammonium acetate	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.		
Ammonium bicarbonate		302	301+312+330
Butyl chloroformate		226, 314, 331	210, 280, 301+330+331, 303+361+353, 304+340+311, 305+351+338
butyryl chloride		225, 314	210, 280, 305+351+338, 310
butyl carbonochloridate		226, 314, 331	210, 280, 301+330+331, 303+361+353, 304+340+311, 305+351+338
tert-butyldimethylsilyl chloride		228, 314	210, 260, 280, 370+378, 305+351+338, 303+361+353,
Dichloromethane		315, 319, 336, 351	201, 302+352, 308+313, 305+351+338
tert-Butanol		225, 319, 332, 335, 336	210, 304+340+312, 305+351+338
Chloroform		302, 315, 319, 331, 351, 361, 372	302+352, 304+340, 305+351+338, 308+310
Chloroform-*d*		302, 315, 319, 331, 336, 351, 361d, 372	201, 273, 301+312+330, 302+352, 304+340+311, 308+313

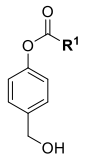
Celite® S		372	260, 264, 270, 314, 501
N-Chlorosuccinimide		302, 314	280, 310, 305+351+338
Cyclohexane		225, 304, 315, 336, 410	210, 273, 302+352, 301+310+331
Deuterium oxide	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.		
Decanoyl chloride		314	280, 310, 305+351+338
Dichloromethane		315, 319, 336, 351	201, 302+352, 305+351+338, 308+313
Diethyl ether		224, 302, 336	210, 301+312+330, 403+233
4-Dimethylaminopyridine		301, 310, 315, 319, 335	280, 301+310+330, 302+352+310, 304+340+312, 305+351+338, 337+313
1-Decanol		319, 412	264, 273, 280, 305+351+338, 337+313, 501
Diphenyl phosphonate		302, 315, 318, 335	280, 301+312+330, 302+352, 305+351+338+310
Dodecylmagnesium bromide solution		224, 250, 261, 302, 314, 336	210, 222, 231+232, 261, 280, 422, EUH014, EUH019
Di*iso*propylamine		225, 302, 314, 331	210, 280, 303+361+353, 304+340+310, 305+351+338, 403+233
Diethyl chlorophosphite		225, 314, 335	210, 261, 280, 305+351+338, 310, EUH014
N,*N*-Dimethylacetamide		312+332, 319, 360D	201, 280, 302+352+312, 304+340+312, 305+351+338, 308+313
Dowex® 50WX8		319	305+351+338
Dodecanoyl chloride		314	280, 305+351+338, 310
Ethanol		225, 319	210, 305+351+338
Ethyl carbonochloridate		225, 301, 314, 330	210, 280, 301+310+330, 303+361+353, 304+340+310, 305+351+338
Ethyl acetate		225, 319, 336	210, 305+351+338

9-Fluorenemethanol	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.		
1-Hexadecanol	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.		
Heptanoyl chloride		314, 330	280, 301+330+331, 303+361+353, 304+340+310, 305+351+338
n-Hexane		225, 304, 315, 336, 361f, 373, 411	210, 260, 280, 301+310, 370+378, 403+235
Hydrochloric acid		290, 314, 335	260, 280, 303+361+353, 304+340+310, 305+351+338
4-Hydroxybenzyl alcohol		319	305+351+338
1-Hexanol		226, 302+312, 319	210, 280, 301+312+330, 305+351+338, 370+378
3-Hydroxypropionitrile	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.		
Isovaleryl chloride		226, 314, 331	210, 280, 301+330+331, 303+361+353, 304+340+311, 305+351+338
Lithium aluminium hydride		260, 314	223, 231+232, 280, 422, 305+351+338, 370+378
Methanol		225, 301+311+331+370	210, 280, 301+310+330, 302+352+312, 304+340+311
Methyl carbonochloridate		225, 302+312, 330	210, 260, 280, 284, 305+351+338, 310
Methanol-d		225, 301+311+331+370	210, 280, 301+310+330, 302+352+312, 304+340+311
Methanesulfonyl chloride		301+311, 317, 330, 335	280, 301+310+330, 301+330+331, 303+361+353, 304+340+310, 305+351+338
1-Methylimidazole		302, 311, 314	208, 301+312+330, 301+330+331, 303+361+353, 305+351+338
3 M methyl-magnesium bromide in diethyl ether		225, 260, 302, 314, 336	210, 223, 261, 422, 231+232, 370+378
nonanoyl chloride		314	280, 305+351+338, 310
1-Nonanol		319, 412	273, 305+351+338
1-Octadecanol	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.		

Octadecanoyl chloride		314	280, 310, 305+351+338
Octadecylmagnesium chloride solution		225, 302, 314, 335, 351	210, 260, 280, 403+235, 305+351+338, 370+378
Palmitoyl chloride		314, EUH014	
Petroleum ether 50-70		225, 304, 315, 336, 361f, 373, 411	210, 240, 273, 301+330+331, 310, 302+352, 403+233
Phosphorus oxychloride		302, 314, 330, 372	280, 301+330+331, 303+361+353, 304+340+310, 305+351+338, 314
Potassium permanganate		272, 302, 314, 410	210, 220, 260, 273, 280, 303+361+353, 304+340+310, 305+351+338+310, 370+378, 391
1-Pentadecanol	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.		
2-Propanol		225, 319, 336	210, 305+351+338
Propionyl chloride		225, 302, 314, 331	210, 280, 303+361+353, 304+340+310, 305+351+338, 403+233
Pyridine		225, 302+312+332, 315, 319	210, 280, 301+312+330, 302+352+312, 304+340+312, 305+351+338
Potassium carbonate		315, 319, 335	305+351+338
Potassium-*tert*-butoxide		228, 260, 314	210, 231+232, 260, 280, 303+361+353, 305+351+338
isoButyryl chloride		225, 314	210, 280, 305+351+338, 310
Silica gel	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.		
Sodium bicarbonate	Not a hazardous substance or mixture.		
Sodium carbonate		319	264, 280, 305+351+338, 337+313
Sodium chloride	Not a hazardous substance or mixture according to Regulation		
Sodium hydroxide		290, 314	260, 280, 301+330+331, 303+361+353, 305+351+338
Sodium sulfate	Not a hazardous substance or mixture according to Regulation		

Sulfuric acid		290, 314	280, 301+330+331, 303+361+353, 305+351+338+310
Sodium thiosulfate	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.		
Tetrabutylammonium hydroxide (40% in H2O)		314	280, 305+351+338, 310
Tetrahydrofuran		225, 302, 319, 335, 351	201, 210, 301+312+330, 305+351+338, 308+313
Triethylamine		225, 302, 311+331, 314, 335	210, 280, 301+312+330, 303+361+353, 304+340+311, 305+351+338+310
Triphosgene		314, 330	260, 284, 303+361+353, 304+340+310, 305+351+338, 403+233
Tetradecylmagnesium chloride solution		225, 250, 261, 314, 335, 351	210, 231+232, 280, 305+351+338, 370+378, 422
Toluene		225, 304, 315, 336, 361d, 373, 412	201, 210, 273, 301+310+331, 302+352, 308+313
Triethyl phosphate		302, 319	301+312+330, 305+351+338
Thymidine	Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.		
Thymine			
p-Toluenesulfonyl chloride		290, 315, 317, 318	280, 302+352, 305+351+338+310
Trifluoroacetic anhydride		314, 332, 412	273, 280, 301+330+331, 303+361+353, 304+340+312, 305+351+338+310
1-Tetradecanol		319, 410	273, 305+351+338
1-Undecanol		315, 317, 411	273, 280
Valeroyl chloride		226, 290, 314, 331, 412	210, 301+330+331, 273, 303+361+353, 273, 305+351+338

8.2 Overview of the Compound Structures



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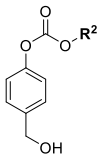

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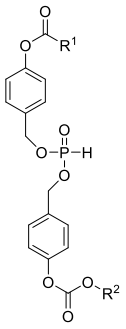
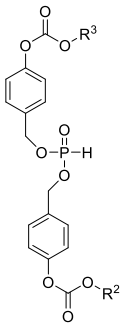


77

R¹: **a**=CH_3, **b**=C_2H_5, **c**=C_3H_7 (n-propyl), **d**=C_3H_7 (isopropyl), **e**=C_4H_9 (n-butyl), **f**=C_4H_9 (isobutyl), **g**=C_6H_{13}, **h**=C_8H_{17}, **i**=C_9H_{17}, **j**=$C_{11}H_{23}$

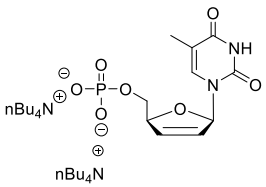
R²: **k**=CH_3, **l**=C_2H_5, **m**=C_4H_9, **r**=C_6H_{13}, **s**=C_9H_{19}, **t**=$C_{10}H_{21}$, **u**=$C_{11}H_{23}$, **v**=$C_{12}H_{25}$, **w**=$C_{14}H_{29}$, **x**=$C_{15}H_{31}$, **y**=$C_{16}H_{33}$, **z**=$C_{18}H_{37}$

77ay: $R^1 = CH_3$, $R^2 = C_{16}H_{33}$
77by: $R^1 = C_2H_5$, $R^2 = C_{16}H_{33}$
77ey: $R^1 = n\text{-}C_4H_9$, $R^2 = C_{16}H_{33}$
77fy: $R^1 = iso\text{-}C_4H_9$, $R^2 = C_{16}H_{33}$
77gy: $R^1 = C_6H_{13}$, $R^2 = C_{16}H_{33}$
77hy: $R^1 = C_8H_{17}$, $R^2 = C_{16}H_{33}$
77iy: $R^1 = C_9H_{19}$, $R^2 = C_{16}H_{33}$
77bs: $R^1 = C_2H_5$, $R^2 = C_9H_{19}$
77bt: $R^1 = C_2H_5$, $R^2 = C_{10}H_{21}$
77bu: $R^1 = C_2H_5$, $R^2 = C_{11}H_{23}$
77bv: $R^1 = C_2H_5$, $R^2 = C_{12}H_{25}$
77bw: $R^1 = C_2H_5$, $R^2 = C_{14}H_{29}$
77cv: $R^1 = n\text{-}C_3H_7$, $R^2 = C_{12}H_{25}$
77dv: $R^1 = iso\text{-}C_3H_7$, $R^2 = C_{12}H_{25}$
77ev: $R^1 = C_4H_9$, $R^2 = C_{12}H_{25}$
77ew: $R^1 = C_4H_9$, $R^2 = C_{14}H_{29}$
77ex: $R^1 = C_4H_9$, $R^2 = C_{15}H_{31}$
77ez: $R^1 = C_4H_9$, $R^2 = C_{18}H_{37}$
77is: $R^1 = C_9H_{19}$, $R^2 = C_9H_{19}$
77jr: $R^1 = C_{11}H_{23}$, $R^2 = C_6H_{13}$

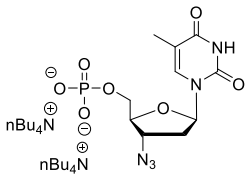


79

79ss: $R^3 = C_9H_{19}$, $R^2 = C_9H_{19}$
79lv: $R^3 = C_2H_5$, $R^2 = C_{12}H_{25}$
79mv: $R^3 = C_4H_9$, $R^2 = C_{12}H_{25}$
79mz: $R^3 = C_4H_9$, $R^2 = C_{18}H_{37}$



d4TMP **1a**



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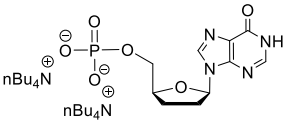
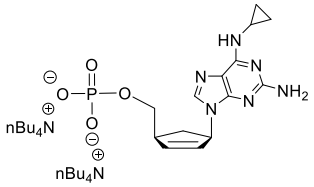
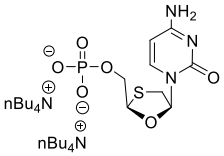


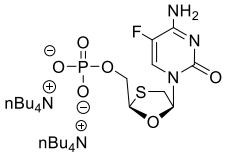
ddIMP **3a**



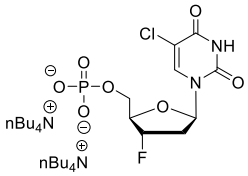
ABCMP **5a**



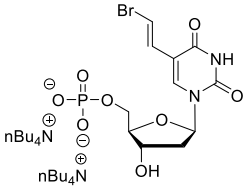
3TCMP **6a**



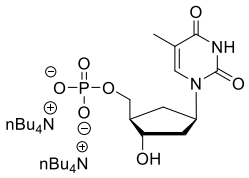
FTCMP **7a**



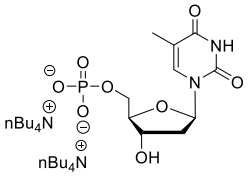
FddClU **8a**



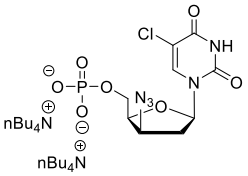
BVdUMP **9a**



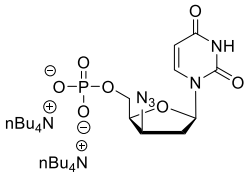
carba-TMP **63a**



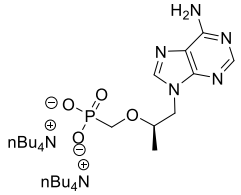
TMP **65a**



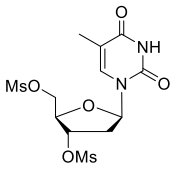
AZddClUMP **87a**



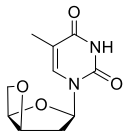
AZUMP **64a**



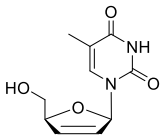
TFVMP **17a**



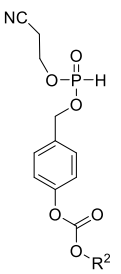
65A



65B

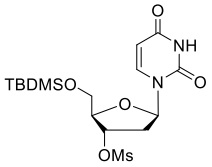


d4T 1

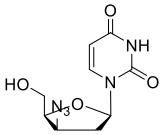


83

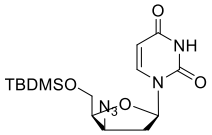
83v: $R^2 = C_{12}H_{25}$
83y: $R^2 = C_{16}H_{33}$



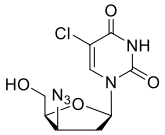
86



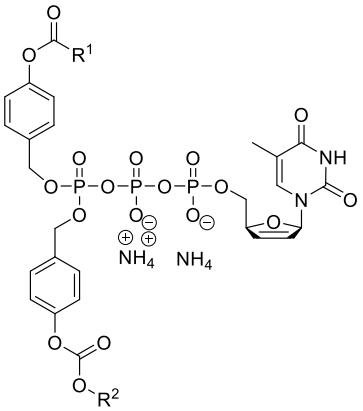
64



87

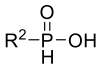


66

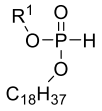


γ-(AB; ACB)-d4TTPs **60**

60ay: $R^1 = CH_3$, $R^2 = C_{16}H_{33}$;
60by: $R^1 = C_2H_5$, $R^2 = C_{16}H_{33}$;
60ey: $R^1 = n\text{-}C_4H_9$, $R^2 = C_{16}H_{33}$;
60fy: $R^1 = iso\text{-}C_4H_9$, $R^2 = C_{16}H_{33}$;
60gy: $R^1 = C_6H_{13}$, $R^2 = C_{16}H_{33}$;
60hy: $R^1 = C_8H_{17}$, $R^2 = C_{16}H_{33}$;
60iy: $R^1 = C_9H_{19}$, $R^2 = C_{16}H_{33}$;
60bs: $R^1 = C_2H_5$, $R^2 = C_9H_{19}$;
60bt: $R^1 = C_2H_5$, $R^2 = C_{10}H_{21}$;
60bu: $R^1 = C_2H_5$, $R^2 = C_{11}H_{23}$;
60bv: $R^1 = C_2H_5$, $R^2 = C_{12}H_{25}$;
60bw: $R^1 = C_2H_5$, $R^2 = C_{14}H_{29}$;
60cv: $R^1 = n\text{-}C_3H_7$, $R^2 = C_{12}H_{25}$;
60dv: $R^1 = iso\text{-}C_3H_7$, $R^2 = C_{12}H_{25}$;
60ev: $R^1 = C_4H_9$, $R^2 = C_{12}H_{25}$;
60ew: $R^1 = C_4H_9$, $R^2 = C_{14}H_{29}$;
60ex: $R^1 = C_4H_9$, $R^2 = C_{15}H_{31}$;
60ez: $R^1 = C_4H_9$, $R^2 = C_{18}H_{37}$;
60is: $R^1 = C_9H_{19}$, $R^2 = C_9H_{19}$;
60jr: $R^1 = C_{11}H_{23}$, $R^2 = C_6H_{13}$



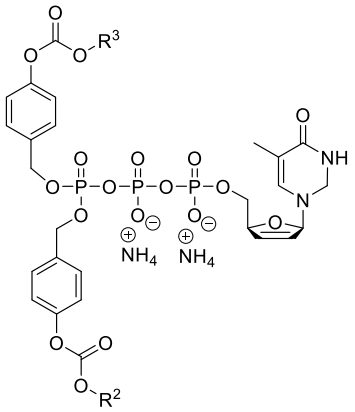
98



113

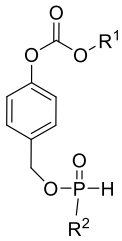
98a: $R^2 = C_{12}H_{25}$;
98b: $R^2 = C_{14}H_{29}$;
98c: $R^2 = C_{18}H_{37}$

113a: $R^1 = CH_3$;
113b: $R^1 = C_4H_9$;
113c: $R^1 = C_8H_{17}$ (2-ethylhexy)



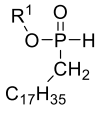
γ-(ACB; ACB)-d4TTPs **61**

61ss: $R^3 = C_9H_{19}$, $R^2 = C_9H_{19}$;
61lv: $R^3 = C_2H_5$, $R^2 = C_{12}H_{25}$;
61mv: $R^3 = C_4H_9$, $R^2 = C_{12}H_{25}$;
61mz: $R^3 = C_4H_9$, $R^2 = C_{18}H_{37}$



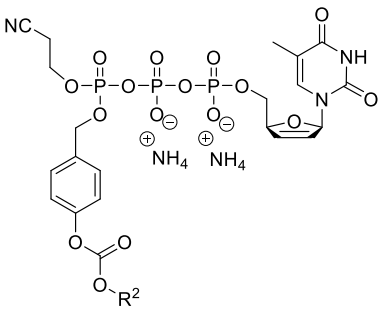
102

102ak: $R^1 = CH_3$, $R^2 = C_{12}H_{25}$
102am: $R^1 = C_4H_9$, $R^2 = C_{12}H_{25}$
102au: $R^1 = C_{11}H_{23}$, $R^2 = C_{12}H_{25}$
102bm: $R^1 = C_4H_9$, $R^2 = C_{14}H_{29}$
102cm: $R^1 = C_4H_9$, $R^2 = C_{18}H_{37}$



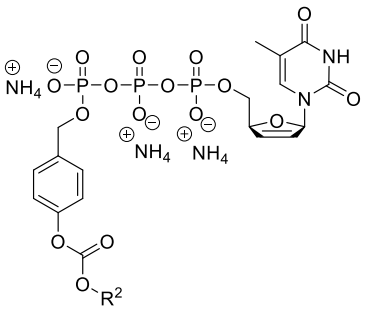
115

115a: $R^1 = CH_3$;
115b: $R^1 = C_4H_9$;
115c: $R^1 = C_8H_{17}$ (2-ethylhexy);
115d: $R^1 = C_{12}H_{25}$



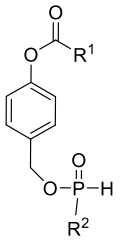
γ-(ACB; β-cyanoethyl)-d4TTPs **85.**

85v: $R^2 = C_{12}H_{25}$;
85y: $R^2 = C_{16}H_{33}$



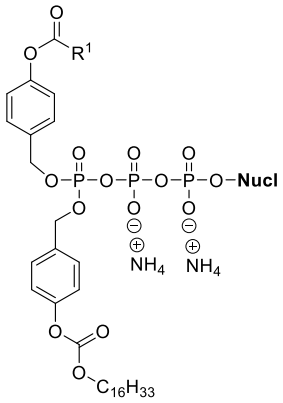
γ-(ACB)-d4TTPs **62.**

62v: $R^2 = C_{12}H_{25}$;
62y: $R^2 = C_{16}H_{33}$

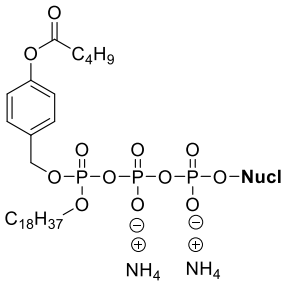


99

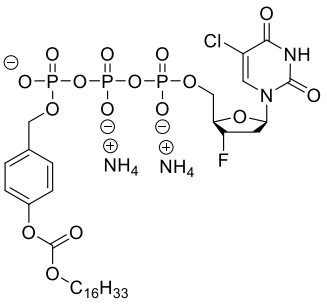
99aa: $R^1 = CH_3$, $R^2 = C_{12}H_{25}$;
99ae: $R^1 = C_4H_9$, $R^2 = C_{12}H_{25}$;
99aj: $R^1 = C_{11}H_{23}$, $R^2 = C_{12}H_{25}$;
99be: $R^1 = C_4H_9$, $R^2 = C_{14}H_{29}$;
99ce: $R^1 = C_4H_9$, $R^2 = C_{18}H_{37}$



γ-(AB; ACB-C16)-NTPs **89**

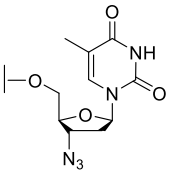


γ-(AB-C4; alkyl-C18)-NTPs **90**

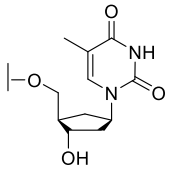


γ-(ACB-C16)-FddClUTPs **95g**

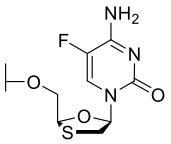
Nucl =



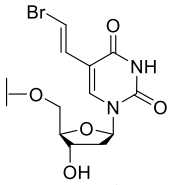
89b1 $R^1 = C_2H_5$
89b2 $R^1 = C_4H_9$
90b $R^1 = C_4H_9$



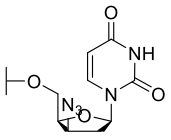
89c1 $R^1 = C_2H_5$



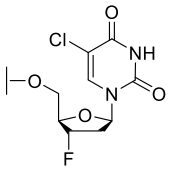
89d1 $R^1 = C_2H_5$
89d2 $R^1 = C_4H_9$
90d $R^1 = C_4H_9$



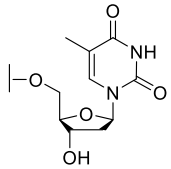
89e1 $R^1 = C_2H_5$
89e2 $R^1 = C_4H_9$
90be $R^1 = C_4H_9$



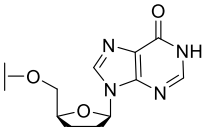
89f1 $R^1 = C_2H_5$



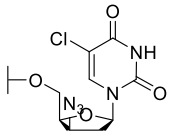
89g1 $R^1 = C_2H_5$
89g2 $R^1 = C_4H_9$
90g $R^1 = C_4H_9$



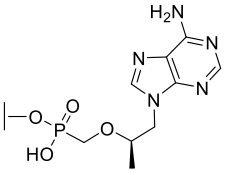
89h1 $R^1 = C_2H_5$



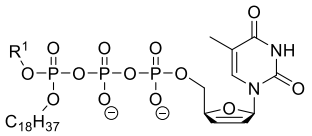
89i2 $R^1 = C_4H_9$
90i $R^1 = C_4H_9$



89j1 $R^1 = C_2H_5$

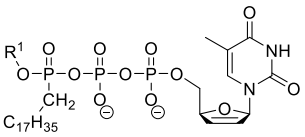


89l2: $R^1 = C_2H_5$



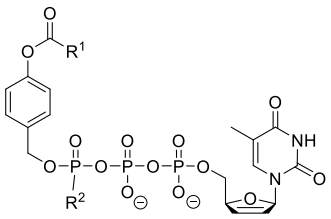
γ-(A; C18)-d4TTPs **70**

70a: $R^1 = CH_3$;
70b: $R^1 = C_4H_9$;
70c: $R^1 = C_8H_{17}$ (2-ethylhexy)



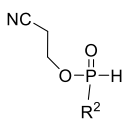
γ-C-(A; C18)-d4TTPs **71**

71a: $R^1 = CH_3$;
71b: $R^1 = C_4H_9$;
71c: $R^1 = C_8H_{17}$ (2-ethylhexy);
71d: $R^1 = C_{12}H_{25}$



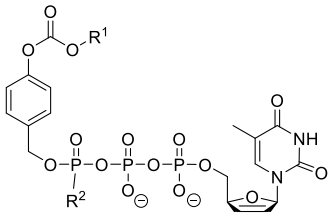
γ-AB-γ-C-alkyl-d4TTPs **67**

67aa: $R^1 = CH_3$, $R^2 = C_{12}H_{25}$;
67ae: $R^1 = C_4H_9$, $R^2 = C_{12}H_{25}$;
67aj: $R^1 = C_{11}H_{23}$, $R^2 = C_{12}H_{25}$;
67be: $R^1 = C_4H_9$, $R^2 = C_{14}H_{29}$;
67ce: $R^1 = C_4H_9$, $R^2 = C_{18}H_{37}$



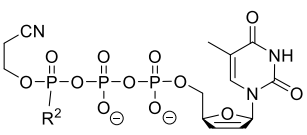
104

104a: $R^2 = C_{12}H_{25}$,
104c: $R^2 = C_{18}H_{37}$



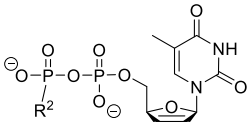
γ-ACB-γ-C-alkyl-d4TTPs **68**

68ak: $R^1 = CH_3$, $R^2 = C_{12}H_{25}$
68am: $R^1 = C_4H_9$, $R^2 = C_{12}H_{25}$
68au: $R^1 = C_{11}H_{23}$, $R^2 = C_{12}H_{25}$
68bm: $R^1 = C_4H_9$, $R^2 = C_{14}H_{29}$
68cm: $R^1 = C_4H_9$, $R^2 = C_{18}H_{37}$



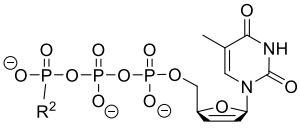
γ-(alky; β-cyanoethyl)-d4TTPs **106**

106a: $R^2 = C_{12}H_{25}$;
106c: $R^2 = C_{18}H_{36}$



γ-C-(alkyl)-d4TDPs **107**

107a: $R^2 = C_{12}H_{25}$



γ-C-(alkyl)-d4TTPs **69**

69a: $R^2 = C_{12}H_{25}$;
69c: $R^2 = C_{18}H_{36}$

8.3 Curriculum Vitae

Not applicable for reasons of protection of personal data

9 Eidesstattliche Versicherung

I hereby declare on oath that I have written the present PhD thesis ``Membrane-Permeable Nucleoside Triphosphate Prodrugs of Anti-HIV Active Nucleoside Analogues: γ-(Phosphate or Phosphonate)-Modified Nucleotide Analogues´´ by myself and that I have not used any aids other than those specified. The submitted written version corresponds to that on the electronic storage medium. I confirm that this dissertation was not submitted in a previous doctoral procedure.

_____ _____

Ort, Datum M.Sc. Xiao Jia