Journal of
Medicinal Chemistry

Article

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J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.0c00271 • Publication Date (Web): 18 May 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Anti-HIV-active Nucleoside Triphosphate Prodrugs

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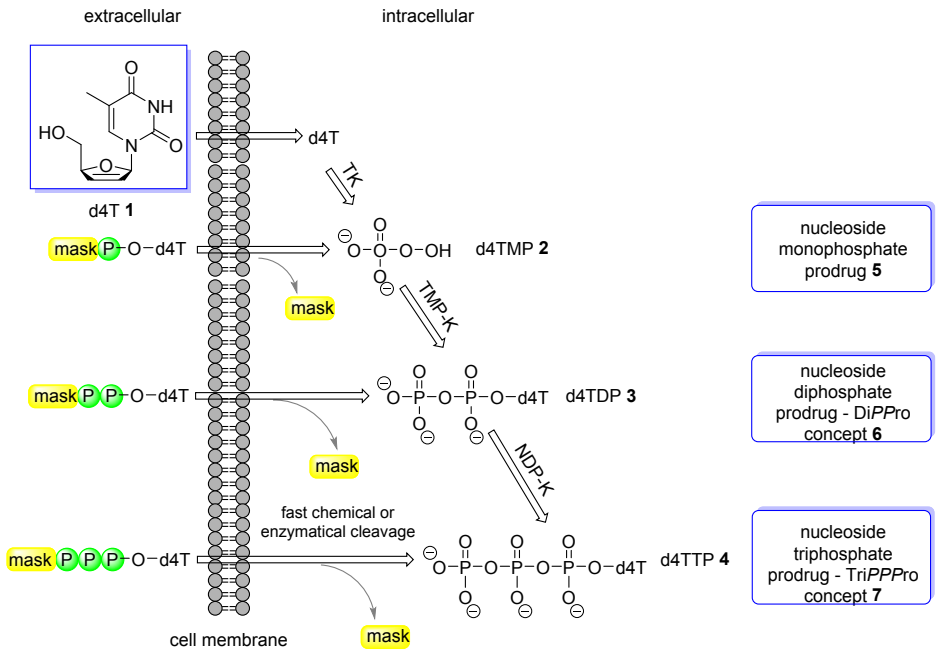
ABSTRACT We disclose a study on nucleoside triphosphate (NTP) analogues in which the γ-phosphate is covalently modified by F8butwo different biodegradable masking units and d4T as nucleoside analogue that enable the delivery of d4TTP with high selectivity in phosphate buffer (pH 7.3) and by enzyme-triggered reactions in human $CD4^+$ T-lymphocyte CEM cell extracts. This allows the bypass of all steps normally needed in the intracellular phosphorylation. These Tri*PPP*ro-nucleotides comprising an acyloxybenzyl- (AB; ester) or an alkoxycarbonyloxybenzyl- (ACB; carbonate) in combination with an ACB-moiety are described as NTP delivery systems. The introduction of these two different groups led to the selective formation of γ-(ACB)-d4TTPs by chemical hydrolysis and in particular by cell extract enzymes. γ-(AB)-d4TTPs are faster cleaved than γ-(ACB)-d4TTPs. In antiviral assays, the compounds are highly active against HIV-1 and HIV-2 in wild-type CEM/O cells and more importantly in thymidine kinase-deficient $CD4^+$ T-cells (CEM/TK^-).

Introduction

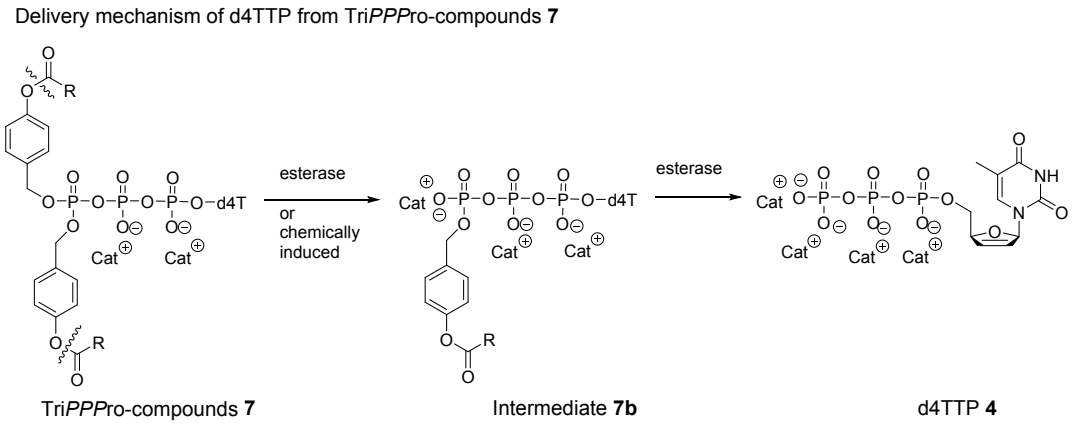
For many decades, nucleoside analogues have been applied in antiviral and antitumoral chemotherapy and they still comprise the frontline of drugs used to combat infections caused by HIV, herpes virus, hepatitis B and C virus.[1,2] The antiviral efficacy of many nucleoside analogues such as 3'-deoxy-2',3'-dehydrothymidine (d4T, **1**; Scheme 1) or 3'-deoxy-3'-azidothymidine (AZT) are strongly dependent on their intracellular activation by host cell kinases to give, via the monophosphate (**2**, NMP) and the diphosphate (**3**, NDP), ultimately the bioactive nucleoside analogue triphosphate derivatives (**4**, NTP).[3,4] The targets of effective nucleoside analogue drugs are the virus-encoded DNA- or RNA polymerases, such as the HIV reverse transcriptase (RT)[5,6] or the HCV-encoded RNA-dependent RNA-polymerase NS5B,[7] which are the key enzymes in the replication cycle of HIV and HCV, respectively. Up to now, many nucleoside analogues have been approved as HIV-RT inhibitors (NRTIs)[8] and they are used as the backbone of the combined antiretroviral therapy (cART).[9] However, cellular kinases often catalyse these biotransformation insufficiently, resulting in low or no biological activity of the given compound.[3,10,11] Moreover, the clinical efficacy of nucleoside analogues is hampered by limitations such as poor biological half-lives due to catabolic elimination from the body, mutations of nucleoside transporters, variable bioavailability after oral administration or development of drug resistance.[12-14] These hurdles can be overcome by using lipophilic prodrugs of the phosphorylated parent nucleosides, which are able to bypass the rate-limiting, kinase-catalyzed conversion steps, such as tenofovir and sofosbuvir.[15,16] In the past, this task has been successfully achieved for the intracellular delivery of NMP using prodrug strategies[17-19] such as the *cyclo*Sal-,[20-22] SATE-,[23,24] bisPOM-[25] or phosphoramidate nucleotides.[26,27]



Scheme 1: Metabolism of nucleoside analogues such as d4T **1** and the corresponding nucleotide prodrugs.

In the case of the anti-HIV drug d4T **1** within the stepwise biotransformation, the first phosphorylation step catalyzed by the host cell enzyme thymidine kinase (TK) has been identified as the metabolism-limiting step because of the rather modest affinity of d4T **1** to TK as an alternative substrate and because TK activity is S-phase dependent.[4,28] In addition to the *cyclo*Sal-nucleoside monophosphate prodrug approach, we have reported on a successful approach to deliver NDPs inside cells using lipophilic, but still partially charged NDP derivatives (Di*PP*ro-approach **6**; Scheme 1).[29-33] However, although both approaches deliver phosphorylated forms of nucleosides, the released nucleotides still need further phosphorylation into their triphosphate forms by cellular kinases in order to interact with the viral polymerases. As a consequence, the development of NTP prodrugs (Tri*PPP*ro-concept **7**; Scheme 1) is still highly interesting and desirable because this would bypass all steps of intracellular phosphorylation and would in principle maximize the intracellular concentration of the ultimately bioactive NTP

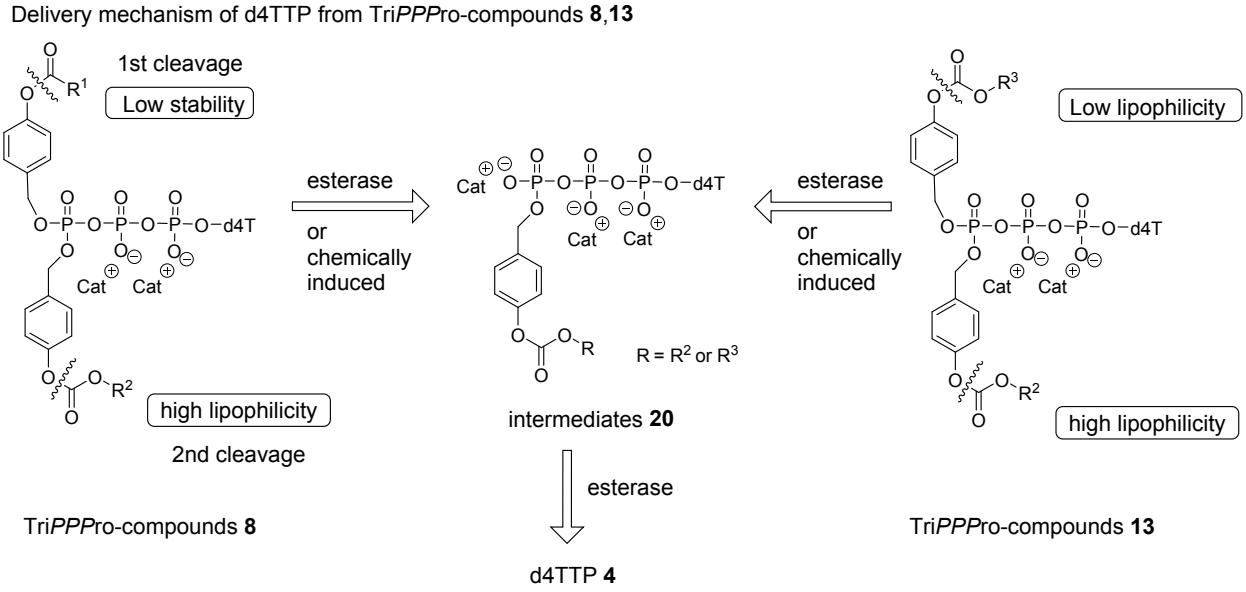
although the formidable challenges are not to be underestimated.[36] A triphosphate has (a) four negative charges that require masking, has (b) an inherent lability within the triphosphate unit due to two reactive phosphate anhydride linkages and (c) the chemical synthesis of a prodrug might be difficult. Earlier, very few reports on potential triphosphate prodrugs have been reported,[37,38] which may be due to their low chemical stability,[39] complicated synthesis, poor deliverability and their high sensitivity for enzymatic dephosphorylation. Recently, we disclosed the first delivery system of NTPs through a prodrug technology (Tri*PPP*ro-approach **7**).[40-42] It was proven for d4T **1** and meanwhile also for other nucleoside analogues that such compounds deliver successfully the corresponding triphosphate inside cells by an uptake study using a fluorescent nucleoside analogue[41] and by the observed significant anti-HIV activity in CEM/TK$^-$ cell cultures whereas the parent **1** was virtually inactive in these cells due to the lack of phosphorylation. The membrane permeability was achieved by esterification of the γ-phosphate group with two covalently attached but bioreversible 4-acceptor-substituted benzyl esters (acyloxybenzyl; AB groups), which led also to a marked increase in enzymatic stability of the triphosphate unit. The enzyme-driven cleavage of both masks by an initial cleavage of the phenolic acyl ester and a subsequent spontaneous cleavage of the remaining part of the mask led to the formation of d4TTP **4** from Tri*PPP*ro-prodrugs **7** (Scheme 2). Further studies showed that the γ-dimasked Tri*PPP*ro-prodrugs were not substrates for polymerases such as HIV-RT or DNA-pol γ.



Scheme 2: Tri*PPP*ro-nucleoside triphosphate prodrugs **7** and the delivery pathway.

Interestingly, in the case of non-symmetric Di*PP*ro-compounds, a highly selective conversion of the Di*PP*ro-compounds into nucleoside analogue diphosphates was finally achieved in CEM cell extracts.[32] We have shown before that the stability of such compounds could be adjusted over a wide range.[30] Moreover, the symmetric Tri*PPP*ro-compounds bearing long alkyl chains such as a 8Z-C17 residue ($t_{1/2}$ = 27 h)[40] proved to be unstable because of altered solubility behavior or micelle formation. 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.[40] These observations guided us here to conduct a study on a series of triphosphate derivatives **8**,**13** bearing two different biodegradable masking units (R^1 or R^3 not identical to R^2). One of the bioreversible groups is an acyloxybenzyl- (AB; ester) or an alkoxycarbonyloxybenzyl- (ACB; carbonate) moiety while the second group is always an ACB-moiety. It was expected that such a combination would be more rapidly cleaved by chemical or particularly by enzymatic means to form the ACB-carbonate-intermediate **20** (Scheme 3) and thereby would help to avoid the side reaction that is responsible for the formation of the unwanted NMP or NDP. The introduced ACB-moiety comprise a long,

lipophilic aliphatic chain, which not only added high lipophilicity to the molecule but also should slowly cleaved to form the triphosphate. It was expected that with these non-symmetric compounds a selective conversion of the Tri*PPP*ro-compounds **8**,**13** into nucleoside triphosphates such as d4TTP **4** can be achieved.



Scheme 3: The prodrug of d4TTP **8**,**13** and the γ-alkoxycarbonyloxybenzyl-modified-d4TTP derivatives **20**.

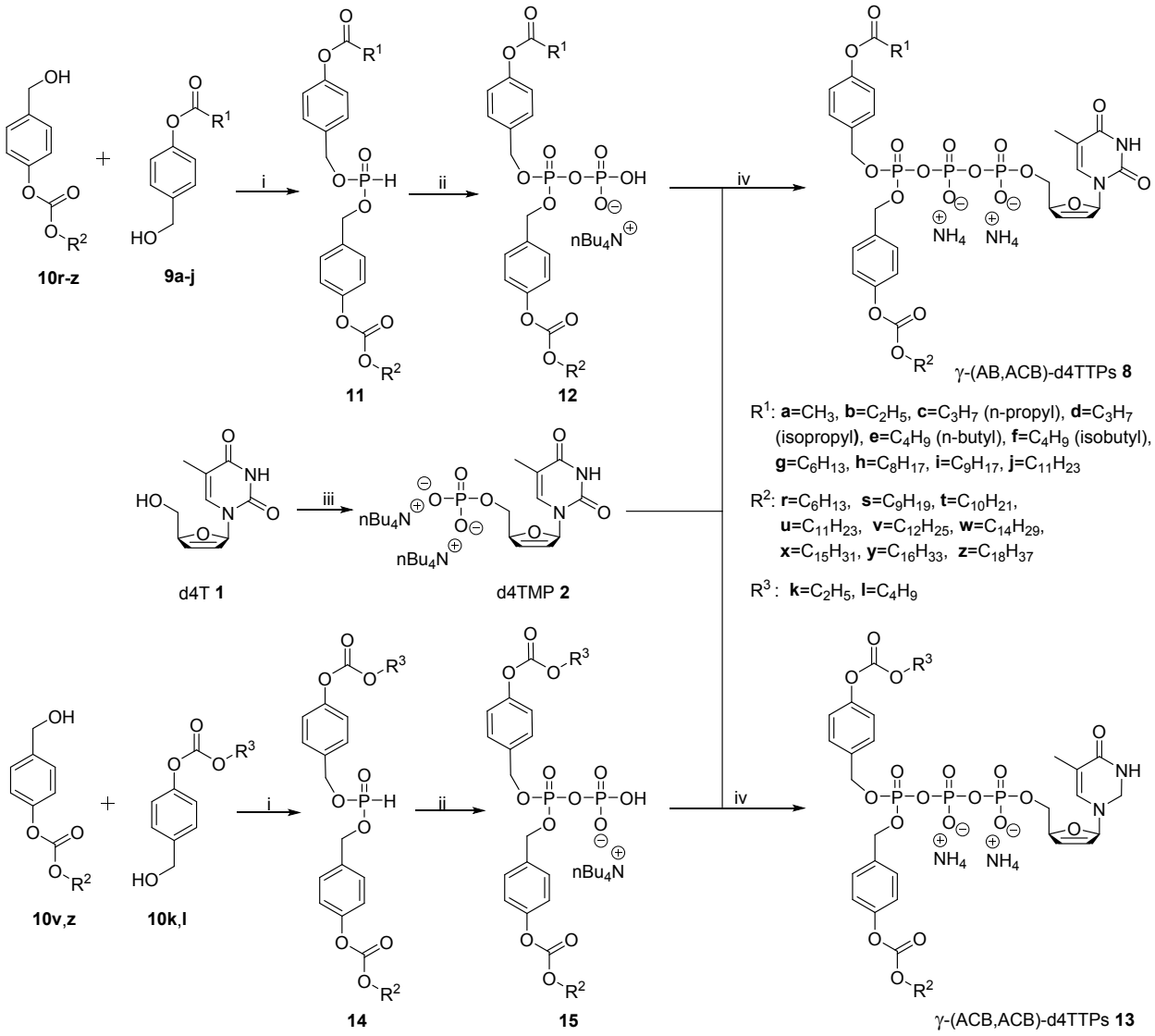
Here we present the synthesis and characterization of these new Tri*PPP*ro-compounds **8**,**13** as well as their hydrolysis behavior in different media and their antiviral activity.

RESULTS AND DISCUSSION.

Synthesis of γ-acyloxybenzyl (AB)-alkoxycarbonyloxybenzyl (ACB)-d4TTPs 8 and γ-(ACB;ACB)-d4TTPs 13

For the synthesis of γ-acyloxybenzyl (AB)-alkoxycarbonyloxybenzyl (ACB)-d4TTPs **8**, the *H*-phosphonate route was used as reported previously by us for the preparation of symmetric

Tri*PPP*ro-derivatives (Scheme 4).[41] In the first step, d4TMP **2** was prepared according to a known procedure.[44] Mixed *H*-phosphonates **11** were prepared from diphenyl hydrogenphosphonate (DPP), 4-acyloxybenzyl alcohols **9** and 4-alkoxycarbonyloxybenzyl alcohols **10**. Next, compounds **11** were converted into the corresponding chlorophosphate using N-chlorosuccinimide (NCS)[45] followed by a phosphorylation with tetra-*n*-butylammonium phosphate to yield pyrophosphates **12** in almost quantitative yield. The final coupling reaction was accomplished using modified literature methods[46,47] by a stepwise activation of **12** with trifluoroacetic acid anhydride (TFAA) and *N*-methylimidazole, followed by addition of d4TMP **2** to give γ-(AB;ACB)-d4TTPs **8** (*n*-Bu_4N^+ form). The different γ-(AB;ACB)-d4TTPs **8** (NH_4^+ form) were isolated as white solids after reversed-phase (rp) column chromatography, a Dowex 50WX8 (NH_4^+) ion exchange and freeze-drying. The advantage of the *H*-phosphonate route used here is that d4TMP was easier to prepare than d4TDP, which was the limiting step in the overall yield of the phosphoramidite method. A second advantage of this route is that after the formation of the P-O-P-linkage, no oxidation is needed in contrast to the phosphoramidite chemistry. The conversion of the parent nucleoside d4T **1** to the target Tri*PPP*ro-compounds **8** was improved and the overall yields varied between 23%-78%. For comparison, three γ-(ACB;ACB)-d4TTPs **13** were synthesized as well using the same approach (Scheme 4). These compounds have two alkoxycarbonyloxybenzyl (ACB)-moieties but bearing different lipophilic alkyloxy residues.

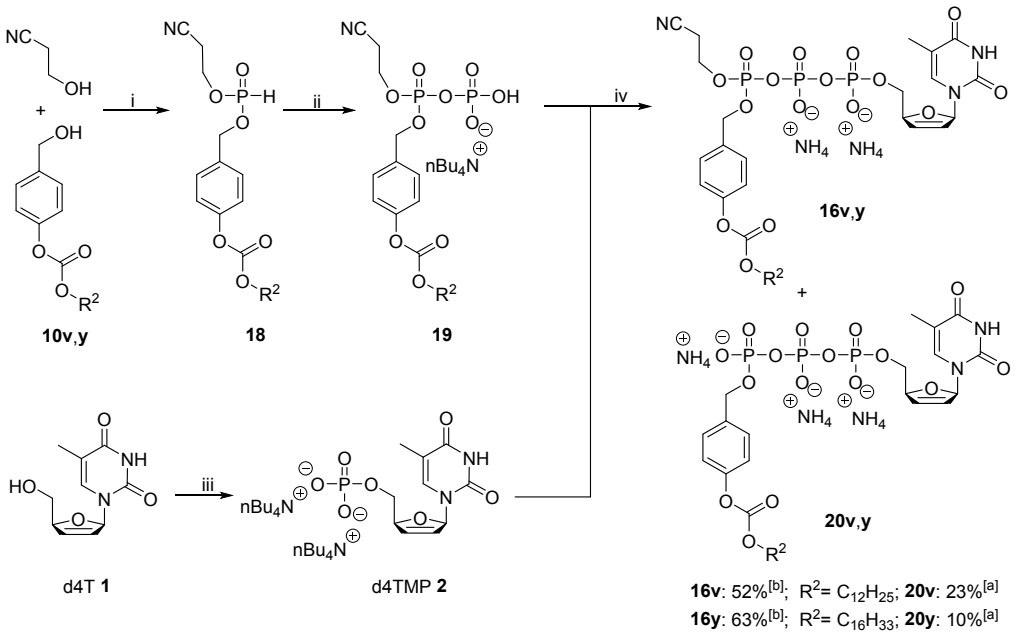


8ay: 50%; **8by**: 51%; **8ey**: 71%; **8fy**: 73%; **8gy**: 50%; **8hy**: 46%; **8iy**: 23%; **8bs**: 51%; **8bt**: 37%; **8bu**: 69%; **8bv**: 43%; **8bw**: 66%; **8cv**: 52%; **8dv**: 44%; **8ev:** 59%; **8ew**: 78%; **8ex**: 74%; **8ez**: 39%; **8is**: 78%; **8jr**: 54%; **13ss**: 70%; **13kv**: 59%; **13lv:** 55%; **13lz**: 52%

Scheme 4. Reagents and conditions: i) DPP, pyridine, 0 °C-rt, 12 h; ii) a. NCS, CH_3CN, rt, 2 h, b) $N(Bu)_4(H_2PO_4)$, CH_3CN, rt, 1 h; iii) d4T **1**, $POCl_3$, pyridine, H_2O, CH_3CN, 0 °C-rt, 5h; iv) a. TFAA, Et_3N, CH_3CN, 0 °C, 10 min, b. 1-methylimidazole, Et_3N, CH_3CN, 0 °C-rt, 10 min, c. d4TMP **2**, rt, 2-5 h.

Synthesis of γ-alkoxycarbonyloxybenzyl (ACB)-d4TTPs 20 and γ-(ACB; β-cyanoethyl)-d4TTPs 16

γ-Alkoxycarbonyloxybenzyl-d4TTPs **20** were synthesized using the *H*-phosphonate route as well. However, the β-cyanoethyl group was introduced as protection group for the γ-phosphate group. In the first step, DPP was successively reacted with 3-hydroxypropionitrile and 4-alkoxycarbonyloxybenzyl alcohols **10** to form *H*-phosphonates **18**. Compounds **18** were converted into the pyrophosphates **19** as above. After the coupling reaction of compounds **19** and d4TMP **3** to give the γ-protected triphosphates **16** (*n*-Bu_4N^+ form), the crude reaction product was deprotected during the ion-exchange to yield the mixture of γ-(ACB; β-cyanoethyl)-d4TTPs **16** (NH_4^+ form) and γ-ACB-d4TTPs **20** (NH_4^+ form). Finally, γ-(ACB)-d4TTPs **20** (NH_4^+ form) were obtained as white solids after rp column chromatography and freeze-drying (Scheme 5).

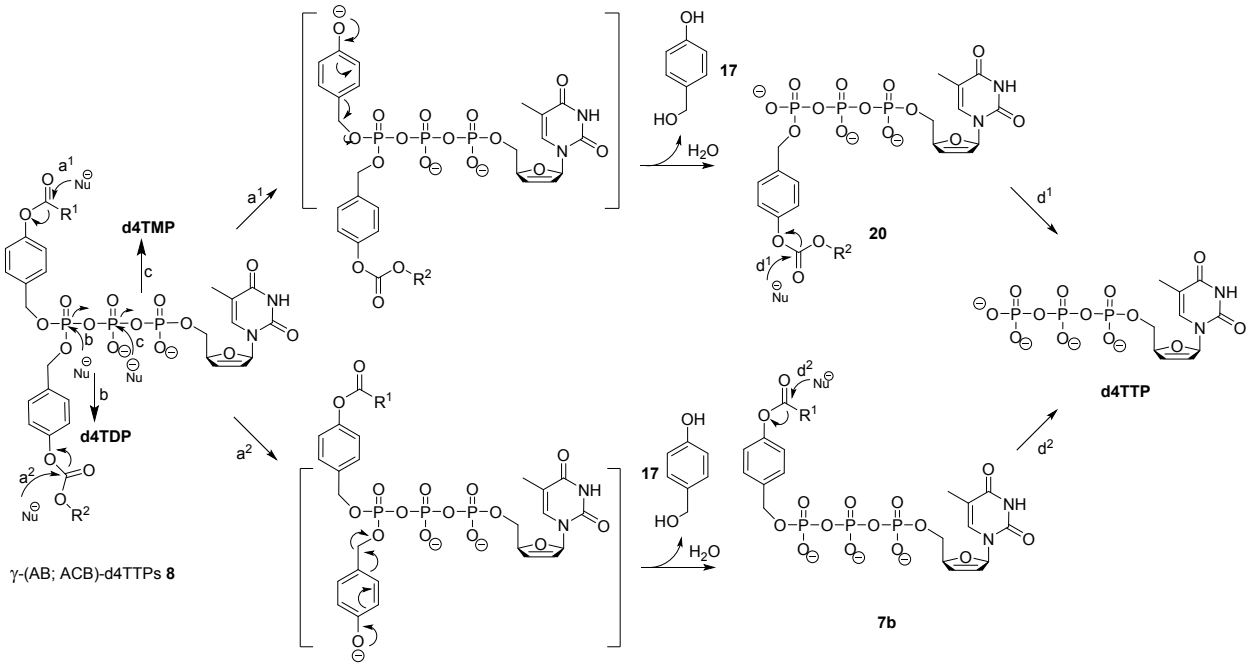


Scheme 5. Reagents and conditions: i) DPP, pyridine, 0 °C-rt, 12 h; ii) a. NCS, CH_3CN, rt, 2 h, b) $N(Bu)_4(H_2PO_4)$, CH_3CN, rt, 1 h; iii) d4T **1**, $POCl_3$, pyridine, H_2O, CH_3CN, 0 °C-rt, 5h; iv) a. TFAA, Et_3N, CH_3CN, 0 °C, 10 min, b. 1-methylimidazole, Et_3N, CH_3CN, 0 °C-rt, 10 min, c.

d4TMP **2**, rt, 5 h. [a] yields are calculated for the conversion from **18** to **20**. [b] yields are calculated for the conversion from **18** to **16**.

Stability studies

The Tri*PPP*ro-d4TTP prodrugs **8**,**13**,**16** and the γ-ACB-d4TTPs **20** were incubated in PBS (25 mM, pH 7.3), or were exposed to human $CD4^+$ T-lymphocyte cell extracts and to pig liver esterase (PLE) to study their stability and to identify the formed hydrolysis products. The hydrolysis mixtures were analyzed by means of analytical RP18-HPLC. The calculated half-lives of prodrugs **8** (Table 1, $t_{1/2}$) reflect either the removal of the bioreversible AB-group or the ACB-group to yield the corresponding intermediates **7b** and **20**, respectively. Possible hydrolysis pathways and products are summarized in Scheme 6.



Scheme 6. Hydrolysis and delivery mechanism of γ-(AB;ACB)-NTP prodrugs **8**.

a. Chemical stability in aqueous phosphate buffer (PBS, pH 7.3).

In PBS, the stability of Tri*PPP*ro-d4TTP prodrugs **8bs**–**8bw** (C2-AB; ACB: C9-C14, Table 1) increased with increasing alkyl chain lengths. However, chemical stabilities of compounds **8ew**–**8ez**,**fy** (C4-AB; ACB: C14-C18) were in the same range as Tri*PPP*ro-d4TTP prodrugs **8cv**–**8dv** (C3-AB; C12-ACB) ($t_{1/2}$= 69-77h, Table 1). The half-lives of intermediates **20** were found to be significantly higher than those of the prodrugs **8**, supposingly caused by repulsive interaction between the increase in negative charges of the intermediate and the approaching nucleophile. Interestingly, as compared to previously studied γ-(C17-AB)-d4TTP **7b** ($t_{1/2}$ = 583 h),[40] the half-lives for γ-(C16-ACB)-d4TTP **20y** ($t_{1/2}$ > 1600 h) was found to be significantly higher by almost a factor of 3. In intermediates γ-(C4-AB)-d4TTP **7be** ($t_{1/2}$ = 270 h)[40] and γ-(C12-ACB)-d4TTP **20v** ($t_{1/2}$ = 625 h), the short alkanoyl ester moieties were more rapidly hydrolyzed as compared to the long alkyl carbonate bearing moieties to form d4TTP **4**. Moreover, in contrast to compounds **8bv** (C2-AB; C12-ACB) and **8ev** (n-C4-AB; C12-ACB), the half-lives of compounds **13kv** (C2-ACB; C12-ACB) and **13lv** (n-C4-ACB; C12-ACB) with two different alkoxycarbonyloxybenzyl groups, which were included for comparative reasons, increased due to altered chemical stability of the two carbonate residues.

Table 1: Half-lives of Tri*PPP*ro-d4TTPs **8**,**13**,**16** and γ-ACB-d4TTPs **20** in PBS, PH 7.3.

Comp.	R^1	R^2	PBS pH=7.3 $t_{1/2}$ [h]	Comp.	R^1 or R^3	R^2	PBS pH=7.3 $t_{1/2}$ [h]
8ay	CH_3	$C_{16}H_{33}$	81	**8ev**	C_4H_9	$C_{12}H_{25}$	87
8by	C_2H_5	$C_{16}H_{33}$	83	**8ew**	C_4H_9	$C_{14}H_{29}$	69
8ey	n-C_4H_9	$C_{16}H_{33}$	74	**8ex**	C_4H_9	$C_{15}H_{31}$	74
8fy	iso-C_4H_9	$C_{16}H_{33}$	77	**8ez**	C_4H_9	$C_{18}H_{37}$	74
8gy	C_6H_{13}	$C_{16}H_{33}$	89	**8is**	C_9H_{19}	C_9H_{19}	81
8hy	C_8H_{17}	$C_{16}H_{33}$	90	**8jr**	$C_{11}H_{23}$	C_6H_{13}	95

8iy	C_9H_{19}	$C_{16}H_{33}$	85	**13ss**	C_9H_{19}	C_9H_{19}	101
8bs	C_2H_5	C_9H_{19}	25	**13kv**	C_2H_5	$C_{12}H_{25}$	84
8bt	C_2H_5	$C_{10}H_{21}$	34	**13lv**	C_4H_9	$C_{12}H_{25}$	107
8bu	C_2H_5	$C_{11}H_{23}$	52	**13lz**	C_4H_9	$C_{18}H_{37}$	111
8bv	C_2H_5	$C_{12}H_{25}$	66	**16v**	C_2H_4CN	$C_{12}H_{25}$	30
8bw	C_2H_5	$C_{14}H_{29}$	74	**16y**	C_2H_4CN	$C_{16}H_{33}$	56
8cv	n-C_3H_7	$C_{12}H_{25}$	75	**20v**		$C_{12}H_{25}$	625
8dv	iso-C_3H_7	$C_{12}H_{25}$	70	**20y**		$C_{16}H_{33}$	>1600
d4TTP			>500				

The hydrolysis experiments of γ-modified-NTP **8**,**13**,**16** and **20** were conducted in aqueous 25 mM phosphate buffer (PBS, pH=7.3). The hydrolysis products were detected by analytical rp18 HPLC.

The cleavage of the AB group or the ACB group was initiated by an ester or a carbonate hydrolysis and thus proceed similar to the previously published cleavage pathway for Tri*PPP*ro-NTPs **7**. However, it can not be excluded that the initial cleavage under chemical conditions proceeded at least in part also by a nucleophilic attack at the benzyl position.[40] Nevertheless, in both cases identical products would be the result.

As an example, the hydrolysis of compound **8by** (C2-AB; C16-ACB) is shown in Figure 1. The chemical hydrolysis was followed over a period of 50 days. Clearly, the starting material disappeared and the expected γ-(C16-ACB)-d4TTP **20y** was formed. The hydrolysis of Tri*PPP*ro-d4TTP prodrugs **8ay**-**8iy** (AB: C1-C9; C16-ACB) in PBS released intermediates γ-(C16-ACB)-d4TTP **20y** and γ-(AB: C1-C9)-d4TTP **7b**, respectively, indicating that both masking groups of Tri*PPP*ro-d4TTP prodrugs **8** were involved in the chemical hydrolysis (pathways a^1 and a^2, Scheme 6). While γ-(C2-AB;C16-ACB)-d4TTPs **8by** is hydrolyzed mainly to γ-(C16-ACB)-d4TTP **20y** with some concomitant cleavage to d4TTP occurring as well. Before complete consumption of the starting material, an increase of d4TTP **4** and γ-(C16-ACB)-d4TTP **20y** concentrations were observed and a very small amount of γ-(C2-AB)-d4TTP was

detected. Because of the very long hydrolysis time periods, also a side-reaction occurred as proven by the appearance of the nucleobase thymine by the cleavage of the glycosidic bond as reported before.[33,40] However, in the case of **13lv** (C4-ACB; C12-ACB), the formation of intermediate γ-(C4-ACB)-d4TTP proceeded with nearly the same rate to γ-(C12-ACB)-d4TTP **20v** (Figure 4, A). In the case of the prodrug **8jr** (C11-AB; C6-ACB), the γ-(C6-ACB)-d4TTP **20r**/γ-(C11-AB)-d4TTP **7bj** ratio was found to be 3:1 (Figure 2, A). The half-lives for γ-(C6-ACB)-d4TTP **20r** ($t_{1/2}$ = 544h) was found to be higher than γ-(C11-AB)-d4TTP **7bj** ($t_{1/2}$ = 460h),[40] which supports that the chemical stability of the carbonate intermediates γ-(ACB)-d4TTP **20** were found to be higher than the corresponding ester intermediates γ-(AB)-d4TTP **7b** (Figure 2, A). Also some d4TDP was formed in this hydrolysis. However, after full conversion of the starting Tri*PPP*ro-compound **8jr**, no further increase of the d4TDP concentration was detected which led to the conclusion that d4TDP was formed directly from the starting compound. The moment a charge appears at the γ-phosphate group due to the cleavage of the first biodegradable masking moiety, the cleavage of the anhydride bond between the β- and the γ-phosphate is prevented. Additionally, no d4TMP could be detected in these hydrolysis studies.

In addition to the two types of bioreversible triphosphate prodrugs, we studied the two β-cyanoethyl-ACB-d4TTP derivatives **16v**,**16y** as well. Both compounds were hydrolysed surprisingly fast and faster than most of the ACB-prodrugs. We concluded that these compounds seem to be cleaved preferentially at the β-cyanoethyl-moiety first and in the second step the ACB-bioreversible groups is hydrolysed. Mechanistically this may happen either by the known β-elimination or a (less probably) nucleophilic attack at the first carbon atom resulting in a substitution reaction leading in both cases to compounds **20v** and **20y**.

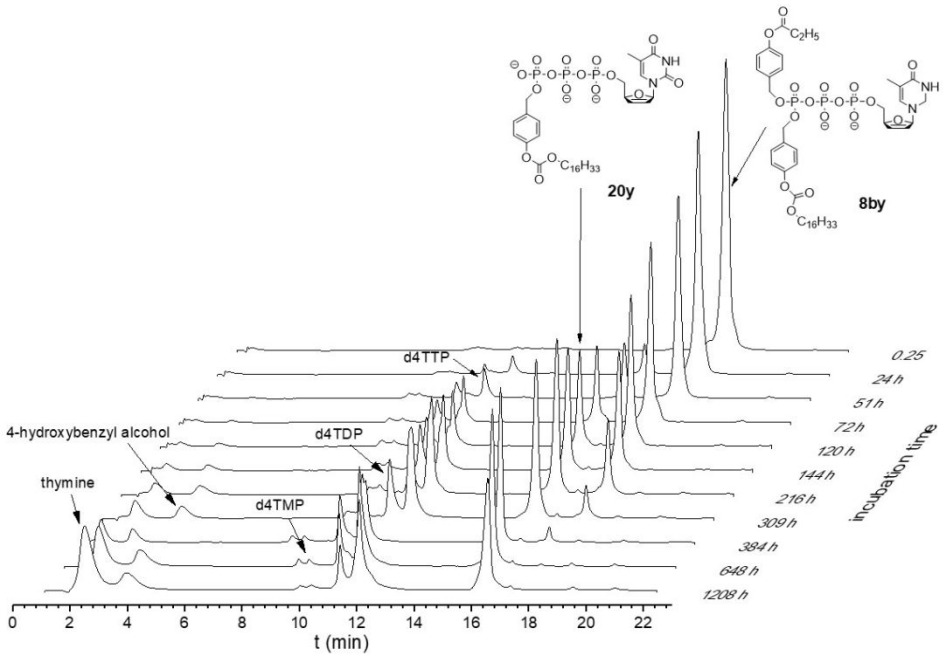
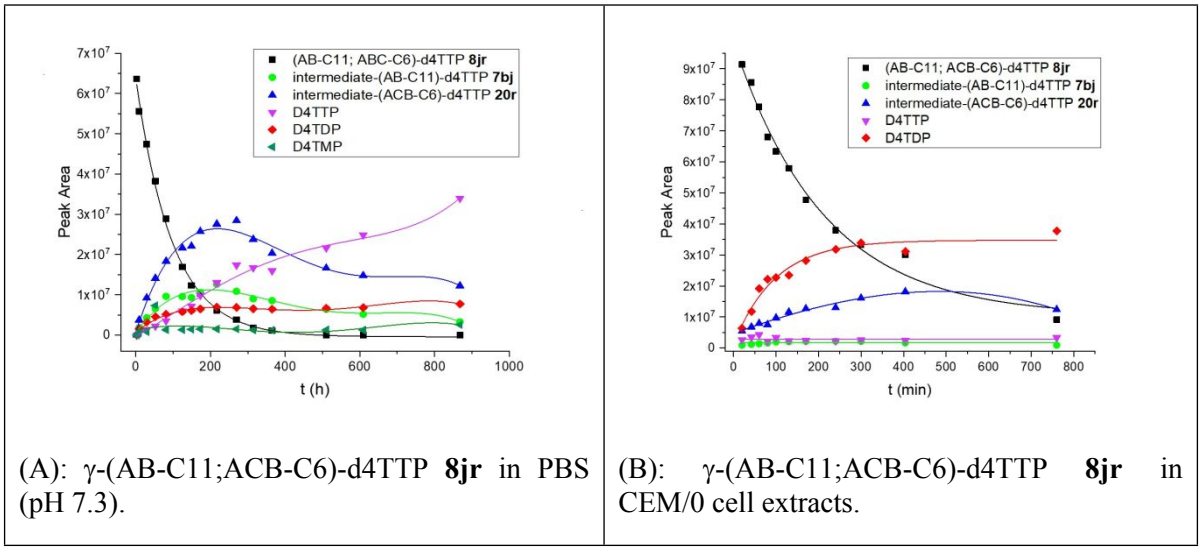
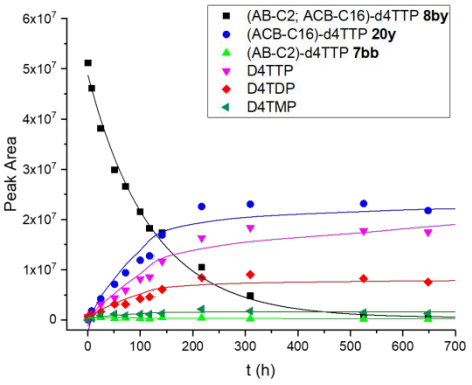


Figure 1: HPLC profile for Tri*PPP*ro-d4TTP prodrug **8by** after incubation in PBS (pH 7.3).

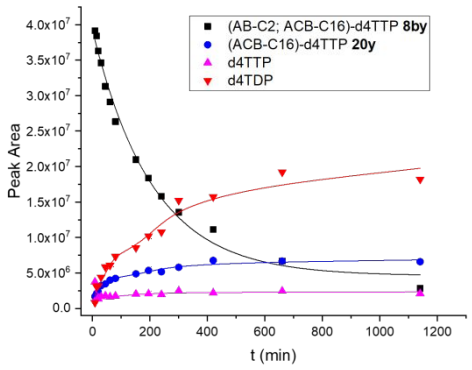


(A): γ-(AB-C11;ACB-C6)-d4TTP **8jr** in PBS (pH 7.3).

(B): γ-(AB-C11;ACB-C6)-d4TTP **8jr** in CEM/0 cell extracts.



(C): γ-(AB-C2;ACB-C16)-d4TTP **8by** in PBS (pH 7.3).



(D): γ-(AB-C2;ACB-C16)-d4TTP **8by** in CEM/0 cell extracts.

Figure 2: Hydrolysis study of **8jr** in PBS (pH 7.3) and in CEM/0 cell extracts.

b. Hydrolysis study using Esterase.

Tri*PPP*ro-d4TTP prodrugs **8** bearing as R^1 a C_2H_5 or a C_4H_9 residue in the AB-group in combination with long alkyl chains in the carbonate masking group such as the $OC_{12}H_{25}$ or the $OC_{16}H_{33}$ residue were incubated with PLE in phosphate buffer (pH 7.3) to investigate the impact of the chain length on the enzymatic cleavage by this esterase and to study the chemoselectivity. The hydrolysis of Tri*PPP*ro-compound **8by** (C2-AB;C16-ACB) in PLE is shown in Figure 3, which was in agreement with the results obtained from the studies of compounds **8by** in PBS. As can be seen in Figure 3, there is a highly selective cleavage of one biodegradable moiety which led to the formation of intermediate **20y**. Intermediate **20y** first accumulated and later is cleaved as well and finally formed d4TTP. Almost no d4TDP and no d4TMP was detected. Furthermore, Tri*PPP*ro-d4TTP prodrug **13kv** (C2-ACB; C12-ACB) was also included to study whether the attached two different carbonate functional group have an effect on the hydrolysis pathway or on the compound stability. As compared to the chemical hydrolyses, all compounds were rapidly hydrolyzed and delivered the nucleoside triphosphates d4TTP much faster than in PBS,

demonstrating a significant contribution of the enzymatic cleavage (Table 2). The half-lives determined for compounds **8bv** (C2-AB; C12-ACB), **8by** (C2-AB; C16-ACB) as well as **8ev** (C4-AB; C12-ABC) and **8ey** (C4-AB; C16-ACB) increased with increasing of the alkyl carbonate chain lengths (R^2). In contrast to the above study with the $OC_{16}H_{33}$-bearing Tri*PPP*ro-compounds **8by**,**8ey**, here the slightly longer aliphatic chain (R^1=C_4H_9) in the AB moiety was cleaved faster than the short chain acyl group (R^1=C_2H_5). The cleavage of the acyloxybenzyl masking unit in **8ev** (C4-AB;C12-ABC) occurred readily under the experimental conditions ($t_{1/2}$ = 0.17 h) leading selectively to the formation of γ-(C12-ACB)-d4TTP **20v**. Moreover, for prodrug **8hy** (C8-AB;C16-ABC) containing a long alkyl chain, the half-life was found to be 13.8 h. Again, the Tri*PPP*ro-NTPs **8** proved to be more stable as compared to the studies of Tri*PPP*ro-compounds **7** described before.[40] Remarkably, in the case of the hydrolysis of compound **13lv** (C4-ACB;C12-ABC) as compared to the hydrolysis in PBS, both hydrolysis intermediates bearing the long aliphatic chain were formed, although in markedly different amounts as can be seen in Figure 4 (B). In chemical hydrolysis also both possible intermediates were formed but in almost identical amounts (Figure 4; A).

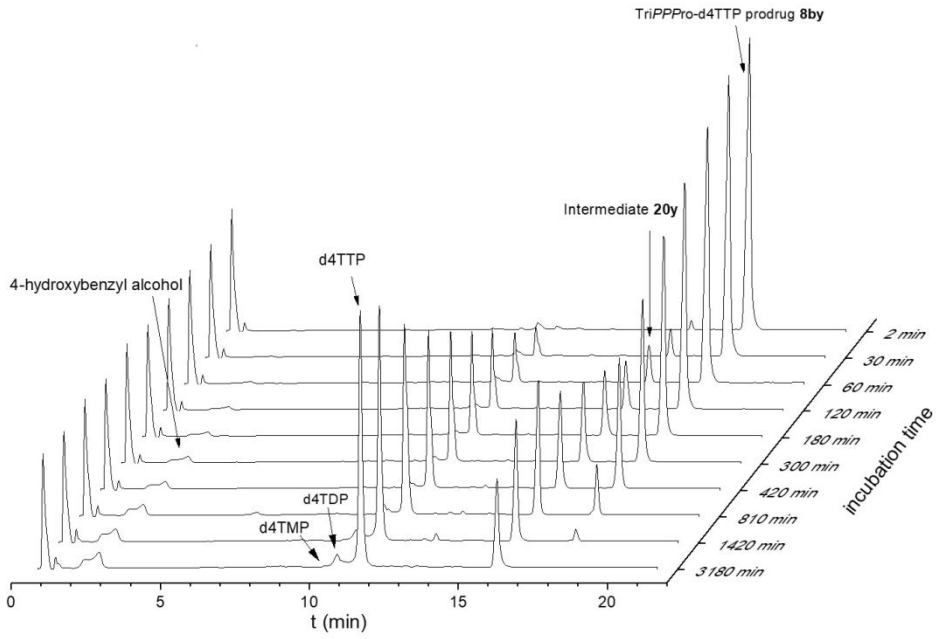
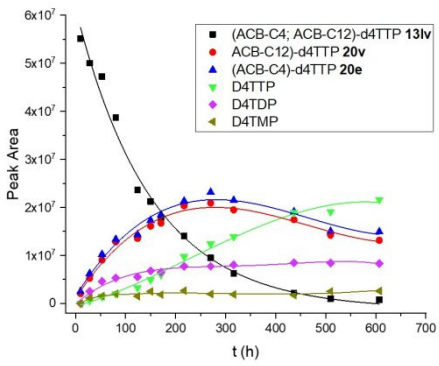
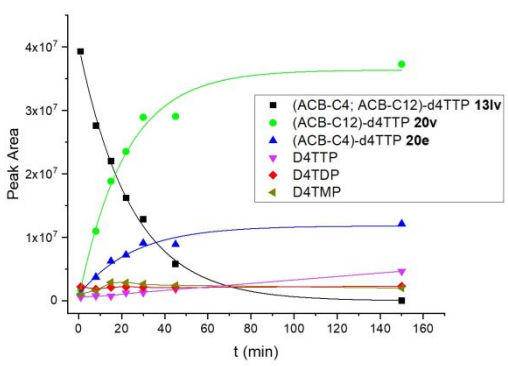


Figure 3: HPLC profile for Tri*PPP*ro-d4TTP prodrug **8by** after incubation in PLE.



(A): γ-(ACB-C4;ACB-C12)-d4TTP **13lv** in PBS.



(B): γ-(ACB-C4;ACB-C12)-d4TTP **13lv** in PLE.

Figure 4: Hydrolysis study of **13lv** in PBS (PH 7.3) and PLE.

Table 2. Half-lives of Tri*PPP*ro-d4TTPs **8** and **13** in the presence of PLE and CEM/0 cell extracts.

Comp.	CEM/0 cell extracts $t_{1/2}$ [h]	PLE $t_{1/2}$ [h]	Comp.	CEM/0 cell extracts $t_{1/2}$ [h]	PLE $t_{1/2}$ [h]
8by	1.9	4.7	**8ev**	1.2	0.17
8ey	3.7	1.6	**8jr**	2.5	n.d.[a]
8hy	6.4	13.8	**13kv**	0.94	0.51
8bv	n.d.[a]	0.44	**13lv**	n.d.[a]	0.28

[a]n.d.: not determined.

c. Hydrolysis in cell extracts.

The hydrolysis of the prodrugs **8**,**13** was further investigated in human $CD4^+$ T-lymphocyte CEM cell extracts. Again, the half-lives of the prodrugs correlated well with the chain length and were found to be significantly lower than the half-lives in PBS. Here, half-lives as low as 0.94 h (**13kv**) to 6.4 h (**8hy**) were determined which clearly points as in the PLE studies to an enzymatic cleavage (Table 2). The prodrug **8by** (C2-AB; C16-ACB) comprising a short AB-group in the prodrug moiety was found to be more readily cleaved to form intermediate γ-(C16-ACB)-d4TTP **20y** shown in Figure 5. In addition, the amount of d4TDP increased most probably because of the presence of dephosphorylating enzymes such as phosphatases/kinases, which is in accordance to our previous results of the Di*PP*ro- or the Tri*PPP*ro-compounds **7**. There, it was almost impossible to detect significant concentrations of d4TTP due to its fast dephosphorylation ($t_{1/2}$= 38 min) to form first d4TDP **3** and ultimately d4TMP **2**. Interestingly, in the case of the hydrolysis of Tri*PPP*ro-prodrug **8jr** (C11-AB; C6-ABC) as compared to the hydrolysis in PBS, γ-(C6-ACB)-d4TTP **20r** was also detected as the main monomasked intermediate product

(Figure 2, B). After 8 h incubation, the ratio of γ-(C6-ACB)-d4TTP and γ-(C11-AB)-d4TTP was 10:1. This means that an almost selective cleavage process took place in cell extracts with the AB-moiety being cleaved first. This was in sharp contrast to the studies performed with Tri*PPP*ro-compounds **7**.

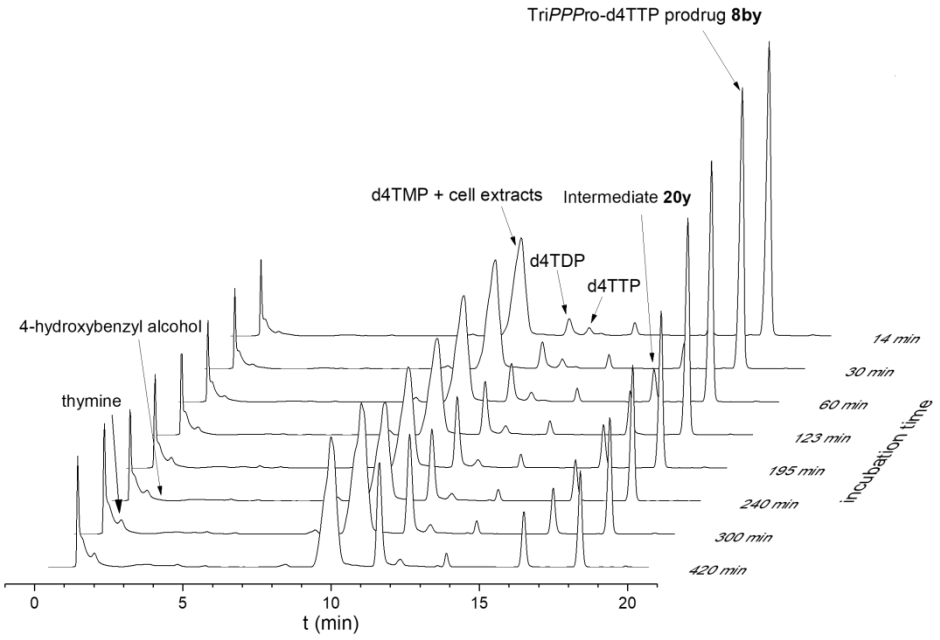


Figure 5: HPLC profile of compound **8by** after incubation in CEM/0 cell extracts at different times.

d. Antiviral evaluation.

Tri*PPP*ro-d4TTP prodrugs **8**,**13**,**16** and γ-alkoxycarbonyloxybenzyl-d4TTPs **20** were evaluated for their activity to inhibit the 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 3 summarizes the antiviral and cytostatic data of the Tri*PPP*ro-d4TTP prodrugs **8**,**13**,**16**, γ-

ACB-d4TTPs **20** and the parent nucleoside analogues d4T **1** as reference compound. As can be seen, most of the Tri*PPP*ro-d4TTP prodrugs showed virtually similar or even slightly better activities against HIV-1 and HIV-2 than the parent nucleoside d4T **1** in wild-type CEM/O cells. In addition and more importantly, all Tri*PPP*ro-d4TTP prodrugs **8**,**13** 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 (EC_{50}: 31.05 μM). However, as compared to Tri*PPP*ro-d4TTP prodrug **8by** (C2-AB; C16-ACB), no increased antiviral activity of prodrug **8iy** (C9-AB; C16-ACB) was observed, although the compound is more lipophilic but maybe also too low in solubility. D4TTP derivatives **8bs-8by** or **8ev-8ez** 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. The three Tri*PPP*ro-compounds comprising either two OC9 chains (**13ss**), C9-AB and C9-ACB alkyl group (**8is**) or a mixture of a short C6-ACB and a long C11-AB alkyl group (**8jr**) were also active in TK-deficient CEM cells in contrast to the parent d4T and d4TTP. Interestingly, Tri*PPP*ro-d4TTP prodrugs **8is** (C9-AB;C9-ACB) and **8jr** (C11-AB;C6-ACB) also showed marked activity in TK-deficient cell cultures due to sufficient lipophilicity of the compounds combined with a relatively slow cleavage of the bioreversible moieties which led to the formation of different long-chain γ-modified-d4TTPs. The β-cyanoethyl-comprising compounds **16** and even more interestingly the monomasked γ-ACB-d4TTPs **20** were found to be in the same range antivirally active in CEM/TK$^-$ cell cultures although the latter compound has an additional charge as compared to all the other prodrugs. 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-d4TTP prodrugs. It should also be noticed that *none* of the Tri*PPP*ro-

d4TTP prodrugs **8**,**13**,**16** and γ-ACB-d4TTPs **20** were endowed with a marked cytotoxicity compared to the parent d4T **1**. Compounds **16v** and **20v** (CC_{50}^{b} [μM] >100) exhibited even lower toxicity than d4T **1**. However, it should be mentioned that it can not be excluded that the antiviral activity observed in the infected CEM/TK^{-}deficient cells is at least in part due to the formation of d4TMP and d4TDP. As seen in the hydrolysis studies particularly in the cell extracts, the d4TTP is quickly dephosphorylated to give d4TDP and d4TMP. So, during the assay the delivered triphosphate as well as the rephosphorylated d4TMP and d4TDP are most probably responsible for the observed antiviral effect.

Table 3. Antiviral activity and cytotoxicity of Tri*PPP*ro-d4TTPs **8**,**13**,**16** and γ-ACB-d4TTPs **20** in comparison with the parent nucleoside d4T **1**.

Comp.	HIV-1 (HE)	HIV-2 (ROD)	CEM/TK^{-} HIV-2 (ROD)	cellular toxicity	selectivity index (SI)
	EC_{50}^{a} [μM]	EC_{50}^{a} [μM]	EC_{50}^{a} [μM]	CC_{50}^{b} [μM]	
8by	0.027 ± 0.0092	0.0048 ± 0.0065	0.11 ± 0.0071	34 ± 9.3	1259
8ey	0.032 ± 0.017	0.014 ± 0.015	0.12 ± 0.048	21 ± 17	656
8iy	0.16 ± 0.085	0.078 ± 0.044	0.24 ± 0.0071	16 ± 1.1	100
8bs	0.073±0.028	0.040±0.011	1.76±0.13	84±23	1150
8bv	0.061±0.027	0.13±0.072	0.64±0.12	33±21	541
8ev	0.040 ± 0.029	0.017 ± 0.015	0.073 ± 0.036	27 ± 4.9	675
8ez	0.055±0.006	0.025±0.007	0.56±0.13	58±22	1054
8is	0.11±0.021	0.09±0.011	0.15±0.02	37±2	336
8jr	0.30±0.18	0.07±0.003	0.21±0.02	41±9	137
13ss	0.34±0.24	0.09±0.03	0.23±0.11	34±2	100
13kv	0.57±0.33	0.24±0.17	1.75±0.25	64±16	112
13lv	0.73±0.53	0.17±0.014	1.12±0.21	54±13	74
16v	0.47±0.29	0.23±0.021	2.48±0.46	>100	>212
16y	0.53±0.26	0.30±0.05	3.26±0.28	53±22	100
20v	0.33±0.13	0.25±0.06	1.98±1.67	>100	>303

20y	0.50±0.29	0.29±0.06	1.46±1.34	61±36	122
d4T	0.43±0.23	0.31±0.13	31.05±5.25	>50	>116

[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.

The cleavage product in all cases is 4-hydroxybenzyl alcohol which is known to be mainly and quickly oxidized to 4-hydroxybenzoic acid which is a non-toxic compound. Previously, this compound has been added to the antiviral assays and CC50 values >100 μM were observed. However, from the report, when applying the water-soluble tetrazolium (WST-1) assay to eEND2 cells incubated with a range of concentrations of 4-hydroxybenzyl alcohol, a loss in cell viability was found with a LD 50 of ~50 mM. In line with these findings, cytotoxicity of 4-hydroxybenzyl alcohol progressively increased between 1 and 100 mM, as indicated by an enhanced lactate dehydrogenase (LDH) release from damaged eEND2 cells. However, these are concentrations that are about a 1000-fold higher than the concentration that we generate with our compounds.[48]

CONCLUSIONS

In summary, Tri*PPP*ro-NTPs **8** and **13** of the nucleoside analogue d4T **1** bearing two different biodegradable masking units attached to the γ-phosphate group of the corresponding nucleoside triphosphate are disclosed here. The Tri*PPP*ro-d4TTP prodrugs **8**,**13** were synthesized using the *H*-phosphonate approach described previously with modest to high yields (up to 78%). Most of the enzyme-cleavable Tri*PPP*ro-d4TTPs **8**,**13** were as active as or even more active against HIV-1 and HIV-2 in wild-type CEM/0 cell cultures. Moreover, also high activities were obtained depending on the lipophilicity of the Tri*PPP*ro-d4TTP prodrugs **8**,**13** against HIV-2 in mutant

CEM/ TK^- cell cultures. Interestingly, as compared to the symmetric ester bearing AB groups Tri*PPP*ro-NTPs **7** with two identical acyloxybenzyl masks reported previously,[40,41] we have proven that the AB-prodrug group was more readily cleaved to give γ-(C_nH_{2n+1}-ACB)-nucleoside triphosphates **20** by chemical hydrolysis (slow process) and in particular by cell extract enzymes (fast process). The extent of differentiation was dependent on the medium. It is lower in PBS but very pronounced in PLE.

The γ-alkoxycarbonyloxybenzyl (ACB)-d4TTPs **20** were also highly potent in CEM/TK^- cell cultures. This confirmed that these compounds were taken-up by the cells and delivered intracellularly a phosphorylated form of d4T, most likely d4T triphosphate or it acted as such. Thus, 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. We disclosed the non-symmetric 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. This concept is warrant to be applied to nucleoside analogues that show severe limitations in their activation to give the corresponding nucleoside triphosphates, e.g. nucleoside analogs such as AZT or FTC. We are convinced 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, PK studies, testing phases and the development of reaction routes that allow production of industrial size quantities of the compounds.

EXPERIMENTAL SECTION

General: All experiments involving water-sensitive compounds were carried out under anhydride conditions and nitrogen atmosphere. *Solvents and Reagents*: Acetonitrile, pyridine and THF were purchased from Acros Organics (Extra Dry over molecular sieves) and dried with activated molecular sieves. 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 commercially available were used as received. *Thin layer chromatography (TLC):* For thin layer chromatography Macherey-Nagel pre-coated TLC sheets Alugram® Xtra SIL G/UV254 were used. *Column chromatography:* Normal phase column chromatography were performed with Macherey-Nagel silica gel 60 M (0.04-0.063 mm). *Automatic RP-18 chromatography:* For reversed phase chromatography an Interchim Puriflash 430 in combination with Chromabond® Flash RS40 C_{18} ec was used. *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 or Nucleodur 100-5 C_8ec (Macherey-Nagel) was available. Acetonitrile for HPLC was obtained from VWR (HPLC grade) and ultrapure water was produced by a Sartorius Aurium® pro (Sartopore 0.2 µm, UV). 2 mM tetra-*n*-Butylammonium acetate solution (TBAA, pH 6.3) or 10 mM triethylammonium acetate (TEAA, pH 6.2) were used for buffering. Method: Nucleodur 100-5 C18ec; 0-20 min: TBAA buffer/acetonitrile gradient (5-80%); 20-30 min: buffer/acetonitrile (80%); 30-33 min: buffer/acetonitrile (80-5%); 33-38 min: buffer/acetonitrile (5%); flow: 1 mL/min. Compound purity: All final compounds were isolated analytically pure, ≥95% purity by HPLC and NMR spectroscopy.

Nuclear Magnetic Resonance (NMR): 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. *Mass Spectrometry (MS)*: HRMS (ESI) mass spectra were acquired with a VG Analytical Finnigan ThermoQuest MAT 95 XL or an Agilent 6224 EIS-TOF spectrometer. MALDI measurements (matrix: 9-aminoacridine [9-AA] or 2,5-dihydroxybenzoic acid [DHB]) were performed with a Bruker UltrafleXtreme spectrometer. *Infrared spectroscopy (IR)*: IR spectra were recorded on a Bruker Alpha P FT-IR at room temperature in the range of 400-4000 cm^{-1}.

Syntheses and characterization

The syntheses and characterization of 4-(hydroxymethyl)phenylalkanoates **9** were described previously.[29,32] The synthesis of (n-$Bu_4N)_2$▪d4TMP **2** was performed using the Sowa-Ouichi procedure starting from d4T **1**.[44]

General Procedure 1: Preparation of 4-(hydroxymethyl)phenylalkylcarbonate 10.

a) The reactions carried out under nitrogen (N_2) atmosphere under dry conditions. A mixture of triphosgene (1.0 equiv.), K_2CO_3 (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 $C_nH_{2n+1}OH$ 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. b) 4-Hydroxybenzyl alcohol **17** and

trimethylamine (TEA) in DCM or THF were cooled to 0 °C. The corresponding alkyl chloroformate in DCM 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 $MgSO_4$ and the solvent was removed in vaccum. The crude material was purified using column chromatography to give compound 4-(hydroxymethyl)phenylalkylcarbonate **10**.

General Procedure 2: Preparation of *H*-phosphonate 11

General Procedure b1: Under dry conditions, diphenyl *H*-phosphonate (DPP, 1.0 equiv.) was dissolved pyridine and cooled to 0 °C. 4-(Hydroxymethyl)phenylalkanoate **9** (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 **10** (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 EtOAc/petroleum ether/0.5% acetic acid as eluent.

General Procedure b2: Under dry conditions, DPP (1.0 equiv.) was dissolved in pyridine and cooled to 0 °C. 4-(Hydroxymethyl)phenylalkylcarbonate **10** (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-(hydroxymethyl)phenylalkanoate **9** (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 EtOAc/petroleum ether/0.5% acetic acid as eluent.

General Procedure 3: Preparation of γ-(AB;ACB)-d4TTPs 8 and γ-(ACB;ACB)-d4TTPs 13

The reactions were performed in a nitrogen (N_2) atmosphere and dry conditions. a) *H*-phosphonate (1.0 equiv.) was dissolved in 3 mL CH_3CN and *N*-chlorosuccinimide (NCS, 2.0 equiv.) was added. After stirring for 2 h at room temperature, tetrabutylammonium phosphate

solution (0.4 M in acetonitrile) (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, 5.0 equiv.) and Et_3N (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 (3.0 equiv.) and Et_3N (TEA, 5.0 equiv.) was added. The mixture was warmed to room temperature and stirred for 10 min. The resulting activated imidazolidate formed and d4TMP (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.

Synthesis of 4-(hydroxymethyl)phenylalkylcarbonate 10.

Butyl (4-(hydroxymethyl)phenyl) carbonate 10l

According to general procedure 1 with 4.47 g 4-hydroxybenzyl alcohol **17** (36 mmol, 1.0 equiv.) and 5.0 mL triethylamine (36 mmol, 1.0 equiv.) in 40 mL THF at 0 °C and dropwise addition of 4.6 mL butyl chloroformate (36 mmol, 1.0 equiv.) in 10 mL THF. 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. ^{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, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 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). HRMS (ESI^+, m/z): calculated for $C_{12}H_{16}O_4$, $[M+Na]^+$ 247.0941; found 247.0901. IR: ν [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 10r

According to general procedure 1 with 1.48 g triphosgene (5.0 mmol, 1.0 equiv.), 1.38 g K_2CO_3 (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 **17** (9.1 mmol, 1.1 equiv.) and 1.15 mL TEA (8.3 mmol 1.0 equiv.) in 10 mL DCM were cooled to 0 °C followed by a dropwise addition of hexyl chloroformate (8.3 mmol, 1.0 equiv.) in 10 mL DCM. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v). Yield: 1.60 g (6.4 mmol, 77%) white solid. ^{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, $^{3}J_{HH}$= 6.7 Hz, 2H, H-g), 2.55 (s, 1H, OH), 1.73 (quint, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 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). HRMS (ESI^+, m/z): calculated for $C_{14}H_{20}O_4$, $[M+Na]^+$ 275.1254; found 275.1234. IR: ν [cm^{-1}] = 3387, 2957, 2929,

2871, 2157, 1757, 1607, 1508, 1466, 1392, 1247, 1209, 1046, 1014, 920, 848, 779, 603, 504, 404.

4-(Hydroxymethyl)phenyl nonyl carbonate 10s

According to general procedure 1 with 2.97 g triphosgene (10.0 mmol, 1.0 equiv), 2.76 g K_2CO_3 (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 **17** (5.9 mmol, 1.1 equiv.) and 0.74 mL TEA (5.3 mmol 1.0 equiv.) in 10 mL DCM were cooled to 0 °C followed by a dropwise addition of nonyl chloroformate (5.3 mmol, 1.0 equiv.) in 10 mL DCM. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v). Yield: 1.10 g (10.5 mmol, 70%) white solid. ^{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). HRMS (ESI$^+$, m/z): calculated for $C_{17}H_{26}O_4$, $[M+Na]^+$ 317.1723; found 317.1701. IR: ν [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 10t

According to general procedure 1 with 4.45 g triphosgene (15.0 mmol, 1.0 equiv.), 4.15 g K_2CO_3 (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 **17** (21.5 mmol, 1.1 equiv.) and 2.72 mL TEA (19.5 mmol 1.0 equiv.) in 20 mL DCM were cooled to 0 °C followed by a dropwise addition of decyl chloroformate (19.5 mmol, 1.0 equiv.) in 20 mL DCM. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v). Yield: 4.89 g (6.4 mmol, 81.5%) yellow solid. ^{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, $^{3}J_{HH}$= 6.7 Hz, 2H, H-g), 2.13 (s, 1H, OH), 1.74 (quint, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 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, $^{4}J_{CP}$= 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). HRMS (ESI$^+$, m/z): calculated for $C_{18}H_{28}O_4$, $[M+Na]^+$ 331.1880; found 331.1872. 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 10u

According to general procedure 1 with 5.10 g triphosgene (17.1 mmol, 1.0 equiv), 4.56 g K_2CO_3 (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 **17** (30.9 mmol, 1.1 equiv.) and TEA (28.1 mmol 1.0 equiv.) in 30 mL DCM were cooled to 0 °C. Dropwise addition of undecyl chloroformate (28.1 mmol, 1.0 equiv.) in 30 mL DCM. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v). Yield: 4.80 g (13.8 mmol, 49%) white solid. ^{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). HRMS (ESI$^+$, m/z): calculated for $C_{19}H_{30}O_4$, $[M+Na]^+$ 345.2036; found 345.1980. IR: ν [cm^{-1}] = 3274, 2955, 2916, 2848, 1750, 1506, 1464, 1397, 1255, 1214, 1041, 1013, 955, 820, 776, 720, 521, 472.

4-(Hydroxymethyl)phenyl tetradecyl carbonate 10w

According to general procedure 1 with 4.45 g triphosgene (15.0 mmol, 1.0 equiv), 4.15 g K_2CO_3 (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 **17** (17.9 mmol, 1.1 equiv.) and 2.3 mL TEA (16.3 mmol 1.0 equiv.) in 20 mL DCM were cooled to 0 °C. Dropwise addition of tetradecyl chloroformate (16.3 mmol, 1.0 equiv.) in 20 mL DCM. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v). Yield: 5.30 g (14.5 mmol, 89%) white solid. ^{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).

HRMS (ESI$^+$, m/z): calculated for $C_{22}H_{36}O_4$, $[M+Na]^+$ 387.2506; found 387.2398. 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 10x

According to general procedure 1 with 1.61 g triphosgene (5.4 mmol, 1.0 equiv.), 1.49 g K_2CO_3 (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 **17** (9.0 mmol, 1.1 equiv.) and 1.18 mL TEA (8.2 mmol 1.0 equiv.) in 10 mL DCM were cooled to 0 °C. Dropwise addition of pentadecyl chloroformate (8.2 mmol, 1.0 equiv.) in 10 mL DCM. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v). Yield: 2.54 g (6.7 mmol, 82%) white solid. ^{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). HRMS (ESI$^+$, m/z): calculated for $C_{23}H_{38}O_4$, $[M+Na]^+$ 401.2662; found 401.2557. 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 10y

According to general procedure 1 with 2.97 g triphosgene (10 mmol, 1.0 equiv), 2.76 g K_2CO_3 (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 **17** (14.9 mmol, 1.1 equiv.) and 1.88 mL TEA (13.5 mmol 1.0 equiv.) in 30 mL DCM were cooled to 0 °C. Dropwise addition of hexadecyl chloroformate (13.5 mmol, 1.0 equiv.) in 20 mL DCM. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v). Yield: 3.60 g (9.2 mmol, 68%) white solid. ^{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). HRMS (ESI$^+$, m/z): calculated for $C_{24}H_{40}O_4$, $[M+Na]^+$ 415.2819; found 415.2831. 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 10z

According to general procedure 1, with 2.97 g triphosgene (10 mmol, 1.0 equiv), 2.76 g K_2CO_3 (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 **17** (18 mmol, 1.2 equiv.) and

2.1 mL TEA (15 mmol 1.0 equiv.) in 30 mL DCM were cooled to 0 °C. Dropwise addition of octadecyl chloroformate (15 mmol, 1.0 equiv.) in 20 mL DCM. Column chromatography (petroleum ether/ethyl acetate 8:2 v/v). Yield: 4.00 g (10.5 mmol, 70%) white solid. ^{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). HRMS (ESI^+, m/z): calculated for $C_{26}H_{44}O_4$, $[M+Na]^+$ 443.3132; found 443.3102. IR: ν [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.

(C1-AB; C16-ACB)-*H*-phosphonate 11ay

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.27 g 4-(hydroxymethyl)phenyl acetate **9a** (1.65 mmol, 1.05 equiv.) was added and following with 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **10y** (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. ^{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, PH), 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 H_Z, $^{3}J_{CP}$= 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 H_Z, $^{3}J_{CP}$= 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. HRMS (ESI^+, m/z): calculated for $C_{33}H_{49}O_8P$, $[M+Na]^+$ 627.3057; found 627.3078. 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.

(C2-AB; C16-ACB)-*H*-phosphonate 11by

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **9b** (1.65 mmol, 1.05 equiv.) was added and following with 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **10y** (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. ^{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, $^{1}J_{HP}$= 709.6 Hz, 1H, PH), 5.10-4.95 (m, 4H, H-a^1, H-a^2), 4.22 (t, $^{3}J_{HH}$= 6.8 Hz, 2H, H-g^2), 2.56 (q, $^{3}J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.74 (quint, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 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, $^{3}J_{CP}$= 5.9 H_Z, $^{3}J_{CP}$= 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, $^{3}J_{CP}$= 5.5 H_Z, $^{3}J_{CP}$= 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. HRMS (ESI^+, m/z): calculated for $C_{34}H_{51}O_8P$, $[M+Na]^+$ 641.3214; found 641.3149. IR: ν [cm^{-1}] = 2924, 2853, 1758, 1711, 1610, 1509, 1463, 1390, 1359, 1249, 1218, 1143, 958, 892, 780, 606, 504, 479, 451.

(C4-AB;C16-ACB)-*H*-phosphonate 11ey

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.34 g 4-(hydroxymethyl)phenyl pentanoate **9e** (1.65 mmol, 1.05 equiv.) was added and following with 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **10y** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI^+, m/z): calculated for $C_{36}H_{55}O_8P$, $[M+Na]^+$ 669.3530; found 669.3506. IR: ν [cm^{-1}] = 2956, 2915, 2872, 2849, 1753, 1607, 1509, 1465, 1382, 1285, 1218, 1168, 1056, 996, 961, 835, 786, 719, 506, 452.

(C4-AB; C16-ACB)-*H*-phosphonate 11fy

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.34 g 4-(hydroxymethyl)phenyl 3-methylbutanoate **9f** (1.65 mmol, 1.05 equiv.) was added and following with 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **10y** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{36}H_{55}O_8P$, $[M+Na]^+$ 669.3530; found 669.3484. 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.

(C6-AB; C16-ACB)-*H*-phosphonate 11gy

According to general procedure b2, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **10y** (1.57 mmol, 1.0 equiv.) was added and following with 0.39 g 4-(hydroxymethyl)phenyl heptanoate **9g** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{38}H_{59}O_8P$, $[M+Na]^+$ 697.3840; found 697.3855. IR: ν [cm^{-1}] = 2956, 2915, 2849, 1753, 1607, 1509, 1464, 1382, 1286, 1250, 1219, 1057, 961, 835, 747, 720, 608, 509, 448.

(C8-AB; C16-ACB)-*H*-phosphonate 11hy

According to general procedure b2, with 0.30 mL DPP (1.57mmol, 1.0 equiv.) at 0 °C. 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **10y** (1.57 mmol, 1.0 equiv.) was added and following with 0.44 g 4-(hydroxymethyl)phenyl nonanoate **9h** (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. ^{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, $^{1}J_{HP}$= 709.4 Hz, 1H, PH), 5.10-4.96 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^{3}J_{HH}$= 6.80 Hz, 2H, H-g^2), 2.55 (t, $^{3}J_{HH}$= 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 ($^{4}J_{CP}$= 1.5 H_Z, C-e^2), 151.0 ($^{4}J_{CP}$= 1.5 H_Z, 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, $^{3}J_{CP}$= 3.6 H_Z, $^{3}J_{CP}$= 5.8 Hz, $^{3}J_{CP}$= 3.6 H_Z, $^{3}J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{40}H_{63}O_8P$, $[M+Na]^+$ 725.4153; found 725.4235. IR: ν [cm^{-1}] = 2955, 2916, 2849, 1753, 1607, 1509, 1466, 1381, 1250, 1220, 1167, 1057, 997, 878, 786, 748, 513, 479, 447, 423.

(C9-AB; C16-ACB)-*H*-phosphonate 11iy

According to general procedure b2, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **10y** (1.57 mmol, 1.0 equiv.) was added and following with 0.46 g 4-(hydroxymethyl)phenyl decanoate **9i** (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. ^{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, $^{1}J_{HP}$= 709.4 Hz, 1H, PH), 5.11-4.97 (m, 4H, H-a^1, H-a^2), 4.24 (t, $^{3}J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.55 (t, $^{3}J_{HH}$= 7.5 Hz, 2H, H-g^1), 1.79-

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 H_Z, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 2.7 H_Z, $^3J_{CP}$= 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. HRMS (ESI^+, m/z): calculated for $C_{41}H_{65}O_8P$, $[M+Na]^+$ 739.4309; found 739.3924. IR: ν [cm^{-1}] = 2956, 2917, 2849, 1750, 1606, 1558, 1509, 1466, 1412, 1250, 1220, 1106, 1059, 997, 924, 786, 770, 720, 581, 540.

(C4-AB; C12-ACB)-*H*-phosphonate 11ev

According to general procedure b2, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **10v** (1.57 mmol, 1.0 equiv.) was added and following with 0.34 g 4-(hydroxymethyl)phenyl pentanoate **9e** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, C-d[2]), 69.1 (C-g[2]), 66.7, 66.5 (2 × d, $^3J_{CP}$= 5.5 H_Z, $^3J_{CP}$= 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. HRMS (ESI^+, m/z): calculated for $C_{32}H_{47}O_8P$, $[M+Na]^+$ 613.2901; found 613.2841. IR: ν [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.

(C4-AB; C14-ACB)-*H*-phosphonate 11ew

According to general procedure b2, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.57 g 4-(hydroxymethyl)phenyl tetradecyl carbonate **10w** (1.57 mmol, 1.0 equiv.) was added and following with 0.34 g 4-(hydroxymethyl)phenyl pentanoate **9e** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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]).

HRMS (ESI$^+$, m/z): calculated for $C_{34}H_{51}O_8P$, $[M+Na]^+$ 641.3214; found 641.3201. ^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.73. IR: ν [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.

(C4-AB; C15-ACB)-*H*-phosphonate 11ex

According to general procedure b2, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.59 g 4-(hydroxymethyl)phenyl pentadecyl carbonate **10x** (1.57 mmol, 1.0 equiv.) was added and following with 0.34 g 4-(hydroxymethyl)phenyl pentanoate **9e** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{35}H_{53}O_8P$, $[M+Na]^+$ 655.3370; found 655.3357. IR: ν [cm^{-1}] = 2955, 2915, 2871, 2849, 1753, 1607, 1509, 1465, 1382, 1251, 1218, 1155, 996, 895, 787, 719, 559, 451, 421.

(C4-AB; C18-ACB)-*H*-phosphonate 11ez

According to general procedure b2, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.66 g 4-(hydroxymethyl)phenyl octadecyl carbonate **10z** (1.57 mmol, 1.0 equiv.) was added and following with 0.34 g 4-(hydroxymethyl)phenyl pentanoate **9e** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{38}H_{59}O_8P$, $[M+Na]^+$ 697.3840; found 697.3795. 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.

(C2-AB; C9-ACB)-*H*-phosphonate 11bs

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **9b** (1.65 mmol, 1.05 equiv.) was added and following with

0.46 g 4-(hydroxymethyl)phenyl nonyl carbonate **10s** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{27}H_{37}O_8P$, $[M+Na]^+$ 543.2118; found 543.2095. 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.

(C2-AB; C10-ACB)-*H*-phosphonate 11bt

According to general procedure b2, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **9b** (1.65 mmol, 1.05 equiv.) was added and following with 0.48 g decyl (4-(hydroxymethyl)phenyl) carbonate **10t** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{28}H_{39}O_8P$, $[M+Na]^+$ 557.2275; found 557.2295. 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.

(C2-AB; C11-ACB)-*H*-phosphonate 11bu

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **9b** (1.65 mmol, 1.05 equiv.) was added and following with 0.51 g 4-(hydroxymethyl)phenyl undecyl carbonate **10u** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{29}H_{41}O_8P$, $[M+Na]^+$ 571.2431; found 571.2386. IR: ν [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.

(C2-AB; C12-ACB)-*H*-phosphonate 11bv

According to general procedure b1, with 0.30 mL DPP (1.57mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **9b** (1.65 mmol, 1.05 equiv.) was added and following with 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **10v** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{30}H_{43}O_8P$, $[M+Na]^+$ 585.2588; found 585.2572. IR: ν [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.

(C2-AB; C14-ACB)-*H*-phosphonate 11bw

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.30 g 4-(hydroxymethyl)phenyl propionate **9b** (1.65 mmol, 1.05 equiv.) was added and following with 0.57 g 4-(hydroxymethyl)phenyl tetradecyl carbonate **10w** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{32}H_{47}O_8P$, $[M+Na]^+$ 613.2901; found 613.2845. 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.

(C3-AB; C12-ACB)-*H*-phosphonate 11cv

According to general procedure b1, with 0.30 mL DPP (1.57mmol, 1.0 equiv.) at 0 °C. 0.32 g 4-(hydroxymethyl)phenyl butyrate **9c** (1.65 mmol, 1.05 equiv.) was added and following with 0.53

g dodecyl (4-(hydroxymethyl)phenyl) carbonate **10v** (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. ^{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, PH), 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 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{31}H_{45}O_8P$, $[M+Na]^+$ 599.2744; found 599.2692. 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.

(C3-AB; C12-ACB)-*H*-phosphonate 11dv

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.32 g 4-(hydroxymethyl)phenyl isobutyrate **9d** (1.65 mmol, 1.05 equiv.) was added and following with 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **10v** (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. ^{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, $^1J_{HP}$= 709.4 Hz, 1H, PH), 5.04-

4.93 (m, 4H, H-a^1, H-a^2), 4.20 (t, $^3J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.75 (hept, $^3J_{HH}$= 7.0 Hz, 2H, H-g^1), 1.69 (quint, $^3J_{HH}$= 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, $^3J_{HH}$= 7.2 Hz, 6H, H-h^1), 0.85 (t, $^3J_{HH}$= 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, $^3J_{CP}$= 6.4 H_Z, $^3J_{CP}$= 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, $^3J_{CP}$= 5.5 H_Z, $^3J_{CP}$= 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. HRMS (ESI$^+$, m/z): calculated for $C_{31}H_{45}O_8P$, $[M+Na]^+$ 599.2744; found 599.2742. 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.

(C2-ACB; C12-ACB)-*H*-phosphonate 14kv

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.32 g ethyl (4-(hydroxymethyl)phenyl) carbonate **10k** (1.65 mmol, 1.05 equiv.) was added and following with 0.48 g decyl (4-(hydroxymethyl)phenyl) carbonate **10v** (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. ^{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, PH), 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 H_Z, $^4J_{CP}$= 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. HRMS (ESI^+, m/z): calculated for $C_{30}H_{43}O_9P$, $[M+Na]^+$ 601.2537; found 601.2485. 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.

(C4-ACB; C12-ACB)-*H*-phosphonate 14lv

According to general procedure b2, with 0.30 mL DPP (1.57mmol, 1.0 equiv.) at 0 °C. 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **10v** (1.57 mmol, 1.0 equiv.) was added and following with 0.35 g butyl (4-(hydroxymethyl)phenyl) carbonate **10l** (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. ^{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, PH), 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. HRMS (ESI^+, m/z): calculated for $C_{32}H_{47}O_9P$, $[M+Na]^+$ 629.2850; found 629.2876. IR: ν [cm^{-1}] = 2957, 2923, 2853, 1757, 1609, 1509, 1464, 1390, 1246, 1204, 1170, 1064, 949, 820, 777, 725, 633, 601, 510, 424.

(C4-ACB; C18-ACB)-*H*-phosphonate 14lz

According to general procedure b2, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.66 g 4-(hydroxymethyl)phenyl octadecyl carbonate **10z** (1.57 mmol, 1.0 equiv.) was added and following with 0.34 g butyl (4-(hydroxymethyl)phenyl) carbonate **10l** (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. ^{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, PH), 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. HRMS (ESI$^+$, m/z): calculated for $C_{38}H_{59}O_9P$, $[M+Na]^+$ 713.3789; found 713.3738. 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.

(C9-AB; C9-ACB)-*H*-phosphonate 11is

According to general procedure b2, with 0.15 mL DPP (0.79 mmol, 1.0 equiv.) at 0 °C. 0.23 g 4-(hydroxymethyl)phenyl nonyl carbonate **10s** (0.79 mmol, 1.0 equiv.) was added and following

with 0.21 g 4-(hydroxymethyl)phenyl decanoate **9i** (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. ^{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, PH), 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 H_Z, C-e^2), 150.9 (C-e^1), 133.1, 132.8 (2 × dd, $^3J_{CP}$= 2.2 H_Z, $^3J_{CP}$= 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 H_Z, $^3J_{CP}$= 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. HRMS (ESI^+, m/z): calculated for $C_{34}H_{51}O_8P$, $[M+Na]^+$ 641.3214; found 641.3203. 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.

(C9-ACB; C9-ACB)-*H*-phosphonate 14ss

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.97 g 4-(hydroxymethyl)phenyl nonyl carbonate **10s** (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. ^{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, PH), 5.10-4.96 (m, 4H, H-a), 4.23 (t, $^3J_{HH}$=

6.7 Hz, 4H, H-g), 1.72 (quint, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 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, $^{3}J_{CP}$= 5.5 H_Z, C-b), 129.1 (C-c), 121.3 (C-d), 69.0 (C-g), 66.44 (d, $^{3}J_{CP}$= 6.4 H_Z, 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. HRMS (ESI^+, m/z): calculated for $C_{34}H_{51}O_9P$, $[M+Na]^+$ 657.3163; found 657.3159. IR: ν [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.

(C11-AB; C6-ACB)-*H*-phosphonate 11jr

According to general procedure b2, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.40 g hexyl (4-(hydroxymethyl)phenyl) carbonate **10r** (1.57 mmol, 1.0 equiv.) was added and following with 0.51 g 4-(hydroxymethyl)phenyl dodecanoate **9j** (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. ^{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, PH), 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, $^{3}J_{CP}$= 6.4 H_Z, $^{3}J_{CP}$= 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 (2 × d, $^{3}J_{CP}$= 5.5 H_Z, $^{3}J_{CP}$= 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, 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. HRMS (ESI^+, m/z): calculated for $C_{33}H_{49}O_8P$, $[M+Na]^+$ 627.3057; found 627.2886. 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.

(β-cyanoethyl; C12-ACB)-*H*-phosphonate 18v

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.12 g 3-hydroxypropionitrile (1.65 mmol, 1.05 equiv.) was added and following with 0.53 g dodecyl (4-(hydroxymethyl)phenyl) carbonate **10v** (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. ^{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, PH), 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 H_Z, 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 H_Z, C-a), 59.8 (d, $^3J_{CP}$= 5.5 H_Z, 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 H_Z, C-t), 14.0 (C-r). ^{31}P-NMR (202 MHz, $CDCl_3$): δ [ppm] = 7.65. HRMS (ESI^+, m/z): calculated for $C_{23}H_{36}NO_5P$, $[M+Na]^+$ 476.2172; found 476.2179. IR: ν [cm^{-1}] = 2923, 2853, 1757, 1720, 1608, 1509, 1466, 1391, 1248, 1217, 1052, 959, 823, 777, 722, 685, 606, 511.

(β-cyanoethyl; C16-ACB)-*H*-phosphonate 18y

According to general procedure b1, with 0.30 mL DPP (1.57 mmol, 1.0 equiv.) at 0 °C. 0.12 g 3-hydroxypropionitrile (1.65 mmol, 1.05 equiv.) was added and following with 0.62 g hexadecyl (4-(hydroxymethyl)phenyl) carbonate **10v** (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. ^{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, PH), 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 H_Z, 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 H_Z, C-a), 59.8 (d, $^3J_{CP}$= 5.8 H_Z, 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 H_Z, C-x), 14.1 (C-v). ^{31}P-NMR (162 MHz, $CDCl_3$): δ [ppm] = 7.66. HRMS (ESI$^+$, m/z): calculated for $C_{27}H_{44}NO_5P$, $[M+Na]^+$ 532.2798; found 532.2791. 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-(C1-AB;C16-ACB)-d4TTP 8ay. According to general procedure C with 91 mg *H*-phosphonate **11ay** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 5 h at room temperature. Yield: 65 mg (0.064 mmol, 50%) white solid. ^{1}H NMR (600 MHz, CD_3OD): 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,

$^{3}J_{HH}$= 3.5 Hz, $^{4}J_{HH}$=1.5 Hz, 1H, H-1´), 6.46 (dt, $^{3}J_{HH}$= 5.9 Hz, $^{4}J_{HH}$=1.5 Hz, 1H, H-3´), 5.79 (ddd, $^{3}J_{HH}$= 6.0 Hz, $^{3}J_{HH}$= 2.4 Hz, $^{4}J_{HH}$= 1.4 Hz, 1H, H-2´), 5.15 (d, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 6.7 Hz, $^{4}J_{HH}$=1.0 Hz, 2H, H-g^{2}), 2.26 (d, $^{4}J_{HH}$= 1.1 Hz, 3H, H-g^{1}), 1.89 (d, $^{4}J_{HH}$= 1.1 Hz, 3H, H-7), 1.73 (quint, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 7.0 Hz, 3H, H-t). ^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 171.0 (d, $^{3}J_{CP}$= 2.2 H_Z, 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, $^{3}J_{CP}$= 7.7 H_Z, C-b^{2}), 134.9 (d, $^{3}J_{CP}$= 7.7 Hz, C-b^{1}), 130.5, 130.4 (2 × d, $^{3}J_{CP}$= 5.5 H_Z, $^{3}J_{CP}$= 5.5 H_Z, C-c^{1}, C-c^{2}), 127.2 (C-2´), 122.9 (d, $^{3}J_{CP}$= 2.2 H_Z, C-d^{1}), 122.3 (d, $^{3}J_{CP}$= 2.2 H_Z, C-d^{2}), 112.0 (C-5), 90.8 (C-1´), 87.1 (d, $^{3}J_{CP}$= 8.8 H_Z, C-4´), 70.4, 70.2 (2 × dd, $^{3}J_{CP}$= 3.3 H_Z, $^{3}J_{CP}$= 5.5 Hz, $^{3}J_{CP}$= 3.3 H_Z, $^{3}J_{CP}$= 5.5 Hz, C-a^{1}, C-a^{2}), 70.0 (C-g^{2}), 67.9 (d, $^{3}J_{CP}$= 5.5 H_Z, 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_3OD): δ [ppm] = -11.81 (d, $^{2}J_{pp}$= 18.6 Hz, P-α), -13.20 (d, $^{2}J_{pp}$= 17.7 Hz, P-γ), -23.77 (t, $^{2}J_{pp}$= 18.2 Hz, P-β). MALDI-MS (m/z): calculated for $C_{43}H_{61}N_2O_{18}P_3$ $[M-H]^-$ 985.306; found, 985.110. 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-(C2-AB;C16-ACB)-d4TTP 8by. According to general procedure C with 93 mg *H*-phosphonate **11by** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 5 h at room temperature. Yield: 67 mg (0.065

mmol, 51%) white solid. ^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.66 (d, $^{4}J_{HH}$= 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, $^{3}J_{HH}$= 3.5 Hz, $^{4}J_{HH}$=1.9 Hz, 1H, H-1′), 6.46 (dt, $^{3}J_{HH}$= 6.1 Hz, $^{4}J_{HH}$=1.8 Hz, 1H, H-3′), 5.79 (ddd, $^{3}J_{HH}$= 6.1 Hz, $^{3}J_{HH}$= 2.4 Hz, $^{4}J_{HH}$= 1.4 Hz, 1H, H-2′), 5.15 (d, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 6.6 Hz, $^{4}J_{HH}$=1.1 Hz, 2H, H-g^{2}), 2.60 (qd, $^{3}J_{HH}$= 6.6 Hz, $^{4}J_{HH}$= 1.3 Hz, 2H, H-g^{1}), 1.89 (d, $^{4}J_{HH}$= 1.1 Hz, 3H, H-7), 1.73 (quint, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 7.5 Hz, $^{4}J_{HH}$=0.9 Hz, 3H, H-h^{1}), 0.89 (t, $^{3}J_{HH}$= 7.0 Hz, 3H, H-v). ^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 174.5 (d, $^{3}J_{CP}$= 2.2 H_Z, 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, $^{3}J_{CP}$= 7.5 H_Z, C-b^{2}), 134.9 (d, $^{3}J_{CP}$= 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, $^{3}J_{CP}$= 2.2 H_Z, C-d^{1}), 122.3 (d, $^{3}J_{CP}$= 2.2 H_Z, C-d^{2}), 112.0 (C-5), 90.8 (C-1′), 87.1 (d, $^{3}J_{CP}$= 8.8 H_Z, C-4′), 70.4, 70.2 (2 × dd, $^{3}J_{CP}$= 3.4 H_Z, $^{3}J_{CP}$= 5.5 Hz, $^{3}J_{CP}$= 3.4 H_Z, $^{3}J_{CP}$= 5.5 Hz, C-a^{1}, C-a^{2}), 70.0 (C-g^{2}), 67.9 (d, $^{3}J_{CP}$= 4.2 H_Z, 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, $^{2}J_{pp}$= 19.9 Hz, P-α), -13.22 (d, $^{2}J_{pp}$= 16.7 Hz, P-γ), -23.67 (t, $^{2}J_{pp}$= 22.4 Hz, P-β). MALDI-MS (m/z): calculated for $C_{44}H_{63}N_2O_{18}P_3$ $[M-H]^-$ 999.322; found, 999.318. 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-(C4-AB; C16-ACB)-d4TTP 8ey. According to general procedure C with 97 mg *H*-phosphonate **11ey** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL

tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 5 h at room temperature. Yield: 97 mg (0.091 mmol, 71%) white solid. ^{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 H_Z, 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 H_Z, 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 H_Z, C-d^1), 122.3 (d, $^3J_{CP}$= 2.1 H_Z, C-d^2), 112.0 (C-5), 90.9 (C-1′), 87.1 (d, $^3J_{CP}$= 8.8 H_Z, C-4′), 70.4, 70.3 (C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 H_Z, 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). MALDI-MS (m/z): calculated for $C_{46}H_{67}N_2O_{18}P_3$ $[M-H]^-$ 1027.353; found, 1027.153. IR: ν [cm^{-1}] = 3065, 2921, 2851, 1757, 1688, 1659, 1452, 1206, 1126, 1062, 1040, 993, 867, 835, 781, 735, 479, 421.

γ-(C4-AB;C16-ACB)-d4TTP 8fy. According to general procedure C with 97.3 mg *H*-phosphonate **11fy** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL

tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 4 h at room temperature. Yield: 114 mg (0.077 mmol, 73%) white solid. ^{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 H_Z, 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 H_Z, C-4′), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 4.3 H_Z, $^3J_{CP}$= 6.5 Hz, $^3J_{CP}$= 3.4 H_Z, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.8 (d, $^3J_{CP}$= 5.5 H_Z, 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 $C_{46}H_{67}N_2O_{18}P_3$ $[M-H]^-$ 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-(C6-AB;C16-ACB)-d4TTP 8gy. According to general procedure C with 101 mg *H*-phosphonate **11gy** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL

tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 5 h at room temperature. Yield: 69 mg (0.064 mmol, 50%) white solid. ^{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 H_Z, 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 H_Z, 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 H_Z, C-d^1), 122.3 (d, $^3J_{CP}$= 2.1 H_Z, C-d^2), 112.0 (C-5), 90.8 (C-1′), 87.1 (d, $^3J_{CP}$= 8.8 H_Z, C-4′), 70.4, 70.3 (C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 H_Z, 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). MALDI-MS (m/z): calculated for $C_{48}H_{71}N_2O_{18}P_3$ $[M-H]^-$ 1055.384; found, 1055.231. 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-(C8-AB;C16-ACB)-d4TTP 8hy. According to general procedure C with 105 mg *H*-phosphonate **11hy** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL

tetrabutylammonium phosphate (0.45mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 5 h at room temperature. Yield: 65 mg (0.059 mmol, 46%) white solid. ^{1}H NMR (600 MHz, CD_3OD): 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_3OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.2 H_Z, 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 H_Z, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 H_Z, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.2 (d, $^3J_{CP}$= 8.8 H_Z, C-4´), 70.4, 70.3 (C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.6 H_Z, 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_3OD): 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). MALDI-MS (m/z): calculated for $C_{50}H_{75}N_2O_{18}P_3$ $[M-H]^-$ 1083.416; found, 1083.272. 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-(C9-AB;C16-ACB)-d4TTP 8iy. According to general procedure C with 108 mg *H*-phosphonate **11iy** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 5 h at room temperature. Yield: 33 mg (0.029 mmol, 23%) white solid. ^{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 H_Z, 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 H_Z, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 H_Z, C-d^2), 112.0 (C-5), 90.8 (C-1′), 87.2 (d, $^3J_{CP}$= 8.8 H_Z, C-4′), 70.4, 70.3 (C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 H_Z, 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). MALDI-MS (m/z): calculated for $C_{51}H_{77}N_2O_{18}P_3$ $[M-H]^-$ 1097.431; found, 1097.289. 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-(C4-AB;C12-ACB)-d4TTP 8ev. According to general procedure C with 91 mg *H*-phosphonate **11ev** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 5 h at room temperature. Yield: 73 mg (0.075 mmol, 59%) white solid. ^{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 H_Z, 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 H_Z, 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 H_Z, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 H_Z, C-d^2), 112.0 (C-5), 90.9 (C-1′), 87.2 (d, $^3J_{CP}$= 8.8 H_Z, C-4′), 70.4, 70.3 (2 × dd, $^3J_{CP}$= 3.3 H_Z, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 H_Z, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 H_Z, 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). MALDI-MS (m/z): calculated for $C_{42}H_{59}N_2O_{18}P_3$ $[M-H]^-$ 971.290; found, 971.135. IR: ν [cm^{-1}] = 2987, 2971, 2901, 1747, 1729, 1451, 1406, 1393, 1381, 1250, 1229, 1075, 1066, 1055, 892, 431.

γ-(C4-AB;C14-ACB)-d4TTP 8ew. According to general procedure C with 93 mg *H*-phosphonate **11ew** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 4 h at room temperature. Yield: 85 mg (0.082 mmol, 78%) white solid. ^{1}H NMR (600 MHz, CD_3OD): 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 H_Z, 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_3OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.2 H_Z, 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 H_Z, 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 H_Z, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 H_Z, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 H_Z, C-4´), 70.4, 70.3 (2 × dd, $^3J_{CP}$= 3.3 H_Z, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 H_Z, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 H_Z, 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_3OD): 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). MALDI-MS (m/z): calculated for $C_{44}H_{63}N_2O_{18}P_3$ $[M-H]^-$ 999.322; found, 999.191. 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-(C4-AB;C15-ACB)-d4TTP 8ex. According to general procedure C with 142 mg *H*-phosphonate **11ex** (0.23 mmol, 1.0 equiv.), 60 mg NCS (0.45 mmol, 2.0 equiv.), 1.7 mL tetrabutylammonium phosphate (0.68 mmol, 3.0 equiv.) and 124 mg d4TMP 2×nBu_4N^+ salt (0.16 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 122 mg (0.17 mmol, 74%) white solid. ^{1}H NMR (600 MHz, CD_3OD): 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 H_Z, 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_3OD): 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 H_Z, 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 H_Z, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 H_Z, C-d^2), 112.0 (C-5), 90.9 (C-1′), 87.1 (d, $^3J_{CP}$= 8.8 H_Z, C-4′), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 3.2 H_Z, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 H_Z, $^3J_{CP}$= 5.5 Hz,C-a^1, C-a^2), 67.9 (d, $^3J_{CP}$= 5.5 H_Z, 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_3OD): 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, $^{2}J_{pp}$= 18.9 Hz, P-β). MALDI-MS (m/z): calculated for $C_{45}H_{65}N_2O_{18}P_3$ $[M-H]^-$ 1013.337; found, 1013.202. 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-(C4-AB;C18-ACB)-d4TTP 8ez. According to general procedure C with 101 mg *H*-phosphonate **11ez** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 4 h at room temperature. Yield: 54 mg (0.041 mmol, 39%) white solid. ^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.64 (d, $^{4}J_{HH}$= 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, $^{3}J_{HH}$= 3.3 Hz, $^{4}J_{HH}$=1.5 Hz,, 1H, H-1′), 6.44 (dt, $^{3}J_{HH}$= 6.0 Hz, $^{4}J_{HH}$= 1.5 Hz, 1H, H-3′), 5.79 (ddd, $^{3}J_{HH}$= 6.0 Hz, $^{3}J_{HH}$= 2.2 Hz, $^{4}J_{HH}$= 1.3 Hz, 1H, H-2′), 5.14 (d, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 6.7 Hz, 2H, H-g^2), 2.58 (t, $^{3}J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.89 (d, $^{4}J_{HH}$= 0.8 H_Z, 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, $^{3}J_{HH}$= 7.3 Hz, 3H, H-j^1), 0.89 (t, $^{3}J_{HH}$= 6.8 Hz, 3H, H-x). ^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 173.7 (d, $^{3}J_{CP}$= 2.2 H_Z, 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, $^{3}J_{CP}$= 7.7 H_Z, C-b^2), 134.8 (d, $^{3}J_{CP}$= 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, $^{3}J_{CP}$= 3.3 H_Z, C-d^1), 122.3 (d, $^{3}J_{CP}$= 2.2 H_Z, C-d^2), 112.0 (C-5), 90.9 (C-1′), 87.1 (d, $^{3}J_{CP}$= 8.9 H_Z, C-4′), 70.4, 70.2 (2 × dd, $^{3}J_{CP}$= 4.3 H_Z, $^{3}J_{CP}$= 6.6 Hz, $^{3}J_{CP}$= 3.3 H_Z, $^{3}J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^{3}J_{CP}$= 5.5 H_Z, 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). MALDI-MS (m/z): calculated for $C_{48}H_{71}N_2O_{18}P_3$ $[M-H]^-$ 1055.384; found, 1055.282. IR: ν [cm^{-1}] = 2987, 2971, 2901, 1759, 1691, 1451, 1406, 1393, 1382, 1250, 1229, 1075, 1055, 892, 427.

γ-(C2-AB;C9-ACB)-d4TTP 8bs. According to general procedure C with 117 mg *H*-phosphonate **11bs** (0.23 mmol, 1.0 equiv.), 60 mg NCS (0.45 mmol, 2.0 equiv.), 1.7 mL tetrabutylammonium phosphate (0.68 mmol, 3.0 equiv.) and 124 mg d4TMP 2×nBu_4N^+ salt (0.16 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 75 mg (0.080mmol, 51%) white solid. ^{1}H NMR (400 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), 7.09-7.03 (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_3OD): δ [ppm] = 174.5 (d, $^4J_{CP}$= 1.5 H_Z, 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 H_Z, 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 H_Z, C-d^1), 122.3 (d, $^4J_{CP}$= 1.4 H_Z, C-d^2), 112.0 (C-5), 90.8 (C-1′), 87.1 (d, $^3J_{CP}$= 8.7 H_Z, C-4′), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 2.2 H_Z, $^3J_{CP}$= 5.9 Hz, $^3J_{CP}$= 2.3 H_Z, $^3J_{CP}$= 5.2 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.8 (d, $^3J_{CP}$= 5.2 H_Z, 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_3OD): 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). MALDI-MS (m/z): calculated for $C_{37}H_{49}N_2O_{18}P_3$ $[M-H]^-$ 901.212; found, 901.135. 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-(C2-AB;C10-ACB)-d4TTP 8bt. According to general procedure C with 80 mg *H*-phosphonate **11bt** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 83 mg d4TMP 2×nBu_4N^+ salt (0.11 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 56 mg (0.039 mmol, 37%) white solid. ^{1}H NMR (600 MHz, CD_3OD): 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_3OD): δ [ppm] = 174.5 (d, $^3J_{CP}$= 2.2 H_Z, 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 H_Z, 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 H_Z, C-d[1]), 122.3 (d, $^3J_{CP}$= 2.2 H_Z, C-d[2]), 112.0 (C-5), 90.9 (C-1′), 87.1 (d, $^3J_{CP}$= 7.7 H_Z, C-4′), 70.4, 70.3 (2 × dd, $^3J_{CP}$= 3.3 H_Z, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 H_Z, $^3J_{CP}$= 5.5 Hz, C-a[1], C-a[2]), 70.0 (C-g[2]), 67.9 (d, $^3J_{CP}$= 5.5 H_Z, 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 MHz, CD_3OD): 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). MALDI-MS (m/z): calculated for $C_{38}H_{51}N_2O_{18}P_3$ [M-H]$^-$ 915.228; found, 915.153. **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-(C2-AB;C11-ACB)-d4TTP 8bu. According to general procedure C with 123 mg *H*-phosphonate **11bu** (0.23 mmol, 1.0 equiv.), 60 mg NCS (0.45 mmol, 2.0 equiv.), 1.7 mL tetrabutylammonium phosphate (0.68 mmol, 3.0 equiv.) and 124 mg d4TMP 2×nBu_4N^+ salt (0.16 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 105 mg (0.11 mmol, 69%) white solid. ^{1}H NMR (400 MHz, CD_3OD): 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_3OD): δ [ppm] = 174.4 (d, $^4J_{CP}$= 1.5 H_Z, 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 H_Z, 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 H_Z, C-d^1), 122.3 (d, $^3J_{CP}$= 2.2 H_Z, C-d^2), 112.0 (C-5), 90.8 (C-1′), 87.1 (d, $^3J_{CP}$= 8.8 H_Z, C-4′), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 2.2 H_Z, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 2.2 H_Z, $^3J_{CP}$= 5.9 Hz, C-a^1, C-a^2), 70.0 (C-g^2),

67.9 (d, $^{3}J_{CP}$= 5.2 H_Z, 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_3OD): δ [ppm] = -11.72 (d, $^{2}J_{pp}$= 19.6 Hz, P-α), -13.17 (d, $^{2}J_{pp}$= 16.9 Hz, P-γ), -23.58 (t, $^{2}J_{pp}$= 18.1 Hz, P-β). MALDI-MS (m/z): calculated for $C_{39}H_{53}N_2O_{18}P_3$ $[M-H]^-$ 929.243; found, 929.182. 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-(C2-AB;C12-ACB)-d4TTP 8bv. According to general procedure C with 169 mg *H*-phosphonate **11bv** (0.30 mmol, 1.0 equiv.), 80 mg NCS (0.60 mmol, 2.0 equiv.), 2.3 mL tetrabutylammonium phosphate (0.90 mmol, 3.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt (0.21 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 66 mg (0.091 mmol, 43%) white solid. ^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.66 (d, $^{4}J_{HH}$= 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, $^{3}J_{HH}$= 3.3 Hz, $^{4}J_{HH}$=1.8 Hz, 1H, H-1′), 6.46 (dt, $^{3}J_{HH}$= 6.0 Hz, $^{4}J_{HH}$=1.8 Hz, 1H, H-3′), 5.79 (ddd, $^{3}J_{HH}$= 6.1 Hz, $^{3}J_{HH}$= 2.5 Hz, $^{4}J_{HH}$= 1.5 Hz, 1H, H-2′), 5.15 (d, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.60 (qd, $^{3}J_{HH}$= 7.6 Hz, $^{4}J_{HH}$= 0.8 Hz, 2H, H-g^1), 1.88 (d, $^{4}J_{HH}$= 1.2 Hz, 3H, H-7), 1.73 (quint, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 7.6 Hz, $^{4}J_{HH}$=0.8 Hz, 3H, H-h^1), 0.89 (t, $^{3}J_{HH}$= 6.9 Hz, 3H, H-r). ^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 174.5 (d, $^{3}J_{CP}$= 2.2 H_Z, 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, $^{3}J_{CP}$= 6.6 H_Z, C-b^2), 134.8 (d, $^{3}J_{CP}$= 7.7 Hz, C-b^1), 130.51, 130.46 (2 × d, $^{3}J_{CP}$= 4.4 H_Z, $^{3}J_{CP}$= 4.4 H_Z, C-c^1, C-c^2), 127.2 (C-2′), 122.9 (d, $^{3}J_{CP}$= 2.2 H_Z, C-d^1), 122.3 (d, $^{3}J_{CP}$= 2.2 H_Z, C-d^2), 112.0 (C-5), 90.9 (C-1′), 87.1 (d, $^{3}J_{CP}$= 8.8 H_Z, C-

4′), 70.4, 70.2 (2 × dd, $^{3}J_{CP}$= 3.3 H_Z, $^{3}J_{CP}$= 5.5 Hz, $^{3}J_{CP}$= 3.3 H_Z, $^{3}J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^{3}J_{CP}$= 5.4 H_Z, 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, $^{2}J_{pp}$= 19.7 Hz, P-α), -13.20 (d, $^{2}J_{pp}$= 15.8 Hz, P-γ), -23.65 (t, $^{2}J_{pp}$= 17.9 Hz, P-β). MALDI-MS (m/z): calculated for $C_{40}H_{55}N_2O_{18}P_3$ $[M-H]^-$ 943.259; found, 943.185. 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-(C2-AB;C14-ACB)-d4TTP 8bw. According to general procedure C with 133 mg *H*-phosphonate **11bw** (0.23 mmol, 1.0 equiv.), 60 mg NCS (0.45 mmol, 2.0 equiv.), 1.7 mL tetrabutylammonium phosphate (0.68 mmol, 3.0 equiv.) and 124 mg d4TMP 2×nBu_4N^+ salt (0.16 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 104 mg (0.11 mmol, 66%) white solid. ^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.62 (d, $^{4}J_{HH}$= 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, $^{3}J_{HH}$= 3.4 Hz, $^{4}J_{HH}$=1.8 Hz, 1H, H-1′), 6.44 (dt, $^{3}J_{HH}$= 6.1 Hz, $^{4}J_{HH}$=1.7 Hz, 1H, H-3′), 5.79 (ddd, $^{3}J_{HH}$= 6.1 Hz, $^{3}J_{HH}$= 2.4 Hz, $^{4}J_{HH}$= 1.4 Hz, 1H, H-2′), 5.15 (d, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 6.5 Hz, 2H, H-g^2), 2.60 (qd, $^{3}J_{HH}$= 7.5 Hz, $^{4}J_{HH}$= 0.8 Hz, 2H, H-g^1), 1.89 (d, $^{4}J_{HH}$= 1.0 Hz, 3H, H-7), 1.72 (quint, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 7.5 Hz, $^{4}J_{HH}$=0.5 Hz, 3H, H-h^1), 0.89 (t, $^{3}J_{HH}$= 6.8 Hz, 3H, H-t). ^{13}C NMR (101 MHz, CD_3OD): δ [ppm] = 174.4 (d, $^{4}J_{CP}$= 1.5 H_Z, 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, $^{3}J_{CP}$= 7.4 H_Z, C-b^2), 134.8 (d, $^{3}J_{CP}$= 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, $^{4}J_{CP}$= 1.5 H_Z, C-

d[1]), 122.3 (d, $^4J_{CP}$= 1.5 H_Z, C-d[2]), 112.0 (C-5), 90.8 (C-1′), 87.1 (d, $^3J_{CP}$= 8.1 H_Z, C-4′), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 2.2 H_Z, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 2.2 H_Z, $^3J_{CP}$= 5.1 Hz, C-a[1], C-a[2]), 70.0 (C-g[2]), 67.9 (d, $^3J_{CP}$= 3.7 H_Z, 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_3OD): 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). MALDI-MS (m/z): calculated for $C_{42}H_{59}N_2O_{18}P_3$ $[M-H]^-$ 971.290; found, 971.204. 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-(C3-AB;C12-ACB)-d4TTP 8cv. According to general procedure C with 130 mg *H*-phosphonate **11cv** (0.23 mmol, 1.0 equiv.), 60 mg NCS (0.45 mmol, 2.0 equiv.), 1.7 mL tetrabutylammonium phosphate (0.68 mmol, 3.0 equiv.) and 124 mg d4TMP 2×nBu_4N^+ salt (0.16 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 81 mg (0.082 mmol, 52%) white solid. ^{1}H NMR (600 MHz, CD_3OD): 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_3OD): δ [ppm] = 173.6 (d, $^3J_{CP}$= 2.2 H_Z, 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 H_Z, 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 H_Z, C-d[1]), 122.3 (d, $^3J_{CP}$= 2.2 H_Z, C-d[2]), 112.0 (C-5), 90.9 (C-1′), 87.1 (d, $^3J_{CP}$= 8.8 H_Z, C-4′), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 3.3 H_Z, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.3 H_Z, $^3J_{CP}$= 5.5 Hz, C-a[1], C-a[2]), 70.0 (C-g[2]), 67.9 (d, $^3J_{CP}$= 5.5 H_Z, 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_3OD): 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). MALDI-MS (m/z): calculated for $C_{41}H_{57}N_2O_{18}P_3$ $[M-H]^-$ 957.275; found, 957.186. 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-(C3-AB;C12-ACB)-d4TTP 8dv. According to general procedure C with 130 mg *H*-phosphonate **11dv** (0.23 mmol, 1.0 equiv.), 60 mg NCS (0.45 mmol, 2.0 equiv.), 1.7 mL tetrabutylammonium phosphate (0.68 mmol, 3.0 equiv.) and 124 mg d4TMP 2×nBu_4N^+ salt (0.16 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 69 mg (0.069 mmol, 44%) white solid. ^{1}H NMR (400 MHz, CD_3OD): 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_3OD): δ [ppm] = 177.0 (d, $^4J_{CP}$= 1.4 H_Z, 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 H_Z, 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 H_Z, C-d[1]), 122.3 (d, $^3J_{CP}$= 2.2 H_Z, C-d[2]), 112.0 (C-5), 90.8 (C-1´), 87.2 (d, $^3J_{CP}$= 8.8 H_Z, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 2.2 H_Z, $^3J_{CP}$= 5.8 Hz, $^3J_{CP}$= 2.2 H_Z, $^3J_{CP}$= 6.5 Hz, C-a[1], C-a[2]), 70.0 (C-g[2]), 67.9 (d, $^3J_{CP}$= 3.0 H_Z, 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_3OD): 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). MALDI-MS (m/z): calculated for $C_{41}H_{57}N_2O_{18}P_3$ $[M-H]^-$ 957.275; found, 957.194. 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-(C2-ACB;C12-ACB)-d4TTP 13kv. According to general procedure C with 130 mg *H*-phosphonate **14kv** (0.23 mmol, 1.0 equiv.), 60 mg NCS (0.45 mmol, 2.0 equiv.), 1.7 mL tetrabutylammonium phosphate (0.68 mmol, 3.0 equiv.) and 124 mg d4TMP 2×nBu_4N^+ salt (0.16 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 93 mg (0.093 mmol, 59%) white solid. ^{1}H NMR (600 MHz, CD_3OD): 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, $^{3}J_{HH}$= 7.1 Hz, $^{4}J_{HH}$=0.7 Hz, 3H, H-h^{1}), 0.89 (t, $^{3}J_{HH}$= 7.0 Hz, 3H, H-r). ^{13}C NMR (151 MHz, CD_3OD): 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, $^{3}J_{CP}$= 7.8 H_Z, C-4´), 70.32, 70.29, 70.26 (C-a^{1}, C-a^{2}), 70.0 (C-g^{2}), 67.9 (d, $^{3}J_{CP}$= 4.4 H_Z, 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_3OD): δ [ppm] = -11.72 (d, $^{2}J_{pp}$= 18.8 Hz, P-α), -13.20 (d, $^{2}J_{pp}$= 17.8 Hz, P-γ), -23.62 (t, $^{2}J_{pp}$= 18.8 Hz, P-β). MALDI-MS (m/z): calculated for $C_{40}H_{55}N_2O_{19}P_3$ $[M-H]^-$ 959.254; found, 959.197. 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-(C4-ACB;C12-ACB)-d4TTP 13lv. According to general procedure C with 137 mg *H*-phosphonate **14lv** (0.23 mmol, 1.0 equiv.), 60 mg NCS (0.45 mmol, 2.0 equiv.), 1.7 mL tetrabutylammonium phosphate (0.68 mmol, 3.0 equiv.) and 124 mg d4TMP 2×nBu_4N^+ salt (0.16 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 88 mg (0.087 mmol, 55%) white solid. ^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.66 (d, $^{4}J_{HH}$= 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, $^{3}J_{HH}$= 3.3 Hz, $^{4}J_{HH}$=1.7 Hz, 1H, H-1´), 6.45 (dt, $^{3}J_{HH}$= 6.1 Hz, $^{4}J_{HH}$=1.8 Hz, 1H, H-3´), 5.79 (ddd, $^{3}J_{HH}$= 6.0 Hz, $^{3}J_{HH}$= 2.3 Hz, $^{4}J_{HH}$= 1.3 Hz, 1H, H-2´), 5.15 (d, $^{3}J_{HH}$= 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, $^{4}J_{HH}$= 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, $^{3}J_{HH}$= 7.4 Hz, 3H, H-j^{1}), 0.89 (t, $^{3}J_{HH}$= 6.9 Hz, 3H, H-r). ^{13}C NMR (151 MHz,

CD_3OD): 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 H_Z, 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 H_Z, 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_3OD): 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). MALDI-MS (m/z): calculated for $C_{42}H_{59}N_2O_{19}P_3$ $[M-H]^-$ 987.285; found, 987.189. 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-(C4-ACB;C18-ACB)-d4TTP 13lz. According to general procedure C with 104 mg *H*-phosphonate **14lz** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 100 mg d4TMP 2×nBu_4N^+ salt (0.13 mmol, 0.85 equiv.). Reaction time was 5 h at room temperature. Yield: 72 mg (0.066 mmol, 52%) white solid. ^{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 H_Z, 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 H_Z, 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). MALDI-MS (m/z): calculated for $C_{48}H_{71}N_2O_{19}P_3$ $[M-H]^-$ 1071.379; found, 1071.243. IR: ν [cm^{-1}] = 2986, 2968, 2923, 1749, 1684, 1507, 1453, 1405, 1393, 1222, 1066, 899, 833, 777, 725, 549, 492, 450.

γ-(C9-AB;C9-ACB)-d4TTP 8is. According to general procedure C with 91 mg *H*-phosphonate **11is** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 83 mg d4TMP 2×nBu_4N^+ salt (0.09 mmol, 0.60 equiv.). Reaction time was 5 h at room temperature. Yield: 94 mg (0.070 mmol, 78%) white solid. ^{1}H NMR (600 MHz, CD_3OD): 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_3OD): δ [ppm] = 173.7 (d, $^3J_{CP}$= 2.2 H_Z, 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

H_Z, C-b^2), 134.8 (d, $^3J_{CP}$= 7.7 H_Z, C-b^1), 130.50, 130.48 (2 × d, $^3J_{CP}$= 2.2 H_Z, $^3J_{CP}$= 3.3 H_Z, C-c^1, C-c^2), 127.2 (C-2´), 122.9 (d, $^3J_{CP}$= 2.2 H_Z, C-d^1), 122.3 (d, $^3J_{CP}$= 2.1 H_Z, C-d^2), 112.0 (C-5), 90.9 (C-1´), 87.1 (d, $^3J_{CP}$= 8.8 H_Z, C-4´), 70.4, 70.2 (2 × dd, $^3J_{CP}$= 3.3 H_Z, $^3J_{CP}$= 5.5 Hz, $^3J_{CP}$= 3.2 H_Z, $^3J_{CP}$= 5.5 Hz, C-a^1, C-a^2), 70.0 (C-g^2), 67.9 (d, $^3J_{CP}$= 5.5 H_Z, 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_3OD): 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). MALDI-MS (m/z): calculated for $C_{44}H_{63}N_2O_{18}P_3$ $[M-H]^-$ 999.322; found, 999.245. IR: ν [cm^{-1}] = 2987, 2971, 2901, 1758, 1694, 1508, 1452, 1406, 1393, 1382, 1250, 1228, 1168, 1075, 1055, 899, 782, 491, 438.

γ-(C9-ACB;C9-ACB)-d4TTP 13ss. According to general procedure C with 95 mg *H*-phosphonate **14ss** (0.15 mmol, 1.0 equiv.), 40 mg NCS (0.30 mmol, 2.0 equiv.), 1.2 mL tetrabutylammonium phosphate (0.45 mmol, 3.0 equiv.) and 83 mg d4TMP 2×nBu_4N^+ salt (0.11 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 77 mg (0.074 mmol, 70%) white solid. ^{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, $^{4}J_{CP}$= 1.4 Hz, C-d), 112.0 (C-5), 90.8 (C-1′), 87.2 (d, $^{3}J_{CP}$= 8.6 H_Z, C-4′), 70.3 (dd, $^{3}J_{CP}$= 2.1 H_Z, $^{3}J_{CP}$= 5.9 Hz, C-a), 70.0 (C-g), 67.9 (d, $^{3}J_{CP}$= 5.0 H_Z, 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, $^{2}J_{pp}$= 19.6 Hz, P-α), -13.21 (d, $^{2}J_{pp}$= 15.8 Hz, P-γ), -23.66 (t, $^{2}J_{pp}$= 18.0 Hz, P-β). MALDI-MS (m/z): calculated for $C_{44}H_{63}N_2O_{19}P_3$ $[M-H]^-$ 1015.317; found, 1015.231. 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-(C11-AB;C6-ACB)-d4TTP 8jr. According to general procedure C with 136 mg *H*-phosphonate **11jr** (0.23 mmol, 1.0 equiv.), 60 mg NCS (0.45 mmol, 2.0 equiv.), 1.7 mL tetrabutylammonium phosphate (0.68 mmol, 3.0 equiv.) and 106 mg d4TMP 2×nBu_4N^+ salt (0.14 mmol, 0.60 equiv.). Reaction time was 5 h at room temperature. Yield: 72 mg (0.073 mmol, 54%) white solid. ^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.64 (d, $^{4}J_{HH}$= 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, $^{3}J_{HH}$= 3.4 Hz, $^{4}J_{HH}$=1.8 Hz, 1H, H-1′), 6.44 (dt, $^{3}J_{HH}$= 6.0 Hz, $^{4}J_{HH}$=1.7 Hz, 1H, H-3′), 5.79 (ddd, $^{3}J_{HH}$= 6.0 Hz, $^{3}J_{HH}$= 3.2 Hz, $^{4}J_{HH}$= 1.4 Hz, 1H, H-2′), 5.14 (d, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 6.6 Hz, 2H, H-g^2), 2.57 (t, $^{3}J_{HH}$= 7.4 Hz, 2H, H-g^1), 1.89 (d, $^{4}J_{HH}$= 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_3OD): 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, $^{3}J_{CP}$= 6.7 H_Z, C-b^2), 134.7 (d, $^{3}J_{CP}$= 7.7 H_Z, C-b^1), 130.47, 130.45, 130.44, 129.6 (C-c^1, C-c^2), 127.2 (C-2′), 122.8 (d, $^{3}J_{CP}$= 2.2 H_Z, C-d^1), 122.3 (d, $^{3}J_{CP}$= 2.2 H_Z, C-d^2), 112.0 (C-5), 90.8 (C-1′), 87.0 (d, $^{3}J_{CP}$= 8.8 H_Z, C-4′),

70.4, 70.2 (2 × dd, $^{3}J_{CP}$= 3.3 H_Z, $^{3}J_{CP}$= 6.5 Hz, $^{3}J_{CP}$= 2.3 H_Z, $^{3}J_{CP}$= 5.5 Hz, C-a^{1}, C-a^{2}), 70.0 (C-g^{2}), 67.9 (d, $^{3}J_{CP}$= 5.6 H_Z, 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_3OD): δ [ppm] = -11.75 (d, $^{2}J_{pp}$= 18.3 Hz, P-α), -13.16 (d, $^{2}J_{pp}$= 17.8 Hz, P-γ), -23.62 (t, $^{2}J_{pp}$= 17.8 Hz, P-β). MALDI-MS (m/z): calculated for $C_{43}H_{61}N_2O_{18}P_3$ $[M-H]^-$ 985.306; found, 985.230. 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;C12-ACB)-d4TTP 16v. According to general procedure C with 136 mg *H*-phosphonate **18v** (0.30 mmol, 1.0 equiv.), 80 mg NCS (0.60 mmol, 2.0 equiv.), 2.3 mL tetrabutylammonium phosphate (0.90 mmol, 3.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt (0.21 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 98 mg (0.11 mmol, 52%) white solid. ^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.65 (d, $^{4}J_{HH}$= 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, $^{3}J_{HH}$= 8.0 Hz, 2H, H-a), 5.01-4.95 (m, 1H, H-4´), 4.33 (q, $^{3}J_{HH}$= 6.1 Hz, 2H, H-s), 4.27-4.15 (m, 2H, H-5´), 4.23 (t, $^{3}J_{HH}$= 6.6 Hz, 2H, H-g), 2.87 (t, $^{3}J_{HH}$= 6.0 Hz, 2H, H-t), 1.90 (s, 3H, H-7), 1.73 (q, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 6.7 Hz, 3H, H-r). ^{13}C NMR (101 MHz, CD_3OD): 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, $^{4}J_{CP}$= 1.5 H_Z, 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, $^{3}J_{CP}$= 8.7 H_Z, C-4´), 70.5 (d, $^{3}J_{CP}$= 5.2 H_Z, C-a), 70.0 (C-g), 67.9 (d, $^{3}J_{CP}$= 5.8 H_Z, C-5´), 64.3 (d, $^{3}J_{CP}$= 5.1 H_Z, 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, $^{3}J_{CP}$= 8.1 H_Z, C-t), 14.5 (C-r), 12.5 (C-7). ^{31}P NMR (162 MHz, CD_3OD): δ [ppm] = -11.67 (d, $^{2}J_{pp}$= 18.5 Hz, P-α), -13.65 (d, $^{2}J_{pp}$= 15.9 Hz, P-γ), -23.47 (t, $^{2}J_{pp}$= 16.7 Hz, P-β). MALDI-MS (m/z): calculated for $C_{33}H_{48}N_3O_{16}P_3$ $[M-H]^-$ 834.218; found, 834.179. 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-(C12-ACB)-d4TTP 20v. According to general procedure C with 136 mg *H*-phosphonate **18v** (0.30 mmol, 1.0 equiv.), 80 mg NCS (0.60 mmol, 2.0 equiv.), 2.3 mL tetrabutylammonium phosphate (0.90 mmol, 3.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt (0.21 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 41 mg (0.048 mmol, 23%) white solid. ^{1}H NMR (400 MHz, CD_3OD): δ [ppm] = 7.65 (d, $^{4}J_{HH}$= 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, $^{3}J_{HH}$= 3.4 Hz, $^{4}J_{HH}$=1.8 Hz, 1H, H-1′), 6.48 (dt, $^{3}J_{HH}$= 6.0 Hz, $^{4}J_{HH}$=1.7 Hz, 1H, H-3′), 5.82 (ddd, $^{3}J_{HH}$= 6.0 Hz, $^{3}J_{HH}$= 3.2 Hz, $^{4}J_{HH}$= 1.3 Hz, 1H, H-2′), 5.05 (d, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 6.6 Hz, 2H, H-g), 1.90 (d, $^{4}J_{HH}$= 1.0 Hz, 3H, H-7), 1.73 (q, $^{3}J_{HH}$= 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, $^{3}J_{HH}$= 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, $^{3}J_{CP}$= 8.9 H_Z, 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, $^{3}J_{CP}$= 8.7 H_Z, C-4′), 69.9 (C-g), 68.2 (d, $^{3}J_{CP}$= 5.1 H_Z, C-a), 67.8 (d, $^{3}J_{CP}$= 5.9 H_Z, 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, $^{2}J_{pp}$= 19.6 Hz, P-α), -11.28 (d, $^{2}J_{pp}$= 17.9 Hz, P-γ), -21.97 (t, $^{2}J_{pp}$= 17.9 Hz, P-β). MALDI-MS (m/z):

calculated for $C_{30}H_{45}N_2O_{16}P_3$ $[M-H]^-$ 781.191; found, 781.162. IR: ν [cm^{-1}] = 2987, 2963, 1699, 1652, 1521, 1507, 1456, 1247, 1231, 1066, 1047, 1027, 668, 548, 471, 436.

γ-(β-cyanoethyl;C16-ACB)-d4TTP 16y. According to general procedure C with 153 mg *H*-phosphonate **18y** (0.30 mmol, 1.0 equiv.), 80 mg NCS (0.60 mmol, 2.0 equiv.), 2.3 mL tetrabutylammonium phosphate (0.90 mmol, 3.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt (0.21 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 123 mg (0.13 mmol, 63%) white solid. ^{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 H_Z, 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 H_Z, C-4′), 70.5 (d, $^3J_{CP}$= 5.8 H_Z, C-a), 70.0 (C-g), 67.9 (d, $^3J_{CP}$= 5.8 H_Z, C-5′), 64.1 (d, $^3J_{CP}$= 5.8 H_Z, 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 H_Z, 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). MALDI-MS (m/z): calculated for $C_{37}H_{56}N_3O_{16}P_3$ $[M-H]^-$ 890.280; found, 890.226. 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-(C16-ACB)-d4TTP 20y. According to general procedure C with 153 mg *H*-phosphonate **18y** (0.30 mmol, 1.0 equiv.), 80 mg NCS (0.60 mmol, 2.0 equiv.), 2.3 mL tetrabutylammonium phosphate (0.90 mmol, 3.0 equiv.) and 165 mg d4TMP 2×nBu_4N^+ salt (0.21 mmol, 0.70 equiv.). Reaction time was 5 h at room temperature. Yield: 19 mg (0.021 mmol, 10%) white solid. ^{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). MALDI-MS (m/z): calculated for $C_{34}H_{53}N_2O_{16}P_3$ $[M-H]^-$ 837.254; found, 837.128. IR: ν [cm^{-1}] = 2987, 2971, 2917, 2850, 1758, 1688, 1508, 1453, 1394, 1220, 1127, 1066, 1014, 904, 869, 836, 782, 644, 491, 427.

Chemical hydrolysis of the γ-(AB, ACB)- or γ-(ACB, ACB)-alkyl-modified-Tri*PPP*ro-d4TTPs 8 and 13 as well as the γ-ACB-d4TTPs 20

Stock solutions (50mM in DMSO-d_6) of compounds **8**, **13**, **20** were prepared. After dilution of 11 µL stock solution with 100 µL milliQ water and 189 µL DMSO-d_6 to 1.9mM hydrolysis

solutions the reaction was started by addition of 300 µL phosphate buffer saline (PBS, 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 265-266 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.

Enzymatic hydrolysis of compounds 8 and 13 with *pig liver esterase* (PLE)

10 µL 50 mM DMSO stock solution of Tri*PPP*ro-d4TTPs **8** or **13** were diluted to 6.0 mM hydrolysis solution by addition of 31.7 µL DMSO and 41.7 µL ultrapure water. Then 83.3 µl of the 6.0 mM solution was diluted with 125 µL DMSO and 833 µl 50 mM PBS buffer (pH 7.3). The reaction was started by addition of 62.5 µl of PLE in PBS buffer (3 mg/mL) and the mixture was incubated with 800 rpm at 37 °C in a thermomixer. At different times, aliquots (100 µl) were taken and the reaction was stopped by addition to 106 mL MeOH. The mixture was kept for 5 min on ice followed by centrifugation for 5 min (13000 rpm). The mixture was filtered (Chromafil RC-20/15 MS, 0.2 mm) and stored in liquid nitrogen. When testing, the samples were defrosted and injection volume with 80 µL was used for HPLC analysis.

Enzyme-catalyzed hydrolysis of Tri*PPP*ro-d4TTPs 8 or 13

18 µL of the appropriate 50 mM DMSO-d_6 stock solution was diluted to 6.0 mM hydrolysis solution by addition of 132.0 µL DMSO-d_6. 7-10 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 (80ul) were directly injected to HPLC. The calculation of $t_{1/2}$ was performed analogously to that for the chemical hydrolysis studies.

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 PBS, 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.

Anti-HIV activity assay: Inhibition of HIV-1(III_B)- and HIV-2(ROD)-induced cytopathicity in wild-type CEM/0 and $CD4^+$ T-cells 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%.

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Funding Sources

The work conducted by CM was supported by the Deutsche Forschungsgemeinschaft (DFG; Me1161/13-1, Me1161/15-1, Me1161/17-1) and that of DS has been supported by the KU Leuven (GOA 15/19 TBD).

Author contributions

CM headed the project; XJ performed the chemical synthesis and did the biochemical assays, DS carried out the antiviral testing of the synthesized compounds. All authors were involved in the preparation of the manuscript.

ACKNOWLEDGMENTS

The authors are grateful to Ria Van Berwaer, Sandra Claes, Daisy Ceusters and Evelyne Van Kerckhove for excellent technical assistance.

ABBREVIATIONS USED

AZT, 3'-azido-3'-deoxythymidine; d4T, 3'-deoxy-2',3'-didehydrothymidine; NTP, nucleoside triphosphate; NDP, nucleoside diphosphate; NMP, nucleoside monophosphate; PLE, pig liver esterase; TK, thymidine kinase

ASSOCIATED CONTENT

Supporting Information NMR-spectra of all compounds and Molecular Formula Strings. This material is available free of charge via the Internet at http://pubs.acs.org.

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