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FULL PAPER

Phosphate-Based Self-Immolative Linkers for Tunable Double Cargo Release

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We dedicate this paper to the memory of Dr. John C. Martin (1951–2021), head of Gilead Sciences, to commemorate his achievements in the development of anti-HIV drugs (acyclic nucleoside phosphonates, “Holy Trinity”: A. Holý, E. De Clercq, J. C. Martin).

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Abstract: Phosphorus-based self-immolative (SI) linkers offer a wide range of applications, such as smart materials and drug delivery systems. Phosphorus SI linkers are ideal candidates for double cargo delivery platforms because they have a higher valency than carbon. Accordingly, we designed a series of substituted phosphate linkers for releasing two phenolic cargos through SI followed by chemical hydrolysis. Suitable modifications of the lactate spacer increased the cargo release rate significantly, from 1 day to 2 hours or 5 minutes, as shown for linkers containing *p*-fluoro phenol. In turn, double cargo linkers bearing *p*-methyl phenol released their cargo more slowly (4 days, 4 hours, and 15 minutes, respectively) than their *p*-fluoro analogues. The *α*-hydroxyisobutyrate linker released both cargos in 25 minutes. Our study expands the current portfolio of SI constructs by providing a double cargo delivery option, which is crucial to develop universal SI platforms.

Introduction

Self-immolative (SI) linkers are chemical constructs subjected to irreversible fragmentation triggered by external stimuli.[1] After external activation, SI linkers disassemble (e.g., via cyclisation or electronic cascade), thereby releasing a leaving group (cargo). Triggered cargo release can be used in drug delivery[2] (prodrugs,[3] antibody-drug conjugates,[4] and chemosensors[5]), smart materials[6] (stimuli-responsive SI dendrimers[7] and polymers[8]), or *in vivo* cell labelling,[9] thus highlighting the wide range of applications of SI linkers. In turn, different structural motifs, including carbamate[3,6,10] or phosphate,[11] can be used to attach chemically variable cargos to the SI linker.

Phosphorus-based SI linkers can offer higher versatility than their carbamate analogues because they allow us to attach an additional substituent (a second cargo), which significantly broadens their potential applications. For example, a double cargo linker can be used to simultaneously tether a drug (warhead, first cargo) and a reporter molecule (chromogenic molecule, second cargo).[12] Systems combining double (multi) cargo release have been studied[13] to pursue effective cancer chemotherapy utilising complementary drug combination,[14] antibiotic drug resistance[15] or novel fluorescent reporters/signal amplification chemosensors.[5a,16] In addition, phosphorus linkers enable us to monitor the reaction pathway by ^{31}P NMR spectroscopy in real-time,[17] providing detailed structural and kinetic information, and to even detect the cyclic intermediates in some cases,[18] confirming cargo release *via* Self-immolation, more specifically intramolecular cyclisation, and not *via* chemical hydrolysis.

Self-immolation, and consequently the rate of the cargo release reaction, can be tuned up by varying substituents on the phosphorus atom and is mainly directed by two effects: 1) the Thorpe-Ingold[19] effect and 2) the *pKa* effect of the leaving groups. The Thorpe-Ingold effect refers to the spacer – sterically demanding substituents in the *α*-position accelerate intramolecular cyclisation.[20] Conversely, the *pKa* effect is related to the cargo – the more acidic the cargo is (lower *pKa*), the faster the cargo will be released upon external activation.[18] Fast cargo release systems are usually designed for biological applications. However, slow SI may also be advantageous when constructing slowly–reacting (decomposing) polymers[8,21] or developing prodrugs with delayed cargo release (e.g., antibiotics).[22] Notwithstanding these advances and the potential of SI linkers, no phosphate-based, double cargo release system has been reported yet.

Considering the above, we designed a novel set of phosphate linkers bearing a lactate spacer (Figure 1) to attach two cargos (double cargo option). We also fine-tuned the release of both cargos by introducing a suitable modification in the lactate spacer and by adjusting the *pKa* of the leaving groups. SI was triggered by UV light (365 nm) and monitored by ^{31}P NMR spectroscopy. The structures of intermediates and products were determined *in situ* by combining ^{13}C and ^{31}P NMR spectra. Our findings indicate that SI linkers with controlled double cargo release may be applied to develop novel combination therapies and smart materials.

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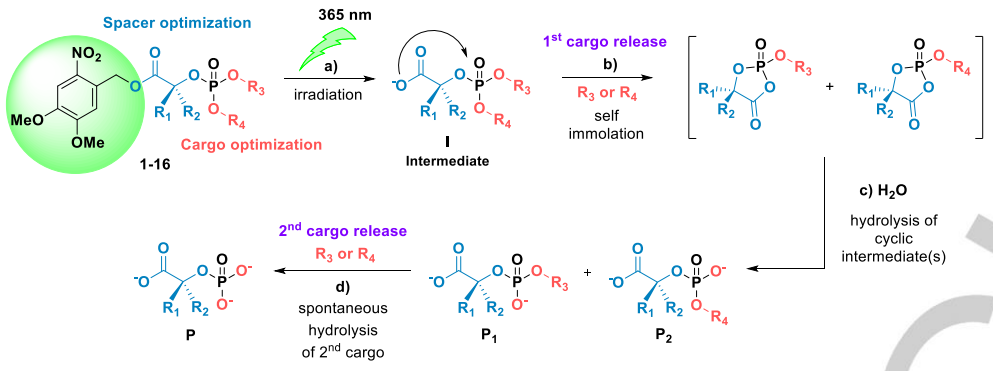


Cpd	R_1	R_2	R_3	R_4
1	Me	H	Ph	*p*-F-Ph
2	Me	H	Ph	*p*-Me-Ph
3	Me	H	*p*-NO_2-Ph	Et
4	Me	H	*p*-F-Ph	Et
5	Me	H	Ph	Et
6	Me	H	*p*-Me-Ph	Et
7	Me	H	*p*-OMe-Ph	Et
8	*i*-Pr	H	Ph	Et
9	Me	Me	Ph	Et
10	*i*-Pr	H	Ph	*p*-F-Ph
11	*i*-Pr	H	Ph	*p*-Me-Ph
12	Me	Me	Ph	*p*-F-Ph
13	Me	Me	Ph	*p*-Me-Ph
14	Me	H	Et	Et
15	*i*-Pr	H	Et	Et
16	Me	Me	Et	Et

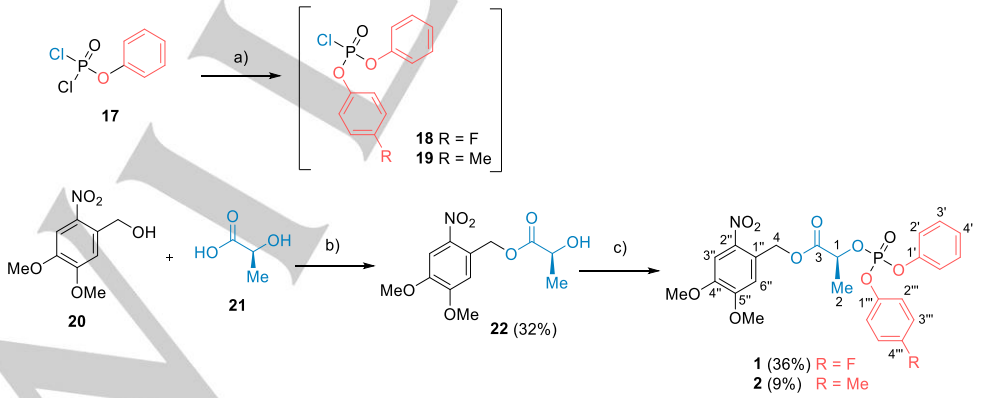
Figure 1. Chemical structure of phosphate-based linkers **1**–**16** and the proposed mechanism of self-immolation; a) photoactivation; b) intramolecular cyclisation leading to 1st cargo release; c) 2nd cargo release (via chemical hydrolysis).

Results and Discussion

Double cargo system: proof of concept

Our initial strategy was to prepare the two model double cargo linkers with a lactate spacer as proof of concept. Compounds **1** and **2** were prepared by phosphorylation[23] of **22** using the corresponding *in situ*-generated diphenyl phosphoro-chloridates **18** and **19** (Scheme 1) in dichloromethane (DCM) at room temperature. Photocleavable dimethoxy nitrobenzyl (DMNB)[24] ester **22** was prepared from DMNB-alcohol **20** and the lactic acid **21** *via* acid-catalysed esterification in refluxing toluene. Phosphorochloridates **18** and **19** were synthesized from phenyl dichloridate **17** and the corresponding phenol in toluene at room temperature (Scheme 1), and **1** and **2** were synthesized using *N*-methylimidazole (NMI)[25] as a base/catalyst (Scheme 1c). Other bases, such as triethylamine (TEA), pyridine, and 4-(dimethylamino)pyridine (DMAP), were also tested during reaction optimisation, albeit without success.[26] The reaction progress was monitored by ^{31}P NMR spectroscopy (for NMR chemical shifts in $CDCl_3$, see Table S9 in ESI).

We performed irradiation NMR experiments on **1** and **2**, in a previously optimised mixture of cacodylate buffer/DMSO (1/1, v/v). Indeed, both pilot compounds **1** and **2** cyclised upon UV light irradiation, releasing the cargos overnight (Figure 2). Compound **1**, bearing the electron-withdrawing (EWG) *p*-F substituent, provided two ^{31}P NMR signals at δ_P = –13.02 and –13.10 ppm, corresponding to two diastereoisomers resulting from a stereogenic centre on the phosphorus atom, and carbon in the lactate spacer. Upon UV light irradiation, DMNB was cleaved off, and intermediate **1-I** (δ_P = –12.55 and –12.64 ppm) was formed in 5 minutes (full conversion of **1** to **1-I** in 15 minutes). The activated linker **1-I** slowly cyclised and afforded mono-phenyl products **1-P1** (δ_P = –6.17 ppm) and **1-P2** (δ_P = –5.98 ppm) overnight. The more acidic *p*-F-phenyl substituent (*pKa* 9.95[27]) was released by SI first (**1-P1**), while the phenyl



Scheme 1. Synthesis of the two model double cargo linkers **1** and **2** prepared for a proof of concept study. Reaction conditions: a) "the corresponding phenol", TEA, toluene, 25 °C, 12 hours; b) *p*-toluenesulfonic acid, toluene, reflux, 16 hours; c) diphenyl chlorophosphate **18** (for **1**) or **19** (for **2**) NMI, DCM, 25 °C, 12 hours.

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substituent (with higher *pKa* 9.98[28]) remained mostly unscathed (**1-P2**). A trace amount of the fully hydrolysed product **P** (δ_P = 0.06 ppm) was observed after 4 days. Compound **2**, with the electron-donating (EDG) *p*-Me group (δ_P = –12.92 and –13.09 ppm), also afforded the activated intermediate **2-I** (δ_P = –12.57 ppm), but its cyclisation proceeded significantly slower than that of **1-I**. After 24 hours, **2-I** was still the major component (Figure 2). The desired products **2-P1** (δ_P = –6.19 ppm) and **2-P2** (δ_P = –6.02 ppm) were identified, but the more acidic phenol (**2-P2**) was preferentially released.

Both linkers (**1** and **2** differing in R_4, Figure 1) provided the same mono-phenyl product **P1** (**1-P1** and **2-P1**), albeit in significantly different timescales (in 15 minutes and 24 hours, respectively). Phenol release can be controlled by a nature of the second cargo. The ability to attach cargos with different release rates may be hence useful for further applications, such as generating phosphorylated metabolites in biology experiments and drug delivery, among others.

The structures of the two intermediates (**1-I** and **2-I**) and of products **P1** and **P2** were determined *in situ* by combining ^{13}C and ^{31}P NMR spectra. The key connectivity information was derived from the ^{13}C signal splitting caused by ^{13}C-^{31}P spin-spin interaction (J_{CP}), typically through two or three chemical bonds, with J_{CP} = 3–8 Hz (Table S3–8 in ESI). The ^{13}C-^{19}F spin-spin interactions (J_{CF} = 4–244 Hz) enabled us to easily identify the phenyl that was preferentially released from **1**.

pKa effect on single-cargo release

To better understand the *pKa* effect on cargo release, we prepared a series of compounds **3**–**7** bearing only one releasable phenolic cargo differing in *para* substitution (Scheme 2). The lactate derivative **22** was treated with highly reactive ethyl dichloridate **23** and with one equivalent of TEA in toluene at room temperature to give the corresponding phosphorochloridate **24** (not isolated). Toluene was removed at low pressure, and crude **24** was subsequently used in reactions with the corresponding phenols in DCM, in the presence of TEA, to give **3**–**7**. The reaction progress was monitored by ^{31}P NMR spectroscopy (for NMR chemical shifts in $CDCl_3$, see Table S10 in ESI).

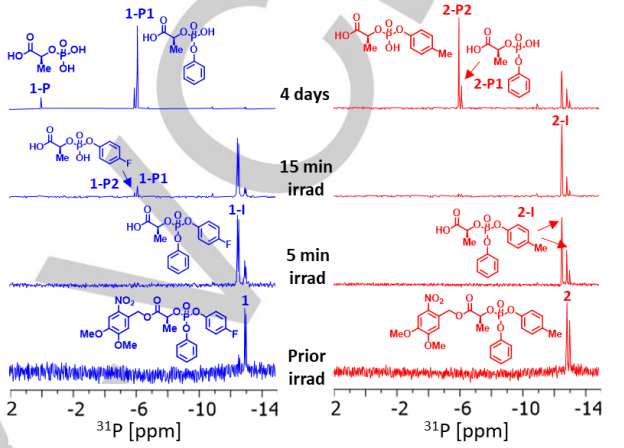
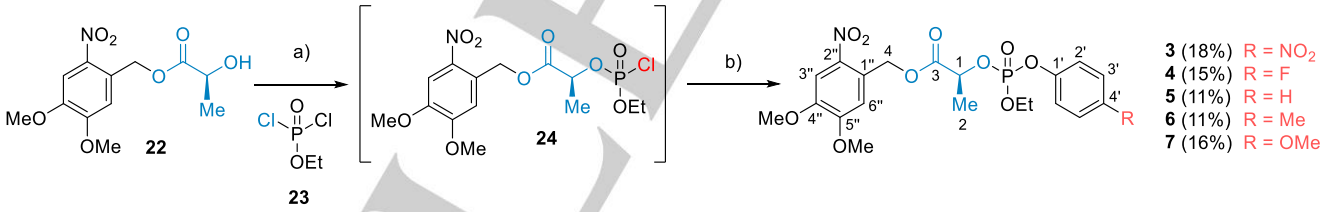


Figure 2. Figure Series of ^{31}P NMR spectra of 5 mM **1** (left) and **2** (right) in 50% CACO/DMSO-d_6 recorded before and after UV light irradiation (365 nm) at room temperature. In both cases, the more acidic phenol (*p*-F-phenol in **1** and the unsubstituted phenol in **2**) was released preferentially. The high signal-to-noise ratios of the first spectra (the prior irrad row) are caused by the lower solubility of the starting compounds in 50% CACO/DMSO-d_6.



Scheme 2. Synthesis of lactate linkers **3**–**7**. Reaction conditions: a) TEA, toluene, 25 °C, 12 hours, and then: b) "corresponding phenol", TEA, DCM, 25 °C, 12 hours.

Compounds **3**–**7** released the phenolic cargo successfully at various rates, and the same final product **P2** (δ_P = –1.14 ppm) was detected in all cases (Figure 3). In **3** (EWG NO_2 group), the SI was so fast that **3-I** was not detected, and *p*-NO_2-phenol was released in an hour. Moreover, we observed spontaneous partial hydrolysis of **3** overnight, which released *p*-NO_2-phenol without photoactivation; therefore, no SI could proceed (hydrolytic product **hP**, Figure 3, left).

Such a hydrolytic decomposition of **3** may be easily misinterpreted for SI when using common optical methods.[18] SI was slower In **4** than in **3**, the intermediate **4-I** was detected, and the corresponding phenol was released in 24 hours. The relative concentration of products **3-P2** and **4-P2** was significantly higher than that of their unsubstituted phenol counterpart **5**. The SI reaction in **3**, **4** and **5** matches the corresponding *pKa* values of *p*-NO_2, *p*-F, and *p*-H phenols (7.15[28], 9.95, and 9.98, respectively). The lower the *pKa* of phenol is, the faster SI will be. Conversely linkers bearing EDG phenols with *p*-Me (**6**) and *p*-OMe (**7**) released the corresponding phenol in 96 and 24 hours, respectively. The higher *pKa* values of EDG-phenols in **6** and **7** (10.14[28] and 10.55[29], respectively) resulted in slower cargo release in **6**; as such, only traces of **6-P2** were detected overnight. Yet, in contrast to **6**, linker **7** did not fully match its *pKa* value and led to a faster cargo release than **5**. The 15-minute trace in Figure

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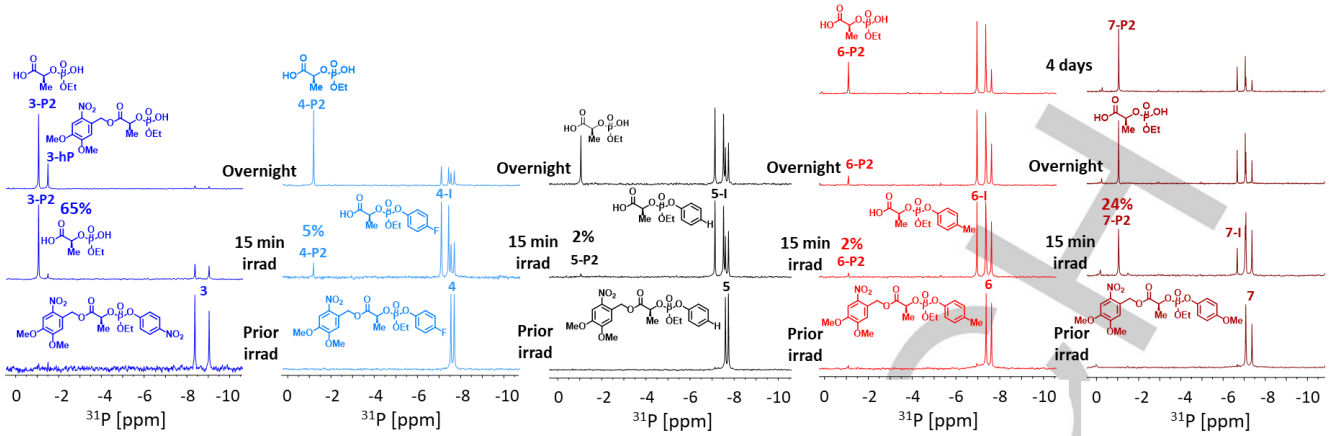


Figure 3. Series of ^{31}P NMR spectra of compounds **3**–**7** (5 mM, 50% CACO/DMSO-d_6) recorded upon UV light irradiation (365 nm) at room temperature.

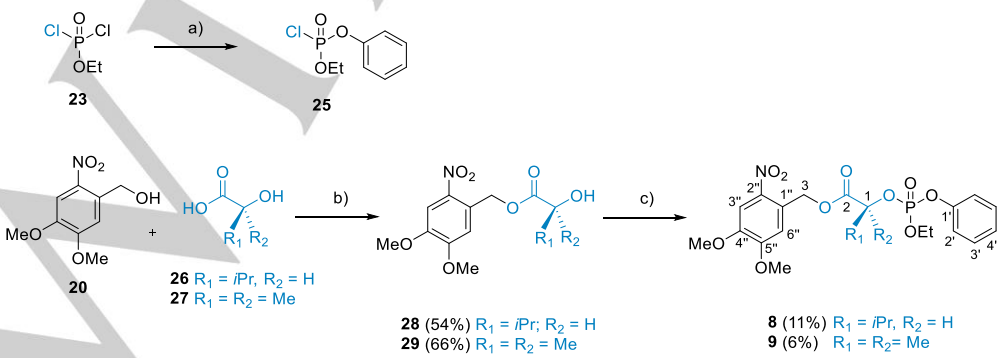
3 shows the relative concentration of the final product **P2** of **3**–**7** as follows: 65%, 5%, 2%, 2% and 24%.

We monitored the cyclisation of **3**–**7** by ^{31}P NMR spectra with *in situ* irradiation (details in ESI) and extracted the concentration profiles of intermediates within 60 minutes of UV irradiation. Based on our previous study,[20] the photoactivation minutes (kinetic curves in Figure S1 in ESI). The SI rates in **3**–**7** did not fully match the *p*Ka values of the leaving groups, showing the following trend: **6** (*p*-Me) < **5** (*p*-H) < **4** (*p*-F) < **7** (*p*-OMe) < **3** (*p*-NO_2). Most likely, the pKa value is not the only parameter that affects SI. We may, nevertheless, speculate that a resonance-based change of electron density on phosphorus is mediated by *p*-OMe (free electron pair of oxygen), which supports SI.

Spacer optimisation

To accelerate cargo release, we used the Thorpe-Ingold effect[19] and modified the lactate spacer responsible for cyclisation in **5** by introducing either a sterically demanding or an additional α-substituent. Thus, we prepared model *α*-hydroxyisovalerate and *α*-hydroxyisobutyrate linkers (**8** and **9**, respectively). For this purpose, photocleavable (DMNB)-esters **28** and **29** were synthesized from DMNB-alcohol **20** and the corresponding carboxylic acids, α-hydroxyisovaleric **26** and *α*-hydroxyisobutyric **27**, via an acid-catalysed esterification in is similar among **3**–**7**, which bear the same lactate spacer. Thus, alterations in intermediate concentrations represent differences in cyclisation rates. For example, in 30 minutes, we obtain 0% of **3-I,** meaning that cyclisation is fast and that photoactivation is the rate-limiting step. Conversely, linkers **4**–**7** provided 32% **4-I**, 48% **5-I** and 55% **6-I**, and 18% **7- I** in 30 refluxing toluene using a condenser trap to remove the reaction water (Scheme 3). However, the synthetic approach used for compounds **3**–**7** failed in the derivatives of *α*-hydroxyisovalerate **8** and α-hydroxyisobutyrate **9**, most likely due to the degradation of the starting materials **26** and **27** (dehydration of branched acid esters **26** and **27**). Therefore, we came up with an alternative synthetic approach, similar to **1** and **2**, generating the phosphorylating agent **25** *in situ* to phosphorylate compounds **28** and **29** and thus yielding **8** and **9** (Scheme 3).

Monochloridate **25** was prepared in toluene using TEA. However, the phosphorylation of the sterically hindered alcohols **28** and **29** was challenging. Several conditions (solvents, bases and temperatures) were tested, but only limited combinations gave the desired products, as monitored by ^{31}P NMR (see Table S11 in ESI). The secondary alcohol **28** yielded the desired product **8** only when using the DMAP base, and the tertiary alcohol **29** gave product **9** when using NMI, both of which in DCM.



Scheme 3. Synthesis of linkers **8** and **9** with branched substituents in α position. Reaction conditions: a) phenol, TEA, toluene, 25° C, 12 hours; b) *p*-toluenesulfonic acid, toluene, reflux, 16 hours; c) for **8**: compound **25**, DMAP, DCM, 25 °C, 12 hours; for **9**: compound **25**, NMI, DCM, 25 °C, 12 hours.

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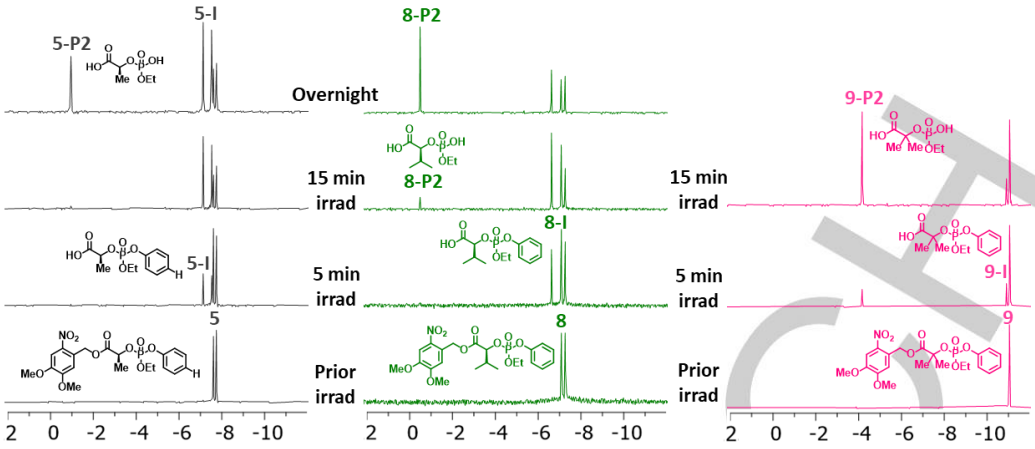


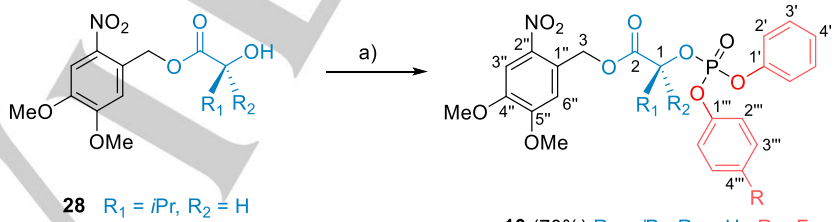
Figure 4. Series of ^{31}P NMR spectra of linkers **5**, and **8**–**9**, (5 mM, 50% CACO/DMSO-d_6) recorded upon UV light irradiation (365 nm) at room temperature.

Surprisingly, despite the increase of steric demands in the *α* position, SI was not significantly better in **8** than in **5** (Figure 4). Although traces of **8-P2** (δ_P –0.60 ppm) were detected after 15 minutes, a comparable amount of **P2** from both analogues (**5** and **8**) was detected within 24 hours. This finding contrasts with our previous observation in the phosphoramidate linker series,[20] wherein the increase in the *α*-substitution effect (Me versus *i*-Pr) markedly increased the cargo release rate. Conversely, linker **9** (δ_P –10.99 ppm) increased the cargo release considerably, with traces of **9-P2** (δ_P –4.22 ppm) being detected within 5 minutes. After 15 minutes, **9-P2** was the main component in the reaction mixture. This trend is also clearly visible in the concentration profiles of intermediates **5-I**, **8-I** and **9-I** (Figure S1 in ESI), where **9-I** remains at approximately 20% (in 20–60 minutes), which means that **9-I** cyclises more quickly than **5-I** and **8-I**. In contrast, the concentration of **5-I** and **8-I** increases from 40 to 70% (in 20–60 minutes), indicating significantly slower cyclisation and, thus, slower cargo release.

Double cargo linkers with a tunable release rate

Our structure-activity relationship study, including spacer and cargo modifications, provided us with deeper insights into SI and its limitations, encouraging us to design other double-cargo systems with a wider range of release rates as the basis for linkers with timed, double-cargo sequential release.

The third class of linkers, **10**–**13**, containing diphenyl substituted phosphorus, was prepared similarly to **1** and **2**. *In situ*-generated phosphorochloridates **18** and **19** (Scheme 1) were directly used to phosphorylate **28** and **29** (Scheme 4), but sterically hindered alcohols **28** and **29** showed low reactivity to **18** and **19**. Thus, the reaction conditions required optimisation. For *α*-hydroxyisovalerate **28**, using DMAP in DCM was the most effective approach. In contrast, for *α*-hydroxyisobutyrate **29**, using one equivalent of TEA in DCM with DMAP catalysis led to the highest yields (Scheme 4). Tertiary alcohol **29** did not react under NMI conditions (as in **9**), nor did DMAP (without TEA) or TEA (without DMAP). This difference in reactivity is likely caused by the low reactivity of diphenyl monochloridates **18** and **19** combined with the bulky alcohols **28** and **29**. Hence, synthetic access to asymmetric diphenol-phosphates with a bulky alcohol spacer should be optimised for particular substrates. In this study, we monitored the reaction progress by ^{31}P NMR spectroscopy (for NMR chemical shifts in $CDCl_3$, see Table S12 in ESI; for the synthetic note page S23).



28 R_1 = *i*Pr, R_2 = H
29 R_1 = R_2 = Me

10 (70%) R_1 = *i*Pr, R_2 = H, R = F
11 (58%) R_1 = *i*Pr, R_2 = H, R = Me
12 (10%) R_1 = R_2 = Me, R = F
13 (54%) R_1 = R_2 = Me, R = Me

Scheme 4. Synthesis of branched double-cargo linkers **10**–**13**. Reaction conditions: a) for **10** and **11**: "diaryl-chlorophosphate **18** or **19**", DMAP, DCM, 25 °C, 12 hours; for **12** and **13**: "diaryl-chlorophosphate **18** and **19**", respectively, TEA, DMAP (cat.), DCM, 25 °C, 12 hours.

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All double-cargo linkers **10**–**13** displayed the desired properties, covering a wide range of cargo release rates – from minutes to days – and enabling sequential cargo release. Modifying the lactate spacer increased SI significantly, from 24 hours in **1** and **2** to 2 hours in *α*-hydroxyisovalerate analogues **10** and **11** or to 15 minutes in their *α*-hydroxybutyrate counterparts **12** and **13**, as shown in Figures 2 and 5. The SI of **10**–**13** matches the trend found in single-cargo linkers **5**, **8** and **9** (Figure 4) where butyrate spacer showed faster cyclisation (also supported by the concentration profiles of the intermediates, Figure S1 in ESI). Moreover, the relative concentrations of **12-I** and **13-I** are approximately 15% and 35%, which proves the faster SI and cargo release of *p*-F linker **12**. We also noticed that the cargo release rates of **10** and **12** (EWG cargos, *p*-F phenyl group) are similar to those of **1** and **11** and that the cargo release rate of **13** (EDG cargos, *p*-Me phenyl moiety) is similar to that of **2**. In general, linkers **1**, **10**, and **12** with EWG cargo yielded a significantly higher amount of **P1**/**P2** than their EDG cargo counterparts **2**, **11**, and **13**, respectively, as shown in Figures 2 and 5 (see the 15-minute row). Moreover, the *α*-hydroxyisovalerate analogues **10** and **11** were measured in 25% CACO/DMSO because of their low solubility in the 50% solvent system (the solvent effect is shown in Figure S2, in ESI, and is in line with our previous study[31]).

Interestingly, in **12,** both phenolic cargos were released within 25 minutes, exclusively yielding the final product **12-P**, while compound **13** gave a mixture of **13-P2** and **13-P** (=**12-P**) in 3 hours, showing similar characteristics to **11** but a faster release rate. Importantly, **12** and **13** are stable in 50% CACO/DMSO mixture at room temperature for seven days (Figure S3 in ESI), which is enough time for most biological applications.

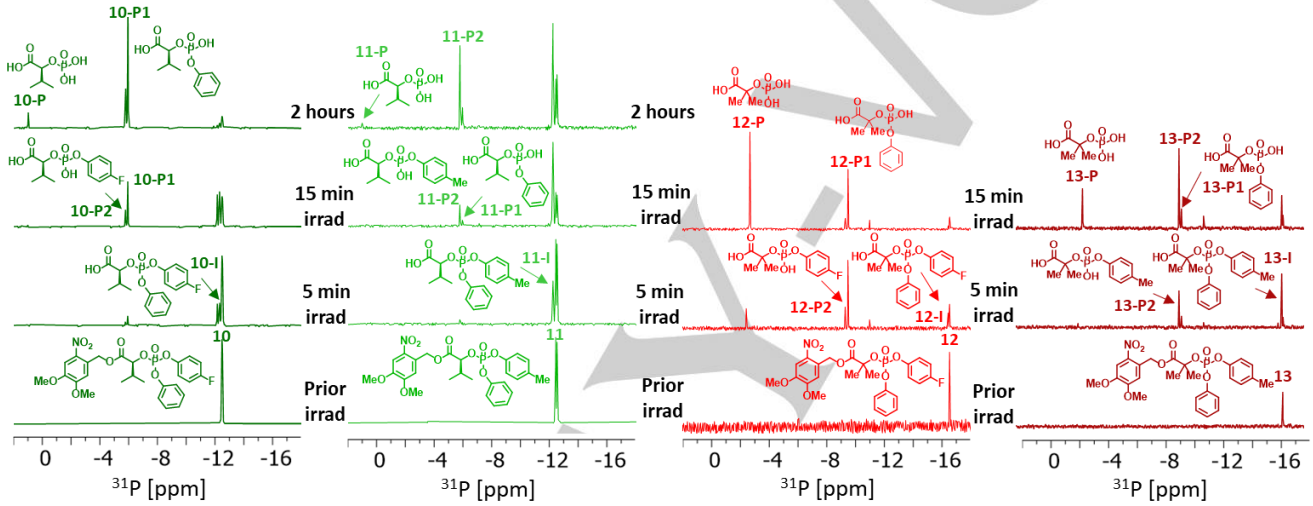
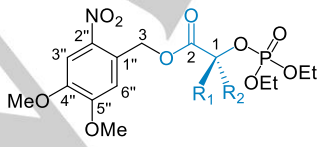


Figure 5. Series of ^{31}P NMR spectra of compounds **10**–**13** (5 mM, 25% (**10**, **11**) or 50% (**12**, **13**) CACO/DMSO-d_6) recorded upon UV light irradiation (365 nm) at room temperature. The more acidic phenolic cargo is preferentially released, and the α-hydroxybutyrate linkers **12** and **13** released the cargo within minutes, while the α-hydroxyisovalerate analogues **10** and **11** released the cargo within hours.

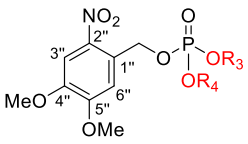
Negative controls

We examined three linkers, **14**–**16**, differing in the spacer (lactate, *α*-hydroxyisovalerate and *α*-hydroxybutyrate, respectively) and bearing ethyl moieties instead of phenyl groups serving as negative controls. We expected that the photoactivation step would result in the formation of intermediate **I** without any further change (no cargo release).

As a second negative control, we included three derivatives, **32**–**34**, bearing no SI spacer. All negative controls, **14**–**16** and **32**–**34**, confirmed the importance of a suitable cargo (appropriate leaving group) and a spacer, which responsible for SI. Without them, no SI cascade is possible, as shown in Figure S5, and Section 2 in ESI.



14 (13%) R_1 = Me, R_2 = H
15 (17%) R_1 = *i*Pr, R_2 = H
16 (11%) R_1 = Me, R_2 = Me



32 (21%) R_3 = Et, R_4 = Et
33 (17%) R_3 = Ph, R_4 = Et
34 (11%) R_3 = Ph, R_4 = *p*-F-Ph

Scheme 5. Negative controls: linkers **14**–**16** bearing no releasable ethanol cargo (left), and linkers **32**–**34** with no spacer responsible for SI (right).

Conclusion

We developed a novel class of phosphate-based SI linkers with a tuneable double-cargo release option. The first cargo is released through SI, while the second cargo is released through chemical hydrolysis. Suitable modifications of the lactate spacer increased the cargo release rate significantly, from 1 day to 2 hours or to 5 minutes, as shown for the linkers containing *p*-F phenol **1**, **10**, or **12**, respectively. In turn, the double cargo linkers **2**, **11**, and **13**, bearing *p*-Me phenyl, released their cargo more slowly (4 days, 4 hours, and 15 minutes, respectively) than their *p*-F analogues. Our linkers provide the: a) programmable release of the first cargo in 3 hours (**10-P1**, **11-P2**); b) simultaneous release of both cargos within 25 minutes (**12-P**); or c) sequential release of the first cargo within 15 minutes (**13-P2**) followed by the second cargo release within 3 hours (**13-P**). Linkers **12** and **13**, with the fastest cargo release rates, have shown satisfying stability in a 50% buffer/DMSO mixture for seven days at room temperature. Overall, we are now able to drive the sequential release of two cargos from minutes to days by controlling SI. Our systems also provide phosphorylated products **P1**, **P2**, and **P** in a wide range of time scales. These systems may thus find further applications, such as the development of new smart materials and multiple drug delivery or the generation of phosphorylated species. Ultimately, our study pioneers a novel route for the design of phosphorus-based, self-immolative systems for double-cargo release.

Experimental Section

General. All reagents were purchased from commercial suppliers and used as received. 4,5-Dimethoxy-2-nitrobenzyl alcohol was purchased from Fluorochem Ltd. (United Kingdom). All reactions were performed under an inert argon atmosphere. Thin layer chromatography (TLC) was performed on TLC aluminium sheets (silica-gel 60 F_{254}; Merck). Reaction progress was monitored using TLC and/or ^{31}P NMR spectroscopy in $CDCl_3$. Flash-column chromatography was performed on a Compact (ECOM s.r.o.) chromatography system using silica-gel or C18 silica-gel 230–400 mesh, 60 Å (Merck KGaA, Germany). The final products were recovered by solvent evaporation. All products were viscous oils, semi-solids or non-crystalline solids. The reaction yields were not optimised.

Synthesis

4,5-Dimethoxy-2-nitrobenzyl L-lactate (**22**). 4,5-Dimethoxy-2-nitrobenzyl alcohol **20** (213 mg, 1.00 mmol, 1.00 eq.) and L-lactic acid (90 mg, 1.00 mmol, 1.00 eq.) were suspended in toluene (50 mL), subsequently adding *p*-toluenesulfonic acid (50 mg, 0.26 mmol, 0.26 eq.) at 25 °C. The mixture was refluxed for 12 hours, evaporated to dryness in *vacuo* with silica-gel, and the title compound was isolated by normal-phase flash chromatography (DCM – methanol gradient on silica-gel) and followed by reverse-phase flash chromatography (water – acetonitrile gradient on C18 silica-gel). Yield **22** (90 mg, 32%) of an off-white semisolid. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 7.71 (s, 1H, 3''), 7.21 (s, 1H, 6''), 5.55 (d, 1H, $J_{OH\text{-}3}$ = 5.9, -OH), 5.46 (d, 1H, J_{GEM} = 14.1, 4a), 5.39 (d, 1H, J_{GEM} = 14.1, 4b), 4.25 (m, 1H, 1), 3.90 (s, 3H, 5''-O-C**H$_3$**), 3.87 (s, 3H, 4''-O-C**H$_3$**), 1.29 ppm (d, 3H, $J_{2\text{-}1}$ = 6.8, 2). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 174.07 (3), 153.18 (5''), 147.98 (4''), 139.69 (2''), 126.16 (1''), 111.35 (6''), 108.28 (3''), 65.99 (1), 62.62 (4), 56.26 (5''-O-**C**H$_3$), 56.12 (4''-O-**C**H$_3$), 20.32 ppm (2). HRMS (ESI+) calculated for $C_{12}H_{15}O_7NNa$ 308.07407, found $[M+Na]^+$ 308.07381.

4,5-dimethoxy-2-nitrobenzyl (S)-2-hydroxy-3-methylbutanoate (**28**). 4,5-Dimethoxy-2-nitrobenzyl alcohol **20** (2.55 g, 12.0 mmol, 1.20 eq.) and *p*-toluenesulfonic acid (172 mg, 1.00 mmol, 0.10 eq.) were suspended in toluene (100 mL), subsequently adding (*S*)-2-hydroxy-3-methylbutanoic acid (1.18 g, 10.0 mmol, 1.00 eq.) after 45 minutes of azeotropic distillation. The mixture was refluxed overnight and washed with saturated $NaHCO_3$ (60 mL), water (60 mL), and saturated NaCl (60 mL). The organic phase was dried with Na_2SO_4 and evaporated to dryness in *vacuo* with silica-gel. The title compound was isolated by normal-phase flash chromatography (DCM – methanol gradient on silica-gel) followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **28** (1.68 g, 54%) of a red-brown semisolid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.75 (s, 1H, 3''), 7.01 (s, 1H, 6''), 5.67 (d, J_{GEM} = 14.3, 3a), 5.59 (d, J_{GEM} = 14.3, 3b), 4.16 (d, 1H, $J_{1\text{-}CH(iPr)}$ = 3.5, 1), 4.00 (s, 3H, 5''-O-C**H$_3$**), 3.99 (s, 3H, 4''-O-C**H$_3$**), 2.14 (m, C**H**^{iPr}), 1.07 (d, 3H, $J_{CH3(iPr)\text{-}CH(iPr)}$ = 7.0, C**H**$_3^{iPr}$), 0.92 ppm (d, 3H, $J_{CH3(iPr)\text{-}CH(iPr)}$ = 7.0, C**H**$_3^{iPr}$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 174.38 (2), 153.45 (5''), 148.57 (4''), 140.20 (2''), 125.90 (1''), 110.89 (6''), 108.33 (3''), 75.16 (1), 64.19 (3), 56.42−56.46 (m, 4''-O-C**H**$_3$ and 5''-O-C**H**$_3$), 32.26 (C**H**^{iPr}), 18.78 and 16.03 ppm (C**H**$_3^{iPr}$). HRMS (ESI+) calculated for $C_{14}H_{19}O_7NNa$ 336.10537, found $[M+Na]^+$ 336.10506.

4,5-Dimethoxy-2-nitrobenzyl 2-hydroxy-2-methylpropanoate (**29**). 4,5-Dimethoxy-2-nitrobenzyl alcohol **20** (2.13 g, 10.0 mmol, 1.00 eq.) and 2-hydroxy-2-methylpropanoic acid (1.04 g, 10.0 mmol, 1.00 eq.) were suspended in toluene (100 mL), subsequently adding *p*-toluenesulfonic acid (200 mg, 1.04 mmol, 0.10 eq.) at 25 °C. The mixture was refluxed for 12 hours and evaporated to dryness in *vacuo* with silica-gel, isolating the title compound by normal-phase flash chromatography (DCM – methanol gradient on silica-gel) followed by reverse-phase flash chromatography (water – acetonitrile gradient on C18 silica-gel). Yield **29** (1.97 mg, 66%) of a greyish semisolid. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.75 (s, 1H, 3''), 6.98 (s, 1H, 6''), 5.61 (s, 2H, 3), 3.99 and 3.98 (s, 6H, 5''-O-C**H$_3$** and 4''-O-C**H$_3$**), 1.52 ppm (s, 6H, 1-(C**H$_3$**)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 176.69 (2), 153.49 and 148.42 (5'' and 4''), 139.96 (2''), 126.32 (1''), 110.16 (6''), 108.34 (3''), 72.19 (1), 64.34 (3), 56.42 and 56.38 (5''-O-**C**H$_3$ and 4''-O-**C**H$_3$), 27.21 ppm (1-(**C**H$_3$)$_2$). HRMS (ESI+) calculated for $C_{13}H_{17}O_7NNa$ 322.08972, found $[M+Na]^+$ 322.08944.

4,5-Dimethoxy-2-nitrobenzyl (2S)-2-(((4-fluorophenoxy)(phenoxy)phosphoryl)oxy)propanoate (**1**). Phenyl dichlorophosphate **17** (60 µL, 0.40 mmol, 1.00 eq.) was dissolved in toluene (3 mL), subsequently adding TEA (100 µL, 0.72 mmol, 1.80 eq.) and 4-fluorophenol (45 mg, 40 mmol, 1.00 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The solid residue was dissolved in DCM (3 mL) and 4,5-dimethoxy-2-nitrobenzyl L-lactate **22** (110 mg, 0.39 mmol, 0.98 eq.), subsequently adding NMI (35 µL, 0.44 mmol, 1.10 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The title compound was isolated by normal-phase flash chromatography (*n*-hexane – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – acetonitrile gradient on C18 silica-gel). Yield **1** (76 mg, 36%) of a yellow oil. NOTE – approximately 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.71 (s, 1H, 3''), 7.71 (s, 1H, 3''), 7.35 (m, 2H, 3'), 7.29 (m, 2H, 3'), 7.14−7.24 (m, 10H, 4', 2''', 2'), 7.02 (m, 2H, 3'''), 6.97 (m, 2H, 3'''), 7.00−7.01 (m, 2H, 6''), 5.62 (dd, 1H, J_{GEM} = 14.9, $J_{4a\text{-}6''}$ = 0.6, 4a), 5.61 (dd, 1H, J_{GEM}= 14.7, $J_{4a\text{-}6''}$ = 0.6, 4a), 5.56 (dd, 1H, J_{GEM} = 14.7, $J_{4b\text{-}6''}$ = 0.6, 4b), 5.53 (dd, 1H, J_{GEM} = 14.9, $J_{4b\text{-}6''}$ = 0.6, 4b), 5.15−5.24 (m, 2H, 1), 3.96 (s, 3H, 4''-O-C**H$_3$**), 3.95 (s, 3H, 4''-O-C**H$_3$**), 3.94 (s, 3H, 5''-O-C**H$_3$**), 3.92 (s, 3H, 5''-O-C**H$_3$**), 1.58−1.64 ppm (m, 6H, 2). ^{13}C NMR

(100 MHz, $CDCl_3$, 25 °C) δ 169.47 (d, $J_{3\text{-}P}$ = 5.0, 3), 169.38 (d, $J_{3\text{-}P}$ = 4.7, 3), 160.13 (dd, $J_{4'''\text{-}F}$ = 244.8, $J_{4'''\text{-}P}$ = 1.1, 4'''), 160.08 (dd, $J_{4'''\text{-}F}$ = 244.2, $J_{4'''\text{-}P}$ = 1.1, 4'''), 153.89 and 153.88 (5''), 150.25 (d, $J_{1'\text{-}P}$ = 7.3, 1'), 150.16 (d, $J_{1'\text{-}P}$ = 7.3, 1'), 148.54 and 148.50 (4''), 146.15−146.45 (m, 1'''), 139.76−139.94 (m, 2''), 130.04 and 129.91 (3'), 126.33 and 126.24 (1''), 125.87 (d, $J_{4'\text{-}P}$ = 1.4, 4'), 125.78 (d, $J_{4'\text{-}P}$ = 1.5, 4'), 121.86 (d, $J_{2'''\text{-}P}$ = 4.6, 2'''), 121.70 (d, $J_{2'''\text{-}P}$ = 4.9, 2'''), 120.24 (d, $J_{2'\text{-}P}$ = 4.7, 2'), 120.20 (d, $J_{2'\text{-}P}$ = 5.4, 2'), 116.59 (d, $J_{3'''\text{-}F}$ = 23.6, 3'''), 116.43 (d, $J_{3'''\text{-}F}$ = 23.6, 3'''), 110.43 and 110.37 (6''), 108.31 and 108.30 (3''), 73.65 (d, $J_{1\text{-}P}$ = 6.1, 1), 73.64 (d, $J_{1\text{-}P}$ = 5.9, 1), 64.53 (4), 56.75 (5''-O-**C**H_3), 56.55 (4''-O-**C**H_3), 19.16 (d, $J_{2\text{-}P}$ = 5.9, 2), 19.13 ppm (d, $J_{2\text{-}P}$ = 6.2, 2). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ −12.33 ppm. HRMS (ESI+) calculated for $C_{24}H_{23}O_{10}NFNaP$ 558.09358, found $[M+Na]^+$ 558.09332.

4,5-Dimethoxy-2-nitrobenzyl (2S)-2-(((4-methylphenoxy)(phenoxy)phosphoryl)oxy)propanoate (**2**). Phenyl dichlorophosphate **17** (60 µL, 0.40 mmol, 1.00 eq.) was dissolved in toluene (3 mL), subsequently adding TEA (100 µL, 0.72 mmol, 1.80 eq.) and 4-methylphenol (45 mg, 0.40 mmol, 1.00 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The solid residue was dissolved in DCM (3 mL) and 4,5-dimethoxy-2-nitrobenzyl L-lactate **22** (114 mg, 0.40 mmol, 1.02 eq.), adding NMI (40 µL, 0.50 mmol, 1.26 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The title compound was isolated by normal-phase flash chromatography (n-hexane – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **2** (20 mg, 9%) of a yellowish oil. NOTE – approximately 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.72 (s, 1H, 3''), 7.71 (s, 1H, 3''), 7.31–7.37 (m, 2H, 3'), 7.26–7.31 (m, 2H, 3'), 7.19–7.24 (m, 4H, 2'''or 2'), 7.12–7.19 (m, 2H, 4'), 7.09–7.12 (m, 2H, 3'''), 7.06–7.09 (m, 6H, 3''', 2' or 2'''), 7.02−7.04 (m, 2H, 6''), 5.51–5.64 (m, 4H, 4), 5.16−5.25 (m, 2H, 1), 3.95−3.96 (m, 6H, 4''-O-C**H$_3$**), 3.92 (s, 3H, 5''-O-C**H$_3$**), 3.91 (s, 3H, 5''-O-C**H$_3$**), 2.32 (s, 3H, 4'''-C**H$_3$**), 2.28 (s, 3H, 4'''-C**H$_3$**), 1.61 (dd, 3H, $J_{2\text{-}1}$ = 6.9, , $J_{2\text{-}P}$ = 0.9, 2), 1.61 ppm (dd, 3H, $J_{2\text{-}1}$ = 6.9, , $J_{2\text{-}P}$ = 0.8, 2). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 169.37 (d, $J_{3\text{-}P}$ = 4.9, 3), 169.34 (d, $J_{3\text{-}P}$ = 5.2, 3), 153.83 (5''), 150.23−150.43 (m, 1'), 148.26 and 148.25 (4''), 148.16 (d, $J_{1'''\text{-}P}$ = 7.2, 1'''), 148.07 (d, $J_{1'''\text{-}P}$ = 7.6, 1'''), 139.54 and 139.51 (2''), 135.29 (d, $J_{4'''\text{-}P}$ = 1.5, 4'''), 135.29 (d, $J_{4'''\text{-}P}$ = 1.5, 4'''), 130.26 (3'''), 130.15 (3'), 126.47 and 126.45 (1''), 129.83 (d, $J_{4'\text{-}P}$ = 1.6, 4'), 125.71 (d, $J_{4'\text{-}P}$ = 1.6, 4'), 120.15 (d, $J_{2'\text{-}P}$ = 4.6, 2'), 120.10 (d, $J_{2'\text{-}P}$ = 4.5, 2'), 119.84 (d, $J_{2'''\text{-}P}$ = 5.2, 2'''), 119.78 (d, $J_{2'''\text{-}P}$ = 5.1, 2'''), 110.02 and 109.99 (6''), 108.10 and 108.08 (3''), 73.38 (d, $J_{1\text{-}P}$ = 5.8, 1), 64.28 (4), 56.64 (5''-O-**C**H_3), 56.39 (4''-O-**C**H_3), 20.73 and 20.68 (4'''-**C**H_3), 19.01 (d, $J_{2\text{-}P}$ = 5.7, 2), 18.98 ppm (d, $J_{2\text{-}P}$ = 5.9, 2). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ −12.27 and −12.29 ppm. HRMS (ESI+) calculated for $C_{25}H_{27}O_{10}NP$ 532.13671, found $[M+H]^+$ 532.13678.

4,5-Dimethoxy-2-nitrobenzyl (2S)-2-((ethoxy(4-nitrophenoxy)phosphoryl)oxy)propanoate (**3**). 4,5-Dimethoxy-2-nitrobenzyl L-lactate **22** (110 mg, 0.39 mmol, 1.00 eq.) was dissolved in toluene (4 mL), subsequently adding ethyl dichlorophosphate **23** (50 µL, 0.40 mmol, 1.03 eq.) and TEA (100 µL, 0.72 mmol, 1.85 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The solid residue was dissolved in DCM (4 mL), subsequently adding 4-nitrophenol (56 mg, 0.40 mmol, 1.03 eq.) and then TEA (100 µL, 0.72 mmol, 1.85 eq.). The reaction mixture was stirred at 25 °C for 12 hours. The title compound was isolated after evaporating volatiles by normal-phase flash chromatography (n-hexane – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – acetonitrile gradient on C18 silica-gel). Yield **3** (34 mg, 18%) of yellowish oils. NOTE – approximately 1:1 mixture of diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) δ 8.27 (m, 2H, 3'), 8.20 (m, 2H, 3'), 7.70 (s, 1H, 3''), 7.67 (s, 1H, 3''), 7.46 (m, 2H, 2'), 7.43 (m, 2H, 2'), 7.21 (s, 1H, 6''), 7.15 (s, 1H, 6''), 5.42–5.55 (m, 4H, 4), 5.18–5.27 (m, 2H, 1), 4.18–4.27 (m, 4H, -O-C**H$_2$**-CH$_3$), 3.89 (s, 3H, 5''-O-C**H$_3$**), 3.87 (s, 3H, 4''-O-C**H$_3$**), 3.86 (s, 6H, 4''-O-C**H$_3$** and 5''-O-C**H$_3$**), 1.54 (dd, 3H, $J_{2\text{-}1}$ = 7.0, $J_{2\text{-}P}$ = 0.5, 2), 1.45 (dd, 3H, $J_{2\text{-}1}$ = 7.0, $J_{2\text{-}P}$ = 0.6, 2), 1.25–1.28 ppm (m, 6H, -O-CH$_2$-C**H$_3$**). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C) δ 169.35 (d, $J_{3\text{-}P}$ = 4.5, 3), 169.19 (d, $J_{3\text{-}P}$ = 4.9, 3), 154.83 (d, $J_{1'\text{-}P}$ = 6.4, 1'), 153.20 and 153.15 (5''), 148.16 and 148.11 (4''), 144.43 and 144.28 (4'), 139.74 and 139.67 (2''), 125.91 and 125.74 (3'), 125.25 and 125.21 (1''), 121.01 (d, $J_{2'\text{-}P}$ = 5.5, 2'), 120.93 (d, $J_{2'\text{-}P}$ = 5.5, 2'), 111.67 and 111.57 (6''), 108.27 and 108.18 (3''), 72.66 (d, $J_{1\text{-}P}$ = 5.6, 1), 65.49 (d, $J_{CH2\text{-}P}$ = 6.0, -O-**C**H$_2$-CH$_3$), 65.38 (d, $J_{CH2\text{-}P}$ = 6.3, -O-**C**H$_2$-CH$_3$), 63.93 and 63.88 (4), 56.31 and 53.25 and 56.13 and 56.08 (4''-O-**C**H$_3$ and 5''-O-**C**H$_3$), 18.80 (d, $J_{2\text{-}P}$ = 5.6, 2), 18.71 (d, $J_{2\text{-}P}$ = 6.3, 2), 15.70−15.83 ppm (m, -O-CH$_2$-**C**H$_3$). ^{31}P NMR (202 MHz, DMSO-d_6, 25 °C) δ −8.15 and −8.18 ppm. HRMS (ESI+) calculated for $C_{20}H_{23}O_{12}N_2NaP$ 537.08808, found $[M+Na]^+$ 537.08765.

4,5-Dimethoxy-2-nitrobenzyl (2S)-2-((ethoxy(4-fluorophenoxy)phosphoryl)oxy)propanoate (**4**). 4,5-Dimethoxy-2-nitrobenzyl L-lactate **22** (110 mg, 0.39 mmol, 1.00 eq.) was dissolved in toluene (4 mL), subsequently adding ethyl dichlorophosphate **23** (50 µL, 0.40 mmol, 1.03 eq.) and TEA (100 µL, 0.72 mmol, 1.85 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 h and evaporated to dryness in *vacuo*. The solid residue was dissolved in DCM (4 mL), subsequently adding 4-fluorophenol (45 mg, 0.40 mmol, 1.03 eq.) and then TEA (100 µL, 0.72 mmol, 1.85 eq.). The reaction mixture was stirred at 25 °C for 12 hours. The title compound was isolated after evaporating volatiles by normal-phase flash chromatography (n-hexane – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – acetonitrile gradient on C18 silica-gel). Yield **4** (30 mg, 15%) of slightly yellow oils. NOTE – approximately 1:1 mixture of diastereomers. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) δ 7.71 (s, 1H, 3''), 7.70 (s, 1H, 3''), 7.23−7.24 (m, 2H, 6''), 7.15−7.23 (m, 8H, 2', 3'), 5.51 (d, 1H, J_{GEM} = 13.9, 4a), 5.49 (d, 1H, J_{GEM} = 13.9, 4a), 5.48 (d, 1H, J_{GEM} = 13.9, 4b), 5.46 (d, 1H, J_{GEM} = 13.9, 4b), 5.09–5.19 (m, 2H, 1), 4.12–4.21 (m, 4H, -O-C**H$_2$**-CH$_3$), 3.89 (s, 3H, 5''-O-C**H$_3$** or 4''-O-C**H$_3$**), 3.87 (s, 3H, 5''-O-C**H$_3$** or 4''-O-C**H$_3$**), 3.86−3.87 (s, 6H, 4''-O-C**H$_3$** and/or 5''-O-C**H$_3$**), 1.52 (d, 3H, $J_{2\text{-}1}$ = 6.9, 2), 1.45 (dd, 3H, $J_{2\text{-}1}$ = 6.9, $J_{2\text{-}P}$ = 0.6, 2), 1.20–1.25 ppm (m, 6H, -O-CH$_2$-C**H$_3$**). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C) δ 169.53 (d, $J_{3\text{-}P}$ = 4.6, 3), 169.36 (d, $J_{3\text{-}P}$ = 5.4, 3), 159.12 (d, $J_{4'\text{-}F}$ = 241.5, 4'), 159.08 (d, $J_{4'\text{-}F}$ = 241.5, 4'), 153.26 and 153.24 (5''), 148.17 and 148.15 (4''), 146.14−146.31 (m, 1'), 139.74 and 139.71 (2''), 125.40 and 125.38 (1''), 121.68−121.94 (m, 2'), 116.53 (d, $J_{3'\text{-}F}$ = 23.7, 3'), 116.39 (d, $J_{3'\text{-}F}$ = 23.7, 3'), 111.62 and 111.57 (6''), 108.32 and 108.29 (3''), 72.28 (d, $J_{1\text{-}P}$ = 5.5, 1), 72.27 (d, $J_{1\text{-}P}$ = 5.5, 1), 65.00 (d, $J_{CH2\text{-}P}$ = 6.2, -O-**C**H$_2$-CH$_3$), 64.91 (d, $J_{CH2\text{-}P}$ = 6.3, -O-**C**H$_2$-CH$_3$), 63.86 and 63.83 (4), 56.34 and 53.29 and 56.17 and 56.15 (4''-O-**C**H$_3$ and 5''-O-**C**H$_3$), 18.89 (d, $J_{2\text{-}P}$ = 5.7, 2), 18.74 (d, $J_{2\text{-}P}$ = 6.2, 2), 15.74−15.85 ppm (m, -O-CH$_2$-C**H$_3$**). ^{31}P NMR (202 MHz, DMSO-d_6, 25 °C) δ −7.03 and −7.31 ppm. HRMS (ESI+) calculated for $C_{20}H_{23}O_{10}NFNaP$ 510.09358, found $[M+Na]^+$ 510.09302.

4,5-Dimethoxy-2-nitrobenzyl (2S)-2-((ethoxy(4-methylphenoxy)phosphoryl)oxy)propanoate (**5**). Ethyl dichlorophosphate **23** (60 µL, 0.47 mmol, 1.00 eq.) was dissolved in toluene (3 mL), subsequently adding TEA (100 µL, 0.72 mmol, 1.53 eq.) and phenol (44 mg, 0.47 mmol, 1.0 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in vacuo. Solid residue was dissolved in DCM (3 mL), adding 4,5-dimethoxy-2-nitrobenzyl L-lactate **22** (110 mg, 0.39 mmol, 0.83 eq.) and NMI (35 µL; 0.43 mmol, 0.91 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours. The title compound was isolated (direct injection) by normal-phase flash chromatography (n-hexane – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). NOTE – approximately 1:1 mixture of diastereomers. Yield **5** (20 mg, 11%) of a yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) δ 7.72 (s, 1H, 3''), 7.71 (s, 1H, 3''), 7.40 (m, 2H, 3'), 7.35 (m, 2H, 3'), 7.23 (s, 1H, 6''), 7.17–7.22 (m, 7H, 2', 4', 6''), 5.43–5.54 (m, 4H, 4), 5.08–5.18 (m, 2H, 1), 4.12–4.20 (m, 4H, -O-C**H$_2$**-CH$_3$), 3.89 (s, 3H, 4''-O-C**H$_3$** or 5''-O-C**H$_3$**), 3.88 (s, 3H, 4''-O-C**H$_3$** or 5''-O-C**H$_3$**), 3.87 (s, 3H, 4''-O-C**H$_3$** or 5''-O-C**H$_3$**), 3.87 (s, 3H, 4''-O-C**H$_3$** or 5''-O-C**H$_3$**), 1.52 (dd, 3H, $J_{2\text{-}1}$ = 6.8, $J_{2\text{-}P}$ = 0.4, 2), 1.45 (dd,

3H, $J_{2\text{-}1}$ = 6.9, $J_{2\text{-}P}$ = 0.6, 2), 1.23 (td, 3H, $J_{CH3\text{-}CH2}$ = 7.1, $J_{CH3\text{-}P}$ = 1.0, -O-CH_2-C**H_3**), 1.22 ppm (td, 3H, $J_{CH3\text{-}CH2}$ = 7.2, $J_{CH3\text{-}P}$ = 1.0, -O-CH_2-C**H_3**). ^{13}C NMR (125 MHz, DMSO-*d*$_6$, 25 °C) *δ* 169.53 (d, $J_{3\text{-}P}$ = 4.6, 3), 169.35 (d, $J_{3\text{-}P}$ = 5.3, 3), 153.25 and 153.23 (5''), 150.12 (d, $J_{1'\text{-}P}$ = 6.4, 1'), 148.13 and 148.11 (4''), 139.70 and 139.68 (2''), 129.96 and 129.84 (3'), 125.42 (1''), 125.35 and 125.22 (4'), 119.99 (d, $J_{2'\text{-}P}$ = 5.1, 2'), 119.89 (d, $J_{2'\text{-}P}$ = 4.5, 2'), 111.56 and 111.51 (6''), 108.30 and 108.28 (3''), 72.17 (d, $J_{1\text{-}P}$ = 5.5, 1), 72.14 (d, $J_{1\text{-}P}$ = 5.5, 1), 64.83 (d, $J_{CH2\text{-}P}$ = 6.4, -O-**C**H_2-CH_3), 64.76 (d, $J_{CH2\text{-}P}$ = 6.1, -O-**C**H_2-CH_3), 63.80 and 63.76 (4), 56.31 (4''-O-**C**H_3 or 5''-O-**C**H_3), 56.26 (4''-O-**C**H_3 or 5''-O-**C**H_3), 56.11−56.16 (m, 4''-O-**C**H_3 or/and 5''-O-**C**H_3), 18.87 (d, $J_{2\text{-}P}$ = 5.5, 2), 18.71 (d, $J_{2\text{-}P}$ = 6.3, 2), 15.70−15.84 ppm (m, -O-CH_2-**C**H_3). ^{31}P NMR (202 MHz, DMSO-*d*$_6$, 25 °C) *δ* −7.14 and −7.47 ppm. HRMS (ESI+) calculated for $C_{20}H_{24}O_{10}$NNaP 492.10300, found $[M+Na]^+$ 492.10263.

4,5-Dimethoxy-2-nitrobenzyl (2S)-2-((ethoxy(4-methylphenoxy)phosphoryl)oxy)propanoate (**6**). 4,5-Dimethoxy-2-nitrobenzyl L-lactate **22** (110 mg, 0.39 mmol, 1.00 eq.) was dissolved in toluene (3 mL), subsequently adding ethyl dichlorophosphate **23** (50 µL, 0.40 mmol, 1.03 eq.) and TEA (100 µL, 0.72 mmol, 1.85 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The solid residue was dissolved in DCM (3 mL), adding 4-methylphenol (45 mg, 0.42 mmol, 1.08 eq.) and then TEA (100 µL, 0.72 mmol, 1.85 eq.). The reaction mixture was stirred at 25 °C for 12 hours. The title compound was isolated after evaporating volatiles by normal-phase flash chromatography (n-hexane – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – acetonitrile gradient on C18 silica-gel). Yield **6** (21 mg, 11%) of slightly yellow oil. NOTE – approximately 1:1 mixture of diastereomers. ^{1}H NMR (500 MHz, DMSO-*d*$_6$, 25 °C) *δ* 7.72 (s, 1H, 3''), 7.71 (s, 1H, 3''), 7.04–7.23 (m, 10H, 2', 3', 6''), 5.52 (d, 1H, J_{GEM} = 13.8, 4a), 5.47 (d, 1H, J_{GEM} = 13.8, 4b), 5.50 (d, 1H, J_{GEM} = 14.0, 4a), 5.45 (d, 1H, J_{GEM} = 14.0, 4b), 5.06–5.16 (m, 2H, 1), 4.11–4.19 (m, 4H, -O-C**H_2**-CH_3), 3.89 (s, 3H, 5''-O-C**H_3**), 3.87 (s, 3H, 4''-O-C**H_3**), 3.87 (s, 3H, 4''-O-C**H_3**), 3.86 (s, 3H, 5''-O-C**H_3**), 2.27 (s, 3H, 4'-C**H_3**), 2.24 (s, 3H, 4'-C**H_3**), 1.51 (d, 3H, $J_{2\text{-}1}$ = 6.9, 2), 1.45 (dd, 3H, $J_{2\text{-}1}$ = 6.8, $J_{2\text{-}P}$ = 0.5, 2), 1.22 (td, 3H, $J_{CH3\text{-}CH2}$ = 7.0, $J_{CH3\text{-}P}$ = 1.0, -O-CH_2-C**H_3**), 1.21 ppm (td, 3H, $J_{CH3\text{-}CH2}$ = 7.1, $J_{CH3\text{-}P}$ = 1.0, -O-CH_2-C**H_3**). ^{13}C NMR (125 MHz, DMSO-*d*$_6$, 25 °C) *δ* 169.56 (d, $J_{3\text{-}P}$ = 4.8, 3), 169.36 (d, $J_{3\text{-}P}$ = 5.3, 3), 153.25 (5''), 148.13 and 148.10 (4''), 148.00–147.86 (m, 1'), 139.69 and 139.65 (2''), 134.51 (d, $J_{4'\text{-}P}$ = 1.5, 4'), 134.37 (4'), 130.22 and 130.09 (3'), 125.45 and 125.43 (1''), 119.73 (d, $J_{2'\text{-}P}$ = 4.6, 2'), 119.64 (d, $J_{2'\text{-}P}$ = 4.6, 2'), 111.55 and 111.47 (6''), 108.29 and 108.26 (3''), 72.12 (d, $J_{1\text{-}P}$ = 5.5, 1), 72.10 (d, $J_{1\text{-}P}$ = 5.5, 1), 64.75 (d, $J_{CH2\text{-}P}$ = 6.2, -O-**C**H_2-CH_3), 64.68 (d, $J_{CH2\text{-}P}$ = 6.2, -O-**C**H_2-CH_3), 63.79 and 63.75 (4), 56.31 and 53.26 (4''-O-**C**H_3 or 5''-O-**C**H_3), 56.12–56.16 (m, 4''-O-**C**H_3 or/and 5''-O-**C**H_3), 20.26 and 20.21 (4'-**C**H_3), 18.88 (d, $J_{2\text{-}P}$ = 5.5, 2), 18.74 (d, $J_{2\text{-}P}$ = 6.3, 2), 15.81 (d, $J_{CH3\text{-}P}$ = 6.3, -O-CH_2-**C**H_3), 15.76 ppm (d, $J_{CH3\text{-}P}$ = 6.3, -O-CH_2-**C**H_3). ^{31}P NMR (202 MHz, DMSO-*d*$_6$, 25 °C) *δ* −6.97 and −7.26 ppm. HRMS (ESI+) calculated for $C_{21}H_{26}O_{10}$NNaP 506.11865, found $[M+Na]^+$ 506.11847.

4,5-Dimethoxy-2-nitrobenzyl (2S)-2-((ethoxy(4-methoxyphenoxy)phosphoryl)oxy)propanoate (**7**). 4,5-Dimethoxy-2-nitrobenzyl L-lactate **22** (500 mg, 1.75 mmol, 1.00 eq.) was dissolved in toluene (10 mL), subsequently adding ethyl dichlorophosphate **23** (250 µL, 1.98 mmol, 1.13 eq.) and TEA (300 µL, 2.16 mmol, 1.23 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The solid residue was dissolved in DCM (10 mL), adding 4-methoxyphenol (90 mg, 0.73 mmol, 0.42 eq.) and then TEA (100 µL, 0.72 mmol, 0.41 eq.). The reaction mixture was stirred at 25 °C for 12 hours. The title compound was isolated after evaporating volatiles by normal-phase flash chromatography (DCM – methanol gradient on silica-gel) followed by reverse-phase flash chromatography (water – acetonitrile gradient on C18 silica-gel). Yield **7** (56 mg, 16%) of a yellow oil. NOTE – approximately 1:0.7 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) *δ* 7.74 and 7.73 (s, 2H, 3''), 7.10−7.15 (m, 4H, 2'), 7.08 (s, 1H, 6''), 7.05 (s, 1H, 6''), 6.84 (m, 2H, 3'), 6.77 (m, 2H, 3'), 5.65 (d, 1H, J_{GEM} = 15.1, 4a), 5.60 (d, 1H, J_{GEM} = 15.1, 4b), 5.63 (d, 1H, J_{GEM} = 14.9, 4a), 5.55 (d, 1H, J_{GEM} = 14.9, 4b), 5.03−5.16 (m, 2H, 1), 4.19−4.31 (m, 4H, -O-C**H_2**-CH_3), 4.00 and 3.97 and 3.97 and 3.95 (s, 12H, 5''-O-C**H_3** and 4''-O-C**H_3**), 3.79 (s, 3H, 4'-O-C**H_3**), 3.75 (s, 3H, 4'-O-C**H_3**), 1.67 (dd, 3H, $J_{2\text{-}1}$ = 6.9, $J_{2\text{-}P}$ = 0.6, 2), 1.56 (dd, 3H, $J_{2\text{-}1}$ = 7.0, $J_{2\text{-}P}$ = 0.9, 2), 1.35 (td, 3H, $J_{CH3\text{-}CH2}$ = 6.3, $J_{CH3\text{-}P}$ = 1.2, -O-CH_2-C**H_3**), 1.33 ppm (td, 3H, $J_{CH3\text{-}CH2}$ = 6.3, $J_{CH3\text{-}P}$ = 1.2, -O-CH_2-C**H_3**). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) *δ* 169.90 (d, $J_{3\text{-}P}$ = 4.2, 3), 169.53 (d, $J_{3\text{-}P}$ = 5.4, 3), 156.77 and 156.75 (4'), 153.79 and 153.76 (5'' or 4''), 148.29 and 148.22 (4'' or 5''), 143.97 (d, $J_{1'\text{-}P}$ = 7.6, 1'), 143.92 (d, $J_{1'\text{-}P}$ = 7.2, 1'), 139.61 and 139.51 (2''), 126.44 (1''), 120.96 (d, $J_{2'\text{-}P}$ = 4.6, 2'), 120.88 (d, $J_{2'\text{-}P}$ = 4.6, 2'), 114.58 and 114.47 (3'), 110.11 and 110.03 (6''), 108.14 and 108.07 (3''), 72.50 (d, $J_{1\text{-}P}$ = 5.3, 1), 72.48 (d, $J_{1\text{-}P}$ = 5.1, 1), 65.18 (d, $J_{CH2\text{-}P}$ = 6.2, -O-**C**H_2-CH_3), 64.94 (d, $J_{CH2\text{-}P}$ = 6.1, -O-**C**H_2-CH_3), 64.18 and 64.14 (4), 56.67 and 56.60 and 56.38 and 56.35 (5''-O-**C**H_3 and 4''-O-**C**H_3), 55.56 and 55.50 (4'-O-**C**H_3), 19.16 (d, $J_{2\text{-}P}$ = 5.4, 2), 18.99 (d, $J_{2\text{-}P}$ = 6.2, 2), 16.00 (d, $J_{CH3\text{-}P}$ = 6.4, -O-CH_2-**C**H_3), 15.95 ppm (d, $J_{CH3\text{-}P}$ = 6.6, -O-CH_2-**C**H_3). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) *δ* –6.48, −6.67 ppm. HRMS (ESI+) calculated for $C_{21}H_{27}O_{11}$NP 500.13162, found $[M+H]^+$ 500.13106.

4,5-dimethoxy-2-nitrobenzyl (2S)-2-((ethoxy(phenoxy)phosphoryl)oxy)-3-methylbutanoate (**8**). Ethyl dichlorophosphate **23** (50 µL, 0.40 mmol, 1.00 eq.) was dissolved in toluene (3 mL), subsequently adding TEA (100 µL, 0.72 mmol, 1.80 eq.) and phenol (40 mg, 0.43 mmol, 1.08 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in vacuo. The solid residue was dissolved in DCM (2 mL), adding 4,5-dimethoxy-2-nitrobenzyl (*S*)-2-hydroxy-3-methylbutanoate **28** (120 mg, 0.38 mmol, 0.95 eq.) and DMAP (100 mg, 0.82 mmol, 2.05 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours. The title compound was isolated (direct injection) by normal-phase flash chromatography (n-hexane – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **8** (20 mg, 11%) of a yellowish oil. NOTE – approximately 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) *δ* 7.74 (s, 1H, 3''), 7.72 (s, 1H, 3''), 7.25–7.31 (m, 4H, 3'), 7.17–7.25 (m, 4H, 2'), 7.13–7.17 (m, 2H, 4'), 7.12 (s, 1H, 6''), 7.07 (s, 1H, 6''), 5.66 (d, J_{GEM} = 14.8, 3a), 5.60 (d, J_{GEM} = 14.8, 3b), 5.60 (d, J_{GEM} = 15.0, 3a), 5.54 (d, J_{GEM} = 15.0, 3b), 4.81–4.88 (m, 2H, 1), 4.21–4.33 (m, 4H, -O-C**H_2**-CH_3), 4.02 (s, 3H, 5''-OC**H_3**), 3.95 (s, 3H, 5''-OC**H_3**), 3.98 (s, 3H, 4''-OC**H_3**), 3.97 (s, 3H, 4''-OC**H_3**), 2.34 (m, 1H, C**H**^{iPr}), 2.27 (m, 1H, C**H**^{iPr}), 1.35 (td, 3H, $J_{CH2\text{-}CH3}$ = 7.1, $J_{CH3\text{-}P}$ = 1.1, -O-CH_2-C**H_3**), 1.34 (td, 3H, $J_{CH2\text{-}CH3}$ = 7.1, $J_{CH3\text{-}P}$ = 1.1, -O-CH_2-C**H_3**), 1.09 (d, 3H, $J_{CH3(iPr)\text{-}CH(iPr)}$ = 6.9, C**H_3**^{iPr}), 1.03 (d, 3H, $J_{CH3(iPr)\text{-}CH(iPr)}$ = 6.9, C**H_3**^{iPr}), 0.97 ppm (d, 6H, $J_{CH3(iPr)\text{-}CH(iPr)}$ = 6.8, C**H_3**^{iPr}). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) *δ* 169.23 (d, $J_{2\text{-}P}$ = 1.6, 2), 168.86 (d, $J_{2\text{-}P}$ = 2.1, 2), 153.83 and 153.78 (5''), 148.31 and 148.23 (4''), 150.60 (1'), 139.67 and 139.60 (2''), 129.68 and 129.56 (3'), 126.57 and 126.53 (1''), 125.17 (d, $J_{4'\text{-}P}$ = 1.6, 4'), 125.11 (d, $J_{4'\text{-}P}$ = 1.5, 4'), 120.02 (d, $J_{2'\text{-}P}$ = 4.6, 2'), 119.97 (d, $J_{2'\text{-}P}$ = 4.7, 2'), 110.37 and 110.27 (6''), 108.12 and 108.04 (3''), 80.78 (d, $J_{1\text{-}P}$ = 6.5, 1), 65.24 (d, $J_{CH2\text{-}P}$ = 6.3, -O-**C**H_2-CH_3), 64.99 (d, $J_{CH2\text{-}P}$ = 6.3, -O-**C**H_2-CH_3), 64.01 and 63.93 (3), 56.74 and 56.66 (5''-O-**C**H_3), 56.39 and 56.38 (4''-O-**C**H_3), 31.78 (d, $J_{CH(iPr)\text{-}P}$ = 6.9, **C**H^{iPr}), 31.69 (d, $J_{CH(iPr)\text{-}P}$ = 7.1, **C**H^{iPr}), 18.47 and 18.37 and 16.76 and 16.61 (C**H_3**^{iPr}), 16.03 (d, $J_{CH3\text{-}P}$ = 7.4, -O-CH_2-**C**H_3), 15.94 ppm (d, $J_{CH3\text{-}P}$ = 6.9, -O-CH_2-**C**H_3). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) *δ* –6.67 ppm. HRMS (ESI+) calculated for $C_{22}H_{28}O_{10}$NNaP 520.13430, found $[M+Na]^+$ 520.13434.

4,5-Dimethoxy-2-nitrobenzyl 2-((ethoxy(phenoxy)phosphoryl)oxy)-2-methylpropanoate (**9**). Ethyl dichlorophosphate **23** (60 µL, 0.47 mmol, 1.00 eq.) was dissolved in toluene (3 mL), subsequently adding TEA (100 µL, 0.72 mmol, 1.80 eq.) and phenol (45 mg, 0.48 mmol, 1.02 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The solid residue was dissolved in DCM (3 mL), adding 4,5-dimethoxy-2-nitrobenzyl (2-methyl)propanoate **29** (140 mg, 0.47 mmol, 1.00 eq.) and NMI (50 µL, 0.61 mmol, 1.30 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The title compound was isolated by normal-phase flash chromatography (n-hexane – ethyl acetate gradient on silica-gel)

followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **9** (14 mg, 6%) of a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.72 (s, 1H, 3''), 7.30 (m, 2H, 3'), 7.20 (m, 2H, 2'), 7.15 (m, 1H, 4'), 7.14 (s, 1H, 6''), 5.63 (dd, J_{GEM} = 14.9, $J_{3a\text{-}6''}$ = 0.6, 3a), 5.57 (dd, J_{GEM} = 14.9, $J_{3b\text{-}6''}$ = 0.6, 3b), 4.23 (m, 2H, -O-C**H$_2$**-CH_3), 3.97 (s, 3H, 5''-O-C**H$_3$**), 3.97 (s, 3H, 4''-O-C**H$_3$**), 1.76 (s, 3H, 1-C**H$_3$**), and 1.75 (s, 3H, 1-C**H$_3$**), 1.32 ppm (td, $J_{CH3\text{-}CH2}$ = 7.1, $J_{CH3\text{-}P}$ = 1.2, -O-CH_2-C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.64 (d, $J_{2\text{-}P}$ = 3.9, 2), 153.75 (5''), 150.61 (d, $J_{1'\text{-}P}$ = 6.9, 1'), 148.20 (4''), 139.62 (2''), 129.54 (3'), 126.69 (1''), 124.99 (4'), 120.10 (d, $J_{2'\text{-}P}$ = 4.7, 2'), 110.40 (6''), 108.04 (3''), 82.05 (d, $J_{1\text{-}P}$ = 6.2, 1), 64.71 (d, $J_{CH2\text{-}P}$ = 6.2, -O-**C**H_2-CH_3), 64.50 (3), 56.69 and 56.36 (5''-O-**C**H_3 and 4''-O-**C**H_3), 26.56 (d, $J_{CH3\text{-}P}$ = 5.5, 1-**C**H_3), 26.08 (d, $J_{CH3\text{-}P}$ = 4.1, 1-**C**H_3), 15.92 ppm (d, $J_{CH3\text{-}P}$ = 7.0, -O-CH_2-**C**H_3). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ –10.38 ppm. HRMS (ESI+) calculated for $C_{21}H_{27}O_{10}NP$ 484.13671, found $[M+H]^+$ 484.13656.

4,5-dimethoxy-2-nitrobenzyl (2S)-2-(((4-fluorophenoxy)(phenoxy)phosphoryl)oxy)-3-methylbutanoate (**10**). Phenyl dichlorophosphate **17** (60 µL, 0.40 mmol, 1.00 eq.) was dissolved in toluene (3 mL), subsequently adding TEA (100 µL, 0.72 mmol, 1.80 eq.) and 4-fluorophenol (45 mg, 0.40 mmol, 1.00 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in vacuo. The solid residue was dissolved in DCM (2 mL), adding 4,5-dimethoxy-2-nitrobenzyl (*S*)-2-hydroxy-3-methylbutanoate **28** (120 mg, 0.38 mmol, 0.95 eq.) and DMAP (100 mg, 0.82 mmol, 2.05 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours. The title compound was isolated (direct injection) by normal-phase flash chromatography (hexanes – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **10** (149 mg, 70%) of a yellowish oil. NOTE – approximately 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.68 (s, 1H, 3''), 7.68 (s, 1H, 3''), 7.32 (m, 2H, 3'), 7.26 (m, 2H, 3'), 7.10–7.22 (m, 10H, 2', 4', 2'''), 6.90–7.03 (m, 6H, 6'', 3'''), 5.51–5.61 (m, 4H, 3), 4.92 (dd, $J_{1\text{-}CH(iPr)}$ = 4.2, $J_{1\text{-}P}$ = 7.6, 1), 4.91 (dd, $J_{1\text{-}CH(iPr)}$ = 4.2, $J_{1\text{-}P}$ = 7.4, 1), 3.92−3.94 (m, 9H, 4''-O-C**H$_3$**), 3.91 (s, 3H, 5''-O-C**H$_3$**), 2.30 (m, 2H, **C**H^{iPr}), 0.94–1.00 ppm (m, 12H, **C**H$_3^{iPr}$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 168.56 (d, $J_{2\text{-}P}$ = 1.9, 2), 168.46 (d, $J_{2\text{-}P}$ = 1.9, 2), 159.70 (dd, $J_{4'''\text{-}F}$ = 245.0, $J_{4'''\text{-}P}$ = 1.2, 4'''), 159.66 (dd, $J_{4'''\text{-}F}$ = 244.3, $J_{4'''\text{-}P}$ = 1.5, 4'''), 153.58 (5''), 150.22 (d, $J_{1'\text{-}P}$ = 6.7, 1'), 150.15 (d, $J_{1'\text{-}P}$ = 6.6, 1'), 148.22 and 148.18 (4''), 146.04−146.23 (m, 1'''), 139.62 and 139.58 (2''), 129.71 and 129.54 (3'), 126.09 and 126.00 (1''), 125.47 and 125.39 (4'), 121.56 (dd, $J_{2'''\text{-}F}$ = 8.6, $J_{2'''\text{-}P}$ = 4.8, 2'''), 121.35 (dd, $J_{2'''\text{-}F}$ = 8.4, $J_{2'''\text{-}P}$ = 5.4, 2'''), 119.97 (d, $J_{2'\text{-}P}$ = 4.7, 2'), 119.82 (d, $J_{2'\text{-}P}$ = 4.6, 2'), 116.25 (d, $J_{3'''\text{-}F}$ = 23.7, 3'''), 116.03 (d, $J_{3'''\text{-}F}$ = 23.8, 3'''), 110.35 and 110.30 (6''), 107.94 (3''), 81.59 (d, $J_{1\text{-}P}$ = 6.6, 1), 64.01 (3), 56.49 (5''-O-**C**H_3), 56.22 (4''-O-**C**H_3), 31.59 (d, $J_{CH(iPr)\text{-}P}$ = 7.2, **C**H^{iPr}), 18.23 and 18.20 and 16.48 and 16.44 ppm (**C**H$_3^{iPr}$). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ −11.96 and −11.98 ppm. HRMS (ESI+) calculated for $C_{26}H_{28}O_{10}NFP$ 564.14294, found $[M+H]^+$ 564.14368.

4,5-dimethoxyn-2-nitrobenzyl (2S)-3-methyl-2-((phenoxy(p-tolyloxy)phosphoryl)oxy)butanoate (**11**). Phenyl dichlorophosphate **17** (66 µL, 0.44 mmol, 1.00 eq.) was dissolved in toluene (3 mL), subsequently adding TEA (66 µL, 0.47 mmol, 1.07 eq.) and 4-methylphenol (45 mg, 0.42 mmol, 0.95 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in vacuo. The solid residue was dissolved in DCM (2 mL), adding 4,5-dimethoxy-2-nitrobenzyl (*S*)-2-hydroxy-3-methylbutanoate **28** (100 mg, 0.32 mmol, 0.73 eq.) and DMAP (60 mg, 0.49 mmol, 1.11 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours. The title compound was isolated (direct injection) by normal-phase flash chromatography (hexanes – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **11** (103 mg, 58%) of yellowish oil. NOTE – approximately 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.70 (s, 1H, 3''), 7.70 (s, 1H, 3''), 7.25−7.35 (m, 4H, 3'), 7.18−7.24 (m, 4H, 2'), 7.11−7.16(m, 2H, 4'), 7.02−7.11 (m, 10H, 2''', 3''', 6''), 5.55−5.57 (m, 4H, 3), 4.92−4.95 (m, 2H, 1), 3.95 (s, 6H, 4''-O-C**H$_3$**), 3.92 (s, 3H, 5''-O-C**H$_3$**), 3.92 (s, 3H, 5''-O-C**H$_3$**), 2.25−2.36 (m, 8H, **C**H^{iPr}, 4'''-C**H$_3$**) 0.97−1.01 ppm (m, 12H, **C**H$_3^{iPr}$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 168.64 (d, $J_{2\text{-}P}$ = 1.9, 2), 153.72 (5''), 150.40 (d, $J_{1'\text{-}P}$ = 7.6, 1'), 150.36 (d, $J_{1'\text{-}P}$ = 7.0, 1'), 148.09−148.23 (m, 1''', 4'''), 139.49 and 139.45 (2''), 135.06 (4'''), 135.00 (d, $J_{4'''\text{-}P}$ = 1.2, 4'''), 130.12 and 129.97 (3'''), 129.70 and 129.53 (3'), 126.46 and 126.43 (1''), 125.37 and 125.30 (4'), 120.08 (d, $J_{2'\text{-}P}$ = 4.7, 2'), 119.92 (d, $J_{2'\text{-}P}$ = 4.9, 2'), 119.78 (d, $J_{2'''\text{-}P}$ = 4.7, 2'''), 119.59 (d, $J_{2'''\text{-}P}$ = 4.7, 2'''), 110.17 and 110.13 (6''), 107.93 and 107.92(3''), 81.53 (d, $J_{1\text{-}P}$ = 6.9, 1), 63.97 (3), 56.59 (5''-O-C**H$_3$**), 56.28 (4''-O-C**H$_3$**), 31.70 (d, $J_{CH(iPr)\text{-}P}$ = 7.1, **C**H^{iPr}), 31.69 (d, $J_{CH(iPr)\text{-}P}$ = 7.1, **C**H^{iPr}), 20.62 and 20.58 (4'''-**C**H_3), 18.28 and 18.26 and 16.61 and 16.59 ppm (**C**H$_3^{iPr}$). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ –11.91 and –11.96 ppm. HRMS (ESI+) calculated for $C_{27}H_{31}O_{10}NP$ 560.16801, found $[M+H]^+$ 560.16748.

4,5-Dimethoxy-2-nitrobenzyl 2-(((4-fluorophenoxy)(phenoxy)phosphoryl)oxy)-2-methylpropanoate (**12**). Phenyl dichlorophosphate **17** (60 µL, 0.40 mmol, 1.00 eq.) was dissolved in toluene (3 mL), subsequently adding TEA (100 µL, 0.72 mmol, 1.80 eq.) and 4-fluorophenol (45 mg, 40 mmol, 1.00 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The solid residue was dissolved in DCM (3 mL), adding 4,5-dimethoxy-2-nitrobenzyl (2-methyl)propanoate **29** (120 mg, 0.40 mmol, 1.00 eq.), TEA (100 µL, 0.72 mmol, 1.80 eq.) and a catalytic amount of DMAP at 25 °C. The mixture was stirred at 25 °C for 1 hour and evaporated to dryness in *vacuo*. The title compound was isolated by normal-phase flash chromatography (n-hexane – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **12** (21 mg, 10%) of a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.70 (s, 1H, 3''), 7.31 (m, 2H, 3'), 7.14−7.21 (m, 5H, 2', 4', 2'''), 7.07 (s, 1H, 6''), 6.98 (m, 2H, 3'''), 5.58 (dd, J_{GEM} = 14.9, $J_{3a\text{-}6''}$ = 0.6, 3a), 5.54 (dd, J_{GEM} = 14.9, $J_{3b\text{-}6''}$ = 0.6, 3b), 3.96 (s, 3H, 4''-O-C**H$_3$**), 3.94 (s, 3H, 5''-O-C**H$_3$**), 1.76 (s, 3H, 1-C**H$_3$**), 1.75 ppm (s, 3H, 1-C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.23 (d, $J_{2\text{-}P}$ = 3.9, 2), 159.77 (dd, $J_{4'''\text{-}F}$ = 244.0, $J_{4'''\text{-}P}$ = 1.5, 4'''), 153.62 (5''), 150.36 (d, $J_{1'\text{-}P}$ = 7.4, 1'), 148.25 (4''), 146.30 (dd, $J_{1'''\text{-}P}$ = 7.7, $J_{1'''\text{-}F}$ = 3.1, 1'''), 139.71 (2''), 129.64 (3'), 126.26 (1''), 125.38 (d, $J_{4'\text{-}P}$ = 1.4, 4'), 121.61 (dd, $J_{2'''\text{-}F}$ = 8.5, $J_{2'''\text{-}P}$ = 4.7, 2'''), 120.09 (d, $J_{2'\text{-}P}$ = 4.7, 2'), 116.18 (d, $J_{3'''\text{-}F}$ = 23.9, 3'''), 110.54 (6''), 108.02 (3''), 83.28 (d, $J_{1\text{-}P}$ = 6.6, 1), 64.67 (3), 56.59 (5''-O-C**H$_3$**), 56.32 (4''-O-C**H$_3$**), 26.39 (d, $J_{CH3\text{-}P}$ = 5.0, 1-C**H$_3$**), 26.28 ppm (d, $J_{CH3\text{-}P}$ = 4.9, 1-C**H$_3$**). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ –15.92 and –15.93 ppm. HRMS (ESI+) calculated for $C_{25}H_{26}O_{10}NFP$ 550.12729, found $[M+H]^+$ 550.12715.

4,5-Dimethoxy-2-nitrobenzyl 2-(((phenoxy)(p-tolyloxy)phosphoryl)oxy)-2-methylpropanoate (**13**). Phenyl dichlorophosphate **17** (66 µL, 0.44 mmol, 1.00 eq.) was dissolved in toluene (3 mL), subsequently adding TEA (66 µL, 0.47 mmol, 1.07 eq.) and 4-methylphenol (45 mg, 0.42 mmol, 0.95 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The solid residue was dissolved in DCM (2 mL), adding 4,5-dimethoxy-2-nitrobenzyl (2-methyl)propanoate **29** (100 mg, 0.33 mmol, 0.75 eq.) and DMAP (60 mg, 0.49 mmol, 1.11 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours and evaporated to dryness in *vacuo*. The title compound was isolated by normal-phase flash chromatography (n-hexane – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **13** (97 mg, 54%) of a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.70 (s, 1H, 3''), 7.30 (m, 2H, 3'), 7.20 (m, 2H, 2'), 7.16 (m, 4'), 7.11 (s, 1H, 6''), 7.07−7.08 (m, 4H, 2''', 3'''), 5.56 (s, 2H, 3), 3.96 (s, 3H, 4''-O-C**H$_3$**), 3.92 (s, 3H, 5''-O-C**H$_3$**), 2.30 (d, 3H, $J_{CH3\text{-}P}$ = 0.8, 4'''-C**H$_3$**), 1.76 ppm (s, 6H, 1-(C**H$_3$**)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.34 (d, $J_{2\text{-}P}$ = 4.2, 2), 153.71 (5''), 150.48 (d, $J_{1'\text{-}P}$ = 7.7, 1'), 148.25 (d, $J_{1'''\text{-}P}$ = 7.7, 1'''), 148.12 (4''), 139.51 (2''), 134.89 (4'''), 130.00 (3'''), 129.56 (3'), 126.61 (1''), 125.22 (d, $J_{4'\text{-}P}$ = 1.0, 4'), 120.14 (d, $J_{2'\text{-}P}$ = 4.7, 2'), 119.81 (d, $J_{2'''\text{-}P}$ = 4.7, 2'''), 110.31 (6''), 107.93 (3''), 83.06 (d, $J_{1\text{-}P}$ = 6.6, 1), 64.57 (3), 56.62 (5''-O-C**H$_3$**), 56.30 (4''-O-C**H$_3$**), 26.33 (d, $J_{CH3\text{-}P}$ = 5.2, 1-(C**H$_3$**)$_2$), 20.63 ppm (4'''-C**H$_3$**). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ –

15.90 ppm. HRMS (ESI+) calculated for $C_{26}H_{29}O_{10}NP$ 546.15236, found $[M+H]^+$ 546.15200.

4,5-dimethoxy-2-nitrobenzyl (S)-2-((diethoxyphosphoryl)oxy)propanoate (**14**). 4,5-Dimethoxy-2-nitrobenzyl L-lactate **22** (114 mg, 0.40 mmol, 1.00 eq.) was dissolved in dry DCM (3 mL), subsequently adding diethyl chlorophosphate **30** (60 µL, 0.41 mmol, 1.04 eq.) and TEA (100 µL, 0.72 mmol, 1.80 eq.) at 25 °C. The mixture was stirred at 25 °C for 36 hours and directly injected to normal-phase flash chromatography system (hexanes – ethyl acetate gradient on silica-gel), followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **14** (18 mg, 11%) of a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.75 (s, 1H, 3''), 7.11 (s, 1H, 6''), 5.66 (d, J_{GEM} = 14.8, 3a), 5.62 (d, J_{GEM} = 14.8, 3b), 5.03 (m, 1), 4.10−4.22 (m, 4H, O-C**H$_2$**-CH$_3$), 4.03 (s, 3H, 5''-O-C**H$_3$**), 3.98 (s, 3H, 4''-O-C**H$_3$**), 1.64 (dd, 3H, $J_{2\text{-}1}$ = 6.9, $J_{2\text{-}P}$ = 0.6, 1-Me), 1.36 (td, 3H, $J_{2'\text{-}1'}$ = 7.1, $J_{CH3\text{-}P}$ = 1.0, O-CH$_2$-C**H$_3$**), 1.33 ppm (td, 3H, $J_{CH3\text{-}1'}$ = 7.1, $J_{2'\text{-}P}$ = 1.0, O-CH$_2$-C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 170.13 (d, $J_{2\text{-}P}$ = 4.8, 2), 153.81 (5''), 148.32 (4''), 139.6 (2''), 126.53 (1''), 110.16 (6''), 108.19 (3''), 71.72 (d, $J_{1\text{-}P}$ = 5.4, 1), 64.32 (d, $J_{CH2\text{-}P}$ = 5.9, O-**C**H$_2$-CH$_3$), 64.08 (d, $J_{CH2\text{-}P}$ = 6.2, O-**C**H$_2$-CH$_3$), 64.12 (3), 56.70 (5''-O-**C**H$_3$), 56.41 (4''-O-**C**H$_3$), 19.20 (d, $J_{2\text{-}P}$ = 5.5, 1-Me), 16.04 (d, $J_{CH3\text{-}P}$ = 6.9, O-CH$_2$-**C**H$_3$), 16.00 ppm (d, $J_{CH3\text{-}P}$ = 7.0, O-CH$_2$-**C**H$_3$). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ –1.87 ppm. HRMS (ESI+) calculated for $C_{16}H_{25}O_{10}NP$ 422.12106, found $[M+H]^+$ 422.12143.

4,5-dimethoxy-2-nitrobenzyl (S)-2-((diethoxyphosphoryl)oxy)-3-methylbutanoate (**15**). 4,5-Dimethoxy-2-nitrobenzyl (*S*)-2-hydroxy-3-methylbutanoate **28** (120 mg, 0.38 mmol, 1.00 eq.) was added to a premixed solution of dry DCM (3 mL), diethyl chlorophosphate **30** (60 µL, 0.41 mmol, 1.08 eq.) and NMI (50 µL, 0.63 mmol, 1.66 eq.) at 25 °C. The mixture was stirred at 25 °C for 12 hours. The title compound was isolated (direct injection) by normal-phase flash chromatography (hexanes – ethyl acetate gradient on silica-gel) followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **15** (29 mg, 17%) of a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.74 (s, 1H, 3''), 7.13 (s, 1H, 6''), 5.66 (dd, J_{GEM} = 14.9, $J_{3a\text{-}6''}$ = 0.6, 3a), 5.61 (d, J_{GEM} = 14.9, $J_{3b\text{-}6''}$ = 0.6, 3b), 4.74 (dd, $J_{1\text{-}CH(iPr)}$ = 4.4, $J_{1\text{-}P}$ = 7.9, 1), 4.09−4.20 (m, 4H, O-C**H$_2$**-CH$_3$), 4.03 (s, 3H, 5''-O-C**H$_3$**), 3.97 (s, 3H, 4''-O-C**H$_3$**), 2.28 (m, **C**H^{iPr}), 1.34 (td, 3H, $J_{CH3\text{-}CH2}$ = 7.1, $J_{CH3\text{-}P}$ = 1.1, O-CH$_2$-C**H$_3$**), 1.31 (td, 3H, $J_{CH3\text{-}CH2}$ = 7.1, $J_{CH3\text{-}P}$ = 1.1, O-CH$_2$-C**H$_3$**), 1.08 (d, $J_{CH3(iPr)\text{-}CH(iPr)}$ = 6.9, **C**H$_3^{iPr}$), 1.01 ppm (d, $J_{CH3(iPr)\text{-}CH(iPr)}$ = 6.8, **C**H$_3^{iPr}$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 169.45 (d, $J_{2\text{-}P}$ = 1.5, 2), 153.81 (5''), 148.26 (4''), 139.63 (2''), 126.63 (1''), 110.32 (6''), 108.09 (3''), 79.89 (d, $J_{1\text{-}P}$ = 6.2, 1), 64.22 (d, $J_{CH2\text{-}P}$ = 6.1, O-**C**H$_2$-CH$_3$), 64.02 (d, $J_{CH2\text{-}P}$ = 6.2, O-**C**H$_2$-CH$_3$), 63.84 (3), 56.73 (5''-O-**C**H$_3$), 56.37 (4''-O-**C**H$_3$), 31.69 (d, $J_{CH(iPr)\text{-}P}$ = 7.0, **C**H^{iPr}), 18.52 and 16.71 (CH$_3^{iPr}$), 16.05 (d, $J_{CH3\text{-}P}$ = 7.2, O-CH$_2$-**C**H$_3$), 15.97 ppm (d, $J_{CH3\text{-}P}$ = 7.0, O-CH$_2$-**C**H$_3$). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ –1.36 ppm. HRMS (ESI+) calculated for $C_{18}H_{28}O_{10}NNaP$ 472.13430, found $[M+Na]^+$ 472.13438.

4,5-dimethoxy-2-nitrobenzyl 2-((diethoxyphosphoryl)oxy)-2-methylpropanoate (**16**). 4,5-Dimethoxy-2-nitrobenzyl (2-methyl)propanoate **29** (120 mg, 0.40 mmol, 1.00 eq.) was dissolved in dry DCM (3 mL), subsequently adding diethyl chlorophosphate **30** (60 µL, 0.41 mmol, 1.04 eq.) and NMI (50 µL, 0.63 mmol, 1.57 eq.) at 25 °C. The mixture was stirred at 25 °C for 36 hours and directly injected into a normal-phase flash chromatography system (hexanes – ethyl acetate gradient on silica-gel), followed by reverse-phase flash chromatography (water – methanol gradient on C18 silica-gel). Yield **16** (23 mg, 13%) of a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.74 (s, 1H, 3''), 7.19 (s, 1H, 6''), 5.63 (s, 2H, 3), 4.12 (m, 4H, O-C**H$_2$**-CH$_3$), 4.03 (s, 3H, 5''-O-C**H$_3$**), 3.97 (s, 3H, 4''-O-C**H$_3$**), 1.75 (s, 6H, 1-(C**H$_3$**)$_2$), 1.32 ppm (td, 6H, $J_{CH3\text{-}1'}$ = 7.1, $J_{CH3\text{-}P}$ = 1.0, O-CH$_2$-C**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 171.96 (d, $J_{2\text{-}P}$ = 3.9, 2), 153.78 (5''), 148.23 (4''), 139.67 (2''), 126.81 (1''), 110.48 (6''), 108.09 (3''), 80.92 (d, $J_{1\text{-}P}$ = 6.2, 1), 64.41 (3), 63.76 (d, $J_{CH2\text{-}P}$ = 6.1, O-**C**H$_2$-CH$_3$), 56.76 (5''-O-**C**H$_3$), 56.38 (4''-O-**C**H$_3$), 26.30 (d, $J_{CH3\text{-}P}$ = 5.1, 1-(**C**H$_3$)$_2$), 16.00 ppm (d, $J_{CH3\text{-}P}$ = 7.1, O-CH$_2$-**C**H$_3$). ^{31}P NMR (161 MHz, $CDCl_3$, 25 °C) δ –4.95 ppm. HRMS (ESI+) calculated for $C_{17}H_{27}O_{10}NP$ 436.13671, found $[M+H]^+$ 436.13666.

*Characterization of intermediates (**I**) and products identified after irradiation with UV light*

1-I. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 174.92 (d, $J_{3\text{-}P}$ = 5.1, 3), 160.88 (d, $J_{4'''\text{-}F}$ = 242.6, 4'''), 151.02−151.23 (m, 1'), 147.11−147.31 (m, 1'''), 131.61 (3'), 127.40 (4'), 123.11−123.33 (m, 2'''), 121.37 (d, $J_{2'\text{-}P}$ = 4.6, 2'), 121.35 (d, $J_{2'\text{-}P}$ = 4.7, 2'), 118.03 (d, $J_{3'''\text{-}F}$ = 23.7, 3'''), 118.00 (d, $J_{3'''\text{-}F}$ = 23.6, 3'''), 78.25 (d, $J_{1\text{-}P}$ = 7.1, 1), 20.79 ppm (d, $J_{2\text{-}P}$ = 5.0, 2). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −12.55 and −12.64 ppm. HRMS (ESI-) calculated for $C_{15}H_{13}O_6FP$ 339.04393, found $[M-H]^-$ 339.04370.

1-P1, 2-P1. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) 130.76 (3'), 124.66 (4'), 121.56 (d, $J_{2'\text{-}P}$ = 4.7, 2'), 74.19 (d, $J_{1\text{-}P}$ = 6.4, 1), 21.32 ppm (d, $J_{2\text{-}P}$ = 2.7, 2). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −6.17 ppm. HRMS (ESI-) calculated for $C_9H_{10}O_6P$ 245.02205, found $[M-H]^-$ 245.02221.

1-P, 2-P. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 180.53 (d, $J_{3\text{-}P}$ = 5.5, 3), 73.24 (d, $J_{1\text{-}P}$ = 5.5, 1), 21.39 ppm (d, $J_{2\text{-}P}$ = 4.3, 2). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −0.22 ppm. HRMS (ESI-) calculated for $C_3H_6O_6P$ 168.99075, found $[M-H]^-$ 168.99092.

2-I. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 175.93 (d, $J_{3\text{-}P}$ = 5.4, 3), 151.10−151.27 (m, 1'), 148.83−149.08 (m, 1'''), 136.88−136.99 (m, 4'''), 131.80−131.90 (m, 3'''), 131.52−131.60 (m, 3'), 127.31 and 127.29 (4'), 121.29−121.42 (m, 2'), 121.04−121.18 (m, 2'''), 78.06 (d, $J_{1\text{-}P}$ = 6.6, 1), 21.39−21.46 (m, 4'''-**C**H$_3$), 20.83 ppm (d, $J_{2\text{-}P}$ = 5.3, 2). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −12.57 ppm. HRMS (ESI-) calculated for $C_{16}H_{16}O_6P$ 335.06900, found $[M-H]^-$ 335.06906.

2-P2 ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 179.17 (d, $J_{3\text{-}P}$ = 7.3, 3), 151.50 (d, $J_{1'''\text{-}P}$ = 7.0, 1'''), 133.81 (4'''), 131.10 (3'''), 121.30−121.44 (m, 2'''), 74.13 (d, $J_{1\text{-}P}$ = 6.0, 1), 21.41 (d, $J_{CH3\text{-}P}$ = 1.8, 4'''-**C**H$_3$), 21.33 ppm (d, $J_{2\text{-}P}$ = 3.1, 2). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −6.01 ppm. HRMS (ESI-) calculated for $C_{10}H_{12}O_6P$ 259.03770, found $[M-H]^-$ 259.03787.

4-I. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 123.11−123.33 (m, 2'), 117.90 (d, $J_{3'\text{-}F}$ = 23.7, 3'), 77.18 (d, $J_{1\text{-}P}$= 6.4, 1), 66.90−67.06 (m, -O-**C**H$_2$-CH$_3$), 20.73−20.92 (m, 2), 16.84−16.99 ppm (m, -O-CH$_2$-C**H$_3$**). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −7.05 and −7.38 ppm. HRMS (ESI-) calculated for $C_{11}H_{13}O_6FP$ 291.04393, found $[M-H]^-$ 291.04359.

5-I. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 176.47 (d, $J_{3\text{-}P}$ = 5.6, 3), 175.40 (d, $J_{3\text{-}P}$ = 5.8, 3), 151.29 (d, $J_{1'\text{-}P}$ = 7.0, 1'), 151.25 (d, $J_{1'\text{-}P}$ = 6.7, 1'), 131.48 and 131.48 (3'), 127.04 and 127.01 (4'), 121.42 (d, $J_{2'\text{-}P}$ = 4.5, 2'), 121.37 (d, $J_{2'\text{-}P}$ = 4.6, 2'), 77.08 (d, $J_{1\text{-}P}$ = 6.6, 1), 77.06 (d, $J_{1\text{-}P}$ = 6.3, 1), 66.85 (d, $J_{CH2\text{-}P}$ = 6.5, -O-**C**H$_2$-CH$_3$), 66.81 (d, $J_{CH2\text{-}P}$ = 6.3, -O-**C**H$_2$-CH$_3$), 20.86 (d, $J_{2\text{-}P}$ = 4.8, 2), 20.79 (d, $J_{2\text{-}P}$ = 5.1, 2), 16.94 (d, $J_{CH3\text{-}P}$ = 6.7, -O-CH$_2$-**C**H$_3$), 16.91 ppm (d, $J_{CH3\text{-}P}$ = 6.7, -O-CH$_2$-**C**H$_3$). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −7.14 and −7.53 ppm. HRMS (ESI-) calculated for $C_{11}H_{14}O_6P$ 273.05335, found $[M-H]^-$ 273.05358.

6-I. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 176.52 (d, $J_{3\text{-}P}$ = 5.4, 3), 176.45 (d, $J_{3\text{-}P}$ = 5.8, 3), 149.09 (d, $J_{1'\text{-}P}$ = 7.1, 1'), 149.06 (d, $J_{1'\text{-}P}$ = 7.3, 1'), 136.60 and 136.56 (4'), 131.78 and 131.77 (3'), 121.18 (d, $J_{2'\text{-}P}$ = 4.5, 2'), 121.13 (d, $J_{2'\text{-}P}$ = 4.6, 2'), 77.02 (d, $J_{1\text{-}P}$ = 6.5, 1), 77.00 (d, $J_{1\text{-}P}$ = 6.3, 1), 66.77 (d, $J_{CH2\text{-}P}$ = 6.4, -O-**C**H$_2$-CH$_3$), 66.74 (d, $J_{CH2\text{-}P}$ =

6.3, -O-**C**H$_2$-CH$_3$), 21.43 and 21.42 (4'-**C**H$_3$), 20.87 (d, $J_{2\text{-}P}$ = 4.9, 2), 20.80 (d, $J_{2\text{-}P}$ = 5.3, 2), 16.94 (d, $J_{CH3\text{-}P}$ = 6.7, -O-CH$_2$-**C**H$_3$), 16.91 ppm (d, $J_{CH3\text{-}P}$ = 6.4, -O-CH$_2$-**C**H$_3$). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −6.96 and −7.37 ppm. HRMS (ESI-) calculated for $C_{12}H_{16}O_6P$ 287.06900, found [M-H]$^-$ 287.06893.

7-I. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 176.37–176.47 (m, 3), 157.66 and 157.61 (4'), 144.89−145.04 (m, 1'), 122.57 (d, $J_{2'\text{-}P}$ = 4.4, 2'), 122.52 (d, $J_{2'\text{-}P}$ = 4.5, 2'), 116.33 and 116.24 (3'), 77.01 (d, $J_{1\text{-}P}$ = 6.8, 1), 77.00 (d, $J_{1\text{-}P}$ = 6.4, 1), 66.75 (d, $J_{CH2\text{-}P}$ = 6.4, -O-**C**H$_2$-CH$_3$), 66.73 (d, $J_{CH2\text{-}P}$ = 6.4, -O-**C**H$_2$-CH$_3$), 56.91 and 56.84 (4'-O-**C**H$_3$), 20.87 (d, $J_{2\text{-}P}$ = 5.1, 2), 20.80 (d, $J_{2\text{-}P}$ = 5.3, 2), 16.94 (d, $J_{CH3\text{-}P}$ = 6.4, -O-CH$_2$-**C**H$_3$), 16.92 ppm (d, $J_{CH3\text{-}P}$ = 6.3, -O-CH$_2$-**C**H$_3$). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −6.68, −7.06 ppm. HRMS (ESI-) calculated for $C_{12}H_{16}O_7P$ 303.06391, found [M-H]$^-$ 303.06411.

3-P2, **4-P2**, **5-P2**, **6-P2** and **7-P2**. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 179.87 (d, $J_{3\text{-}P}$ = 6.5, 3), 73.52 (d, $J_{1\text{-}P}$ = 5.4, 1), 62.42 (d, $J_{CH2\text{-}P}$ = 5.9, -O-**C**H$_2$-CH$_3$), 21.42 (d, $J_{2\text{-}P}$ = 3.2, 2), 17.33 ppm (d, $J_{CH3\text{-}P}$ = 7.5, -O-CH$_2$-**C**H$_3$). ^{31}P NMR (202MHz, 50% CACO/DMSO-d_6, 25 °C) δ −1.04 ppm. HRMS (ESI-) calculated for $C_5H_{10}O_6P$ 197.02205, found [M-H]$^-$ 197.02187.

8-I. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 175.36 (d, $J_{2\text{-}P}$ = 2.8, 2), 175.29 (d, $J_{2\text{-}P}$ = 2.8, 4), 151.31–151.53 (m, 1'), 131.40 (3'), 126.93 and 126.87 (4'), 121.45 (d, $J_{2'\text{-}P}$ = 4.4, 2'), 121.38 (d, $J_{2'\text{-}P}$ = 4.4, 2'), 85.66 (d, $J_{1\text{-}P}$ = 7.0, 1), 85.59 (d, $J_{1\text{-}P}$ = 6.2, 1), 66.66–66.84 (m, -O-**C**H$_2$-CH$_3$), 32.29–32.46 (m, **C**H^{iPr}), 20.11 and 20.08 and 18.04 and 17.86 (**C**H$_3^{iPr}$), 16.95 ppm (d, $J_{CH3\text{-}P}$ = 6.8, -O-CH$_2$-**C**H$_3$). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −6.64 and −7.09 ppm. HRMS (ESI-) calculated for $C_{13}H_{18}O_6P$ 301.08465, found [M-H]$^-$ 301.08489.

8-P2. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 178.68 (d, $J_{2\text{-}P}$ = 3.1, 2), 82.29 (d, $J_{1\text{-}P}$ = 5.9, 1), 62.38 (d, $J_{CH2\text{-}P}$ = 5.8, -O-**C**H$_2$-CH$_3$), 32.73 (d, $J_{CH(iPr)\text{-}P}$ = 5.2, **C**H^{iPr}), 19.97 and 18.93 (**C**H$_3^{iPr}$), 17.37 ppm (d, $J_{CH3\text{-}P}$ = 8.0, -O-CH$_2$-**C**H$_3$). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −0.60 ppm. HRMS (ESI-) calculated for $C_7H_{14}O_6P$ 225.05335, found [M-H]$^-$ 225.05350.

9-P2. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 181.68 (2), 81.23 (d, $J_{1\text{-}P}$ = 7.9, 1), 62.21 (d, $J_{CH2\text{-}P}$ = 5.5, -O-**C**H$_2$-CH$_3$), 27.32 (d, $J_{CH3\text{-}P}$ = 1.8, 1-(**C**H$_3$)$_2$), 17.33 ppm (d, $J_{CH3\text{-}P}$ = 7.7, -O-CH$_2$-**C**H$_3$). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ –4.22 ppm. HRMS (ESI-) calculated for $C_6H_{12}O_6P$ 211.03770, found [M-H]$^-$ 211.03777.

10-P1. ^{13}C NMR (125 MHz, 25% CACO/DMSO-d_6, 25 °C) δ 129.82 (3'), 123.01 (4'), 120.84 (d, $J_{2'\text{-}P}$ = 4.9, 2'), 82.20 (d, $J_{1\text{-}P}$ = 6.5, 1), 32.05 (d, $J_{CH(iPr)\text{-}P}$ = 4.6, **C**H^{iPr}), 19.92 and 18.47 ppm (**C**H$_3^{iPr}$). C2 and C1' were not detected. ^{31}P NMR (202 MHz, 25% CACO/DMSO-d_6, 25 °C) δ −5.91 ppm. HRMS (ESI-) calculated for $C_{11}H_{14}O_6P$ 273.05335, found [M-H]$^-$ 273.05330.

10-P and **11-P**. ^{13}C NMR (125 MHz, 25% CACO/DMSO-d_6, 25 °C) δ 178.38 (2), 81.02 (d, $J_{1\text{-}P}$ = 6.5, 1), 31.65 (d, $J_{CH(iPr)\text{-}P}$ = 7.6, **C**H^{iPr}), 20.39 and 17.74 ppm (**C**H$_3^{iPr}$). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −0.99 ppm. HRMS (ESI-) calculated for $C_5H_{10}O_6P$ 197.02205, found [M-H]$^-$ 197.02181.

11-I. ^{13}C NMR (125 MHz, 25% CACO/DMSO-d_6, 25 °C) δ 172.80 (m, 2), 148.82−149.01 (m, 1'''), 135.57 (4'''), 131.12 and 131.03 and 130.84 and 130.75 (3''', 3'), 126.25 (4'), 121.13 (d, $J_{2'/2'''\text{-}P}$ = 4.8, 2' or 2'''), 120.90 (d, $J_{2'/2'''\text{-}P}$ = 4.5, 2' or 2'''), 120.83 (d, $J_{2'/2'''\text{-}P}$ = 4.6, 2' or 2'''), 120.55−120.67 (m, 2' or 2'''), 86.13−86.25 (m, 1), 31.74 (d, $J_{CH(iPr)\text{-}P}$ = 7.2, **C**H^{iPr}), 21.06 and 21.04 (4'''-**C**H$_3$), 19.99 and 19.97 and 17.54 and 17.53 ppm (**C**H$_3^{iPr}$). ^{31}P NMR (202 MHz, 25% CACO/DMSO-d_6, 25 °C) δ –12.16 and –12.19 ppm. HRMS (ESI-) calculated for $C_{18}H_{20}O_6P$ 363.10030, found [M-H]$^-$ 363.10056.

11-P2. ^{13}C NMR (125 MHz, 25% CACO/DMSO-d_6, 25 °C) δ 176.85 (d, $J_{2\text{-}P}$ = 3.1, 2), 151.92 (d, $J_{1'''\text{-}P}$ = 6.4, 1'''), 131.79 (4'''), 130.16 (3'''), 120.63 (d, $J_{2'''\text{-}P}$ = 4.9, 2'''), 82.11 (d, $J_{1\text{-}P}$ = 6.9, 1), 32.05 (d, $J_{CH(iPr)\text{-}P}$ = 5.2, **C**H^{iPr}), 21.04 (4'''-**C**H$_3$), 19.94 and 18.48 ppm (**C**H$_3^{iPr}$). ^{31}P NMR (202 MHz, 25% CACO/DMSO-d_6, 25 °C) δ –5.76 ppm. HRMS (ESI-) calculated for $C_{12}H_{16}O_6P$ 287.06900, found [M-H]$^-$ 287.06927.

12-P and **13-P**. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 182.51–182.64 (m, 2), 81.41 (d, $J_{1\text{-}P}$ = 7.5, 1), 28.05 ppm (d, $J_{CH3\text{-}P}$ = 3.7, 1-(**C**H$_3$)$_2$). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ –2.68 ppm. HRMS (ESI-) calculated for $C_4H_8O_6P$ 183.00640, found [M-H]$^-$ 183.00654.

13-P2. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 133.48 (4'''), 131.04 (3'''), 121.16 (d, $J_{2'''\text{-}P}$ = 4.7, 2'''), 81.97 (d, $J_{1\text{-}P}$ = 7.9, 1), 27.32 (d, $J_{CH3\text{-}P}$ = 2.2, 1-(**C**H$_3$)$_2$), 21.40 ppm (4'''-**C**H$_3$). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ –9.30 ppm. HRMS (ESI+) calculated for $C_{11}H_{14}O_6P$ 273.05335, found [M-H]$^-$ 273.05389.

14-I. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 176.89 ($J_{3\text{-}P}$ = 5.5, 3), 76.89 (d, $J_{1\text{-}P}$ = 6.0, 1), 65.76 (d, $J_{1'\text{-}P}$ = 5.6, 1'), 65.71 (d, $J_{1'\text{-}P}$ = 5.4, 1'), 20.90 (d, $J_{2\text{-}P}$ = 5.0, 2), 16.97 (d, $J_{2'\text{-}P}$ = 6.6, 2'), 16.96 ppm (d, $J_{2'\text{-}P}$ = 6.4, 2'). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ –2.01 ppm. HRMS (ESI-) calculated for $C_7H_{14}O_6P$ 225.05335, found [M-H]$^-$ 225.05355.

15-I. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 175.78 (d, $J_{2\text{-}P}$ = 1.8, 2), 84.72 (d, $J_{1\text{-}P}$ = 6.8, 1), 65.65−65.75 (m, 1'), 32.36 (d, $J_{CH(iPr)\text{-}P}$ = 6.8, **C**H^{iPr}), 20.14 (**C**H$_3^{iPr}$), 18.08 (**C**H$_3^{iPr}$), 17.01 (d, $J_{2'\text{-}P}$ = 6.3, 2'), 16.99 ppm (d, $J_{2'\text{-}P}$ = 6.4, 2'). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −1.52 ppm. HRMS (ESI-) calculated for $C_9H_{18}O_6P$ 253.08465, found [M-H]$^-$ 253.08479.

16-I. ^{13}C NMR (125 MHz, 50% CACO/DMSO-d_6, 25 °C) δ 178.58 (d, $J_{2\text{-}P}$ = 6.6, 2), 86.18 (d, $J_{1\text{-}P}$ = 7.4, 1), 65.31 (d, $J_{1'\text{-}P}$ = 6.1, 1'), 27.53 (d, $J_{CH3\text{-}P}$ = 3.6, 1-(**C**H$_3$)$_2$), 16.96 ppm (d, $J_{2'\text{-}P}$ = 6.9, 2'). ^{31}P NMR (202 MHz, 50% CACO/DMSO-d_6, 25 °C) δ −5.44 ppm. HRMS (ESI-) calculated for $C_8H_{16}O_6P$ 239.06900, found [M-H]$^-$ 239.06903.

NMR Spectroscopy. For compound characterization, NMR spectra were recorded on a Bruker Avance III spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161 MHz for ^{31}P. Irradiation NMR experiments were performed on a Bruker Avance III spectrometer with a broad-band cryo probe with an ATM module (5 mm CPBBO BB-^{1}H/^{19}F/^{15}N/D Z-GRD) operating at 500 MHz for ^{1}H, 125.7 MHz for ^{13}C and 202 MHz for ^{31}P. For NMR signal assignment, standard Bruker pulse sequences were employed for both 1D (^{1}H, ^{13}C-APT, ^{31}P) and 2D (COSY, ROESY, HSQC, HMBC) NMR experiments at a corrected temperature of 25 °C. The structure of each intermediate was determined *in situ*, as recently reported.[17] All NMR data was interpreted using Topspin 3.5. For reference, the following solvent signals were used: DMSO-d_6: 2.50 (^{1}H) and 39.5 (^{13}C) ppm; $CDCl_3$: 7.27 (^{1}H) and 77.0 (^{13}C). ^{31}P NMR spectra were referenced to H_3PO_4 with 0 ppm.

For NMR experiments with *in situ* irradiation, a light emitting diode (LED; Thorlabs, Germany) was used at 365 nm. The light was guided into the spectrometer, directly into the NMR tube, via a multimode silica optical fiber with 1-mm diameter, 0.39 NA, and a high amount of OH (Thorlabs, Germany). The irradiation setup was described in detail in our previous work.[30] For *in situ* irradiation NMR experiments, we used 0.5 mM solutions of the corresponding linkers **1**−**13** in a mixture of cacodylate buffer (CACO) with DMSO-d_6 (1:1, v/v or, in some case, 1:3, v/v). All irradiation experiments were performed at room temperature.

Mass spectrometry. Mass spectra were measured on an LTQ Orbitrap XL (Thermo Fisher Scientific) by electrospray ionisation (ESI).

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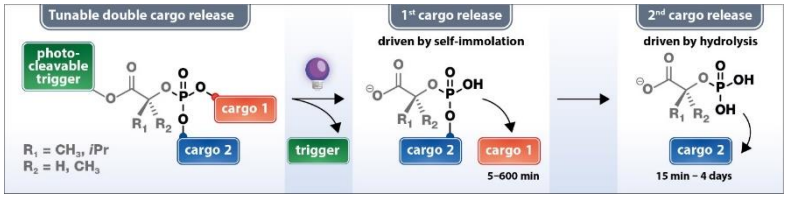

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