# Design and Synthesis of an $\alpha,\alpha$-Difluorophosphinate Hapten for Antibody-Catalyzed Hydrolysis of Organophosphorus Nerve Agents

**Philippe Vayron,[a,c] Pierre-Yves Renard,*[a,c] Alain Valleix,[a] and Charles Mioskowski*[a,b]**

**Abstract:** In a new approach to the safe neutralization of organophosphorus chemical weapons, we designed a hapten to elicit catalytic antibodies with phosphatase activity. Here we report the synthesis of this $\alpha,\alpha$-difluorophosphinate hapten **6**. Various methods for the introduction of the key $\alpha,\alpha$-difluoromethyl feature into the phosphinate hapten are discussed. The best results were obtained with the electrophilic *gem*-difluorinating agent *N*-fluorobenzenesulfonimide.

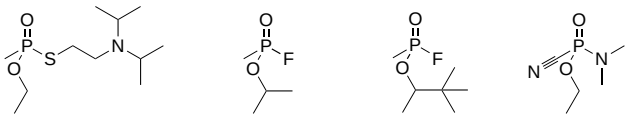
**Keywords:** catalytic antibodies · fluorine · organophosphates · phosphatases · protein mimetics

## Introduction

Inactivation of extremely toxic organophosphorus chemical weapons has become a subject of major importance. The international control of their proliferation is thwarted by the ease of their synthesis, and by the similarity between their chemical precursors and widely used pest-control agents. Mild means of decontamination on the battlefield or in laboratories and tools for the in vivo degradation of organophosphorus compounds have both been investigated.[1]

The main effect of organophosphorus poisons is related to their potent and irreversible inhibition of mammalian acetylcholinesterase (AChE),[2] the enzyme responsible for regulating the concentration of the neurotransmitter acetylcholine at cholinergic synapses. Of the four major chemical warfare organophosphorus agents (Scheme 1), thiophosphonate VX (**1**) exhibits the highest toxicity. The usual methods for decontamination include hydrolysis in strongly alkaline media, oxidation (both require highly corrosive solutions, although milder media have been proposed)[3] or nucleophile-assisted substitution.[4]

Considerable work has been done with a view to destruction of these organophosphorus nerve agents,[5] but two issues have to be addressed:




Scheme 1. Main organophosphorus chemical warfare nerve agents.

Environmentally compatible solutions are required for decontamination of sensitive equipment.

New and efficient substances must be able to remove or neutralize the effects of toxins in vivo,[6] since, once present in the body, organophosphorus nerve agents are only partially hydrolyzed by native esterases and phosphatases before hitting their target.

Genetically engineered cholinesterases[7] and phosphatases[8] probably represent the most interesting of the approaches described so far to the inactivation of organophosphorus chemical weapons under physiological conditions. However, these strategies require expensive and time-consuming preparation of large amounts of the modified enzymes, whose in vivo half-life is short, even when they are stabilized.

The ability of antibodies to bind strongly to foreign molecules has long been exploited therapeutically. Their power to immobilize natural poisons or toxins in vivo is still used in treatment of snakebite, for example. Progress in the production of monoclonal antibodies (multigram quantities of antibodies are now easily available)[9] has revived interest in these proteins, notably because of their potential clinical applications against organophosphorus nerve agents.[10] More recently, the discovery of catalytic antibodies[11] has broadened the scope for their therapeutic use. Indeed, antibodies able to destroy a toxin catalytically rather than simply bind to it would be of great use in therapy. This strategy has been successfully applied against cocaine addiction: serotherapy

[a] Dr. C. Mioskowski, Dr. P.-Y. Renard, P. Vayron, A. Valleix
CEA, Service des Molécules Marquées, CE-Saclay
F-91191 Gif sur Yvette Cedex (France)
Fax: (+33) 1-69-08-79-91
E-mail: pierre-yves.renard@cea.fr

[b] Dr. C. Mioskowski
Laboratoire de Synthèse Bioorganique associé au CNRS
Faculté de Pharmacie, Université Louis Pasteur
74 route du Rhin, F-67401 Illkirch (France)
E-mail: mioskow@aspirine.u-strsbg.fr

[c] Dr. P.-Y. Renard, P. Vayron
CEB, BP 3
F-91710 Vert le Petit (France)



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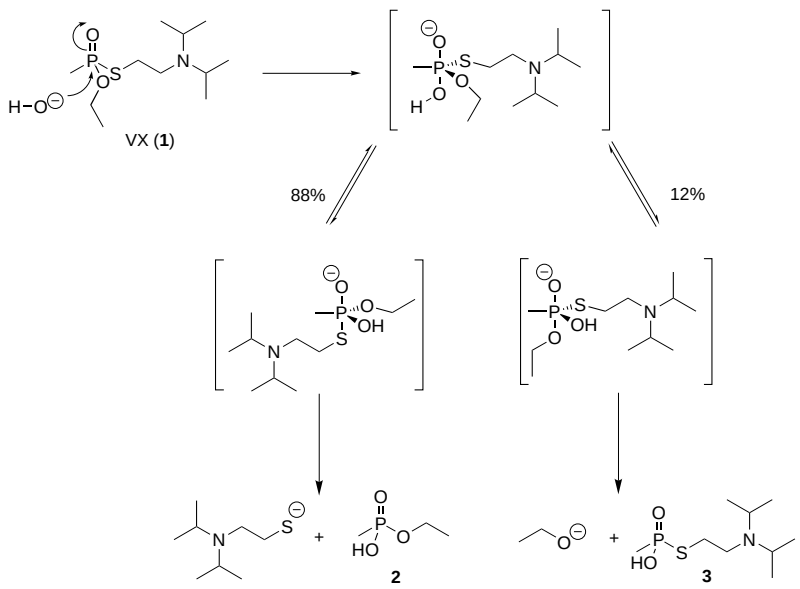
using a monoclonal antibody (mAb) that speeds the degradation of cocaine into nontoxic, nonaddictive compounds stopped the drug-seeking behavior of cocaine-addicted rats, and protected them against an overdose that was lethal for controls.[12]

Our aim is to apply this active immunization strategy to the degradation of the exceedingly toxic organophosphorus nerve agent VX (**1**). A preliminary study based on a first-generation hapten bearing an $\alpha$-hydroxyphosphinate moiety mimicking the early approach of an incoming water molecule to the phosphorus center gave encouraging results, despite the modest acceleration factor of the catalytic antibody PAR-15.[13] Here we describe the synthesis of a second-generation hapten which is charged and mimics the transition state of another hydrolysis pathway.

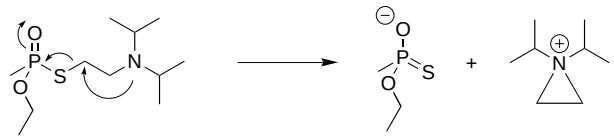



Scheme 2. Mechanism of hydrolysis of VX (**1**) by $HO^-$ nucleophilic addition to phosphorus, predominant in strongly basic media.

Few antibodies endowed with phosphatase-like activity have been described to date, and the major problem is how to mimic the putative pentacoordinated anionic transition state. Use of a water stable phosphorane led to a debatable catalytic activity,[14] and the only successful strategy was based on a pentacoordinated metallochelate.[15] Other phosphatase catalytic activities have been observed with haptens mimicking phosphatase inhibitors,[16] or by using a bait-and-switch strategy.[17]

## Results and Discussion

The mechanism of the hydrolysis or perhydrolysis of VX (**1**) is still under study. At least four mechanisms have been considered and are believed to occur simultaneously.[18] First, hydroxide ion attack on phosphorus yields pentacoordinated phosphorane, which decomposes with an approximately 88/12 mixture of P–S and P–O bond cleavage, yielding both nontoxic methyl-*O*-ethylphosphonic acid (**2**), and toxic methyl-*S*-(2-diisopropylaminoethyl)phosphonic acid (**3**), as depicted in Scheme 2. Unlike the perhydroxide ion attack on VX, for which the concerted $S_N2(P)$ mechanism has been demonstrated, it is still an open question whether this nucleophilic attack on phosphorus is concerted or occurs after pseudorotational interconversion.[19, 20] However, this hydroxide ion attack is pH-dependent, and the pseudo-first-order rate constant $k_{OH}$ has been estimated as $\approx 5 \times 10^{-3}\,M^{-1}s^{-1}$. For the three other mechanisms, the hydrolysis is promoted by the intramolecular amino group, via a) a neighboring N-assisted displacement to cleave S–C bonds, as depicted in Scheme 3



Scheme 3. Mechanism of hydrolysis of VX (**1**) by intramolecular S–C bond cleavage.

($k \approx 4.6 \times 10^{-7}\,s^{-1}$),[18] or general base catalyses, with either b) the *O*-ethyl (Scheme 4), or c) the *S*-alkyl (Scheme 5) group apical to the attacking water molecule (in both cases, $k \approx 4 \times 10^{-6}\,s^{-1}$).[18] In dilute aqueous solution (pH 6–9), the latter two mechanisms predominate and give an approximately 50/50 mixture of P–S and P–O bond cleavage.

We chose to select catalytic antibodies which favor the latter mechanism (c), in order to simultaneously accelerate the P–S bond cleavage reaction and minimize the amount of P–O bond cleavage (which yields the still extremely toxic thiophosphonic acid **3**). This aim can be achieved with the use of conveniently designed haptens.

In a first series of experiments, to avoid handling exceedingly toxic VX (**1**), we selected the less toxic phenylthiophosphonate PhX (**4**; Scheme 6) as target. PhX reversibly inhibits AChE with a 20 nM $IC_{50}$,[13] whereas VX (**1**) almost irreversibly inhibits AChE with a 0.2 nM $IC_{50}$ (intravenous

**Abstract in French:** *Dans cet article, nous décrivons la synthèse de l'haptène* ***6****, de structure α,α-difluorophosphinate. Cet haptène est destiné à être utilisé dans une nouvelle approche pour neutraliser les agents de guerre chimiques organophosphorés, grâce à des anticorps à activité catalytique de type phosphatase. Diverses méthodes d'introduction d'un motif gem-difluoromethyl en α du phosphore ont été testées; les meilleurs résultats ont été obtenus en utilisant un agent de difluoration électrophile, le N-fluorobenzene sulfonimide.*

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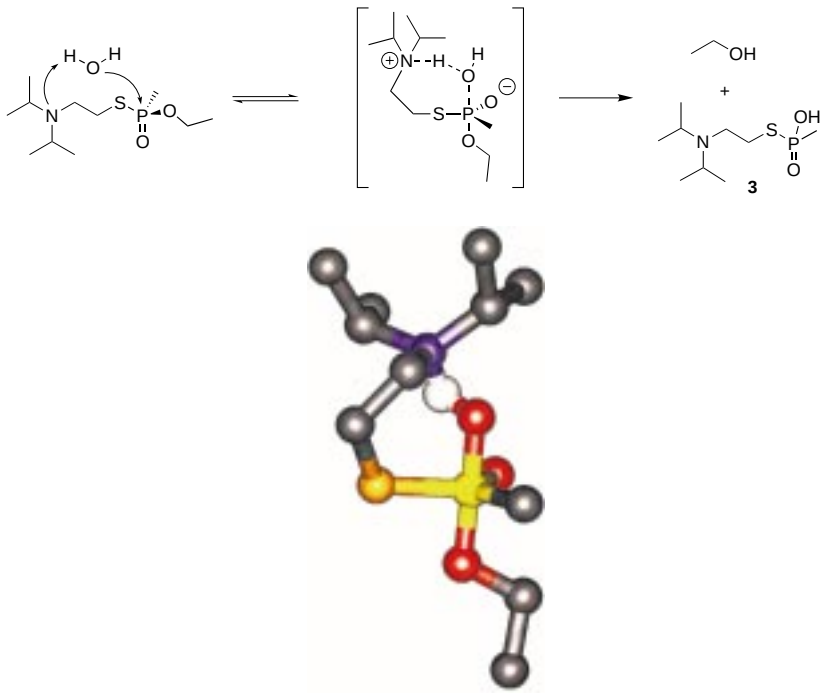
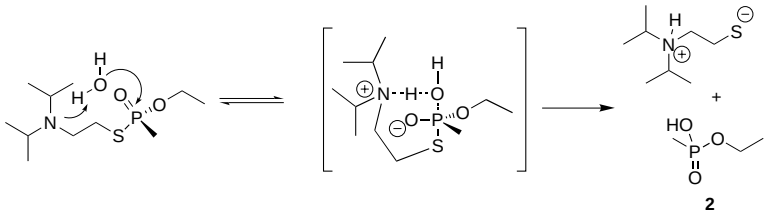
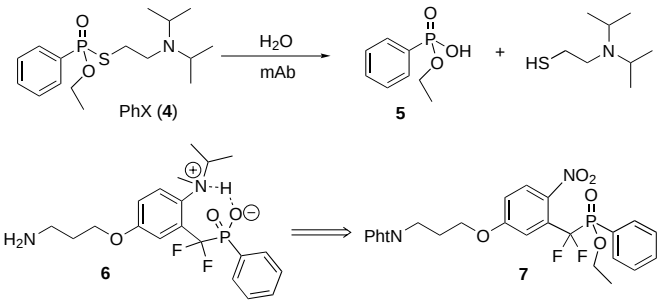



Scheme 4. VX (**1**) hydrolysis mechanism involving apical oxygen-bearing side chain.




Scheme 5. VX (**1**) hydrolysis mechanism involving apical sulfur-bearing side chain.




Scheme 6. Hydrolysis of PhX (**4**) and hapten structure.

$LD_{50} = 8\ \mu g\,kg^{-1}$ and percutaneous $LD_{50} = 28\ \mu g\,kg^{-1}$ in rabbits).[1b] We therefore designed hapten **6** bearing the structural features listed below.

- A charged nitrogen atom brought artificially close to the phosphorus in order both a) to force the folding of the lateral chain of VX (the entropy reduction required for the substrate to reach a reactive form is thus minimized), and b) to introduce an anionic amino acid at the antibody-binding site, which would promote a general acid/base catalysis known in the case of catalytic antibodies as the bait-and-switch strategy.[21] The side chain is folded by means of conformational strain caused by introduction of an aromatic ring on the side chain of hapten **6** (Scheme 6), and through an intramolecular zwitterionic bond between the acidic moiety and the charged amine.
- We decided not to introduce the two isopropyl groups of PhX (**4**) on the nitrogen of the side chain, but only one, along with a methyl group, in order not to center the immunological response on this particularly immunogenic structural feature.
- We included a hydrolytically stable $\alpha,\alpha$-difluorophosphinate moiety, on the grounds that substitution of phosphate groups, in natural and unnatural products with the $\alpha,\alpha$-difluoromethylenephosphonate moiety, results in a significant enhancement of their biological properties.[22] More particularly, one of the most striking examples is the inhibition of protein tyrosine phosphatases (PTPs) with peptides containing the non-hydrolyzable phosphotyrosine mimetic (phosphonodifluoromethyl)phenylalanine.[23] This can be understood first by the mimicry of the P–O (or P–S) bond[24] with a significantly longer, non-hydrolyzable $P–CF_2$ bond. It can be understood too by the steric and electronic equivalence between the oxygen of the phosphate and the $CF_2$ moiety replacing it in difluoromethylenephosphonate, which are known to be isosteric with the corresponding phosphates.[25] This point is illustrated by the fact that $\alpha,\alpha$-difluorophosphonate has a lower $pK_a$ than the corresponding phosphate,[26] and finally by specific interactions between the fluorine atom with the amino acid side chains in the PTP active sites.[23d] As far as the P–S bond is concerned, the $P–CF_2$ bond is slightly shorter than the P–S one. Yet steric and electronic equivalence is even closer since the $CF_2$ moiety



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mimics the bulk of the sulfur atom better than that of the oxygen atom, and the electronic density is also better adjusted.

- Moreover, on analogy with the hydration of difluoromethyl ketones,[27] it was expected that the enhancement of the electrophilicity at the phosphorus of phosphinates bearing a $CF_2$ moiety would make them prone to hydration, yielding the corresponding pentacoordinated phosphorane.
- We designed in two strongly antigenic aromatic moieties in order to reinforce the immunological response of immunized mice.
- We included a partially deprotonated phosphinic acid moiety, which should mimic an incoming water molecule on phosphorus, as in Scheme 5. The partially negative charge on the oxygen atom is increased by the strong electron-withdrawing effect of the neighboring electronegative fluorine atoms.
- An aliphatic linker was necessary for coupling to the carrier protein through the homobifunctional cross-linking reagent glutaraldehyde; it was situated opposite the $\alpha,\alpha$-difluorophosphate moiety, in order to target the immunological response on this moiety.

Retrosynthesis of hapten **6** leads to the intermediate **7** (Scheme 6). The ethyl phosphinate ester should either be saponified (the presence of the strongly electron-withdrawing fluorine atoms should facilitate saponification of the phosphate by increasing the fragility of the O–C bond), or removed with trimethylsilyl halide.[28] The nitro function should easily be transformed to a tertiary amine.

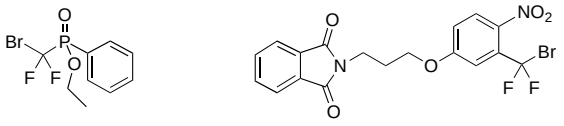
The key feature in intermediate **7** is the $\alpha,\alpha$-difluorophosphinate moiety. Although synthesis of $\alpha,\alpha$-difluorinated phosphonate and particularly benzylic phosphonates is well documented,[29] when we began this study, data on the synthesis of $\alpha,\alpha$-fluorinated phosphinates were scarce. Since then, the $PCF_2$ key moiety has been introduced into $\alpha,\alpha$-difluorophosphinates and $\alpha,\alpha$-difluorophosphinites of biological interest in six different ways:

- Nucleophilic addition of the phosphinyl anion to chlorodifluoromethane.[30]
- Michaelis–Arbuzov-like addition of iodo-[31] or bromodifluoroalkanes to phosphonites.[32]
- Radical addition of phosphinyl radical to $\alpha,\alpha$-difluorovinylalkanes,[33] as described more recently and more extensively for phosphonyl radicals.[34]
- Addition of iododifluoroalkane to a phosphate by metallation of the iodide with Zn/Cu.[35]
- Electrophilic fluorination with perchloryl fluoride as "$F^+$" transfer agent.[36]
- [2,3]-Wittig rearrangement of highly electrophilic $\gamma,\gamma$-difluoroallylphosphinites.[37]

None of these methods is of general use; yields are often quite low (except for the first one), and preparation of a completely and conveniently functionalized molecule thus appears tedious and time-consuming. In order to obtain a more general method of introducing the $PCF_2$ moiety into benzylic phosphinates, and using literature findings on $\alpha,\alpha$-difluorinated phosphonates,[29] we made the efforts reported here to introduce this $PCF_2$ moiety.

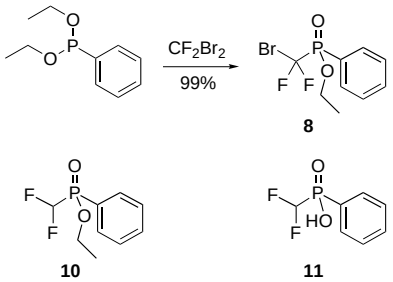
These methods follow one of two different strategies: a) the use of a fluorinated synthon, or b) a direct *gem*-difluorination by nucleophilic or electrophilic addition.

a) *Fluorinated synthons*: Two fluorinated synthons attracted our attention: *O*-ethyl bromodifluoromethyl phosphinate (**8**), and bromodifluoromethylbenzene (**9**) (Scheme 7). *O*-Ethyl bromodifluoromethyl phenyl phosphinate (**8**), which has been previously described,[32] was synthesized by a Michaelis–Arbuzov addition of dibromodifluoromethane to phenyl diethyl phosphonite (Scheme 8). Yields were greatly improved and




**8** **9**

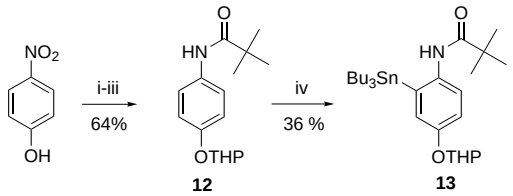
Scheme 7. Difluorinated synthons.




Scheme 8. $\alpha,\alpha$-Difluoromethylene phosphinates.

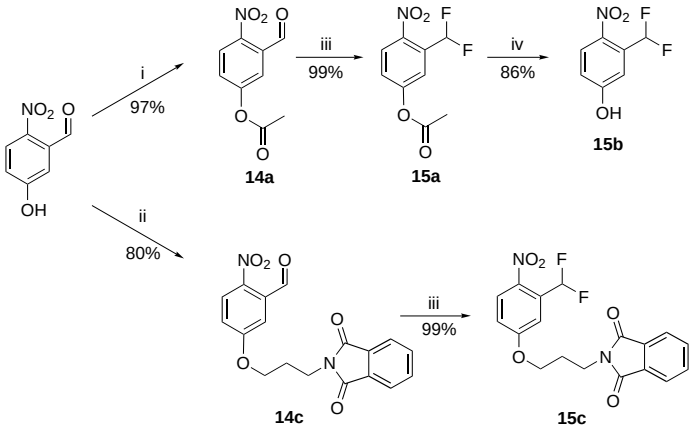
amounts of by-products minimized by performing the reaction at room temperature with dibromodifluoromethane as solvent. The use of fluorinated organometallic reagents is widely documented,[38] but with aromatic electrophiles, only the CuBr-promoted addition of dialkoxyphosphinyl difluoromethyl zinc derivative[39] and CuCl-promoted addition of cadmium derivatives[40] to aryl iodide have been successful. In our hands, under the conditions described, the formation of the organozinc reagent was observed with phosphinate **8**; it proved to be rather stable (unlike the corresponding magnesium bromide), but its addition to iodobenzene failed, and the only product isolated was difluoromethyl phosphinate **10** (Scheme 8). Our efforts to form an anion from **8** or **10** with the use of various organometallic reagents (*n*BuLi, sodium hexamethyldisilazane—NaHMDS, lithium diisopropylamide—LDA) and to add it to electrophiles (alkyl iodide, triflates, or even simple aldehydes) showed that the strong electronegativity of the fluorine atoms makes the $CF_2P(O)O$–C bond too unstable,[41] and despite the very low temperature ($-90\,^\circ C$), the only isolated product was the corresponding phosphinic acid **11** (Scheme 8), with no trace of coupling reagent. The same product was observed when aryl carbanions (PhLi, PhMgBr, or $Ph_2CuLi$) were used as "nucleophile"[42] on **8**. With tin derivative **13** (Scheme 9[+]) and $Pd(PPh_3)_4$ no change was detected after one week at room temperature.

[+] Compound **13** was easily obtained from *p*-nitrophenol in four steps and 15% yield as described in Scheme 9.




Scheme 9. Synthesis of *m*-metallated aniline **13**. i) DHP, PPTS, $CH_2Cl_2$; ii) $H_2$, Pd/C 10%, EtOH; iii) *t*BuC(O)Cl, pyridine; iv) 3 *n*BuLi, THF, 0°C, then 4.5 $ClSnBu_3$, 0°C to room temperature.

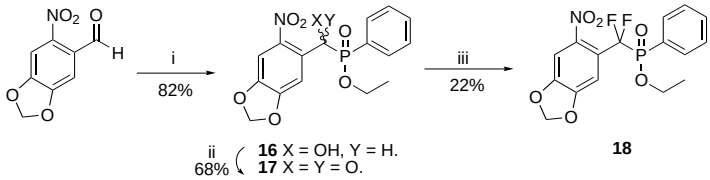
Bromodifluoromethylbenzene derivative **9** was first designed to be used in a Michaelis–Arbuzov rearrangement, also known as the Arbuzov reaction, which is a very versatile way to create a phosphorus–carbon bond from a trialkyl phosphite, phosphinite, or phosphonite and an alkyl halide.[43] Its use for the formation of the P–$CF_n$ bond is quite rare,[44] and is often limited to dihalogenodifluoromethylenes by a mechanism claimed to involve the generation of difluorocarbenes.[45] Yet benzylic bromides such as the nonfluorinated equivalent of **9** are usually particularly reactive halogenides for the Arbuzov rearrangement.[46] Moreover, **9** could be used as a substrate in Arbuzov-like reactions, either radical-induced,[47] $S_N2$-like[45c, 48] displacements or addition of the corresponding magnesium bromide onto chlorophosphinate.[49] In order to evaluate these approaches to $\alpha,\alpha$-difluorophosphinate, we decided to synthesize bromodifluoromethylbenzene derivative **9**. The synthesis of halogenodifluoromethylbenzene derivatives is best accomplished by a radical bromination[50] or chlorination[51] of the corresponding difluoromethylene compound. Compounds **15a–c** were thus synthesized from the corresponding aldehydes with diethylaminosulfur trifluoride (DAST)[52] as described in Scheme 10,




Scheme 10. Synthesis of difluoromethylbenzenes. i) $Ac_2O$, pyridine, RT; ii) (*N*-3-bromopropyl)phthalimide, $K_2CO_3$, $CH_3CN$, 80°C; iii) DAST, $CH_2Cl_2$; iv) $NaHCO_3$, $H_2O$/MeOH.

but whatever conditions were used ($Br_2$, *N*-bromosuccinimide (NBS), with or without radical initiator or $K_2CO_3$) for the radical bromination, none of them gave satisfactory yields of the bromodifluoromethyl benzenes. This radical bromination procedure was also tested without success on other difluoromethylbenzene derivatives. The requirements of excessively harsh conditions and overly long reaction times (*p*-nitrodifluoromethylbenzene with NBS plus irradiation is reported to give a 69% yield of *p*-nitrobromodifluoromethylbenzene, but in 63 days)[50b] for this bromination mean that it is of no practical use. We are currently working on a more appropriate and general approach to such bromodifluoromethylbenzenes.

b) *Direct gem-difluorination*: Since the approaches with difluoromethylene synthons proved unsuccessful, we turned to direct methods using fluorinating reagents, either nucleophilic or electrophilic.[29, 53] This strategic scheme was strengthened by our experience of the easy access to difluoromethylbenzenes **15a–c** from the corresponding benzaldehydes, by means of nucleophilic addition to the carbonyl with DAST,[52] and the numerous examples of conversion of $\alpha$-keto esters[54] and $\alpha$-oxophosphonates[55] to the corresponding $\alpha,\alpha$-difluoro esters and $\alpha,\alpha$-difluorophosphonates, respectively. Yet this latter transformation requires a large excess of expensive DAST (5 to 20 equivalents), and when performed on a multigram scale can sometimes cause explosions.[56] Moreover, the reaction conditions and yields vary greatly according to the stability of the $\alpha$-oxophosphonate or ester, which is linked to the nature of the substrate, of the protective groups, and of the ester functions on the phosphonate.[57] As an illustration, we synthesized $\alpha$-oxophosphinate **17** in two steps and 56% yield from 6-nitropiperonaldehyde as shown in Scheme 11, by means of Abramov–Pudovik addition[58] of the




Scheme 11. *gem*-Difluorination of $\alpha$-oxophosphinate **17** with DAST. i) PhP(OH)OEt, $Et_3N$, DME; ii) PDC, Celite, $CH_2Cl_2$; iii) 14 equiv DAST, neat.

anion of the corresponding phosphinite, and subsequent benzylic oxidation of the $\alpha$-hydroxyphosphinate **16** (in our hands, PDC proved to be the reagent of choice for this transformation, and gave better yields of $\alpha$-oxophosphinate than $MnO_2$ or the Swern oxidation). Although further purification of the $\alpha$-oxophosphinate on silica gel was possible, it resulted in a drop in yield to 45% owing to the poor stability of the product, which was in fact sufficiently pure to be used without further purification. *Gem*-difluorination was then performed overnight at room temperature with 14 equivalents of DAST, and gave $\alpha,\alpha$-difluorophosphinate **18** in a modest 22% yield, certainly because of the instability of the starting material. To our knowledge this is the first successful difluorination of $\alpha$-oxophosphinate by this strategy. We then applied this difluorination strategy to other diversely substituted $\alpha$-oxophosphinates (**21a–d**; Scheme 12). These $\alpha$-oxophosphinates were obtained by the same synthetic scheme from the corresponding aldehydes: Abramov–Pudovik addition to the aldehydes **19a–d** gave the $\alpha$-hydroxyphosphinates **20a–d** in 84.5%, 98%, 89.5%, and 96% yield; by oxidation with PDC (pyridinium dichromate), these gave, after filtration on Celite, the corresponding $\alpha$-oxophosphinates in 70%,



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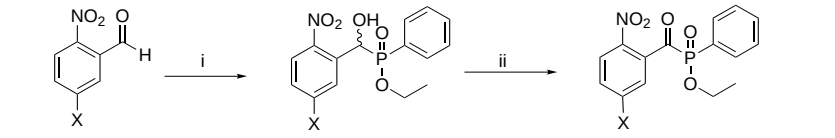



**19a** : X = H
**19b** : X = OTHP
**14c** : X = $O(CH_2)_3NPht$
**19d** : X = F

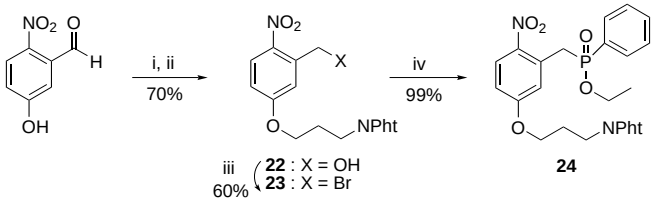
**20a** : X = H, 85%
**20b** : X = OTHP, 98%
**20c** : X = $O(CH_2)_3NPht$, 89%
**20d** : X = F, 96%

**21a** : X = H, 70%
**21b** : X = OTHP, 95%
**21c** : X = $O(CH_2)_3NPht$, 91%
**21d** : X = F, 78%

Scheme 12. Synthesis of $\alpha$-oxophosphinates. i) PhP(OH)OEt, $Et_3N$, DME; ii) PDC, Celite, $CH_2Cl_2$, except for **21c**: Swern oxidation.

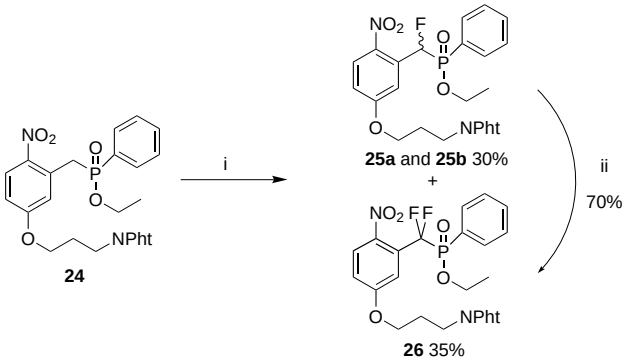
95%, and 77.5% yield for **21a**, **21b**, and **21d**, respectively; Swern oxidation of **18c** gave $\alpha$-oxophosphinates **21c** in 91% yield after successive precipitations in hexane. $\alpha$-Oxophosphinates **21a** and **21d** could not be further purified owing to their complete degradation on silica gel; **21b** could be flash chromatographed on silica gel (57.5% yield, but NMR spectra showed no difference in purity from precipitated **21b**). The four $\alpha$-oxophosphinates, either crude or purified, were mixed with 2–20 equivalents of DAST, either with or without solvent ($CH_2Cl_2$), but in any case only degradation products were observed and even with crude material the $\mathbf{P}(O)CF_2$ characteristic triplet at $\delta \approx 30$ in $^{31}P$ NMR was never observed.

To overcome the difficulties generated by the lack of stability of the $\alpha$-oxophosphinates, in contrast to the easy-to-handle and quite stable $\alpha,\alpha$-difluorophosphinates such as **18**, we turned to electrophilic difluorination. Although the hazardous and nonselective nature of the traditional "$F^+$"-transfer reagents such as perchloryl fluoride ($FClO_3$)[36, 59] has limited the use of this pathway to fluorinated products, there has been a surge over the last 15 years in the development of stable, mild, and highly selective electrophilic *N*-fluoro "$F^+$"-transfer reagents.[60] Difluorination of active methylene compounds (such as benzylic phosphinates or phosphonates) still results in generally modest yields since reaction of the excess base with fluorinating agent becomes deleteriously competitive with the second deprotonation and fluorination. Best results for the difluorination of benzylic phosphonates have thus been obtained from a two-step reaction.[61] A recent publication[62] attracted our attention because of good difluorination yields obtained in one step when NaHMDS was used for the deprotonation and *N*-fluorobenzene sulfonimide (NFBS) as the fluorinating agent. Benzylic phosphinate **24** was therefore synthesized in four steps and high yields from 5-hydroxy-2-nitrobenzaldehyde (Scheme 13). The phenolic function was first etherified with an *N*-phthalimido-protected propylamine moiety, to be used as the aliphatic linker to the



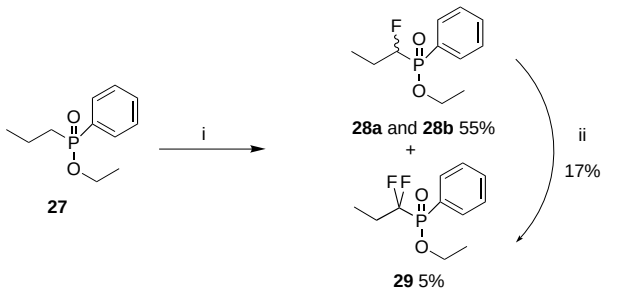

Scheme 13. Synthesis of benzylic phosphinate **24**. i) (*N*-3-bromopropyl)phthalimide, $K_2CO_3$, $CH_3CN$, 80°C; ii) $NaBH_4$, THF, 0°C; iii) $PPh_3Br_2$, $CH_2Cl_2$; iv) $PhP(OEt)_2$, toluene, 120°C.

carrier protein. Reduction of the benzaldehyde to benzyl alcohol ($NaBH_4$) and substitution of the hydroxyl by a bromine ($PPh_3 \cdot Br_2$) gave benzyl bromide **23**, which underwent a very efficient Michaelis–Arbuzov condensation on phenyldiethylphosphonite to yield phosphinate **24**. Deprotonation was then tested with *n*BuLi, KDA, and NaHMDS, with NFBS as the fluorination reagent. The deprotonation temperature of −80°C had to be closely monitored, and a mixture of mono- and difluorinated compounds was obtained. Best results were obtained with NaHMDS, with an overall 56% yield of $\alpha,\alpha$-difluorophosphinate **26** in two steps, once monofluorinated products **25a,b** have been recycled (Scheme 14). This difluorination proce-




Scheme 14. *gem*-Difluorination of benzylic phosphinate **24**. i) a) 2.2 NaHMDS, THF, −80°C, b) 2.2 NFBS, THF, −80°C to RT; ii) a) 1.1 NaHMDS, THF, −90°C, b) 1.1 NFBS, THF, −90°C to RT.

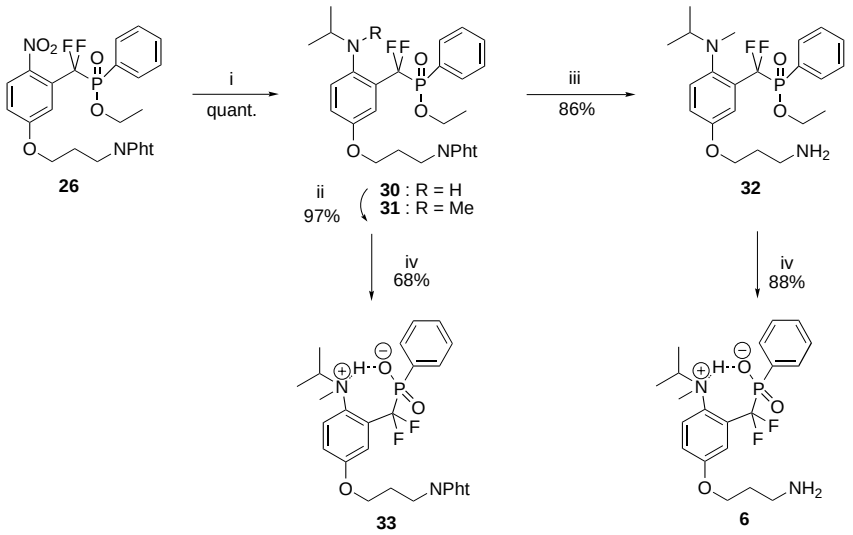
dure was also tested on an alkylphosphonite (compound **27**, Scheme 15). None of the tested bases (NaHMDS, *n*BuLi, KDA, NaDA) gave satisfactory results. Yet deprotonation with *t*BuLi gave a modest 14% difluorination yield of




Scheme 15. *gem*-Difluorination of benzylic phosphinate **27**; i) a) 2.2 *t*BuLi, THF, −90°C, b) 2.2 NFBS, THF, −90°C to RT; ii) a) 1.1 *t*BuLi, THF, −90°C, b) 1.1 NFBS, THF, −90°C to RT.

phosphinate **29** in two steps, showing that with an appropriate base for the deprotonation, this electrophilic *gem*-difluorination procedure could be extended to a nonactivated position.

With the $\alpha,\alpha$-difluorophosphinate in hand, we then synthesized hapten **6** in four steps (Scheme 16). Hydrogenation of




Scheme 16. Final access to hapten **6**. i) Acetone, MeOH, $MgSO_4$, Pd/C, $H_2$; ii) $K_2CO_3$, MeI, $CH_3CN$; iii) $H_2N{-}NH_2 \cdot H_2O$, MeOH; iv) TMSI, $CH_3CN$.

the nitro function of **26** gave an unstable aniline, which could be alkylated only in very low yields. We thus decided to test a one-pot reduction of the nitro function and subsequent reductive amination by performing the hydrogenation in the presence of magnesium sulfate and excess acetone. By this procedure, secondary amine **30** was obtained in nearly quantitative yields. Methylation of **30** afforded the methylisopropylaniline **31** in 97% yield. The primary amine on the aliphatic linker required for the coupling to the carrier protein was then released with excess hydrazine, yielding primary amine **32**, and hapten **6** was obtained following the classical phosphinic acid deprotection method with TMSI. Analytical studies of phosphinic acid **33** (obtained in 68% yield by treatment of phosphinate **31** with TMSI) and hapten **6** confirmed their zwitterionic and cyclic character: the $^1H$ NMR chemical shifts of the protons vicinal to the aniline showed that the nitrogen atom is quaternized. No alien counterion was detected in the elemental analysis or by FAB mass spectroscopy, which confirms an intra- (or inter-)molecular zwitterionic character for **33** and **6**. Moreover, **33** and **6** are not present as dimers, and $^1H$ NMR spectroscopy showed that the acidic proton is shared by a nitrogen atom and an oxygen atom present on the same molecule, since in $[D_6]$DMSO, whatever the concentration, the signal for this acidic proton was unchanged at $\delta = 14.91$ for **33** and 14.94 for **6**, and since $^1H-^1H$ COSY of **33** in $[D_6]$DMSO exhibited a scalar coupling between this acidic proton and the protons on the *N*-methyl group.

The conformations of both hapten **6** and the transition state it mimics have been determined by means of MM3 force-field minimization with the AccuModel 1.1 simulation program (MicroSimulations); results are displayed in Figure 1.

Hapten **6** was then covalently coupled to KLH (keyhole limpet hemocyanin) via the homobifunctional cross-coupling reagent glutaraldehyde, for injection into three Biozzi mice, and to maleimidated AChE, for use as enzymatic tracer in enzyme immunoassay (EIA),[63] *via* heterobifunctional cross-coupling reagent SATA (*N*-succinimidyl *S*-acetylthioacetate) as described previously.[64]

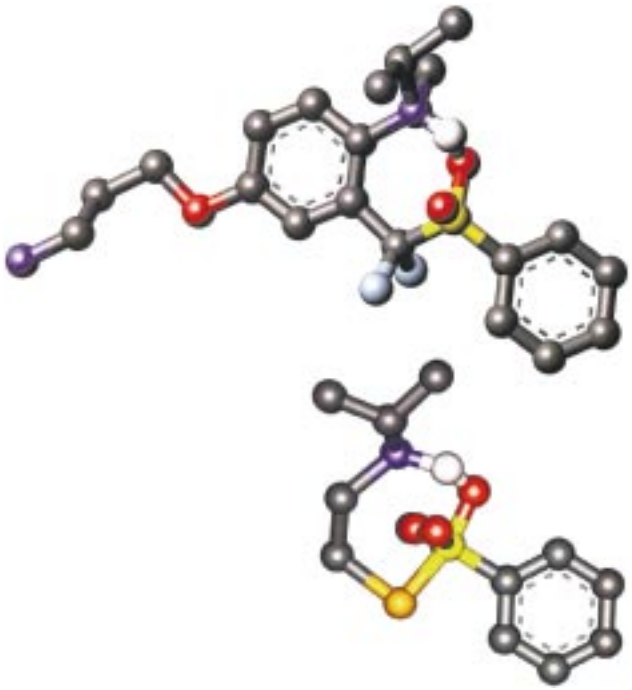


Figure 1. Conformations of hapten **6** (top) and of the transition state. The conformations were calculated at the semiempirical level with the MM3 force field implemented in AccuModel v1.1 from MicroSimulations, Mahwak (NJ, USA).

In conclusion, we have tested various methods for the *gem*-difluorination of benzylic phosphinates in our attempts to synthesize $\alpha,\alpha$-difluorophosphinate hapten **6** to be used for the selection of catalytic antibodies with phosphatase-like activity against the exceedingly toxic organophosphorus compounds PhX (**4**) and VX (**1**). $\alpha,\alpha$-Phosphinates proved to be much more sensitive and difficult to synthesize than the corresponding phosphonates, and the only method which gave satisfactory results and acceptable yields was direct *gem*-difluorination with electrophilic *N*-fluorination agent NFBS using NaHMDS as a base. This difference in stability can be explained both by the greater fragility of the $CF_2P(O)O{-}C$ bond in benzylic phosphinates than in benzylic phosphonates, and by the much lower partial positive charge borne by the benzylic carbon in benzylic phosphinates than in benzylic phosphonates. An exact equilibrium between the base strength required for the deprotonation and the stability of the forming $\alpha,\alpha$-difluorophosphinate has to be carefully established, and depends on the substrate to be *gem*-difluorinated, since we have shown



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that excess base not only reacts with fluorinating agent, but also with the nascent $\alpha,\alpha$-difluorophosphinate.

We thus synthesized hapten **6** in nine steps and 17% overall yield from 5-hydroxy-2-nitro-benzaldehyde, once the yield of the limiting *gem*-difluorination step was improved to 56%. Immunization results and monoclonal antibody activities will be reported in due course.

## Experimental Section

**General remarks**: Reagents were from Aldrich. TLC was performed with fluorescent Merck F254 glass plates. NMR spectra were recorded on a Bruker AC-300 MHz. Chemical shifts ($\delta$) are given in ppm, and the coupling constant $J$ is expressed in Hertz. IR spectra were recorded on a Perkin–Elmer spectrophotometer 2000-FT/IR, and MS were obtained with a Finnigan–Mat 4600 quadrupole system. Elemental analysis was carried out by the "Institut des Substances Naturelles" in Gif sur Yvette. High-resolution mass spectroscopy was performed by the "Centre Régional des Mesures Physiques de l'Ouest" in Rennes.

**Ethyl (1-bromo-1,1-difluoromethyl)-phenylphosphinate (8)**: Diethylphenylphosphonite (1 mL, 5.2 mmol) was added to dibromodifluoromethane (10 mL, 109 mmol). TLC showed that the reaction was complete within 2 h at room temperature. Excess dibromodifluoromethane was then removed under vacuum, and the crude material was chromatographed on silica gel (1% acetone in $CH_2Cl_2$) yielding 1.54 g phosphinate **8** ($C_9H_{10}BrF_2O_2P$; $M_r = 299.05$; 99%) as a colorless oil. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta =$ 7.93–7.87 (m, 2H), 7.68–7.62 (m, 1H), 7.54–7.48 (m, 2H), 4.48–4.38 (m, 2H), 1.40 (t, 3H, $^3J = 7$ Hz); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 134.4$ (CH), 133.4 (d, 2CH, $^2J$(P,C) = 10 Hz), 128.9 (d, 2CH, $^3J$(P,C) = 14 Hz), 123.5 (d, Cq, $^1J$(P,C) = 145 Hz), 124.2 (td, $CF_2Br$, $^1J$(P,C) = 149 Hz, $^1J$(C,F) = 334 Hz), 64.5 (d, $CH_2$, $^2J$(P,C) = 6 Hz), 16.5 (d, $CH_3$, $^3J$(P,C) = 4.5 Hz); $^{31}$P NMR (121.5 MHz,$CDCl_3$): $\delta = 21.7$ (t, $^2J$(P,F) = 100 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta = 41.0$ (m); MS (CI/$NH_3$): $m/z$ 316 (80%), 317 (20%), 318 (100%), 319 (20%) [$M$+$NH_4^+$]; IR (neat): $\tilde{\nu} =$ 3064, 2987, 1592, 1440, 1262, 1120, 1086, 1021, 966, 868 cm$^{-1}$.

**2,2-Dimethyl-*N*-[4-tetrahydropyran-2-yloxy)-phenyl]-propionamide (12)**: Dihydropyran (1.31 mL, 14.4 mmol) and pyridinium *p*-toluenesulfonate (181 mg, 0.72 mmol) in dry $CH_2Cl_2$ (20 mL) were added to *p*-nitrophenol (1.0 g, 7.2 mmol). After 18 h at room temperature, excess reagents and solvents were removed under vacuum. The crude reaction mixture was diluted in dry methanol (20 mL), and 10% Pd/C (50 mg) was added. The reaction flask was purged thrice with nitrogen and then thrice with hydrogen, and the reaction mixture was left for 10 h under hydrogen. Once TLC indicated that the reaction was complete, the reaction mixture was filtered through Celite, and the solvents were removed under vacuum. The crude reaction mixture was dissolved in pyridine (15 mL), and pivaloyl chloride (2.5 mL, 9.3 mmol) was added. After 1 h at room temperature, the reaction mixture was filtered and excess reagents were removed under vacuum. The crude material was chromatographed on silica gel (pentane/EtOAc 85/15), and yielded 1.27 g protected aniline **12** ($C_{16}H_{23}NO_3$; $M_r =$ 277.36; 64%) as a white powder. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 7.41$ (d, 2H, $^3J = 9$ Hz), 7.35 (br s, 1H, NH), 6.99 (d, 2H, $^3J = 9$ Hz), 5.35 (t, 1H, $^3J = 3$ Hz), 3.89 (td, 1H, $^3J = 3$ Hz, $^3J = 10$ Hz), 3.61–3.55 (m, 1H), 1.99–1.95 (m, 1H), 1.86–1.81 (m, 2H), 1.70–1.57 (m, 3H), 1.29 (s, 9H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 176.5$ (C=O), 153.8 (Cq), 132.1 (Cq), 121.8 (2CH), 117.0 (2CH), 96.8 (CH), 62.1 ($CH_2$), 39.5 (Cq), 30.4 ($CH_2$), 27.7 (3$CH_3$), 25.3 ($CH_2$), 18.9 ($CH_2$); MS (CI/$NH_3$): $m/z$ 278 [$M$+$H^+$], 295 [$M$+$NH_4^+$]; IR (KBr): $\tilde{\nu} =$ 3314, 2949, 2872, 1650, 1602, 1512, 1409, 1363, 1319, 1235, 1168, 1110 cm$^{-1}$; HRMS (FAB, $M^+$, $C_{16}H_{23}NO_3$) calcd: 277.1678, found: 277.1686; $C_{16}H_{23}NO_3$ (277.36): calcd C 69.29, H 8.36; found C 69.09, H 8.35.

**2,2-Dimethyl-*N*-[4-(tetrahydropyran-2-yloxy)-2-tributylstannanylphenyl]-propionamide (13)**: *n*-Butyllithium (820 µL; 1.6 M in hexane, 1.3 mmol) was added to aniline **12** (121.2 mg; 0.44 mmol) dissolved in THF (5 mL) at 0 °C. The solution turned yellow. After one hour, tri-*n*-butylstannyl chloride (550 µL, 2 mmol) was added, and the reaction mixture was left at room temperature for 48 h. The reaction was then quenched with water, and extracted thrice with diethyl ether. The combined organic layers were washed with brine and dried on $MgSO_4$. Flash chromatography (pentane/AcOEt 90/10) of the crude material yielded 89 mg stannyl derivative **13** ($C_{28}H_{49}NO_3Sn$; $M_r = 566.39$; 36%) as a white powder. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 7.54$ (dd, 1H, $J = 2.5$ Hz, $J = 9$ Hz), 7.28 (d, 1H, $J = 2.5$ Hz), 7.25 (se, 1H, NH), 7.08 (d, 1H, $J = 9$ Hz), 5.38 (t, 1H, $^3J =$ 2.5 Hz), 3.86 (td, 1H, $^3J = 2.5$ Hz, $^3J = 7.5$ Hz), 3.63–3.60 (m, 1H), 2.05–1.48 (m, 3 + 6H), 1.40–1.26 (m, 9 + 9H), 1.11–1.05 (m, 3H), 0.95–0.86 (m, 9H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 176.3$ (C=O), 158.5 (Cq), 131.9 (Cq), 130.6 (Cq), 128.8 (CH), 122.4 (CH), 112.7 (CH), 96.3 (CH), 61.6 ($CH_2$), 39.5 (Cq), 30.5 ($CH_2$), 29.2 (3$CH_2$), 27.8 (3$CH_3$), 27.5 (3$CH_2$), 25.3 ($CH_2$), 18.8 ($CH_2$), 13.8 (3$CH_3$), 9.9 (3$CH_2$); MS (CI/$NH_3$): $m/z$ 567 [$M$+$H^+$], 584 [$M$+$NH_4^+$]; IR (KBr): $\tilde{\nu} =$ 2957, 2929, 2872, 1649, 1529, 1474, 1372, 1219, 1109, 967 cm$^{-1}$.

**5-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-propoxy]-2-nitrobenzaldehyde (14c)**: *N*-(3-bromopropyl)phthalimide (3.53 g, 13.16 mmol) was added to a mixture of 6-hydroxy-3-nitrobenzaldehyde (2 g, 11.97 mmol) and potassium bicarbonate (1.98 g, 14.36 mmol) in acetonitrile (40 mL), with stirring. The mixture was then refluxed at 80 °C. When TLC indicated that the reaction was complete, the mixture was diluted in $CH_2Cl_2$ and the carbonates were filtered off. The crude mixture was evaporated and diluted in a minimum of $CH_2Cl_2$, and the product was precipitated with hexane to yield 3.35 g phthalimide **14c** ($C_{18}H_{14}N_2O_6$; $M_r = 354.31$; 80%) as a white powder, m.p. 143–145 °C (decomp). $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 10.45$ (s, 1H), 8.12 (d, $^2J = 9$ Hz, 1H), 7.84 (m, 2H), 7.75 (m, 2H), 7.20 (d, $^2J = 2.5$ Hz, 1H), 7.04 (dd, $^2J = 9$ Hz, $^2J = 2.5$ Hz, 1H), 4.18 (t, $^3J = 6$ Hz, 2H), 3.94 (t, $^3J = 6.5$ Hz, 2H), 2.25 (tt, $^3J = 6$ Hz, $^3J = 6.5$ Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 188.4$ (C=O), 168.4 (2C=O), 163.2 (Cq), 142.4 (Cq), 134.2 (2CH), 132.1 (2Cq), 127.3 (CH), 123.4 (2CH), 118.8 (CH), 113.8 (CH), 67.0 ($CH_2$), 35.1 ($CH_2$), 28.05 ($CH_2$); MS (CI/$NH_3$): $m/z$ 355 [$M$+$H^+$], 372 [$M$+$NH_4^+$]; IR (KBr): $\tilde{\nu} = 3109$ ($\tilde{\nu}_{CHar}$), 1698 ($\tilde{\nu}_{C=O}$) cm$^{-1}$.

**2-{3-[3(1,1-Difluoromethyl)-4-nitrophenoxy]-propyl}-isoindole-1,3-dione (15c)**: DAST (136 µL, 1.034 mmol) was added to a solution of aldehyde **14c** (305 mg, 0.86 mmol) in $CH_2Cl_2$ (20 mL). After 1 h at room temperature, TLC showed that the reaction was complete. The reaction mixture was quenched by addition of ice, and extracted twice with 10 mL $CH_2Cl_2$. The combined organic layers were washed successively with water (5 mL) and brine (5 mL), and dried over $MgSO_4$, yielding 320 mg difluoromethylbenzene **15c** as a white powder after removal of the solvent under vacuum ($C_{18}H_{14}F_2N_2O_5$; $M_r = 376.31$; 99%). $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta =$ 8.16 (d, 1H, $J = 9$ Hz), 7.85–7.82 (m, 2H), 7.75–7.72 (m, 2H), 7.38 (t, 1H, $^2J$(F,H) = 55 Hz), 7.15 (d, 1H, $J = 2.5$ Hz), 6.95 (dd, 1H, $J = 2.5$ Hz, $J =$ 9 Hz), 4.17 (t, 2H, $J = 6$ Hz), 3.93 (t, 2H, $J = 6.5$ Hz), 3.05–2.97 (m, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 168.4$ (C=O), 163.1 (Cq), 134.2 (2CH), 132.1 (Cq), 128.2 (CH), 123.4 (2CH), 115.8 (CH), 113.1 (t, CH, $^3J$(F,C) = 9.5 Hz), 110.5 (t, $CHF_2$, $^1J$(F,C) = 240 Hz), 67.0 ($CH_2$), 35.2 ($CH_2$), 28.0 ($CH_2$); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $-12.3$ (d, $^2J$(F,H) = 55 Hz); MS (CI/$NH_3$): $m/z$ 394 [$M$+$NH_4^+$]; IR (neat): $\tilde{\nu} =$ 3115, 3083, 2955, 1712, 1593, 1515, 1379, 1326, 1256, 1181, 1043, 988 cm$^{-1}$; HRMS (FAB, $M^+$, $C_{18}H_{14}F_2N_2O_5$) calcd: 376.0871, found: 376.0869.

**3-(1,1-Difluoromethyl)-4-nitrophenyl acetate (15b)**: Acetic anhydride (350 µL, 3.6 mmol) was added to a solution of 6-hydroxy-3-nitrobenzaldehyde (500 mg, 3 mmol) in pyridine (10 mL). The reaction mixture was left for 2 h at room temperature, and the excess reagents were removed under vacuum yielding protected phenol **14b** as a white powder. The aldehyde was then directly dissolved in $CH_2Cl_2$ (20 mL). DAST (450 µL) was added, and the reaction mixture was left at room temperature for 14 h. Similar treatment as for **15c** yielded 665 mg difluoromethylbenzene compound **15b** ($C_9H_7F_2NO_4$; $M_r = 231.15$; 96%) as a pale yellow oil. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 8.20$ (d, 1H, $J = 9$ Hz), 7.60 (d, 1H, $J = 2$ Hz), 7.42 (dd, 1H, $J = 9$ Hz, $J = 2$ Hz), 7.38 (t, 1H, $^2J$(F,H) = 55 Hz), 2.36 (s, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 168.3$ (C=O), 154.8 (Cq), 144.1 (Cq), 131.3 (Cq), 127.2 (CH), 124.6 (CH), 120.8 (t, CH, $^3J$(F,C) = 17 Hz), 110.3 (t, $CHF_2$, $^1J$(F,C) = 240 Hz), 21.0 ($CH_3$); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta =$ $-12.4$ (d, $^2J$(F,H) = 55 Hz); MS (CI/$NH_3$): $m/z$ 249 [$M$+$NH_4^+$]; IR (neat): $\tilde{\nu} =$ 3123, 3085, 1776, 1593, 1537, 1371, 1349, 1191, 1054, 914 cm$^{-1}$.

**3-(1,1-Difluoromethyl)-4-nitrophenol (15a)**: A saturated aqueous solution of sodium bicarbonate (3 mL) was added to a solution of **15b** (390 mg, 1.69 mmol) in methanol. After 2 h at room temperature, the reaction mixture was acidified to pH 2 with 1.0 N HCl. The aqueous layer was extracted thrice with $CH_2Cl_2$. The combined organic layers were washed with brine and dried over $MgSO_4$, yielding 275 mg phenol **14a** ($C_7H_5F_2NO_3$; $M_r = 189.11$; 86%) as a pale orange powder. $^1$H NMR

(300.125 MHz, $CDCl_3$): $\delta = 8.20$ (d, 1H, $J = 9$ Hz), 7.42 (t, 1H, $^2J(F,H) = 55$ Hz), 7.31 (d, 1H, $J = 2$ Hz), 7.05 (dd, 1H, $J = 9$ Hz, $J = 2$ Hz), 6.30 (br s, 1H, OH); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta = 161.1$ (Cq), 135.2 (Cq), 128.6 (CH), 117.6 (CH), 114.1 (t, CH, $^3J(F,C) = 9$ Hz), 110.4 (t, $CHF_2$, $^1J(F,C) = 240$ Hz); $^{19}F$ NMR (282.2 MHz, $CDCl_3$): $\delta = -12.5$ (d, $^2J(F,H) = 55$ Hz); MS (CI/$NH_3$): $m/z$ 207 $[M+NH_4^+]$.

**Ethyl [1-hydroxy-1-(6-nitro-1,3-benzodioxol-5-yl)-methyl]-phenylphosphinate (16)**: Triethylamine (345 µL, 2.6 mmol) was added to a mixture of 6-nitropiperonaldehyde (500 mg, 2.6 mmol) and phenyl *O*-ethylphosphonite (386 µL, 2.6 mmol) in DME (10 mL), with stirring. The mixture was stirred at ambient temperature for 12 h. Solvents were removed under vacuum. Flash chromatography on silica gel (15% acetone in $CH_2Cl_2$) yielded 767 mg $\alpha$-hydroxyphosphinate **16** ($C_{16}H_{16}NO_7P$; $M_r = 365.27$; 82%) as a yellow powder (two diastereoisomers). $^1H$ NMR (300.125 MHz, $CDCl_3/CD_3OD$ 50/50): $\delta = 7.60-7.54$ (m, 4H), 7.43–7.23 (m, 8H), 7.08 (d, 1H, $J = 2$ Hz), 6.85 (d, 1H, $J = 2$ Hz), 6.22 (d, 1H, $J = 11$ Hz), 6.18 (d, 1H, $J = 13$ Hz), 5.97 (s, 2H), 5.94 (d, 2H), 3.92–3.69 (m, 4H), 1.10 (t, 3H, $^3J = 7$ Hz), 1.03 (t, 3H, $^3J = 7$ Hz); $^{13}C$ NMR (75.4 MHz, $CDCl_3/CD_3OD$ 50/50): $\delta = 152.1$ (Cq), 151.9 (Cq), 147.35 (2Cq), 141.6 (2Cq), 132.8 (2CH), 132.5 (d, 2CH, $^3J(P,C) = 9$ Hz), 132.4 (d, 2CH, $^3J(P,C) = 9$ Hz), 130.4 (Cq), 130.3 (Cq), 128.4 (d, 2CH, $^2J(P,C) = 13$ Hz), 128.2 (d, 2CH, $^2J(P,C) = 13$ Hz), 127.3 (d, Cq, $^1J(P,C) = 120$ Hz), 108.0 ($CH_2$), 107.7 ($CH_2$), 105.4 (CH), 103.1 (CH), 67.9 (d, CH, $^2J(P,C) = 116$ Hz), 67.1 (d, CH, $^1J(P,C) = 118$ Hz), 62.2 (d, $CH_2$, $^2J(P,C) = 7$ Hz), 62.0 (d, $CH_2$, $^2J(P,C) = 7$ Hz), 16.0 (d, $CH_3$, $^3J(P,C) = 6$ Hz); $^{31}P$ NMR (121.5 MHz, $CDCl_3$): $\delta = 39.27$ (s), 37.23 (s); MS (CI/$NH_3$): $m/z$ 366 $[M+H^+]$, 383 $[M+NH_4^+]$.

**Ethyl [1-(6-nitro-1,3-benzodioxol-5-yl)-methanoyl]-phenylphosphinate (17)**: Pyridinium dichromate (891 mg, 2.4 mmol) and Celite were added to a solution of hydroxyphosphinate **16** (345 mg, 0.948 mmol) in $CH_2Cl_2$ (20 mL), with stirring. The mixture was stirred at ambient temperature for 72 h and was then evaporated. The crude mixture was diluted with diethyl ether and filtered over Celite. Celite and chromium salts were washed several times with diethyl ether. Evaporation of the solvents under vacuum yielded 235 mg $\alpha$-oxophosphinate **17** ($C_{16}H_{14}NO_7P$; $M_r = 363.26$; 68%) as a white powder. $^1H$ NMR (300.125 MHz, $CDCl_3$): $\delta = 7.93-7.86$ (m, 2H), 7.62–7.59 (m, 1H), 7.59 (s, 1H), 7.54–7.47 (m, 2H), 6.69 (s, 1H), 6.20 (s, 2H), 4.20–4.15 (m, 2H), 1.34 (t, 3H, $^3J = 7$ Hz); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta = 204.0$ (d, C=O, $^1J(P,C) = 120$ Hz), 153.2 (Cq), 150.3 (Cq), 142.5 (Cq), 133.5 (CH), 133.0 (d, 2CH, $^2J(P,C) = 10$ Hz), 131.3 (Cq), 128.7 (d, 2CH, $^2J(P,C) = 13.5$ Hz), 106.9 ($CH_2$), 104.8 (CH), 104.0 (CH), 62.9 (d, $CH_2$, $^2J(P,C) = 7$ Hz), 16.0 (d, $CH_3$, $^3J(P,C) = 5$ Hz); $^{31}P$ NMR (121.5 MHz, $CDCl_3$): $\delta = 17.52$ (s); MS (CI/$NH_3$): $m/z$ 381 $[M+NH_4^+]$; IR (neat): $\tilde{\nu} =$ 3059, 2986, 2920, 1682, 1605, 1524, 1507, 1481, 1332, 1273, 1032 $cm^{-1}$.

**Ethyl [1,1-difluoro-1-(6-nitro-1,3-benzodioxol-5-yl)-methyl]phenylphosphinate (18)**: DAST (1.2 mL, 9.08 mmol, 14 equiv) was added to a solution of $\alpha$-oxophosphinate **17** (234 mg, 0.644 mmol) in $CH_2Cl_2$ (2 mL), with stirring. The mixture was stirred at ambient temperature for 20 h and was then diluted with $CH_2Cl_2$ (5 mL) and carefully quenched with aqueous 1N KOH. The aqueous layer was extracted thrice with $CH_2Cl_2$ (10 mL). The combined organic layers were dried over magnesium sulfate and then evaporated. Flash chromatography on silica gel (2.5% acetone in $CH_2Cl_2$) yielded 55 mg $\alpha,\alpha$-difluorophosphinate **18** ($C_{16}H_{14}F_2O_6P$; $M_r = 385.26$; 22%) as a white powder. $^1H$ NMR (300.125 MHz, $CDCl_3$): $\delta = 7.92-7.85$ (m, 2H), 7.69–7.64 (m, 1H), 7.57–750 (m, 2H), 7.21 (s, 1H), 7.09 (s, 1H), 6.17 (s, 2H), 4.31–4.21 (m, 2H), 1.39 (t, 3H, $^3J = 7$ Hz); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta = 149.9$ (Cq), 149.8 (Cq), 143.5 (Cq), 133.6 (1CH), 133.3 (d, 2CH, $^2J(P,C) = 10$ Hz), 128.7 (d, 2CH, $^2J(P,C) = 13.5$ Hz), 125.5 (d, Cq, $^1J(P,C) = 139$ Hz), 119.5 (td, $CF_2$, $^1J(P,C) = 90$ Hz, $^1J(C,F) = 240$ Hz), 108.8 (t, CH, $^2J(C,F) = 16$ Hz), 105.2 ($CH_2$), 103.5 (CH), 63.6 (d, $CH_2$, $^2J(P,C) = 6.5$ Hz), 16.5 (d, $CH_3$, $^3J(P,C) = 6$ Hz); $^{31}P$ NMR (121.5 MHz, $CDCl_3$): $\delta = 26.77$ (t, $^2J(P,F) = 100$ Hz); $^{19}F$ NMR (282.2 MHz, $CDCl_3$): $\delta = 3.69$ (dd, $^2J(P,F) = 100$ Hz, $^2J(F,F) = 300$ Hz), $-0.17$ (dd, $^2J(P,F) = 100$ Hz, $^2J(F,F) = 300$ Hz); MS (CI/$NH_3$): $m/z$ 403 $[M+NH_4^+]$; IR (neat): $\tilde{\nu} = 2919$, 1541, 1510, 1493, 1266, 1242, 1031 $cm^{-1}$; HRMS (LSIMS, $[M+H^+]$, $C_{16}H_{15}F_2O_6P$) calcd: 386.0605, found: 386.0607; E.A. for $C_{16}H_{14}F_2O_6P$ (385.26): calcd. C 49.88, H 3.66; found C 49.73, H 3.71.

**Ethyl [1-hydroxy-(2-nitrophenyl)-methyl]-phenylphosphinate (20a)**: Compound **20a** was prepared from 3-nitrobenzaldehyde (1.345 g, 8.9 mmol) by the procedure described for **16**, with phenyl *O*-ethylphosphonite (1.34 mL, 8.9 mmol) and triethylamine (1.2 mL, 8.9 mmol). Chromatography on silica gel of the crude material (5% acetone in $CH_2Cl_2$) yielded 2.42 g $\alpha$-hydroxyphosphinate **20a**, in a 1/1 mixture of diastereoisomers ($C_{15}H_{16}NO_5P$; $M_r = 321.27$; 84.5%), as a pale yellow oil. $^1H$ NMR (300.125 MHz, $CDCl_3$): $\delta = 7.98-7.86$ (m, 1+1H), 7.70–7.64 (m, 2H), 7.60–7.55 (m, 1+1H), 7.50–7.23 (m, 5+5H), 6.46 (d, 1H, $^2J(P,H) = 15$ Hz), 6.33 (d, 1H, $^2J(P,H) = 9$ Hz), 4.05–3.98 (m, 2H), 3.89–3.76 (m, 2H), 1.17 (t, 3H, $^3J = 7$ Hz), 1.05 (t, 3H, $^3J = 7$ Hz); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta = 147.7$ (2Cq), 133.5 (2CH), 133.2 (2CH), 132.9 (2CH), 132.6 (2CH), 132.4 (2Cq), 129.5 (2CH), 129.1 (2CH), 128.7 (2CH), 128.5 (2CH), 128.4 (2CH), 128.2 (2CH), 126.5 (d, 2Cq, $^1J(P,C) = 120$ Hz), 124.7 (2CH), 124.6 (2CH), 68.6 (CH), 67.1 (CH), 62.5 (d, $CH_2$, $^2J(P,C) = 7$ Hz), 62.3 (d, $CH_2$, $^2J(P,C) = 7$ Hz), 16.2 ($2CH_3$); $^{31}P$ NMR (121.5 MHz, $CDCl_3$): 39.6 and 37.1; MS (CI/$NH_3$): $m/z$ 322 $[M+H^+]$, 339 $[M+NH_4^+]$; IR (KBr): $\tilde{\nu} = 3209$, 2987, 2905, 1749, 1608, 1531, 1440, 1350, 1122, 1030, 961 $cm^{-1}$.

**Ethyl {1-hydroxy-[2-nitro-5-(tetrahydropyran-2-yloxy)-phenyl]-methyl}-phenylphosphinate (20b)**: Dihydropyran (1.18 mL, 13 mmol) was added to a mixture of 6-hydroxy-3-nitrobenzaldehyde (720 mg, 4.32 mmol) and pyridinium *p*-toluenesulfonate (0.2 mmol) in dry $CH_2Cl_2$ (50 mL). The reaction mixture was allowed to stand at room temperature for 16 h. Solvent and excess dihydropyran were removed under vacuum, and the crude material chromatographed on silica gel (10% AcOEt in pentane) yielding 650 mg protected phenol **19b** ($C_{12}H_{13}NO_5$; $M_r = 251.23$; 60%) as a pale yellow oil. The aldehyde was reacted with phenyl *O*-ethylphosphonite (390 µL, 2.6 mmol) and triethylamine (350 µL, 2.6 mmol) as described for **16**, yielding 1.07 g $\alpha$-hydroxyphosphinate **20b**, in a 1/1/1/1 mixture of four diastereoisomers ($C_{20}H_{24}NO_7P$; $M_r = 421.39$; 98%), as a white powder. $^1H$ NMR (300.125 MHz, $CDCl_3$): $\delta = 8.08$ (d, 1H, $J = 9$ Hz), 8.06 (d, 1H, $J = 9$ Hz), 7.98 (d, 1+1H, $J = 9$ Hz), 7.87–7.76 (m, 2+2H), 7.64–7.27 (m, 18H), 7.13–7.01 (m, 4+2H), 6.95 (d, 1H, $J = 9$ Hz), 6.94 (d, 1H, $J = 9$ Hz), 6.57 (d, 1H, $^2J(P,H) = 15$ Hz), 6.55 (d, 1H, $^2J(P,H) = 15$ Hz), 6.52–6.40 (m, 1+1H), 5.98 (t, 1+1H, $^3J = 5$ Hz), 5.59 (br s, 1H), 5.51 (br s, 1H), 5.37–5.25 (m, 1+1H), 4.18–4.13 (m, 2H), 4.05–3.75 (m, 8H), 3.75–3.50 (m, 6H), 2.10–1.50 (m, 6+6+6+6H), 1.29 (t, 3+3H, $^3J = 7$ Hz), 1.14 (t, 3H, $^3J = 7$ Hz), 1.12 (t, 3H, $^3J = 7$ Hz); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta = 161.3$, 160.9, 141.0, 136.3, 136.1, 133.0, 132.9, 132.5, 129.4, 128.7, 128.6, 128.1, 127.9, 127.7, 127.5, 127.3, 125.9, 117.1, 116.2, 115.4, 115.2, 114.9, 114.8, 96.4, 96.3, 96.1, 68.8 (d, $^1J(P,C) = 107$ Hz), 68.6 ($^1J(P,C) = 108$ Hz), 68.3 (d, $^1J(P,C) = 109$ Hz), 62.5, 62.4, 62.1, 62.0, 61.9, 30.0, 29.8, 25.0, 18.3, 16.4, 16.3, 16.2; $^{31}P$ NMR (121.5 MHz, $CDCl_3$): $\delta = 39.5$ (s), 37.2 (s); MS (CI/$NH_3$): $m/z$ 439 $[M+NH_4^+]$; IR (KBr): $\tilde{\nu} = 3214$, 2947, 2875, 1610, 1579, 1517, 1476, 1439, 1340, 1205, 1120, 1036, 905 $cm^{-1}$.

**Ethyl (1-hydroxy-{5-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propoxy]-2-nitrophenyl}-methyl)-phenylphosphinate (20c)**: Ester **20c** was prepared from **14c** (1.6 g, 4.5 mmol) by the procedure described for **16**, with phenyl *O*-ethylphosphinite (680 µL, 4.5 mmol) and triethylamine (610 µL, 4.5 mmol). Chromatography on silica gel yielded 2.1 g $\alpha$-hydroxyphosphinate **20c**, in a 1/1 mixture of diastereoisomers ($C_{26}H_{25}N_2O_8P$; $M_r = 524.47$; 89.5%), as a white powder. $^1H$ NMR (300.125 MHz, $CDCl_3$): $\delta = 7.98$ (d, 2+2H, J = 9 Hz), 7.97–7.75 (m, 4+4H), 7.68–7.65 (m, 1+1H), 7.54–7.39 (m, 4+4H), 7.05 (m, 1H), 6.95 (m, 1H), 6.75–6.73 (m, 1+1H), 6.49 (d, 1H, $^2J(P,H) = 14$ Hz), 6.40 (d, 1H, $^2J(P,H) = 14$ Hz), 4.05–3.83 (m, 6+6H), 2.13 (m, 2+2H), 1.29 (t, 3H, $^3J = 7$ Hz), 1.22 (t, 3H, $^3J = 7$ Hz); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta = 168.3$ (2C=O), 162.3 (2Cq), 136.6 (Cq), 136.4 (Cq), 135.1 (Cq), 134.1 (2CH), 133.0 (CH), 132.9 (CH), 132.6 (CH), 132.5 (CH), 132.4 (2CH), 132.1 (2Cq), 128.6 (d, 2CH, $^3J(P,C) = 12$ Hz), 128.0 (d, 2CH, $^3J(P,C) = 12$ Hz), 127.5 (CH), 127.2 (CH), 126.4 (d, 2Cq, $^1J(P,C) = 115$ Hz), 123.3 (2CH), 114.6 (CH), 113.6 (CH), 113.0 (CH), 68.6 (d, CH, $^1J(P,C) = 110$ Hz), 68.3 (d, CH, $^1J(P,C) = 110$ Hz), 66.4 ($CH_2$), 66.2 ($CH_2$), 62.5 ($CH_2$), 35.2 ($CH_2$), 28.1 ($CH_2$), 27.9 ($CH_2$), 16.3 ($CH_3$); $^{31}P$ NMR (121.5 MHz, $CDCl_3$): $\delta = 39.6$ (s), 37.3 (s); MS (CI/$NH_3$): $m/z$ 341, 358; IR (KBr): $\tilde{\nu} =$ 3448, 3191, 1984, 1710, 1583, 1512, 1398, 1342, 1035 $cm^{-1}$; HRMS (LSIMS; $[M+H^+]$, $C_{26}H_{26}N_2O_8P$) calcd: 525.1427, found: 525.1426.

**Ethyl [1-hydroxy-(2-nitro-5-fluorophenyl)-methyl]-phenylphosphinate (20d)**: Ester **20d** was prepared from 6-fluoro-2-nitrobenzaldehyde (500 mg, 2.96 mmol) by the procedure described for **16**, with phenyl *O*-ethylphosphinite (445 µL, 3 mmol) and triethylamine (400 µL, 3 mmol). Chromatography on silica gel (5% MeOH in $CH_2Cl_2$) yielded 966 mg $\alpha$-hydroxyphosphinate **20d**, in a 1/1 mixture of diastereoisomers ($C_{15}H_{15}FNO_5P$; $M_r = 339.26$; 96%), as a yellow foam. $^1H$ NMR (300.125 MHz, $CDCl_3$): $\delta = 8.01-7.97$ (m, 1+1H), 7.74–7.66 (m, 2H), 7.52–7.30 (m, 2+3+3+1H), 7.16–7.13 (m, 1H), 7.10–6.96 (m, 1+1H),



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6.52 (d, 1H, $^2J$(P,H) = 15.5 Hz), 6.41 (d, 1H, $^2J$(P,H) = 10 Hz), 4.08–4.00 (m, 2H), 3.93–3.82 (m, 2H), 1.20 (t, 3H, $^3J$ = 7 Hz), 1.09 (t, 3H, $^3J$ = 7 Hz); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 165.2 (d, CF, $^1J$(C,F) = 255 Hz), 164.8 (d, CF, $^1J$(C,F) = 255 Hz), 143.6 (Cq), 137.6 (d, Cq, $^3J$(C,F) = 8 Hz), 137.3 (d, Cq, $^3J$(C,F) = 9 Hz), 133.0 (2CH), 132.8 (d, CH, $^2J$(P,C) = 9.5 Hz), 132.5 (d, CH, $^2J$(P,C) = 9.5 Hz), 128.6 (d, CH, $^2J$(P,C) = 12 Hz), 128.2 (d, CH, $^2J$(P,C) = 12 Hz), 127.6 (CH), 127.5 (CH), 126.1 (d, Cq, $^2J$(P,C) = 120 Hz), 116.7 (d, CH, $^2J$(C,F) = 28 Hz), 116.3 (d, CH, $^2J$(C,F) = 28 Hz), 115.2 (d, CH, $^2J$(C,F) = 22 Hz), 114.9 (d, CH, $^2J$(C,F) = 22 Hz), 67.9 (d, CH, $^1J$(P,C) = 113 Hz), 62.7 (d, $CH_2$, $^2J$(P,C) = 7 Hz), 62.4 (d, $CH_2$, $^2J$(P,C) = 7 Hz), 16.1 (d, $CH_3$, $^3J$(P,C) = 5 Hz), 16.0 (d, $CH_3$, $^3J$(P,C) = 5 Hz); MS (CI/$NH_3$): *m*/*z* 340 [*M*+H$^+$], 357 [*M*+$NH_4^+$].

**Ethyl [1-(2-nitrophenyl)-methanoyl]phenylphosphinate (21a)**: Ester **21a** was prepared from **20a** (439 mg; 1.36 mmol) by the procedure described for **17**, with PDC (1 g, 2.73 mmol), yielding $\alpha$-oxophosphinate **21a** ($C_{15}H_{14}NO_5P$; $M_r$ = 319.27; 70%) as a white powder. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta$ = 8.10 (d, 1H, $J$ = 8 Hz), 7.87–7.81 (m, 2H), 7.73–7.68 (m, 1H), 7.65–7.53 (m, 2H), 7.47–7.41 (m, 2H), 7.31 (d, 1H, $J$ = 7 Hz), 4.18–4.08 (m, 2H), 1.27 (t, 3H, $^3J$ = 7 Hz); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 205.5 (d, C=O, $^1J$(P,C) = 130 Hz), 146.8 (Cq), 135.1 (CH), 133.6 (CH), 133.0 (d, CH, $^2J$(P,C) = 10 Hz), 132.2 (CH), 131.5 (Cq), 128.8 (d, CH, $^2J$(P,C) = 13 Hz), 128.1 (CH), 126.8 (d, Cq, $^1J$(P,C) = 130 Hz), 124.1 (CH), 63.0 (d, $CH_2$, $^2J$(P,C) = 7 Hz), 16.5 (d, $CH_3$, $^3J$(P,C) = 6 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 17.6 (s); MS (CI/$NH_3$): *m*/*z* 337 [*M*+$NH_4^+$]; IR (KBr): $\tilde{\nu}$ = 3061, 2986, 1725, 1684, 1532, 1348, 1235, 1125, 1027, 965 cm$^{-1}$.

**Ethyl {1-[2-nitro-5-(tetrahydropyran-2-yloxy)-phenyl]-methanoyl}phenylphosphinate (21b)**: Ester **21b** was prepared from **20b** (441 mg; 1.05 mmol) by the procedure described for **17**, with PDC (590 mg, 1.57 mmol), yielding after flash chromatography (5% MeOH in $CH_2Cl_2$) $\alpha$-oxophosphinate **21b** (252 mg), in a 1/1 mixture of diastereoisomers ($C_{20}H_{22}NO_7P$; $M_r$ = 419.39; 57.5%), as a pale yellow powder. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta$ = 8.12 (d, 1H, $J$ = 9 Hz), 8.11 (d, 1H, $J$ = 9 Hz), 7.94–7.84 (m, 2+2H), 7.60–7.57 (m, 1+1H), 7.52–7.45 (m, 2+2H), 7.25 (dd, 1H, $J$ = 9 Hz, $J$ = 2.5 Hz), 7.22 (dd, 1H, $J$ = 9 Hz, $J$ = 2.5 Hz), 6.91 (d, 1H, $J$ = 2.5 Hz), 6.87 (d, 1H, $J$ = 2.5 Hz), 5.50 (s, 1H), 5.49 (s, 1H), 4.23–4.13 (m, 2+2H), 3.72–3.68 (m, 1+1H), 3.60–3.56 (m, 1+1H), 1.94–1.84 (m, 3+3H), 1.70–1.61 (m, 3+3H), 1.34 (t, 3H, $^3J$ = 7.5 Hz), 1.32 (t, 3H, $^3J$ = 7.5 Hz); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 206.0 (d, C=O, $^1J$(P,C) = 120 Hz), 162.4 (Cq), 140.0 (Cq), 137.5 (Cq), 133.5 (CH), 133.1 (CH), 133.0 (CH), 132.9 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 126.5 (CH), 118.3 (CH), 118.2 (CH), 115.2 (CH), 115.1 (CH), 96.9 (CH), 96.8 (CH), 96.7 (CH), 62.9 ($CH_2$), 62.8 ($CH_2$), 62.7 ($CH_2$), 62.0 ($CH_2$), 29.7 ($CH_2$), 24.8 ($CH_2$), 18.1 ($CH_2$), 16.55 (d, $CH_3$), 16.45 (d, $CH_3$); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 17.5 (s), 17.3 (s); MS (CI/$NH_3$): *m*/*z* 437 [*M*+$NH_4^+$]; IR (KBr): $\tilde{\nu}$ = 2927, 1739, 1686, 1583, 1515, 1442, 1328, 1203 cm$^{-1}$.

**Ethyl (1-{5-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propoxy]-2-nitrophenyl}-methanoyl)-phenylphosphinate (21c)**: Dimethyl sulfoxide (300 µL; 4.2 mmol) was added under argon at −78°C to oxalyl chloride (200 µL; 2.1 mmol) in $CH_2Cl_2$ (2 mL). After 15 min at −78°C, **20c** (1 g; 1.9 mmol) dissolved in $CH_2Cl_2$ (15 mL) was added dropwise. After an extra 30 min at −78°C, triethylamine (1.2 mL; 8.6 mmol) was added. The reaction mixture was allowed to reach room temperature slowly (2 h), and then 0.1N HCl (10 mL) and water (30 mL) were added. The aqueous layer was extracted twice with $CH_2Cl_2$ (50 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was then removed under vacuum, dissolved in a minimum amount of $CH_2Cl_2$, and precipitated with hexane, yielding 904 mg $\alpha$-oxophosphinate **21c** ($C_{26}H_{23}N_2O_8P$; $M_r$ = 522.47; 91%) as a white powder. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta$ = 8.10 (d, 1H, $J$ = 9 Hz), 7.92–7.80 (m, 4H), 7.74–7.70 (m, 2H), 7.63–7.58 (m, 1H), 7.53–7.46 (m, 2H), 6.95 (dd, 1H, $J$ = 9 Hz, $J$ = 2.5 Hz), 6.61 (d, 1H, $J$ = 2.5 Hz), 4.23–4.13 (m, 2H), 4.09 (t, 2H, $^3J$ = 6 Hz), 3.89 (t, 2H, $^3J$ = 6.5 Hz), 2.20 (m, 2H), 1.37 (t, 3H, $^3J$ = 7 Hz); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 205.5 (d, C=O, $^1J$(P,C) = 120 Hz), 168.4 (2C=O), 163.8 (Cq), 139.8 (Cq), 134.2 (2CH), 133.5 (CH), 133.0 (d, 2CH, $^2J$(P,C) = 10 Hz), 132.1 (Cq), 128.7 (d, 2CH, $^3J$(P,C) = 13 Hz), 127.5 (d, Cq, $^2J$(P,C) = 120 Hz), 126.9 (CH), 123.4 (2CH), 116.5 (CH), 113.2 (CH), 67.1 ($CH_2$), 63.0 (d, $CH_2$, $^2J$(P,C) = 6 Hz), 35.1 ($CH_2$), 28.1 ($CH_2$), 16.5 (d, $CH_3$, $^3J$(P,C) = 5 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 17.5 (s); MS (CI/$NH_3$): *m*/*z* 540 [*M*+$NH_4^+$]; IR (KBr): $\tilde{\nu}$ = 3067, 2982, 1771, 1709, 1585, 1516, 1397, 1336, 1284, 1240, 1029, 724 cm$^{-1}$; HRMS (LSIMS; [*M*+H$^+$], $C_{26}H_{23}N_2O_8P$) calcd: 523.1270, found: 523.1273.

**Ethyl [1-(2-nitro-5-fluorophenyl)-methanoyl]phenylphosphinate (21d)**: Ester **21d** was prepared from **20d** (278 mg; 0.88 mmol) by the procedure described for **17**, with PDC (662 mg; 1.76 mmol), which yielded 230 mg $\alpha$-oxophosphinate **21d** ($C_{15}H_{13}FNO_5P$; $M_r$ = 337.26; 77.5%) as white crystals. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta$ = 8.20 (dd, 1H, $J$ = 9 Hz, $^4J$(F,H) = 4 Hz), 7.90–7.83 (m, 2H), 7.63–7.58 (m, 1H), 7.52–7.46 (m, 2H), 7.34–7.27 (m, 1H), 7.00 (dd, 1H, $J$ = 2.5 Hz, $^3J$(F,H) = 7 Hz), 4.20–4.12 (m, 2H), 1.32 (t, 3H, $^3J$ = 7 Hz); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 204.0 (d, C=O, $^1J$(P,C) = 133 Hz), 165.7 (d, CF, $^1J$(C,F) = 260 Hz), 143.0 (Cq), 133.8 (CH), 132.9 (d, CH, $^2J$(P,C) = 10 Hz), 131.0 (d, Cq, $^3J$(C,F) = 12 Hz), 128.8 (d, CH, $^2J$(P,C) = 14 Hz), 127.2 (d, CH, $^3J$(C,F) = 10 Hz), 126.5 (d, Cq, $^1J$(P,C) = 120 Hz), 118.7 (d, CH, $^2J$(C,F) = 24 Hz), 115.4 (d, CH, $^2J$(C,F) = 26 Hz), 63.1 (d, $CH_2$, $^2J$(P,C) = 7 Hz), 16.5 (d, $CH_3$, $^3J$(P,C) = 6 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 17.5 (s); MS (CI/$NH_3$): *m*/*z* 338 [*M*+H$^+$], 355 [*M*+$NH_4^+$]; IR (KBr): $\tilde{\nu}$ = 3080, 2993, 1727, 1690, 1585, 1524, 1472, 1440, 1342, 1273, 1238, 1122, 1019, 961 cm$^{-1}$.

**2-[3-(3-Hydroxymethyl-4-nitrophenoxy)-propyl]-isoindole-1,3-dione (22)**: Aldehyde **14c** (2.6 g, 7.3 mmol) in THF (60 mL) was stirred at 0°C and sodium borohydride (277 mg, 7.3 mmol) was added. When TLC indicated that the reaction was complete, the mixture was quenched with saturated aqueous ammonium chloride (50 mL). The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate (100 mL). The combined organic layers were dried over magnesium sulfate and then evaporated. Flash chromatography on silica gel (2 to 5% MeOH in $CH_2Cl_2$) yielded 2.27 g alcohol **22** ($C_{18}H_{16}N_2O_6$; $M_r$ = 356.33; 87%) as a white powder. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta$ = 8.13 (d, $^2J$ = 9 Hz, 1H), 7.84 (m, 2H), 7.74 (m, 2H), 7.12 (d, $^2J$ = 2.5 Hz, 1H), 6.78 (dd, $^2J$ = 9 Hz, $^2J$ = 2.5 Hz, 1H), 4.96 (s, 2H), 4.16 (t, $^3J$ = 6 Hz, 2H), 3.93 (t, $^3J$ = 6.5 Hz, 2H), 2.24 (tt, $^3J$ = 6 Hz, $^3J$ = 6.5 Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 168.5 (2C=O), 163.4 (Cq), 140.4 (Cq), 134.2 (2CH), 132.2 (2Cq), 128.1 (CH), 123.5 (2CH), 114.8 (CH), 113.65 (CH), 66.6 ($CH_2$), 63.1 ($CH_2$), 35.3 ($CH_2$), 29.2 ($CH_2$); MS (CI/$NH_3$): *m*/*z* 374 [*M*+$NH_4^+$]; IR (KBr): $\tilde{\nu}$ = 3489 ($\tilde{\nu}_{OH}$), 3063 ($\tilde{\nu}_{CHar}$), 1766 ($\tilde{\nu}_{C=O}$), 1702 cm$^{-1}$.

**2-[3-(3-Bromomethyl-4-nitrophenoxy)-propyl]-isoindole-1,3-dione (23)**: A solution of bromine in $CH_2Cl_2$ was added dropwise to triphenylphosphine (1.838 g, 7.0 mmol) in $CH_2Cl_2$ (40 mL) at 0°C. The addition was stopped when a yellow coloration persisted. Alcohol **22** (2.27 g, 6.37 mmol) in $CH_2Cl_2$ was then added dropwise and the resulting mixture was stirred for 1 h at ambient temperature. Solvent was evaporated and flash chromatography on silica gel (1 to 2% acetone in $CH_2Cl_2$) yielded 1.6 g bromide **23** ($C_{18}H_{15}BrN_2O_5$; $M_r$ = 419.23; 60%) as a white powder m.p. 140.5–142.5°C. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta$ = 8.10 (d, $^2J$ = 9 Hz, 1H), 7.84 (m, 2H), 7.75 (m, 2H), 6.88 (d, $^2J$ = 3 Hz, 1H), 6.82 (dd, $^2J$ = 9 Hz, $^2J$ = 3 Hz, 1H), 4.80 (s, 2H), 4.14 (t, $^3J$ = 6 Hz, 2H), 3.93 (t, $^3J$ = 6.5 Hz, 2H), 2.24 (tt, $^3J$ = 6 Hz, $^3J$ = 6.5 Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 168.4 (2C=O), 162.6 (Cq), 135.7 (Cq), 134.2 (2CH), 132.1 (2Cq), 128.4 (CH), 123.4 (2CH), 118.1 (CH), 114.3 (CH), 66.7 ($CH_2$), 35.3 ($CH_2$), 29.9 ($CH_2$), 29.1 ($CH_2$); MS (CI/$NH_3$): *m*/*z* 436 [*M*+$NH_4^+$]; IR (neat): $\tilde{\nu}$ = 3058 ($\tilde{\nu}_{CHar}$), 1768 ($\tilde{\nu}_{C=O}$), 1705 cm$^{-1}$; $C_{18}H_{15}BrN_2O_5$ (419.23): calcd C 51.57, H 3.61, found C 51.34, H 3.71.

**Ethyl {5-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propoxy]-2-nitrobenzyl}-phenylphosphinate (24)**: Diethylphenylphosphonite (706 µL, 3.67 mmol) was added to a suspension of bromide **23** (1.46 g, 3.5 mmol) in degassed toluene (15 mL) under nitrogen. The mixture was refluxed under a gentle stream of nitrogen for 18 h. Solvent was evaporated, and flash chromatography on silica gel (5% MeOH in $CH_2Cl_2$) yielded 1.77 g phosphinate **24** ($C_{26}H_{25}N_2O_7P$; $M_r$ = 508.46; 99%) as a white powder, m.p. 148–150°C. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta$ = 7.87 (d, $^2J$ = 9 Hz, 1H), 7.80–7.77 (m, 2H), 7.69–7.66 (m, 2H), 7.63–7.56 (m, 2H), 7.49–7.47 (m, 1H), 7.40–7.36 (m, 2H), 6.69 (d, $^2J$ = 1 Hz, 1H), 6.68 (dd, $^2J$ = 9 Hz, $^2J$ = 1 Hz, 1H), 4.02–3.63 (m, 6H), 3.84 (t, $^3J$ = 6.5 Hz, 2H), 2.14 (tt, $^3J$ = 6 Hz, $^3J$ = 6.5 Hz, 2H), 1.16 (t, $^3J$ = 7 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 168.3 (2C=O), 161.8 (Cq), 142.4 (d, Cq, $^3J$(P,C) = 4.5 Hz), 134.1 (2CH), 132.6 (CH), 132.1 (2Cq), 131.9 (d, 2CH, $^3J$(P,C) = 9.5 Hz), 130.05 (d, Cq, $^2J$(P,C) = 8 Hz), 129.9 (d, Cq, $^1J$(P,C) = 127 Hz), 128.6 (d, 2CH, $^2J$(P,C) = 12.5 Hz), 127.8 (CH), 123.3 (2CH), 118.0 (d, CH, $^3J$(P,C) = 4 Hz), 113.75 (CH), 66.35 ($CH_2$), 61.25 (d, $CH_2$, $^2J$(P,C) = 5 Hz), 35.6 (d, $CH_2$, $^1J$(P,C) = 92 Hz), 35.2 ($CH_2$), 28.1 ($CH_2$), 16.3 (d, $CH_3$, $^3J$(P,C) = 7 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta$ = 39.61 (s); MS (CI/$NH_3$): *m*/*z* 509 [*M*+H$^+$], 526 [*M*+$NH_4^+$]; IR (neat): $\tilde{\nu}$ = 3074, 1766, 1708, 1605, 1591, 1260 cm$^{-1}$; HRMS (LSIMS; [*M*+H$^+$], $C_{26}H_{26}N_2O_7P$) calcd: 509.1478, found: 509.1480.

**Ethyl (1-{5-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propoxy]-2-nitrophenyl}-1,1-difluoromethyl)phenylphosphinate (26)**: Phosphinate **24** (2.5 g, 4.92 mmol) in THF (80 mL) was added dropwise to sodium hexamethyldisilazide (10.82 mL, 1M solution in THF, 10.82 mmol) diluted in THF (20 mL), at $-80\,^{\circ}C$ under inert atmosphere, at such a rate that the temperature was carefully maintained at $-80\,^{\circ}C$. The purple mixture was stirred at $-80\,^{\circ}C$ for 15 min. *N*-Fluorobenzenesulfonimide (3.41 g, 10.82 mmol) in THF (20 mL) was then added dropwise and the resulting orange mixture was stirred at ambient temperature; around $-30\,^{\circ}C$ a white precipitate formed. The reaction was quenched with water (50 mL) and the mixture diluted with ethyl acetate. The aqueous layer was extracted twice with ethyl acetate (100 mL). The combined organic layers were dried over magnesium sulfate and then evaporated. Flash chromatography on silica gel (pentane 40% in ethyl acetate) yielded 947 mg $\alpha,\alpha$-difluorophosphinate **26** ($C_{26}H_{23}F_2N_2O_7P$; $M_r = 544.44$, 35%) as a white powder, m.p. 123.5–126 °C, and 790 mg of $\alpha$-fluorophosphinates **25a** and **25b** ($C_{26}H_{24}FN_2O_7P$; $M_r = 526.45$, 30%) as an inseparable, approximately 1/1 mixture of diastereoisomers. This mixture of diastereoisomers could be further fluorinated by the same methodology with both 1.1 equivalent sodium hexamethlydisilazide and *N*-fluorobenzene sulfonimide, to yield 70% **26**, and thus altogether a 56% global yield for **26**.

**Difluorinated phosphinate 26**: $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 7.89-7.82$ (m, 4H), 7.75–7.70 (m, 2H), 7.67–7.64 (m, 1H), 7.66 (d, $^2J = 9$ Hz, 1H), 7.54–7.48 (m, 2H), 7.13 (d, $^2J = 2.5$ Hz, 1H), 6.68 (dd, $^2J = 9$ Hz, $^2J = 2.5$ Hz, 1H), 4.27–4.15 (m, 2H), 4.10 (t, $^3J = 6$ Hz, 2H), 3.91 (t, $^3J = 6.5$ Hz, 2H), 2.21 (tt, $^3J = 6$ Hz, $^3J = 6.5$ Hz, 2H), 1.35 (t, $^3J = 7$ Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 168.3$ (2C=O), 160.7 (Cq), 142.2 (d, Cq, $^3J$(P,C) = 4.5 Hz), 134.1 (2CH), 133.8 (CH), 133.3 (d, 2CH, $^3J$(P,C) = 10 Hz), 132.1 (2Cq), 128.65 (d, 2CH, $^2J$(P,C) = 13 Hz), 127.9 (dt, Cq, $^2J$(P,C) = 13 Hz, $^2J$(C,F) = 22.5 Hz), 126.7 (CH), 125.6 (d, Cq, $^1J$(P,C) = 139 Hz), 123.4 (2CH), 118.3 (dt, $CF_2$, $^1J$(P,C) = 145.5 Hz, $^1J$(C,F) = 269.5 Hz), 116.8 (CH), 115.2 (t, CH, $^3J$(C,F) = 8.5 Hz), 66.7 ($CH_2$), 63.6 (d, $CH_2$, $^2J$(P,C) = 6 Hz), 35.2 ($CH_2$), 28.1 ($CH_2$), 16.5 (d, $CH_3$, $^3J$(P,C) = 5.5 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 27.02$ (t, $^2J$(P,F) = 100 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): 3.36 (dd, $^2J$(P,F) = 100 Hz, $^2J$(F,F) = 307 Hz), $-0.36$ (dd, $^2J$(P,F) = 100 Hz, $^2J$(F,F) = 307 Hz); MS (CI/$NH_3$): *m*/*z* 545 [*M*+H$^+$], 562 [*M*+$NH_4^+$]; IR (neat): $\tilde{\nu} = 2936$, 1770, 1713, 1264, 1247 cm$^{-1}$; $C_{26}H_{23}F_2N_2O_7P$ (544.44): calcd C 57.36, H 4.26; found C 57.21, H 4.31.

**Monofluorinated phosphinates** ethyl (1-{5-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propoxy]-2-nitrophenyl}-1-fluoromethyl)phenylphosphinates **25a** and **25b** (roughly 1/1 mixture of diastereoisomers): $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 8.06$ (d, $^2J = 10$ Hz, 1H), 8.02 (d, $^2J = 10$ Hz, 1H), 7.79–7.74 (m, 4H), 7.72–7.64 (m, 6H), 7.64–7.50 (m, 4H), 7.50–7.38 (m, 4H), 7.09 (dd, $^2J$(H,F) = 45 Hz, $^2J$(P,H) = 7.5 Hz, 1H), 6.99 (dd, $^2J$(H,F) = 45 Hz, $^2J$(P,H) = 7.5 Hz, 1H), 6.84–6.83 (2 dd, 2H), 6.79–6.76 (2dd, 2H), 4.09–3.89 (m, 8H), 3.86–3.80 (2t, 4H), 2.16–2.09 (2tt, 4H), 1.35 (2t, 6H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 168.3$ (2C=O), 162.7 (Cq), 139.8 (Cq), 134.1 (2CH), 133.25, 132.9, 132.75, 132.6, 132.4, 132.1 (3CH, 2Cq), 128.7, 128.6, 128.5, 128.45 (2CH), 127.85 (CH), 126.4 (d, Cq, $^1J$(P,C) = 51.5 Hz), 123.3 (2CH), 114.95, 114.7 (CH), 112.8, 112.6 (CH), 88.4 (dd, CHF, $^1J$(P,C) = 112 Hz, $^1J$(C,F) = 205 Hz), 87.3 (dd, CHF, $^1J$(P,C) = 112 Hz, $^1J$(C,F) = 205 Hz), 66.55 ($CH_2$), 62.5, 62.4, 62.3, 62.2 ($CH_2$), 35.15 ($CH_2$), 28.0 ($CH_2$), 16.4, 16.3, 16.3 (d, $CH_3$, $^3J$(P,C) = 5.5 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 31.89$ (d, $^2J$(P,F) = 85 Hz), 30.84 (d, $^2J$(P,F) = 85 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta = -99.06$ (dd, $^2J$(P,F) = 85 Hz, $^2J$(F,H) = 45 Hz), $-99.39$ (dd, $^2J$(P,F) = 85 Hz, $^2J$(C,F) = 45 Hz); MS (CI/$NH_3$): *m*/*z* 527 [*M*+H$^+$], 544 [*M*+$NH_4^+$]; IR (neat): $\tilde{\nu} = 3061$, 1772, 1712, 1610, 1584, 1032 cm$^{-1}$; HRMS (LSIMS, [*M*+H]$^+$, $C_{26}H_{25}FN_2O_7P$): calcd: 527.1383, found: 527.1383.

**Ethyl (1,1-difluoropropyl)phenylphosphinate (29)**: Diethylphenylphosphonite (1.0 mL; 5.2 mmol) and bromopropane (15 mL) were gently refluxed together overnight. Excess bromopropane was removed under vacuum, and the crude material was purified by chromatography on silica gel (3% MeOH in $CH_2Cl_2$) yielding 1.07 g phosphinate **27** ($C_{11}H_{17}O_2P$; $M_r = 212.23$, 97%) as a colorless oil. Phosphinate **27** (205 mg; 0.97 mmol) was dissolved in 5 mL THF, and cooled to $-80\,^{\circ}C$. *tert*-Butyllithium (0.97 mmol, 1.6M in hexane) was then added dropwise. The reaction mixture turned bright yellow. After 2 h at $-80\,^{\circ}C$, *N*-fluorobenzenesulfonimide (365 mg, 1.16 mmol) dissolved in precooled THF (5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature over 2 h. Saturated $NH_4Cl$ solution (5 mL) was added, and the aqueous layer was extracted twice with ethyl acetate. The organic layers were pooled and dried on $MgSO_4$. Solvents were removed under vacuum, and the crude material was chomatographed on silica gel (10% acetone in $CH_2Cl_2$), yielding 10 mg difluorinated phosphinate **38** ($C_{11}H_{15}F_2O_2P$; $M_r = 248.21$; 5%) and 120 mg monofluorinated phosphinates **28a** and **28b**, in a 2/1 mixture of diastereoisomers ($C_{11}H_{16}FO_2P$; $M_r = 230.22$; 54%), as colorless oils. Phosphinates **28a** and **28b** were transformed into difluorinated phosphinate **29** in 17% yield by the same procedure. **29**: $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 7.92-7.85$ (m, 2H), 7.66–7.61 (m, 1H), 7.58–7.49 (m, 2H), 4.33–4.17 (m, 2H), 2.17–1.91 (m, 2H), 1.40 (t, $^3J = 7$ Hz, 3H), 1.06 (t, $^3J = 7.5$ Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 133.6$ (CH), 133.1 (d, 2CH, $^3J$(P,C) = 10 Hz), 128.7 (d, 2CH, $^2J$(P,C) = 13 Hz), 128.2 (d, Cq, $^1J$(P,C) = 140 Hz), 124.2 (td, Cq, $^1J$(P,C) = 130 Hz, $^1J$(C,F) = 235 Hz), 62.7 (d, $CH_2$, $^2J$(P,C) = 8 Hz), 26.4 (td, $CH_2$, $^2J$(P,C) = 15 Hz, $^2J$(C,F) = 21 Hz), 16.6 (d, $CH_3$, $^3J$(P,C) = 5 Hz), 4.8 ($CH_3$); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 27.6$ (t, $^2J$(P,F) = 100 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta = -12.0$ (m); MS (CI/$NH_3$): *m*/*z* 249 [*M*+H$^+$], 266 [*M*+$NH_4^+$]; IR (neat): $\tilde{\nu} = 3064$, 2987, 1592, 1440, 1248, 1034 cm$^{-1}$; HRMS (FAB, $M^+$, $C_{11}H_{15}F_2O_2P$): calcd: 248.0778; found : 248.0767.

**Monofluorinated phosphinate 28a**: $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 7.85-7.78$ (m, 2H), 7.60–7.55 (m, 1H), 7.51–7.44 (m, 2H), 4.76 (ddt, 1H, $^1J$(F,H) = 47.5 Hz, $^2J$(P,H) = 8.5 Hz, $^3J$(H,H) = 5 Hz), 4.19–3.96 (m, 2H), 1.99–1.54 (m, 2H), 1.33 (t, $^3J$(H,H) = 7 Hz, 3H), 1.06 (t, $^3J$(H,H) = 7.5 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 133.0$ (CH), 132.7 (d, 2CH, $^3J$(P,C) = 10 Hz), 128.6 (d, 2CH, $^2J$(P,C) = 12.5 Hz), 127.2 (d, Cq, $^1J$(P,C) = 127 Hz), 92.7 (dd, CH, $^1J$(P,C) = 120 Hz, $^1J$(C,F) = 185 Hz), 61.7 (d, $CH_2$, $^2J$(P,C) = 5 Hz), 23.0 (d, $CH_2$, $^2J$(C,F) = 18.5 Hz), 16.5 (d, $CH_3$, $^3J$(P,C) = 5 Hz), 10.0 ($CH_3$); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 35.8$ (d, $^2J$(P,F) = 70 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta = -105.2$ (dd, $^1J$(F,H) = 47.5 Hz, $^2J$(P,F) = 70 Hz); MS (CI/$NH_3$): *m*/*z* 231 [*M*+H$^+$], 248 [*M*+$NH_4^+$]; IR (neat): $\tilde{\nu} = 3061$, 2981, 2939, 1439, 1219 cm$^{-1}$; HRMS (FAB, $M^+$, $C_{11}H_{15}FO_2P$):calcd: 230.0872; found: 230.0848.

**Monofluorinated phosphinate 28b**: $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 7.85-7.78$ (m, 2H), 7.60–7.55 (m, 1H), 7.51–7.44 (m, 2H), 4.62 (ddt, 1H, $^1J$(F,H) = 47.5 Hz, $^2J$(P,H) = 8.5 Hz, $^3J$(H,H) = 5 Hz), 4.19–3.96 (m, 2H), 1.99–1.54 (m, 2H), 1.32 (t, $^3J$(H,H) = 7 Hz, 3H), 1.00 (t, $^3J$(H,H) = 7.5 Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 133.0$ (CH), 132.7 (d, 2CH, $^3J$(P,C) = 10 Hz), 128.6 (d, 2CH, $^2J$(P,C) = 12.5 Hz), 127.2 (d, Cq, $^1J$(P,C) = 127 Hz), 92.7 (dd, CH, $^1J$(P,C) = 120 Hz, $^1J$(C,F) = 185 Hz), 61.7 (d, $CH_2$, $^2J$(P,C) = 5 Hz), 22.6 (d, $CH_2$, $^2J$(C,F) = 20 Hz), 16.5 (d, $CH_3$, $^3J$(P,C) = 5 Hz), 9.86 ($CH_3$); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 34.3$ (d, $^2J$(P,F) = 65 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta = -106.3$ (dd, $^1J$(F,H) = 47.5 Hz, $^2J$(P,F) = 65 Hz); MS (CI/$NH_3$): *m*/*z* 231 [*M*+H$^+$], 248 [*M*+$NH_4^+$]; IR (neat): $\tilde{\nu} = 3061$, 2981, 2939, 1439, 1219 cm$^{-1}$.

**Ethyl (1-{5-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propoxy]-2-isopropylaminophenyl}-1,1-difluoromethyl)phenylphosphinate (30)**: Pd/C 10% (100 mg) and magnesium sulfate (5 g) were added to a solution of $\alpha,\alpha$-difluorophosphinate **26** (947 mg, 1.75 mmol) in methanol (20 mL) and acetone (20 mL). The reaction mixture was stirred under an atmosphere of hydrogen at ambient temperature for 120 h. The mixture was filtered and solvents were evaporated. Flash chromatography on silica gel (5% MeOH in $CH_2Cl_2$) yielded 970 mg *N*-isopropylaniline (**30**) ($C_{29}H_{31}F_2N_2O_5P$; M.W = 556.54; 99%) as a yellow oil. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 7.78-7.71$ (m, 4H), 7.67–7.62 (m, 2H), 7.55–7.50 (m, 1H), 7.44–7.37 (m, 2H), 6.75 (dd, $^2J = 9$ Hz, $^2J = 2$ Hz, 1H), 6.62 (d, $^2J = 9$ Hz, 1H), 7.57 (d, $^2J = 2$ Hz, 1H), 4.23–4.04 (m, 2H), 3.84–3.71 (m, 4H), 3.53 (m, 1H), 2.02 (tt, 2H), 1.30 (t, $^3J = 8$ Hz, 3H), 1.19 (d, $^3J = 6$ Hz, 3H), 1.18 (d, $^3J = 6$ Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 168.4$ (2C=O), 150.3 (Cq), 139.6 (Cq), 134.1 (CH), 134.0 (2CH), 133.7 (CH), 132.95 (d, 2CH, $^3J$(P,C) = 10 Hz), 132.2 (2Cq), 128.6 (d, 2CH, $^2J$(P,C) = 12.5 Hz), 125.5 (d, Cq, $^1J$(P,C) = 135 Hz), 123.3 (2CH), 120.3 (dt, $CF_2$, $^1J$(P,C) = 150 Hz, $^1J$(C,F) = 268 Hz), 119.5 (CH), 116.3 (dt, Cq), 114.3 (t, CH, $^3J$(C,F) = 10 Hz), 66.8 ($CH_2$), 63.6 (d, $CH_2$, $^2J$(P,C) = 6 Hz), 46.2 (CH), 35.5 ($CH_2$), 28.35 ($CH_2$), 22.3 ($CH_3$), 22.1 ($CH_3$), 16.6 (d, $CH_3$, $^3J$(P,C) = 5 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta = -3.0$ (dd, $^2J$(P,F) = 115 Hz, $^2J$(F,F) = 300 Hz), $-5.1$ (dd, $^2J$(P,F) = 115 Hz, $^2J$(F,F) = 300 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 28.93$ (t, $^2J$(P,F) = 115 Hz); MS (CI/$NH_3$): *m*/*z* 557 [*M*+H$^+$]; IR (neat): $\tilde{\nu} = 3390$, 2971, 1772, 1714, 1397 cm$^{-1}$; HRMS (LSIMS, [*M*+H]$^+$, $C_{29}H_{32}F_2N_2O_5P$): calcd: 557.2017, found: 557.2015.

**Ethyl (1-{5-[3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propoxy]-2-(isopropylmethylamino)phenyl}-1,1-difluoromethyl)-phenylphosphinate (31)**: Iodo-



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methane (2 mL; large excess) was added to a mixture of *N*-isopropylaniline **30** (760 mg, 1.36 mmol) and of dry potassium bicarbonate (190 mg, 1.38mmol) in acetonitrile (10 mL). The reaction mixture was stirred at ambient temperature for 48 h, diluted with $CH_2Cl_2$, and filtered, and the solvents were evaporated. Flash chromatography on silica gel (2.5 to 5% MeOH in $CH_2Cl_2$) yielded 760 mg tertiary aniline **31** ($C_{30}H_{33}F_2N_2O_5P$; $M_r = 570.56$; 97%) as a yellow oil. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta =$ 7.87–7.84 (m, 2H), 7.81–7.76 (m, 2H), 7.74–7.71 (m, 2H), 7.56–7.58 (m, 1H), 7.47–7.41 (m, 2H), 7.09 (d, $^2J = 9$ Hz, 1H), 7.91 (d, $^2J = 3$ Hz, 1H), 6.84 (dd, $^2J = 9$ Hz, $^2J = 3$ Hz, 1H), 4.25–4.14 (m, 2H), 3.96 (t, $^3J = 6$ Hz, 2H), 3.90 (t, $^3J = 7$ Hz, 2H), 3.02 (m, 1H), 2.28 (s, 3H), 2.16 (tt, 2H), 1.34 (t, $^3J =$ 7 Hz, 3H), 0.91 (d, $^3J = 6.5$ Hz, 3H), 0.83 (d, $^3J = 6.5$ Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 168.1$ (2C=O), 154.6 (Cq), 146.2 (Cq), 133.7 (2CH), 132.7 (d, 2CH, $^3J$(P,C) = 10 Hz), 131.9 (2Cq), 130.75 (d, Cq, $^1J$(P,C) = 149 Hz), 127.9 (d, 2CH, $^2J$(P,C) = 13 Hz), 127.8 (Cq), 126.2 (CH), 123.0 (2CH), 120.1 (dt, $CF_2$, $^1J$(P,C) = 151 Hz, $^1J$(C,F) = 244.5 Hz), 117.1 (CH), 113.7 (t, CH, $^3J$(C,F) = 9 Hz), 65.7 ($CH_2$), 62.4 (d, $CH_2$, $^2J$(P,C) = 7 Hz), 55.8 ($CH_3$), 35.2 ($CH_2$), 34.35 ($CH_3$), 28.0 ($CH_2$), 18.6 ($CH_3$), 17.35 ($CH_3$), 16.3 (d, $CH_3$, $^3J$(P,C) = 5.5 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta =$ 28.17 (t, $^2J$(P,F) = 105 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta = 3.55$ (dd, $^2J$(P,F) = 105 Hz, $^2J$(F,F) = 290 Hz), 1.09 (dd, $^2J$(P,F) = 105 Hz, $^2J$(F,F) = 290 Hz); MS (CI/$NH_3$): $m/z$ 571 [$M$+H$^+$]; IR (neat): $\tilde{\nu} = 3059$, 2971, 1772, 1714, 1500, 1395, 1247, 1035 cm$^{-1}$; HRMS (LSIMS, [$M$+H]$^+$, $C_{30}H_{34}F_2N_2O_5P$): calcd: 571.2173, found: 571.2172.

**{1-[5-[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-propoxy]-2-(isopropylmethylamino)-phenyl]-1,1-difluoromethyl)phenylphosphinic acid (33)**: Iodotrimethylsilane (30 μL; 0.2 mmol) was added to aniline **31** (80 mg, 0.144 mmol) in $CH_2Cl_2$ (1 mL) under an inert atmosphere. The reaction mixture was stirred at ambient temperature for 1 h. $CH_2Cl_2$ was then evaporated and the crude mixture was stirred in methanol at ambient temperature for 10 min. Methanol was evaporated and flash chromatography on silica gel (5 to 10% MeOH in $CH_2Cl_2$) yielded 53 mg phosphinic acid **33** ($C_{28}H_{29}F_2N_2O_5P$; $M_r = 542.51$; 68%) as a white powder. Acid **33** was recrystallized from warm ethanol to yield colorless crystals. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 7.97$–$7.91$ (m, 2H), 7.76–7.73 (m, 2H), 7.65–7.61 (m, 2H), 7.44–7.35 (m, 3H), 7.30 (d, $^2J = 9$ Hz, 1H), 7.12 (d, $^2J = 2.5$ Hz, 1H), 6.87 (dd, $^2J = 9$ Hz, $^2J = 2.5$ Hz, 1H), 3.98 (t, $^3J = 6$ Hz, 2H), 3.81 (t, $^3J = 6.5$ Hz, 2H), 3.74 (m, 1H), 2.98 (s, 3H), 2.10 (tt, 2H), 1.40 (d, $^3J =$ 6.5 Hz, 3H), 1.29 (d, $^3J = 6.5$ Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta =$ 168.3 (2C=O), 159.05 (Cq), 134.1 (2CH), 133.7 (d, 2CH, $^3J$(P,C) = 8.5 Hz), 132.2 (d, Cq, $^1J$(P,C) = 149 Hz), 132.0 (CH), 131.75 (CH and 3Cq), 127.9 (d, 2CH, $^2J$(P,C) = 12 Hz), 124.35 (CH), 123.3 (2CH), 120.2 (dt, $CF_2$, $^1J$(P,C) = 153 Hz, $^1J$(C,F) = 264 Hz), 121.1 (CH), 118.0 (t, CH, $^3J$(C,F) = 9 Hz), 70.0 ($CH_2$), 61.1 (CH), 37.9 ($CH_3$), 35.2 ($CH_2$), 28.1 ($CH_2$), 19.2 ($CH_3$), 15.6 ($CH_3$); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.0$ (t, $^2J$(P,F) = 85 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta = 3.28$ (dd, $^2J$(P,F) = 85 Hz, $^2J$(F,F) = 128 Hz), $-5.18$ (dd, $^2J$(P,F) = 85 Hz, $^2J$(F,F) = 128 Hz); MS (CI/$NH_3$): $m/z$ 543 [$M$+H$^+$], 523, 399; IR (neat): $\tilde{\nu} = 3435$, 3065, 2948, 1772, 1712, 1397, 720 cm$^{-1}$; HRMS (LSIMS, [$M$+H]$^+$, $C_{28}H_{30}F_2N_2O_5P$): calcd: 543.1860, found: 543.1860.

**Ethyl {1-[5-(3-aminopropoxy)-2-(isopropylmethylamino)-phenyl]-1,1-difluoromethyl}phenylphosphinate (32)**: Hydrazine hydrate (250 μL) was added to aniline **31** (500 mg, 0.877 mmol) in methanol (3 mL). The reaction mixture was stirred at ambient temperature for 18 h, during which a white precipitate formed. The reaction mixture was diluted in diethyl ether and the precipitate was filtered. The solvents were evaporated to yield 323 mg pure amine **32** ($C_{22}H_{31}F_2N_2O_5P$; $M_r = 440.46$; 86%) as a colorless oil. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 7.76$–$7.69$ (m, 2H), 7.66–7.61 (m, 1H), 7.53–7.47 (m, 2H), 7.19 (d, $^2J = 9$ Hz, 1H), 7.00 (dd, $^2J = 9$ Hz, $^2J =$ 2.5 Hz, 1H), 6.95 (d, $^2J = 2.5$ Hz, 1H), 4.18 (m, 2H), 3.97 (t, $^3J = 6$ Hz, 2H), 2.98 (m, 1H), 2.85 (t, $^3J = 7$ Hz, 2H), 2.26 (s, 3H), 1.93 (tt, 2H), 1.31 (t, $^3J =$ 7 Hz, 3H), 0.91 (d, $^3J = 6.5$ Hz, 3H), 0.84 (d, $^3J = 6.5$ Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 159.3$ (Cq), 150.3 (Cq), 137.45 (CH), 136.7 (d, 2CH, $^3J$(P,C) = 10 Hz), 133.55 (dt, Cq, $^2J$(P,C) = 12 Hz, $^2J$(C,F) = 17 Hz), 132.4 (d, 2CH, $^2J$(P,C) = 14 Hz), 130.65 (CH), 130.4 (d, Cq, $^1J$(P,C) = 136.5 Hz), 124.3 (dt, $CF_2$, $^1J$(P,C) = 125 Hz, $^1J$(C,F) = 271 Hz), 117.1 (CH), 114.5 (t, CH, $^3J$(C,F) = 9 Hz), 69.9 ($CH_2$), 67.15 (d, $CH_2$, $^2J$(P,C) = 7 Hz), 60.15 (CH), 42.2 ($CH_2$), 38.0 ($CH_3$), 35.3 ($CH_2$), 22.1 ($CH_3$), 20.8 ($CH_3$), 19.7 (d, $CH_3$, $^3J$(P,C) = 5.5 Hz); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 29.8$ (t, $^2J$(P,F) = 110 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta = 3.63$ (dd, $^2J$(P,F) = 110 Hz, $^2J$(F,F) = 292 Hz), 1.13 (dd, $^2J$(P,F) = 110 Hz, $^2J$(F,F) = 292 Hz); IR (neat): $\tilde{\nu} = 3343$, 2924, 1622, 1432, 1470, 1261, 1216, 1130 cm$^{-1}$; MS (CI/$NH_3$): $m/z$ 441 [$M$+H$^+$].

**{1-[5-(3-Aminopropoxy)-2-(isopropylmethylamino)-phenyl]-1,1-difluoromethyl}phenylphosphinic acid (6)**: Iodotrimethylsilane (100 μL; 0.7 mmol) was added to amine **32** (194 mg, 0.441 mmol) in $CH_2Cl_2$ (1 mL) under an inert atmosphere. The reaction mixture was stirred at ambient temperature for 18 h. $CH_2Cl_2$ was then evaporated and the crude mixture was stirred in MeOH at ambient temperature for 10 min. The mixture was concentrated in vacuo and precipitated with diethyl ether to yield 153 mg phosphinic acid **6** ($C_{20}H_{27}F_2N_2O_3P$; $M_r = 412.41$, 84%) as a pale yellow powder. $^1$H NMR (300.125 MHz, $CDCl_3$): $\delta = 7.93$–$7.87$ (m, 3H, 3), 7.63–7.58 (m, 1H), 7.54–7.48 (m, 2H), 7.33 (dd, $^2J = 9$ Hz, $^2J = 3$ Hz, 1H), 6.24 (d, $^2J = 3$ Hz, 1H); 4.20 (t, $^3J = 6$ Hz, 2H), 4.06 (m, 1H), 3.28 (s, 3H), 3.17 (t, $^3J = 7$ Hz, 2H), 2.18 (tt, 2H), 1.51 (d, $^3J = 6.5$ Hz, 3H), 1.45 (d, $^3J = 6.5$ Hz, 3H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta = 160.4$ (Cq), 134.4 (d, 2CH, $^3J$(P,C) = 9 Hz), 133.5 (CH), 132.4 (d, Cq, $^1J$(P,C) = 131.5 Hz), 131.9 (dt, Cq, $^2J$(P,C) = 10 Hz, $^2J$(C,F) = 21.5 Hz), 129.2 (d, 2CH, $^2J$(P,C) = 12 Hz), 126.4 (CH), 126.0 (Cq), 121.0 (dt, $CF_2$, $^1J$(P,C) = 133 Hz, $^1J$(C,F) = 266 Hz), 118.5 (CH), 115.9 (t, CH, $^3J$(C,F) = 11.5 Hz), 67.1 ($CH_2$), 64.0 (CH), 40.6 ($CH_3$), 38.4 ($CH_2$), 28.0 ($CH_2$), 19.5 ($CH_3$), 16.3 ($CH_3$); $^{31}$P NMR (121.5 MHz, $CDCl_3$): $\delta = 21.71$ (t, $^2J$(P,F) = 90 Hz); $^{19}$F NMR (282.2 MHz, $CDCl_3$): $\delta = 3.38$ (dd, $^2J$(P,F) = 90 Hz, $^2J$(F,F) = 297 Hz), $-0.85$ (dd, $^2J$(P,F) = 90 Hz, $^2J$(F,F) = 297 Hz); MS (CI/$NH_3$): $m/z$ 413 [$M$+H$^+$]; IR (neat): $\tilde{\nu} = 3450$, 2971, 1606, 1500, 1441, 1286, 1239, 1192, 1126, 1026 cm$^{-1}$; HRMS (LSIMS, [$M$+H]$^+$, $C_{20}H_{28}F_2N_2O_3P$): calcd: 413.1806, found: 413.1806.

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