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# Formation of 1-Hydroxymethylene-1,1-Bisphosphinates through the Addition of a Silylated Phosphonite on various Trivalent Derivatives

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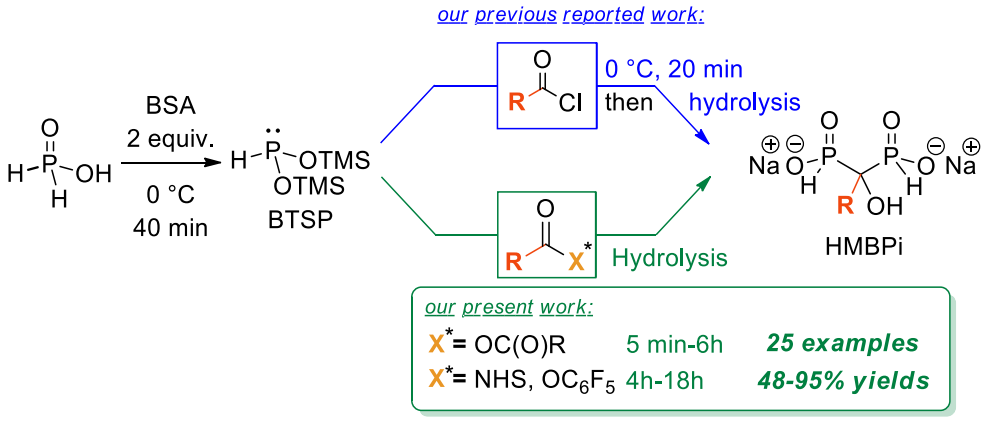


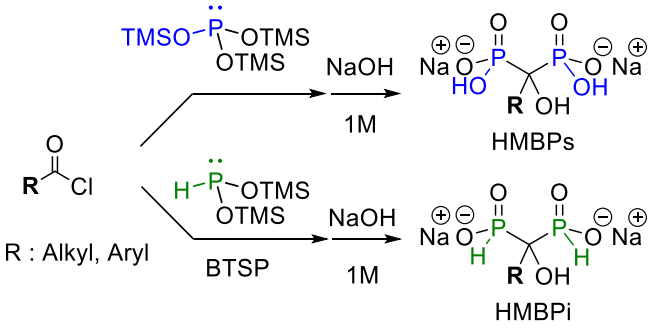

**ABSTRACT**: An easily handled one-pot synthetic procedure was previously developed for the synthesis of bisphosphinates starting from acyl chlorides. Herein, other trivalent derivatives as acid anhydrides and activated esters were tested in order to form various bisphosphinates. This modulation of the reactivity can be controlled according to the nature of the acid derivative for the use of sensitive and functionalized substrates.

## INTRODUCTION

1-Hydroxymethylene-1,1-bisphosphonates (HMBPs) are phosphorylated molecules which occupy a prominent place in clinic.[1] Indeed, bisphosphonates are well known for their clinical use on bone diseases and also for their antitumor potential activity.[2] HMBPs have high affinity for hydroxyapatite,[3] which is the main mineral found in bones, and they can chelate several metal ions, such as Mg(+II), Ca(+II), and Fe(+II). HMBPs which are easily taken up by the bone tissue,[4] are usually used as inhibitors of bone resorption, and more precisely in osteoporosis, solid tumor bone metastases and myeloma bone disease.[5] These compounds also exhibit interesting antitumor effects on soft tissue primary tumor models (breast, prostate…).[5,6] However, their uses are limited by their unfavorable pharmacokinetics and biodistribution. In fact, bisphosphonates hardly pass the biological membranes due to their negative charges at physiological pH. Furthermore, their high hydrophilic nature causes a weak plasma half-life. Moreover, because of their strong chelating properties, the biodistribution of bisphosphonates is exclusively limited on bone tissue. These parameters therefore make them particularly difficult to impregnate soft tissues and thus target soft tumors.[7]

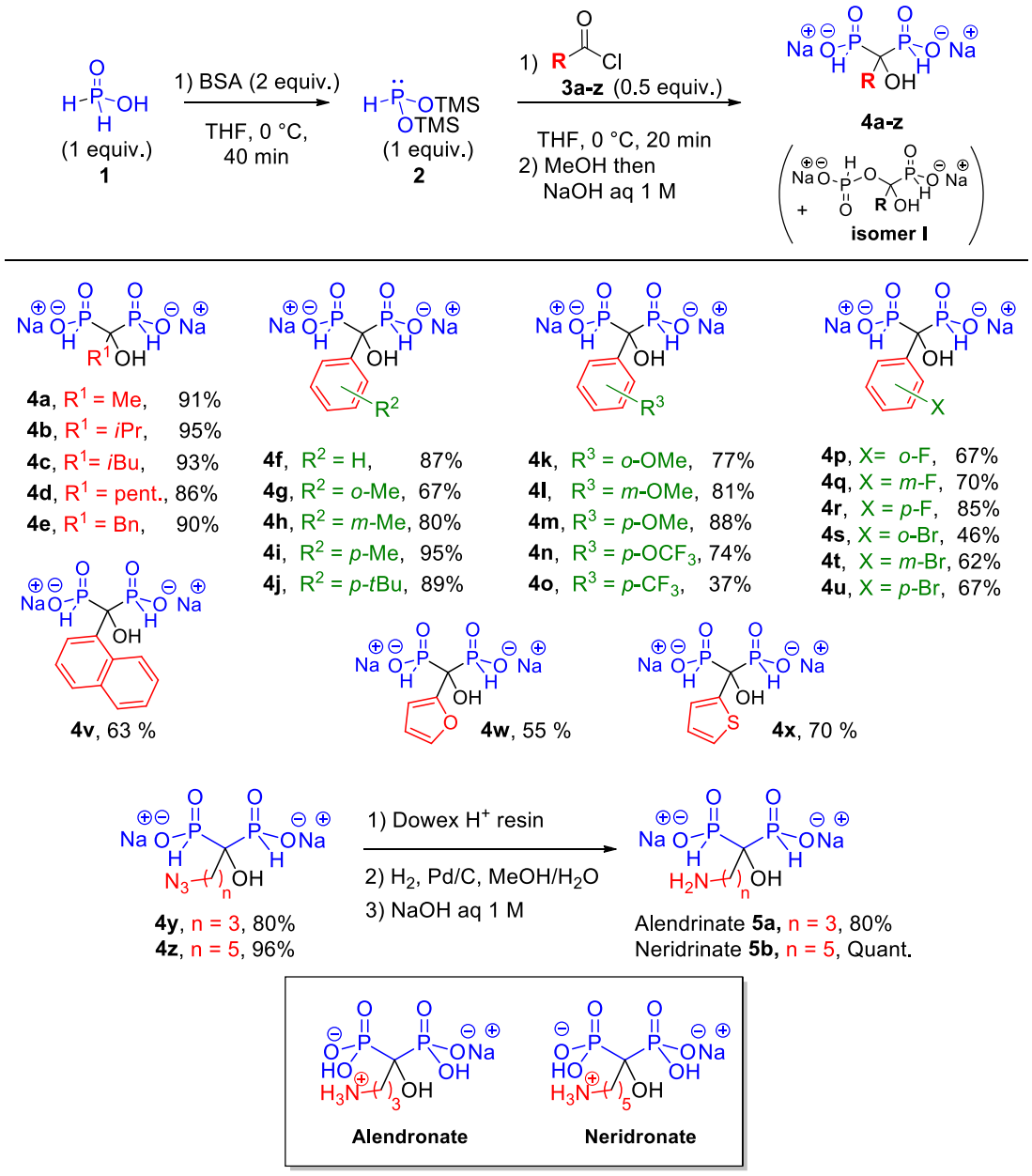
In this context, several strategies were developed to improve their cell uptake.[8] One of them consists in the replacement of the phosphonic acid group by a phosphinic acid moiety. This function should represent a good compromise in terms of hydrophobicity by decreasing both acidity and ionicity at physiological pH and chelating properties.

For the past years, our laboratory have developed efficient methodologies allowing the access to various 1-hydroxymethylene-1,1-bisphosphonates (HMBPs)[9] and more recently to easily purified 1-hydroxymethylene-1,1-bis(*H*-phosphinates) (HMBPi)[10] in short reaction times, and in rather good to excellent yields. In both cases, HMBPs and HMBPi are synthesized starting from an acyl chloride respectively in the presence of a commercially available silylated phosphite or a pre-formed silylated phosphonite (Scheme 1).[11]




**Scheme 1** Synthesis of HMBPs and HMBPi starting from acyl chloride and respectively in the presence of $P(OTMS)_3$ or $HP(OTMS)_2$.

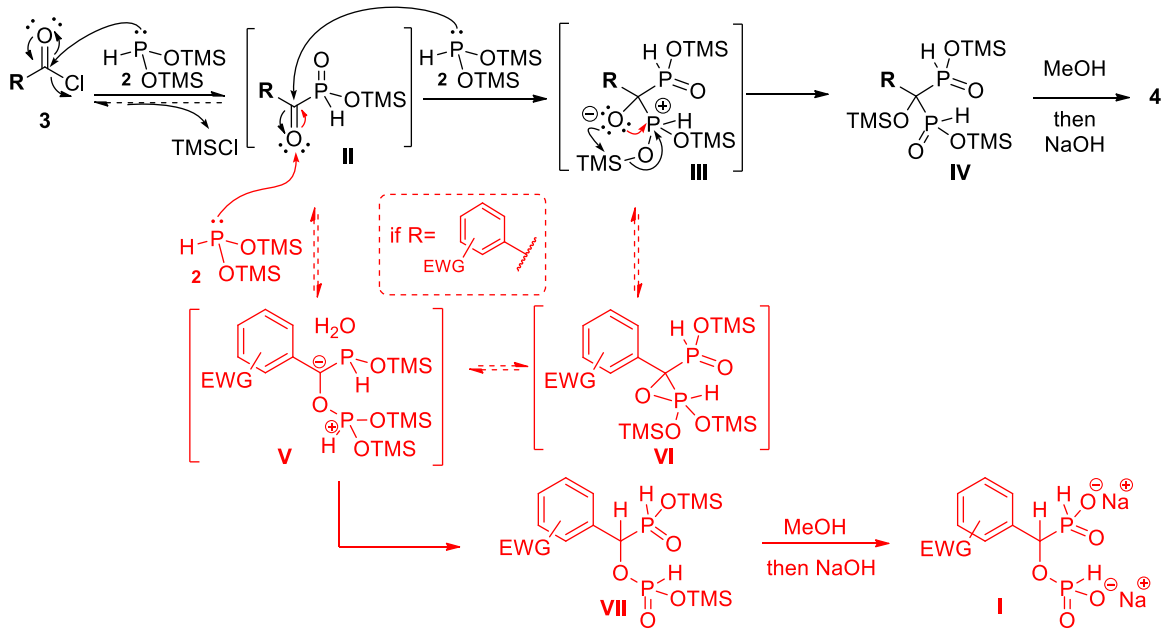
For our latest study, the synthesis of HMBPi required to manage properly the formation of BTSP **2** starting from hypophosphorous acid **1** in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) as silylating agent. Indeed, although numerous reports described the use of BTSP, its synthesis was usually performed in the excess of silylating agent and hence appears inconvenient.[12,13] Thanks to a careful NMR monitoring, the reaction was successfully achieved after 40 minutes by mixing only 2 equivalents of BSA and 1 equivalent of hypophosphorous acid **1** to *in situ* generate bis(trimethylsilyl)phosphonite BTSP **2**. After several optimizations in terms of temperature, concentrations, and reagent additions, the subsequent addition of 1 equivalent of BTSP **2** to 0.5 equivalent of acyl chloride **3** finally led to the corresponding HMBPi. Therefore, these more eco-compatible conditions were retained to enlarge the scope of the reaction. Several bisphosphinates **4** have been synthesized starting from alkyl or (hetero)aromatic acyl chlorides **3** in good yields after only 25 min (Scheme 2).[10,11]




**Scheme 2** Scope of the reaction between hypophosphorous acid **1** and various acyl chlorides **3a-z** in the presence of BSA.

The preparation of biorelevant analogues of HMBP was also considered in bisphosphinate series such as alendrinate **5a** and neridrinate **5b**, analogues of HMBP alendronate and neridronate (Scheme 2). Under our optimal conditions, the reaction was conducted between the azido acyl chlorides **3** and BTSP **2** to afford the expected HMBPi in excellent yields (80% and 96%) after methanolysis and basic treatment. Afterward, the bisphosphinates **5a-b** were treated with Dowex $H^+$ resin to form the corresponding bisphosphinic acids. The catalytic hydrogenation of the azido function was subsequently carried out in the presence of palladium on activated charcoal to finally give the targeted bisphosphinates **5a-b** in excellent yields (80% and quantitative).

During this study, we tried at best to manage the high reactivity of acyl chlorides. Unfortunately, starting from some electro-withdrawing substituted aromatic acyl chlorides, the formation of a side product was also observed in various amounts (beyond 10%). Theses by-products have been identified as phosphinylphosphonate isomers **I** (depicted in scheme 2) and resulted from a transposition during the reaction. Regarding our experiments and also those reported in the literature, we have proposed a postulated mechanism for HMBPi syntheses including alternative routes towards the formation of the phosphinylphosphinate isomer **I** (Scheme 3).[10]




**Scheme 3** postulated mechanism for the formations of HMBPi **4** or **7** and phosphinylphosphonate isomer **A**.

In most of the cases, the first attack of BTSP **2** onto the trivalent electrophile could generate a silylated α-ketophosphinate **II** which could undergo a second attack of BTSP **2** to form a tetravalent phosphonium **III**. After an intramolecular transilylation of **III**, the resulting silylated HMBPi **IV** finally furnishes the expected HMBPi **4** after methanolysis and pH adjustment. However, two side pathways could also occur especially in the presence of aromatic acyl chlorides **3** bearing electro-withdrawing substituents. In this cases, we have considered the silylated α-ketophosphinate **10** could move towards a stabilized benzylic carbanion **V**. His formation could be explained either by the second attack of BTSP **2** onto the carbonyl

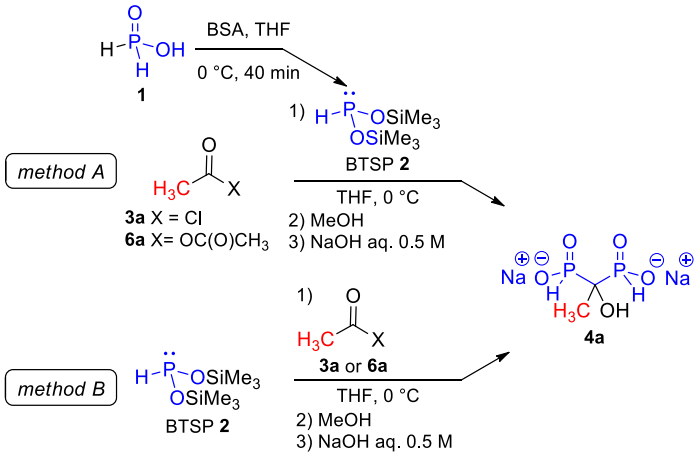
oxygen atom of **II** or by the opening of **VI** obtained by intramolecular cyclization of **III**. The intermediate **V** could then give the silylated phosphinylphosphinate **VII** and finally the isomer **I** after methanolysis and pH adjustment. In view of our latest works, the use of less reactive trivalent substrates could consequently be a good alternative to limit the formation of isomer **I** and hence enabled us to access to sensitive or more functionalized HMBPi.

In bisphosphonate series, our laboratory has already reported an efficient Sila Arbuzov reaction starting from acid anhydrides and silylated phosphites.[14] In this context, the reaction between silylated phosphonite BTSP **2** and other trivalent electrophiles was investigated in order to smoothly form 1-hydroxymethylene-1,1-bis(*H*-phosphinate) scaffold which has not been reported yet as much as we know. Herein we described our detailed study for the synthesis of substituted and functionalized HMBPi.

## RESULTS ANS DISCUSSION

**Reaction on acid anhydride substrates.** At the outset of this study, the reaction was conducted with hypophosphorous acid **1** and acetic anhydride **6a** in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in tetrahydrofuran at 0 °C. The results are presented in the table 1 below in comparison with the yields obtained with the acyl chlorides as starting reagents (Table 1, entries 1, 3 *versus* 2, 4).

**Table 1** Reaction between acetyl chloride **3a** or acetic anhydride **6a** and hypophosphorous acid **1** in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[a]




| entry | trivalent derivative **3a** or **6a** | method[b] | time[c] | yield **4a** (%)[d] |
|---|---|---|---|---|
| 1 | **3a** | **A** | 18 h | - |
| 2 | **6a** | **A** | 45 min | 84 |
| 3 | **3a** | **B** | 20 min | 91 |
| 4 | **6a** | **B** | 5 min | 90 |

[a]Reagents and conditions: **1** (10 mmol), BSA (20 mmol), **3a** or **6a** (5 mmol), THF, Ar, 0 °C. [b]For details see experimental section. [c]The reaction completion was monitored by $^{31}P\{^{1}H\}$ and $^{31}P$ NMR; the indicated time includes the time of addition. [d]Isolated yield of HMBPi **4a**.

First of all, the silylated phosphonite **2** was generated *in situ* in 40 minutes in anhydrous THF at 0 °C as previously mentioned. BTSP **2** was then added to a solution of acetic anhydride **6a** diluted in anhydrous THF at 0 °C (Table 1, entry 2: method A) Surprisingly, we found that the reaction was already complete

after only 45 minutes at 0 °C and the expected bisphosphinate **4a** was obtained in an excellent yield of 84%. Conversely, the same reaction with acetyl chloride **3a** did not proceed. Indeed, after methanolysis, only the hypophosphorous acid, phosphorous acid and methyl ester were recovered (Table 1, entries 1 *versus* 2).

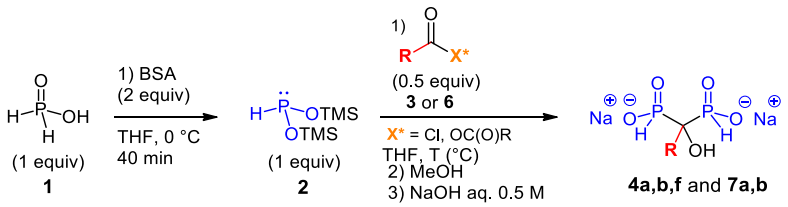
Thereafter, the influence of reagent additions was studied to easily handle the reaction (Table 1, entries 3-4 *versus* 1-2; method B). This time, the solution of acetic anhydride **6a** in THF was added dropwise to the silylated phosphonite BTSP **2** at 0 °C (method B). The reaction was successful in shorter reaction time as only 5 min (acetic anhydride addition) were only necessary to reach a complete conversion. In this case, the reaction appears to be less exothermic in the presence of acid anhydride **6a** than acetyl chloride **3a** which enables faster reagent addition (Table 1, entries 4 *versus* 3). The methanolysis step finally leads to the bisphosphinate disodium salt **4a** in an excellent yield of 90% after pH adjustment and purification by simple washes (Table 1, entry 4: method B).

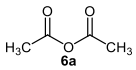
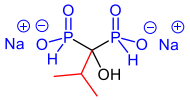
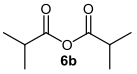
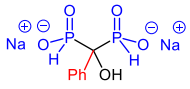
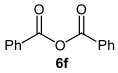
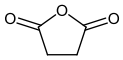
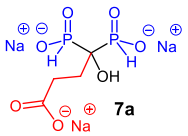
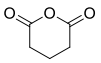
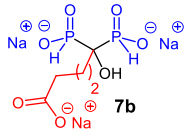
**Scope of the reaction.** Under the previous optimized conditions, the scope of the reaction was studied on various aliphatic and cyclic acid anhydrides **6** (Table 2).

**Reaction on acyclic acid anhydrides.** The reaction performed between a bulkier isobutyric anhydride **6b** and the bis(trimethylsilyl)phosphonite **2** was finished after only 9 minutes to afford *H*-HMBPi **4b** in a very good yield of 86% (Table 2, entry 4). Thereafter, these conditions were tested on benzoic anhydride **6f** (table 2, entry 6). The expected compound **4f** was isolated in an excellent yield of 92 % after only 10 minutes. In both cases, the acid anhydrides **6b** and **6f** were added faster to the phosphonite solution because of the lower exothermicity observed compared to what was found in the presence of acyl chlorides **3b** and **3f**. Thus, the reaction completions were faster reached in the presence of acid anhydrides than acyl chlorides (Table 2, entries 2, 4 *versus* 1, 3). Moreover, the expected compound **4f** was isolated in a yield of 92% instead of 87% (Table 2, entries 6 *versus* 5).

**Reaction on cyclic anhydrides.** Afterwards, the reactivity of cyclic anhydride reagents was investigated such as succinic and glutaric anhydride. This approach should enable the access to functionalized HMBPi **7a-b** bearing a carboxylate on its side chain which could subsequently undergo a peptidic coupling for instance, or other post-functionalization step. In this cases, the bis(trimethylsilyl)phosphonite **2** and the cyclic anhydrides were mixed at 0 °C and then, the mixture was stirred at room temperature respectively for 6h and 4h in order to totally achieve the reaction. After the methanolysis step and the pH adjustment, the functionalized HMBPi **7a,b** were isolated in similar yields (89 and 86%). These reactions required longer reaction times. Moreover, it was noted that a considerable quantity of a five-membered ring HMBPi lactone was also formed during this reaction in the presence of succinic anhydride. However, the mixture of cyclized and linear HMBPi was stirred in an aqueous solution of NaOH and this treatment was sufficient to give the desired compound **7a** in the indicated yield of 89%. The lactonization was never observed starting from glutaric anhydride.

**Table 2** Reaction between acyl chloride **3** or acid anhydride **6** and hypophosphorous acid **1** in the presence of BSA[a]



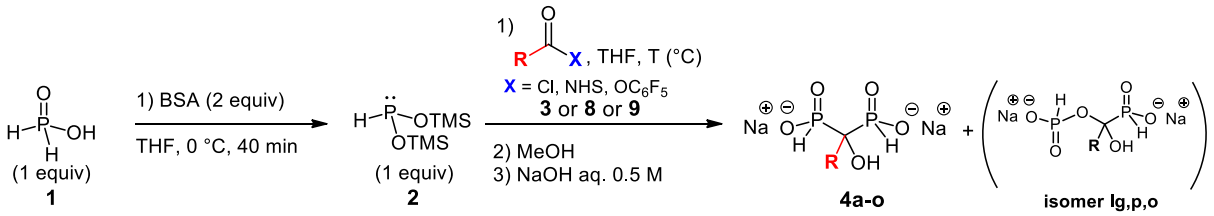

| entry | trivalent derivative **3** or **6** | temp | Time[b] | HMBPi **4** or **7** | Yield[c] (%) |
|---|---|---|---|---|---|
| 1 |  **3a** | 0 °C | 20 min |  **4a** | 91 |
| 2 |  **6a** | 0 °C | 5 min | | 90 |
| 3 |  **3b** | 0 °C | 20 min |  **4b** | 95 |
| 4 |  **6b** | 0 °C | 9 min | | 86 |
| 5 |  **3f** | 0 °C | 20 min |  **4f** | 87 |
| 6 |  **6f** | 0 °C | 10 min | | 92 |
| 7 |  | 0 °C to rt | 6h |  **7a** | 89 |
| 8 |  | 0 °C to rt | 4h |  **7b** | 86 |

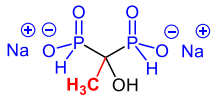
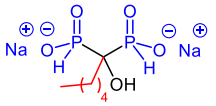
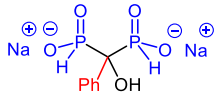
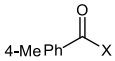
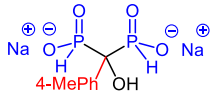
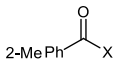
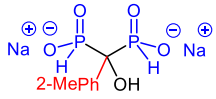
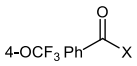
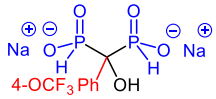
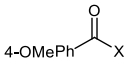
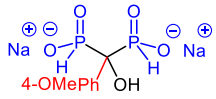
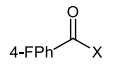
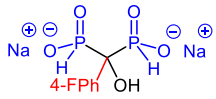
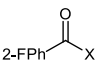
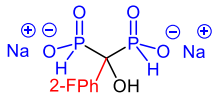
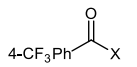
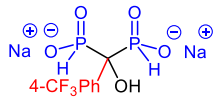
[a]Reaction conditions: **1** (10 mmol), BSA (20 mmol), **3** (5 mmol), THF, Ar. Concentrations were adjusted depending on addition method and temperature in order to obtain sufficient solution volumes to allow the reaction occurring. For details see experimental section. [b] The reaction completion was monitored by $^{31}P\{^{1}H\}$ and $^{31}P$ NMR; the indicated time includes the time of addition. [c]Isolated yield of HMBPi **4a,b,f** or **7a,b**.

**Reaction on activated esters.** Another study was then considered and the objective was to evaluate the reactivity of other trivalent substrates such as esters. Indeed, the reaction between BTSP **2** and esters should be easier to control due to their lesser reactivity. However no reaction occurred when an aliphatic or aromatic esters with electron-donating groups were chosen. As a result, we opted for the use of activated esters **8-9** with electron-withdrawing groups which would be more reactive than conventional esters but less than acyl chlorides or anhydrides (Table 3).

The syntheses of activated esters as NHS esters **8** and pentafluorophenyl (PFP) esters **9** were firstly performed under standard conditions and the corresponding esters were obtained in excellent yields (see the experimental section for details).[15]

**Table 3** Reaction between activated esters **8** and **9** and hypophosphorous acid **1** in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA)[a]




| entry | electrophile | X | temp | Time[c] | HMBPi **4** | Isomer **I** (%)[d] | Yield[e] (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | **3a**: X = Cl | 0°C | 20 min |  | - | 91 |
| 2 | | **8a**: X = NHS[b] | 0°C to rt | 18h | | - | 90 |
| 3 | | **9a**: X = $OC_6F_5$ | 0°C to rt | 5h | **4a** | - | 95 |
| 4 |  | **3d**: X = Cl | 0°C | 20 min |  | - | 86 |
| 5 | | **8d**: X = NHS | 0°C to rt | 18h | | - | 87 |
| 6 | | **9d**: X = $OC_6F_5$ | 0°C to rt | 5h | **4d** | - | 93 |
| 7 |  | **3f**: X = Cl | 0°C | 20 min |  | - | 87 |
| 8 | | **8f**: X = NHS[b] | 0°C to rt | 18h | | - | 85 |
| 9 | | **9f**: X = $OC_6F_5$[b] | 0°C to rt | 5h | **4f** | - | 84 |
| 10 |  | **3i**: X = Cl | 0°C | 20 min |  | - | 95 |
| 11 | | **8i**: X = NHS[b] | 0°C to rt | 18h | | - | 80 |
| 12 | | **9i**: X = $OC_6F_5$ | 0°C to rt | 5h | **4i** | - | 86 |
| 13 |  | **3g**: X = Cl | 0°C | 20 min |  | 32 | 67 |
| 14 | | **8g**: X = NHS[b] | 0°C to rt | 18h | | 23 | 61 |
| 15 | | **9g**: X = $OC_6F_5$ | 0°C to rt | 5h | **4g** | - | 60 |
| 16 |  | **3n**: X = Cl | 0°C | 20 min |  | - | 74 |
| 17 | | **8n**: X = NHS[b] | 0°C to rt | 4h | | - | 71 |
| 18 | | **9n**: X = $OC_6F_5$ | 0°C to rt | 4h | **4n** | - | 77 |
| 19 |  | **3m**: X = Cl | 0°C | 20 min |  | - | 88 |
| 20 | | **8m**: X = NHS[b] | 0°C to rt | 6h30 | | - | 58 |
| 21 | | **9m**: X = $OC_6F_5$[b] | 0°C to rt | 6h30 | **4m** | - | 61 |
| 22 |  | **3r**: X = Cl | 0°C | 20 min |  | - | 85 |
| 23 | | **8r**: X = NHS[b] | 0°C to rt | 5h | | - | 91 |
| 24 | | **9r**: X = $OC_6F_5$ | 0°C to rt | 4h | **4r** | - | 86 |
| 25 |  | **3p**: X = Cl | 0°C | 20 min |  | 16 | 67 |
| 26 | | **8p**: X = NHS[b] | 0°C to rt | 5h | | 3 | 93 |
| 27 | | **9p**: X = $OC_6F_5$ | 0°C to rt | 4h | **4p** | 5 | 94 |
| 28 |  | **3o**: X = Cl | 0°C | 20 min |  | 52 | 37 |
| 29 | | **8o**: X = NHS[b] | 0°C to rt | 4h | | 16 | 30 |
| 30 | | **9o**: X = $OC_6F_5$ | 0°C to rt | 4h | **4o** | 16 | 48 |

[a]Reaction conditions: **1** (10 mmol), BSA (20 mmol), **8-9** (5 mmol), THF, Ar. [b]The concentrations were adjusted in order to solubilize the various activated esters. [c]The reaction completions were monitored by $^{31}P\{^1H\}$ and $^{31}P$ NMR; the indicated time includes the time of addition. [d]NMR ratio in crude mixture. [e]Isolated yields of HMBPi **4a-o**.

Several aliphatic, aromatic activated esters which were substituted by an electron-donating or an electron-withdrawing group at the *ortho*- or *para*- position were tested. As a general trend, from the reaction on activated esters permits to form HMBPi in good or even better yields than those obtained with acyl chlorides. However, the reaction rates appeared slower, as the reaction completions were observed after 5h for the PFP esters and 18h for the NHS esters. Indeed, after adding the silylated phosphonite at 0 °C, the temperature was increased at room temperature in order to reach total conversion. Otherwise, the degradation of the phosphonite occurred faster than the expected reaction. Furthermore, the reaction between the silylated phosphonite with the activated ester NHS is faster (4h) in the presence of electron-withdrawing groups at the *para*- and *ortho*- positions.

The first reactions were carried out between the aliphatic activated esters (**8a,d**; **9a,d**) and BTSP **2** under the optimal conditions B (Table 3, entries 2,3,5,6). In all cases, the corresponding bisphosphinates **4a** and **4d** were isolated in excellent yields (**4a**: 90% and 95%; **4d**: 87% and 93%). We even observed better yields for aliphatic bisphosphinates starting from the PFP esters **9**. The reaction was also successful in the presence of unsubstituted aromatic activated esters **8f** and **9f** (85% and 84% *versus* 87% from acyl chloride **3f**) (Table 3, entries 8,9 *versus* 7).

Various substituted aromatic activated esters **8** and **9** were studied under the optimized conditions (entries 10-30) and the corresponding bisphosphinates were isolated in moderate to excellent yields (30% to 94%) (Table 3, entries 10-30). The presence of an alkyl group at the *para*- position of the activated esters **8i** and **9i** provided the expected HMBPi **4i** in very good yields (80% and 86%). However a slight lower yield was observed for **4g,** bearing a methyl in *ortho*- position, compared to those obtained from acyl chloride (61% and 60% *versus* 67%) (Table 3, entries 13-15). In this case, we considerable prevented the formation of the phosphinylphosphonate isomer **Ig** (23% of isomer for NHS and no isomer for PFP *versus* 32% for acyl chloride). Nevertheless, we noted that BTSP **2** and the final product can unfortunately decompose into silylated phosphorous acid over time due to the slower reaction rate. This observation explains the yield of 61% starting from PFP ester after 18h, even if no isomer **Ig** was formed.

In the presence of 4-trifluoromethoxy group at the *para*- position of the activated esters **8n-9n**, the reaction gives the desired product **4n** in the indicated similar yields (71% and 77%), (Table 3, entries 17-18). Moreover, concerning the presence of methoxy group, the corresponding bisphosphinates **4m** were isolated in moderate yields (58% and 61%) while the same product **4m** starting from acyl chloride **3m** was obtained with an excellent efficiency (86%) (Table 3, entries 19-21). This can be explained by the presence of the electron-donating group which decreases the reactivity of the trivalent electrophile.

In the presence of *para*-fluoro- substituent on the activated esters **8r-9r**, the reaction also successfully led to the expected bisphosphinate **4r** in excellent yields (91% and 86%), (Table 3, entries 23-24).

Then, we decided to evaluate the reactivity of specific substituted aromatic substrates for which a significant amount of phosphinylphosphonate isomer **I** was observed in acyl chloride series. Thus, the

substitution of an electron-withdrawing group at the *ortho*- position of the aromatic activated esters **8p-9p** afforded the bisphosphinate **4p** in an excellent yield (93% and 94% *versus* 67% starting from acyl chloride **3p**) (Table 3, entries 25-27). A minor quantity of by-product **Ip** was only detected when the reaction was carried out on those activated esters **8p** and **9p**.

The reaction was also conducted in the presence of the esters **8o** and **9o** substituted by a highly electro-withdrawing 4-trifluoromethyl group. HMBPi **4o** was obtained in yields of 30% and 47% starting from **8o** and **9o** respectively. These results are in accordance with those obtained from the corresponding acyl chloride **3o** (37%). These yields are moderate probably due to the high electronegativity of this substituent (Table 3, entries 28-30). Moreover, starting from **3o**, a large amount of the phosphinylphosphonate isomer **Io** was detected (52%) as well as the disproportionation of BTSP into silylated phosphorous acid (11%). In contrast, only 16% of isomer **Io** was observed starting from **8o** and **9o** while a significant quantity of silylated phosphorous acid were formed due to their lack of reactivity. However, the synthesis of HMBPi **4o** from **9o** remains much better than those obtained from the corresponding acyl chloride **3o**.

In our past study, we have shown the phosphinylphosphinate **I** could be produced in larger amount when the silylated α-ketophosphinate **II** was *in situ* generated in high quantity.[10a] When the reactions were performed starting from acyl chlorides, a high exothermicity was indeed observed with fast reaction rates since a total conversions were reached at the end of acyl chloride additions. In the present study, the use of activated ester allowed to decrease the reaction rates which formed the silylated α-ketophosphinate **II**. In those conditions, the side reactions seemed to be limited. However, the disproportionation of BTSP could also take place if the reaction rate became too slow.

## CONCLUSION

In conclusion, we proposed an efficient easily handled methodology which successfully gave various 1-hydroxymethylene-1,1-bis(*H*-phosphinates) HMBPi. These optimized conditions could be applied onto various trivalent derivative substrates as acyl chlorides as well as acid anhydrides and activated esters. Moreover, depending on the nature of the starting materials, we can choose the adequate electrophile in order to manage the reactivity. For the synthesis of HMBPi starting from acid anhydrides, the exothermicity of the reaction can be perfectly controlled and no side product was observed. Furthermore, the use of cyclic acid anhydrides offers the advantage to provide HMBPi bearing a carboxylic acid on its side chain which could be an anchor for the synthesis of more functionalized molecules. NHS and PFP esters exhibit also several advantages such as their easy preparation, their relative stability which permits to preserve and to purify them. So they can be adapted to several types of substrates. Indeed, the reaction could be implemented on sensitive functionalized substrates which are incompatible with the preparation of an acyl chloride. Moreover, the formation of side product as isomer could be limited depending on the nature of the trivalent derivative into consideration.

This methodology should allow us to access to other biological relevant bisphosphonate analogues. Their synthesis and biological evaluation will be reported soon.

## EXPERIMENTAL SECTION

**General.** Reagents were purchased from common commercial suppliers (*Sigma-Aldrich, Alfa Aesar, Acros Organics*) and used as delivered. All solvents were extra-dried grade prior used. *N,O*-bis(trimethylsilyl)acetamide (BSA) was purchased from *Alfa Aesar* (LOT: J24T014). Anhydrous $H_3PO_2$ was prepared from commercially aqueous $H_3PO_2$ solution (50% w/w) according to the procedure reported by Montchamp *et al.*[16] Reactions requiring inert conditions were carried out in flame-dried glassware under an argon atmosphere.

NMR spectra were recorded at 20 °C on a Bruker Avance-III-400 spectrometer ($^1$H: 400 MHz, $^{13}$C: 101 MHz, $^{31}$P: 162 MHz, $^{19}$F: 377 MHz). Chemical shifts (δ) were given in ppm, the number of protons (n) for a given resonance was indicated by nH, and coupling constants *J* in Hz. $^1$H NMR spectra were calibrated on non-deuterated solvent residual peak ($H_2O$: 4.79 ppm) while $H_3PO_4$ (85% in water) was used as an external standard for $^{31}$P NMR notably for the reaction monitoring. The following abbreviations were used for $^1$H, $^{13}$C, $^{31}$P and $^{19}$F NMR spectra to indicate the signal multiplicity: s (singlet), bs (broad singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets), dm (doublet of multiplets), ddm (doublet of doublets of multiplets) and m (multiplet). All $^{13}$C NMR spectra were measured with $^1$H-decoupling while $^{31}$P and $^{19}$F NMR spectra were measured with $^1$H coupling and $^1$H decoupling. $^1$H NMR experiments with water presaturation were performed with $D_1$ = 2 s and 128 scans. The reactions were followed by $^{31}$P and $^{31}$P{$^1$H} NMR experiments (the spectra were recorded without lock and shims). High-resolution mass spectra (HRMS) were performed on a Bruker maXis mass spectrometer in negative (ESI-) or positive (ESI+) mode (ESI) by the "Fédération de Recherche" ICOA/CBM (FR2708) platform. MS analyses were performed using a Q-TOF Impact HD mass spectrometer equipped with the electrospray (ESI) ion source (Bruker Daltonics). The instrument was operated in the negative or positive mode with an ESI source on a Q-TOF mass spectrometer with an accuracy tolerance of 2 ppm. The mass profiles obtained by ESI-MS were analyzed using DataAnalysis software (Bruker Daltonics). Infrared spectra were recorded on a *ThermoFisher scientific* Nicolet 380 FT-IR Spectrometer. Smart OMNI-Sampler Germanium ATR Sampling accessory was used. The Smart OMNI-Sampler utilizes an extremely rugged germanium ATR crystal. The wave numbers were expressed in $cm^{-1}$ and comprised between 4000 and 675 $cm^{-1}$. The samples were analyzed neat. The following abbreviations were used for IR spectra to indicate the signal intensities: w (weak), m (medium), s (strong), br (broad). The melting point of HMBPi cannot be measured because the disodium salts decomposed up to 250 °C.

Thin Layer Chromatography were performed on commercial silica plates (silica-coated aluminum plates of MERK 5179, 250 mesh) with fluorescent indicator 60 PF254, 0.25 mm thick and UV revealed at 254 nm and a basic solution of $KMnO_4$.

**Synthesis of activated esters 8 and 9.**

To a solution of carboxylic acid (8.00 mmol, 1.00 equiv.) and NHS or pentafluorophenol (12.0 mmol, 1.50 equiv.) in anhydrous $CH_2Cl_2$ (32.0 mL) at 0 °C were added EDC (12.0 mmol, 1.50 equiv.) and DMAP (16.0 mmol, 2.00 equiv.). The mixture was stirred for 16h at room temperature. The organic layer was successively washed twice with an aqueous solution of HCl 1 M and a saturated aqueous solution of $NaHCO_3$. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to form a pure product. The activated esters were synthesized according the reported procedure and were used directly for the synthesis of bisphosphinates **4** without any further purification.

**2,5-dioxopyrrolidin-1-yl acetate 8a.** White solid (1.26 g, 100% yield). $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.91 – 2.75 (m, 4H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$,101 MHz) δ 169.2 (2C), 165.6, 25.6 (2C), 17.6. These data are in agreement with those previously reported.[17]

**2,5-dioxopyrrolidin-1-yl hexanoate 8d.** White solid (1.69 g, 99% yield). $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.88 – 2.76 (m, 4H), 2.58 (t, 2H, J = 7.5 Hz), 1.79 – 1.69 (m, 2H), 1.43 – 1.29 (m, 4H), 0.90 (t, 3H, J = 7.2 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$,101 MHz) δ 169.3 (2C), 168.8, 31.0 (2C), 25.7 (2C), 24.4, 22.3, 14.0. MS (ESI+) m/z: 214.10 $[M+H]^+$. HRMS (ESI+) m/z: $[M+H]^+$ Calcd. for $[C_{10}H_{16}NO_4]$: 214.1074, found: 214.1072.

**2,5-dioxopyrrolidin-1-yl benzoate 8f.** White solid (1.73 g, 100% yield). $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.18 – 8.11 (m, 2H), 7.71 – 7.65 (m, 1H), 7.55 – 7.48 (m, 2H), 3.01 – 2.83 (m, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$,101 MHz) δ 169.3 (2C), 161.9, 135.0, 130.6 (2C), 128.9 (2C), 125.1, 25.7 (2C). These data are in agreement with those previously reported.[18]

**2,5-Dioxopyrrolidin-1-yl 4-methylbenzoate 8i.** White solid (1.81 g, 97% yield). $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, 2H, J = 8.3 Hz), 7.31 (d, 2H, J = 8.0 Hz), 2.99 – 2.84 (m, 4H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$,101 MHz) δ 169.4 (2C), 161.9, 146.1, 130.6 (2C), 129.6 (2C), 122.3, 25.6 (2C), 21.9. These data are in agreement with those previously reported.[18]

**2,5-Dioxopyrrolidin-1-yl 2-methylbenzoate 8g.** White solid (1.86 g, 100% yield). $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.12 (dd, 1H, J = 8.3 Hz, J = 1.4 Hz), 7.58 – 7.47 (m, 1H), 7.36 – 7.29 (m, 2H), 2.90 – 2.76 (m, 4H), 2.62 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$,101 MHz) δ 169.4 (2C), 162.1, 142.1, 134.0, 132.0, 131.4, 126.1, 124.3, 25.7 (2C), 21.6. MS (ESI+) m/z: 234.07 $[M+H]^+$. HRMS (ESI+) m/z: $[M+H]^+$ Calcd. for $[C_{12}H_{12}NO_4]$: 234.0761, found: 234.0760.

**2,5-dioxopyrrolidin-1-yl 4-methoxybenzoate 8m.** White solid (1.91 g, 96% yield). $^1$H NMR ($CDCl_3$, 400 MHz) δ 8.13 – 8.05 (m, 2H), 7.01 – 6.93 (m, 2H), 3.93 – 3.85 (m, 4H), 2.89 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$,101 MHz) δ 169.5 (2C), 164.9, 161.5, 132.9 (2C), 117.1, 114.2 (2C), 55.6, 25.7 (2C). These data are in agreement with those previously reported.[19]

**2,5-dioxopyrrolidin-1-yl 4-(trifluoromethoxy)benzoate 8n.** White solid (2.38 g, 98% yield). $^{19}F\{^1H\}$ NMR ($CDCl_3$, 377 MHz) δ -57.6 (s). $^{19}$F NMR ($CDCl_3$, 377 MHz) δ -57.6 (bs). $^1$H NMR ($CDCl_3$, 400

MHz) δ 8.20 (d, 2H, J = 8.8 Hz), 7.35 (d, 2H, J = 8.5 Hz), 3.00 – 2.85 (m, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 169.0 (2C), 160.8, 154.0 (d, 1C, J = 1.5 Hz), 132.8 (2C), 123.5, 120.6 (2C), 120.2 (q, 1C, J = 259.6 Hz), 25.7 (2C). MS (ESI+) m/z: 304.04 $[M+H]^+$. HRMS (ESI+) m/z: $[M+H]^+$ Calcd. for $[C_{12}H_9F_3NO_5]$: 304.0427, found: 304.0427.

**2,5-dioxopyrrolidin-1-yl 4-fluorobenzoate 8r.** White solid (1.88 g, 99% yield). $^{19}F\{1H\}$ NMR ($CDCl_3$, 377 MHz) δ -101.3 (s). $^{19}F$ NMR ($CDCl_3$, 377 MHz) δ -101.2 – -101.4 (m). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.21 – 8.13 (m, 2H), 7.24 – 7.16 (m, 2H), 2.99 – 2.84 (m, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 169.2 (2C), 166.9 (d, 1C, J = 257.8 Hz), 160.9, 133.4 (d, 2C, J = 9.8 Hz), 121.4, 116.3 (d, 2C, J = 22.3 Hz), 25.7 (2C). These data are in agreement with those previously reported.[19]

**2,5-Dioxopyrrolidin-1-yl 2-fluorobenzoate 8p.** White solid (1.86 g, 98% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -105.3 (s). $^{19}F$ NMR ($CDCl_3$, 377 MHz) δ -105.3 – -105.4 (m). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.14 – 8.02 (m, 1H), 7.74 – 7.61 (m, 1H), 7.34 – 7.27 (m, 2H), 3.01 – 2.76 (m, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 169.1 (2C), 162.5 (d, 1C, J = 263.2 Hz), 159.3, 136.8 (d, 1C, J = 9.3 Hz), 132.6, 124.5, 117.4 (d, 1C J = 21.9 Hz), 113.8 (d, 1C, J = 9.3 Hz), 25.6 (2C). These data are in agreement with those previously reported.[20]

**2,5-dioxopyrrolidin-1-yl 4-(trifluoromethyl)benzoate 8o.** White solid (2.23 g, 97% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -63.5 (s). $^{19}F$ NMR ($CDCl_3$, 377 MHz) δ -63.5 (bs). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, 2H, J = 8.1 Hz), 7.80 (d, 2H, J = 8.2 Hz), 2.91 – 2.83 (m, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 168.9 (2C), 160.9, 136.2 (q, 1C, J = 33.2 Hz), 131.0 (2C), 128.5, 125.9 (q, 2C, J = 3.7 Hz), 123.3 (q, 1C, J = 273.2 Hz), 25.7 (2C). These data are in agreement with those previously reported.[20]

**Pentafluorophenyl acetate 9a.** Pale yellow oil (1.81 g, 100% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -152.8 (dm, 2F, J = 17.3 Hz), -158.1 (t, 1F, J = 21.7 Hz), -162.4 (ddm, 2F, J = 21.8 Hz, 17.3 Hz). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 166.8, 141.3 (dm, 2C, J = 251.3 Hz), 139.7 (dtt, 1C, J = 252.3 Hz, J = 13.5 Hz, J = 4.1 Hz), 139.7 (dm, 2C, J = 252.1 Hz), 125.3 (tdt, 1C, J = 14.5 Hz, J = 4.3 Hz, J = 2.0 Hz), 19.9. These data are in agreement with those previously reported. [21]

**Pentafluorophenyl hexanoate 9d.** Pale yellow oil (2.26 g, 100% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -153.1 (dm, 2F, J = 18.7 Hz), -158.4 – -158.8 (m, 1F), -162.7 – 163.0 (m, 2F). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 2.66 (t, 2H, J = 7.4 Hz), 1.83 – 1.74 (m, 2H), 1.46 – 1.33 (m, 4H), 0.93 (t, 3H, J = 6.9 Hz). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 169.9, 141.4 (dm, 2C, J = 250.9 Hz), 139.5 (dtt, 1C, J = 253.9 Hz, J = 13.3 Hz, J = 3.9 Hz), 138.1 (dm, 2C, J = 254.5 Hz), 125.3 (tdt, 1C, J = 14.2 Hz, J = 4.1 Hz, J = 1.8 Hz), 33.4, 31.2, 24.6, 22.4, 13.9. MS (ESI+) m/z: 283.07 $[M+H]^+$. HRMS (ESI+) m/z: $[M+H]^+$ Calcd. for $[C_{12}H_{12}F_5O_2]$: 283.0752, found: 283.0752.

**Pentafluorophenyl benzoate 9f.** Pale yellow solid (2.26 g, 98% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -152.4 (dm, 2F, J = 17.3 Hz), -157.9 (t, 1F, J = 21.7 Hz), -162.3 (ddm, 2F, J = 21.8 Hz, 17.3 Hz). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.24 – 8.18 (m, 2H), 7.75 – 7.68 (m, 1H), 7.59 – 7.52 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 162.6, 141.3 (dm, 2C, J = 252.3 Hz), 139.4 (dtt, 1C, J = 252.6 Hz, J = 13.2 Hz, J = 4.1 Hz), 139.2 (dm, 2C, J = 252.8 Hz), 134.8, 130.8 (2C), 128.9 (2C), 125.1 (tdt, 1C, J = 14.5 Hz, J = 4.3 Hz, J = 2.0 Hz), 19.7. These data are in agreement with those previously reported. [22]

**Pentafluorophenyl 4-methylbenzoate 9i.** Pale yellow oil (2.39 g, 99% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -152.6 (dm, 2F, J = 17.2 Hz), -158.3 (t, 1F, J = 21.7 Hz), -162.4 – 162.7 (m, 2F). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, 2H, J = 8.2 Hz), 7.35 (d, 2H, J = 8.0 Hz), 2.48 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 162.5, 141.4 (dm, 2C, J = 252.3 Hz), 139.5 (dm, 1C, J = 253.0 Hz), 138.0 (dm, 2C, J = 254.3 Hz), 130.8 (2C), 129.6 (2C), 125.7 – 125.2 (m, 1C), 145.9, 124.2, 21.8. MS (ESI+) m/z: 303.04 $[M+H]^+$. HRMS (ESI+) m/z: $[M+H]^+$ Calcd. for $[C_{14}H_8F_5O_2]$: 303.0439, found: 303.0439.

**Pentafluorophenyl 2-methylbenzoate 9g.** White solid (2.39 g, 99% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -152.5 (dm, 2F, J = 22.1 Hz), -158.4 (t, 1F, J = 21.6 Hz), -162.5 – 162.7 (ddm, 2F, J = 21.6 Hz, 17.3 Hz). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.19 (dd, 1H, J = 8.2 Hz, J = 1.4 Hz), 7.55 (dd, 1H, J = 7.6 Hz, J = 1.4 Hz), 7.42 – 7.32 (m, 2H), 2.66 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 162.8, 142.3, 141.5 (dm, 2C, J = 251.5 Hz), 139.5 (dm, 1C, J = 253.1 Hz), 139.2 (dm, 2C, J = 253.4 Hz), 133.8, 132.2, 131.7, 126.2, 125.6 – 125.2 (m, 1C), 126.0, 21.7. MS (ESI+) m/z: 303.04 $[M+H]^+$. HRMS (ESI+) m/z: $[M+H]^+$ Calcd. for $[C_{14}H_8F_5O_2]$: 303.0439, found: 303.0438.

**Pentafluorophenyl 4-(trifluoromethoxy)benzoate 9n.** White solid (2.95 g, 99% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -57.6 (s, 3F), -152.4 (dm, 2F, J = 17.3 Hz), -157.4 (t, 1F, J = 21.7 Hz), -162.0 (ddm, 2F, J = 21.2 Hz, J =17.5 Hz). $^{19}F$ NMR ($CDCl_3$, 377 MHz) δ -57.6 (bs), -152.4 (dm, 2F, J = 17.3 Hz), -157.4 (t, 1F, J = 21.7 Hz), -162.0 (ddm, 2F, J = 21.2 Hz, J =17.5 Hz). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, 2H, J = 8.8 Hz), 7. 38 (d, 2H, J = 8.5 Hz). $^{13}C\{^{1}H\}$NMR ($CDCl_3$,101 MHz) δ 161.4, 154.0, 141.4 (dm, 2C, J = 253.8 Hz), 139.7 (dm, 1C, J = 255.5 Hz), 138.0 (dm, 2C, J = 252.2 Hz), 132.9 (2C), 125.5 – 124.9 (m, 1C), 125.2, 120.6 (2C), 120.3 (q, 1C, J = 259.5 Hz). MS (ESI+) m/z: 373.02 $[M+H]^+$. HRMS (ESI+) m/z: $[M+H]^+$ Calcd. for $[C_{14}H_5F_8O_3]$: 373.0105, found: 373.0104.

**Pentafluorophenyl 4-methoxybenzoate 9m.** White solid (2.49 g, 98% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -152.6 (dm, 2F, J = 17.2 Hz), -158.5 (t, 1F, J = 21.7 Hz), -162.7 (ddm, 2F, J = 21.9 Hz, J =17.1 Hz). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, 2H, J = 8.7 Hz), 7.01 (d, 2H, J = 8.8 Hz), 3.91 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 164.8, 162.3, 141.4 (dm, 2C, J = 255.9 Hz), 139.4 (dm, 1C, J = 253.0 Hz), 137.9 (dm, 2C, J = 251.6 Hz), 133.0 (2C), 125.8 – 125.3 (m, 1C), 119.1, 114.2 (2C), 55.6. These data are in agreement with those previously reported.[23]

**Pentafluorophenyl 4-fluorobenzoate 9r.** White solid (2.43 g, 99% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -102.0 (s, 1F), -152.6 (dm, 2F, J = 18.5 Hz), -157.9 (t, 1F, J = 21.6 Hz), -162.3 (ddm, 2F, J = 20.7 Hz, J =18.3 Hz). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.29 – 8.19 (m, 2H), 7.23 (t, 2H, J = 8.6 Hz). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 166.8 (d, 1C, J = 257.4 Hz), 161.6, 141.4 (dm, 2C, J = 251.5 Hz), 139.6 (dm, 1C, J = 253.6 Hz), 138.0 (dm, 2C, J = 252.5 Hz), 133.5 (d, 2C, J = 9.8 Hz), 125.5 – 124.9 (m, 1C), 123.2 (d, 1C, J = 3.0 Hz), 116.3 (d, 2C, J = 22.3 Hz). These data are in agreement with those previously reported. [24]

**Pentafluorophenyl 2-fluorobenzoate 9p.** White solid (2.38 g, 97% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -106.5 (s, 1F), -152.3 (dm, 2F, J = 17.0 Hz), -157.8 (t, 1F, J = 21.6 Hz), -162.0 – 162.7 (ddm, 2F, J = 21.8 Hz, J = 16.9 Hz). $^{19}F$ NMR ($CDCl_3$, 377 MHz) δ -106.5 – 106.6 (m), -152.3 (dm, 2F, J = 17.0 Hz), -157.8 (t, 1F, J = 21.6 Hz), -162.0 – 162.7 (ddm, 2F, J = 21.8 Hz, J = 16.9 Hz). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.12 (td, 1H, J = 7.7 Hz, J = 1.8 Hz), 7.73 – 7.64 (m, 1H), 7.32 (dd, 1H, J = 7.8 Hz, J = 1.0 Hz), 7.28 – 7.22 (m, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 162.7 (d, 1C, J = 263.9 Hz), 159.9 (d, 1C, J = 4.1 Hz), 141.4 (dm, 2C, J = 251.9 Hz), 139.7 (dm, 1C, J = 253.6 Hz), 137.8 (dm, 2C, J = 254.8 Hz), 136.5 (d, 1C, J = 9.3 Hz), 132.8, 125.3 – 124.8 (m, 1C), 124.4 (d, 1C, J = 3.9 Hz), 117.5 (d, 1C, J = 21.8 Hz), 115.6 (d, 1C, J = 9.3 Hz). MS (ESI+) m/z: 307.01 $[M+H]^+$. HRMS (ESI+) m/z: $[M+H]^+$ Calcd. for $[C_{13}H_5F_6O_2]$: 307.0188, found: 307.0187.

**Pentafluorophenyl 4-(trifluoromethyl)benzoate 9o.** White solid (2.74 g, 96% yield). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 377 MHz) δ -63.5 (s, 3F), -152.5 (dm, 2F, J = 17.2 Hz), -157.3 (t, 1F, J = 21.6 Hz), -162.0 (ddm, 2F, J = 21.6 Hz, J = 17.3 Hz). $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 8.33 (d, 2H, J = 8.1 Hz), 7.83 (d, 2H, J = 8.2 Hz). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,101 MHz) δ 161.5, 141.5 (dm, 2C, J = 253.6 Hz), 139.7 (dm, 1C, J = 255.1 Hz), 138.1 (dm, 2C, J = 252.4 Hz), 136.1 (q, 1C, J = 32.8 Hz),131.1 (2C), 130.2, 126.0 (2C), 125.4 – 124.8 (m, 1C), 123.3 (q, 1C, J = 260.5 Hz). These data are in agreement with those previously reported.[22]

**Synthesis of HMBPi 4a-o, 5a-b** and **7a-b.**

**General procedure for method A.** To a dry and argon flushed 100 mL three-necked flask equipped with a thermometer, an argon inlet and an addition funnel, were successively introduced anhydrous hypophosphorous acid **1** (660 mg, 10.0 mmol, 2.00 equiv.) and anhydrous tetrahydrofuran (1.00 mL) under argon atmosphere. *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (3.055 g, 20.0 mmol, 4.00 equiv.) was added dropwise at 0 °C under argon and the mixture was stirred for 40 minutes. The reaction conversion was monitored by $^{31}P$ NMR spectroscopy. To another dry and argon flushed 100 mL three-necked flask equipped with a thermometer, an argon inlet and an addition funnel, were successively introduced acyl chloride **3** (5.00 mmol, 1.00 equiv.) and anhydrous tetrahydrofuran (2.25 mL for acyl chloride and 1.00 mL for acid anhydride). The bis(trimethylsilyl)phosphonite **2** was added dropwise (at -70 °C for acyl chloride and 0 °C for acid anhydride). The reaction was monitored by $^{31}P$ NMR spectroscopy. The

reaction mixture was quenched with methanol (10.0 mL) at 0 °C and the mixture was stirred for 25 minutes. Then, methanol was evaporated under reduced pressure. The residue was dissolved in water (2mL) and the pH was adjusted to 7.0 by adding an aqueous solution of sodium hydroxide (0.5 M) and the solution was lyophilized. The crude residue was washed with methanol ($Na_2HPO_3$ removal) and ethanol (acetamide removal) to give a pure solid **4**.

**Optimized experimental procedure for method B.** To a dry and argon flushed 100 mL three-necked flask equipped with a thermometer, an argon inlet and an addition funnel, were successively introduced anhydrous hypophosphorous acid **1** (660 mg, 10.0 mmol, 2.00 equiv.) and anhydrous tetrahydrofuran (2.00 mL) under argon atmosphere. *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (3.055 g, 20.0 mmol, 4.00 equiv.) was added dropwise at 0 °C under argon and the mixture was stirred for 40 minutes. The reaction conversion was monitored by $^{31}P$ NMR spectroscopy. A solution of acyl chloride **3** or acid anhydride **6** or activated ester **8-9** (5.00 mmol, 1.00 equiv.) in anhydrous tetrahydrofuran (1.00 mL) was added dropwise at 0 °C. The reaction completion was monitored by $^{31}P$ NMR spectroscopy.

For acyl chlorides **3** and acid anhydrides **6** the reaction was already completed after addition except for cyclic acid anhydrides. For cyclic acid anhydrides and activated esters **8-9**, the reaction was stirred at room temperature until reaction completion.

The reaction mixture was quenched with methanol (10.0 mL) at 0 °C and the mixture was stirred for 25 minutes. Then, methanol was evaporated under reduced pressure. The residue was dissolved in water (2mL) and the pH was adjusted to 7.0 by adding an aqueous solution of sodium hydroxide (0.5 M) and the solution was lyophilized. The crude residue was washed with methanol ($Na_2HPO_3$ removal) and ethanol (acetamide removal) to give a pure solid **4**.

**1-Hydroxyethane-1,1-bis(*H*-phosphinate) disodium salt 4a.** White powder (0.99 g, 91% yield (from acyl chloride **3a**), 0.98 g, 90% yield (from acid anhydride **6a**), 0.98 g, 90% yield (from NHS ester **8a**), 1.03 g, 95% yield (from pentafluorophenyl ester **9a**)). IR (neat, $cm^{-1}$) ν = 3301br, 2375w, 1187s, 1072m, 962m, 742m. $^{31}P\{^1H\}$ NMR ($D_2O$, 162 MHz) δ 25.9 (s). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 25.9 (dm, P-H, J = 524.8 Hz). $^1H$ NMR ($D_2O$, 400 MHz) δ 6.84 (dm, 2H, J= 524.8 Hz), 1.31 (t, 3H, J = 15.3 Hz). $^{13}C\{^1H\}$ NMR ($D_2O$, 101 MHz) δ 71.4 (t, 1C, J = 96.3 Hz), 14.4. These data are in agreement with those previously reported.[13c]

**1-Hydroxy-2-methylpropane-1,1-bis(*H*-phosphinate) disodium salt 4b.** White powder (1.17 g, 95% yield (from acyl chloride **3b**), 1.06 g, 86% yield (from acid anhydride **7b**). IR (neat, $cm^{-1}$) ν = 3361br, 2969w, 2371w, 1185s, 1106m, 974m, 755m. $^{31}P\{^1H\}$ NMR ($D_2O$, 162 MHz) δ 24.8 (s). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 24.8 (dm, P-H, J = 529.6 Hz). $^1H$ NMR ($D_2O$, 400 MHz) δ 7.02 (dm, 2H, J = 529.6 Hz), 2.39 – 2.22 (m, 1H), 1.11 (d, 6H, J = 6.8 Hz). $^{13}C\{^1H\}$ NMR ($D_2O$, 101 MHz) δ 76.5 (t, 1C, J = 92.8 Hz), 31.1, 17.4 (2C). These data are in agreement with those previously reported.[10]

**1-Hydroxyhexane-1,1-bis(*H*-phosphinate) disodium salt 4d.** White powder (1.17 g, 86% yield (from acyl chloride **3d**), 1.18 g, 87% yield (from NHS ester **9d**), 1.26 g, 93% yield (from PFP ester **10e**). IR (neat, $cm^{-1}$) ν = 3328br, 2956w, 2303w, 1182s, 1105m, 959m, 746w. $^{31}P\{^{1}H\}$ NMR ($D_2O$, 162 MHz) δ 25.1 (s). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 25.1 (dm, P-H, J = 525.6 Hz). $^{1}H$ NMR ($D_2O$, 400 MHz) δ 6.92 (dm, 2H, J = 525.6 Hz), 1.87 – 1.69 (m, 2H), 1.61 –1.43 (m, 2H), 1.38 – 1.18 (m, 4H), 0.93 – 0.75 (m, 3H). $^{13}C\{^{1}H\}$ NMR ($D_2O$, 101 MHz) δ 74.2 (t, 1C, J = 94.9 Hz), 32.0, 30.6, 22.2 (t, 1C, J = 6.5 Hz), 21.8, 13.3. These data are in agreement with those previously reported.[10]

**1-Hydroxy-1-phenylmethane-1,1-bis(*H*-phosphinate) disodium salt 4f.** White powder (1.22 g, 87% yield (from acyl chloride **3f**), 1.29 g, 92% yield (from acid anhydride **6f**), 1.19 g, 85% yield (from NHS ester **8f**), 1.18 g, 84% yield (from PFP ester **9f**)). IR (neat, $cm^{-1}$) ν = 3263br, 2973w, 2317w, 1601w, 1489w, 1446w, 1395w, 1195s, 1119m, 975m, 732m. $^{31}P\{^{1}H\}$ NMR ($D_2O$, 162 MHz) δ 24.4 (s). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 24.4 (dm, P-H, J = 538.2 Hz). $^{1}H$ NMR ($D_2O$, 400 MHz) δ 7.48 – 7.42 (m, 2H), 7.34 (t, 2H, J = 7.0 Hz), 7.26 – 7.16 (m, 1H), 6.94 (dm, 2H, J = 538.2 Hz). $^{13}C\{^{1}H\}$ NMR ($D_2O$, 101 MHz) δ 136.1, 128.5 (2C), 127.2, 125.4 (2C), 77.4 (t, 1C, J = 91.8 Hz). These data are in agreement with those previously reported.[10]

**1-Hydroxy-1-(4-tolyl)methane-1,1-bis(*H*-phosphinate) disodium salt 4i.** White powder **(**1.39 g, 95% yield (from acyl chloride **3i**), 1.17 g, 80% yield (from NHS ester **8i**), 1.26 g, 86% yield (from PFP ester **9i**)). IR (neat, $cm^{-1}$) ν = 3236br, 2978w, 2900w, 2310w, 1647w, 1510w, 1335w, 1188s, 1095s, 976m, 753m. $^{31}P\{^{1}H\}$ NMR ($D_2O$, 162 MHz) δ 24.4 (s). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 24.4 (dm, P-H, J = 537.0 Hz). $^{1}H$ NMR ($D_2O$, 400 MHz) δ 7.42 (dt, 2H, J = 8.1 Hz, J = 1.7 Hz), 7.25 (d, 2H, J = 8.1 Hz), 7.02 (dm, 2H, J = 537.0 Hz), 2.31 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($D_2O$, 101 MHz) δ 137.0 (t, 1C, J = 2.6 Hz), 132.8, 128.8 (2C), 125.3 (t, 2C, J = 4.4 Hz), 77.0 (t, 1C, J = 92.1 Hz), 20.1. These data are in agreement with those previously reported.[10]

**1-Hydroxy-1-(2-tolyl)methane-1,1-bis(*H*-phosphinate) disodium salt 4g.** White powder (0.99 g, 67% yield (from acyl chloride **3g**), 0.90 g, 61% yield (from NHS ester **8g**), 0.89 g, 60% yield (from PFP ester **9g**). IR (neat, $cm^{-1}$) ν = 3217br, 2898m, 2901m, 2327w, 1452w, 1394w, 1178m, 1080s, 975w, 753w. $^{31}P\{^{1}H\}$ NMR ($D_2O$, 162 MHz) δ 24.7 (s). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 24.7 (dm, P-H, J = 540.7 Hz). $^{1}H$ NMR ($D_2O$, 400 MHz) δ 7.65 – 7.58 (m, 1H), 7.28 – 7.14 (m, 3H), 7.12 (dm, 2H, J = 540.7 Hz), 2.56 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($D_2O$, 101 MHz) δ 137.7 – 137.3 (m, 1C), 134.7, 132.7, 127.2, 126.9 (t, 1C, J = 5.3 Hz), 125.4, 80.0 (t, 1C, J = 89.4 Hz), 22.2. These data are in agreement with those previously reported.[10]

**1-Hydroxy-1-(4-trifluoromethoxyphenyl)methane-1,1-bis(*H*-phosphinate) disodium salt 4n.** White powder **(**1.35 g, 74% yield (from acyl chloride **3n**), 1.30 g, 71% yield (from NHS ester **8n**), 1.40 g, 77% yield (from PFP ester **9n**). IR (neat, $cm^{-1}$) ν = 3258br, 2989w, 2315w, 1610w, 1507w, 1192s, 1118m, 1098m, 1056w, 975w, 742w. $^{31}P\{^{1}H\}$ NMR ($D_2O$, 162 MHz) δ 23.8 (s). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 23.8 (dm, P-H, J = 539.3 Hz). $^{19}F$ $\{^{1}H\}$ NMR ($D_2O$, 377 MHz) δ -57.8 (s). $^{19}F$ NMR ($D_2O$, 377 MHz) δ -57.8 (bs); $^{1}H$ NMR ($D_2O$, 400 MHz) δ 7.59 (dm, 2H, J = 8.6 Hz), 7.33 (d, 2H, J = 8.6 Hz), 7.03 (dm, 2H, J = 539.3 Hz). $^{13}C\{^{1}H\}$ NMR ($D_2O$, 101 MHz) δ 147.9 (d, 1C, J = 1.7 Hz), 135.0, 126.8 (t, 2C, J = 4.3 Hz), 120.7 (2C), 120.3 (q, 1C, J = 256.1 Hz), 77.0 (t, 1C, J = 90.9 Hz). These data are in agreement with those previously reported.[10]

**1-Hydroxy-1-(4-methoxyphenyl)methane-1,1-bis(*H*-phosphinate) disodium salt 4m.** White powder (1.36 g, 88% yield (from acyl chloride **3m**), 0.90 g, 58% yield (from NHS ester **8m**), 0.94 g, 61% yield (from PFP ester **9m**). IR (neat, $cm^{-1}$) ν = 3247br, 3001w, 2902w, 2313w, 1609w, 1509m, 1467w, 1191s, 1117m, 1034m, 975w, 740w. $^{31}P\{^{1}H\}$ NMR ($D_2O$, 162 MHz) δ 24.3 (s). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 24.3 (dm, P-H, J = 535.9 Hz); $^{1}H$ NMR ($D_2O$, 400 MHz) δ 7.52 – 7.43 (m, 2H), 7.01 (dm, 2H, J = 535.9 Hz), 7.01 (d, 2H, J = 8.9 Hz), 3.81 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($D_2O$, 101 MHz) δ 157.8, 128.4, 126.7 (t, 2C, J = 4.5 Hz), 113.8 (2C), 76.7 (t, 1C, J = 92.9 Hz), 55.3. These data are in agreement with those previously reported.[10]

**1-Hydroxy-1-(4-fluorophenyl)methane-1,1-bis(*H*-phosphinate) disodium salt 4r.** White powder **(**1.26 g, 85% yield (from acyl chloride **3j**), 1.35 g, 91% yield (from NHS ester **8r**), 1.27 g, 86% yield (from PFP ester **9r**). IR (neat, $cm^{-1}$) ν = 3224br, 2987m, 2309w, 1606w, 1507m, 1194s, 1090s, 1056s, 975w, 748m. $^{31}P\{^{1}H\}$ NMR ($D_2O$, 162 MHz) δ 24.0 (d, J = 2.6 Hz). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 24.0 (dm, P-H, J = 537.5 Hz). $^{19}F$ $\{^{1}H\}$ NMR ($D_2O$, 377 MHz) δ -116.7 – -116.8 (m). $^{19}F$ NMR ($D_2O$, 377 MHz) δ -116.6 – -116.8 (m). $^{1}H$ NMR ($D_2O$, 400 MHz) δ 7.59 – 7.50 (m, 2H), 7.20 – 7.12 (m, 2H), 7.04 (dm, 2H, J = 537.5 Hz). $^{13}C\{^{1}H\}$ NMR ($D_2O$, 101 MHz) δ 161.9 (d, 1C, J = 242.5 Hz), 131.8, 127.4 – 127.0 (m, 2C), 115.1 (d, 2C, J = 21.5 Hz), 77.0 (t, 1C, J = 91.6 Hz). These data are in agreement with those previously reported.[10]

**1-Hydroxy-1-(2-fluorophenyl)methane-1,1-bis(*H*-phosphinate) disodium salt 4p.**

White powder (1.00 g, 67% yield (from acyl chloride **3p**), 1.39 g, 93% yield (from NHS ester **8p**), 1.40 g, 94% yield (from PFP ester **9p**). IR (neat, $cm^{-1}$) ν = 3261br, 3036w, 2325w, 1614w, 1485w, 1447w, 1194s, 1116m, 1089m, 968w, 753w. $^{31}P\{^{1}H\}$ NMR ($D_2O$, 162 MHz) δ 22.0 (d, J = 14.9 Hz). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 22.0 (dm, P-H, J = 549.6 Hz). $^{19}F$ $\{^{1}H\}$ NMR ($D_2O$, 377

MHz) δ -108.8 (t, J = 15.0 Hz). $^{19}$F NMR ($D_2O$, 377 MHz) δ -108.7 – -109.0 (m). $^{1}$H NMR ($D_2O$, 400 MHz) δ 7.65 – 7.51 (m, 1H), 7.41 – 7.29 (m, 1H), 7.29 – 7.19 (m, 1H), 7.17 (dm, 2H, J = 549.6 Hz), 7.16 – 7.05 (m, 1H). $^{13}$C{$^{1}$H} NMR ($D_2O$, 101 MHz) δ 159.1 (dt, 1C, J = 243.9 Hz, J = 3.4 Hz), 129.2 – 129.0 (m, 1C), 128.1 – 127.1 (m, 1C), 124.3, 123.7 (dm, 1C, J = 14.7 Hz), 115.7 (d, 1C, J = 22.6 Hz), 77.4 (td, 1C, J = 87.2 Hz, J = 6.2 Hz). These data are in agreement with those previously reported.[10]

**1-Hydroxy-1-(4-(trifluoromethyl)phenyl)methane-1,1-bis(*H*-phosphinate) disodium salt 4o.**

White powder (0.64 g, 37% yield (from acyl chloride **3o**), (0.52 g, 30% yield (from NHS ester **8o**), 0.83 g, 48% yield (from PFP ester **9o**). IR (neat, cm$^{-1}$) ν = 3321br, 2983w, 2320w, 1651w, 1611w, 1193s, 1116m, 1069s, 977w, 762m. $^{31}$P{$^{1}$H} NMR ($D_2O$, 162 MHz) δ 23.6 (s). $^{31}$P NMR ($D_2O$, 162 MHz) δ 23.6 (dm, P-H, J = 540.4 Hz). $^{19}$F {$^{1}$H} NMR ($D_2O$, 377 MHz) δ -61.9 – -62.3 (m). $^{19}$F NMR ($D_2O$, 377 MHz) δ -61.9 – -62.3 (m); $^{1}$H NMR ($D_2O$, 400 MHz) δ 7.74 – 7.67 (m, 4H), 7.07 (dm, 2H, J = 540.4 Hz). $^{13}$C{$^{1}$H} NMR ($D_2O$, 101 MHz) δ 140.6, 128.3 (dt, 1C, J = 32.0 Hz, J = 2.8 Hz), 125.8 – 125.7 (m, 2C), 125.2 – 125.0 (m, 2C), 124.4 (q, 1C, J = 271.0 Hz), 77.6 (t, 1C, J = 90.0 Hz). These data are in agreement with those previously reported.[10]

**1-Hydroxy-1-(5-azidopentyl)methane-1,1-bis(*H*-phosphinate) disodium salt 5a.** White powder (1.51 g, 96% yield). IR (neat, cm$^{-1}$): 3328br, 2956w, 2303w, 2121w, 1182s, 1105m, 959m, 746w. $^{31}$P{$^{1}$H} NMR ($D_2O$, 162 MHz) δ 24.9 (s). $^{31}$P NMR ($D_2O$, 162 MHz) δ 24.9 (dm, P-H, J = 526.4 Hz). $^{1}$H NMR ($D_2O$, 400 MHz) δ 6.93 (dm, 2H, J = 526.4 Hz), 3.32 (t, 2H, J = 6.2 Hz), 1.89 – 1.73 (m, 2H), 1.69 – 1.50 (m, 4H), 1.44 – 1.31 (m, 2H). $^{13}$C{$^{1}$H} NMR ($D_2O$, 101 MHz) δ 74.1 (t, 1C, J = 94.6 Hz), 51.1, 30.4, 27.7, 26.9, 22.2 (t, 1C, J = 6.5 Hz). MS (ESI-) m/z: 270.04 [M-H]$^-$, 292.02 [M-2H+Na]$^-$, 252.03 [M-H-$H_2O$]$^-$, 227.04 [M-H-$N_3$]$^-$, 204.05 [M-H-$H_3PO_2$]$^-$. HRMS (ESI-) m/z: [M-H]$^-$ Calcd. for [$C_6H_{14}N_3O_5P_2$]: 270.0414, found: 270.0415.

**1-Hydroxy-1-(5-aminopentyl)methane-1,1-bis(*H*-phosphinate) disodium salt 5b.** White solid (0.06 g, quantitative yield). IR (neat, cm$^{-1}$): 3318br, 2952w, 2309w, 1204w, 1178s, 1102m, 975m, 739w. $^{31}$P{$^{1}$H} NMR ($D_2O$, 162 MHz) δ = 24.8 (s).$^{31}$P NMR ($D_2O$, 162 MHz) δ 24.8 (dm, P-H, J = 525.6 Hz). $^{1}$H NMR ($D_2O$, 400 MHz) δ 6.90 (dt, 2H, J = 525.8 Hz, J = 17.8 Hz), 2.95 (t, 2H, J = 7.1 Hz), 1.85 – 1.72 (m, 2H), 1.71 – 1.45 (m, 4H), 1.42 – 1.24 (m, 2H). $^{13}$C{$^{1}$H} NMR ($D_2O$, 101 MHz) δ 74.0 (t, 1C, J = 95.2 Hz), 39.2, 30.1, 26.4, 26.2, 22.0. MS (ESI-) m/z: 244.05 [M-H]$^-$. HRMS (ESI-) m/z: [M-H]$^-$ Calcd. for [$C_6H_{16}NO_5P_2$ ]: 244.0509, found: 244.0513.

**Sodium 4-hydroxy-4,4-bis(*H*-phosphinyl)butanoate 7a.** White powder **(**1.31 g, 89% yield (from succinic anhydride)). IR (neat, $cm^{-1}$): 3320br, 2950w, 2309w, 1725m,1204w, 1178s, 1102m, 975m, 739w. $^{31}P\{^{1}H\}$ NMR ($D_2O$, 162 MHz) δ 25.2 (s). $^{31}P$ NMR ($D_2O$, 162 MHz) δ 25.2 (dm, P-H, J = 526.9 Hz). $^{1}H$ NMR ($D_2O$, 400 MHz) δ 6.90 (dm, 2H, J = 526.9 Hz), 2.54 – 2.42 (m, 2H), 2.14 – 1.93 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($D_2O$, 101 MHz) δ 182.9, 73.4 (t, 1C, J = 95.3 Hz), 31.7 (t, 1C, J = 7.2 Hz), 26.4; MS (ESI-) m/z: 230.98 $[M-H]^-$, 252.96 $[M-2H+Na]^-$, 212.97 $[M-H-H_2O]^-$, 165.00 $[M-H-H_3PO_2]^-$. HRMS (ESI-) m/z: $[M-H]^-$ Calcd. for $[C_4H_9O_7P_2]$: 230.9831, found: 230.9829.

**Sodium 5-hydroxy-5,5-bis(*H*-phosphinyl)pentanoate 7b.** White powder **(**1.34 g, 86% yield (from glutaric anhydride)); IR (neat, $cm^{-1}$): 3321br, 2951w, 2310w, 1725m, 1205w, 1177s, 1100m, 975m, 740w; $^{31}P\{^{1}H\}$ NMR ($D_2O$, 162 MHz) δ 24.9 (s); $^{31}P$ NMR ($D_2O$, 162 MHz) δ 24.9 (dm, PH, J = 526.9 Hz); $^{1}H$ NMR ($D_2O$, 400 MHz) δ 6.92 (dm, 2H, J = 526.9 Hz), 2.25 – 2.07 (m, 2H), 1.89 – 1.70 (m, 4H); $^{13}C\{^{1}H\}$ NMR ($D_2O$, 101 MHz) δ 183.2, 74.0 (t, 1C, J = 94.9 Hz), 38.1, 30.2, 19.9 (t, 1C, J = 7.1 Hz); MS (ESI-) m/z: 245.00 $[M-H]^-$, 266.98 $[M-2H+Na]^-$, 179.01 $[M-H-H_3PO_2]^-$; HRMS (ESI-) m/z: $[M-H]^-$ Calcd. for $[C_5H_{11}O_7P_2]$: 256.9447, found: 256.9444.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Copies of $^{1}H$, $^{13}C\{^{1}H\}$, $^{31}P$ {1H}, $^{31}P$ and $^{19}F$ NMR spectra (PDF)

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## REFERENCES

(1) (a) Iaroshenko, V., Phosphorus in Chemical Biology and Medicinal Chemistry. In Organophosphorus Chemistry: , V. Iaroshenko (Ed.): 2019; pp 499-544; (b) Hudson, H. R.; Wardle, N. J.; Bligh, S. W.A.; Greiner, I.; Grun, A.; Keglevich, G., N-Heterocyclic Dronic Acids: Applications and Synthesis. *Mini Rev. Med. Chem.* **2012,** *12*, 313-325; (c)Abdou, W. M.; Shaddy, A. A., The development of bisphosphonates for therapeutic uses, and bisphosphonate structure-activity consideration *ARKIVOC* **2009,** *ix*, 143-182.

(2) (a) Verron, E.; Gauthier, O.; Janvier, P.; Pilet, P.; Lesoeur, J.; Bujoli, B.; Guicheux, J.; Bouler, J.-M., In vivo bone augmentation in an osteoporotic environment using bisphosphonate-loaded calcium deficient apatite. *Biomaterials* **2010,** *31*, 7776-7784; (b) Galezowska, J.; Gumienna-Kontecka, E., Phosphonates, their complexes and bio-applications: A spectrum of surprising diversity. *Coord. Chem. Rev.* **2012,** *256*, 105-124; (c) Clezardin, P.; Massaia, M., Nitrogen-Containing Bisphosphonates and Cancer Immunotherapy. *Curr. Pharm. Des.* **2010,** *16*, 3007-3014. (d) Braza, M. S.; Klein, B., Anti-tumour immunotherapy with Vγ9Vδ2 T lymphocytes: from the bench to the bedside. *Br. J. Haematol.* **2013,** *160*, 123-132. (e) Giger, E. V.; Castagner, B.; Leroux, J.-C., Biomedical applications of bisphosphonates. *J Control. Release* **2013,** *167*, 175-188

(3) (a) Russell, R.; Watts, N. B. F.; Ebetino, F.; Rogers, M., Mechanism of action of bisphosphonates: Similarities and differences and their potential influence in clinical efficacy. *Osteoporos. int.* **2008,** *19*, 733-759; (b) Nancollas, G. H.; Tang, R.; Phipps, R. J.; Henneman, Z.; Gulde, S.; Wu, W.; Mangood, A.; Russell, R. G. G.; Ebetino, F. H., Novel insights into actions of bisphosphonates on bone: Differences in interactions with hydroxyapatite. *Bone* **2006,** *38*, 617-627.

(4) Gumienna-Kontecka, E.; Silvagni, R.; Lipinski, R.; Lecouvey, M.; Cesare Marincola, F.; Crisponi, G.; Nurchi, V. M.; Leroux, Y.; Kozlowski, H., Bisphosphonate chelating agents: complexation of Fe(III) and Al(III) by 1-phenyl-1-hydroxymethylene bisphosphonate and its analogues. *Inorg. Chim. Acta* **2002,** *339*, 111-118.

(5) (a) Clézardin, P., Bisphosphonates' antitumor activity: An unravelled side of a multifaceted drug class. *Bone* **2011,** *48*, 71-79; (b) Mongerard-Coulanges, M.; Migianu-Griffoni, E.; Lecouvey, M.; Jolles, B., Impact of alendronate and VEGF-antisense combined treatment on highly VEGF-expressing A431 cells. *Biochem. Pharmacol.* **2009,** *77*, 1580-1585; (c) Muller, S.; Migianu-Griffoni, E.; Lecouvey, M.; Kraemer, M.; Oudar, O., Alendronate Inhibits Proliferation and Invasion of Human Epidermoid Carcinoma Cells In Vitro. *Anticancer Res.* **2005,** *25*, 2655-2660.

(6) Dunford, J. E.; Kwaasi, A. A.; Rogers, M. J.; Barnett, B. L.; Ebetino, F. H.; Russell, R. G. G.; Oppermann, U.; Kavanagh, K. L., Structure–Activity Relationships Among the Nitrogen Containing Bisphosphonates in Clinical Use and Other Analogues: Time-Dependent Inhibition of Human Farnesyl Pyrophosphate Synthase. *J. Med. Chem.* **2008,** *51*, 2187-2195.

(7) Lin J.H., Bisphosphonates: a Review of the Pharmacokinetic Properties. *Bone* **1996**, *18*, 75-85.

(8) (a) Chebbi, I.; Migianu-Griffoni, E.; Sainte-Catherine, O.; Lecouvey, M.; Seksek, O., In vitro assessment of liposomal neridronate on MDA-MB-231 human breast cancer cells. *Int. J. Pharm.* **2010,** *383*, 116-122; (b) Lalatonne, Y.; Paris, C.; Serfaty, J. M.; Weinmann, P.; Lecouvey, M.; Motte, L., Bis-phosphonates–ultra small superparamagnetic iron oxide nanoparticles: a platform towards diagnosis and therapy. *Chem. Comm.* **2008,** *22*, 2553-2555 ; (c) Migianu-Griffoni, E.; Chebbi, I.; Kachbi, S.; Monteil, M.; Sainte-Catherine, O.; Chaubet, F.; Oudar, O.; Lecouvey, M., Synthesis and Biological Evaluation of New Bisphosphonate-Dextran Conjugates Targeting Breast Primary Tumor. *Bioconjugate Chemistry* **2014,** *25*, 224-230.

(9) (a) Lecouvey, M.; Mallard, I.; Bailly, T.; Burgada, R.; Leroux, Y., A mild and efficient one-pot synthesis of 1-hydroxymethylene-1,1-bisphosphonic acids. Preparation of new tripod ligands. *Tetrahedron Lett.* **2001,** *42*, 8475-8478. (b) Lecouvey, M.; Leroux, Y.; Kraemer, M.; Crepin, M.; El Manouni, D.; Louriki, M. New bisphosphonates derivatives, their preparation and use. WO03/008425, 2003; *Chem. Abstr.* **2003**, *138*, 122736; (c) Migianu, E.; Mallard, I.; Bouchemal, N.; Lecouvey, M., One-pot synthesis of 1-hydroxymethylene-1,1-bisphosphonate partial esters. *Tetrahedron Lett.* **2004,** *45*, 4511-4513; (d) Monteil, M.; Guenin, E.; Migianu, E.; Lutomski, D.; Lecouvey, M., Bisphosphonate prodrugs: synthesis of new aromatic and aliphatic 1-hydroxy-1,1-bisphosphonate partial esters. *Tetrahedron* **2005,** *61*, 7528-7537; (e) Guénin, E.; Monteil, M.; Bouchemal, N.; Prangé, T.; Lecouvey, M., Syntheses of Phosphonic Esters of Alendronate, Pamidronate and Neridronate. *Eur. J. Org. Chem.* **2007,** 3380-3391; (f) Migianu, E.; Guenin, E.; Lecouvey, M., New efficient synthesis of 1-hydroxymethylene-1,1-bisphosphonate monomethyl esters. *Synlett* **2005**, 425-428.

(10) (a) Dussart, J.; Guedeney, N.; Deschamp, J.; Monteil, M.; Gager, O.; Legigan, T.; Migianu-Griffoni, E.; Lecouvey, M., A convenient synthetic route towards H-bisphosphinates. *Org. Biomol. Chem.* **2018,** *16*, 6969-6979; (b) Guedeney, N.; Dussart, J.; Deschamp, J.; Ouechtati, M.; Migianu-Griffoni, E.; Lecouvey, M., A convenient one-pot synthesis of 1-hydroxymethylene-1,1-bisphosphinic acids. *Phosphorus, Sulfur Silicon Relat. Elem.* **2019,** *194*, 323-325.

(11) Dussart, J.; Deschamp, J.; Migianu-Griffoni, E.; Lecouvey, M., From Industrial Method to the Use of Silylated P(III) Reagents for the Synthesis of Relevant Phosphonylated Molecules. *Org. Process Res. Dev.* **2020**. *24*, 637-651.

(12) For review: Montchamp, J.-L., Recent advances in phosphorus–carbon bond formation: synthesis of H-phosphinic acid derivatives from hypophosphorous compounds. *J. Organomet. Chem.* **2005,** *690*, 2388-2406.

(13) (a) Issleib, K.; Mögelin, W.; Balszuweit, A., 1-Hydroxy-alkan-1,1-diphosphonigsäurederivate. *Z. Chem.* **1985,** *25*, 370-371; (b) David, T.; Procházková, S.; Kotek, J.; Kubícek, V.; Hermann, P.; Lukes, I., Aminoalkyl-1,1-bis(phosphinic acids): Stability, Acid–Base, and Coordination Properties. *Eur. J. Inorg. Chem.* **2014**, 4357-4368; (c) David, T.; Kreckova, P.; Kotek, J.; Kubícek, V.; Lukes, I., 1-Hydroxy-1,1-bis(H-phosphinates): Synthesis, Stability, and Sorption Properties. *Heteroat. Chem.* **2012,** *23*, 195-201; (d) Kaboudin, B.; Ezzati, A.; Faghihi, M. R.; Barati, A.; Kazemi, F.; Abdollahi, H.; Yokomatsu, T., Hydroxy-bisphosphinic acids: synthesis and complexation properties with transition metals and lanthanide ions in aqueous solution. *J. Iran. Chem. Soc.* **2016,** *13*, 747-752.

(14) Guenin, E.; Degache, E.; Liquier, J.; Lecouvey, M., Synthesis of 1-Hydroxymethylene-1,1-bis(phosphonic acids) from Acid Anhydrides: Preparation of a New Cyclic 1-Acyloxymethylene-1,1-bis(phosphonic acid). *Eur. J. Org. Chem*. **2004**, 2983-2987.

(15) Legigan, T.; Riss-Yaw, B.; Clavel, C.; Coutrot, F., Active Esters as Pseudostoppers for Slippage Synthesis of [2]Pseudorotaxane Building Blocks: A Straightforward Route to Multi-Interlocked Molecular Machines. *Chem. Eur. J.* **2016,** *22*, 8835-8847. For some details see experimental section.

(16) Deprèle, S.; Montchamp, J.-L., Triethylborane-Initiated Room Temperature Radical Addition of Hypophosphites to Olefins: Synthesis of Monosubstituted Phosphinic Acids and Esters. *J. Org. Chem.* **2001,** *66*, 6745-6755.

(17) Chapman, T. M.; Freedman, E. A., Nucleophilic reactions N-hydroxyimide-O-triflates. *J. Org. Chem.* **1973,** *38*, 3908-3911.

(18) Tan, B.; Toda, N.; Barbas III, C. F., Organocatalytic Amidation and Esterification of Aldehydes with Activating Reagents by a Cross-Coupling Strategy. *Angew. Chem., Int. Ed.* **2012,** *51*, 12538-12541.

(19).Xu, X.; Sun, J.; Lin, Y.; Cheng, J.; Li, P.; Jiang, X.; Bai, R.; Xie, Y., Iron-Nitrate-Catalyzed Oxidative Esterification of Aldehydes and Alcohols with N-Hydroxyphthalimide: Efficient Synthesis of N-Hydroxyimide Esters. *Eur. J. Org. Chem.* **2017,** *2017*, 7160-7166.

(20) Xu, X.; Li, P.; Huang, Y.; Tong, C.; Yan, Y.; Xie, Y., Atmospheric oxidative catalyst-free cross-dehydrogenative coupling of aldehydes with N-hydroxyimides. *Tetrahedron Lett.* **2017,** *58*, 1742-1746.

(21) Das, R.; Chakraborty, D., Silver Triflate Catalyzed Acetylation of Alcohols, Thiols, Phenols, and Amines. *Synthesis* **2011,** *2011*, 1621-1625.

(22) Bao, Y.-S.; Chen, C.-Y.; Huang, Z.-Z., Transesterification for Synthesis of Carboxylates Using Aldehydes as Acyl Donors via C–H and C–O Bond Activations. *J. Org. Chem.* **2012,** *77*, 8344-8349.

(23) Li, H.; Hou, Y.; Liu, C.; Lai, Z.; Ning, L.; Szostak, R.; Szostak, M.; An, J., Pentafluorophenyl Esters: Highly Chemoselective Ketyl Precursors for the Synthesis of α,α-Dideuterio Alcohols Using SmI2 and D2O as a Deuterium Source. *Org. Lett.* **2020,** *22*, 1249-1253.

(24) de Almeida, A. M.; Andersen, T. L.; Lindhardt, A. T.; de Almeida, M. V.; Skrydstrup, T., General Method for the Preparation of Active Esters by Palladium-Catalyzed Alkoxycarbonylation of Aryl Bromides. *J. Org. Chem.* **2015,** *80*, 1920-1928.