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A convenient synthetic route towards 1-hydroxymethylene-1,1-bis(*H*-phosphinates)[†]

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Jade Dussart, Nicolas Guedeney, Julia Deschamp, Maëlle Monteil, Olivier Gager, Thibaut Legigan, Evelyne Migianu-Griffoni* and Marc Lecouvey*

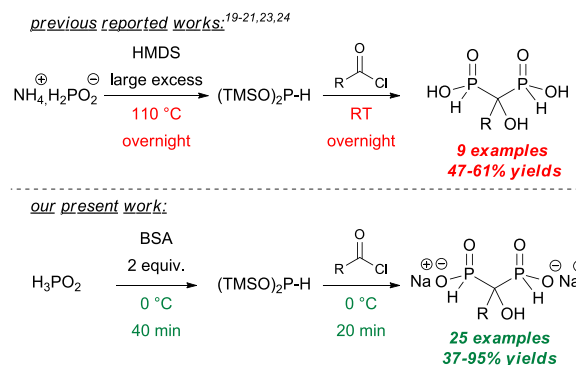
A practical general route to 1-hydroxymethylene-1,1-bis(*H*-phosphinates) has been developed. Diverse alkyl or (hetero)aryl bisphosphinates were rapidly obtained in satisfying to excellent yields from corresponding acid chlorides and *in situ* generated bis(trimethylsilyl)phosphonite. This work is complementary to previous approaches. A generalisable procedure was optimised allowing the description of numerous compounds. To check the literature data, a pK_a value study was also performed.

Introduction

Tetracoordinate pentavalent phosphorus compounds are broadly represented as pharmacophores in various classes of therapeutic agents.^{1–3} Among phosphorylated molecules used in clinic, 1-hydroxymethylene-1,1-bisphosphonates (HMBPs) occupy a prominent place. Because of their affinity for the calcium ions, they are currently the most widely used treatment of bone pathologies.⁴ They are used as inhibitors of bone resorption, in particular osteoporosis, solid tumor bone metastases and myeloma bone disease. Moreover, these compounds have interesting antitumor effects on soft tissue primary tumor models (breast, prostate...) as well *in vitro* as *in vivo*. HMBPs exhibit two distinct action mechanisms depending on their side chain nature. The first leads to the cytotoxic ATP derivative formation at high concentration.^{4,5} In the second mechanism, farnesylpyrophosphate synthase (FPPS), a key enzyme in the mevalonate pathway, is inhibited at low concentration (especially true for HMBPs having a nitrogen on the side chain).^{6–8} More recently, a new allosteric pocket on FPPS has been discovered, opening a novel pharmacological field for HMBPs and derivatives as SAR studies have shown that farnesylpyrophosphate itself is inhibitor.⁹ However, while they have demonstrated great promise, the bisphosphonate main drawback is their weak bioavailability.¹⁰ HMBPs carry two or three negative charges at physiological pH making them very polar, thus limiting their cell uptake. To improve their pharmacological properties, lipophilic prodrug strategies in which HMBP negative charges were partially masked have been evaluated.^{11–16} In this context, our laboratory has proposed several methodologies to synthesise regioselectively various HMBP cleavable mono-, di- and triesters.^{17,18} Another few described strategy is the replacement of the phosphonic group

by a phosphinic moiety. This function presents some advantages such as lower acidity and ionicity at physiological pH and lower affinity for bone to targeting soft tissues. In contrast to bisphosphonates, limited number of studies have focused on the synthesis and chemical properties of bisphosphinates.^{19–24} David *et al.* described only 3 examples of 1-hydroxymethylene-1,1-bis(*H*-phosphinic acids) to study their bone affinity and one aminoalkyl-1-hydroxymethylene-1,1-bis(*H*-phosphinic acid) in order to assess their stability, acid/base and coordination properties.²¹ They proposed a procedure using a large excess of bis(trimethylsilyl)phosphonite (8 equivalents) to obtain total conversion of acid chloride (Scheme 1). After ethanolysis, expected compounds were obtained with a large quantity of phosphorous acid. Difficulties are often observed to separate phosphorous acid from 1-hydroxymethylene-1,1-bis(*H*-phosphinic acids) requiring tedious purifications and thus decreasing the yields.

Here, we take advantage of our former work on bisphosphonates in order to develop a convenient methodology to access to 1-hydroxymethylene-1,1-bis(*H*-phosphinic acid) (*H*-HMBPi) derivatives.

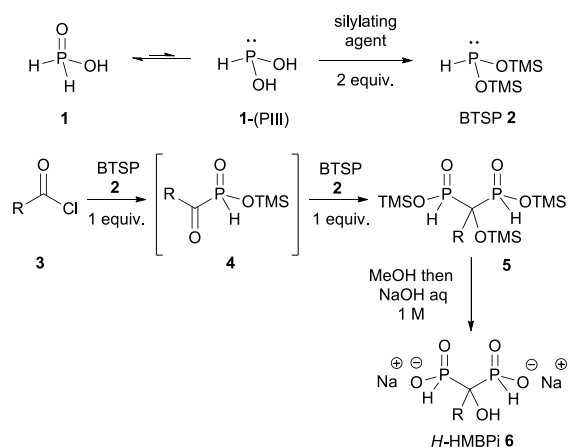


Scheme 1 Syntheses of *H*-HMBPi scaffolds.

Université Paris 13, Sorbonne Paris Cité, Laboratoire CSPBAT, CNRS UMR 7244, F-93017 Bobigny Cedex, France.

E-mail: migianu@univ-paris13.fr, marc.lecouvey@univ-paris13.fr

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Scheme 2 Postulated pathway to *H*-HMBPi **6** synthesis.

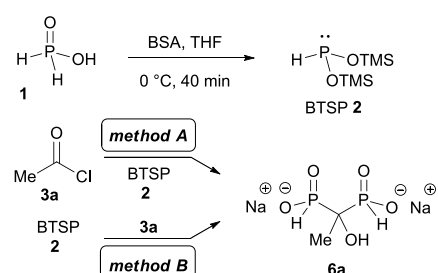
The synthetic pathway started from substituted acid chlorides and readily available hypophosphorous acid in presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) as silylating agent. This procedure provides easily purified *H*-HMBPi disodium salts in higher yields, shorter reaction times and a wide range of aliphatic and (hetero)aromatic substituents than previously reported^{19-21,23,24} (Scheme 1).

Results and discussion

This present work builds on the following postulated pathway inspiring by our previous works on 1-hydroxymethylene-1,1-bisphosphonate (HMBP) syntheses¹⁸ (Scheme 2). The access to *H*-HMBPi scaffold relies on the existing equilibrium between hypophosphorous acid **1** and its *H*-phosphonite form **1-(PIII)** that could be trapped in presence of a silylating agent to afford the well-known bis(trimethylsilyl)phosphonite (BTSP) **2**. The first addition of **2** on an acid chloride could generate a silylated α -ketophosphinate **4** which could subsequently react with a second equivalent of BTSP **2**. Then, the resulting silylated *H*-bisphosphinate **5** could undergo a methanolysis step following by a pH adjustment to **7**, at which the *H*-HMBPi disodium salt **6** should be expected.

Our first experiments were performed with hypophosphorous acid **1** and acetyl chloride **3a** in presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) as a silylating agent under argon atmosphere (Table 1). Indicated concentrations of reagents corresponded to solvent volumes required for a homogeneous reaction mixture stirring at the considered temperature. Initially, the silylated phosphonite **2** which was *in situ* generated by adding two equivalents of BSA to H_3PO_2 was added portionwise to an acetyl chloride **3a** solution at -70 °C (entry 1; **method A**). We were pleased to observe the formation of the expected *H*-HMBPi **6a** after 1.5 hours in an average yield of 47% after purification. The reaction progress was routinely monitored by $^{31}P\{^1H\}$ and ^{31}P NMR (for more details, see Scheme 1 in ESI). First of all, we expectedly observed the fast appearance of the silylphosphonite **2** (141.4 ppm) starting from **1** (12.8 ppm). When the acetyl chloride **3a** solution underwent the attack of **2**, its signal disappeared in favor of several emer-

Table 1 Reaction between acetyl chloride **3a** and hypophosphorous acid **1** in presence of *N,O*-bis(trimethylsilyl)acetamide (BSA).^a

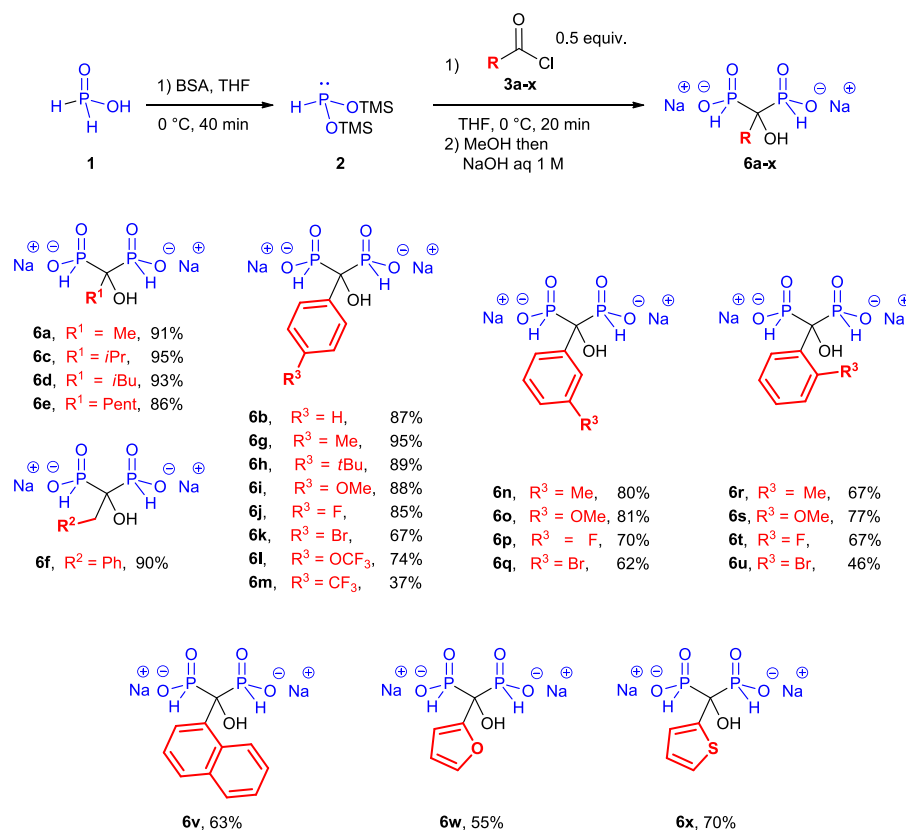


Entry	Method ^b	Temp (°C)	[3a] (M)	[2] (M)	Time	Yield ^f (%)
1	A	-70	2.25 ^c	10 ^c	1.5 h ^d	47
2	A	0	5 ^c	10 ^c	18 h	-
3	B	-70	5 ^c	1 ^c	25 min ^e	54
4	B	0	5 ^c	1 ^c	10 min ^e	65
5	B	0	5	10	20 min ^e	55
6	B	0	2.25	10	20 min ^e	57
7	B	0	5	5	20 min ^e	91
8	B	-25	5	5	20 min ^e	88

^aReaction conditions: **1** (10 mmol), BSA (20 mmol), **3a** (5 mmol), THF, Ar, 0 °C.

^bFor details see Experimental section. ^cConcentrations were adjusted depending on addition method and temperature in order to obtain sufficient solution volumes to allow the reaction occurring. ^dTime of reaction completion monitored by $^{31}P\{^1H\}$ and ^{31}P NMR; the indicated time includes the time of addition. ^eTime of reaction completion monitored by $^{31}P\{^1H\}$ and ^{31}P NMR; the indicated time corresponds to the addition time. ^fIsolated yield of *H*-HMBPi **6a**.

ging signals in P(III)/P(V) species region (142-144 and 20-25 ppm). A sole signal corresponding to the bisphosphinic acid was observed after methanolysis of the reaction mixture following by a pH adjustment to 7. Unfortunately, we never were able to identify the signal corresponding to the α -ketophosphinate intermediate **4** even after adding only few drops of BTSP **2** solution at -70 °C. This intermediate **4** should be highly reactive and thus, instantly react to give the corresponding silylated bisphosphinate **5**.²⁵ It was also noted that small amounts of hypophosphorous acid (7%) and phosphorous acid (11%) were detected in the reaction mixture probably due to BTSP disproportionation (see Scheme 1 in ESI). Surprisingly, when the reaction was conducted at 0 °C, no reaction occurred. Only hypophosphorous acid, phosphorous acid and acetic acid were recovered after methanolysis (entries 2 vs 1). The reagent addition order was then studied (entries 3 vs 1-2; **method B**). The acetyl chloride solution was this time added onto BTSP **2** at -70 °C, the temperature at which *H*-HMBPi **6a** was formed during the first assay. In this case, the reaction was already completed at the end of the acetyl chloride addition (25 min), and *H*-HMBPi disodium salt **6a** was isolated in a better yield of 54%. We were also delighted to find that the same reaction could be succeeded in only 10 min at 0 °C in 65% yield (entries 4 vs 3). Thereafter, we investigated the influence of the reagent concentrations in order to enhance the reaction process (entries 5-7).



Scheme 3 Scope of the reaction between hypophosphorous acid **1** and various acid chlorides **3a-x** in presence of *N,O*-bis(trimethylsilyl)acetamide (BSA).

Higher concentration of the silylated phosphonite **2** allowed to perform the reaction in 20 min at 0 °C in a lower yield (55%, entries 5 vs 4) while the acetyl chloride dilution did not influence the outcome of the reaction (entries 6 vs 5). Finally, we found that the same reagent concentrations (5M) were the best compromise in terms of short reaction time and improved yields (entries 7 vs 4-6). A last assay was carried out at -25 °C in the same concentration and time conditions as entry 7 to check the temperature influence on the reaction efficiency (entry 8). The obtained 88% yield encouraged us to select entry 7 parameters as the best and convenient conditions of addition and temperature.

We have simultaneously studied the same parameter variations on presence of the aromatic acid chloride **3b** instead of acetyl chloride **3a** to ensure the procedure viability (see Table 1 in ESI). We were pleased to observe the same improvement for this aromatic substrate suggesting that this methodology is generalisable as well as aliphatic as aromatic acid chlorides. Under the previous optimised conditions, the expected bisphosphinate disodium salt **6b** was obtained in a very satisfying yield of 87% in 20 min.

We consequently pursued our investigation by studying the scope of the reaction on various acid chlorides (Scheme 3). The reaction was carried out between aliphatic acid chlorides **3c-f** and BTSP **2**. In all cases, the corresponding *H*-bisphosphinates **6c-f** were isolated in excellent yields of 86 to 95%. The reaction rate was very fast as all the reactions were complete at the end of alkyl acid chloride additions. It was noted the reaction is very

effective even in the presence of bulkier acid chloride **3c** (R¹ = *i*Pr) as the corresponding *H*-HMBPI **6c** was obtained in 95% yield. Moreover, it should be noticed that enol formation was never observed after attack of BTSP **2** on phenyl acetyl chloride **3f** as reported by Burgada in bisphosphonate series.²⁶ Then, the screening of various substituted aromatic acid chlorides **3g-u** was performed under optimised conditions. Reactions were generally successful in moderate to excellent yields (37-95%). The presence of alkyl or methoxy groups at the para position of benzoyl chloride provided the expected *H*-HMBPI **6g-i** in very good yields (88-95%). When the reaction was conducted in presence of halogenated substituents (4-fluoro, 4-bromo and 4-trifluoromethoxy), the bisphosphinates **6j-l** were also isolated in satisfying to good yields (67-85%). However, electro-withdrawing trifluoromethyl group gave the corresponding para-substituted bisphosphinate **6m** in the lowest yield of 37%.

The introduction of electro-donating and electro-withdrawing substituents at meta- and ortho- positions of benzoyl chloride were also considered (compounds **6n-u**). As a general trend, the presence of a methyl- or a methoxy- group at meta- or ortho- position led to similar behaviours. Indeed, these expected *H*-HMBPI were obtained in very good yields of 80% and 81% for **6n** and **6o** while it decreased for **6r** and **6s** (67% and 77%) probably due to steric hindrance. Concerning the halogen substituted compounds, the yield decreased from 85% for the para- position (**6j**) to 70% and 67% for meta- and ortho- fluoro-derivatives respectively (**6p** and **6t**). In the same way, the yield declined drastically with the bromo substitution from 67% (**6k**,

para- compound) to 62% and 46% (**6q**, meta- and **6u**, ortho-derivatives).

Finally, the reaction was extended to 1-naphtyl- and heteroaromatic (2-furyl and 2-thiophenyl) substituted acid chlorides **3v-x**, and we were pleased to isolate the corresponding *H*-HMBP*i* **6v-x** in moderate to rather good yields (55-70%).

For some aromatic *H*-HMBP*i* analogues (**6k-m**, **6p-r**, **6t-v**), we also observed the formation of a side product in various amounts (beyond 10%). It was noted that this quantity could be negligible for the other aromatic substrates. Indeed, the $^{31}\text{P}\{^1\text{H}\}$ NMR monitoring of the reaction showed the presence of the expected silylated *H*-HMBP*i* **5** signal and another silylated species in the P(V) spectral area as two doublets. After methanolysis and pH adjustment to 7, $^{31}\text{P}\{^1\text{H}\}$ NMR analysis presented similar two doublets in the same proportion around 23 and 6 ppm (P(V) region again) indicating two different non-equivalent phosphorus atoms. According to NMR spectra, this compound represented 10 to 40% proportion (^{31}P NMR) of crude products mixed with the corresponding *H*-HMBP*i* **6**, phosphorous acid and acetamide. However, *H*-HMBP*i* **6** could be easily separated from crude product thanks to washes with ethanol then methanol. The side product could not be isolated in pure form nevertheless we were able to distinguish its signals. ^1H and ^{13}C 1D and 2D NMR and mass spectrometry experiments allowed identification of a phosphino-

phosphonate isomer as the by-product (see Figures 1a-f in ESI). Indeed, ^1H NMR spectrum showed a new signal compared to *H*-HMBP*i* **6** about 5 ppm assigned to a proton in benzylic position. The presence of this group was confirmed by ^{13}C NMR spectrum with a doublet of doublets around 74 ppm (instead of a triplet for *H*-HMBP*i* **6**) and a one-bond correlation in HMQC NMR of these two chemical signals. It should be noted that this by-product was never formed in aliphatic series.

In order to understand how phosphino-phosphonate isomer was formed, $^{31}\text{P}\{^1\text{H}\}$ NMR studies were set up. As it appeared before methanolysis, the first investigation was to determine if this isomer resulted from a rearrangement of the silylated intermediate **5** or from a reaction starting with the silylated α -ketophosphinate **4**. Benzoyl acid chloride **3b** (R = Ph) which gave only 6% amount of the silylated phosphino-phosphonate isomer (about 14 and 31 ppm) in optimised conditions (**method B**) was selected for this study (Figure 1a). The first experiment was carried out adding benzoyl acid chloride **3b** in one portion onto BTSP **2** (**method B**) at 50 °C in the aim of promoting rapidly the silylated *H*-HMBP*i* **5** formation. Indeed, under **method B** conditions, the high BTSP **2** concentration would disfavour the silylated α -ketophosphinate **4** accumulation. After 5 minutes, the $^{31}\text{P}\{^1\text{H}\}$ NMR analysis indicated the isomer presence in comparable amount (9%) as reference spectrum (a).

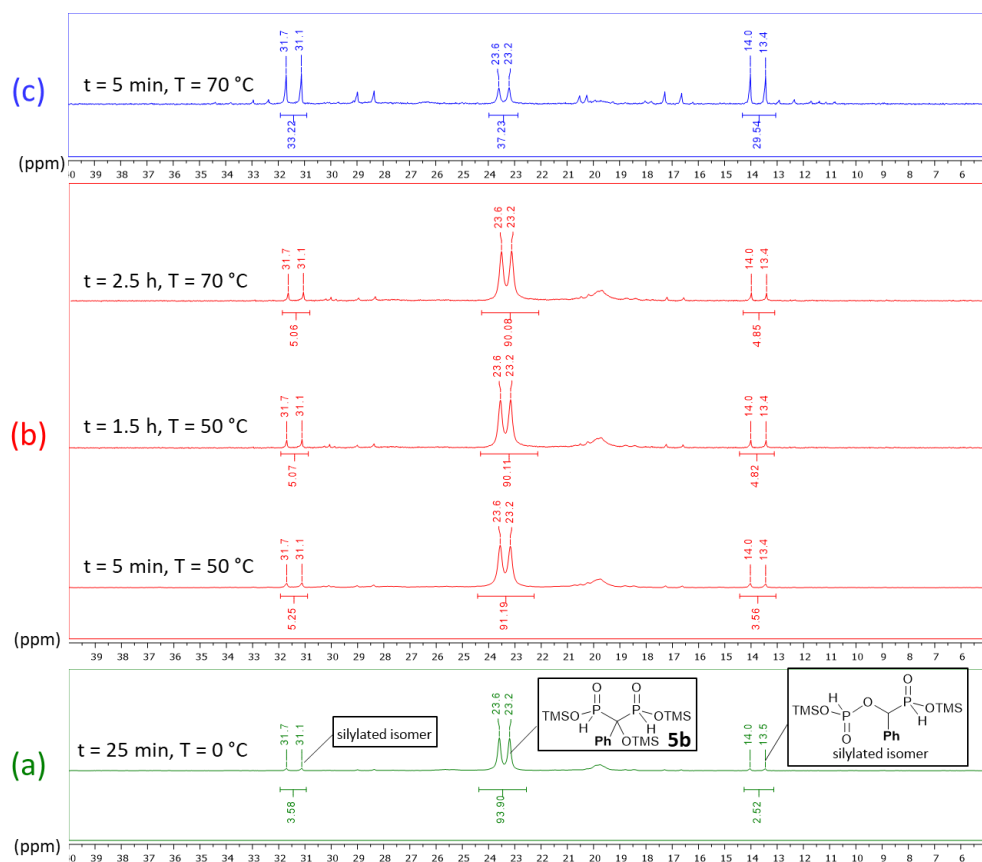


Figure 1 ^{31}P NMR monitoring of phosphino-phosphonate isomer formation (a) by **method B** at 0 °C; (b) by **method B** at 50 then 70 °C; (c) by **method A** at 70 °C.

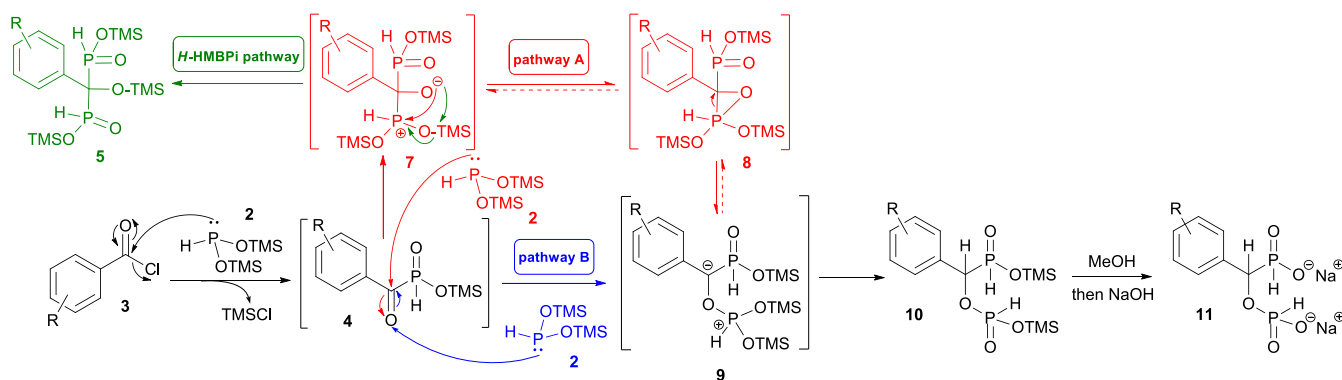
This proportion did not change over time or increasing temperature (Figure 1b). This result suggested that bis-silylated phosphino-phosphonate was not formed from silylated *H*-bisphosphinate **5b** but might result from a rearrangement during the reaction or from another reaction starting from silylated α -ketophosphinate **4**. Besides, bis-silylated phosphino-phosphonate isomer seemed to be rapidly formed at the beginning of the reaction. In the second experiment, BTSP **2** was added dropwise on benzoyl chloride **3b** (method A) at 70 °C in order to promote more the formation of silylated α -ketophosphinate **4** than in method B. In these conditions, the ratio silylated *H*-bisphosphinate/ silylated isomer was totally different after only 5 minutes from 90/10 in the first assay (Figure 1b, T = 70 °C) to 37/63 (Figure 1c). These ratios might suggest the bis-silylated phosphino-phosphonate was more formed from silylated α -ketophosphinate **4**.

Based on those structure/formation elucidation and previous observation on BP tetraester rearrangement,²⁷ we envisioned a first plausible mechanistic pathway of phosphino-phosphonate isomer **11** formation (Scheme 4, pathway A). As earlier reported in Scheme 2, the silylated α -ketophosphinate **4** could be firstly generated from the reaction between BTSP **2** and aryl acid chloride **3**. A nucleophilic addition of the second equivalent of BTSP **2** on the carbon atom of **4** would lead to intermediate **7**. Whereas phosphonium transilylation led to the silylated *H*-HMBPi **5** (*H*-HMBPi pathway), we proposed here the formation of the 1,2-oxaphosphirane **8**, because of a low steric hindrance of this phosphonium. The unfavourable pentacoordinate phosphorus and three-membered ring could generate the intermediate **9**. However, we had also considered another mechanism from silylated α -ketophosphinate **4** inspired by reported reactions between aromatic dialkyl α -ketophosphonates and trialkyl phosphites.^{28,29} In this way, the addition of the second equivalent of BTSP **2** directly on the carbonyl oxygen atom could furnish the same proposed carbanion **9**. In both pathways A and B, the formation of this

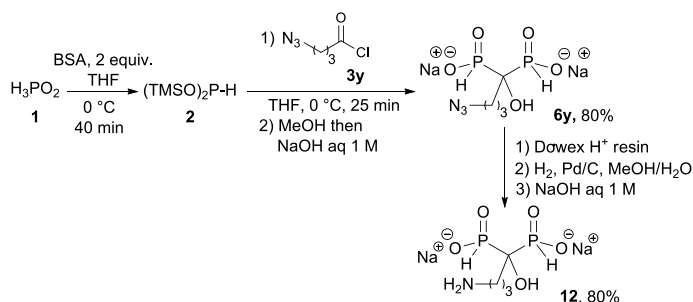
negative charge in benzylic position may explain why phosphino-phosphonate isomer was exclusively obtained in aromatic series. Indeed, this carbanion could be stabilised especially with electro-withdrawing substituents, as observed. The phosphonium **9** could then move towards bis-silylated phosphino-phosphonate **10** giving the phosphino-phosphonate isomer **11** after methanolysis and pH adjustment to 7.

To complete our study, we investigated pK_a values of synthesised *H*-HMBPi derivatives, especially as only few contradictory data are available in the literature.¹⁹⁻²⁰ Surprisingly, Kaboudin *et al.* reported two unexpected pK_a values between 8.1 and 8.7 and 9.3 and 11.9 respectively for aliphatic and aromatic HMBPi.¹⁹ These surprising results encouraged us to determine pK_a values of some synthesised *H*-HMBPi derivatives **6**. Molecules **6c** ($R^1 = iPr$, branched alkyl chain) and **6g** ($R^1 = p\text{-MePh}$, substituted aryl) were chosen. Titrations by an aqueous solution of NaOH (0.04M) were performed with a pure product in its acidic form (adjustment pH step to 7 was omitted here). Purifications and titrations had to be carried out rapidly due to the low stability of the compounds under acidic conditions. pH data exploitation indicated two pK_a values are 1.89 and 1.97 for *H*-HMBPi **6c** and 1.81 and 1.86 for *H*-HMBPi **6g** (for more details, see Figures 2a and 2b in ESI). These results are in contradiction with Kaboudin's values but in accordance with David's study.²⁰ Indeed, reported pK_a values for bis(methylphosphinic acid) are 1.95 and 3.63 corresponding to the two phosphinic acids and are in agreement with our experimental values for bis(*H*-phosphinic acid).

An additional study of *H*-HMBPi **6g** pH evolution depending on chemical shift in $^{31}P\{^1H\}$ NMR was led (see Figure 2c in ESI). Results were in agreement with pK_a values around 2. Moreover, this study showed the *H*-HMBPi **6** existed exclusively on disodium salt form at pH = 7.



Scheme 4 Proposed mechanistic pathways of phosphino-phosphonate isomer **11** formation.



Scheme 5 Synthesis of alendronate *H*-HMBPi analogue **12**.

Afterwards, we aimed at applying our optimised methodology to the synthesis of biologically relevant compounds. We focused on the synthesis of one *H*-HMBPi which is alendronate bisphosphinate analogue **12** (Scheme 5). Our one-pot procedure was performed with 4-azidobutanoyl chloride³⁰ **3y** which underwent the attack of BTSP **2** to afford the corresponding *H*-HMBPi **6y** in 80% yield after methanolysis and basic treatment. After treatment of bisphosphinate **6y** with Dowex H⁺ resin, the catalytic hydrogenation of the azido function was carried out with palladium on carbon. After pH adjustment and simple washes, the disodium salt alendronate bisphosphinate analogue **12** was obtained in better yield (80%) than previously reported.²⁰

Conclusions

To conclude, we have developed an efficient userfriendly methodology allowing the access to various 1-hydroxymethylene-1,1-bis(*H*-phosphinates) in short reaction times, easy purification steps and rather good to excellent yields. Our general optimised procedure can be successfully applied as well as alkyl than (hetero)aromatic acid chlorides and allowed the preparation of biologically relevant organophosphorus compounds such as the alendronate bisphosphinate analogue.

Synthesis and biological evaluation of other bisphosphinates of interest will be reported soon.

Experimental section

General information. Chemicals were purchased from common commercial suppliers (*Sigma-Aldrich*, *Alfa Aesar*, *Acros Organics*) and used as delivered. Anhydrous H₃PO₂ was prepared from aqueous H₃PO₂ solution (50% w/w) according to the procedure reported by Montchamp et al.³¹ *N,O*-Bis(trimethylsilyl)acetamide (BSA) was purchased from Alfa Aesar (LOT: J24T014). All solvents were extra-dried grade or distilled prior used. Reactions requiring inert conditions were carried out in flame-dried glassware under an argon atmosphere.

NMR spectra were recorded at room temperature on a Bruker Avance-III-400 spectrometer (¹H: 400 MHz, ¹³C: 101 MHz, ³¹P: 162 MHz, ¹⁹F: 377 MHz). Chemical shifts (δ) were given in ppm and coupling constants *J* in Hz. ¹H NMR spectra were calibrated on non-deuterated solvent residual peak (H₂O: 4.79 ppm) while H₃PO₄ (85% in water) was used as an external standard for ³¹P NMR notably for

the monitoring of the reaction. The following abbreviations were used for ¹H, ¹³C, ³¹P and ¹⁹F NMR spectra to indicate the signal multiplicity: s (singlet), bs (broad singlet), d (doublet), dt (doublet of triplets), dm (doublet of multiplets), t (triplet), td (triplet of doublets) and m (multiplet). All ¹³C NMR spectra were measured with ¹H decoupling while ³¹P and ¹⁹F NMR spectra were measured with ¹H coupling (zoom on the spectrum) and ¹H decoupling. The reactions were followed by ³¹P and ³¹P{¹H} 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-) mode 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 mode with an ESI source on a Q-TOF mass spectrometer with an accuracy tolerance of 2 ppm. Samples were diluted with acetonitrile and water (15:85) and were analysed by mass spectrometry in continuous infusion using a syringe pump at 200 μL/min. The mass profiles obtained by ESI-MS were analysed 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 used 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 analysed neat. The following abbreviations were used for IR spectra to indicate the signal intensities: w (weak), m (medium), s (strong), br (broad).

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 (660 mg, 10.0 mmol) and anhydrous tetrahydrofuran (1 mL) under argon atmosphere. *N,O*-Bis(trimethylsilyl)acetamide (BSA) (3.055 g, 20.0 mmol) was added dropwise at 0 °C under argon and the mixture was stirred for 40 minutes. The reaction conversion was monitored by ³¹P 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 acid chloride (5.0 mmol) and anhydrous tetrahydrofuran (2.25 mL). The bis(trimethylsilyl)phosphonite was added dropwise at -70 °C. The reaction was monitored by ³¹P NMR spectroscopy. The reaction mixture was quenched by methanol (10 mL) and the mixture was stirred for 25 minutes. Then, methanol was evaporated under reduced pressure following by a pH adjustment to 7.0 with an aqueous solution of sodium hydroxide (0.5 M) and the solution was lyophilised. The crude residue was washed with methanol (Na₂HPO₃ removal) and ethanol (acetamide removal) to give a pure solid.

Optimised 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 (660 mg, 10.0 mmol) and anhydrous tetrahydrofuran (2 mL) under argon atmosphere. *N,O*-Bis(trimethylsilyl)acetamide (BSA) (3.055 g, 20.0 mmol) 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 acid chloride (5.0 mmol) in anhydrous tetrahydrofuran (1 mL) was added dropwise at 0 °C. The reaction was monitored by ^{31}P NMR spectroscopy. The reaction mixture was quenched by methanol (10 mL) and the mixture was stirred for 25 minutes. Then, methanol was evaporated under reduced pressure following by a pH adjustment to 7.0 with an aqueous solution of sodium hydroxide (0.5 M) and the solution was lyophilised. The crude residue was washed with methanol (Na_2HPO_3 removal) and ethanol (acetamide removal) to give a pure solid.

1-Hydroxyethane-1,1-bis(*H*-phosphinate) disodium salt (6a).

White powder (0.99 g, 4.55 mmol, 91% yield); IR (neat, cm^{-1}) $\nu = 3301\text{br}, 2375\text{w}, 1187\text{s}, 1072\text{m}, 962\text{m}, 742\text{m}$; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D_2O) δ 25.9 (s); ^{31}P NMR (162 MHz, D_2O) δ 25.9 (dm, $^1J_{\text{P-H}} = 524.8$ Hz); ^1H NMR (400 MHz, D_2O) δ 6.84 (dm, $^1J_{\text{P-H}} = 524.8$ Hz, 2H), 1.31 (t, $^3J_{\text{P-H}} = 15.3$ Hz, 3H); ^{13}C NMR (101 MHz, D_2O) δ 71.4 (t, $^1J_{\text{P-C}} = 96.3$ Hz), 14.4. These data are in agreement with those previously reported.²¹

1-Hydroxy-1-phenylmethane-1,1-bis(*H*-phosphinate) disodium salt (6b).

White powder (1.22 g, 4.36 mmol, 87% yield); IR (neat, cm^{-1}) $\nu = 3263\text{br}, 2973\text{w}, 2317\text{w}, 1601\text{w}, 1489\text{w}, 1446\text{w}, 1395\text{w}, 1195\text{s}, 1119\text{m}, 975\text{m}, 732\text{m}$; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D_2O) δ 24.4 (s); ^{31}P NMR (162 MHz, D_2O) δ 24.4 (dm, $^1J_{\text{P-H}} = 538.2$ Hz); ^1H NMR (400 MHz, D_2O) δ 7.48 – 7.42 (m, 2H), 7.34 (t, $^3J = 7.0$ Hz, 2H), 7.26 – 7.16 (m, 1H), 6.94 (dm, $^1J_{\text{P-H}} = 538.2$ Hz, 2H); ^{13}C NMR (101 MHz, D_2O) δ 136.1, 128.5 (2C), 127.2, 125.4 (2C), 77.4 (t, $^1J_{\text{P-C}} = 91.8$ Hz). These data are in agreement with those previously reported.²¹

1-Hydroxy-2-methylpropane-1,1-bis(*H*-phosphinate) disodium salt (6c).

White powder (1.17 g, 4.76 mmol, 95% yield); IR (neat, cm^{-1}) $\nu = 3361\text{br}, 2969\text{w}, 2371\text{w}, 1185\text{s}, 1106\text{m}, 974\text{m}, 755\text{m}$; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D_2O) δ 24.8 (s); ^{31}P NMR (162 MHz, D_2O) δ 24.8 (dm, $^1J_{\text{P-H}} = 529.6$ Hz); ^1H NMR (400 MHz, D_2O) δ 7.02 (dm, $^1J_{\text{P-H}} = 529.6$ Hz, 2H), 2.39 – 2.22 (m, 1H), 1.11 (d, $^3J = 6.8$ Hz, 6H); ^{13}C NMR (101 MHz, D_2O) δ 76.5 (t, $^1J_{\text{P-C}} = 92.8$ Hz), 31.1, 17.4 (2C); MS (ESI-) m/z : 201.00 [M-H] $^-$, 222.99 [M-2H+Na] $^+$, 183.00 [M-H-H₂O] $^-$, 135.02 [M-H-H₃PO₂] $^-$; HRMS (ESI-) m/z : [M-H] $^-$ Calcd. for [C₄H₁₁O₅P₂] $^-$: 201.0087, found: 201.0088.

1-Hydroxy-3-methylbutane-1,1-bis(*H*-phosphinate) disodium salt (6d).

White powder (1.20 g, 4.63 mmol, 93% yield); IR (neat, cm^{-1}) $\nu = 3215\text{br}, 2955\text{w}, 2314\text{w}, 1185\text{s}, 1107\text{m}, 1049\text{w}, 747\text{w}$; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D_2O) δ 25.1 (s); ^{31}P NMR (162 MHz, D_2O) δ 25.1 (dm, $^1J_{\text{P-H}} = 526.0$ Hz); ^1H NMR (400 MHz, D_2O) δ 6.91 (dm, $^1J_{\text{P-H}} = 526.0$ Hz, 2H), 2.17 – 2.03 (m, 1H), 1.70 (td, $^3J_{\text{P-H}} = 12.9$ Hz, $^3J = 6.0$ Hz, 2H), 0.95 (d, $^3J = 6.5$ Hz, 6H); ^{13}C NMR (101 MHz, D_2O) δ 75.2 (t, $^1J_{\text{P-C}} = 94.2$ Hz), 38.5, 24.2 (2C), 23.8 (t, $^3J_{\text{P-C}} = 7.7$ Hz); MS (ESI-) m/z : 215.02 [M-H] $^-$, 237.01 [M-2H+Na] $^+$, 197.01 [M-H-H₂O] $^-$, 149.04 [M-H-H₃PO₂] $^-$; HRMS (ESI-) m/z : [M-H] $^-$ Calcd. for [C₅H₁₃O₅P₂] $^-$: 215.0244, found: 215.0243.

1-Hydroxyhexane-1,1-bis(*H*-phosphinate) disodium salt (6e).

White powder (1.17 g, 4.27 mmol, 86% yield); IR (neat, cm^{-1}) $\nu = 3328\text{br}, 2956\text{w}, 2303\text{w}, 1182\text{s}, 1105\text{m}, 959\text{m}, 746\text{w}$; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D_2O) δ 25.1 (s); ^{31}P NMR (162 MHz, D_2O) δ 25.1 (dm, $^1J_{\text{P-H}} = 525.6$ Hz); ^1H NMR (400 MHz, D_2O) δ 6.92 (dm, $^1J_{\text{P-H}} = 525.6$ Hz, 2H), 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 NMR (101 MHz, D_2O) δ 74.2 (t, $^1J_{\text{P-C}} = 94.9$ Hz), 32.0, 30.6, 22.2 (t, $^3J_{\text{P-C}} = 6.5$ Hz), 21.8, 13.3; MS (ESI-) m/z : 229.04 [M-H] $^-$;

251.02 [M-2H+Na] $^+$, 211.03 [M-H-H₂O] $^-$, 163.05 [M-H-H₃PO₂] $^-$; HRMS (ESI-) m/z : [M-H] $^-$ Calcd. for [C₆H₁₅O₅P₂] $^-$: 229.0400, found: 229.0402.

1-Hydroxy-2-phenylethane-1,1-bis(*H*-phosphinate) disodium salt (6f).

White powder (1.24 g, 4.5 mmol, 90% yield); IR (neat, cm^{-1}) $\nu = 3288\text{br}, 2987\text{m}, 2901\text{m}, 2314\text{w}, 1188\text{s}, 1122\text{m}, 1057\text{m}, 757\text{m}$; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D_2O) δ 23.8 (s); ^{31}P NMR (162 MHz, D_2O) δ 23.8 (dm, $^1J_{\text{P-H}} = 532.2$ Hz); ^1H NMR (400 MHz, D_2O) δ 7.36 – 7.27 (m, 2H), 7.26 – 7.12 (m, 3H), 6.71 (dm, $^1J_{\text{P-H}} = 532.2$ Hz, 2H), 3.04 (t, $^3J = 12.4$ Hz, 2H); ^{13}C NMR (101 MHz, D_2O) δ 135.3 (t, $^3J_{\text{P-C}} = 7.9$ Hz), 131.2 (2C), 128.0 (2C), 126.7, 73.6 (t, $^1J_{\text{P-C}} = 94.9$ Hz), 35.3. These data are in agreement with those previously reported.²¹

1-Hydroxy-1-(4-tolyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6g).

White powder (1.39 g, 4.73 mmol, 95% yield); IR (neat, cm^{-1}) $\nu = 3236\text{br}, 2978\text{w}, 2900\text{w}, 2310\text{w}, 1647\text{w}, 1510\text{w}, 1335\text{w}, 1188\text{s}, 1095\text{s}, 976\text{m}, 753\text{m}$; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D_2O) δ 24.4 (s); ^{31}P NMR (162 MHz, D_2O) δ 24.4 (dm, $^1J_{\text{P-H}} = 537.0$ Hz); ^1H NMR (400 MHz, D_2O) δ 7.42 (dt, $^3J = 8.1$ Hz, $^4J_{\text{P-H}} = 1.7$ Hz, 2H), 7.25 (d, $^3J = 8.1$ Hz, 2H), 7.02 (dm, $^1J_{\text{P-H}} = 537.0$ Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, D_2O) δ 137.0 (t, $^5J_{\text{P-C}} = 2.6$ Hz), 132.8, 128.8 (2C), 125.3 (t, $^3J_{\text{P-C}} = 4.4$ Hz, 2C), 77.0 (t, $^1J_{\text{P-C}} = 92.1$ Hz), 20.1; MS (ESI-) m/z : 249.01 [M-H] $^-$, 270.99 [M-2H+Na] $^+$, 231.00 [M-H-H₂O] $^-$, 183.02 [M-H-H₃PO₂] $^-$; HRMS (ESI-) m/z : [M-H] $^-$ Calcd. for [C₈H₁₁O₅P₂] $^-$: 249.0087, found: 249.0089.

1-Hydroxy-1-(4-(*tert*-butyl)phenyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6h).

White powder (1.73 g, 4.41 mmol, 89% yield); IR (neat, cm^{-1}) $\nu = 3346\text{br}, 2988\text{m}, 2901\text{m}, 2322\text{w}, 1662\text{w}, 1598\text{w}, 1509\text{w}, 1394\text{w}, 1182\text{s}, 1081\text{s}, 970\text{w}, 774\text{m}$; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D_2O) δ 24.5 (s); ^{31}P NMR (162 MHz, D_2O) δ 24.5 (dm, $^1J_{\text{P-H}} = 537.7$ Hz); ^1H NMR (400 MHz, D_2O) δ 7.53 – 7.45 (m, 4H), 7.01 (dm, $^1J_{\text{P-H}} = 537.7$ Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (101 MHz, D_2O) δ 150.4, 133.1, 125.3 – 125.2 (m, 4C), 77.1 (t, $^1J_{\text{P-C}} = 91.8$ Hz), 33.8, 30.5 (3C); MS (ESI-) m/z : 291.06 [M-H] $^-$, 313.04 [M-2H+Na] $^+$, 273.05 [M-H-H₂O] $^-$, 225.07 [M-H-H₃PO₂] $^-$; HRMS (ESI-) m/z : [M-H] $^-$ Calcd. for [C₁₁H₁₇O₅P₂] $^-$: 291.0557, found: 291.0557.

1-Hydroxy-1-(4-methoxyphenyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6i).

White powder (1.36 g, 4.38 mmol, 88% yield); IR (neat, cm^{-1}) $\nu = 3247\text{br}, 3001\text{w}, 2902\text{w}, 2313\text{w}, 1609\text{w}, 1509\text{m}, 1467\text{w}, 1191\text{s}, 1117\text{m}, 1034\text{m}, 975\text{w}, 740\text{w}$; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D_2O) δ 24.3 (s); ^{31}P NMR (162 MHz, D_2O) δ 24.3 (dm, $^1J_{\text{P-H}} = 535.9$ Hz); ^1H NMR (400 MHz, D_2O) δ 7.52 – 7.43 (m, 2H), 7.01 (dm, $^1J_{\text{P-H}} = 535.9$ Hz, 2H), 7.01 (d, $^3J = 8.9$ Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, D_2O) δ 157.8, 128.4, 126.7 (t, $^3J_{\text{P-C}} = 4.5$ Hz, 2C), 113.8 (2C), 76.7 (t, $^1J_{\text{P-C}} = 92.9$ Hz), 55.3; MS (ESI-) m/z : 265.00 [M-H] $^-$, 286.99 [M-2H+Na] $^+$, 246.99 [M-H-H₂O] $^-$, 199.02 [M-H-H₃PO₂] $^-$, 201.03 [M-H-HPO₂] $^-$; HRMS (ESI-) m/z : [M-H] $^-$ Calcd. for [C₈H₁₁O₆P₂] $^-$: 265.0036, found: 265.0036.

1-Hydroxy-1-(4-fluorophenyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6j).

White powder (1.26 g, 4.24 mmol, 85% yield); IR (neat, cm^{-1}) $\nu = 3224\text{br}, 2987\text{m}, 2309\text{w}, 1606\text{w}, 1507\text{m}, 1194\text{s}, 1090\text{s}, 1056\text{s}, 975\text{w}, 748\text{m}$; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D_2O) δ 24.0 (d, $^6J_{\text{P-F}} = 2.6$ Hz); ^{31}P NMR (162 MHz, D_2O) δ 24.0 (dm, $^1J_{\text{P-H}} = 537.5$ Hz); ^{19}F { ^1H } NMR (377 MHz, D_2O) δ -116.7 – -116.8 (m); ^{19}F NMR (377 MHz, D_2O) δ -116.6 – -116.8 (m); ^1H NMR (400 MHz, D_2O) δ 7.59 – 7.50 (m, 2H), 7.20 – 7.12 (m, 2H), 7.04 (dm, $^1J_{\text{P-H}} = 537.5$ Hz, 2H); ^{13}C NMR (101 MHz, D_2O) δ 161.9 (d, $^1J_{\text{C-F}} = 242.5$ Hz), 131.8, 127.4 – 127.0

(m, 2C), 115.1 (d, $^2J_{C-F}$ = 21.5 Hz, 2C), 77.0 (t, $^1J_{P-C}$ = 91.6 Hz); MS (ESI-) *m/z*: 252.98 [M-H]⁻, 274.97 [M-2H+Na]⁺, 234.97 [M-H-H₂O]⁻, 187.00 [M-H-H₃PO₂]⁻, 189.01 [M-H-HPO₂]⁻; HRMS (ESI-) *m/z*: [M-H]⁻ Calcd. for [C₇H₈FO₅P₂]: 252.9836, found: 252.9836.

1-Hydroxy-1-(4-bromophenyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6k). White powder (1.19 g, 3.35 mmol, 67% yield); IR (neat, cm⁻¹) ν = 3300br, 2309w, 3100w, 1581w, 1485w, 1195s, 1119m, 975w, 760w; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D₂O) δ 23.8 (s); ^{31}P NMR (162 MHz, D₂O) δ 23.8 (dm, $^1J_{P-H}$ = 539.5 Hz); ^1H NMR (400 MHz, D₂O) δ 7.58 (d, 3J = 7.1 Hz, 2H), 7.46 (d, 3J = 7.1 Hz, 2H), 7.02 (dm, $^1J_{P-H}$ = 539.5 Hz, 2H); ^{13}C NMR (101 MHz, D₂O) δ 135.3, 131.2 (2C), 127.2 (2C), 120.5, 77.1 (t, $^1J_{P-C}$ = 91.1 Hz); MS (ESI-) *m/z*: 312.90 [M-H]⁻, 334.88 [M-2H+Na]⁺, 294.89 [M-H-H₂O]⁻, 246.92 [M-H-H₃PO₂]⁻; HRMS (ESI-) *m/z*: [M-H]⁻ Calcd. for [C₇H₈BrO₅P₂]: 312.9036, found: 312.9036.

1-Hydroxy-1-(4-trifluoromethoxyphenyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6l). White powder (1.35 g, 3.7 mmol, 74% yield); IR (neat, cm⁻¹) ν = 3258br, 2989w, 2315w, 1610w, 1507w, 1192s, 1118m, 1098m, 1056w, 975w, 742w; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D₂O) δ 23.8 (s); ^{31}P NMR (162 MHz, D₂O) δ 23.8 (dm, $^1J_{P-H}$ = 539.3 Hz); $^{19}\text{F}\{^1\text{H}\}$ NMR (377 MHz, D₂O) δ -57.8 (s); ^{19}F NMR (377 MHz, D₂O) δ -57.8 (bs); ^1H NMR (400 MHz, D₂O) δ 7.59 (dm, 3J = 8.6 Hz, 2H), 7.33 (d, 3J = 8.6 Hz, 2H), 7.03 (dm, $^1J_{P-H}$ = 539.3 Hz, 2H); ^{13}C NMR (101 MHz, D₂O) δ 147.9 (d, $^2J_{C-F}$ = 1.7 Hz), 135.0, 126.8 (t, $^3J_{P-C}$ = 4.3 Hz, 2C), 120.7 (2C), 120.3 (q, $^1J_{C-F}$ = 256.1 Hz), 77.0 (t, $^1J_{P-C}$ = 90.9 Hz); MS (ESI-) *m/z*: 318.96 [M-H]⁻, 337.95 [M-2H+Na]⁺, 300.96 [M-H-H₂O]⁻, 255.00 [M-H-H₃PO₂]⁻, 252.99 [M-H-HPO₂]⁻; HRMS (ESI-) *m/z*: [M-H]⁻ Calcd. for [C₈H₈F₃O₆P₂]: 318.9754, found: 318.9753.

1-Hydroxy-1-(4-(trifluoromethyl)phenyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6m). White powder (0.644 g, 1.85 mmol, 37% yield); IR (neat, cm⁻¹) ν = 3321br, 2320w, 1651w, 1611w, 1193s, 1116, 1069s, 977w, 762m; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D₂O) δ 23.6 (s); ^{31}P NMR (162 MHz, D₂O) δ 23.6 (dm, $^1J_{P-H}$ = 540.4 Hz); $^{19}\text{F}\{^1\text{H}\}$ NMR (377 MHz, D₂O) δ -61.9 – -62.3 (m); ^{19}F NMR (377 MHz, D₂O) δ -61.9 – -62.3 (m); ^1H NMR (400 MHz, D₂O) δ 7.74 – 7.67 (m, 4H), 7.07 (dm, $^1J_{P-H}$ = 540.4 Hz, 2H); ^{13}C NMR (101 MHz, D₂O) δ 140.6, 128.3 (dt, $^2J_{C-F}$ = 32.0 Hz, $^5J_{P-C}$ = 2.8 Hz), 125.8 – 125.7 (m, 2C), 125.2 – 125.0 (m, 2C), 124.4 (q, $^1J_{C-F}$ = 271.0 Hz), 77.6 (t, $^1J_{P-C}$ = 90.0 Hz); MS (ESI-) *m/z*: 302.98 [M-H]⁻; HRMS (ESI-) *m/z*: [M-H]⁻ Calcd. for [C₈H₈F₃O₅P₂]: 302.9799, found: 302.9798.

1-Hydroxy-1-(3-tolyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6n). White powder (1.18 g, 4.00 mmol, 80% yield); IR (neat, cm⁻¹) ν = 3414br, 2986w, 2900w, 2317w, 1602w, 1487w, 1405w, 1119s, 1121m, 993w, 727w (P-C); $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D₂O) δ 24.5 (s); ^{31}P NMR (162 MHz, D₂O) δ 24.5 (dm, $^1J_{P-H}$ = 538.1 Hz); ^1H NMR (400 MHz, D₂O) δ 7.41 (s, 1H), 7.39 – 7.30 (m, 2H), 7.19 (d, 3J = 6.3 Hz, 2H), 7.05 (dm, $^1J_{P-H}$ = 538.1 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, D₂O) δ 138.3 (t, $^4J_{P-C}$ = 2.0 Hz), 136.0, 128.3, 127.6 (t, $^4J_{P-C}$ = 2.3 Hz), 125.9 (t, $^3J_{P-C}$ = 4.4 Hz), 122.3 (t, $^3J_{P-C}$ = 4.4 Hz), 77.3 (t, $^1J_{P-C}$ = 91.7 Hz), 20.8; MS (ESI-) *m/z*: 249.01 [M-H]⁻; HRMS (ESI-) *m/z*: [M-H]⁻ Calcd. for [C₈H₁₁O₅P₂]: 249.0082, found: 249.0077.

1-Hydroxy-1-(3-methoxyphenyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6o). White powder (1.25 g, 4.03 mmol, 81% yield); IR (neat, cm⁻¹) ν = 3399br, 2320w, 3001w, 2819w, 1601w, 1580w, 1484w, 1432w, 1193s, 1120m, 1052m, 979w, 771w; $^{31}\text{P}\{^1\text{H}\}$

NMR (162 MHz, D₂O) δ 24.3 (s); ^{31}P NMR (162 MHz, D₂O) δ 24.3 (dm, $^1J_{P-H}$ = 539.3 Hz); ^1H NMR (400 MHz, D₂O) δ 7.36 (t, 3J = 8.2 Hz, 1H), 7.20 – 7.14 (m, 2H), 7.05 (dm, $^1J_{P-H}$ = 539.3 Hz, 2H), 6.96 – 6.90 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, D₂O) δ 158.8, 138.1, 129.6, 118.3 (t, $^3J_{P-C}$ = 4.0 Hz), 112.7, 111.2 (t, $^3J_{P-C}$ = 3.8 Hz), 77.5 (t, $^1J_{P-C}$ = 93.3 Hz), 55.5; MS (ESI-) *m/z*: 265.00 [M-H]⁻, 286.99 [M-2H+Na]⁺, 246.99 [M-H-H₂O]⁻, 199.02 [M-H-H₃PO₂]⁻, 201.03 [M-H-HPO₂]⁻; HRMS (ESI-) *m/z*: [M-H]⁻ Calcd. for [C₈H₁₁O₆P₂]: 265.0036, found: 265.0037.

1-Hydroxy-1-(3-fluorophenyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6p). White powder (1.04 g, 3.50 mmol, 70% yield); IR (neat, cm⁻¹) ν = 3307br, 2988m, 2322w, 1738w, 1614w, 1587w, 1481w, 1188m, 1076s, 1051s, 1012m, 740w; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D₂O) δ 23.8 (s); ^{31}P NMR (162 MHz, D₂O) δ 23.8 (dm, $^1J_{P-H}$ = 540.2 Hz); $^{19}\text{F}\{^1\text{H}\}$ NMR (377 MHz, D₂O) δ -113.3 (s); ^{19}F NMR (377 MHz, D₂O) δ -113.3 – -113.4 (m); ^1H NMR (400 MHz, D₂O) δ 7.46 – 7.37 (m, 1H), 7.37 – 7.26 (m, 2H), 7.05 (dm, $^1J_{P-H}$ = 540.2 Hz, 2H), 7.11 – 7.00 (m, 1H); ^{13}C NMR (101 MHz, D₂O) δ 162.6 (d, $^1J_{C-F}$ = 242.3 Hz), 138.8 (d, $^3J_{C-F}$ = 7.6 Hz), 130.0 (d, $^3J_{C-F}$ = 8.4 Hz), 121.3 – 121.0 (m), 113.7 (dm, $^2J_{C-F}$ = 21.3 Hz), 112.3 (dm, $^2J_{C-F}$ = 23.6 Hz), 77.1 (t, $^1J_{P-C}$ = 90.5 Hz); MS (ESI-) *m/z*: 252.98 [M-H]⁻, 274.97 [M-2H+Na]⁺, 234.97 [M-H-H₂O]⁻, 187.00 [M-H-H₃PO₂]⁻, 189.01 [M-H-HPO₂]⁻; HRMS (ESI-) *m/z*: [M-H]⁻ Calcd. for [C₇H₈FO₅P₂]: 252.9836, found: 252.9836.

1-Hydroxy-1-(3-bromophenyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6q). White powder (1.11 g, 3.10 mmol, 62% yield); IR (neat, cm⁻¹) ν = 3355br, 2979w, 2313w, 1590w, 1562w, 1473w, 1195s, 1089m, 975w, 740w; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D₂O) δ 23.7 (s); ^{31}P NMR (162 MHz, D₂O) δ 23.7 (dm, $^1J_{P-H}$ = 540.4 Hz); ^1H NMR (400 MHz, D₂O) δ 7.79 – 7.67 (m, 1H), 7.60 – 7.45 (m, 2H), 7.30 (t, 3J = 7.8 Hz, 1H), 7.03 (dm, $^1J_{P-H}$ = 540.4 Hz, 2H); ^{13}C NMR (101 MHz, D₂O) δ 138.6, 130.0 (2C), 128.1, 124.1, 122.0, 77.0 (t, $^1J_{P-C}$ = 90.4 Hz); MS (ESI-) *m/z*: 312.90 [M-H]⁻, 334.89 [M-2H+Na]⁺, 296.89 [M-H-H₂O]⁻, 246.92 [M-H-H₃PO₂]⁻, 248.93 [M-H-HPO₂]⁻; HRMS (ESI-) *m/z*: [M-H]⁻ Calcd. for [C₇H₈BrO₅P₂]: 312.9036, found: 312.9037.

1-Hydroxy-1-(2-tolyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6r). White powder (0.99 g, 3.35 mmol, 67% yield); IR (neat, cm⁻¹) ν = 3217br, 2898m, 2901m, 2327w, 1452w, 1394w, 1178m, 1080s, 975w, 753w; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D₂O) δ 24.7 (s); ^{31}P NMR (162 MHz, D₂O) δ 24.7 (dm, $^1J_{P-H}$ = 540.7 Hz); ^1H NMR (400 MHz, D₂O) δ 7.65 – 7.58 (m, 1H), 7.28 – 7.14 (m, 3H), 7.12 (dm, $^1J_{P-H}$ = 540.7 Hz, 2H), 2.56 (s, 3H); ^{13}C NMR (101 MHz, D₂O) δ 137.7 – 137.3 (m), 134.7, 132.7, 127.2, 126.9 (t, $^3J_{P-C}$ = 5.3 Hz), 125.4, 80.0 (t, $^1J_{P-C}$ = 89.4 Hz), 22.2; MS (ESI-) *m/z*: 249.01 [M-H]⁻, 270.99 [M-2H+Na]⁺, 231.00 [M-H-H₂O]⁻, 183.02 [M-H-H₃PO₂]⁻; HRMS (ESI-) *m/z*: [M-H]⁻ Calcd. for [C₈H₁₁O₅P₂]: 249.0087, found: 249.0087.

1-Hydroxy-1-(2-methoxyphenyl)methane-1,1-bis(*H*-phosphinate) disodium salt (6s). White powder (1.19 g, 3.85 mmol, 77% yield); IR (neat, cm⁻¹) ν = 3676w, 2988w, 2900w, 2311w, 1580w, 1489w, 1464w, 1206s, 1119m, 1057w, 967w, 757w; $^{31}\text{P}\{^1\text{H}\}$ NMR (162 MHz, D₂O) δ 23.2 (s); ^{31}P NMR (162 MHz, D₂O) δ 23.2 (dm, $^1J_{P-H}$ = 552.7 Hz); ^1H NMR (400 MHz, D₂O) δ 7.47 (d, 3J = 6.3 Hz, 1H), 7.29 (t, 3J = 7.2 Hz, 1H), 7.14 (dm, $^1J_{P-H}$ = 552.7 Hz, 2H), 7.11 – 6.94 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, D₂O) δ 156.4 (t, $^3J_{P-C}$ = 3.5 Hz), 128.3, 126.6 (t, $^3J_{P-C}$ = 4.6 Hz), 125.5, 120.8, 111.5, 78.1 (t, $^1J_{P-C}$ = 88.6 Hz), 55.1; MS (ESI-) *m/z*: 265.00 [M-H]⁻, 286.99 [M-2H+Na]⁺, 246.99 [M-H-

H₂O⁺; 199.02 [M-H-H₃PO₂]⁺; 201.03 [M-H-HPO₂]⁺; HRMS (ESI-) m/z: [M-H]⁺ Calcd. for [C₈H₁₁O₆P₂]: 265.0036, found: 265.0037.

1-Hydroxy-1-(2-fluorophenyl)methane-1,1-bis(H-phosphinate) disodium salt (6t). White powder (1.00 g, 3.36 mmol, 67% yield); IR (neat, cm⁻¹) ν = 3261br, 3036w, 2325w, 1614w, 1485w, 1447w, 1194s, 1116m, 1089m, 968w, 753w; ³¹P{¹H} NMR (162 MHz, D₂O) δ 22.0 (d, ⁴J_{P-F} = 14.9 Hz); ³¹P NMR (162 MHz, D₂O) δ 22.0 (dm, ¹J_{P-H} = 549.6 Hz); ¹⁹F {¹H} NMR (377 MHz, D₂O) δ -108.8 (t, ⁴J_{P-F} = 15.0 Hz); ¹⁹F NMR (377 MHz, D₂O) δ -108.7 – -109.0 (m); ¹H NMR (400 MHz, D₂O) δ 7.65 – 7.51 (m, 1H), 7.41 – 7.29 (m, 1H), 7.29 – 7.19 (m, 1H), 7.17 (dm, ¹J_{P-H} = 549.6 Hz, 2H), 7.16 – 7.05 (m, 1H); ¹³C NMR (101 MHz, D₂O) δ 159.1 (dt, ¹J_{C-F} = 243.9 Hz, ³J_{P-C} = 3.4 Hz), 129.2 – 129.0 (m), 128.1 – 127.1 (m), 124.3, 123.7 (dm, ²J_{C-F} = 14.7 Hz), 115.7 (d, ²J_{C-F} = 22.6 Hz), 77.4 (td, ¹J_{P-C} = 87.2 Hz, ³J_{C-F} = 6.2 Hz). These data are in agreement with those previously reported.²¹

1-Hydroxy-1-(2-bromophenyl)methane-1,1-bis(H-phosphinate) disodium salt (6u). White powder (0.74 g, 2.30 mmol, 46% yield). IR (neat, cm⁻¹) ν = 3397br, 2986w, 2316w, 1466w, 1302w, 1197s, 1115m, 976w, 754w; ³¹P{¹H} NMR (162 MHz, D₂O) δ 21.4 (s); ³¹P NMR (162 MHz, D₂O) δ 21.4 (dm, ¹J_{P-H} = 554.4 Hz); ¹H NMR (400 MHz, D₂O) δ 7.70 (d, ³J = 6.8 Hz, 1H), 7.63 (d, ³J = 7.7 Hz, 1H), 7.45 (dm, ¹J_{P-H} = 554.4 Hz, 2H), 7.38 (t, ³J = 7.7 Hz, 1H), 7.18 (t, ³J = 7.4 Hz, 1H); ¹³C NMR (101 MHz, D₂O) δ 137.3 – 137.0 (m), 134.4, 128.8 (t, ³J_{P-C} = 4.3 Hz), 128.6, 127.2, 120.0 (t, ³J_{P-C} = 4.4 Hz), 79.0 (t, ¹J_{P-C} = 85.5 Hz); MS (ESI-) m/z: 312.90 [M-H]⁺, 334.88 [M-2H+Na]⁺, 296.89 [M-H-H₂O]⁺, 246.92 [M-H-H₃PO₂]⁺, 248.93 [M-H-HPO₂]⁺; HRMS (ESI-) m/z: [M-H]⁺ Calcd. for [C₇H₈BrO₅P₂]: 312.9036, found: 312.9034.

1-Hydroxy-1-naphthylmethane-1,1-bis(H-phosphinate) disodium salt (6v). White powder (1.04 g, 3.12 mmol, 63% yield); IR (neat, cm⁻¹) ν = 3311br, 2373w, 2994w, 1182s, 1095m, 966m, 784s; ³¹P{¹H} NMR (162 MHz, D₂O) δ 24.6 (s); ³¹P NMR (162 MHz, D₂O) δ 24.6 (dm, ¹J_{P-H} = 544.5 Hz); ¹H NMR (400 MHz, D₂O) δ 8.90 – 8.81 (m, 1H), 7.94 – 7.83 (m, 3H), 7.59 – 7.49 (m, 3H), 7.29 (dm, ¹J_{P-H} = 544.5 Hz, 2H); ¹³C NMR (101 MHz, D₂O) δ 134.2, 133.7 – 133.5 (m), 131.3 – 131.1 (m), 128.6, 128.0, 127.5, 125.7, 125.4, 125.2, 124.8 – 124.6 (m), 80.2 (t, ¹J_{P-C} = 87.9 Hz); MS (ESI-) m/z: 285.01 [M-H]⁺, 306.99 [M-2H+Na]⁺, 267.00 [M-H-H₂O]⁺, 219.02 [M-H-H₃PO₂]⁺, 221.04 [M-H-HPO₂]⁺; HRMS (ESI-) m/z: [M-H]⁺ Calcd. for [C₁₁H₁₁O₅P₂]: 285.0087, found: 285.0086.

1-(Fur-2-yl)-1-hydroxymethane-1,1-bis(H-phosphinate) disodium salt (6w). White powder (0.74 g, 2.75 mmol, 55% yield); IR (neat, cm⁻¹) ν = 3318br, 3104w, 2316w, 1651w, 1579w, 1486w, 1301w, 1198s, 1122m, 989w, 725w; ³¹P{¹H} NMR (162 MHz, D₂O) δ 21.4 (s); ³¹P NMR (162 MHz, D₂O) δ 21.4 (dm, ¹J_{P-H} = 544.2 Hz); ¹H NMR (400 MHz, D₂O) δ 7.52 (bs, 1H), 7.04 (dm, ¹J_{P-H} = 544.2 Hz, 2H), 6.49 – 6.45 (m, 1H), 6.45 – 6.41 (m, 1H); ¹³C NMR (101 MHz, D₂O) δ 149.0, 143.1, 110.6, 107.8 (t, ³J_{P-C} = 4.9 Hz), 74.8 (t, ¹J_{P-C} = 91.8 Hz); MS (ESI-) m/z: 224.97 [M-H]⁺, 246.95 [M-2H+Na]⁺, 206.96 [M-H-H₂O]⁺, 158.99 [M-H-H₃PO₂]⁺, 161.00 [M-H-HPO₂]⁺; HRMS (ESI-) m/z: [M-H]⁺ Calcd. for [C₅H₇O₆P₂]: 224.9723, found: 224.9723.

1-Hydroxy-1-(2-thienyl)methane-1,1-bis(H-phosphinate) disodium salt (6x). White powder (1.00 g, 3.50 mmol, 70% yield); IR (neat, cm⁻¹) ν = 3303br, 2962w, 2309w, 1665w, 1422w, 1433w, 1368w, 1191s, 1096m, 971w, 724w; ³¹P{¹H} NMR (162 MHz, D₂O) δ 23.0 (s); ³¹P NMR (162 MHz, D₂O) δ 23.0 (dm, ¹J_{P-H} = 540.9 Hz);

¹H NMR (400 MHz, D₂O) δ 7.46 – 7.37 (m, 1H), 7.20 – 7.05 (m, 2H), 7.02 (dt, ¹J_{P-H} = 540.9 Hz, 2H); ¹³C NMR (101 MHz, D₂O) δ 139.8, 127.6, 125.0, 123.5, 76.8 (t, ¹J_{P-C} = 91.4 Hz); MS (ESI-) m/z: 240.95 [M-H]⁺, 262.93 [M-2H+Na]⁺, 222.94 [M-H-H₂O]⁺, 174.96 [M-H-H₃PO₂]⁺, 176.98 [M-H-HPO₂]⁺; HRMS (ESI-) m/z: [M-H]⁺ Calcd. for [C₅H₇O₅P₂S]: 240.9495, found: 240.9496.

1-Hydroxy-1-(3-azidopropyl)methane-1,1-bis(H-phosphinate) disodium salt (6y). White powder (1.13 g, 3.94 mmol, 80% yield); IR (neat, cm⁻¹) ν = 3304br, 2962w, 2309w, 1665w, 1422w, 1433w, 1368w, 1191s, 1096m, 971w, 724w; ³¹P{¹H} NMR (162 MHz, D₂O) δ 24.6 (s); ³¹P NMR (162 MHz, D₂O) δ 24.6 (dm, ¹J_{P-H} = 527.6 Hz); ¹H NMR (400 MHz, D₂O) δ 6.85 (dm, ¹J_{P-H} = 527.6 Hz, 2H), 3.60 – 3.06 (m, 2H), 1.85 – 1.67 (m, 4H); ¹³C NMR (101 MHz, D₂O) δ 73.7 (t, ¹J_{P-C} = 94.3 Hz), 51.7, 27.6, 22.5 (t, ³J_{P-C} = 6.6 Hz); MS (ESI-) m/z: 242.01 [M-H]⁺; HRMS (ESI-) m/z: [M-H]⁺ Calcd. for [C₄H₁₀N₃O₅P₂]: 242.0101, found: 242.0103.

1-Hydroxy-1-(3-aminopropyl)methane-1,1-bis(H-phosphinate) disodium salt (12). To a solution of **6y** (59 mg, 0.21 mmol) in H₂O/MeOH: 1/1 (4 mL) was added Pd/C (10%, 6 mg). The system was flushed with a dihydrogen balloon. The reaction mixture was stirred under dihydrogen atmosphere for 2 hours. The end of the reaction was monitored by ³¹P NMR spectroscopy. Then, the mixture was filtered over a pad of celite®. After solvent evaporations, the residue was dissolved in water (2 mL) and an aqueous solution of sodium hydroxide 1M was added until pH = 11. The solution was lyophilised. The crude product was purified by simple washes (ethanol and methanol) to give a white powder (43 mg, 0.16 mmol, 80% yield), ³¹P{¹H} NMR (162 MHz, D₂O) δ 25.0 (s); ³¹P NMR (162 MHz, D₂O) δ 25.0 (dm, ¹J_{P-H} = 525.5 Hz); ¹H NMR (400 MHz, D₂O) δ 6.92 (dt, ¹J_{P-H} = 525.9 Hz, ⁴J = 16.9 Hz, 2H), 2.60 (t, ³J = 6.8 Hz, 2H), 1.91 – 1.75 (m, 2H), 1.75 – 1.62 (m, 2H); ¹³C NMR (101 MHz, D₂O) δ 73.8 (t, ¹J_{P-C} = 96.0 Hz), 41.2, 28.0, 25.9 (t, ³J_{P-C} = 6.7 Hz). These data are in agreement with those previously reported.²⁰

Conflicts of interest

There are no conflicts to declare.

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