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Challenging synthesis of bisphosphonate derivatives with reduced steric hindrance

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ABSTRACT

An alternative approach is reported for the synthesis of methyl ester protected bisphosphonate building blocks, such as methylene bisphosphonate, vinylidenebisphosphonate and aryl substituted prochiral vinylidenebisphosphonates, that cannot be obtained directly from dimethyl phosphite and dichloromethane.

Bone diseases, in particular osteoporosis, are frequently treated with bisphosphonates (BPs, Scheme 1) [1,2] due to their chemical similarity to the phosphate present in hydroxyapatite, which represents the mineral portion of bones. Moreover, the P—C—P group is resistant to pyrophosphatases as well as to chemical hydrolysis [3]. Several studies have underlined the role of the phosphonate units demonstrating the higher affinity of the acid derivatives with respect to the corresponding esters. The biological activity of BPs is a function of their specific molecular structure [4,5], with many reported examples of compounds obtained by varying the R^1 and R^2 side chain attached to the central carbon atom. More specifically, R^1 substituents such as hydroxyl or amino groups enhance chemisorption to hydroxyapatite [6], while varying the R^2 substituents results in differences in the antiresorptive potency of several orders of magnitude.[4] Over the years several BPs have been commercialized [7] as anti-resorption bone drugs, including clodronate, pamidronate, alendronate, ibandronate, zoledronate and risendronate (Scheme 1). BPs with R^1 = OH are usually prepared in a rather straightforward manner from carboxylic acids [8,9], or acyl chlorides.[10] Additionally, the presence of nitrogen atoms or nitrogen containing heterocyclic substituents in the R^2 side chain (e.g. ibandronate, risedronate or zoledronate) leads to very potent anti-resorption bone drugs which are currently employed to treat osteoporosis (Scheme 1).

It is worth noting that Zhang and co-workers reported that lipophilic BPs lacking the OH group in position R^1 and bearing a pyridinium moiety in R^2 are approximately 250 times more effective than any other BP drugs (BPH-715 and BPH-716, Scheme 1) [11]. BPs with R^1 = H are commonly prepared from methylene bisphosphonate tetraethyl ester **1**, which is transformed into vinylidenebisphosphonate tetraethylester **2** or prochiral compounds **3a-c** [12]. Vinylidene bisphosphonates **2** and **3** can undergo Michael addition reactions with many nucleophiles enabling the synthesis of a wide range of new bone anti-resorption drug candidates.

General classes of BPs have also been prepared by the metal catalyzed addition of boronic acids and indoles to **2** as recently disclosed by our group [13,14]. Compounds such as **2** can also be exploited as dienophiles [15] for Diels Alder reactions [16].

The presence of the phosphonate groups ensures the affinity of BPs for the bone matrix, while the specific structure of the R^2 side chain is responsible for their biological activity towards the osteoclast cells responsible for bone resorption. In osteoclasts the BPs inhibit specific enzymes such as farnesyl diphosphate synthase and geranyl geranyl diphosphate synthase [17,18]. While different biological responses to molecules with different stereoisomerism has been proven, the development of chiral BPs is still limited [19]. Chiral BPs can be obtained through stereoselective reactions from BP building blocks. In particular, the use of **2** has been investigated for the synthesis of chiral BPs [20], despite the steric hindrance provided by the four ethyl ester groups limiting its reactivity. Several stereoselective reactions on the prochiral

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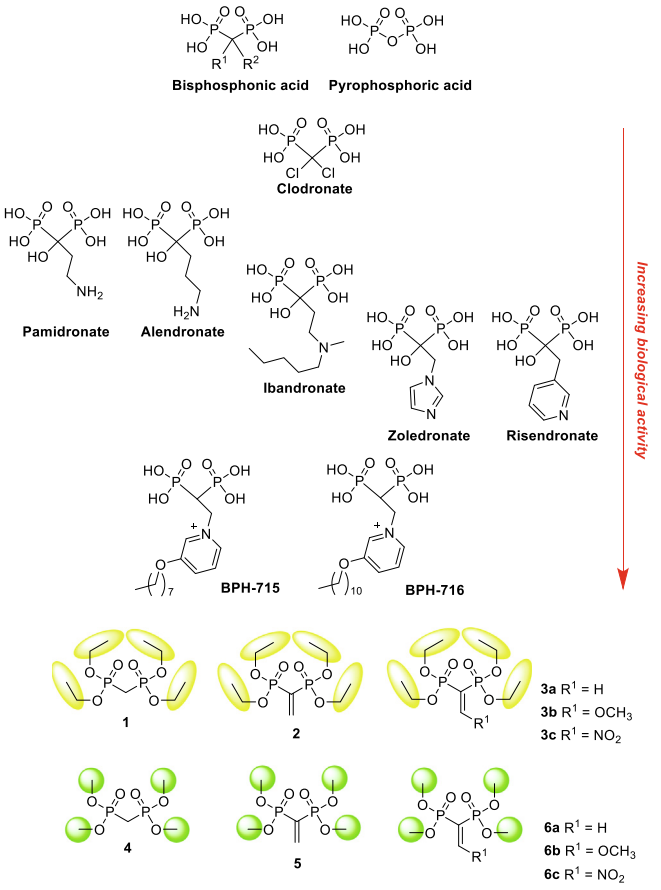


Scheme 1. Structures of bisphosphonic acid, pyrophosphoric acid, commercially available BPs and promising BPs drug candidates. BP building blocks with tetraethyl ester groups **1**, **2**, **3a-c** and tetramethyl ester groups **4**, **5**, **6a-c**.

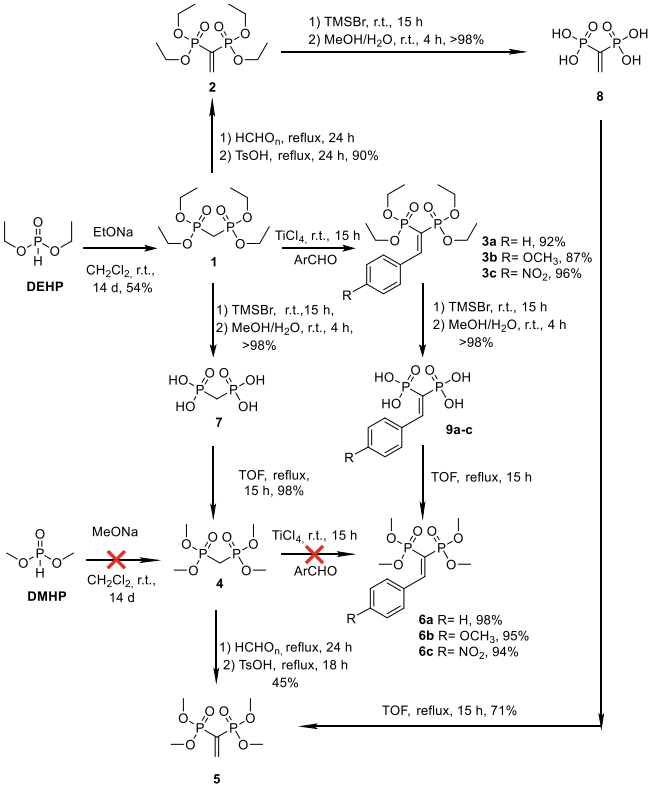
compounds **3a-c** investigated by our group also led to unsatisfactory yields. The ethyl esters are used as protecting groups during the synthesis of the final BP and are generally removed in the last step by treatment with bromo trimethylsilane (TMSBr) and water to give the corresponding bisphosphonic acid [21,22], in quantitative yield as the biologically active species.

With the aim to provide less sterically hindered BP building blocks containing methyl esters in place of ethyl esters, we investigated the preparation of **4**, **5** and **6a-c**. This structural modification seemed trivial but, as described below, a completely different approach was required for the synthesis of such compounds with respect to the procedure used to obtain **1**. For comparison the syntheses of **1**, **2** and **3a-c** were also performed and discussed. Building blocks **1** and **4** are commercially available but at relatively high costs, and therefore a more economical synthetic process is highly desirable. Limited syntheses of **4** have been reported based on the use of carbon disulphide [23] and diazomethane [24]; however, these reagents require special precautions for their use and have severe restrictions due to being toxic, highly flammable, and suspected carcinogens.

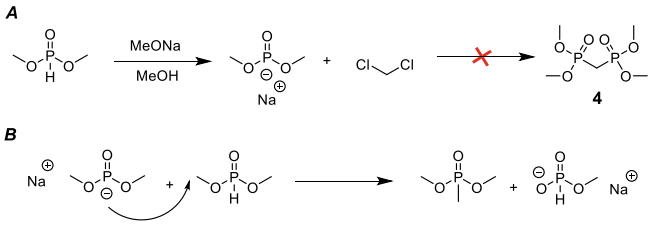
The synthesis of **1** bearing ethyl ester groups was carried out following established procedures [25] *via* the reaction of diethyl phosphite (DEHP) with dichloromethane under basic conditions. The order of addition of the reagents turned out to be crucial in this reaction. Deprotonation of the phosphite occurred using a strong Brønsted base (sodium ethoxylate) generated *in situ* by the addition of metallic sodium to ethanol used as the solvent. Then DEHP was added to the base and the phosphite anion attacked dichloromethane solvent. The reaction was allowed to proceed for two weeks. Meziane and co-workers reported a faster procedure using microwave technologies to synthesize **1** [26], but we preferred to use standard equipment to prove the generality of the procedure. It is noteworthy that the major product is **1** even though a large excess of dichloromethane is used. The reason for this is because the intermediate diethyl chloromethyl phosphonate is more reactive than dichloromethane in the subsequent nucleophilic substitution. This methodology could be performed on a 10 g scale, affording the product in 54% yield. The impurities were removed from the crude reaction mixture by distillation at reduced pressure, leaving **1** in good purity as the residue of distillation (Scheme 2).

The synthesis of **2** typically occurs in two steps *via* the reaction between **1** and formaldehyde [27]. The first step at 60 °C involves deprotonation of the α carbon atom of **1** by diethylamine followed by attack onto formaldehyde to give a 2-hydroxyethan-1,1-bisphosphonate intermediate. The second step carried out at 115 °C affords product **2** *via* the elimination of water under acid catalysis using *p*-toluenesulfonic acid. We were able to carry out the reaction on a 2.5 g scale and product **2** was obtained in 90% yield (Scheme 2).

In order to synthesize methyl ester derivative **4**, we initially modified the synthesis of **1** replacing DEHP with dimethyl phosphite (DMHP) and sodium ethylate with sodium methylate as the base. In contrast to what was expected, the reaction did not provide **4** (Scheme 3A), and instead dimethoxy methyl phosphonate was formed (Scheme 3B). The formation of the latter species from DMHP is known in the presence of methylating agents [28] under classical Michaelis-Arbuzov conditions, or in the absence of an electrophilic species using catalytic amounts of trimethylsilyl halides [29] or other acid species [30], as well as by interaction with silica and polymers [31].



Scheme 2. Overall route for the synthesis of ethyl ester protected **1**, **2** and **3a-c** and alternative methods for the synthesis of reduced steric hindrance BP precursors **4**, **5** and prochiral **6a-c**.



Scheme 3. A) Unsuitable direct synthesis of **4** from DMHP, sodium methylate and dichloromethane; B) plausible mechanism for the formation of dimethoxy methyl phosphonate.

Under basic conditions [30] and in the absence of methylating reagents the formation of dimethoxy methyl phosphonate is unexpected, but can be justified by considering the high nucleophilicity of the dimethylphosphite anion and its attack on the methyl residue of a second molecule of DMHP. The same side reaction cannot occur with DEHP due to the higher steric hindrance on the methylene units connected to the phosphonate moiety and the lower nucleophilicity of the corresponding anion.

Since it was not possible to prepare **4** in a single step starting from DMHP, we decided to investigate the synthesis of this building block in three consecutive steps: i) synthesis of **1** using the procedure reported by Hormi and co-workers [25]; ii) deprotection of the ethyl ester groups with TMSBr followed by hydrolysis to give the corresponding bisphosphonic acid **7**; iii) protection of the acid moieties with trimethyl orthoformate (TOF) to obtain **4** (Scheme 2) [32]. TOF is a reagent employed for the esterification of hydroxyl groups [33] and allowed to obtain **4** from **7** in quantitative yield without the occurrence of undesired side-reactions or partial re-protection, even when the reaction scale was on a 1 g scale.

The same synthetic steps comprising of the deprotection of **2** (to give **8**, Scheme 2) with TMSBr and re-protection using TOF were also applied to the synthesis of **5** in 71% overall yield from **2**. Analysis of the crude reaction mixture by GC–MS showed the formation of **5** together with smaller amounts of two by-products. These are presumably due to the reaction with TMSBr, an extremely aggressive reagent, which tends to react not only with the phosphonic ester groups, but also with the vinyl moiety through a not completely understood mechanism.

As an alternative method for the synthesis of **5**, we adapted the procedure described by Degenhardt and co-workers [27] to obtain **2** from **1**, starting with the reaction of **4** with formaldehyde and subsequent water elimination under acid catalysis (Scheme 2). The reaction was characterized by a conversion of up to 97%; however the isolation and purification of **5** was rather complex. Replacement of the ethyl ester groups in **1** with the methyl ester groups in **4** led to a drastic increase in the hydrophilicity of **5**. As a consequence, during the removal of *p*-toluenesulfonic by aqueous extraction of the reaction mixture, most of **5** moved to the aqueous phase. Multiple extractions of the aqueous phase with ethyl acetate were required to recover the desired product **5**, but at the expense of only 45% yield.

Similarly, it was decided to modify the procedure reported by Lehnert and co-workers [34] for the synthesis of monosubstituted aromatic products **6a-c**. The reaction of **4** with benzaldehyde catalyzed by $TiCl_4$ was initially investigated. Despite high yields in the condensation reaction using **1**, a similar procedure performed on **4** did not give the desired product **6a**. ^{1}H and ^{31}P NMR analysis of the crude reaction mixture demonstrated the total absence of reactivity of the reagents.

We therefore used the deprotection-reprotection method previously developed for the synthesis of **4** and **5** for the preparation of **6a-c** observing that the double bond remained unaltered during the reactions. Starting from **3a-c**, the deprotection step with TMSBr and re-protection with TOF gave **6a-c** in good yields (Scheme 2).

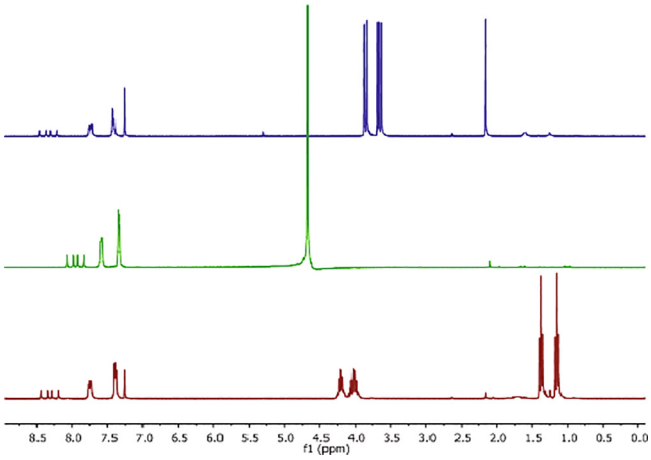


Fig. 1. ^{1}H NMR spectra from bottom to top: ethyl ester derivative **3a** in $CDCl_3$, acid derivative **9a** in D_2O and methyl ester derivative **6a** in $CDCl_3$.

The ^{1}H NMR spectra of **3a**, **9a** and **6a** are reported for comparison in Fig. 1, showing the presence of the aromatic unit and the diagnostic vinylic proton as a doublet of doublets due to the $^{3}J_{P\text{-}H}$ couplings with the P atoms in *cis* and *trans* positions.

The intermediate acids **7**, **8** and **9a-c** turned out to be quite reactive and had to be directly reacted with TOF to obtain the corresponding methyl esters **4**, **5** and **6a-c**, or stored at 4 °C for a few days to prevent decomposition.

Conclusion

An alternative approach is reported for the synthesis of methyl ester protected BPs building blocks such as methylene bisphosphonate **4**, vinylidenebisphosphonate **5** and prochiral vinylidenebisphosphonates **6a-c** that cannot be obtained directly from DMHP and dichloromethane. These BP precursors, characterized by reduced steric hindrance with respect to the most common analogues **1**, **2** and **3a-c**, will favorably spur the development of stereoselective reactions of BPs enabling higher yields.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material containing full experimental conditions and NMR spectra for novel compounds **4**, **5** and **6a-c** is available. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153012.

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