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# One-pot carbanionic access to methylenebis(phosphonate) analogues of natural $P^1$,$P^2$-glycosyl-disubstituted pyrophosphates

Claude Grison,[a,*] Christophe Letondor,[b] Hicham Chibli[a] and Philippe Coutrot[b]

[a]*Laboratoire de Chimie Biomoléculaire, UMR CNRS—UM II—5032—ERT 5, Université Montpellier II, ENSCM, 8 Rue de l'Ecole Normale, 34296 Montpellier, France*
[b]*Laboratoire de Chimie Organique Biomoléculaire, Institut Nancéien de Chimie Moléculaire, UMR 7565, Université Henri Poincaré, Nancy 1, BP 239, 54506 Vandoeuvre cédex, France*

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**Abstract**—Two novel lithiated carbanions derived from ethyl (1,2:3,4-diisopropylidene-α-D-*galacto*pyranosyl) methyl phosphonate **3a** and ethyl (1-*O*-methyl-2,3-*O*-isopropylidene-β-D-*ribo*furanosyl) methylphosphonate **3b** were used in the one-pot alkylidene diphosphorylation of 2,3-*O*-isopropylidene uridine or 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose to synthesise the methylenebis(phosphonate) analogues of natural $P^1$,$P^2$-glycosyl-disubstituted pyrophosphates.
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Analogues of biological pyrophosphates capable to interact with cell metabolism are an attractive goal in therapeutic research. Phosphonic acids and their derivatives are well-known as biological analogues of naturally occurring phosphates with a carbon–phosphorus bond stable to the phosphodiesterases involved in the cleavage of phosphate linkages.[1] Moreover, the C-phosphonate functionality which does not provide a cleavable leaving group can inhibit transglycosylation processing. For instance, C-phosphonate disaccharides which mimic the natural antibiotic moenomycin have been designed to inhibit transglycosylase, a penicillin-binding protein catalysing the connection of the lipid-bearing disaccharide pyrophosphate monomer unit of peptidoglycan.[2,3] Synthesis of a potential mechanism-based bisubstrate inhibitor of the elongating α-D-mannosyl phosphate transferase in *Leishmania*, comprising a guanosine subunit bound to the synthetic acceptor substrate through the methylenebis(phosphonate) linker has been accomplished.[4] Other potential inhibitors of glycosyltransferases with the same linker such as adenosine 5′-[α-D-glucopyranosylhydroxyphosphinylmethyl]phosphonate, uridine 5′-[α-D-*galacto*pyranosylhydroxyphosphinylmethyl]phosphonate, and guanosine 5′-[α-D-mannopyranosylhydroxyphosphinylmethyl]phosphonate, have been prepared.[5] Methylene analogues of thiazole-4-carboxamide adeninedinucleotide (TAD),[6] an antitumour agent analogue of nicotinamide adenine dinucleotide (NAD), fluorinated analogues of TAD,[7] and more recently, mycophenolic adenine dinucleotide analogues (MAD),[8] have been described. Different approaches to the chemical synthesis of such metabolically stable analogues of dinucleotide pyrophosphates have been proposed. Marquez et al. reported several different methods of preparation of TAD analogues where either the α- or the γ-oxygen atom of the pyrophosphate bridge was replaced by a methylene group using the coupling between isosteric phosphonic analogues of adenosine monophosphate (AMP) and tiazofurin monophosphate (TRMP) with, respectively, the morpholidate and imidazolidate activated form of AMP and TRMP. The yields were quite low (3–5%). The symmetric β-methylene-TAD was prepared in 36% yield via the reaction between protected adenosine 5′-(α,β-methylene)diphosphate and 2′,3′-*O*-isopropylidenetiazofurin using dicyclohexylcarbodiimide (DCC) as coupling reagent.[6] A notable improvement was provided by Pankiewicz et al. with nucleoside bicyclic trisanhydrides

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* Corresponding author. Tel./fax: +33 346 714 4342; e-mail: cgrison@univ-montp2.fr

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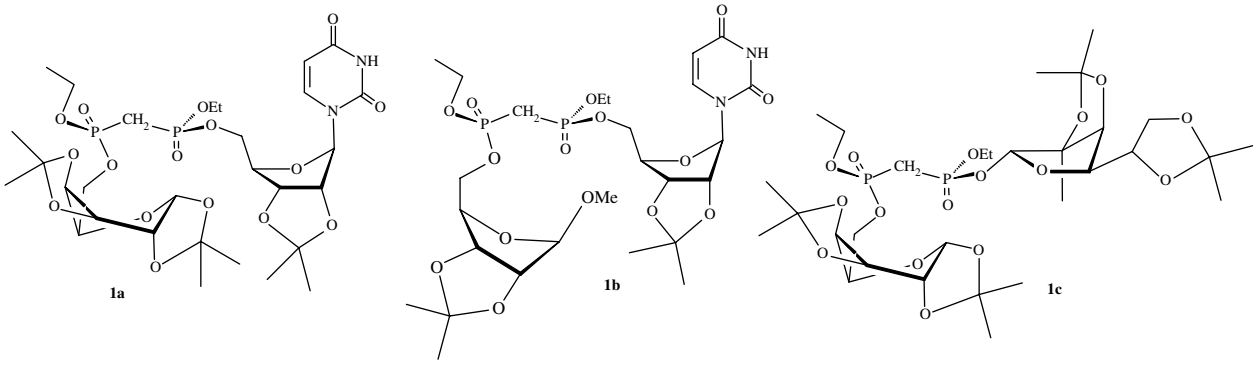
found in the reaction of nucleoside-5′-methylenebis(phosphonate)s with DCC. Thus, the reaction of the trisanhydride derivative of 2′,3′-*O*-isopropylideneadenosin-5′-yl with 2′,3′-*O*-isopropylidenetiazofurin led to the β-methylene-TAD in 92% overall yield.[9] The method was recently used in the synthesis of MAD.[8a] However, these preparations are limited to small scale syntheses, the purification of key intermediates by reversed-phase HPLC being required. More recently, a synthesis of β-methylene-TAD was proposed,[10] based on the use of two rounds of Mitsunobu esterification with conveniently protected nucleosides starting from the partially protected [(bis(benzyloxy)phosphoryl)]methylphosphonic acid monobenzyl ester according to the method of Saddy et al.[11] However, the success of this strategy is still limited by the availability of the tetrabenzyl methylenebis(phosphonate).[10]

We now report on a different approach towards methylenebis(phosphonate) analogues of natural $P^1$,$P^2$-glycosyl-disubstituted pyrophosphates **1a**–**c** based on the adjustment of novel lithiated carbanions **2′** derived from ethyl glycosyl methylphosphonates **2** and on the method of one-pot alkylidene diphosphorylation of nucleophiles previously described by us.[12,13]



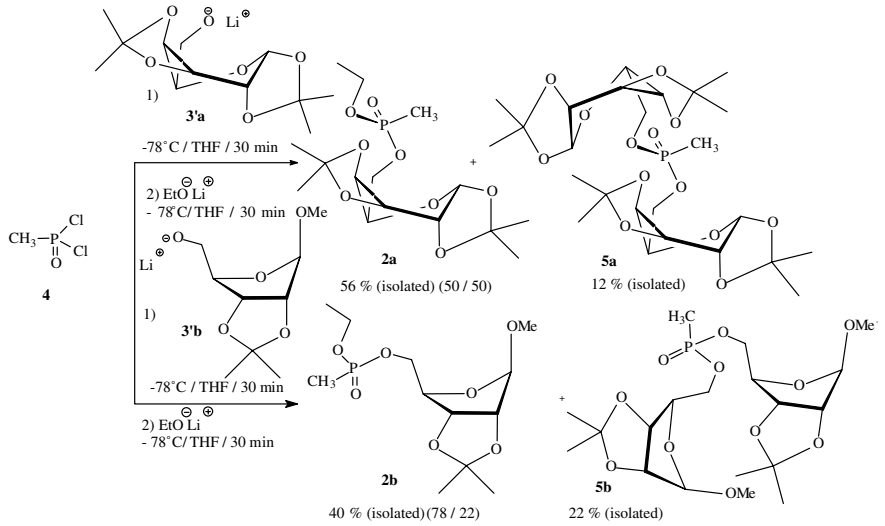

Critical to the success of this approach was the preparation of the starting material ethyl glycosyl methylphosphonates **2**, and the derived lithiated carbanions **2′**, unknown until now. The starting compound **2a** was first prepared drawing one's inspiration from published methods.[13] The 1,2:3,4-α-D-di-*O*-isopropylidene *galacto*pyranose **3a** was slowly added to methylphosphonic dichloride **4** in the presence of tetrazole as a catalyst and diisopropylethylamine. After 5 h stirring, ethanol in excess was added. The double substitution could not be avoided and a mixture of the expected product **2a** accompanied with the disubstituted product **5a** was obtained. After chromatography column over silica gel, compounds **2a** and **5a** were isolated in 39% and 15% yield, respectively. We found a more convenient approach starting from the first addition at −78 °C of the lithium alcoholate **3′a** derived from **3a** onto methylphosphonic dichloride **4**, followed after 30 min by the addition of lithium ethylate at this same temperature (Scheme 1). Although, these conditions could not avoid the double substitution, **2a** and **5a** were isolated in 56% yield and 12% yield, respectively. This last method has several advantages in terms of a better control of the monosubstitution leading to the desired product, ease of purification, and a shorter reaction time. It was noted that the reaction leading to **2a** was not diastereoselective (50/50).

The $^{13}C$ resonance for the $CH_3$–P of the starting compound **2a** was easy to assign as a doublet signal at 11.5 ppm with a coupling constant $J_{C-P} = 144.5$ Hz for one diastereomer and a second doublet at 11.6 ppm with the same coupling constant for the other diastereomer. The $^{31}P$ NMR resonances at 29.3 ppm and 28.8 ppm confirmed the presence of both diastereomers.

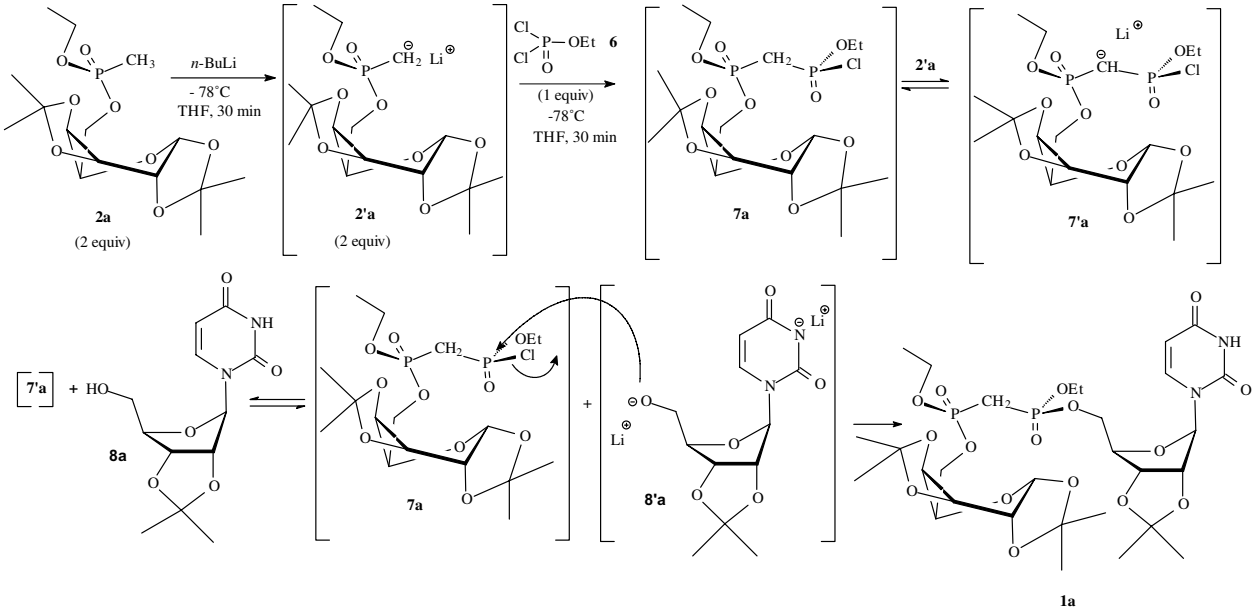
The same method was applied to synthesise the phosphonate **2b** from the alcoholate **3′b** derived from the 1-*O*-methyl-2,3-*O*-isopropylidene-β-D-*ribo*furanose **3b** (40% yield in isolated product). The reaction was here stereoselective (78/22). In this case, **3′b** being less hindered than **3′a** led to a relatively more important amount of disubstituted product **5b** (22% yield in isolated product). It is noteworthy that it is difficult to explain the difference in stereoselectivity obtained while working with **3′a** and **3′b** as a consequence of the complexity of the substitution at *P*(*V*). Moreover, in these cases, the separation of the diastereomers of **2a** and of **2b** was very difficult although the mixture of diastereomers could be purified by flash chromatography over a silica gel column.

The formation of the lithiated carbanion **2′**, exemplified in the case of **2′a**, occurred when the phosphonate **2a** was treated with *n*-BuLi in THF at −78 °C with stirring for 30 min at this temperature. After deuterolysis of the reaction medium, the $^{13}C$ NMR of the crude product showed a complete deuteration (80% in isolated product). The carbon $CH_2D$–P appeared as coupled both to phosphorus and deuterium with a doublet of triplet centred at 11.1 ppm ($J_{C-P} = 144.5$ Hz and $J_{C-D} = 21.5$ Hz) for one diastereomer and at 11.2 ppm for the other. The absence of the $CH_3$–P signal in the crude product of deuterolysis showed the complete metallation of **2a** with *n*-BuLi. This result was confirmed by mass spectrometry with [M+1] = 368 found for the deuterated product coming from **2a**.

This allowed the ensuing assembly of two representative glucides with a methylenebis(phosphonate) link. A typical example is shown in Scheme 2 from the phosphonate




**Scheme 1.**




**Scheme 2.**

**2a**. Thus, once formed, the carbanion **2′a** reacted with ethyl dichlorophosphate **6** to provide the monochlorinated intermediate **7a** which was immediately deprotonated to **7′a** by carbanion **2′a**. As a result two equivalents of **2′a** were required to yield the reaction to completion. Further treatment of carbanion **7′a** with one equivalent of 2,3-*O*-isopropylidene uridine **8a** involved a novel acid–base exchange that led to the reprotonation of **7′a** into **7a** with the concomitant formation of the lithium alcoholate **8′a**. Finally, the lithium alcoholate **8′a** substituted the chlorine of **7a** and led to the desired methylenebis(phosphonate)-$^{1}$P,$^{2}$P-glycosyldisubstituted **1a** in 60% yield of crude product (30% yield in isolated product).

The reaction has been repeated starting from **2a** and with 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose **8c** as the second glucide according to Scheme 2. The expected methylenebis(phosphonate)-$^{1}$P,$^{2}$P-glycosyldisubstituted **1c** was obtained in 98% yield of crude product (67% in isolated product). In this last case, it was noteworthy that the second sugar moiety was linked to the methylenebis(phosphonate) bridge via the anomeric hydroxyl. Owing to the same method, the methylenebis(phosphonate) **1b** was prepared from ethyl (1-*O*-methyl-2,3-*O*-isopropylidene-β-D-*ribo*furanosyl) methylphosphonate **2b** and 2,3-*O*-isopropylidene uridine **8a** (66% in crude product and 41% in isolated product). The $^{31}$P NMR data of products **1a** and **b** presented four singlets as resonance signals between 17.10 ppm and 18.21 ppm corresponding to the four expected diastereomers in a ratio close to 25% for each of them. The product **1c** presented a more complex spectrum with a multiplet between 16.08 ppm and 17.16 ppm which

could be assigned to the mixture of the diastereomers resulting from the two chiral phosphorus atoms and from the α and β anomer configurations of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose moiety.[14]

In conclusion, the preparation of new lithiated carbanions derived from ethyl glycosyl methylphosphonates and their use in the one-pot alkylidene diphosphorylation of 2,3-*O*-isopropylidene uridine or 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose appears as a novel interesting method to approach the methylenebis(phosphonate) analogues of natural $P^1$,$P^2$-glycosyl-disubstituted pyrophosphates. It has to be noted that this four-step reaction that allows the preparation of such relatively complex structures takes place in one-pot and with a total duration of 2 h, at the most, to obtain the crude product. Chemoselective hydrolysis of the ethyl esters which would suppress the phosphorus stereochemistry in the final products and would allow the obtention of **1a**–**c** as diester dianions, closely related to natural compounds, was under investigation.

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14. Product **1b**: IR (KBr film/$cm^{-1}$) $\nu_{max}$: 1720, 1630, 1450, 1250, 1050; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ ppm: 1.18–1.32 (m, 12H), 1.40 (s, 3H), 1.49 (s, 3H), 2.49 (triplet-like, 2H, $^2J_{H-P} = 20$ Hz), 3.25 (s, 3H), 4.00–4.29 (m, 10H), 4.54 (m, 1H), 4.65 (m, 1H), 4.83–4.92 (m, 2H), 5.25 (s, 1H), 5.64–5.74 (m, 2H), 7.43 (m, 1H), 10.06 (s, 1H); $^{13}$C NMR (62.896 MHz, $CDCl_3$) $\delta$ ppm: 16.0, 24.2, 25.0 (triplet-like, $^1J_{C-P} = 135$ Hz), 26.1, 26.8, 27.2, 54.8, 62.8, 65.8, 80.3, 81.2, 83.9, 85.0, 93.4, 102.5, 109.3, 112.3, 114.3, 141.9, 150.1, 163.4; $^{31}$P NMR (101.256 MHz, $CDCl_3$): 17.9 (s, 1P), 17.4 (s, 1P), 17.2 (s, 1P), 17.1 (s, 1P); MS ($FAB^+$) *m*/*z* calculated for $C_{26}H_{42}O_{15}N_2P_2$ $[M]^+$: 684.2. Found: 685.3 $[[M+1]^+$, 60%], 653.2 $[[M+1-MeOH]^+$, 30%].