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One-Pot Carbanionic Synthesis of P^1,P^2-Diglycosyl, P^1,P^1,P^2-Triglycosyl, and P^1,P^1,P^2,P^2-Tetraribosyl Methylenediphosphonates

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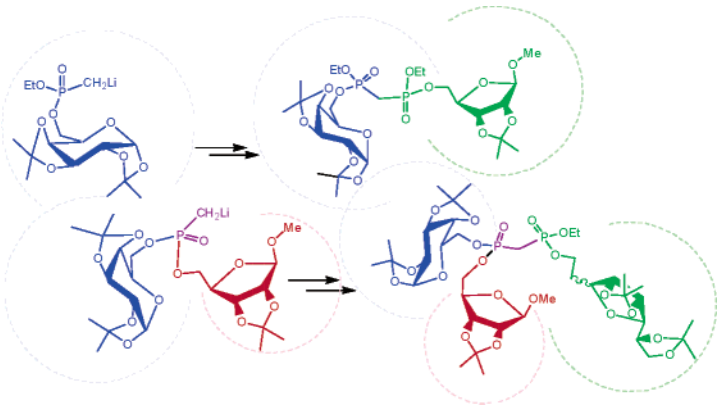

Novel lithiated carbanions derived from ethyl glycosyl- and diglycosyl methylphosphonates were used in a direct and convenient synthesis of P^1,P^2-diglycosyl, P^1,P^1,P^2-triglycosyl, and P^1,P^1,P^2,P^2-tetraribosyl methylenediphosphonates involving a one-pot methylidenediphosphonylation of sugars.

Introduction

The chemical combination of two sugars and the pyrophosphoric acid is a fundamental part of the molecular backbone of reactive biological intermediates. The importance of nucleoside diphosphate sugars is well-known as soluble precursors involved in cell-wall polysaccharide biosynthesis.

Considerable efforts have been made in the structural modifications of nucleoside diphosphate sugars, particularly in the replacement of the phosphodiester linkage. Thus, methylenediphosphonate linkage has been developed as an interesting replacement of the pyrophosphate moiety. Indeed, the isosteric replacement of phosphate with methylenephosphonate or other phosphonates is now well-known and includes resistance to hydrolysis and heightened biochemical stability overall.[1] Furthermore, the methylenediphosphonate moiety should allow decreased hydrophilicity of the substrates and facilitate cell penetration while pyrophosphatases attack. These modified nucleoside diphosphate sugars open different prospects in chemotherapy.[2]

For instance, uridine 5′-[(α-D-galactopyranosylhydroxyphosphinyl)methyl]phosphonate inhibited competively a specific glycoprotein galactosyltransferase.[3] The synthesis, structural features, and biological activity of nucleoside methylenediphosphonate analogues of ADP or GDP have been studied.[4] The synthesis of NAD^+ analogue incorporating a methylenediphos-

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phonate linkage in place of the natural pyrophosphate has been reported to act as an inhibitor of ADP ribosyl cyclase and to resist phosphatase degradation.[5] Recently, methylenediphosphonate analogues of MAD (mycophenolic acid adenine dinucleotide),[6] TAD (thiazole-4-carboxamide adeninedinucleotide),[7] and BAD (benzamide adenine dinucleotide)[7a,8] were synthesized as potential inhibitors of IMPDH (inosine monophosphate deshydrogenase). Synthesis of a possible 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 methylenediphosphonate linker, has been accomplished.[9]

However, rational design of transition-state mimics including trisubstrate analogues (sugar donor, sugar acceptor, and nucleotide) seems unknown.

To the best of our knowledge, only the synthesis of nucleoside methylenediphosphonate sugars or dinucleoside methylenediphosphonates is documented.[2,10] As part of our program in the synthesis of analogues of natural glycosyl-disubstituted pyrophosphates, we have recently described preliminary results on the one-pot alkylidene diphosphorylation of 2,3-*O*-isopropylidene uridine or 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose to synthesize the methylenediphosphonate analogues of natural P^1,P^2-glycosyl-disubstituted pyrophosphates.[11]

We report here the full paper concerning the direct and general procedure for obtaining P^1,P^2-diglycosyl, P^1-glycosyl, P^2-nucleoside methylenediphosphonates, and P^1,P^1,P^2-triglycosyl- and P^1,P^1,P^2,P^2-tetraglycosyl methylenediphosphonates that exploits our carbanionic method based on the alkylidenediphosphorylation of nucleophiles.[12]

Results and Discussion

Our first goal was the preparation of a series of P^1,P^2-diglycosyl and P^1-glycosyl-P^2-nucleoside methylenediphosphonates to investigate the synthetic potential of the strategy.

Synthesis of P^1,P^2-Diglycosyl and P^1-Glycosyl-P^2-Nucleoside Methylenediphosphonates 5-*sugar*-*sugar*. Different approaches to the chemical synthesis of such metabolically stable analogues of dinucleoside pyrophosphates have been proposed. A current synthetic approach to these analogues exploits dicyclohexylcarbodiimide- (DCC-) catalyzed direct coupling of nucleosides and methylenediphosphonate analogues of nucleotides.

For instance, Marquez et al.[13] report the preparation of TAD analogues in 36% yield according to the method. Pankiewicz et al.[8] suggest an interesting process with nucleoside bicyclic trisanhydrides found in the reaction between nucleoside 5′-methylenediphosphonates and DCC. Thus, the reaction of the trisanhydride derivative of 2′,3′-*O*-isopropylideneadenosin-5′-yl with 2′,3′-*O*-isopropylidenetiazofurin leads to the β-methylene-TAD in 92% overall yield.[10a] The method has been recently used in the synthesis of MAD.[6a] However, these preparations are limited to small-scale syntheses, the purification of key intermediates by reversed-phase HPLC being required.

Nucleoside methylenediphosphonate sugars have been prepared by condensation of α-D-glycosyl 1-(methylenediphosphonate) with 2′,3′-di-*O*-acetyladenosine by use of 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole as coupling agent; D-glycosyl 1-(methylenediphosphonate) precursor is obtained in three steps from glycosylpentaacetate and [(diphenoxyphosphinyl)methyl]-phosphonic acid at 170 °C under vacuum.[3] More recently, a synthesis of β-methylene-TAD has been proposed, based on the use of two rounds of Mitsunobu esterification with conveniently protected nucleosides[14] starting from methylenebisphosphonic acid tribenzyl ester according to the method of Saddy et al.[15] However, the success of this strategy is still limited by the availability of the tetrabenzyl methylenediphosphonate precursor.[15]

Our process is exemplified in Scheme 1 in the case of the preparation of P^1,P^2-diglycosyl methylenediphosphonate **5**-*gal*-*rib*. It involved a five-step sequence based on a selective phosphonomethylation of ethyl phosphorodichloridate **2** by use of the lithium anion **1′**-*gal* derived from ethyl glycosyl methylphosphonate **1**-*gal* followed by a direct substitution of the chlorine atom of the intermediate **3**-*gal* by the nucleophilic lithium alcoholate **4′**-*rib* formed in situ after addition of the second sugar **4**-*rib*.

Critical to the success of this approach was the preparation of the starting material, ethyl glycosyl methylphosphonate **1**-*sugar*, and the derived lithiated carbanions **1′**-*sugar*, unknown until now. The model starting compound **1**-*gal* was first prepared. The 1,2:3,4-di-*O*-isopropylidene α-D-galactopyranoside **4**-*gal* (1 equiv) was slowly added to methylphosphonic dichloride **6** in the presence of tetrazole as catalyst and diisopropylethylamine. After 5 h of stirring, ethanol in excess was added.

The double substitution could not be avoided and a mixture of the expected product **1**-*gal* accompanied by the disubstituted product **1**-*gal*-*gal* was obtained. After silica gel chromatography, compounds **1**-*gal* and **1**-*gal*-*gal* were isolated in 39% and 15% yield, respectively (Scheme 2). We found a more convenient approach starting from the first addition at −78 °C of the lithium

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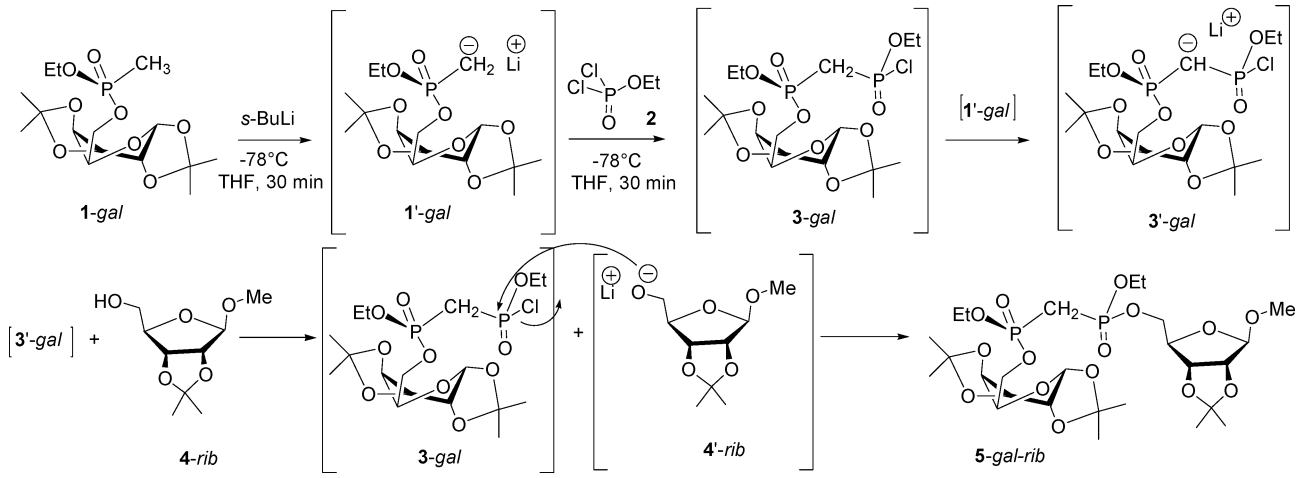
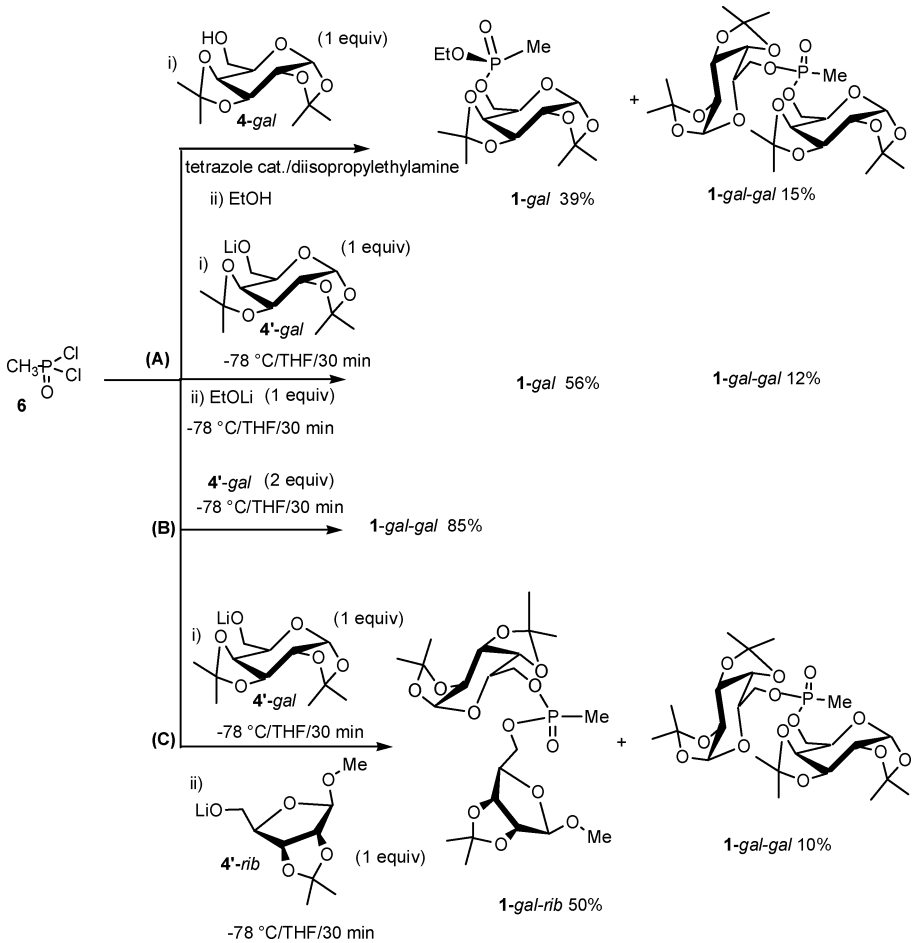
SCHEME 1. Preparation of 5-*gal-rib* as an Example of Synthesis of 5-*sugar-sugar*

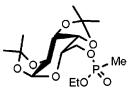
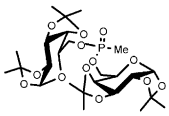
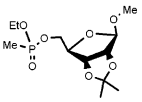
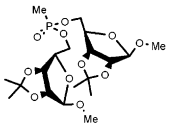
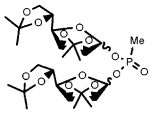
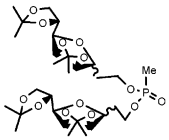
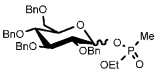
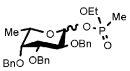


SCHEME 2. Preparation of P-Chiral Ethyl Glycosyl Methylphosphonate 1-*gal*, P-Chiral Galactosyl Ribosyl Methylphosphonate 1-*gal-rib*, and Symmetrical Diglycosyl Methylphosphonate 1-*gal-gal*



alcoholate **4′**-*gal* derived from 1,2:3,4-di-*O*-isopropylidene α-D-galactopyranoside **4**-*gal* onto methylphosphonic dichloride **6**, followed after 30 min by addition of lithium ethylate at this same temperature. Although these conditions could not totally avoid the double substitution, the phosphonate **1**-*gal* was obtained in 56% yield with 12% of the digalactosyl methylphosphonate byproduct **1**-*gal-gal* isolated after column chromatography (Scheme 2, procedure A, and Table 1). This last method has several advantages in terms of better control of the monosubstitution leading to the desired product, ease of purification, and a shorter reaction time. When a stoichiometric amount of the sugar alcoholate **4′**-*gal* was added onto methylphosphonic dichloride at −78 °C, the sole symmetrical diglycosyl methylphosphonate **1**-*gal-gal* was obtained (Scheme 2, procedure B). Interestingly, we noted that the method could also deliver successfully P-chiral diglycosyl methylphosphonates when the sequence used two different lithium sugar alcoholates successively. Only one example was studied with lithium alcoholate **4′**-*gal* as the first reagent and **4′**-*rib* for the second. The bulkier sugar alcoholate **4′**-*gal* must be introduced in the

TABLE 1. Preparation of P-Chiral Ethyl Glycosyl Methylphosphonates 1-*sugar* and Symmetrical Diglycosyl Methylphosphonates 1-*sugar-sugar*

Entry	1-*sugar*(dr)[b]	Procedure %Yield[a]	δ ^{31}P-NMR	1-*sugar-sugar*(dr)[b]	Procedure %Yield[a]	δ ^{31}P-NMR
1	**1**-*gal* (1:1) 	**A:**56 **B:**0	29.33 28.82	**1**-*gal-gal* 	**A:**12 **B:**85	30.10
2	**1**-*rib* (3.5:1) 	**A:**40 **B:**0	28.55[c] 27.92	**1**-*rib-rib* 	**A:**22 **B:**90	29.25
3	**1**-*man*-a (4:1:3.4:1.6) 	**A:**70	*α*: 30.54[d] *β*: 30.05 *β*′: 29.75 *α*′: 29.58	**1**-*man*-a-*man*-a 	**A:**4	*α*: 30.54 *β*: 30.05 *α*′: 29.75 *β*′: 29.58
4	**1**-*man*-b[e] (1.3:1.1:1.3:1) 	**A:** 70 **B:** 0	*α*′: 32.30 *α*: 32.09 *β*: 31.95 *β*′: 31.90	**1**-*man*-b-*man*-b (1.2:1:1.6:1.4) 	**A:** 15 **B:** 85	*β*: 31.50 *α*: 31.40 *α*′: 31.14 *β*′: 30.95
5	**1**-*glc* (3.2: 2.2:1.2:1) 	**A:**15[f]	*β*′: 32.88 *α*′:32.43 *β*: 32.03 *α*: 31.30			
6	**1**-*fuc* 	**A:**15[f]	31.80-31.75 31.22 30.57			

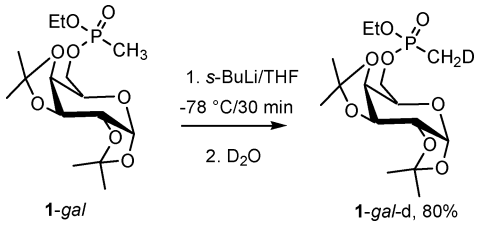
[a] Yield of purified products. [b] Diastereomeric ratios evaluated by ^{31}P NMR on the crude products, specified as *β*: *β*′:α: α′anomer order if necessary. [c] Major isomer. [d] It was possible to separate α-epimer and *β*-epimer and to isolate pure α-epimer. [e] *Thus named as the molecule includes* D-manno moiety. [f] Unstable product.

first step to ensure the best control of the monosubstitution, followed by the addition of the most reactive sugar alcoholate **4′**-*rib* in the second step for an efficient second substitution. As for the phosphonate **1**-*gal*, these conditions could not avoid the partial double substitution of **6** by **4′**-*gal* in the first addition step. Consequently, the phosphonate **1**-*gal*-*rib* was obtained in 50% yield with 10% of the digalactosyl methylphosphonate byproduct **1**-*gal*-*gal* isolated after column chromatography (Scheme 2, procedure C).

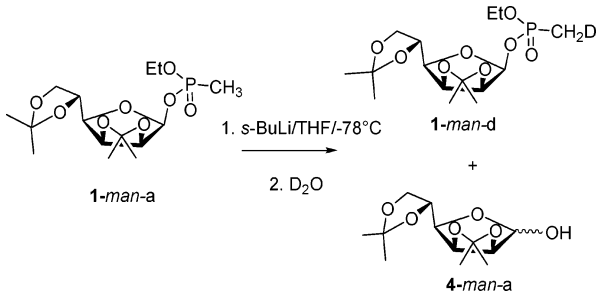
Different P-chiral ethyl glycosyl methylphosphonates **1**-*sugar* and symmetrical diglycosyl methylphosphonate **1**-*sugar*-*sugar* were prepared in that way (Table 1).

As clearly indicated from the ^{31}P NMR spectra of the crude materials, procedure A allows the preparation of glycosyl methylphosphonates **1**-*sugar* with a wide range of sugars (protected D-galactose, D-ribose, and D-mannose). It is possible to introduce the sugar via different hydroxyls (primary alcohol of protected D-galactose or D-ribose, anomeric hydroxyl of protected D-mannose, or primary alcohol of 3,6-anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*manno*-octitol). *O*-benzyl protection is not easily compatible with the basic medium and consequently the yields are decreased to a major extent with tetra-*O*-benzyl-D-glucopyranose and tri-*O*-benzyl-D-fucopyranose (Table 1, entries 5 and 6). Moreover, the corresponding products ethyl glycosyl methylphosphonates **1**-*glc* and **1**-*fuc* are unstable. It can be also observed that relative amounts of the byproduct diglycosyl methylphosphonate **1**-*sugar*-*sugar* formed in procedure A indicate the following reactivity sequence

SCHEME 3. Deuteriolysis of 1-*gal*



SCHEME 4. Deprotonation and Deuteriolysis of 1-*man*-a



for alcoholate **4′**-*sugar*: **4′**-*rib* > **4′**-*man*-b > **4′**-*gal* > **4′**-*man*-a.

In the case of **1**-*sugar*, the reaction leads to the creation of a phosphorus stereogenic center and different diastereomers are observed by NMR analysis. For **1**-*gal* and **1**-*rib*, both epimers are detected by ^{31}P and ^{13}C NMR. In the case of **1**-*man*-a, ^{1}H NMR data confirm the formation of α and β anomers, and ^{31}P NMR reveals the presence of four diastereomers. The ^{1}H NMR spectrum of crude **1**-*man*-a allows the characterization of four stereomers.

In α stereomers, the anomeric hydrogen appears as a doublet at 5.66 ($^{3}J_{H-P}$ = 6 Hz) and 5.58 ppm ($^{3}J_{H-P}$ = 6 Hz), respectively, with a coupling constant J_{H1-H2} = 0 Hz, characteristic of the α-anomer. The ^{13}C NMR spectrum shows a doublet for C-1 at 103.0 and 102.3 ppm.

In ^{1}H NMR, β anomers present a doublet of doublets for H-1 at 5.54 and 5.51 ppm, and in ^{13}C NMR a doublet for C-1 at 96.9 and 96.7 ppm is seen, , characteristic of β-anomer. The carbon C-2 of the sugar is also coupled with the phosphorus atom with a coupling constant J_{C2-P} = 10 Hz for α-anomers and J_{C2-P} = 6 Hz for β-anomers.

Similarly, careful examination of ^{1}H NMR spectra of **1**-*man*-b shows clearly the presence of α- and β-epimers. In α-epimer, the H-4 signal of resonance is a doublet at 4.48 ppm ($^{3}J_{H4-H5}$ = 6 Hz) with a typical negligible coupling with H-3, consistent with α-configuration. In the β-epimer, the H-4 signal is a multiplet between 4.56 and 4.63 ppm, whereas H-6 and H-3 resonances shift toward a higher field at 3.42 and 3.58−3.64 ppm, respectively. As for **1**-*man*-a, the ^{31}P NMR spectrum of **1**-*man*-b confirms the presence of four stereomers (s, 32.30; s, 32.09; s, 31.95; s, 31.90).

It appears that there is little to no control of diastereoselectivity in the different cases, but it is difficult to rationalize the corresponding data as a consequence of the complexity of the substitution mechanism at P(V). Separation of diastereomers succeeded only in the case of **1**-*man*-a, where it was possible to isolate a pure α-anomer and the mixture of both β-anomer and β'-anomer by silica gel chromatography. In other cases, diastereomeric mixtures were obtained after chromatographic purification. However, from a biological point of view, it has to be noted that the obtention of pure diastereomer **1**-*sugar* was not very important as ethyl phosphonates or phosphates were not good prodrugs for phosphonates or phosphates. In return, selective hydrolysis of ethyl ester that removes the chirality at phosphorus was important, as it can afford bioactive glycosyl methylphosphonates. Consequently, selective removal of ethyl protecting group by use of trimethylbromosilane/methanol as reagent was attempted, and this procedure fully succeeded with the phosphonate **1**-*gal*. Unfortunately, in other cases, removal of ethyl group was not selective and was accompanied by a partial glycosyl O−P bond fragmentation.

TABLE 2. Optimization of the Deuteriolysis of 1-*man*-a

reaction time (min)	**4**-*man*-a[a]	**1**-*man*-a	**1**-*man*-d[b]
5	41	38	21
15	59	9	32
30	77	4	19

[a] Values were determined in ^{1}H NMR from the integration of H-1 signals of **4**-*man*-a (α: s, 5.32 ppm; β: d, 4.56 ppm) and H-1 signals of **1**-*man*-a and **1**-*man*-d (m, 5.58−5.52 ppm). [b] Values were determined in ^{1}H NMR from the integration of DCH_2P (dt, 1.57 ppm; dt, 1.46 ppm) and Me of an isopropylidene group (s, 1.39 ppm).

TABLE 3. ^{31}P NMR of the Different Phosphorus Intermediates in the Methylene Diphosphonylation of 4-*sugar*

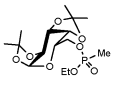
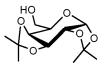
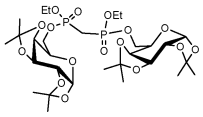
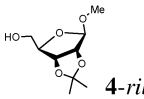
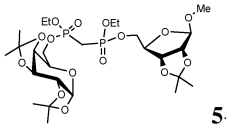
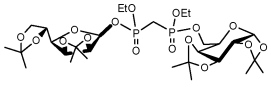
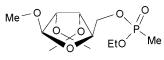
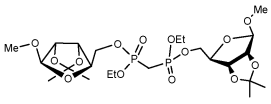
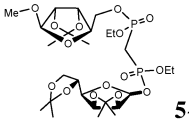
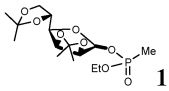
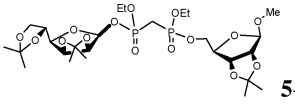
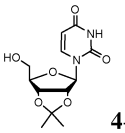
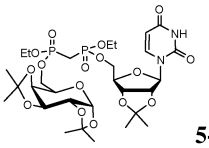
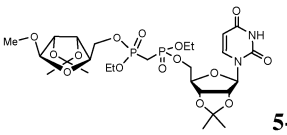
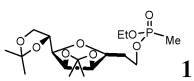
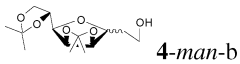
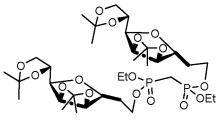
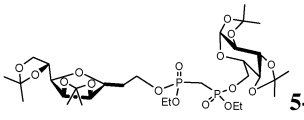
compound	δ ^{31}P (THF)
1-*sugar*	s, ∼29 ppm
1-*sugar*	s, ∼58 ppm
3-*sugar*	d, ∼50 ppm, $^{2}J_{P-P}$ = 76 Hz
	d, ∼36 ppm, $^{2}J_{P-P}$ = 76 Hz
5-*sugar*-*sugar*	d, ∼18 ppm, $^{2}J_{P-P}$ = 5 Hz
	d, ∼16 ppm, $^{2}J_{P-P}$ = 5 Hz

Ethyl glycosyl methylphosphonates **1**-*sugar* being so obtained, a preliminary investigation of the formation and properties of the derived lithiated carbanions **1′**-*sugar* was carried out with the model phosphonate **1**-*gal* as starting material. The formation of the lithiated carbanion **1′**-*gal* occurred when the phosphonate **1**-*gal* was treated with *s*-BuLi in THF at −78 °C with stirring for 30 min at this temperature (Scheme 3). The choice of the base *s*-BuLi was important and resulted from our previous works on alkylidene diphosphorylation, where we showed that *s*-BuLi limits the formation of side products.[12] The carbanion is characterized in THF by a ^{31}P NMR broad signal at 58 ppm, typical of this type of lithiated species. After deuteriolysis of the reaction medium, the ^{13}C NMR of the crude product showed a complete deuteration (80% in isolated pure product, dr 1:1). The carbon *C*H_2D−P appeared as coupled both to phosphorus and deuterium with a doublet of triplets centered at 11.1 ppm (J_{C-P} = 144.5 Hz, J_{C-D} = 21.5 Hz) for one diastereomer and at 11.2 ppm for the other. The absence of the *C*H_3−P signal in the crude product of deuteriolysis showed the complete metalation of **1**-*gal* with *s*-BuLi. This result was confirmed by mass spectroscopy with [M + 1] = 368 found for the deuterated product **1**-*gal*-d.

Surprisingly, the thermal stability of the carbanion **1′**-*gal* is lower than that of the lithium carbanions derived from dialkyl methylphosphonates, where the stability increases with the steric hindrance at phosphorus.[16] On warming to −50 °C the carbanion **1′**-*gal* is degraded after some minutes, as demonstrated by quenching of the reaction mixture with water at this temperature. Only a mixture of complex unidentified degradation products is obtained without any trace of the starting phosphonate **1**-*gal*.

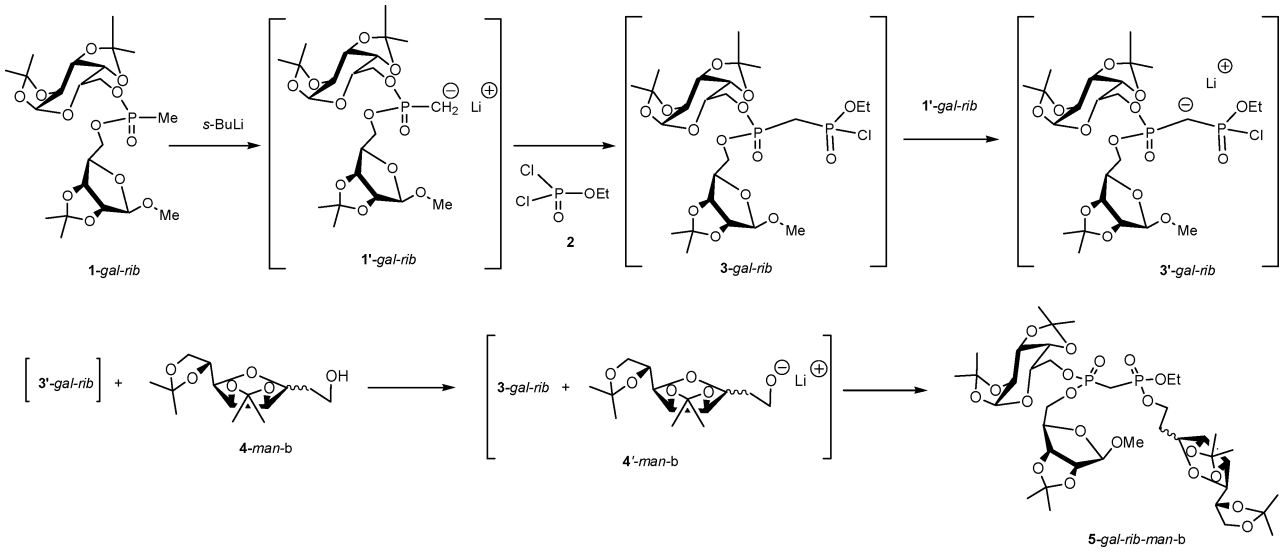
(16) Teulade, M. P.; Savignac, P. *J. Organomet. Chem.* **1986**, *312*, 283−295.

TABLE 4. Preparation of Diglycosyl Methylenediphosphonates 5-*sugar-sugar*

Starting material	Nucleophile	Product	% Yield	δ ^{31}P-NMR
1-*sugar*	**4-***sugar*	**5-***sugar-sugar*		
 **1**-*gal*	 **4**-*gal*	 **5**-*gal-gal*	48[a] (94)[b]	s, 17.97 s, 17.59
1-*gal*	 **4**-*rib*	 **5**-*gal-rib*	73[a] (87)[b]	s, 17.44 s, 17.09
1-*gal*	 **4**-*man*-a	 **5**-*gal-man*-a	67[a] (98)[b]	m, 17.35-15.80
 **1**-*rib*	**4**-*rib*	 **5**-*rib-rib*	56[a] (42)[b]	s, 17.36
1-*rib*	**4**-*man*-a	 **5**-*rib-man*-a	61[a] (93)[b]	s, 16.81 s, 15.67
 **1**-*man*-a	**4**-*gal*	**5**-*gal-man*-a	30[a] (60)[b]	m, 17.35-15.80
1-*man*-a	**4**-*rib*	 **5**-*man*-a-*rib*	22[a] (55)[b]	m, 16.81-15.67
1-*gal*	 **4**-*uri*	 **5**-*gal-uri*	30[a] (60)[b]	m, 18.21-16.8
1-*rib*	**4**-*uri*	 **5**-*rib-uri*	41[a] (66)[b]	s, 17.89(1P) s, 17.42(1P) s, 17.17(2P)
 **1**-*man*-b	 **4**-*man*-b	 **5**-*man-b-man-b*	53[a] (60)[b]	m, 21.65-20.56
1-*man*-b	**4**-*gal*	 **5**-*man-b-gal*	64[a] (80)[b]	m, 21.40-20.41

[a] Isolated yields of analytically pure product. [b] Yields evaluated from ^{31}P NMR analysis of crude product

SCHEME 5. Synthetic Route to 5-*sugar*-*sugar*-*sugar* Exemplified with 5-*gal*-*rib*-*man*-b



Similar conditions for the deprotonation of **1**-*rib* and **1**-*man*-b were investigated. As for **1**-*gal*, metalation was complete after 30 min of stirring with *s*-BuLi at −78 °C.

However, in the case of both β-anomers of **1**-*man*-a, deprotonation with *s*-BuLi was incomplete and was accompanied by 2,3:5,6-di-*O*-isopropylidene α,β-D-mannofuranose **4**-*man*-a as a side product (Scheme 4). It is more than likely that partial dephosphorylation results from O−P bond fragmentation. Indeed, pure starting material **1**-*man*-a itself is fragile and rapidly degrades, leading to **4**-*man*-a in some hours at room temperature. A solution of **1**-*man*-a in methanol also degrades, yielding **4**-*man*-a without a trace of methyl diisopropylidene mannoside, which excludes a substitution of the phosphonate moiety by MeOH at the anomeric carbon with a C−O bond break. Obviously the P−O bond appears to be more fragile than the anomeric C−O bond in **1**-*man*-a. Consequently, the partial dephosphorylation observed in the deuteriolysis of **1′**-*man*-a can be simply explained by nucleophilic assistance of the basic species present in the reaction medium to the natural trend to the P−O break in the starting compound **1**-*man*-a. It cannot be excluded either that a "ketene-like" β-elimination mechanism of the carbanionic species **1′**-*man*-a takes place.

Consequently, deuteriolysis of lithiated carbanion derived from **1**-*man*-a and *s*-BuLi was studied at different reaction times to examine the variation of the metalation/degradation ratio. The best conditions of metalation were obtained with stirring of the reaction medium for 15 min at −78 °C (Table 2).

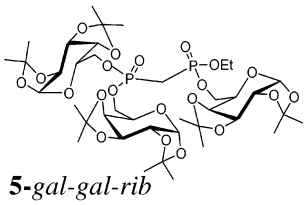
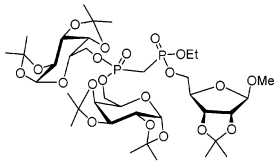
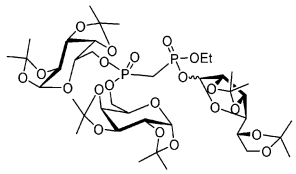
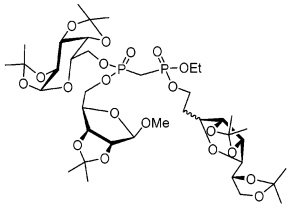
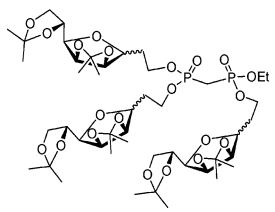
With the conditions of deprotonation of **1**-*sugar* into **1′**-*sugar* in hand, the reactivity of the lithiated carbanion **1′**-*sugar* was then studied in the one-pot methylenediphosphonylation strategy (Scheme 1). Once formed, the carbanion **1′**-*sugar* reacted with the readily available ethyl phosphorodichloridate **2**. The reaction was monitored by ^{31}P NMR spectroscopy to ensure the complete formation of the monochlorinated intermediate **3**-*sugar* (Table 3). As the addition of **2** proceeded, spontaneous metalation of **3**-*sugar* by the carbanion **1′**-*sugar* arose and gave the lithiated diphosphorylated anion **3′**-*sugar*. It was noted that the latter intermediate was stable from −78 °C up to room temperature, which made ^{31}P NMR analyses easier for successive samples of the reaction medium. Thus, to obtain the complete conversion of phosphorodichloridate **2** into **3′**-*sugar*, it was necessary to treat **2** with an excess of carbanion **1′**-*sugar* (2 equiv). Subsequent treatment of the intermediate **3′**-*sugar* with 1 equiv of a suitable protected sugar **4**-*sugar* from −78 °C to room temperature involved a novel acid−base exchange that led to the reprotonation of **3′**-*sugar* into **3**-*sugar* with the concomitant formation of the lithium alcoolate **4′**-*sugar* derived from **4**-*sugar*. Finally, **4′**-*sugar* substituted the chlorine of **3**-*sugar* to afford the desired crude product **5**-*sugar*-*sugar*.

The chromatographic separation of the recovered **1**-*sugar* and **5**-*sugar*-*sugar* was easy, except in the case of **1**-*man*-b and **5**-*man*-b-*man*-b, where a graduated elution was necessary. The excess of ethyl glycosyl methylphosphonate **1**-*sugar* was quantitatively recovered after chromatography.

Different nucleophilic sugars **4** were tested with different ethyl glycosyl methylphosphonates **1**-*sugar* (Table 4). Satisfactory yields were obtained in all cases where the first sugar was linked to the phosphonate **1** by the primary alcohol (48−73% yield in pure product). The reaction was relatively insensitive to changes in the nature of **4**-*sugar* (*gal*, *rib*, *man*-a, *man*-b) and the nature of the nucleophilic hydroxyl group (primary alcohol or anomeric hydroxyl). The particular example of 2,3-*O*-isopropylideneuridine **4**-*uri* as nucleophile has to be noted. The reaction sequence can be used to provide a convenient one-pot synthesis of nucleoside methylenediphosphonate sugars in reasonable yields (respectively 30% and 41% yield for isolated products **5**-*gal*-*uri* and **5**-*rib*-*uri*). The phosphonate **1**-*man*-a as starting material constituted a real difficulty as a result of the great fragility of the anomeric link between the mannosyl and phosphoryl moieties in basic medium. In the conditions defined above (metalation of **1**-*man*-a for 15 min at −78 °C), it was nevertheless possible to effect in 30% yield the methylenediphosphonylation of nucleophilic 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **4**-*gal* into the expected mannosyl galactosyl methylenediphosphonate **5**-*gal*-*man*-a. It was noted that the procedure to prepare the same compound from **1**-*gal* by use of **4**-*man*-a as nucleophilic sugar was better (67% yield in pure product) and showed the versatility of the method.

The presence of a spacer arm of two methylene units between the furanic cycle and the phosphoryl group decreased the nucleophilicity of **1′**-*man*-b so that the reaction of **1′**-*man*-b with **2** had to be carried out at −50 °C for 1.5 h to optimize the formation of **3**-*man*-b. In these conditions, diglycosyl diphosphonates **5**-*man*-b-*man*-b and **5**-*man*-b-*gal* were obtained with-

TABLE 5. Preparation of Triglycosyl Methylenediphosphonates 5-*sugar-sugar-sugar*

5-*sugar-sugar-sugar*	%Yield[a]	(dr)[b]	δ ^{31}P-NMR
5-*gal-gal-gal*	65	1.2:1	18.44(s, 2P), 17.74(s, 1P), 17.42(s, 1P)[c]
			18.44(s, 2P), 17.79(s, 1P)-17.46(s, 1P)
5-*gal-gal-rib*	56	1:1	21.87(s, 2P)-21.30(s, 1P)-21.12(s, 1P)
			21.82(s, 2P)-21.12(s, 1P)-21.06(s, 1P)
5-*gal-gal-man*-a	52	7:2.1:1.7:1	*α*: 22.19(d)-20.55(d)
			*β*: 22.05(d)-19.86(d)
			α′: 21.44(d)-19.59(d)
			β′: 21.12(d)-19.44(d)
5-*gal-rib-man*-b	72	1.8:1	21.46-20.40 (m)[d,e]
			
5-*man*-b-*man*-b-*man*-b	30	1.8:1	21.46-20.40 (m)[d,e]
			

[a] Yield of purified products. [b] Diastereomeric ratios evaluated by ^{31}P NMR on the crude products, specified as α′: α:*β*′: *β* anomer order if necessary. [c] Major isomer. [d] Diastereomeric ratio was determined by integration of H-2 signals of *man*-b moiety by ^{1}H NMR. [e] Only two stereomers could be distinguished in ^{1}H NMR.

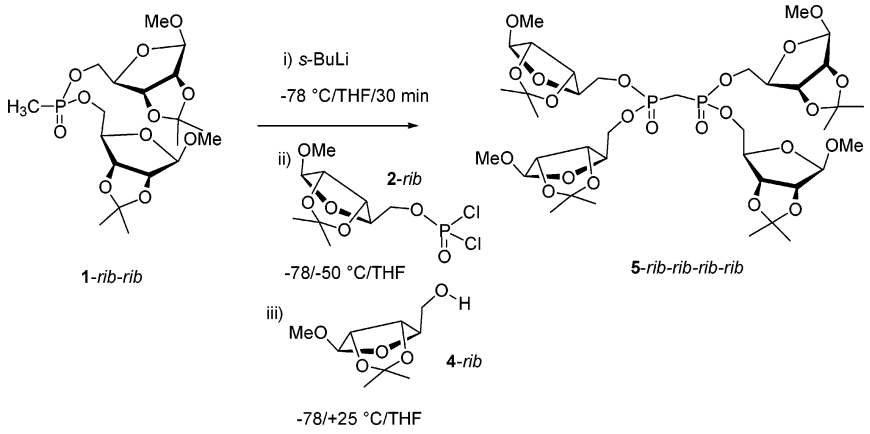
out difficulty in satisfactory yields. The particular example of **5**-*man*-b-*man*-b is interesting as the D-manno configuration is known to confer a specific chemical character to different biological systems and to serve as a recognition site.[17]

In the precedent case of methyl glycosylphosphonates **1**-*sugar*, ^{31}P NMR data allow us to identify all stereomers. In contrast, ^{31}P NMR of P^1,P^2- diglycosyl diphosphonates **5**-*sugar-sugar* cannot be used as stereochemical indicators. Although ^{31}P NMR is generally very sensitive to the stereoelectronic changes at the phosphorus atom, it appears here that a glycosyl substituent at P^1 and another one different at P^2 produce similar environments around the P^1 and P^2 atoms. Thus, according to Table 4, the chemical shifts of **5**-*gal-gal*, **5**-*gal-rib*, **5**-*rib-rib*, and **5**-*rib-man*-a do not differ notably. In the cases of **5**-*gal-uri*, **5**-*rib-uri*, and **5**-*man*-b-*man*-b, the resonances occur at closely related *δ* ^{31}P values. Moreover, products **5**-*sugar-sugar* were obtained as a mixture of inseparable diastereomers after chromatographic purification.

As mentioned above for the simple ethyl glycosyl methylphosphonates **1**-*sugar*, an interesting point was to examine

(17) (a) Ponpipom, M. M.; Shen, T. Y.; Baldeschwieler, J. D.; Wu, P.-S. Modification of liposome surface properties by synthetic glycolipids. In *Liposome Technology*; Gregoriadis, G., Ed.; CRC Press: Boca Raton, FL, 1984; Vol. III, pp 95−115. (b) Slama, J.; Rando, R. R.; *Biochemistry* **1980**, *19*, 4595−4600. (c) Ponpipom, M. M.; Bugianesi, R. L.; Robbins, J. C.; Doebber, T. W.; Shen, T. Y. *J. Med. Chem.* **1981**, *24*, 1388−1395. (d) Doebber, T. W.; Wu, M. S.; Bugianesi, R. L.; Ponpipom, M. M.; Furbisch, F. S.; Barranger, J. A.; Brady, R. O.; Shen, T. Y. *J. Biol. Chem.* **1982**, *257*, 2193−2199.

SCHEME 6. Preparation of 5-*rib-rib-rib-rib*



the removal of the ethyl ester (and consequently the removal of chirality at the phosphorus atom) to obtain potent bioactive compounds. With Me_3SiBr/MeOH or Me_3SiBr/Et_3N/MeOH as reagent, we observed, in the cases of **5**-*man*-b-*gal* and **5**-*man*-b-*man*-b, that removal of ethyl group was slowing down and consequently was not selective and accompanied by mannosyl O−P fragmentation.

Synthesis of P^1,P^1,P^2-Triglycosyl Methylenediphosphonates 5-*sugar-sugar-sugar*. The complete one-pot carbanionic synthesis of P^1,P^2-diglycosyl methylenediphosphonates in hand, our attention was then turned to the possible preparation of the first P^1,P^1,P^2-triglycosyl methylenediphosphonates **5**-*sugar-sugar-sugar* by this way.

Deprotonation of **1**-*sugar-sugar* parallels similarly that described above with **1**-*sugar*, but the conditions have had to be adjusted to the particular structures of **5**-*sugar-sugar-sugar* (Scheme 5, Table 5). Use of *n*-BuLi or *s*-BuLi provided lithium diglycosyl methylphosphonate **1′**-*sugar-sugar* cleanly and quantitatively after 30 min in THF at −78 °C. Contrarily to **1**-*sugar*, the starting phosphonate **1**-*sugar-sugar* was not very sensitive to the nature of the lithiated base, and no significant difference on the formation of byproducts was observed. Generated under these conditions, **1′**-*sugar-sugar* was stable at −78 °C for 30 min, and after addition of **2**, it selectively displaced one chlorine atom of **2** to produce **3**-*sugar-sugar* and then **3′**-*sugar-sugar* after acid−base exchange. However, complete substitution of chlorine atom of **2** was difficult as a result of the steric bulk of the carbanion species **1′**-*sugar-sugar* and was the rate-determining step of the process.

This disadvantage was overcome upon stirring the reaction mixture for 90 min at higher temperature (−50 °C) after addition of **2**. From a practical point of view, we noted a decolorizing of the reaction mixture that indicated the complete substitution and total disappearance of the carbanion **1′**-*sugar-sugar*. Subsequent addition of the nucleophilic **4**-*sugar* provided the reactive intermediate **3**-*sugar-sugar* and the transient lithium alcoholate **4′**-*sugar*. Surprisingly, the displacement of the chlorine atom of **3**-*sugar-sugar* by **4′**-*sugar* required only 1 h at 25 °C for completion. This easy substitution parallels exactly that mentioned above in the preparation of diglycosyl methylenediphosphonates **5**-*sugar-sugar*, where this step was insensitive to the steric effects.

The triglycosyl methylenediphosphonates **5**-*sugar-sugar-sugar* were isolated in moderate to good yields (30−72%). It was noteworthy that the incorporation of a third glycosyl residue did not modify the efficiency of the procedure. The preparation of **5**-*gal-rib-man*-b with two chiral phosphorus atoms confirmed the synthetic interest of the method (72% in pure product), whereas **5**-*man*-b-*man*-b-*man*-b presents a potent biological interest in recognition phenomena.[17] From a practical point of view, it was noted that **5**-*man*-b-*man*-b-*man*-b and **1**-*man*-b-*man*-b in excess were easily separated by chromatography, contrarily to the precedent case of diethyl dimannosyl methylenediphosphonate **5**-*man-b-man*-b, which was difficult to separate from the starting phosphonate **1**-*man*-b. In the case of the chiral P^1,P^2-methylenediphosphonate **5**-*gal-rib-man*-b, the complete structural determination by NMR spectroscopy was difficult and needed heteronuclear single quantum coherence spectroscopy (HSQC), total correlation spectroscopy (TOCSY), and HSQC−TOCSY experiments to facilitate the assignment of individual spin systems (see Supporting Information).

Synthesis of P^1,P^1,P^2,P^2-Tetraglycosyl Methylenediphosphonates 5-*sugar-sugar-sugar-sugar*. To complete the study of the process, we finally described the possible access to tetraglycosyl methylenediphosphonates exemplified in the case of the tetraribosyl methylenediphosphonate **5**-*rib-rib-rib-rib* (Scheme 6). According to the proposed method, the incorporation of a fourth sugar, **4**-*rib*, succeeded after stirring for 48 h at room temperature in the last step of the reaction sequence. Tetraribosyl methylenediphosphonate was so obtained in a reasonable 30% overall yield and constitute the first example of this type of compound. The main difficulty was the final separation of **5**-*rib-rib-rib-rib* from the necessary excess of the starting phosphonate **1**-*rib-rib*, which needed careful chromatography. The symmetry of **5**-*rib-rib-rib-rib* allowed the observation of a typical and unique singlet in ^{31}P NMR at 20.0 ppm, whereas **1**-*rib-rib* gave a singlet at 29.2 ppm. Consequently ^{31}P NMR was used as support to easily control the chromatographic purification of **5**-*rib-rib-rib-rib.*

Conclusion

The preparation of new lithiated carbanions derived from ethyl glycosyl or diglycosyl methylphosphonates and their use in the one-pot alkylidene diphosphonylation of various nucleophilic protected sugars or nucleosides afford a novel and general method to obtain either the methylenediphosphonate analogues of natural P^1,P^2-glycosyl-disubstituted pyrophosphates or a variety of triglycosyl methylenediphosphonates. Moreover, the access to tetraglycosyl methylenediphosphonates appears to be possible. A first structure totally symmetric with the same protected ribosyl phosphonate ester is described. As lithium

carbanions derived from mixed ethyl glycosyl methylphosphonates or from mixed or not mixed diglycosyl methylphosphonates are now accessible, it has to be noted that the method can give the access either to di- or triglycosyl methylenediphosphonates with the same or with different glycosyl phosphonate esters. Combined with the availability of monoglycosyl phosphorodichloridate as electrophilic substrate, the method gives also access to mixed tetraglycosyl methylenediphosphonates. This versatile four-step reaction that provides such relatively complex structures takes place in one pot with easily accessible starting material and in shorter reaction time, in most cases. This new and direct access to di-, tri-, or tetraglycosyl methylenediphosphonates should find different applications in the preparation of compounds of biological interest, if chemoselective hydrolysis of the ethyl ester in the final products can be improved.

Experimental Section

General Procedure for Preparation of P-Chiral Ethyl Glycosyl Methylphosphonates, 1-*sugar* (Protocol A). *n*-BuLi (1 equiv, 5.3 mL, 1.6 M solution in hexanes, 8.5 mmol) was added dropwise to a stirred solution of protected sugar, **4**-*sugar*, or ethanol (1 equiv, 8.5 mmol) in anhydrous THF (15 mL) at −50 °C. After being stirred under nitrogen atmosphere for 30 min, the mixture was allowed to reach room temperature. The so-obtained lithium alcoholate **4′**-*sugar* (1 equiv, 8.5 mmol) was added dropwise to a solution of methyl phosphonic dichloride (1 equiv, 1.13 g, 8.5 mmol) in THF (15 mL) at −78 °C. After the mixture was stirred for 30 min at −78 °C, lithium ethanolate (1 equiv, 8.5 mmol) was added dropwise. The mixture was stirred for 30 min at −50 °C before it was quenched with water (15 mL). The organic layer was extracted with CH_2Cl_2 (3 × 30 mL) and dried over anhydrous sodium sulfate, and solvents were evaporated. Silica gel column chromatography of the residue provided pure **1**-*sugar* in 15−70% yield from **4**-*sugar*.

Ethyl (1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranosyl) Methylphosphonate, 1-*gal*. According to protocol A, 2.21 g (8.5 mmol) of **4**-*gal* yielded 1.74 g (4.7 mmol, 56%) of a 1:1 mixture of **1**-*gal* diastereoisomers and 0.59 g (1.02 mmol, 12%) of **1**-*gal*-*gal*. **1**-*gal*: yellow oil; R_f 0.35 (9:1 ethyl acetate/hexane); IR (KBr plate) 1250, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (d, J = 5.0 Hz, 1 H), 4.61 (dd, J = 7.9, 2.5 Hz, 1 H), 4.33 (dd, J = 5.0, 2.5 Hz, 1 H), 4.24 (dd, J = 7.9, 1.6 Hz, 1 H), 4.20−3.95 (m, 5 H), 1.53 (s, 3 H), 1.50 (d, J = 17.6 Hz, 3 H), 1.43 (s, 3 H), 1.33−1.30 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.2, 109.5, 96.8, 71.5, 70.4, 67.6, 64.8 (d, $^2J_{C-P}$ = 6 Hz), 61.8 (d, $^2J_{C-P}$ = 6 Hz), 26.0−24.5, 16.4 (d, $^3J_{C-P}$ = 6 Hz), 11.2 (d, $^1J_{C-P}$ = 145 Hz); ^{31}P NMR (170 MHz, $CDCl_3$) δ 31.76 (s, 1 P), 31.25(s, 1P). MS (FAB^+): *m*/*z* calcd for $C_{15}H_{27}O_8P$ $[M]^+$ 366.3, found 367.1 $[M + 1]^+$ (100%). Anal. Calcd for $C_{15}H_{27}O_8P$: C, 49.18; H, 7.43; O.34,94; P, 8.45. Found: C, 49.32; H, 7.26; P, 8.64.

General Procedure for Preparation of Diglycosyl Methylphosphonates, 1-*sugar*-*sugar* (Protocol B). The procedure was exactly the same as described above for **1**-*sugar* except that only one lithium alcoholate **4′**-*sugar* (2 equiv, 17 mmol) was added dropwise to a solution of methyl phosphonic dichloride (1 equiv, 1.13 g, 8.5 mmol) in THF (15 mL) at −78 °C. The mixture was stirred for 30 min at −50 °C before it was quenched with water (15 mL). The organic layer was extracted with CH_2Cl_2 (3 × 30 mL) and dried over anhydrous sodium sulfate, and solvents were evaporated. Silica gel column chromatography of the residue provided pure **1**-*sugar*-*sugar* in 85−90% yield from **4**-*sugar*.

Bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl) Methylphosphonate, 1-*gal*-*gal*. According to protocol B, 4.42 g (17 mmol) of **4**-*gal* yielded 4.19 g (7.2 mmol, 85%) of **1**-*gal*-*gal* as a colorless oil: R_f 0.39 (9:1 ethyl acetate/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 5.54 (d, J = 5.0 Hz, 2 H), 4.62 (dd, J = 8.0, 2.5 Hz, 2 H), 4.32 (dd, J = 5.0, 2.5 Hz, 2 H), 4.35−3.95 (m, 8 H), 1.57 (d, J = 17.7 Hz, 3 H), 1.54 (s, 6 H), 1.43 (s, 6 H), 1.32 (s, 12 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 110.2, 109.4, 96.8, 71.09, 71.13, 70.8, 67.6, 64.7 (d, $^2J_{C-P}$ = 6.3 Hz), 26.08, 26.11, 24.6, 24.5, 11.2 (d, $^1J_{C-P}$ = 144 Hz); ^{31}P NMR (101 MHz, $CDCl_3$) δ 29.33 (s, 1 P); MS (FAB^+) *m*/*z* calcd for $C_{25}H_{41}O_{13}P$ $[M]^+$ 580.6, found 581.2 $[M + 1]^+$ (100%). Anal. Calcd for $C_{25}H_{41}O_{13}P$: C, 51.81; H, 6.96; O, 35.89; P, 5.34. Found: C, 51.42; H, 7.18; P, 5.19.

General Procedure for Preparation of P-Chiral Diglycosyl Methylphosphonates, 1-*sugar*-*sugar* (Protocol C). The lithium alcoholate **4′**-*gal* (1 equiv, 8.5 mmol) was prepared as described above in protocol A from **4**-*gal* (1 equiv, 2.21 g, 8.5 mmol) and was added dropwise to a solution of methyl phosphonic dichloride **6** (1 equiv, 1.12 g, 8.5 mmol) in THF (15 mL) at −78 °C. After the reaction mixture was stirred for 30 min at −78 °C, the lithium alcoholate **4′**-*rib* (1 equiv, 8.5 mmol), previously prepared under the same conditions from **4**-*rib* (1 equiv, 1.73 g, 8.5 mmol), was added dropwise to the reaction mixture. The mixture was stirred for 30 min at −50 °C before it was quenched with water (15 mL). The organic layer was extracted with CH_2Cl_2 (3 × 30 mL) and dried over anhydrous sodium sulfate, and solvents were evaporated. Silica gel column chromatography of the residue provided 2.29 g (4.2 mmol, 50%) of a 1:1 mixture of **1**-*gal*-*rib* diastereomers and 0.49 g (0.85 mmol, 10%) of **1**-*gal*-*gal*.

1-*O*-Methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranosyl Methylphosphonate, 1-*gal*-*rib*. Colorless oil; R_f 0.44 (8:1 ethyl acetate/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.54 (d, J = 5.0 Hz, 1 H), 4.97 (s, 1 H), 4.72 (d, J = 4.5 Hz, 1 H), 4.65−4.55 (m, 2 H), 4.35 (dd, J = 2.3, 5.0 Hz, 1 H), 4.26−4.22 (m, 2 H), 4.20−3.94 (m, 5 H), 3.32 (s, 3 H), 1.55−1.47 (m, 9 H), 1.44 (s, 3 H), 1.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.6, 109.6, 109.4, 108.8, 96.3, 85.1, 81.4, 70.7, 70.5, 65.9−64.3, 55.0, 26.4, 26.0, 24.9, 24.5, 11.1 (d, $^1J_{C-P}$ = 145 Hz); ^{31}P NMR (163 MHz, $CDCl_3$) δ 31.78 (s, 1 P), 31.32 (s, 1 P); MS (EI^+) *m*/*z* calcd for $C_{22}H_{37}O_{12}P$ $(M + Na)^+$ 547.5, found 547.5 (100%). Anal. Calcd for $C_{22}H_{37}O_{12}P$: C, 50.38; H, 7.11; O, 36.61; P, 5.91. Found: C, 50.15; H, 7.25; P, 6.10.

Deuteriolysis of 1-*gal*. *n*-BuLi (1 equiv, 1.87 mL, 1.6 M solution in hexanes, 3 mmol) was added dropwise at −78 °C to a stirred solution of **1**-*gal* (1 equiv, 1.098 g, 3 mmol) in THF (15 mL). The mixture was maintained for 30 min at −78 °C before it was quenched with D_2O (10 mL). The organic layer was extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4, concentrated, and purified by silica gel chromatography to give a 1:1 mixture of **1**-*gal*-d diastereomers as a white oil.

Ethyl 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranosyl 1-Deuteriomethylphosphonate, 1-*gal*-d. R_f 0.4 (ethyl acetate); IR (KBr plate) 1255, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.54 (d, J = 5.0 Hz, 1 H), 4.61 (dd, J = 7.9, 2.5 Hz, 1 H), 4.32 (dd, J = 5.0, 2.5 Hz, 1 H), 4.24 (dd, J = 7.9, 1.9 Hz, 1 H), 4.20−3.95 (m, 5 H), 1.54 (s, 3 H), 1.57 (dt, J = 3.9 Hz, 2 H), 1.43 (s, 3 H), 1.33−1.30 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.5, 108.7, 96.2, 70.7, 70.4, 67.3, 64.4 (d, $^2J_{C-P}$ = 6 Hz), 61.4 (d, $^2J_{C-P}$ = 6 Hz), 25.9, 24.9, 16.3 (d, $^3J_{C-P}$ = 6.3 Hz), 10.9 (dt, $^1J_{C-P}$ = 144 Hz, $^1J_{C-D}$ = 21 Hz); ^{31}P NMR (101 MHz, $CDCl_3$) δ 29.33 (s, 1 P), 28.82 (s, 1 P); MS (FAB^+) *m*/*z* calcd for $C_{15}H_{26}DO_8P$ $[M]^+$ 367.3, found 368.2 $[M + 1]^+$ (100%). Anal. Calcd for $C_{15}H_{26}DO_8P$: C, 49.04; H, 7.68; O, 34.84; P, 8.43. Found: C, 49.23; H, 7.32; P, 8.16.

General Procedure for Preparation of P^1,P^2-Diglycosyl Methylenediphosphonates, 5-*sugar*-*sugar*. *s*-BuLi (2 equiv, 1.9 mL, 1.6 M solution in hexanes, 3 mmol) was added dropwise at −78 °C to a stirred solution of **1**-*sugar* (2 equiv, 3 mmol) in THF (15 mL). Stirring was maintained for 30 min at −78 °C. Ethyl phosphorodichloridate **2** (1 equiv, 0.243 g, 1.5 mmol) was added dropwise and the mixture was stirred for 30 min at −78 °C. Then the sugar nucleophile **4** (1 equiv, 1.5 mmol) was added dropwise and the reaction was stirred for 10 min at −78 °C before it was warmed slowly to room temperature. The reaction mixture was then quenched with water (15 mL). The organic layer was extracted with

CH_2Cl_2 (3 × 50 mL) and dried over Na_2SO_4. Evaporation of solvents and silica gel column chromatography provided the product **5**-*sugar*-*sugar* as a mixture of inseparable diastereomers and the recovered **1**-*sugar* in excess.

***P*¹-(Ethyl 1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl) *P*²-(Ethyl 1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl) Methylenediphosphonate, 5-*rib*-*rib*.** According to the general procedure, starting from 0.930 g (3 mmol) of **1**-*rib*, and after successive addition of 0.242 g (1.5 mmol) of ethyl phosphorodichloridate 2 and then 0.306 g (1.5 mmol) of **4**-*rib*, 0.507 g (0.839 mmol, 56%) of **5**-*rib*-*rib* was obtained and 0.450 g (1.45 mmol) of **1**-*rib* was recovered. **5**-*rib*-*rib*: yellow oil; R_f 0.2 (ethyl acetate); IR (KBr plate) 1245, 1035 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.96 (s, 2 H), 4.78−4.70 (m, 2 H), 4.61−4.56 (m, 2 H), 4.37−4.00 (m, 10 H), 3.32 (s, 6 H), 2.54 (t-like, J = 21.0 Hz, 2 H), 1.46 (s, 6 H), 1.41−1.31 (m, 12 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 112.2, 109.1, 84.7, 81.2, 66.0, 65.4, 62.8, 54.7, 24.9 (t, $^1J_{C-P}$ = 136 Hz), 26.1, 22.7, 16.1; ^{31}P NMR (101 MHz) δ 17.36 (s, 2 P); MS (FAB^+) *m*/*z* calcd for $C_{23}H_{42}O_{14}P_2$ $[M]^+$ 604.2, found 605.3 $[M + 1]^+$ (35%), 573.3 $[M - MeOH]^+$ (50%), 311.2 [**1**-*rib* + 1]$^+$ (35%), 279.2 [**1**-*rib*-OMe]$^+$ (60%). Anal. Calcd for $C_{23}H_{42}O_{14}P_2$: C, 45,70; H, 7,00; O, 37,05; P, 10,25. Found: C, 45.37; H, 6.86; P, 9.98.

***P*¹-(Ethyl 1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl) *P*²-(Ethyl 2,3-*O*-isopropylideneuridine) Methylenediphosphonate, 5-*rib*-*uri*.** According to the general procedure, starting from 0.869 g (2.8 mmol) of **1**-*rib*, and after successive addition of 0.227 g (1.4 mmol) of ethyl phosphorodichloridate **2** and then 0.383 g (1.35 mmol) of **4**-*uri*, 0.379 g (0.553 mmol, 41%) of **5**-*rib*-*uri* was obtained and 0.403 g (1.30 mmol) of **1**-*rib* was recovered. **5**-*rib*-*rib*: yellow oil; R_f 0.25 (ethyl acetate); IR (KBr plate) 1720, 1630, 1450, 1250, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.07 (br s, 1 H), 7.46−7.39 (m, 1 H), 5.74−5.64 (m, 2 H), 5.25 (s, 1 H), 4.92−4.77 (m, 2 H), 4.71−4.66 (m, 1 H), 4.57−4.51 (m, 1 H), 4.28−4.00 (m, 10 H), 3.25 (s, 3 H), 2.50 (t-like, J = 21.0 Hz, 2 H), 1.49 (s, 3 H), 1.40 (s, 3 H), 1.33−1.18 (m, 12 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 63.4, 150.1, 141.9, 114.3, 112.3, 109.2, 102.5, 93.4 (d, $^3J_{C-P}$ = 29 Hz), 85.1−83.8, 81.2, 80.3, 65.9, 65.5, 62.8, 54.8, 25.0 (t-like, $^1J_{C-P}$ = 135 Hz), 27.2, 26.9, 26.1, 24.7, 16.0; ^{31}P NMR (101 MHz, $CDCl_3$) δ 17.89 (s, 1 P), 17.42 (s, 1 P), 17.17 (s, 2 P); MS (FAB^+) *m*/*z* calcd for $C_{26}H_{42}N_2O_{15}P_2$ $[M]^+$ 684.2, found 685.3 $[M + 1]^+$ (100%). Anal. Calcd for $C_{26}H_{42}N_2O_{15}P_2$: C, 45.62; H, 6.18; N, 4.09; O, 35.06; P, 9.05. Found: C, 45.74; H, 6.35; N, 3.82; P, 9.22.

General Procedure for Preparation of *P*¹,*P*¹,*P*²-Triglycosyl Methylenediphosphonates, 5-*sugar*-*sugar*-*sugar*. *s*-BuLi (2 equiv, 1.9 mL, 1.6 M solution in hexanes, 3 mmol) was added dropwise at −78 °C to a solution of **1**-*sugar*-*sugar* (2 equiv, 3 mmol) in THF (15 mL). The mixture was stirred for 30 min at −78 °C before ethyl phosphorodichloridate **2** (1 equiv, 1.5 mmol) was added dropwise. After being stirred for 10 min at −78 °C, the mixture was allowed to warm to −50 °C and stirred for ∼90 min at −50 °C until disappearance of the yellow color of the lithium carbanion **1′**-*sugar*-*sugar*. The reaction mixture was then cooled to −78 °C and the nucleophilic **4**-*sugar* was added dropwise. After being stirred for 10 min at −78 °C, the mixture was allowed to warm to room temperature before being quenched with water (15 mL) after 1 h at room temperature. The organic layer was extracted with CH_2Cl_2 (3 × 50 mL) and dried over Na_2SO_4. Evaporation of solvents and column silica gel chromatography provided the triglycosyl methylenediphosphonate product **5**-*sugar*-*sugar*-*sugar* as a mixture of inseparable diastereomers and the recovered **1**-*sugar*-*sugar* in excess.

***P*¹-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranosyl) *P*¹-(1-*O*-Methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)] *P*²-[Ethyl (3,6-anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene)-D-*manno*-octosyl)] Methylenediphosphonate, 5-*gal*-*rib*-*man*-b.** According to the general procedure, starting from 1.52 g (2.9 mmol) of **1**-*gal*-*rib*, and after successive addition of 0.234 g (1.45 mmol) of ethyl phosphorodichloridate **2** and 0.418 g (1.45 mmol) of **4**-*man*-b, 0.942 g (1.04 mmol, 72%) of a 1.8:1 mixture of **5**-*gal*-*rib*-*man*-b diastereomers was obtained and 0.734 g (1.40 mmol) of **1**-*gal*-*rib* was recovered. **5**-*gal*-*rib*-*man*-b: clear oil; R_f 0.22 (6:4 acetone/hexane). α anomer: ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (m, 1 H), 4.96 (s, 1 H), 4.75 (m, 2 H), 4.62−4.55 (m, 3 H), 4.38−4.32 (m, 2 H), 4.26−4.03 (m, 14 H), 3.72 (m, 1 H), 3.32 (s, 3 H), 2.54 (m, 2 H), 1.75 (m, 2 H), 1.49−1.43 (m, 15 H), 1.37−1.25 (m, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 112.5−108.7 (m), 109.3, 96.2, 85,3−84.8 (m), 81.5−80.1 (m), 73.1, 70.6, 70.6−67.3 (m), 66.9−62.8 (m), 55.0, 31.8, 26.9−23.9 (m), 16.4. ^{31}P NMR (163 MHz): δ 20.90−18.93 (m, 2 P). β anomer: ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (m, 1 H), 4.96 (s, 1 H), 4.75 (m, 2 H), 4.67 (m, 1 H), 4.62−4.55 (m, 3 H), 4.38−4.32 (m, 2 H), 4.26−4.03 (m, 14 H), 3.72 (m, 1 H), 3.50 (m, 1 H), 3.32 (s, 3 H), 2.54 (m, 2 H), 2.07 (m, 2 H), 1.49−1.43 (m, 15 H), 1.37−1.25 (m, 18 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 112.5−108.7 (m), 109.3, 96.2, 85.3−84.8 (m), 81.5−80.1 (m), 73.1, 70.6, 70.6−67.3 (m), 66.9−62.8 (m), 55.0, 29.3, 26.9−23.9 (m), 16.4; ^{31}P NMR (163 MHz, $CDCl_3$) δ 20.90−18.93 (m, 2 P). MS (EI^+) *m*/*z* calcd for $C_{38}H_{64}O_{20}P_2$ $[M]^+$ 902.3, found 925.3 $[M + Na]^+$ (25%). Anal. Calcd for $C_{38}H_{64}O_{20}P_2$: C, 50.55; H, 7.14; O, 35.44; P, 6.86. Found: C, 50.70; H, 6.96; P, 6.69.

Preparation of *P*¹,*P*²-tetrakis(1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl) Methylenediphosphonate, 5-*rib*-*rib*-*rib*-*rib*. *s*-BuLi (2 equiv, 1.9 mL, 1.6 M solution in hexanes, 3 mmol) was added dropwise at −78 °C to a solution of **1**-*rib*-*rib* (2 equiv, 1.40 g, 3 mmol) in THF (15 mL). The mixture was stirred for 30 min at −78 °C. The protected ribosyl phosphorodichloridate **2**-*rib* (1 equiv, 0.482 g, 1.5 mmol) was added dropwise. After being stirred for 10 min at −78 °C, the mixture was warmed to −50 °C and stirred for 90 min at this temperature. The reaction mixture was then cooled to −78 °C and the nucleophilic sugar **4**-*rib* (1 equiv, 0.306 g, 1.5 mmol) was added dropwise. After being stirred for 10 min at −78 °C, the mixture was allowed to warm to room temperature. Stirring was pursued for 48 h at room temperature before the mixture was quenched with water (15 mL). The organic layer was extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4, concentrated, and purified by silica gel chromatography and yielded 0.414 g (0.45 mmol, 30%) of **5**-*rib*-*rib*-*rib*-*rib* and 0.65 g (1.30 mmol) of recovered **1**-*rib*-*rib*. **5**-*rib*-*rib*-*rib*-*rib*: colorless oil; R_f 0.22 (4:6 acetone/hexane); IR (KBr plate) 1245, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (s, 4 H), 4.75 (t-like, 4 H), 4.60 (d, J = 5.9 Hz, 4 H), 4.39−4.35 (m, 4 H), 4.15−4.06 (m, 8 H), 3.32 (s, 12 H), 2.62 (t-like, J = 21.3 Hz, 2 H), 1.47 (s, 12 H), 1.32 (s, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.5, 109.4, 85.0, 81.2, 66.4−66.2 (m), 55.1, 25.4 (t-like, $^1J_{C-P}$ = 138 Hz), 26.4, 24.9; ^{31}P NMR (163 MHz, $CDCl_3$) δ 19.98 (s, 1 P); MS (EI^+) *m*/*z* calcd for $C_{37}H_{62}O_{22}P_2$ $[M]^+$ 920.8, found 943.5 $[M + Na]^+$ (90%). Anal. Calcd. for $C_{37}H_{62}O_{22}P_2$: C, 48.26; H, 6.79; O, 38.23; P, 6.73. Found: C, 48.51; H, 6.93; P, 6.42.

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Supporting Information Available: General methods, description of the data, and copies of NMR spectra for new compounds of Tables 1, 4, and 5, including copies of COSY, HMQC, HSQC, TOCSY, and HSQC−TOCSY−NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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