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Preparation of Spiro[4.4]oxaphospholene and -azaphospholene Systems from Carbohydrate Templates

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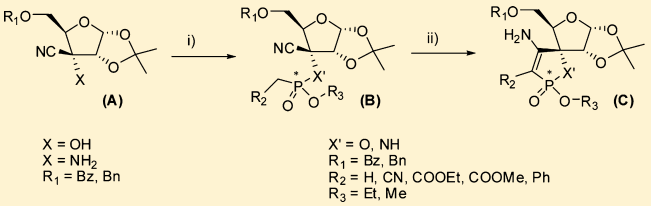
Supporting Information

ABSTRACT: Introduction of a spiro-phosphorus cycle in position 3 of monosaccharidic derivatives was studied starting from cyanohydrin or aminonitrile **A**. A two-step procedure involving (i) phosphonylation and (ii) carbanion-mediated phosphonate intramolecular cyclization (denoted CPIC) was used. The necessity of having an electron-withdrawing group α to the phosphorus atom in order to avoid undesired reactions was demonstrated.



1. INTRODUCTION

[2′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-3′-spiro-5″-(4″-amino-1″,2″-oxathiole-2″,2″-dioxide)thymine (TSAO-T)[1,2] is a nucleoside analogue bearing a spiro heterocycle in position 3′ (Figure 1). It is known to have human immunodeficiency virus type-1 (HIV-1) reverse transcriptase (RT) inhibitory activity and to act through a noncompetitive mechanism.[3−5]

A few years ago we synthesized new TSAO-T analogues where the oxygen of the oxathiol ring was replaced by a nitrogen (Figure 1, ATSAO-T).[6] We recently reported the synthesis of a new *N*-3-acylated TSAO where modifications were performed on the nucleoside base.[7] This new family of TSAO compounds has shown significant activities against RT-HIV-1 and HCV. We thus focused our research on the synthesis of new derivatives by modifying the nature of the spiro ring in position 3′. Different modifications have been described on the oxathiol spiro ring of TSAO-T: in position 3″[8−10] or on the amine in position 4″.[11,12] Starting from A-TSAO-T derivatives, our group reported the synthesis of compounds functionalized at position 5″.[13]

Despite the wide number of modifications described, either on the nucleobase or on the spiro ring, it was not possible to establish a clear structure−activity relationship which could explain the binding of TSAO to RT. Only recently, the crystal structure of TSAO-T with HIV-1-RT has been published by Das and co-workers.[14] It has been demonstrated that the spiro ring was buried inside the non-nucleosidic RT inhibitor binding pocket and that hydrogen bonds were formed between water and the substituents NH_2 and SO_2.

Phosphorus-containing molecules are popular targets for the development of new biologically active compounds. In addition, the difference in electronegativity of the phosphorus atom involved in the P═O bond relative to the sulfur atom induces a difference of polarization of this bond and modifies the hard and soft nature of the atoms involved in the interactions with the binding pockets. As replacement of the sulfur atom by a phosphorus atom has never been undertaken on TSAO-T derivatives, we were interested in the synthesis of new families of these nucleosidic inhibitors with an O−P or N−P bond in the spiro ring at position 3″. Compounds such as P-(A)TSAO-T would also be unusual analogues of nucleoside cyclic phosphates.

Regarding the preparation of 1,2-oxaphosphol-3-ene heterocycles, many examples can be found in the literature. They can be obtained starting from allenylphosphonates using a $CuCl_2$-mediated chlorocyclization reaction,[15] by a Heck cyclization reaction,[16] or a reaction with PhSeCl.[17] 1,2-Oxaphosphol-3-ene heterocycles have also been obtained using RCM reactions.[18,19] The synthesis of trifluoromethylated oxaphospholenes by iodocyclization under mild conditions has been described.[20] The 2,5-dihydro-1,2-oxaphosphole derivatives were described from reactions with phenylsulfenyl bromides and phenylselenenyl bromides.[21] A handy one-step synthesis of oxaphospholenes was developed by a simple treatment of acylallyl phosphonates with *m*-CPBA in the presence of 1 equiv of $MgSO_4$.[22] 2′-Azidoallylphosphonates were used to access 4-amino-1,2-oxaphosphol-3-ene by reaction with tetramethylguanidine azide.[23] Very recently a one-pot, three-component approach was used for the synthesis of novel heterocyclic α-aminophosphonates starting from either 2-hydroxyacetophenones or 2-hydroxybenzaldehydes.[24]

However, there are only a few examples in the literature of the synthesis of 1,2-azaphosphol-3-ene heterocycles. Vinylphosphonamidic anhydrides were derivatized via RCM reactions, leading to the formation of bicyclic phosphonamidic anhydrides.[25,26] After reaction of vinylphosphonochloridate with *N*-allyl-*N*-benzylamine, unsymmetrical allyl vinylphosphonates were obtained and subjected to RCM reactions to give

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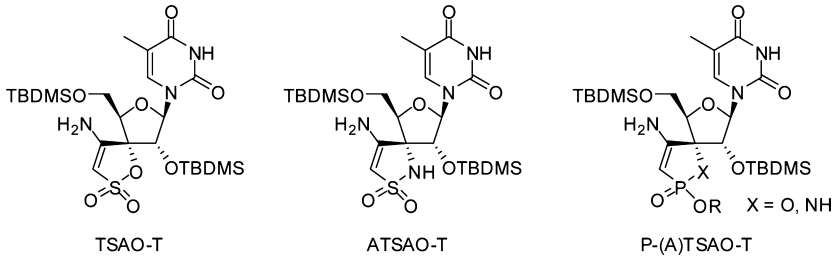


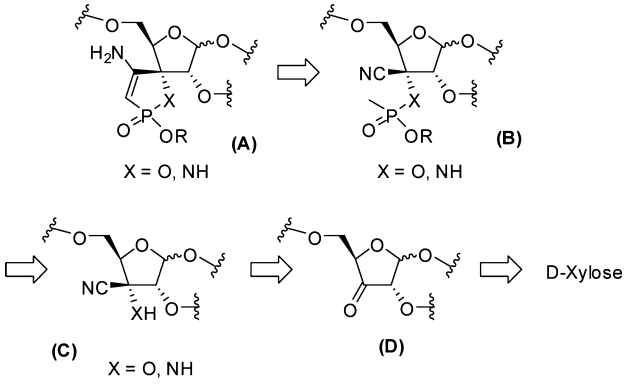
Figure 1. Nucleoside analogues TSAO-T and ATSAO-T and phosphorus derivatives.

access to 1,2-azaphosphol-3-enes.[19] Recently the reaction of 2-(diethoxyphosphorylmethyl)furyl-3-isocyanate with methanol was described for the preparation of cyclic phosphamide derivatives.[27]

Among all the examples found in the literature, the employed strategies seemed not very applicable to saccharidic substrates for the introduction of a phosphonate or phoshonamidate heterocycle in position 3. For this reason, we decided to investigate a phosphonate version of the CSIC reaction (carbanion-mediated sulfonate intramolecular cyclization reaction).[28,29]

With regard to the synthesis of the nucleoside analogues, retrosynthetic analysis of the precursor glycon moiety **A** suggests that the preparation of an oxa or (aza)phospholene ring in position 3′ could be obtained from derivative **B** after a carbanion-mediated phosphonate intramolecular cyclization reaction (CPIC) (Scheme 1). This phosphorus derivative **B** could result from phosphonylation of the ribo-aminonitrile or ribo-cyanohydrin **C** obtained from the well-known ketose **D**.

Scheme 1. Retrosynthetic Analysis of 4-Amino-1,2-oxa(aza)phosphol-3-ene



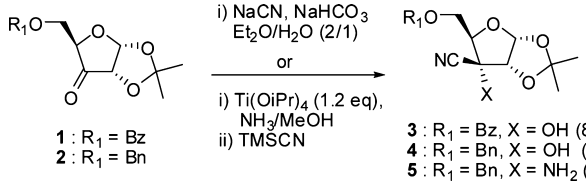
Developing a successful strategy for the synthesis of **A** should allow us to prepare the corresponding nucleoside analogues [P-(A)TSAO-T].

Herein we report our studies affording the targeted 4-amino-1,2-oxa(aza)phosphol-3-ene (**A**) starting from D-xylose.

2. RESULTS AND DISCUSSION

2.1. Chemical Synthesis. Classical Strecker conditions applied to the protected *erythro*-pentofuranose-3-ulose derivatives **1** and **2** obtained from protected D-xylose using PDC oxidation afforded the corresponding *ribo*-cyanohydrins **3** and **4** in 87 and 76% yields, respectively (Scheme 2).[30] The 3-(*R*)-*ribo*-aminonitrile **5** was obtained stereoselectively using NH_3-MeOH, $Ti(OiPr)_4$, and TMSCN in 85% yield.[6]

Scheme 2. Synthesis of Cyanohydrins and Aminonitrile *ribo* Derivatives



The phosphonylation step was performed by the reaction of cyanohydrins or aminonitriles with methyl methylphosphonochloridate, which was prepared from dimethyl methylphosphonate and phosphorus chloride.[31] The reaction of *ribo*-cyanohydrins **3** and **4** and *ribo*-aminonitrile **5** using the conditions described by Raushel et al.[32] were performed (Et_3N (4.2 equiv) and methyl methylphosphonochloridate (2 equiv) at refux in dichloromethane).

In the case of the *ribo*-cyanohydrin **4**, a mixture of both kinetic and thermodynamic products was obtained in 45% yield (Scheme 3).

When starting from the *ribo*-aminonitrile **5**, only kinetic products were observed in 30% yield. Because of the chirality of the phosphorus atom, NMR analyses (^1H, ^{13}C, and ^{31}P) exhibit a doubling of signals that is typical for a pair of diastereomers. In most cases, it was not possible to separate each diastereomer; thus it was not possible to identify each diastereomer. Nevertheless, a determination of the ratio was performed by ^1H NMR, by integration of the H-1 signals.

After modification of the conditions, the use of DMAP (2 equiv) in the presence of 2.4 equiv of methyl methylphosphonochloridate in pyridine allowed the exclusive formation of the kinetic products in 56−90% yields as a mixture of two diastereomers which could not be separated by chromatography (Scheme 4).

In order to access the heterocycle in position 3, cyclization was considered by a CPIC reaction. Unfortunately, under basic conditions compound **9** was not obtained (Table 1).

In the presence of *t*-BuOK, DBU, NaH, or HMDS, only starting material was recovered despite several variations of experimental parameters (temperature, number of equivalents, solvent; entries a−f). In the presence of Cs_2CO_3 or BuLi, a mixture of several derivatives was obtained (TLC analysis). The major product was isolated and characterized as a mixture of *xylo*- and *ribo*-cyanohydrin resulting from isomerization at C3 (entries h and i). The formation of these two isomers could be explained by the mechanism outlined in Scheme 5. In the presence of NaHMDS, only *xylo*-cyanohydrin was isolated. Moreover the ulose derivative formed is unstable, and under the strongly basic conditions, degradation is not surprising.

In the case of the methylphosphonamidate derivative **8**, the reaction with LDA (4 equiv) in THF at −78 °C (the base used

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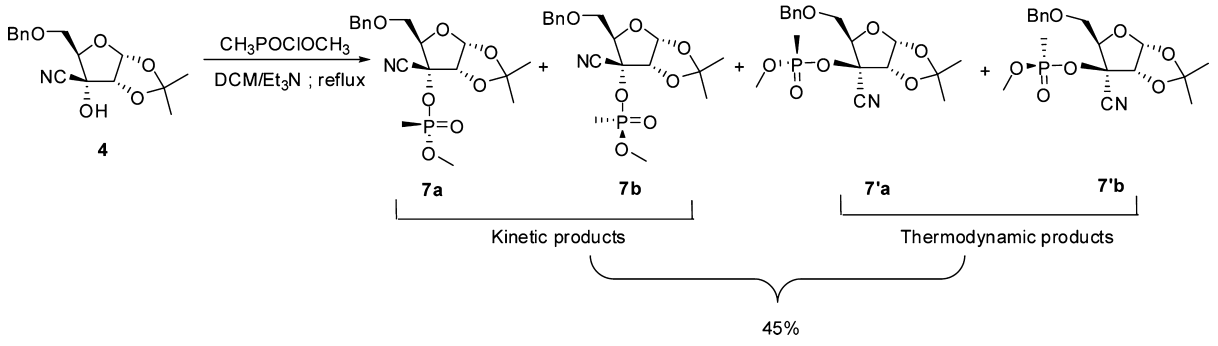
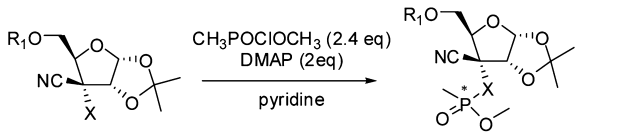
Scheme 3. Kinetic and Thermodynamic Products



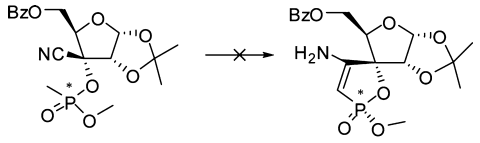
Scheme 4. Synthesis of Phosphonate Derivatives



3 : R_1 = Bz, X = OH
4 : R_1 = Bn, X = OH
5 : R_1 = Bn, X = NH_2

6 : R_1 = Bz, X = O, 90% (55/45)
7 : R_1 = Bn, X = O, 56% (40/60)
8 : R_1 = Bn, X = NH, 86% (55/45)

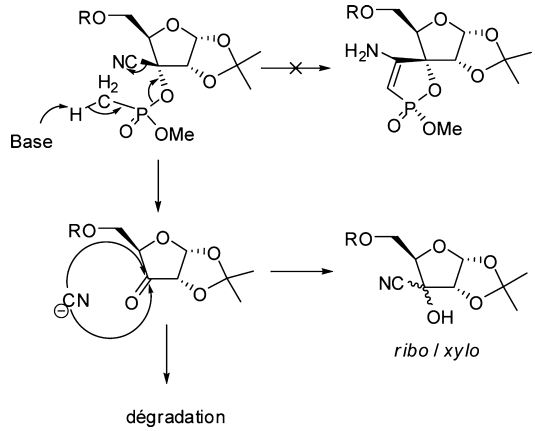
Table 1. Tested Conditions for CPIC Reaction on Phosphonate Derivatives



Entry	Conditions	Results
a	*t*-BuOK (2 equiv), CH_3CN, room temp	starting material
b	*t*-BuOK (2 equiv), CH_3CN, reflux	starting material
c	DBU (2 equiv), CH_3CN, room temp	starting material
d	DBU (2 equiv), CH_3CN, reflux	starting material
e	NaH (1.2 equiv), THF, −78 °C to room temp	starting material
f	NaH (1.2 equiv), DMSO, room temp	starting material
g	Cs_2CO_3 (1 equiv), CH_3CN, 0 °C	starting material
h	Cs_2CO_3 (1 equiv), CH_3CN, room temp	*xylo*- and *ribo*-cyanohydrin
i	BuLi (1.5 equiv), THF, −35 °C	*xylo*- and *ribo*-cyanohydrin
j	LDA (4 equiv), THF, −78 °C	degradation
k	LDA (4 equiv), DMSO, room temp	degradation
l	LDA (4 equiv), THF-HMPA (2 equiv), −78 °C	degradation
m	LDA (4 equiv), THF/HMPA (4/1), −78 °C	*xylo*-cyanohydrin
n	LDA (1.2 equiv), THF/HMPA (4/1), −78 °C	starting material
o	HMDS (1 equiv, 2 equiv, 4 equiv), THF, 0 °C	starting material
p	NaHMDS (1 equiv), THF, 0 °C	*xylo*-cyanohydrin

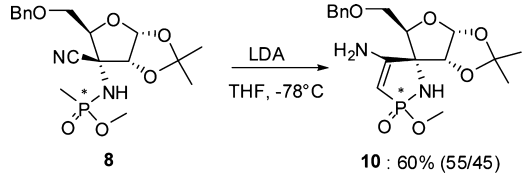
for the carbonate-mediated sulfonate intramolecular cyclization (CSIC) reaction)[6] led to the desired cyclized derivative 4-amino-1,2-(aza)phosphol-3-ene in 60% yield (Scheme 6).

Scheme 5. Proposed Mechanism of Phosphonate Degradation under Basic Conditions



Compound **10** was obtained in the form of two inseparable diastereomers in a 55/45 ratio.

Scheme 6. Synthesis of Azaphospholene Derivative



This difference in reactivity between the oxa and aza analogues was not observed in the case of TSAO and A-TSAO, as in both cases the CSIC was performed in good yield using Cs_2CO_3 for TSAO and LDA for A-TSAO.[6,30]

It was considered that this difference in reactivity might be due to the presence of the hydrogen atom on the nitrogen atom. To this end, alkylation of nitrogen with a methyl group has been performed to give compound **11** in 63% yield. This alkylated derivative gives the azaphospholene ring after cyclization with LDA in 72% yield, demonstrating that the N−H is not necessary for cyclization (Scheme 7).

Presumably the reason for the different behaviors of **6** and **8** is that *β*-fragmentation in **6** gives rise to a carbonyl group (high bond energy, ΔH = 719 kJ mol^{-1}), whereas *β*-fragmentation in **8** gives an imine (lower bond energy, ΔH = 615 kJ mol^{-1}). This difference in behavior was not observed in the case of TSAO and A-TSAO, as sulfur with two doubly bonded oxygens is more stabilizing than a phosphoryl group with one oxygen and

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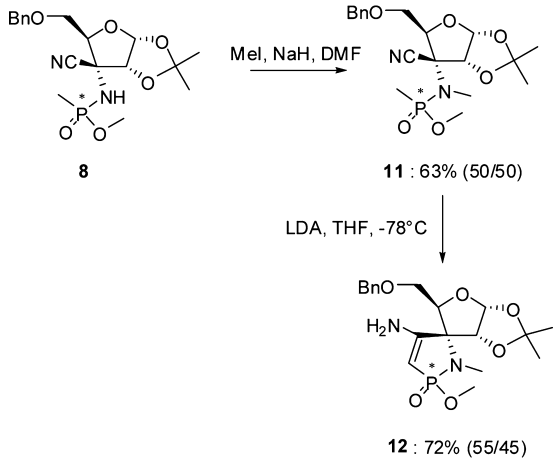
Scheme 7. Synthesis of *N*-Methylazaphospholene Derivative



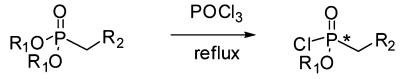
8

therefore promotes the nucleophilic attack on the nitrile rather than the β-fragmentation.

With these results in hand, we envisaged that introduction of an electron-withdrawing group α to the phosphorus atom should facilitate cyclization.

A series of phosphonyl chloride derivatives with electron-withdrawing groups (COOEt, CN, Ph, and COOMe) was prepared by reaction of $POCl_3$ with the corresponding phosphonate according to the procedure described by Rewcastle et al. (Scheme 8).[33] The phosphonochloridates were obtained as liquids and used without any purification.

Scheme 8. Synthesis of Phosphonochloridate Derivatives



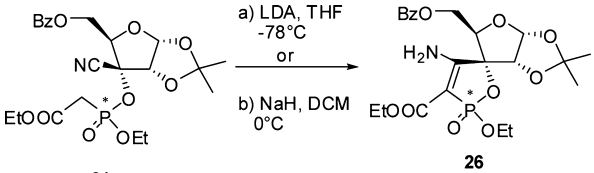
13 : R_1 = Et, R_2 = COOEt
14 : R_1 = Et, R_2 = CN
15 : R_1 = Et, R_2 = Ph
16 : R_1 = Me, R_2 = COOMe

17 : R_1 = Et, R_2 = COOEt
18 : R_1 = Et, R_2 = CN
19 : R_1 = Et, R_2 = Ph
20 : R_1 = Me, R_2 = COOMe

Reaction of these phosphonochloridates with cyanohydrins was thus performed using NaH in DCM at 0 °C (Table 2). The corresponding phosphonate diesters were obtained with high conversion (NMR of the crude mixture) and were isolated in moderate yields. Apparently, some compounds were lost on silica during the purification procedure. Nevertheless, they were all isolated and characterized as mixture of P* diastereomers (all in the *ribo* configuration) with yields ranging from 22% to 65%.

Upon treatment of derivative **21** under basic conditions (LDA or NaH) the desired oxaphospholene derivatives were obtained in 56% or 70% yield, respectively (Scheme 9).

Scheme 9. CPIC Reaction



21

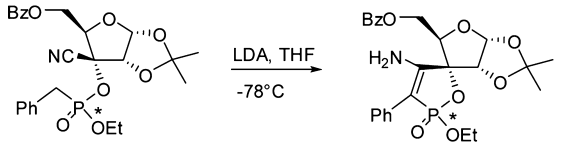
26

a) 56% (55/45)
b) 70% (55/45)

Using NaH, it was possible to carry out the synthesis of the oxaphospholene compounds in a one-pot procedure. This protocol gave us good results, oxaphospholenes being obtained with yields ranging from 41% to 70% as mixtures of separable (**26a,b** and **27a,b**) or inseparable diastereomers (**28**) or as a pure compound (**29**) (Table 3). For this last case, hydrolysis of the CN group was observed during the reaction and amide **29** was the only product obtained.

When using the phosphonochloridate bearing a phenyl group α to the phosphorus (**19**) it was not possible to have a one-pot reaction, as the cyclization step with NaH did not occur. The cyclized compound **30** was obtained only with LDA (78% yield) as a mixture of two diastereomers (Scheme 10).

Scheme 10. CPIC Reaction with LDA



25

30 : 78% (60/40)

2.2. Stereochemical Hypothesis. Examination of the ^{13}C NMR signals of diastereomer **26a** shows two different chemical shifts for the two isopropylidene CH_3 groups (26.6 and 26.2 ppm), whereas for diastereomer **26b** there is only one chemical shift at 26.3 ppm for the two CH_3 (Figure 2).

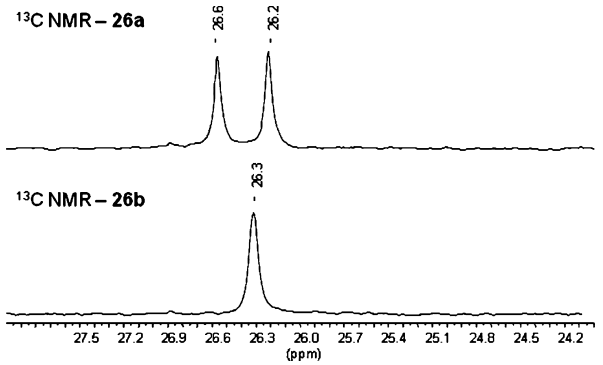


Figure 2. ^{13}C NMR of isopropylidene methyl groups of **26a,b**.

In **26a,b**, the two isopropylidene methyl groups are diastereotopic.

In a modeling study (semiempirical PM3) we can observe that in **26b** (where the P has the *S* configuration), one of the two methyls of the isopropylidene is located much closer to the polar P═O group than the other (Figure 3). This is consistent with the quite different NMR chemical shifts. With **26a** (where the P has the *R* configuration), both CH_3 groups are well away from the P═O group. Thus, we can assume that **26a** corresponds to the *R* diastereomer and **26b** to the *S* diastereomer.

A similar analysis carried out for compound **27** enabled a proposition of identification of the two isolated diastereomers as **27a,b** (Figure 4).

3. CONCLUSION

In conclusion, the synthesis of seven new saccharidic oxa- and azaphospholene derivatives (Figure 5) has been reported. The

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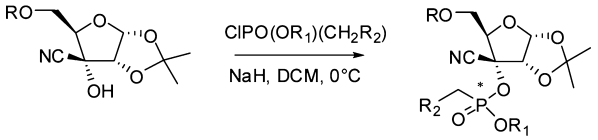
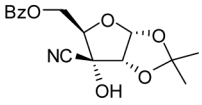
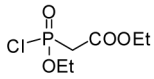
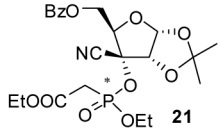
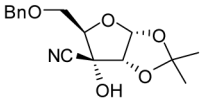
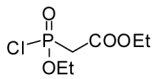
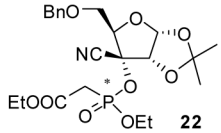
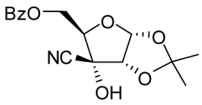
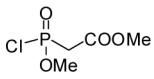
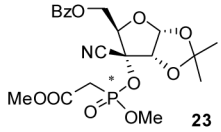
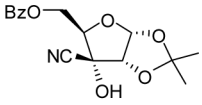
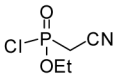
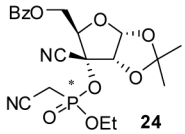
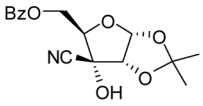
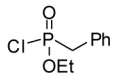
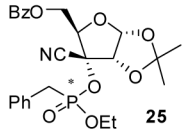
Table 2. Synthesis of Phosphonate Saccharidic Derivatives with Electron-Withdrawing Groups



Cyanohydrins	Phosphinates	Oxaphosphonates	Yield	Diastereomeric ratio
 1	 17	 21	40%	30/70
 2	 17	 22	62%	50/50
 1	 20	 23	22%	60/40
 1	 18	 24	44%	60/40
 1	 19	 25	65%	70/30

strategy for the introduction of these phosphorus heterocyles in position 3 of xylose will be used to synthesize P-TSAO analogues. The synthesis of these nucleosidic derivatives will be reported in due course.

4. EXPERIMENTAL SECTION

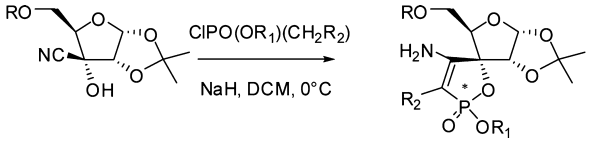
4.1. General Considerations: Materials and Methods. Melting points are uncorrected. Optical rotations were recorded in CH_2Cl_2 solution. ^1H NMR (300.13 MHz), ^{13}C NMR (75.47 MHz), and ^{31}P NMR (121 MHz) (^1H and ^{13}C nondecoupled) spectra were recorded in $CDCl_3$. TLC measurements were performed on Silica F254 and detection by UV light at 254 nm or by charring with cerium molybdate reagent. High-resolution electrospray mass spectra in the positive ion mode were obtained on a Q-TOF Ultima Global hybrid quadrupole/time-of-flight instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source and an additional sprayer (Lock Spray) for the reference compound. The source and desolvation temperatures were kept at 80 and 150 °C, respectively. Nitrogen was used as the drying and nebulizing gas at flow rates of 350 and 50 L/h, respectively. The capillary voltage was 3.5 kV, the cone voltage was 100 V, and the RF lens1 energy was optimized for each sample (40 V). For collision-induced dissociation (CID) experiments, argon was used as the collision gas at an indicated analyzer pressure of 5.10−5 Torr and the collision energy was optimized for each parent ion (50−110 V). Lock mass correction, using appropriate cluster ions of sodium iodide $(NaI)_nNa^+$, was applied for accurate mass measurements. The mass range was typically 50−2050 Da, and spectra were recorded at 2 s/scan in the profile mode at a resolution of 10000 (FWMH). Column chromatography was effected on Silica Gel 60 (230 mesh).

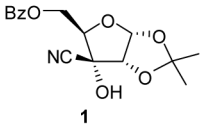
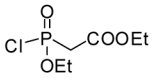
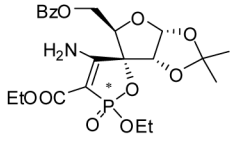
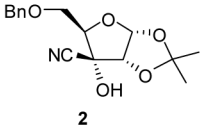
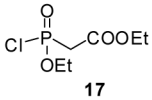
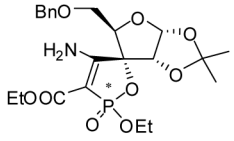
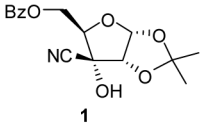
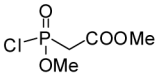
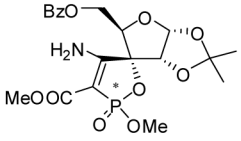
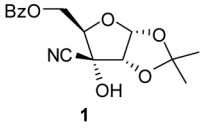
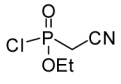
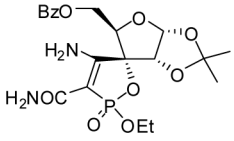
4.2. General Procedure for Phosphonylation with Methyl Methylphosphonochloridate. To a solution of cyanohydrin **3** or **4**[30] or aminonitrile **5**[6] (1 equiv) and DMAP (2 equiv) in dry pyridine at 0 °C was added methyl methylphosphonochloridate (2.4 equiv). After 1 h at room temperature, water and Et_2O were added; the organic phase was separated, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography.

*5-O-Benzoyl-3-C-cyano-1,2-O-isopropylidene-3-O-methoxymethylphosphonyl-α-D-ribofuranose (**6**).* According to the general procedure, compound **3** (103 mg, 0.32 mmol) and DMAP (79 mg, 0.64 mmol) in pyridine (2 mL) were treated with methyl methylphosphonochloridate (76.3 μL, 0.77 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 5/5) to give **6** as a white solid (118 mg, 90%) as a mixture of two diastereomers (55/45). R_f = 0.22 (EtOAc/cyclohexane, 5/5). ^1H NMR ($CDCl_3$; 300 MHz): δ 8.11 (m, 4H), 7.59 (m, 2H), 7.50−7.45 (m, 4H), 6.03 (d, J = 3.8 Hz, 1H), 6.01 (d, J = 3.7 Hz, 1H), 5.28 (d, 1H), 5.19 (d, 1H), 4.77−4.67 (m, 4H), 4.51−4.47 (m, 2H), 3.84 (d, J_{H-P} = 11.7 Hz, 3H), 3.81 (d, J_{H-P} = 11.7 Hz, 3H), 1.63 (d, J_{H-P} = 17.8 Hz, 3H), 1.54 (s, 6H), 1.55 (d, J_{H-P} = 17.1 Hz, 3H), 1.28 (s, 3H), 1.25 (s, 3H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 165.9, 133.4, 129.8, 129.5, 128.4, 115.7, 114.9, 114.3, 104.1, 104.0, 81.9, 81.5, 77.4 (d, J_{C-P} = 9.0 Hz), 77.0 (d, J_{C-P} = 9.0 Hz), 76.7, 62.1, 62.0, 52.7 (d, J_{C-P} = 7.5 Hz), 52.1 (d, J_{C-P} = 7.5 Hz), 26.3, 26.2, 12.2 (d, J_{C-P} = 145.8 Hz). ^{31}P NMR ($CDCl_3$; 121 MHz): δ 36.2−35.8 (m), 34.2−33.7 (m). HRMS: $C_{18}H_{22}NO_8NaP$ calcd 434.0981, found 434.1001.

dx.doi.org/10.1021/jo400954p | J. Org. Chem. 2013, 78, 8994−9003

Table 3. "One Pot−Two Step" Reactions



Cyanhydrins	Phosphinates	Oxaphospholenes	Yield	Diastereomeric ratio
 **1**	 **17**	 **26**	70 %	55/45
 **2**	 **17**	 **27**	42%	70/30
 **1**	 **20**	 **28**	41%	60/40
 **1**	 **18**	 **29**	53%	100/0

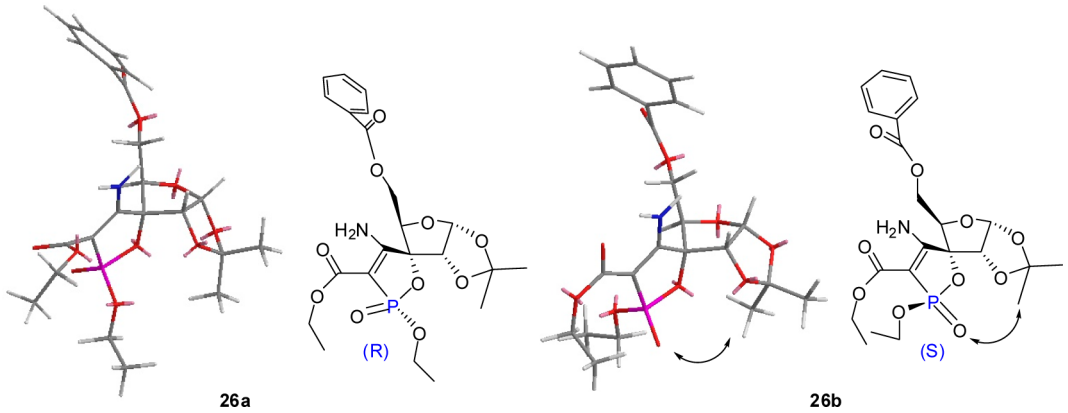


Figure 3. Modeling study of **26a,b**.

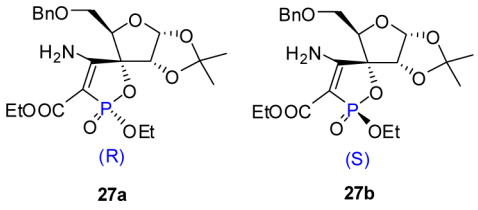


Figure 4. Identification of the two diastereomers **27a,b**.

5-O-Benzyl-3-C-cyano-1,2-O-isopropylidene-3-O-methoxymethylphosphonyl-α-D-ribofuranose (7). According to the general procedure, compound **4** (996 mg, 3.2 mmol) and DMAP (798 mg, 6.53 mmol) in pyridine (20 mL) were treated with methyl methylphosphonochloridate (800 μL, 8.16 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 5/5) to give **7** as a white solid (710 mg, 55%) as a mixture of two diastereomers (40/60). R_f = 0.35 (EtOAc/cyclohexane, 4/6). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 7.39−7.29 (m, 10H), 5.99 (d, J = 4.0 Hz, 1H), 5.97 (d, J = 3.8 Hz, 1H), 5.20 (d, 1H), 5.12 (d, 1H), 4.72 (d, J = 15.6 Hz, 1H), 4.70 (d, J = 15.7 Hz, 1H), 4.62 (d, 1H), 4.57 (d, 1H), 4.40−4.35 (m, 2H), 3.92−3.87 (m, 4H), 3.84 (d, J_{H-P} = 11.6 Hz, 3H), 3.76 (d, J_{H-P} = 11.6 Hz, 3H), 1.65 (d, J_{H-P} = 21.0 Hz, 3H), 1.59 (s, 6H), 1.58 (d, J_{H-P} = 18.0 Hz, 3H), 1.34 (s, 6H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 137.2, 137.1, 128.5, 127.9, 115.1, 114.1, 104.1, 81.8, 81.5, 78.8 (d, J_{C-P} = 9.5 Hz), 78.4 (d, J_{C-P} = 8.8 Hz), 73.9, 68.5, 68.4, 52.7 (d, J_{C-P} = 7.5 Hz), 52.0 (d, J_{C-P} = 7.4 Hz), 27.0, 26.4, 12.2 (d, J_{C-P} =

dx.doi.org/10.1021/jo400954p | J. Org. Chem. 2013, 78, 8994−9003

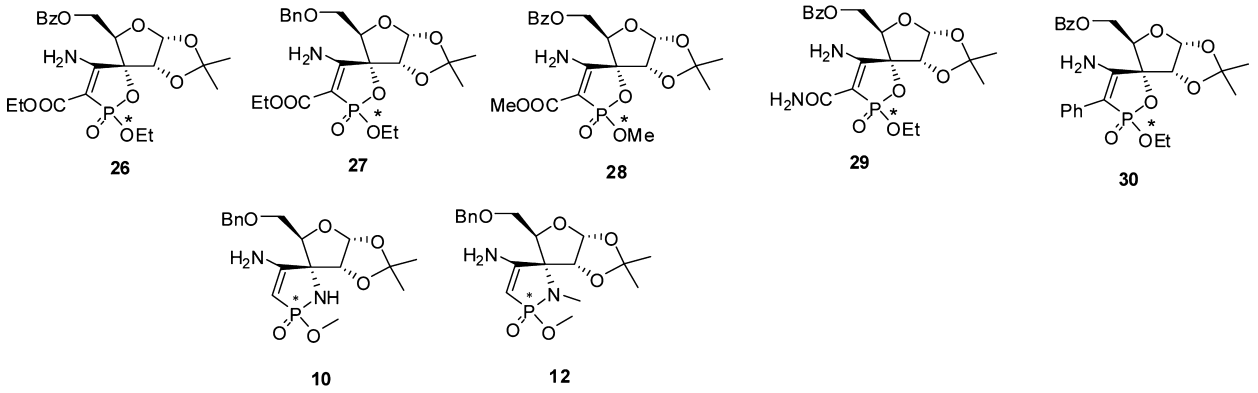


Figure 5. New saccharidic oxa- and azaphospholene derivatives.

146.3 Hz). ^{31}P NMR ($CDCl_3$; 121 MHz): δ 36.2−35.5 (m), 34.2−33.5 (m). HRMS: $C_{18}H_{24}NO_7NaP$ calcd 420.1190, found 420.1188.

*5-O-Benzyl-3-C-cyano-3-desoxy-1,2-O-isopropylidene-3-methoxymethylphosphoramidyl-α-D-ribofuranose (**8**).* According to the general procedure, compound **5** (4 g, 13.1 mmol) and DMAP (3.2 g, 26.2 mmol) in pyridine (20 mL) were treated with methyl methylphosphonochloridate (3.1 mL, 31.6 mmol). The crude product was purified by flash chromatography (EtOAc/cyclohexane, 5/5) to give **8** as a white solid (4.5 g, 86%) as a mixture of two diastereomers (55/45). R_f = 0.5 (CH_2Cl_2/MeOH, 9.5/0.5). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 7.37−7.32 (m, 10H), 5.94 (d, J = 3.7 Hz, 1H), 5.92 (d, J = 3.4 Hz, 1H), 5.15 (d, 1H), 5.03 (d, 1H), 4.60 (m, 4H), 4.15 (m, 2H), 3.90 (m, 4H), 3.70 (d, J_{H-P} = 11.3 Hz, 3H), 3.62 (d, J_{H-P} = 11.4 Hz, 3H), 1.55 (d, J_{H-P} = 14.9 Hz, 3H), 1.54 (s, 6H), 1.52 (d, J_{H-P} = 16.9 Hz, 3H), 1.37 (s, 6H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 137.2, 137.1, 128.5, 128.1, 127.9, 118.1, 117.3, 113.3, 104.4, 104.3, 83.0, 82.7, 78.9 (d, J_{C-P} = 9.8 Hz), 78.6 (d, J_{C-P} = 8.4 Hz), 74.1, 74.0, 69.2, 62.5, 61.8, 51.1 (d, J_{C-P} = 6.8 Hz), 50.4 (d, J_{C-P} = 6.8 Hz), 26.7, 26.3, 14.7 (d, J_{C-P} = 135.1 Hz), 14.4 (d, J_{C-P} = 133.6 Hz). ^{31}P NMR ($CDCl_3$; 121 MHz): δ 34.5−34.1 (m), 32.9−32.5 (m). HRMS: $C_{18}H_{25}N_2O_6PNa$ calcd 419.1348, found 419.1349.

4.3. 1-Aza-7-oxa-2-phosphaspiro[4.4]-(1*S*,3*R*,4*R*,5*R*)-6-benzyloxymethyl-8,9-isopropylidendioxy-2-methoxy-2-oxonon-3-en-4-amine (10). To a solution of diisopropylamine (542 μL, 3.86 mmol) and BuLi (1.45 mL, 3.76 mmol) in dry THF (12 mL) at −78 °C under argon was added compound **8** (373 mg, 0.94 mmol). After 1 h, water was added and the reaction mixture was neutralized with HCl and then extracted with EtOAc. The organic phase was separated, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH) to give **10** as a white solid (225 mg, 60%) as a mixture of two diastereomers (55/45). R_f = 0.31 (CH_2Cl_2/MeOH, 9.8/0.2); ^{1}H NMR ($CDCl_3$; 300 MHz): δ 7.37−7.20 (m, 10H), 5.90 (d, J = 3.0 Hz, 1H), 5.88 (d, J = 3.6 Hz, 1H), 4.66−4.50 (m, 4H), 4.47−4.45 (m, 2H), 4.39 (dd, J = 1.5 Hz, J = 4.5 Hz, 1H), 4.35 (d, J = 3.6 Hz, 1H), 4.18−4.15 (m, 2H), 3.80 (dd, J = 2.1 Hz, J = 11.4 Hz, 1H), 3.72−3.66 (m, 3H), 3.59 (d, J_{H-P} = 12.3 Hz, 3H), 3.50 (d, J_{H-P} = 12.3 Hz, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 159.8 (d, J_{C-P} = 30.6 Hz), 159.3 (d, J_{C-P} = 29.4 Hz), 137.7, 137.5, 128.3, 127.7, 112.9, 103.9, 103.8, 82.8, 82.5, 81.9 (d, J_{C-P} = 19.9 Hz), 80.3 (d, J_{C-P} = 8.4 Hz), 80.1 (d, J_{C-P} = 6.2 Hz), 79.5 (d, J_{C-P} = 19.1 Hz), 73.5, 73.4, 68.6 (d, J_{C-P} = 4.6 Hz), 68.4 (d, J_{C-P} = 5.4 Hz), 67.0, 66.7, 52.8 (d, J_{C-P} = 5.8 Hz), 52.5 (d, J_{C-P} = 6.3 Hz), 26.3, 26.2. ^{31}P NMR ($CDCl_3$; 121 MHz): δ 43.0 (m), 45.9 (m). HRMS: $C_{18}H_{25}N_2O_6PNa$ calcd 419.1348, found 419.1342.

4.4. 5-*O*-Benzyl-3-*C*-cyano-3-desoxy-1,2-*O*-isopropylidene-3-methoxymethylphosphoramidyl-*N*-methyl-α-D-ribofuranose (11). To a solution of **8** (417 mg, 1.03 mmol) in dry DMF (35 mL) were added NaH (84 mg, 2.10 mmol) and then MeI (131 μL, 2.10 mmol). After 1 h at room temperature, 1 N HCl and CH_2Cl_2 were added. The organic phase was separated, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (cyclohexane/EtOAc) to give **11** as a white solid (270 mg, 63%) as a mixture of two diastereomers (50/50). R_f = 0.6 (CH_2Cl_2/MeOH, 9.5/0.5); ^{1}H NMR ($CDCl_3$; 300 MHz): δ 7.42−7.24 (m, 10H), 5.95 (d, J = 3.9 Hz, 1H), 5.93 (d, J = 3.9 Hz, 1H), 5.21 (dd, J = 2.4 Hz, J = 6.8 Hz, 1H), 5.13 (d, 1H,), 4.93−4.90 (m, 2H), 4.71−4.59 (m, 4H), 3.95 (dd, J = 10.9 Hz, 1H), 3.94−3.88 (m, 3H), 3.63 (d, J_{H-P} = 11.5 Hz, 3H), 3.50 (d, J_{H-P} = 11.6 Hz, 3H), 2.77 (d, J_{H-P} = 8.3 Hz, 3H), 2.73 (d, J_{H-P} = 8.7 Hz, 3H), 1.61 (s, 3H), 1.57 (s, 3H), 1.54 (d, J_{H-P} = 20.2 Hz, 3H), 1.46 (d, J_{H-P} = 16.8 Hz, 3H), 1.37 (s, 6H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 138.0, 137.9, 128.4−127.6, 117.3, 116.6, 113.3, 112.9, 103.2, 102.9, 83.6, 82.2, 77.1, 76.7, 76.9, 76.5, 73.4, 73.3, 69.9, 69.5, 50.3 (d, J_{C-P} = 7.0 Hz), 50.0 (d, J_{C-P} = 7.1 Hz), 33.3 (d, J_{C-P} = 33.2 Hz), 32.9 (d, J_{C-P} = 28.7 Hz), 26.9, 26.8, 26.4, 26.2, 12.0 (d, J_{C-P} = 135.7 Hz), 11.8 (d, J_{C-P} = 134.7 Hz). ^{31}P NMR ($CDCl_3$; 121 MHz): δ 36.0−35.8 (m). HRMS: $C_{19}H_{27}N_2O_6PNa$ calcd 433.1504, found 433.1497.

4.5. 1-Aza-7-oxa-2-phospha-spiro[4.4]-(1*S*,3*R*,4*R*,5*R*)-6-benzyloxymethyl-8,9-isopropylidendioxy-2-methoxy-1-methyl-2-oxonon-3-en-4-amine (12). To a solution of diisopropylamine (509 μL, 3.52 mmol) and BuLi (1.40 mL, 3.52 mmol) in dry THF (12 mL) at −78 °C under argon was added a solution of compound **11** (361 mg, 0.88 mmol) in dry THF (12 mL). After 1 h, water was added and the reaction mixture was neutralized with HCl and then extracted with EtOAc. The organic phase was separated, dried (Na_2SO_4), and concentrated. The crude product was purified by reverse phase flash chromatography (C18) (acetonitrile/H_2O) to give **12** as a white solid (260 mg, 72%) as a mixture of two diastereomers (55/45). R_f = 0.45 (CH_2Cl_2/MeOH, 9.5/0.5). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 7.37−7.29 (m, 10H), 5.89 (d, J = 3.9 Hz, 1H), 5.85 (d, J = 3.9 Hz, 1H), 4.87−4.71 (m, 2H), 4.70−4.49 (m, 8H), 3.72−3.66 (m, 4H), 3.58 (d, J_{H-P} = 11.7 Hz, 3H), 3.54 (d, J_{H-P} = 11.6 Hz, 3H), 2.85 (d, J_{H-P} = 7.9 Hz, 3H), 2.79 (d, J_{H-P} = 8.0 Hz, 3H), 1.63 (s, 3H), 1.62 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 160.6 (d, J_{C-P} = 28.8 Hz), 159.9 (d, J_{C-P} = 28.5 Hz), 137.7, 137.5, 129.0−127.8, 113.0, 112.9, 104.0,103.9, 85.9, 85.5, 81.5 (d, J_{C-P} = 19.8 Hz), 80.2 (d, J_{C-P} = 19.2 Hz), 75.0, 74.8, 73.5, 69.7, 67.4, 67.2, 53.5 (d, J_{C-P} = 6.6 Hz), 52.8 (d, J_{C-P} = 6.2 Hz), 27.1−25.9. ^{31}P NMR ($CDCl_3$; 121 MHz): δ 43.2−42.9 (m), 42.5−42.2 (m). HRMS: $C_{19}H_{27}N_2O_6PNa$ calcd 433.1504, found 433.1493.

4.6. General Procedure for Phosphonylation with Electron-Withdrawing Phosphonochloridates. To a solution of furanose derivative (1 equiv) in dry CH_2Cl_2 at 0 °C were added phosphonochloridates (1 equiv) and NaH (1 or 4 equiv). After 1 h at room temperature, the reaction mixture was neutralized with 1 N HCl and then extracted with EtOAc. The organic phase was separated, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography.

*5-O-Benzoyl-3-C-cyano-O-[ethyl-2-(ethoxyphosphonyl)acetate]-1,2-O-isopropylidene-α-D-ribofuranose (**21**).* According to the general procedure, compound **1** (230 mg, 0.72 mmol) was treated with ethyl (ethoxycarbonylmethyl)phosphonochloridate (ClOP(OEt)-(CH_2COOEt); 155 mg, 0.72 mmol) and NaH (29 mg, 0.72 mmol) in CH_2Cl_2 (10 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc, 6/4) to give **21** as a colorless

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oil (150 mg, 40%) as a mixture of two diastereomers (30/70). R_f = 0.33 (EtOAc/cyclohexane, 5/5). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 8.10−7.95 (m, 4H), 7.62−7.58 (m, 2H), 7.49−7.43 (m, 4H), 6.15 (d, J = 4.4 Hz, 1H), 6.02 (d, J = 3.8 Hz, 1H), 5.28 (d, 1H), 5.16 (d, 1H), 4.88 (dd, J = 12.2 Hz, J = 3.4 Hz, 1H), 4,73−4.63 (m, 3H), 4.51−4.45 (m, 2H), 4.35−4.27 (m, 2H), 4.24−4.13 (m, 6H), 3.20−3.07 (m, 4H), 1.63 (s, 3H), 1.60 (s, 3H), 1.41 (s, 3H), 1.43−1.24 (m, 15H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 167.3 (d, J_{C-P} = 33.6 Hz), 165.9, 133.5, 129.9, 129.6, 128.5, 115.2, 114.6, 114.4, 104.1, 103.1, 81.8, 81.6, 77.3 (d, J_{C-P} = 9.5 Hz), 77.2 (d, J_{C-P} = 9.8 Hz), 65.6, 63.0, 63.5, 63.4, 61.9, 61.7, 35.1 (d, J_{C-P} = 137.2 Hz), 27.4, 27.0, 26.9, 26.3, 16.1, 14.0. ^{31}P NMR ($CDCl_3$; 121 MHz): δ 22.2−21.7 (m), 20.3−19.9 (m). HRMS: $C_{22}H_{28}NO_{10}PNa$ calcd 520.1349, found 520.1349.

*5-O-Benzyl-3-C-cyano-O-[ethyl-2-(ethoxyphosphonyl)acetate]-1,2-O-isopropylidene-α-D-ribofuranose (**22**).* According to the general procedure, compound **2** (216 mg, 0.71 mmol) was treated with ethyl (ethoxycarbonylmethyl)phosphonochloridate (ClOP(OEt)-(CH_2COOEt); 456 mg, 2.12 mmol) and NaH (28.3 mg, 0.71 mmol) in CH_2Cl_2 (10 mL). The crude product was purified by reverse flash chromatography (C18, acetonitrile/H_2O) to give **22** as a white solid (212 mg, 62%) as a mixture of two diastereomers (50/50). R_f = 0.36 (EtOAc/cyclohexane, 8/2). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 7.39−7.29 (m, 10H), 5.99 (d, J = 3.8 Hz, 2H), 5.20 (d, 1H), 4.68 (d, 1H), 4.65−4.40 (m, 6H), 4.32−4.22 (m, 4H), 4.22−4.16 (m, 4H), 3.92−3.87 (m, 4H), 3.16 (d, J_{H-P} = 22.7 Hz, 2H), 2.93 (d, J_{H-P} = 21.7 Hz, 2H), 2.03 (s, 6H), 1.38 (s, 6H), 1.48−1.17 (m, 12H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 165.2−164.8, 137.3, 128.6−127.5, 115.5, 114.7, 114.4, 104.5, 104.1, 82.0, 81.6, 81.5, 79.9, 79.6 (d, J_{C-P} = 9.8 Hz), 74.1, 73.9, 68.9, 68.3, 63.4 (d, J_{C-P} = 7.1 Hz), 61.7, 35.2 (d, J_{C-P} = 138.8 Hz), 27.0, 26.9, 26.4, 26.3, 16.0 (d, J_{C-P} = 6.7 Hz), 14.1. ^{31}P NMR ($CDCl_3$; MHz): δ 21.9−21.6 (m), 20.0−19.8 (m). HRMS: $C_{22}H_{30}NO_9PNa$ calcd 506.1556, found 506.1543.

*5-O-Benzoyl-3-C-cyano-1,2-O-isopropylidene-3-O-[methyl-2-(methoxyphosphonyl)acetate]-α-D-ribofuranose (**23**).* According to the general procedure, compound **1** (72 mg, 0.22 mmol) was treated with methyl (methoxycarbonylmethyl)phosphonochloridate (ClOP-(OMe)(CH_2COOMe); 42.1 mg, 0.22 mmol) and NaH (18 mg, 0.40 mmol) in CH_2Cl_2 (10 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc, 5/5) to give **23** as a colorless oil (23 mg, 22%) as a mixture of two diastereomers (60/40). R_f = 0.21 (EtOAc/cyclohexane, 5/5). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 8.14−8.09 (m, 4H), 7.63−7.59 (m, 2H), 7.48−7.45 (m, 4H), 6.04 (d, J = 3.7 Hz, 2H), 5.28 (d, 1H), 5.16 (d, 1H), 4.90 (dd, J = 12.2 Hz, J = 3.4 Hz, 1H), 4,73−4.62 (m, 3H), 4.51 (m), 3.94 (d, J_{H-P} = 11.8 Hz, 3H), 3.83 (d, J_{H-P} = 11.8 Hz, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.18 (d, J_{H-P} = 23.2 Hz, 2H), 3.13 (d, J_{H-P} = 22.3 Hz, 2H), 1.64 (s, 3H), 1.62 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 165.9, 165.0 (d, J_{C-P} = 15.2 Hz), 133.5, 133.4, 129.9, 129.8, 128.5, 115.2, 114.6, 114.4, 104.2, 104.1, 81.8, 81.6, 77.5, 77.3, 61.9, 53.9 (d, J_{C-P} = 7.6 Hz), 53.9 (d, J_{C-P} = 7.3 Hz), 53.0, 52.7, 34.6 (d, J_{C-P} = 139.7 Hz), 34.5 (d, J_{C-P} = 139.7 Hz), 27.0, 26.9, 26.4, 26.3. ^{31}P NMR ($CDCl_3$; 121 MHz): δ 23.5−22.8 (m), 21.6−20.9 (m). HRMS: $C_{20}H_{24}NO_{10}PNa$ calcd 492.1036, found 492.1031.

*5-O-Benzoyl-3-C-cyano-3-O-cyanomethylethoxyphosphonyl-1,2-O-isopropylidene-α-D-ribofuranose (**24**).* According to the general procedure, compound **1** (64 mg, 0.20 mmol) was treated with ethyl (cyanomethyl)phosphonochloridate (ClOP(OEt)(CH_2CN); 33.6 mg, 0.20 mmol) and NaH (16 mg, 0.40 mmol) in CH_2Cl_2 (12 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc, 3/7) to give **24** as a colorless oil (40 mg, 44%) as a mixture of two diastereomers (58/42). R_f = 0.36 (EtOAc/cyclohexane, 5/5). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 8.14−8.11 (m, 4H), 7.66−7.63 (m, 2H), 7.52−7.47 (m, 4H), 6.06 (d, J = 3.8 Hz, 1H), 6.04 (d, J = 3.8 Hz, 1H), 5.28 (d, 1H), 5.16 (d, 1H), 4.78 (dd, J = 12.9 Hz, J = 5.7 Hz, 1H), 4,73−4.56 (m, 3H), 4.44−4.35 (m, 2H), 4.34−4.25 (m, 2H), 4.25−4.16 (m, 2H), 3.24−2.93 (m, 4H), 1.66 (s, 3H), 1.61 (s, 3H), 1.47−1.41 (m, 9H), 1.38−1.33 (m, 3H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 165.9, 133.5, 129.9, 129.1, 128.5, 114.8, 114.6, 114.4, 104.1, 103.9, 81.8, 81.4, 77.2, 77.1, 65.6, 64.6 (d, J_{C-P} = 7.4 Hz), 61.7, 61.5, 26.9, 26.8, 26.2, 17.6 (d, J_{C-P} = 148.7 Hz), 16.1 (d, J_{C-P} = 5.9 Hz), 15.9 (d, J_{C-P} = 6.7 Hz). ^{31}P NMR ($CDCl_3$; 121 MHz): δ 16.4−15.9 (m), 14.5−14.0 (m). HRMS: $C_{20}H_{23}N_2O_8PNa$ calcd 473.1090, found 473.1086.

*5-O-Benzoyl-3-O-benzylethoxyphosphonyl-3-C-cyano-1,2-O-isopropylidene-α-D-ribofuranose (**25**).* According to the general procedure, compound **1** (194 mg, 0.61 mmol) was treated with ethyl (benzyl)phosphonochloridate (ClOP(OEt)(CH_2Ph); 133 mg, 0.61 mmol) and NaH (48.6 mg, 1.21 mmol) in CH_2Cl_2 (30 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc, 6/4) to give **25** as a colorless oil (200 mg, 65%) as a mixture of two diastereomers (70/30). R_f = 0.5 (EtOAc/cyclohexane: 5/5). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 8.13 (d, J = 7.9 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H), 7.59−7.32 (m, 6H), 7.30−7.25 (m, 10H), 6.03 (d, J = 3.7 Hz, 1H), 6.00 (d, J = 3.7 Hz, 1H), 5.33 (d, 1H), 5.18 (d, 1H), 4.76−4.65 (m, 4H), 4.55−4.39 (m, 2H), 4.26−4.10 (m, 2H), 4.03−3.98 (m, 2H), 3.38−3.29 (m, 4H), 1.68 (s, 3H), 1.59 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.29−1.25 (m, 3H), 1.19−1.15 (m, 3H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 165.8, 133.5, 133.4, 129.9−127.1, 115.4, 114.9, 114.5, 114.2, 104.0, 81.9, 81.7, 77.6, 77.4 (d, J_{C-P} = 7.5 Hz), 77.0 (d, J_{C-P} = 9.7 Hz), 63.3 (d, J_{C-P} = 7.7 Hz), 62.9 (d, J_{C-P} = 7.6 Hz), 62.0, 61.9, 34.5 (d, J_{C-P} = 138.7 Hz), 34.3 (d, J_{C-P} = 138.4 Hz), 26.9, 26.5, 26.3, 26.2, 16.1 (d, J_{C-P} = 6.5 Hz), 15.8 (d, J_{C-P} = 6.8 Hz). ^{31}P NMR ($CDCl_3$; 121 MHz): δ 28.0−27.4 (m), 26.8−26.5 (m). HRMS: $C_{25}H_{28}NO_8PNa$ calcd 524.1450, found 524.1437.

*Ethyl 1,7-Dioxa-2-phosphaspiro[4.4]-(1S,3R,4R,5R)-4-amino-6-benzoyloxymethyl-2-ethoxy-8,9-isopropylidenedioxy-2-oxonon-3-en-3-carboxylate (**26**).* According to the general procedure, compound **1** (626 mg, 1.96 mmol) was treated with ethyl (ethoxycarbonylmethyl)phosphonochloridate (ClOP(OEt)-(CH_2COOEt); 421 mg, 1.96 mmol) and NaH (157 mg, 3.92 mmol) in CH_2Cl_2 (50 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc, 6/4) to give **26a** (370 mg) and **26b** (310 mg) as white solids (70%). Data for **26a** are as follows. R_f = 0.18 (EtOAc/cyclohexane, 5/5). Mp: 235−236 °C. $[\alpha]^{20}_D$ = −5 (c 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 7.97 (d, J = 7.2 Hz, 2H), 7.83 (s, 1H), 7.49 (m, 1H), 7.38−7.30 (m, 2H), 6.55 (s, 1H), 6.06 (d, J = 3.9 Hz, 1H), 4.71 (dd, J = 2.8 Hz, J = 7.2 Hz, 1H), 4,62−4.45 (m, 2H), 4.52 (d, 1H), 4.22−4.02 (m, 4H), 1.57 (s, 3H), 1.31 (s, 3H), 1.27−1.17 (m, 6H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 167.3 (d, J_{C-P} = 33.6 Hz), 165.9, 164.3 (d, J_{C-P} = 14.3 Hz), 133.5, 129.8, 129.4, 128.3, 114.2, 104.0, 84.8, 82.7 (d, J_{C-P} = 196.2 Hz), 81.4, 77.3 (d, J_{C-P} = 7.0 Hz), 63.7 (d, J_{C-P} = 6.5 Hz), 61.0, 60.4, 26.6, 26.2, 16.3 (d, J_{C-P} = 6.3 Hz), 14.2. ^{31}P NMR ($CDCl_3$; 121 MHz): δ 33.7 (t, J_{P-H} = 3.0 Hz). HRMS: $C_{22}H_{28}NO_{10}PNa$ calcd 520.1349, found 520.1340. Data for **26b** are as follows: R_f = 0.07 (EtOAct/cyclohexane, 5/5). Mp: 153−154 °C. $[\alpha]^{20}_D$ = +16 (c 0.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 8.01 (d, J = 7.3 Hz, 2H), 7.83 (s, 1H), 7.49 (m, 1H), 7.45−7.40 (m, 2H), 6.23 (s, 1H), 6.06 (d, J = 3.8 Hz, 1H), 4.68 (m, 2H), 4,35−4.24 (m, 2H), 4.21−4.06 (m, 4H), 1.64 (s, 3H), 1.30 (s, 3H), 1.35−1.21 (m, 6H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 166.7 (d, J_{C-P} = 33.8 Hz), 166.0, 165.3 (d, J_{C-P} = 14.3 Hz), 133.3, 129.8, 129.3, 128.4, 114.4, 103.8, 84.9, 83.9 (d, J_{C-P} = 197.1 Hz), 81.8, 77.1 (d, J_{C-P} = 8.5 Hz), 64.1 (d, J_{C-P} = 6.2 Hz), 61.2, 60.4, 26.3, 16.4 (d, J_{C-P} = 5.6 Hz), 14.2. ^{31}P NMR ($CDCl_3$; 121 MHz): δ 34.1 (t, J_{P-H} = 3.0 Hz). HRMS: $C_{22}H_{28}NO_{10}PNa$ calcd 520.1349, found 520.1340.

*Ethyl 1,7-Dioxa-2-phosphaspiro[4.4]-(1S,3R,4R,5R)-4-amino-6-benzyloxymethyl-2-ethoxy-8,9-isopropylidenedioxy-2-oxonon-3-en-3-carboxylate (**27**).* According to the general procedure, compound **2** (203 mg, 0.66 mmol) was treated with ethyl (ethoxycarbonylmethyl)phosphonochloridate (ClOP(OEt)-(CH_2COOEt); 143 mg, 0.66 mmol) and NaH (80 mg, 1.99 mmol) in CH_2Cl_2 (50 mL). The crude product was purified by flash chromatography (cyclohexane/EtOAc) to give **27a** (95 mg) and **27b** (40 mg) as white solids (42%). Data for **27a** are as follows. R_f = 0.43 (EtOAc/cyclohexane, 8/2). Mp: 180−184 °C. ^{1}H NMR ($CDCl_3$; 300 MHz): δ 7.35−7.27 (m, 5H), 5.96 (d, J = 3.9 Hz, 1H), 4.56−4.52 (m, 2H), 4.49 (d, 1H), 4.38−4.16 (m, 5H), 3.81 (dd, J = 2.5 Hz, J = 11.3 Hz, 1H), 3.70 (dd, J = 6.5 Hz, 1H), 1.62 (s, 3H), 1.37 (s, 3H), 1.39−1.26 (m, 6H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 168.3 (d, J_{C-P} = 33.4 Hz), 165.4 (d, J_{C-P} = 14.2 Hz), 137.4, 129.9, 128.4, 127.8, 114.5,

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103.9, 83.3 (d, J_{C-P} = 220.9 Hz), 82.1, 78.8 (d, J_{C-P} = 5.8 Hz), 77.5, 73.6, 66.6, 63.7 (d, J_{C-P} = 6.4 Hz), 60.5, 26.7, 26.3, 16.3 (d, J_{C-P} = 6.1 Hz), 14.3. ^{31}P NMR ($CDCl_3$; 121 MHz): δ 33.7 (t, J_{P-H} = 9.7 Hz). HRMS: $C_{22}H_{30}NO_9PNa$ calcd 506.1556, found 506.1559. Data for **27b** are as follows. R_f = 0.15 (EtOAc/cyclohexane, 8/2). Mp: 127−129 °C. ^{1}H NMR ($CDCl_3$; 300 MHz): δ 7.39−7.30 (m, 5H), 5.94 (d, J = 3.8 Hz, 1H), 4.65−4.51 (m, 4H), 4.36−4.14 (m, 4H), 3.76 (dd, J = 3.0 Hz, J = 12.0 Hz, 1H), 3.66 (dd, J = 6.0 Hz, 1H), 1.66 (s, 3H), 1.38 (s, 3H), 1.39−1.28 (m, 6H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 167.8 (d, J_{C-P} = 33.2 Hz), 165.4 (d, J_{C-P} = 14.3 Hz), 137.3, 129.8−127.7, 114.5, 103.7, 84.7 (d, J_{C-P} = 219.1 Hz), 84.8 (d, J_{C-P} = 3.6 Hz), 82.2 (d, J_{C-P} = 2.6 Hz), 76.6, 73.6, 66.2, 63.8 (d, J_{C-P} = 6.3 Hz), 60.5, 26.4, 26.3, 16.5 (d, J_{C-P} = 6.0 Hz), 14.3. ^{31}P NMR ($CDCl_3$; MHz): δ 33.8 (t, J_{P-H} = 7.2 Hz). HRMS: $C_{22}H_{30}NO_9PNa$ calcd 506.1556, found 506.1541.

*Methyl 1,7-Dioxa-2-phosphaspiro[4.4]-(1S,3R,4R,5R)-4-amino-6-benzoyloxymethyl-8,9-isopropylidenedioxy-2-methoxy-2-oxonon-3-en-3-carboxylate (**28**).* According to the general procedure, compound **1** (380 mg, 1.19 mmol) was treated with methyl (methoxycarbonylmethyl)phosphonochloridate (ClOP(OMe)-(CH_2COOMe); 222 mg, 1.19 mmol) and NaH (190 mg, 4.76 mmol) in CH_2Cl_2 (40 mL). The crude product was purified by reverse flash chromatography (C18, acetonitrile/H_2O) to give **28** as a colorless oil (180 mg, 41%) as a mixture of two diastereomers (60/40). R_f = 0.13 (EtOAc/cyclohexane, 5/5). ^{1}H NMR (MeOD; 300 MHz): δ 8.05−8.02 (m, 4H), 7.68−7.62 (m, 2H), 7.54−7.48 (m, 4H), 6.16 (d, J = 3.8 Hz, 2H), 4.70 (d, 1H), 4.63 (d, 1H), 4.61−4.43 (m, 6H), 3.81 (d, J_{H-P} = 11.7 Hz, 3H), 3.79 (s, 6H), 3.78 (d, J_{H-P} = 11.7 Hz, 3H), 1.64 (s, 3H), 1.63 (s, 3H), 1.41 (s, 6H). ^{13}C NMR (MeOD; 75 MHz): δ 168.1, 166.0 (d, J_{C-P} = 3.8 Hz), 165.2 (d, J_{C-P} = 15.0 Hz), 133.2, 133.1, 129.5, 129.4, 128.3, 113.9, 113.8, 104.2, 104.1, 85.6, 81.9, 77.2 (d, J_{C-P} = 4.6 Hz), 77.0 (d, J_{C-P} = 4.4 Hz), 61.1, 60.8, 53.7 (d, J_{C-P} = 6.2 Hz), 50.5, 50.4, 25.3, 25.2. ^{31}P NMR ($CDCl_3$; MHz): δ 38.7 (q, J_{P-H} = 11.7 Hz). HRMS: $C_{20}H_{24}NO_{10}PNa$ calcd 492.1036, found 492.1031.

*1,7-Dioxa-2-phosphaspiro[4.4]-(1S,3R,4R,5R)-4-amino-6-benzoyloxymethyl-2-ethoxy-8,9-isopropylidenedioxy-2-oxonon-3-en-3-carboxamide (**29**).* According to the general procedure, compound **1** (204 mg, 0.64 mmol) was treated with ethyl (cyanomethyl)-phosphonochloridate (ClOP(OEt)(CH_2CN); 107 mg, 0.64 mmol) and NaH (102 mg, 2.55 mmol) in CH_2Cl_2 (20 mL). The crude product was purified by reverse flash chromatography (C18, acetonitrile/H_2O) to give **29** as a white solid (160 mg, 53%) (only one diastereomer). R_f = 0.1 (EtOAc). Mp: 209−211 °C. $[\alpha]^{20}_D$ = −40 (c 0.1, CH_2Cl_2). ^{1}H NMR (MeOD; 300 MHz): δ 9.43 (d, J = 7.1 Hz, 2H), 9.04 (m, 1H), 8.95−8.90 (m, 2H), 7.62 (d, J = 3.8 Hz, 1H), 6.33 (d, 1H), 6.29 (m, 1H), 6.00 (dd, J = 5.4 Hz, J = 11.7 Hz, 1H), 5.75 (dd, J = 7.4 Hz, 1H), 5.11−5.05 (m, 2H), 3.05 (s, 3H), 2.83 (s, 3H), 2.52 (t, J = 7.1 Hz, 3H). ^{13}C NMR (MeOD; 75 MHz): δ 178.6 (d, J_{C-P} = 17.3 Hz), 175.2 (d, J_{C-P} = 6.9 Hz), 167.0, 134.8, 130.8, 129.8, 129.6, 115.9, 105.6, 97.9 (d, J_{C-P} = 132.2 Hz), 95.0 (d, J_{C-P} = 10.6 Hz), 83.0, 75.7, 62.1, 61.7 (d, J_{C-P} = 5.3 Hz), 26.7, 26.6, 16.8 (d, J_{C-P} = 7.5 Hz). ^{31}P NMR ($CDCl_3$; 121 MHz): δ 2.65 (t, J_{P-H} = 6.0 Hz). HRMS: $C_{20}H_{26}N_2O_9P$ calcd 469.1376, found 469.1380.

4.7. 1,7-Dioxa-2-phosphaspiro[4.4]-(1*S*,3*R*,4*R*,5*R*)-6-benzoyloxymethyl-2-ethoxy-8,9-isopropylidenedioxy-2-oxo-3-phenylnon-3-en-4-amine (30). To a solution of diisopropylamine (52 μL, 0.36 mmol) and BuLi (144 μL, 0.36 mmol) in dry THF (2 mL) at −78 °C under argon was added a solution of compound **25** (45 mg, 0.089 mmol) in dry THF (3 mL). After 1 h, water was added and the reaction mixture was neutralized with HCl and then extracted with EtOAc. The organic phase was separated, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography (cyclohexane/EtOAc, 5/5) to give **30** as a colorless oil (35 mg, 78%) as a mixture of two diastereomers (60/40). R_f = 0.15 (EtOAc/cyclohexane, 5/5). ^{1}H NMR ($CDCl_3$; 300 MHz): δ 7.77−7.73 (m, 2H), 7.48−7.45 (m, 2H), 7.48−7.45 (m, 6H), 7.29−7.26 (m, 10H), 5.75 (d, J = 3.7 Hz, 2H), 4.69 (m, 2H), 4.45 (m, 2H), 4.30−4.04 (m, 8H,), 1.65 (s, 6H), 1.52−1.48 (m, 6H), 1.31 (s, 6H). ^{13}C NMR ($CDCl_3$; 75 MHz): δ 164.3, 163.2, 145.5, 144.9, 132.8, 132.6, 129.5−127.3, 114.0, 113.9, 104.0, 103.9, 87.3 (d, J_{C-P} = 5.1 Hz), 81.5, 81.4, 79.9 (d, J_{C-P} = 4.8 Hz), 79.4 (d, J_{C-P} = 3.4 Hz), 64.7 (d, J_{C-P} = 7.4 Hz), 64.5 (d, J_{C-P} = 6.5 Hz), 57.8, 57.2, 26.6, 26.5, 26.3, 16.4−16.1. ^{31}P NMR ($CDCl_3$; 121 MHz): δ 34.1 (t, J_{P-H} = 8.5 Hz), 33.7 (t, J_{P-H} = 9.5 Hz). HRMS: $C_{25}H_{28}NO_8PNa$ calcd 524.1450, found 524.1459.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra of compounds **6**−**8**, **10**−**12**, and **21**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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