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SOME PROPERTIES OF CYCLIC PHOSPHORAMIDITES AND THEIR PHOSPHITES: PHOSPHITYLATION, ESTER EXCHANGE, AND HYDROLYSIS[#]

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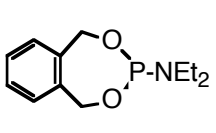
Abstract — Phosphorylation of diols using sterically bulky cyclic phosphoramidites was performed in a good selectivity. Their phosphite derivatives underwent tetrazole-catalyzed hydrolysis and transesterification. The reaction was shown to proceed *via* a phosphorane intermediate by NMR analysis.

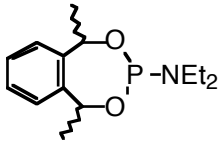
Various phosphoramidites have been utilized for phosphorylation of alcohols mainly in nucleotide and phospholipid chemistry.[1] However, their and related cyclic derivatives have rarely attracted attention for study on synthesis and reactivity,[2, 3] although there have been a number of reports on structure analysis of cyclic phosphorus compounds.[4] We released xylylene *N,N*-diethylphosphoramidite (XEPA)[5] as a powerful phosphitylating reagent for phosphorylation of polyols such as inositol derivatives.[6] In contrast to the methodology, so called exhaustive phosphorylation, selective phosphorylation strategy is also a synthetically useful tool. In order to develop such a method, XEPA was modified to produce a sterically hindered derivative. During this study, we found phosphorous triesters (phosphites) were activated even by a weak acid, 1*H*-tetrazole (p*K*a 4.89), resulting in hydrolysis and ester exchange in the presence of water and an alcohol respectively.[7] In this paper, we describe the selective phosphorylation ability of the cyclic phosphoramidites and ester exchange and hydrolysis of their phosphite versions.

RESULTS AND DISCUSSION

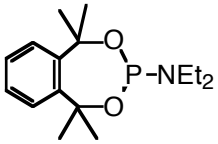
Synthesis of cyclic phosphoramides and phosphorylation



XEPA



1 (*dl* and *meso*)

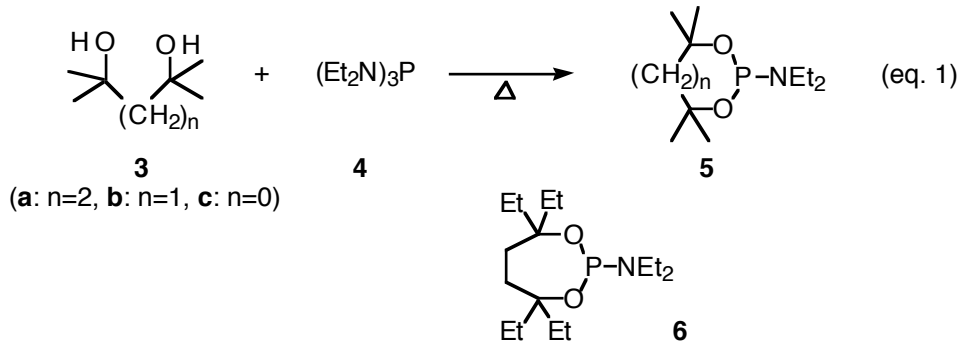


2

Dimethyl and tetramethyl phosphoramidites (**1**) and (**2**) were first candidates for modified XEPA derivatives bearing substituents at the benzylic positions. The former (**1**) was shown to be usable for phosphorylation, however, selective reaction towards a primary *vs* secondary alcohol did not proceed

[#]This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

and also diastereomeric products were troublesome. Since more hindered **2** could not be prepared, several analogous alicyclic phosphoramidites (**5**) and (**6**) including six- and five-membered rings as well as seven were synthesized according to the following equation (eq. 1):



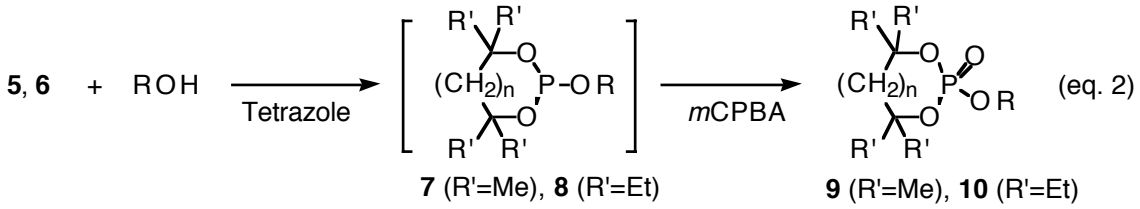


Table 1. Phosphorylation using phosphoramidites

ROH	Yield, %							
	9a$_1$	**9a$_2$**	**9b$_1$**	**9b$_2$**	**9c$_1$**	**9c$_2$**	**10a$_1$***	**10a$_2$***
Ph⌒⌒OH **11**	86		93		76		84	
Ph, OH **12**		91		96		88		86
11 + **12**	91 (82/18)#		87 (73/27)#		78 (66/34)#		50 (86/14)#	

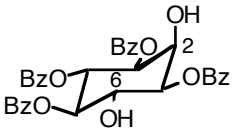
*1.4 Equiv of pyridine based on alcohol employed was added.

#Ratio of primary ester/secondary ester.

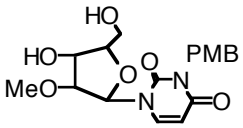
The reactivity of phosphoramidites (**5**) thus obtained was first evaluated by phosphorylation of simple alcohols. They were first treated with 3-phenylpropyl alcohol (PPrOH, **11**) or *dl*-1-phenyl-1-pentyl alcohol (**12**) in the presence of 1*H*-tetrazole to form phosphites (**7**) and (**8**), which were then oxidized with *m*-chloroperbenzoic acid (*m*CPBA) to give phosphates (**9**) and (**10**) in good yields (Table 1). Although their reactivity was lower than that of XEPA and other common acyclic phosphitylating reagents such as dibenzyl and dimethyl phosphoramidite, phosphorylation yields were generally as high as those for the latter amidite reagents. It is interesting to note that five-membered ring products (**9c**) were so fairly stable that they were isolate by a preparative silica gel TLC, whereas five-membered cyclic phosphates are generally known to be quite unstable.[8]

Reaction of equimolar amounts of both alcohols with **5** or **6** at 0 ℃ proceeded in good selectivity, resulting in the predominant formation of primary esters (**9$_1$**) and (**10$_1$**). Selectivity decreased with the ring size of reagents from seven to five. Methyl and ethyl substituents on the seven-membered ring did not affect the

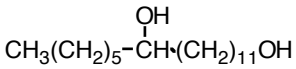
selectivity, however, morpholino version instead of diethylamino one decreased selectivity in some extent. On the basis of these results, some substrates (**13**-**15**) bearing two hydroxyl groups in the same molecules were treated with **5a** and phosphoric esters of higher reactive equatorial and primary alcohols were obtained accompanied with a small amount of diphosphates. Thus, completely selective phosphorylation could not be realized.



13
6-P: 77%
2,6-P_2: 2%

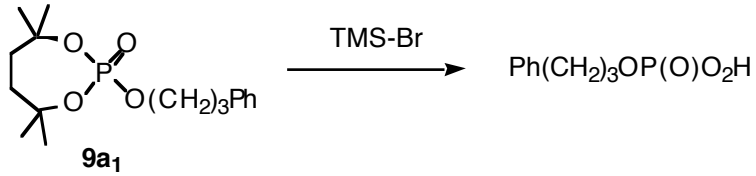


14
5'-P: 75%
3',5'-P2: 6%



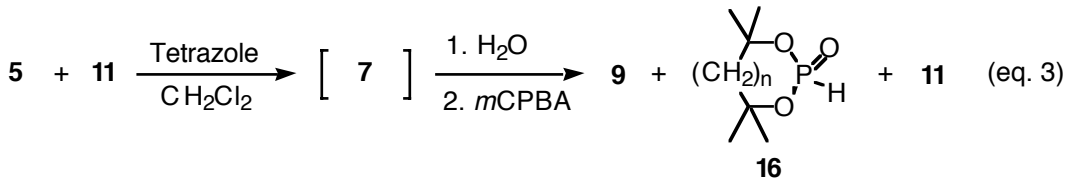
15
1-P: 69%
1,12-P_2: 10%

Deprotection of **9a1** was accomplished by the reaction with bromotrimethylsilane, combination of chlorotrimethylsilane and NaI, or diluted HCl to afford 3-phenylpropyl phosphate in 95% yield.



9a1

Hydrolysis of cyclic phosphites (7)



16

Table 2. Hydrolysis of phosphites (7)

	Yield (%)#		
	9	**16**	**11**
7a	44 (0 ˚C: 74%) *	18	29
7b	47 (0 ˚C: 79%) *	33	45
7c	6 (0 ˚C: 9%) *	-	82

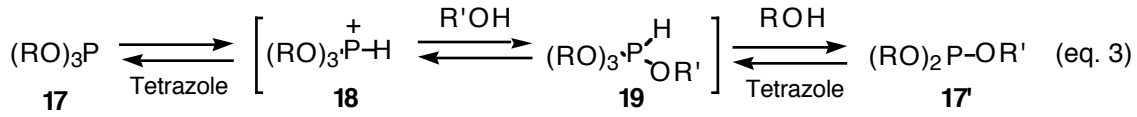
#Isolated yield by preparative TLC.
*Other products were not isolated.

Treatment of cyclic phosphites (**7**), derived *in situ* from amidites (**5**) and PPrOH (**11**), with water for 1 h at an ambient temperature followed by oxidation with *m*CPBA, which was done to isolate P(III) compound(s) without decomposition, yielded hydrolysis products (**16**) and the alcohol (**11**) to a fairly extent along with

phosphorylation product (**9**), while the reaction at 0 ℃ furnished phosphorylation products (**9**) predominantly (eq. 3 and Table 2). The yield of H-phosphonates (**16**) was expected to be comparable with that of alcohol (**11**) recovered, however, their isolation yields were decreased because of their instability on silica gel. Especially, five-membered ring phosphonate (**16c**) was not isolated.[9] It should be noted that, as suggested based on the sum of yields of **9b** and **11**, hydrolysis occurred at the exocyclic position almost exclusively and also a remaining phosphorus-containing product was phosphorylation one (**9b**). In the case of **5a**, one more product, presumably a ring-cleavage derivative was formed, resulting in decrease of the amount of alcohol compared with results in the case of **5b** and **5c** as expected from the ester exchange experiments described below. Since, in independent experiments, hydrolysis of phosphites (**7**) was not observed in the absence of tetrazole and diethylammonium tetrazolide[10] which is generated during the phosphitylation, the former weak acid catalyst and even the less acidic latter became apparent to accelerate the hydrolysis.[11, 12] Thus, hydrolysis of phosphite is assumed to take place by protonation on the phosphorus atom.

Hydrolysis of the five-membered phosphite (**5c**) was faster than that of others. However, the ring size of **5** did not influenced enormously their hydrolytic reactivity, while five-membered ring phosphates are known to be much more reactive than six- and seven-membered cyclic phosphates as well as acyclic esters.[8]

Ester exchange reaction of phosphites

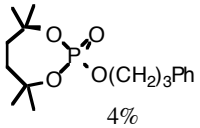
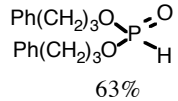
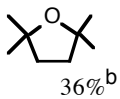
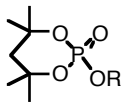
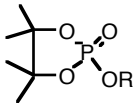
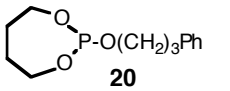
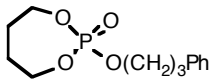
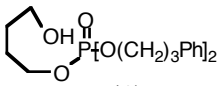
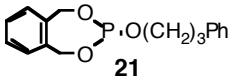
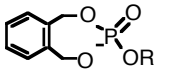
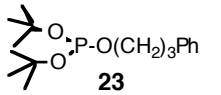
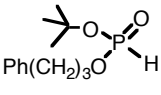


In order to understand the hydrolysis process described above and a catalytic ability of tetrazole in the reaction of a phosphites with nucleophiles, the reaction with an alcohol instead of water was then explored. Thus, equimolar amounts of a phosphite, alcohol, and tetrazole were stirred in CH_2Cl_2 for 22 h at ambient temperature (around 27 ℃), and then the mixture was treated with *m*CPBA to isolate P(III) products without decomposition by transforming to P(V) derivatives. Six- and five-membered cyclic phosphites (**7b**) and (**7c**) were converted in the presence of benzyl alcohol to the corresponding 3-phenylpropyl and benzyl phosphoric triesters resulting from ester exchange without any other side-reaction (run 3, 5 in Table 3) as ^{31}P NMR spectroscopy of the reaction of **7b** with PPrOH (**11**) in the presence of tetrazole in $CDCl_3$ showed only one peak at 128.12 ppm due to **7b** even after 3 days.

On the other hand, the tetrazole-catalyzed reaction of seven-membered **7a** with PPrOH (**11**) proceeded differently to afford bis(3-phenylpropyl) hydrophosphonate as a major product (63% yield) along with 4% of phosphoric triester and 36% of 2,2,5,5-tetramethyltetrahydrofuran (run 1). Analogous seven-membered phosphites (**20**) and (**21**), however, gave only ester exchange products (run 6, 7) as **7b** and **7c**. A simple acyclic tributyl phosphite (**22**) was also smoothly transesterified resulting in the formation of three phosphoric triesters (run 8). Therefore, structural feature of **7a**, that is, tertiary ester changed the pathway dramatically. It is interesting to compare the result of the cyclic di-tertiary ester (**7a**) with that of an acyclic analogue, di-*tert*-butyl 3-phenylpropyl phosphite (**23**) (run 9). In the absence of PPrOH (**11**), **23** decomposed on treatment with tetrazole within 3 h at room temperature to form *tert*-butyl 3-phenylpropyl

hydrophosphonate quantitatively, and even in the presence of the alcohol, transesterification product was not observed. The results can be explained in terms of protonation on the phosphorus atom in **23** with tetrazole and spontaneous formation of trimethylcarbocation, resulting in the formation of the H-phosphonate. In contrast, **7a** did not decompose on treatment with tetrazole in the absence of an alcohol for 2 h at room temperature and then for 2 h under refluxing in CH_2Cl_2.

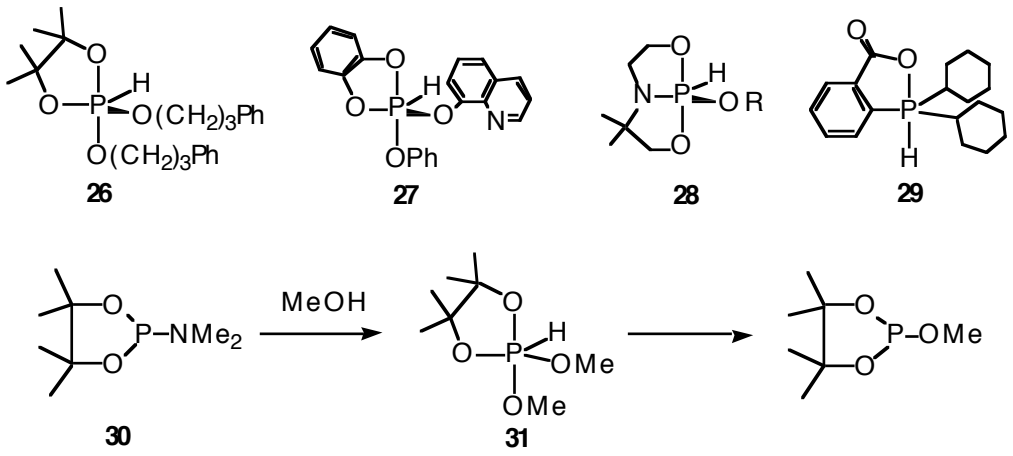
Table 3. Tetrazole-catalyzed reaction of phosphites in the presence of an alcohol

Run	Phosphite	Alcohol [a]	Products and yields
1	**7a**	**24**	 4%  63%  36%[b]
2	**7b**	**24**	 R = $Ph(CH_2)_3$: 85%
3	**7b**	**25**	R = $Ph(CH_2)_3$: 41% **24**: 46%, **25**: 49% R = $PhCH_2$: 30%
4	**7c**	**24**	 R = $Ph(CH_2)_3$: 69%
5	**7c**	**25**	R = $Ph(CH_2)_3$: 42% **24**: 46%, **25**: 48% R = $PhCH_2$: 15%
6	 **20**	**24**	 55%  4% $[Ph(CH_2)_3O]_3P(O)$ 14%
7	 **21**	**25**	 R = $Ph(CH_2)_3$: 34% **24**: 34%, **25**: 42% R = $PhCH_2$: 28%
8	$(n\text{-BuO})_3P$ **22**	**24**	$(n\text{-BuO})_3P(O)$: 21% $(n\text{-BuO})_2P(O)\text{-}O(CH_2)_3Ph$: 36% $n\text{-BuOP(O)}[O(CH_2)_3Ph]_2$: 16%
9	 **23**	**24**	 85% quant. (rt, 3 h without alcohol)

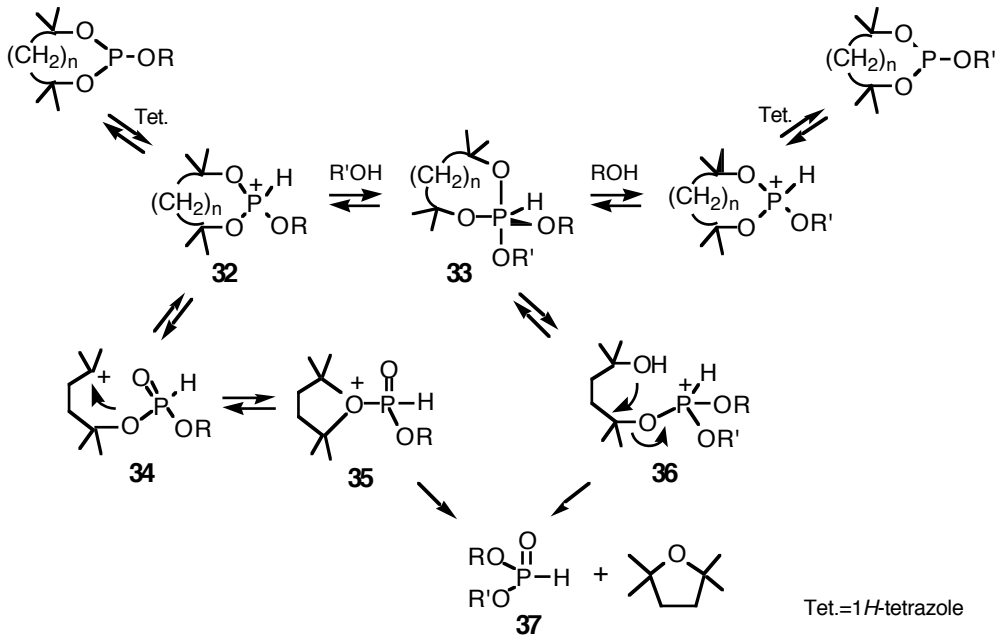
[a] **24**=$Ph(CH_2)_3OH$, **25**=$PhCH_2OH$. [b]GLC analysis

The transesterification of trialkyl phosphites[11] was reported to be catalyzed by acids such as phosphoric acid,[13] diethyl hydrophosphonate,[14] aluminum chloride,[14] and protonated phosphonium salt intermediates were postulated.[14] Alkylation of *p*-toluenesulfonic acid with phosphites *via* phosphonium salts was also reported.[15] Protonated species, phosphonium salts derived from phosphites with strong acids such as 100% sulfuric acid,[16] FSO_3H,[17] and HCl[18] were detected by NMR study. To our knowledge, however, there is no report on direct observation of the intermediate in the transesterification of phosphites. We propose that a phosphorane such as **19** is a key intermediate in transesterification of phosphites (eq. 3) based on direct observation of hydrophosphorane (**26**) by NMR spectroscopy.[19]

When the reaction of **7c** with PPrOH (**11**) in the presence of tetrazole in $CDCl_3$ was monitored by ^{31}P NMR spectroscopy, the spectrum exhibited doublet of quintets as a minor peak due to the coupling with the proton on the phosphorus (J = 666.5 Hz) and two alcoholic methylene (J=18.7 Hz) at -24.95 ppm

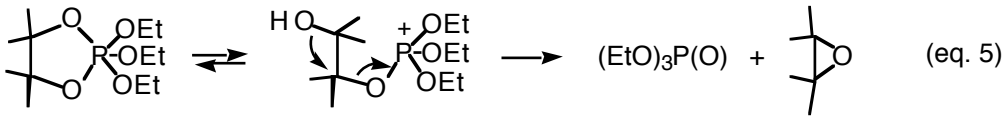


(80% H_3PO_4 as external standard), indicating the existence of hydrophosphorane (**26**). Its concentration during the reaction was kept constantly from 10 min to more than 2 days under anhydrous conditions, suggesting that **26** exists in an equilibrium reaction. This signal was not observed in a spectrum of a mixture of **7c** and tetrazole. Boisdon *et al.* observed hydrophosphorane (**31**) (δ_P -26 ppm) in an NMR study of the reaction of phosphoramidite (**30**) with methanol (eq. 4).[20] As a special case, transesterification of *o*-phenylene 8-quinolyl phosphite with phenol was reported to proceed *via* hydrophosphorane (**27**) which was observed by ^{31}P NMR.[21] Novel bicyclo phosphoramidites were demonstrated to react with alcohols to yield the hydrophosphoranes (**28**) which transesterified with other alcohols without any catalyst.[22] Intramolecular adduct (**29**) between a carboxyl group and phosphine was also reported.[7] A pentacoordinate intermediate like **26** was not detected in the cases of **7a**, **7b**, and **22** by the same analysis. These differences are mainly attributed that phosphorane containing a five-membered ring is more stable than cyclic and acyclic ones.[23] From these facts, it is reasonable to consider that the tetrazole-catalyzed ester exchange reaction of phosphites proceeds by way of **32** and **33** (Scheme 1).



Scheme 1. Mechanism of the tetrazole-catalyzed reactions

A mechanistic feature of the reaction of **7a** is decomposition of the seven-membered ring with the formation of tetramethyltetrahydrofuran. Its process seems to involve the formation of **36** led from **33**. Another pathway including **34** and **35** is at least not important, because **7a** was not decomposed by treatment with tetrazole without an alcohol. Analogous reaction was reported in which phosphorane (**38**) decomposed *via* **39** at room temperature, forming oxirane and triethyl phosphate (eq. 5).[24] We could not detect the same oxirane in the reaction of **9c** whereas a trace of bis(3-phenylpropyl) hydrophosphonate was observed by NMR analysis.



38 **39**

Finally, we would like to warn a possibility that phosphitylation using a phosphoramidite in the presence of tetrazole induces decomposition of the resultant phosphite by the excess of the catalyst and the alcohol, and by a prolonged reaction time. Indeed, glycosyl phosphites[25] and a phosphite of a tertiary alcohol[26] was converted to the *N*-alkylation products by replacement of the hydroxyl groups with tetrazole.

EXPERIMENTAL

All NMR spectra were taken in $CDCl_3$. In the case of ^{31}P NMR, 85% H_3PO_4 (δ=0.0) was used as an external standard. Extracts obtained after work-up were dried over $MgSO_4$ or Na_2SO_4. All compounds isolated were oily except for 1,3,4,5-Tetra-*O*-benzoyl-*myo*-inositol 6-(4,4,7,7-tetramethylbutylene phosphate).

2-Diethylamino-4,4,7,7-tetramethyl-1,3,2-dioxaphosphepane (5a). A mixture of 2,5-dimethyl-2,5-hexanediol (10.0 g, 68.4 mmol) and tris(diethylamino)phosphine (22.6 mL, 82.1 mmol) was heated at 100 ℃ for 2 h and distilled under reduced pressure to give **5a** (10.1 g, 60%): bp 51 ℃/0.4 mmHg; ^1H NMR (90 MHz) δ 1.03 (6H, t, *J*=8.0 Hz), 1.19 (6H, s), 1.37 (6H, s), 1.77 (4H, br), 3.01 (4H, dq, *J*=12.0 and 8.0 Hz); ^{31}P NMR (109 MHz) δ 137.23; *Anal.* Calcd for $C_{12}H_{26}NO_2P$: C, 58.28; H, 10.60; N, 5.66. Found: C, 57.97; H, 10.65; N, 5.87.

2-Diethylamino-4,4,6,6-tetramethyl-1,3,2-dioxaphosphane (5b). According to the procedure for **5a**, **5b** was obtained (100 ℃, 3 h, 66%): bp 53-54 ℃/0.09 mmHg; ^1H NMR (90 MHz) δ 1.00 (6H, t, *J*=8.0 Hz), 1.25 (6H, s), 1.40 (6H, s), 1.65 (2H, br), 3.40 (4H, dq, *J*=12.0 and 8.0 Hz); ^{31}P NMR (109 MHz) δ 137.99; *Anal.* Calcd for $C_{11}H_{24}NO_2P$: C, 56.63; H, 10.37; N, 6.00. Found: C, 56.60; H, 10.35; N, 6.23.

2-Diethylamino-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane (5c). 5c was similarly prepared (100 ℃, 2 h, 73%): bp 65-68 ℃/1.5 mmHg; ^1H NMR (90 MHz) δ 1.10 (6H, t, *J*=8.0 Hz), 1.25 (6H, s), 1.31 (6H, s), 3.12 (4H, dq, *J*=12.0 and 8.0 Hz); ^{31}P NMR (109 MHz) δ 145.84; *Anal.* Calcd for $C_{10}H_{22}NO_2P$: C, 54.78; H, 10.11; N, 6.39. Found: C, 54.66; H, 10.16; N, 6.73.

2-Diethylamino-4,4,7,7-tetraethyl-1,3,2-dioxaphosphepane (6). A mixture of 3,6-diethyl-3,6-octanediol (5.0 g, 24.7 mmol) and tris(diethylamino)phosphine (8.84 mL, 32.1 mmol) was heated at 130 ℃ for 5 h. Distillation and subsequent flash column chromatography (AcOEt/Hexane, 1:10 including 1% of Et_3N) gave **6**: bp 95-100 ℃/0.4 mmHg; ^1H NMR (270 MHz) δ 0.75 (12H, t, *J*=7.3 Hz), 0.95 (6H, s), 1.49 (8H, s), 1.83 (4H, br), 2.90 (4H, dq, *J*=11.7 and 7.3 Hz); ^{31}P NMR (109 MHz) δ 136.13; *Anal.* Calcd for $C_{16}H_{34}NO_2P$: C, 63.34; H, 11.29; N, 4.62. Found: C, 63.37; H, 11.21; N, 4.56.

Representative procedure for phosphorylation. A mixture of PPrOH (**11**) (54 mg, 0.40 mmol), **5a** (108 mg, 0.44 mmol), and 1*H*-tetrazole (31 mg, 0.44 mmol) in CH_2Cl_2 (1.5 mL) was stirred for 1 h at rt, and after being cooled to -78 ℃, treated with *m*CPBA (6 mg, 0.56 mmol). The solution was stirred at rt for an additional 30 min and AcOEt was added. The resulting solution was washed successively with a 10% aq. Na_2SO_3 solution, saturated $NaHCO_3$ solution, and brine, dried and evaporated. The residue was subjected to flash column chromatography on silica gel eluting with AcOEt and hexane (1:1) to give **9a1** (111 mg, 86%). Selective phosphorylation experiments were carried out at 0 ℃.

4,4,7,7-Tetramethyl-2-oxo-2-(3-phenylpropyloxy)-1,3,2-dioxaphosphepane (9a1). ^1H NMR (270 MHz) δ 1.41 (6H, d, *J*=1.22 Hz), 1.54 (6H, s), 1.92-2.06 (6H, complex), 2.72 (2H, t, *J*=6.4 Hz), 4.05 (2H, dt, *J*=6.4 and 6.4 Hz), 7.15-7.35 (5H, complex); ^{31}P NMR (109 MHz) δ -5.06; *Anal.* Calcd for $C_{16}H_{25}O_4P \cdot 1/2H_2O$: C, 59.81; H, 8.16. Found: C, 60.08; H, 8.00.

4,4,7,7-Tetramethyl-2-oxo-2-(1-phenylpentyloxy)-1,3,2-dioxaphosphepane (9a2). ^1H NMR (90 MHz) δ 0.91 (3H, t, *J*=6.5 Hz), 1.07-1.60 (18H, complex), 1.92 (4H, br s), 5.25 (1H, dt, *J*=7.4 and 6.5 Hz), 7.28 (5H, complex); ^{31}P NMR (109 MHz) δ -5.69; *Anal.* Calcd for $C_{19}H_{31}O_4P \cdot 1/5H_2O$: C, 63.74; H, 8.84. Found: C, 63.74; H, 8.64.

4,4,7,7-Tetramethyl-2-oxo-2-(3-phenylpropyloxy)-1,3,2-dioxaphosphane (9b1). ^1H NMR (270 MHz) δ 1.49 (6H, s), 1.56 (6H, s), 2.02 (2H, complex), 2.72 (2H, t, *J*=7.6 Hz), 4.09 (2H, dt, *J*=7.6 and 6.4 Hz), 7.15-7.35 (5H, complex); ^{31}P NMR (109 MHz) δ -6.99.

4,4,7,7-Tetramethyl-2-oxo-2-(1-phenylpentyloxy)-1,3,2-dioxaphosphane (9b2). ^1H NMR (90 MHz) δ 0.85 (3H, t, *J*=5.8 Hz), 1.25-1.50 (18H, complex), 1.92 (2H, s), 5.28 (1H, dt, *J*=6.7 and 5.8 Hz), 7.22 (5H, complex); ^{31}P NMR (109 MHz) δ -7.94; *Anal.* Calcd for $C_{18}H_{29}O_4P \cdot 1/2H_2O$: C, 61.88; H, 8.65. Found: C, 62.04; H, 8.46.

4,4,7,7-Tetramethyl-2-oxo-2-(3-phenylpropyloxy)-1,3,2-dioxaphospholane (9c1). ^1H NMR (90 MHz) δ 1.43 (6H, s), 1.49 (6H, s), 2.01 (2H, complex), 2.70 (2H, t, *J*=7.3 Hz), 4.10 (2H, dt, *J*=7.3 and 7.4 Hz), 7.13 (5H, complex); ^{31}P NMR (109 MHz) δ 12.60.

4,4,7,7-Tetramethyl-2-oxo-2-(1-phenylpentyloxy)-1,3,2-dioxaphospholane (9c2). ^1H NMR (90 MHz) δ 0.81 (3H, t, *J*=8.0 Hz), 1.00-1.45 (6H, br), 1.32 (12H, s), 4.50 (1H, m), 7.16 (5H, complex); ^{31}P NMR (109 MHz) δ 12.60; *Anal.* Calcd for $C_{17}H_{27}O_4P$: C, 62.57; H, 8.34. Found: C, 62.44; H, 8.34.

4,4,7,7-Tetraethyl-2-oxo-2-(3-phenylpropyloxy)-1,3,2-dioxaphosphepane (10a1). ^1H NMR (90 MHz) δ 0.88 (12H, t, *J*=6.1 Hz), 1.50-2.20 (14H, complex), 2.68 (2H, t, *J*=6.1 Hz), 3.97 (2H, dt, *J*=6.1 and 6.1 Hz), 7.08 (5H, complex); ^{31}P NMR (109 MHz) δ -6.12

4,4,7,7-Tetraethyl-2-oxo-2-(1-phenylpentyloxy)-1,3,2-dioxaphosphepane (10a2). ^{1}H NMR (90 MHz) δ 0.50-0.97 (15H, complex), 1.07-2.00 (18H, complex), 5.09 (1H, dt, *J*=6.4 and 6.4 Hz), 7.11 (5H, complex); ^{31}P NMR (109 MHz) δ -5.41.

1,3,4,5-Tetra-*O*-benzoyl-*myo*-inositol 6-(4,4,7,7-tetramethylbutylene phosphate). rt, 3 h then reflux, 1 h for phosphitylation: mp 194-195 ℃ (from AcOEt); ^{1}H NMR (270 MHz) δ 0.86 (3H, s), 0.91 (3H, s), 0.94 (3H, s), 1.05 (3H, s), 1.63 and 1.74 (ABq, *J*=14.3 Hz), 4.66 (1H, br), 5.44-5.57 (3H, complex), 5.80 (1H, t, *J*=9.5 Hz), 6.27 (1H, t, *J*=9.5 Hz), 7.26-8.27 (20H, complex); ^{31}P NMR (109 MHz) δ -4.99; *Anal.* Calcd for $C_{34}H_{43}O_{12}P$: C, 64.12; H, 5.51. Found: C, 64.08; H, 5.51.

3-*N*-(*p*-Methoxybenzyl)-2'-*O*-methyluridine 5'-(4,4,7,7-tetramethylbutylene phosphate). 3.3 Equiv. of pyridine based on the alcohol was additionally used to promote the reaction (rt, 3 h). ^{1}H NMR (270 MHz) δ 1.39 (3H, d, *J*=1.5 Hz), 1.40 (3H, s), 1.53 (6H, s), 2.02 (4H, m), 3.60 (3H, s), 3.72 (1H, dd, *J*=5.2 and 2.1 Hz), 3.76 (3H, s), 4.06 (1H, dt, *J*=7.3 and 2.1 Hz), 4.18 (1H, dd, *J*=7.3 and 5.2 Hz), 4.26 and 4.37 (2H, dddx2, *J*=12.5, 6.4, and 2.1 Hz), 4.97 and 5.09 (ABq, *J*=13.7 Hz), 5.74 (1H, d, *J*=7.9 Hz), 5.93 (1H, d, *J*=2.1 Hz), 6.81 (2H, d, *J*=8.8 Hz), 7.42 (2H, d, *J*=8.8 Hz), 7.71 (1H, d, *J*=7.9 Hz); ^{31}P NMR (109 MHz) δ -4.59; *Anal.* Calcd for $C_{26}H_{37}N_2O_{10}P$: C, 54.93; H, 6.56; N, 4.93. Found: C, 54.98; H, 6.63; N, 5.06.

1,12-Octadecanediol 1-(4,4,7,7-tetramethylbutylene phosphate). 0 ℃, 6.5 h: ^{1}H NMR (270 MHz) δ 0.88 (3H, t, *J*=4.6 Hz), 1.41 (6H, s), 1.53 (6H, s), 1.27-1.67 (30H, complex), 1.95 (4H, m), 3.58 (1H, br), 4.02 (2H, q *J*=6.7 Hz); ^{31}P NMR (109 MHz) δ -5.31; *Anal.* Calcd for $C_{26}H_{53}O_5P$: C, 65.51; H, 11.21. Found: C, 65.62; H, 11.25.

Hydrolysis experiment (typical). A solution of phosphoramidite (**5a**) (91.7 mg, 0.37 mmol), PPrOH (45.9 mg, 0.34 mmol), and tetrazole (28.3 mg, 0.40 mmol) in CH_2Cl_2 (1 mL) was stirred at ambient temperature for 2 h and water (18 mg, 1.00 mmol) was added. The mixture was vigorously stirred for 1 h and cooled to -78 ℃. After addition of *m*CPBA (87.2 mg, 0.51 mmol), the mixture was stirred at ambient temperature for 30 min and AcOEt was added. The organic solution was washed with 10% Na_2SO_3 solution, sat. $NaHCO_3$ solution, and brine, dried and evaporated. The residue was subjected to PTLC (AcOEt/CH_2Cl_2, 1:4) to give **9a** (48.9 mg, 44%), **16a** (13.1 mg, 18%), and PPrOH (13.1 mg, 29%). In a similar manner, **5b** and **5c** were treated.

Synthesis of hydrophosphonate 16 (typical). A mixture of phosphoramidite **5a** (121 mg, 0.49 mmol), tetrazole (134 mg, 0.49 mmol), water (44 mg, 2.46 mmol), and CH_2Cl_2 (5 mL) was stirred for 1 h at rt, and volatile materials were evaporated. The residue was extracted with ether (84 mg) and the soluble fraction was subjected to a bulb to bulb distillation to afford **16a** (31 mg, 33%).

2-Hydro-4,4,7,7-tetramethyl-1,3,2-dioxaphosphepane (16a): R_f 0.3 (AcOEt/CH_2Cl_2, 1:4); bp 110 ℃ (bath temp.)/0.4 mmHg; ^{1}H NMR (90 MHz) δ 1.30 (6H, s), 1.43 (6H, s), 1.89 (4H, br), 6.59 (1H, d, *J*=705.6 Hz); ^{31}P NMR (109 MHz) δ 1.58; IR (neat) 2430 cm^{-1}; *Anal.* Calcd for $C_8H_{17}O_3P \cdot 3/4H_2O$: C, 46.71; H, 9.06. Found: C, 46.43; H, 8.72.

2-Hydro-4,4,6,6-tetramethyl-1,3,2-dioxaphosphane (16b). R_f 0.2 (AcOEt/Hexane, 2:1); bp 110 ℃ (bath temp.)/0.5 mmHg; ^{1}H NMR (90 MHz) δ 1.48 (6H, s), 1.52 (6H, s), 1.65 (2H, br), 1.91

and 2.10 (2H, ABq, J=13.7 Hz), 6.94 (1H, d, *J*=694.8 Hz); ^{31}P NMR (109 MHz) δ -3.14; IR (neat) 2430 cm^{-1}; *Anal*. Calcd for $C_7H_{15}O_3P \cdot 1/5H_2O$: C, 46.25; H, 8.54. Found: C, 46.31; H, 8.39.

2-Hydro-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane (16c): bp 115-120 ℃ (bath temp.)/0.3 mmHg; ^{1}H NMR (90 MHz) δ 1.40 (6H, s), 1.51 (6H, s), 7.25 (1H, d, *J*=706.5 Hz); ^{31}P NMR (109 MHz) δ 17.37.

Tetrazole-catalyzed reaction (Typical). Phosphite (**5a**), which was prepared as described above was isolated in 88% by flash column chromatography (AcOEt/hexane containing 1% Et_3N, 1:14). A mixture of **5a** (384.7 mg, 1.24 mmol), PPrOH (168.8 mg, 1.24 mmol), and tetrazole (86.8 mg, 1.24 mmol) in CH_2Cl_2 (2 mL) was stirred for 22 h at rt. The solution was subjected to GLC analysis to measure the quantity of 2,2,5,5-tetramethylhydrofuran (36%). The mixture was then cooled to -78 ℃ and after addition of *m*CPBA (213.9 mg, 1,24 mmol), the solution was stirred for 30 min at rt. After a usual work-up procedure as above (hydrolysis experiment), bis(3-pheylpropyl) hydrophosphonate (132 mg, 63%) and **9a$_1$** (7.8 mg, 4%) were isolated by PTLC (Et_2O/hexane, 3:1).

4,4,7,7-Tetramethyl-2-(3-phenylpropyloxy)-1,3,2-dioxaphosphepane (7a). ^{1}H NMR (90 MHz) δ 1.42 (12H, s), 1.87 (4H, br), 1.93 (2H, m), 2.70 (2H, t, *J*=7.4 Hz), 3.82 (2H, dt, *J*=9.0 and 7.4 Hz), 7.20 (5H, br); ^{31}P NMR (109 MHz) δ 135.3.

4,4,7,7-Tetramethyl-2-(3-phenylpropyloxy)-1,3,2-dioxaphosphane (7b). ^{1}H NMR (270 MHz) δ 1.41 (6H, s), 1.43 (6H, s), 1.48 (1H, d, *J*=22 Hz), 1.61 (1H, d, *J*=22 Hz), 1.95 (2H, m), 2.71 (2H, t, *J*=7.6 Hz), 3.78 (2H, dt, *J*=8.2 and 6.4 Hz), 7.25 (5H, complex); ^{31}P NMR (109 MHz) δ 128.10.

4,4,7,7-Tetramethyl-2-(3-phenylpropyloxy)-1,3,2-dioxaphospholane (7c). ^{1}H NMR (90 MHz) δ 1.25 (6H, s), 1.38 (6H, s), 1.90 (2H, m), 2.67 (2H, t, *J*=7.3 Hz), 3.85 (2H, dt, *J*=10.4 and 6.1 Hz), 7.17 (1H, t, *J*=7.0 Hz), 7.18 (2H, d, *J*=7.0 Hz), 7.27 (2H, t, *J*=7.0 Hz); ^{31}P NMR (109 MHz) δ 148.20.

3-Phenylpropyl *o*-xylylene phosphite (21): ^{1}H NMR (90 MHz) δ 2.05 (2H, m), 2.77 (2H, t, *J*=6.4 Hz), 3.94 (2H, dt, *J*=7.4 and 6.4 Hz), 4.57 (2H, dd, *J*=13.0 and 8.9 Hz), 5.67 (2H, dd, *J*=13.0 and 9.4 Hz), 7.22 (9H, complex).

Di-*t*-butyl 3-phenylpropyl phosphite (23): ^{1}H NMR (90 MHz) δ 1.41 (18H, s), 1.91 (2H, m), 2.69 (2H, t, *J*=6.2 Hz), 3.80 (2H, q, *J*=6.2 Hz), 7.20 (5H, complex).

2-(3-Phenylpropyloxy)-1,3,2-dioxaphosphepane (**20**) prepared from the corresponding amidite and PPrOH was used after chromatographic purification and TLC analysis. 2-Diethylamino-1,3,2-dioxaphosphepane: bp 120-130 ℃ (bath temp.)/5 mmHg; ^{1}H NMR (90 MHz) δ 1.00 (6H, t, *J*=8.5 Hz), 1.70 (4H, m), 3.12 (4H, dq, *J*=10.8 and 8.5 Hz), 3.90 (4H, m); ^{31}P NMR (109 MHz) δ 131.42.

Bis(3-phenylpropyl) hydrophosphonate: bp 205 ℃ (bath temp.)/0.4 mmHg (*lit.*,[27] 186 ℃/0.2 mmHg); ^{1}H NMR (270 MHz) δ 2.02 (4H, tt, *J*=7.3 and 6.4 Hz), 2.73 (4H, t, *J*=7.3 Hz), 4.08 (4H, dt, *J*=7.9 and 6.4 Hz), 6.83 (1H, d, *J*=694.6 Hz), 7.08-7.18 (10H, complex); ^{31}P NMR (109 MHz) δ 8.52; IR (neat) 2450 cm^{-1}.

2-Benzyloxy-4,4,7,7-tetramethyl-2-oxo-1,3,2-dioxaphosphane. ^{1}H NMR (90 MHz) δ 1.28 (6H, s), 1.40 (6H, s), 1.85 (2H, br), 4.93 (2H, d, *J*=6.7 Hz), 7.20 (5H, complex); ^{31}P NMR (109 MHz) δ -7.11; *Anal*. Calcd for $C_{14}H_{21}O_4P$: C, 59.15; H, 7.45. Found: C, 59.44; H, 7.22.

2-Oxo-2-(3-phenylpropyloxy)-1,3,2-dioxaphosphepane. ^{1}H NMR (90 MHz) δ 1.58-2.10 (6H, complex), 2.67 (2H, t, *J*=6.4 Hz), 3.53-4.30 (6H, complex), 7.18 (5H, complex); ^{31}P NMR (109 MHz) δ 3.86; *Anal*. Calcd for $C_{13}H_{19}O_4P$: C, 57.78; H, 7.09. Found: C, 57.11; H, 7.10.

4-Hydroxybutyl bis(3-phenylpropyl) phosphate: ^{1}H NMR (270 MHz) δ 1.59-1.82 (4H, complex), 2.00 (4H, m), 2.72 (4H, t, *J*=7.3 Hz), 3.67 (2H, t, *J*=6.1 Hz), 4.05 (4H, q, *J*=6.4 Hz), 4.09 (2H, dt, *J*=10.1 and 6.1 Hz), 7.12 (10H, complex); ^{31}P NMR (109 MHz) δ 0.06; IR (neat, cm^{-1}) 3450; *Anal*. Calcd for $C_{22}H_{31}O_5P \cdot 1/2H_2O$: C, 63.60; H, 7.76. Found: C, 63.71; H, 7.70.

Tri-3-phenylpropyl phosphate: ^{1}H NMR (90 MHz) δ 2.01 (6H, quint, *J*=6.4 Hz), 2.70 (6H, t, *J*=6.4 Hz), 4.01 (6H, q, *J*=6.4 Hz), 7.13 (15H, complex); ^{31}P NMR (109 MHz) δ 0.00

3-Phenylpropyl *o*-xylylene phosphate: ^{1}H NMR (90 MHz) δ 1.98 (2H, quint, *J*=6.9 Hz), 2.67 (2H, t, *J*=6.9 Hz), 4.08 (2H, q, *J*=6.9 Hz), 5.07 (4H, m), 7.18 (5H, complex); ^{31}P NMR (109 MHz) δ 0.74; *Anal*. Calcd for $C_{17}H_{19}O_4P \cdot 2/3H_2O$: C, 61.81; H, 6.19. Found: C, 61.57; H, 5.79.

Benzyl *o*-xylylene phosphate: ^{1}H NMR (90 MHz) δ 4.89 (6H, complex), 7.10-7.40 (9H, complex); ^{31}P NMR (109 MHz) δ 0.10.

Dibutyl 3-phenylpropyl phosphate: ^{1}H NMR (90 MHz) δ 0.90 (6H, t, *J*=6.4 Hz), 1.17-1.87 (8H, br), 2.00 (2H, m), 2.70 (2H, t, *J*=6.4 Hz), 4.01 (6H, q, *J*=6.4 Hz), 7.16 (5H, complex); ^{31}P NMR (109 MHz) δ 0.08. The authentic specimen was prepared according to a usual procedure from dibutyl phosphorochloridate and PPrOH.

Butyl bis(3-phenylpropyl) phosphate: ^{1}H NMR (90 MHz) δ 0.83 (3H, t, *J*=6.0 Hz), 1.10-1.70 (4H, br), 1.89 (4H, m), 2.65 (4H, t, *J*=6.4 Hz), 3.94 (6H, q, *J*=6.4 Hz), 7.13 (10H, complex); ^{31}P NMR (109 MHz) δ 0.07. The authentic specimen was prepared according to a usual procedure from butyl phosphorodichloridate and PPrOH.

***tert*-Butyl 3-phenylpropyl hydrophosphonate:** ^{1}H NMR (90 MHz) δ 1.53 (9H, s), 2.01 (2H, m), 2.70 (2H, t, *J*=6.4 Hz), 4.01 (2H, dt, *J*=8.3 and 6.4 Hz), 6.79 (1H, d, *J*=680.4 Hz), 7.21 (5H, complex); ^{31}P NMR (109 MHz) δ 9.78; IR (neat) 2430 cm^{-1}.

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9. PTLC induced decomposition of H-phosphonates as confirmed by independent experiments where purified ones (**16**) were subjected to PTLC respectively (30-50% of decomposition for **16a** and **16b**, >80% for **16c**).
10. The reaction of **7b** with diethylammonium tetrazolide, prepared independently, in the presence of water afforded hydrolysis products predominantly, while interestingly analogous cyclic phosphite (**21**) was not catalyzed by the tetrazolide.
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