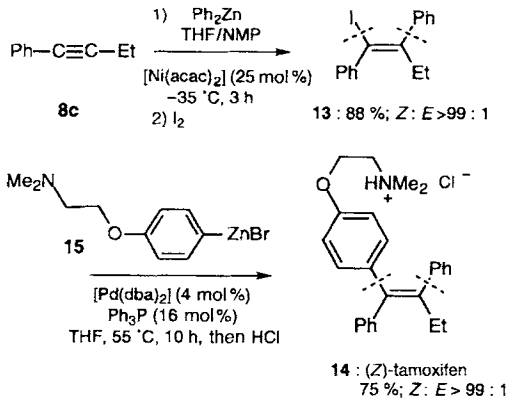

Scheme 4. Synthesis of (*Z*)-tamoxifen (**14**).

In summary, we have reported a new intramolecular *syn* carbonickelation leading to alkylated *exo*-alkylidenecyclopentane derivatives, as well as an intermolecular carbozincation of substituted phenylacetylenes that allows stereoselective (>98% *syn* addition) synthesis of tri- and tetrasubstituted phenylalkenes.

Experimental Procedures

(**12b**): [Ni(acac)$_2$] (320 mg, 1.25 mmol, 25 mol%) and **8d** (0.89 g, 5 mmol, 1 equiv) were dissolved in THF (3.75 mL) and NMP (1.25 mL) at −40 °C under argon. Diethylzinc (1.0 mL, 10 mmol, 2 equiv) was carefully added via syringe at −78 °C. The reaction mixture was allowed to warm to −35 °C and stirred for 2.5 h. Meanwhile a mixture of CuCN (1.79 g, 20 mmol, 4 equiv) and LiCl (1.69 g, 40 mmol, 8 equiv) was dried in vacuo at 130 °C for 2 h and then dissolved in THF (10 mL). The solution was cooled to −60 °C and added by syringe to the reaction mixture at −78 °C. The resulting dark solution was warmed to 0 °C for a few minutes and then again cooled to −78 °C. Ethyl (α-bromomethyl)acrylate[9] (4.82 g, 25 mmol, 5 equiv) was added, and the reaction mixture warmed to 25 °C and worked up. The crude product was purified by flash-chromatography (hexanes/ether 20/1), affording the ester **12b** (1.13 g, 3.53 mmol, 71% yield; *Z*:*E*>99:1) as a white powder.

(**5c**): [Ni(acac)$_2$] (96 mg, 0.37 mmol, 7 mol%) was dissolved in THF (3.75 mL) and NMP (1.25 mL) at −40 °C under argon, and 1-iodo-4-phenyl-5-hexyne (**4b**) (1.41 g, 5 mmol, 1 equiv) was added. At ≅78 °C, $Pent_2Zn$ (2.0 mL, 10 mmol, 2 equiv) was carefully added by syringe. The reaction mixture was stirred for 30 h at −40 °C. After the usual workup, the solvents were distilled off, and the crude residue was purified by chromatography (hexanes) to give the cyclized product **5c** (0.74 g, 3.24 mmol, 65% yield; *E*:*Z*>99:1) as a colorless oil.

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Hydroxyamines as a New Motif for the Molecular Recognition of Phosphodiesters: Implications for Aminoglycoside–RNA Interactions**

Martin Hendrix, Phil B. Alper, E. Scott Priestley, and Chi-Huey Wong*

The molecular recognition of phosphodiesters has received much attention due to their biological importance. In protein–nucleic acid complexes, binding of the phosphodiester backbone is often achieved through a dense network of hydrogen bonding frequently involving a bidentate interaction with the guanidinium group of arginine.[1, 2] In order to identify the underlying principles of phosphodiester recognition in biological systems, various phosphate receptor models have been developed, including synthetic receptors incorporating guanidinium moieties,[3] linear and macrocyclic polyamines,[4] ureas,[5] amidines,[6] aminopyridines,[7] porphyrins,[8, 9] and uranyl complexes.[10]

Aminoglycoside antibiotics[11] have been shown to directly interact with a number of RNA sequences[12] including two important HIV regulatory domains, RRE[13] and TAR.[14] We speculated that the hydroxyamine substructures often found in these molecules may play an important role in recognition. A typical member of the class, neomycin B (**1**, Scheme 1), has a number of different 1,2- and 1,3-hydroxyamine substructures. We therefore prepared the model compounds **2**–**5** to first evaluate their individual binding capacities to dimethylphosphate as a model phosphodiester. To compare our results for phosphodiester binding by hydroxyamines we chose the well-characterized bicyclic guanidine **6**, since it has been used as a standard model for phosphate recognition.[3a] Compound **6** is symmetrical and presents only one hydrogen bond donor, unlike arginine, which has two, allowing straightforward interpretation of spectroscopically derived binding data.

1,3-Hydroxyamines **2**–**4**[15] were synthesized conveniently from the respective diol precursors via cyclic sulfate[16] intermediates as shown in Scheme 2. The *galacto*-configured hydroxyamine **4** was designed to mimic the 4‴, 6‴-hydroxyamine substructure found in the L-*ido* ring of neomycin B, which exists in a triaxial $^4C_1$ chair conformation as shown in Scheme 1.[17]

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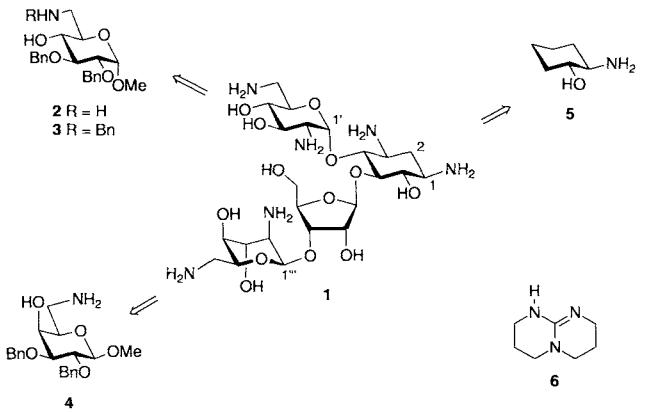
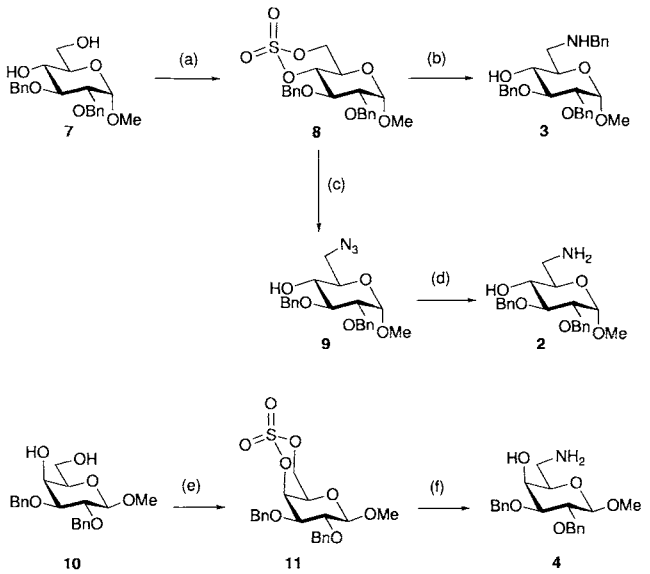


Scheme 1. Structure of neomycin B (**1**) and model compounds **2**–**5**, designed to isolate 1,3- and 1,2-*trans*-hydroxyamine substructures for the study of their phosphodiester recognition capabilities. Bicyclic guanidine **6** is a known phosphate binder included as a reference.



Scheme 2. Synthesis of hydroxyamine model compounds. a) 1. *N*-methylmorpholine (NMM), $SOCl_2$, CH_2Cl_2, room temperature (RT), 2 h; 2. NaIO4, cat. $RuCl_3$, CH_2Cl_2, CH_3CN, H_2O, 0 °C → RT (76%); b) 1. $BnNH_2$, DMF, RT, 10 h; 2. 60% $HClO_4$, THF (70%); c) 1. NaN_3, DMF, RT, 10 h; 2. 60% $HClO_4$, THF (97%); d) 1. PMe_3, THF, 0.1 N NaOH; 2. HCl, Et_2O (84%); e) 1. NMM, $SOCl_2$, CH_2Cl_2, RT, 2 h; 2. $NaIO_4$, cat. $RuCl_3$, CH_2Cl_2, CH_3CN, H_2O, 0 °C → RT (52%); f) 1. NaN_3, DMF, RT, 10 h; 2. 60% $HClO_4$, THF (87%); 3. PMe_3, THF, 0.1 N NaOH; 4. HCl, Et_2O (84%).

Table 1. Binding constants K_a and maximum shifts $\Delta\delta_{max}$ for the OH ^{1}H NMR signals of the hydroxyamines **2**–**5** and for guanidine on complexation of chloride and dimethylphosphate.

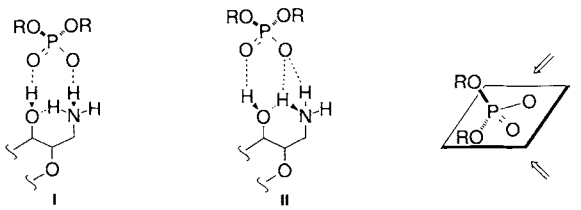
Receptor	Anion	K_a [M^{-1}] [a]	$\Delta\delta_{max}$(OH) [b]
2·H$^+$	Cl^-	49 ± 3	+0.11
	$(MeO)_2PO_2^-$	490 ± 12	+0.84
3·H$^+$	Cl^-	36 ± 6	+0.09
	$(MeO)_2PO_2^-$	254 ± 27	+0.66
4·H$^+$	Cl^-	51 ± 1	−0.01
	$(MeO)_2PO_2^-$	132 ± 19	+0.38
5·H$^+$	Cl^-	53 ± 4	+0.08
	$(MeO)_2PO_2^-$	230 ± 25	+0.56
6·H$^+$	Cl^-	27 ± 1	–
	$(MeO)_2PO_2^-$	342 ± 51	–

[a] NMR dilution experiments with the preformed 1:1 salt complexes were performed in [D_6]DMSO at 293 ± 1 K. [b] calculated maximum shift at full complexation.

While the absolute configuration of the hydroxyamine substructure in **4** is enantiomeric to that of L-idose, the relative orientation of the equatorial aminomethyl and the axial hydroxyl groups is the same and therefore their interactions with achiral compounds will be equivalent.

To determine binding constants we prepared defined 1:1 salt complexes and measured their dissociation upon stepwise dilution in [D_6]DMSO by following the ^{1}H NMR shifts of the NH and OH signals. The chemical shift values of the totally uncomplexed state (δ_0) and the fully complexed state (δ_∞) and the stability constant K_a were subsequently determined by curve fitting. This procedure has the advantage that it does not rely on experimentally determined values of δ_0, which require separate measurements with a noncomplexing counterion that may nonetheless have some residual binding affinity.[18] Table 1 shows the results of dilution experiments with chloride and phosphodiester counterions for compounds **2**–**6**.[19] In all cases, data could be fitted to a 1:1 binding isotherm. Importantly, the *gluco*-configured 1,3-hydroxyamine **2** binds dimethylphosphate with higher affinity than bicyclic guanidine **6**. In contrast, the *galacto* epimer **4** shows reduced binding. The 1,2-*trans*-hydroxyamine **5** binds dimethylphosphate with lower affinity than either **2** or **6**, but is still superior to **4**. All three hydroxyamines show substantial selectivity for dimethylphosphate over chloride (Table 1), suggesting the involvement of hydrogen bonds in addition to ionic contributions, which are typically somewhat larger for the more localized charge of protonated amines.[3c] Evidence for the involvement of a bidentate[20] mode of recognition for **2** was provided by the large downfield shift of its OH resonance upon complexation ($\Delta\delta_{max}$ = 0.84). A smaller shift of the OH signal was seen in **5** ($\Delta\delta_{max}$ = 0.56) and in **4** ($\Delta\delta_{max}$ = 0.38). This order mirrors the order of binding affinities and is consistent with the interpretation that differential involvement of the hydroxyl group in hydrogen bonding accounts for the energetic differences in complexation.

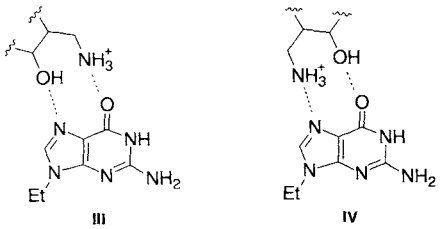
A structural model for the interaction of 1,3-hydroxyamines with phosphodiesters could include either two (**I**) or three (**II**)



hydrogen bonds. In the latter arrangement the hydrogen bonds are formed simultaneously above and below the OPO plane, which is common for coordination of phosphates in biological systems.[21] Results obtained with compound **3**, which features one more benzyl substituent than **2**, are consistent with this model. The intrinsic ion binding capability of **3** is reduced by this substitution as can be seen from its chloride binding ability, which is less than that of **2**, **4**, and **5**. This may be due to added steric bulk and higher basicity of the secondary amine, which decreases its hydrogen bonding donor strength. However, the selectivity for dimethylphosphate over chloride is only slightly diminished (sevenfold vs. tenfold for **2**), suggesting that the principal hydrogen bonding network involved in recognition is still intact. The clear difference in the phosphate recognition abilities of **2** and **4** is interesting. Careful analysis of the coupling constants $J_{5,6a}$ and $J_{5,6b}$ in **2** indicates that in the uncomplexed state a single rotamer around the C5–C6 bond dominates

($J_{5,6a} \leq 2$, $J_{5,6b} = 8-9$ Hz), which does not change significantly upon binding of the phosphodiester. This contrasts with *galacto* epimer **4**, which in the uncomplexed state ($J_{5,6a} = 4.5$, $J_{5,6b} = 8.5$ Hz at 17% complexation) is probably an equilibrium mixture of two rotamers. Upon complexation of dimethylphosphate the molecule rearranges and the torsional angle for the C5–C6 bond changes ($J_{5,6a} \approx J_{5,6b} = 6.5$ Hz at 65% complexation). Thus it is likely that **2** is perfectly preorganized for binding of phosphodiesters, while **4** must undergo rearrangement, accounting for its reduced binding affinity.

The results from the phosphodiester binding studies suggest that hydroxyamines share some of the molecular recognition properties of guanidines, and it is known that in protein–nucleic acid complexes the guanidinium group of arginine frequently makes contact to the Hoogsten face of guanosine.[22] When 9-ethylguanine was titrated with **4**, a downfield shift of the H8 signal due to hydroxyamine binding was indeed observed. Possible complex structures as shown in **III** and **IV** are therefore proposed.



III

IV

To investigate whether 1,3-hydroxyamine substructures may be involved in binding in aqueous solution, we turned our attention to the binding of neamine (**12**), a pseudodisaccharide substructure commonly found in a wide range of aminoglycoside antibiotics. However, initial studies with dimethylphosphate in water showed no detectable binding in the concentration ranges accessible by NMR. This may not be surprising since ionic and hydrogen bonding interactions are severely reduced in water. These weak forces may, however, be enhanced by increasing the charge of the interacting species. In fact, many recognition events involving nucleic acids—including those by aminoglycosides—are likely to have a strong contribution from their polyionic character. We therefore turned our attention to the binding of sulfate, as it is a tetrahedral oxyanion similar to phosphate and its double negative charge mimics the effect of a polyanion. Furthermore, it has a defined ionization state. Since the ^{1}H NMR spectra of aminoglycosides are highly dependent on pH, and even minor pH changes can outweigh any small complexation-induced shifts, we performed binding studies at low pH, where neamine is fully protonated. Upon addition of sodium sulfate to a solution of neamine·4HCl at pH 3.5, only small changes were observed in the ^{1}H NMR spectrum and their interpretation was complicated by severe overlap of signals. Analysis of ^{13}C NMR spectra provided a clearer picture (Figure 1). Signals for all carbons were assigned unambigously through 2D COSY and NOESY spectra and were in full agreement with the assignments made earlier[23] based on comparison of chemical shift values with model compounds. By following the shift of the C1′ signal, an apparent binding constant $K_{app} = 294 \pm 26\ \text{M}^{-1}$ was calculated for the competitive binding of sulfate over chloride through curve-fitting procedures.[24] In-

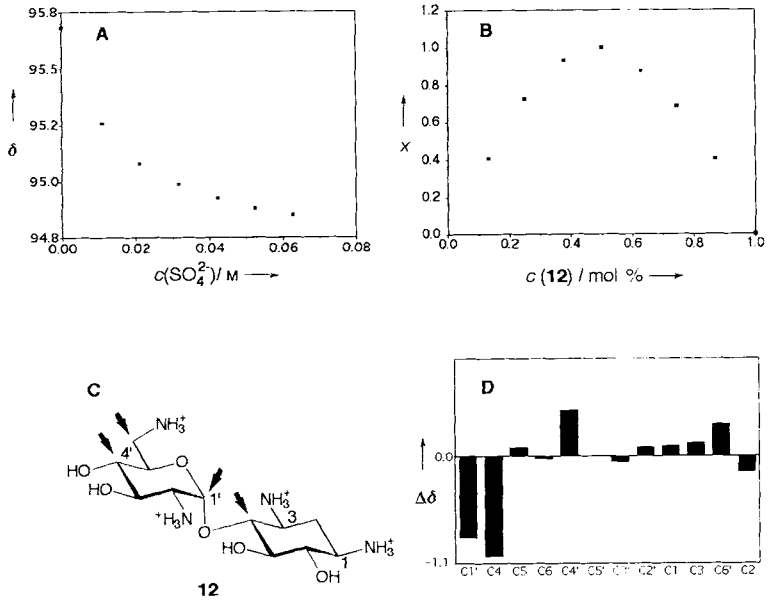


Figure 1. Titration of neamine (**12**) with sodium sulfate at pH 3.5. A) ^{13}C NMR titration curve (C1′ signal). B) Job plot; x = amount [%] of complex formation. C) Structure of neamine indicating the C atoms having the maximum observed shifts. D) Maximum observed shifts of the ^{13}C NMR signals.

vestigation of the binding stoichiometry by the method of Job[25] revealed the predominant existence of a 1:1 complex with only minor contributions from two sulfates binding simultaneously. Tabulation of the maximum observed shifts $\Delta\delta_{max}$ provides an interesting picture: significant changes are seen for the C4, C1′, C4′, and C6′ signals. The changes for the C4 and C1′ signals are opposite in sign to all other shifts and can be interpreted as resulting from a change in glycosidic torsion angles[26] due to altered electrostatic repulsion after complexation of sulfate. The changes for the C4′ and C6′ signals are indicative of binding at the respective sites. In particular, C4′ is the only hydroxyl-substituted carbon showing a large shift. These observations provide clear evidence for anion recognition by a 1,3-hydroxyamine substructure in water.[27] Thus, the selectivity found in aqueous solution is in full agreement with the order of binding affinities determined in the model compounds.

In conclusion, we have identified 1,3-hydroxyamines commonly found in aminoglycoside antibiotics as a new recognition motif for the complexation of phosphodiesters and probably the Hoogsten face of guanosine. This core structure should find useful applications in many molecular recognition systems in which the complexation of phosphodiesters is desired. Work is in progress to combine hydroxyamines with other nucleic acid binding motifs to generate molecules targeting specific nucleic acid sequences.

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[15] **2**: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.16–8.11 (m, 3H, NH$_3$), 7.36–7.23 (m, 10H, 2 × C$_6$H$_5$), 5.66 (d, 1H, J = 7 Hz, OH), 4.77 (AB, 2H, J = 12 Hz, $\Delta\nu$ = 21 Hz, CH_2Ph), 4.77 (d, 1H, J = 3.5 Hz, H1), 4.63 (pseudo-s, 2H, CH_2Ph), 3.62 (m, 1H, H5), 3.58 (dd, 1H, J_1 = J_2 = 10 Hz, H3), 3.39 (dd, 1H, J_1 = 3.5, J_2 = 10 Hz, H2), 3.33 (s, 3H, OCH$_3$), 3.27 (m, 1H, H4), 3.15 (m, 1H, H6a), 2.83 (m, 1H, H6b); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 139.3, 138.6, 128.2, 128.0 (2×), 127.6, 127.5, 127.3, 97.2 80.7, 78.7, 74.1, 71.6, 70.9, 68.5, 54.9, 51.5; HRMS: m/z: 506.0959, calcd for C$_{21}$H$_{25}$NO$_5$Cs (M − HCl + Cs): 506.0944. **3**: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.52 (br. s, 1H, NH), 9.11 (br. s, 1H, NH), 7.58–7.24 (m, 15H, 3 × C$_6$H$_5$), 5.69 (d, 1H, J = 6.5 Hz, OH), 4.78 (d, 1H, J = 3.5 Hz, H1), 4.76 (AB, 2H, J = 11.5 Hz, $\Delta\nu$ = 17 Hz, OCH_2Ph), 4.62 (pseudo-s, 2H, OCH_2Ph), 4.17 (AB, 2H, J = 10 Hz, $\Delta\nu$ = 16 Hz, NCH_2Ph), 3.79 (m, 1H, H5), 3.57 (dd, 1H, J_1 = J_2 = 9 Hz, H3), 3.39 (dd, 1H, J_1 = 3.5, J_2 = 9 Hz, H2), 3.34 (s, 3H, OCH$_3$), 3.26–3.20 (m, 2H, H4, H6a), 2.90 (m, 1H, H6b); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 139.1, 138.5, 131.7, 130.4, 129.0, 128.7, 128.2, 128.0, 127.7, 127.5 (2×), 127.2, 97.4, 80.4, 78.6, 74.2, 71.6, 71.5, 67.7, 55.4, 50.5, 47.4; HRMS: m/z: 596.1420, calcd for C$_{28}$H$_{33}$NO$_5$Cs (M − HCl + Cs): 596.1413. **4**: ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.01 (br. s, 3H, NH$_3$), 7.38–7.25 (m, 10H, 2 × C$_6$H$_5$), 5.14 (br. s, 1H, OH), 4.73 (d, 1H, J = 11.5 Hz, CHPh), 4.70 (d, 1H, J = 12 Hz, CHPh), 4.64 (d, 1H, J = 11.5 Hz, CHPh), 4.52 (d, 1H, J = 12 Hz, CHPh), 4.23 (d, 1H, J = 7.5 Hz, H1), 3.97 (s, 1H, J_1 = 3.5, J_2 = 9 Hz, H5), 3.50–3.39 (m, 5H, OCH$_3$, H2, H3), 3.02 (m, 2H, H6a, H6b); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 138.9, 138.6, 128.1 (2×), 127.5 (2×), 127.3 (2×), 103.9, 80.2, 78.1, 73.9, 70.7, 70.3 (2×), 65.1, 56.5; HRMS: m/z: 374.1973, calcd for C$_{21}$H$_{28}$NO$_5$ (M − Cl): 374.1967.

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A Straightforward Access to α-Functional Phospholide Ions

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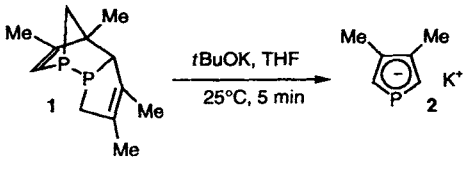
Despite their highly delocalized electronic structure,[1, 2] phospholide ions are functionalized exclusively at the phosphorus atom.[3] To develop the chemistry at the carbon atoms of the ring and to assemble porphyrin-like arrays based upon this heteroatomic unit, we need a straightforward access to functional phospholides. Previous attempts to synthesize such derivatives lacked the necessary simplicity and generality.[4] Perhaps the most characteristic feature of phospholes is their easy interconversion of 1*H*- into 2*H*-phosphole derivatives through [1,5] sigmatropic shifts of the phosphorus substituents.[5, 6] The 2*H*-phospholes generated by these shifts tend to dimerize by [4 + 2] cycloaddition, but this dimerization is known to be reversible.[5a] We reasoned that the treatment of these [4 + 2] dimers with a base, at a temperature high enough to establish the monomer–dimer equilibrium, could yield the corresponding phospholide ions. To check the feasibility of this crucial step, we heated the well-defined [4 + 2] dimer of 3,4-dimethyl-2*H*-phosphole **1**[7] with a variety of bases. Potassium *tert*-butoxide appeared to be the reagent of choice.



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