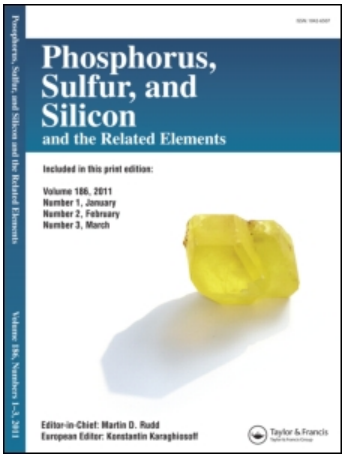

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EVIDENCE IN SUPPORT OF TETRAOXASPIROPHOSPHORANE INTERMEDIATES WITH A SIX-MEMBERED RING AND A P-H BOND IN INTRAMOLECULAR TRANSESTERIFICATION REACTIONS

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EVIDENCE IN SUPPORT OF TETRAOXASPIRO-PHOSPHORANE INTERMEDIATES WITH A SIX-MEMBERED RING AND A P—H BOND IN INTRAMOLECULAR TRANSESTERIFICATION REACTIONS

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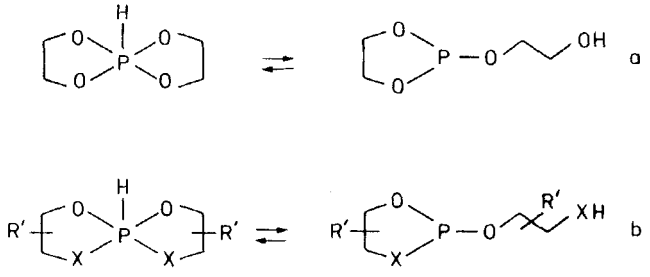
Preparation of tetraoxaspirophosphorane **5** via two possible routes, starting from the isomeric P(V) precursors **10** and **11** results in identical ^{31}P NMR spectra indicative of various P(III) compounds. By analysis of the products and application of low-temperature ^{31}P NMR techniques it is shown that the phosphorane **5** is involved as an intermediate in the intramolecular transesterification **10** ⇄ **11**. Closure of the six-membered ring in **11** proceeds more slowly than closure of the five-membered ring in **10** due to the difference in translational entropy. The rate of the interconversion is enhanced upon addition of excess base. This base-catalyzed proton transfer mimics the role of the bases Histidine 12 and Histidine 119 in the active site of RNase A during hydrolysis of ribonucleic acids. A similar behaviour is observed by using glycol instead of 1,2-dihydroxybenzene. In the case of the isomeric P(V) precursors **27** and **28** no evidence is found indicative of an equilibrium **27** ⇄ **28** which rules out spirophosphorane **7**. These results are rationalized on the basis of orientation effects and Pearson's HASB theory.

INTRODUCTION

The most remarkable property of tetraoxaspirophosphoranes with a P—H bond and two five-membered rings is their ability to give rise to a tautomeric equilibrium between the tri- and penta-coordinated form. The first example of this P(III)—P(V) equilibrium was offered by Burgada et al.[1] (Scheme 1a). It was later demonstrated that the phenomenon was quite general and could be represented by Scheme 1b.[2–6]

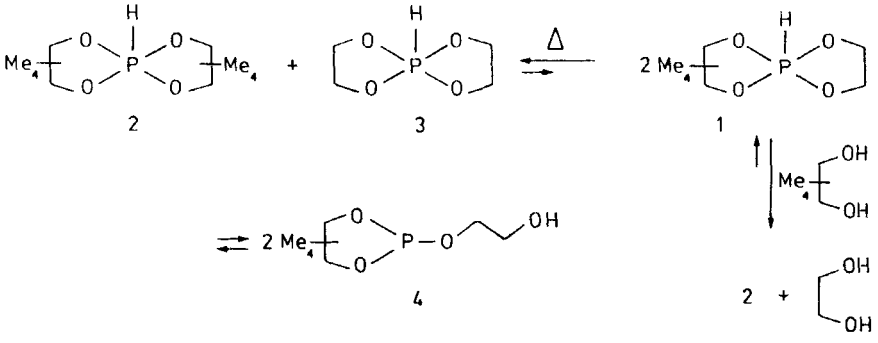
The equilibrium is controlled by electronic factors, steric factors, symmetry properties of the tri- and penta-coordinated molecules or external factors such as temperature and basicity of the solvent.[7] An example of symmetry properties and electronic factors is given in Scheme 2.

Upon heating of the asymmetrical tetraoxaspirophosphorane (**1**), a mixture of the symmetrical compounds (**2**) and (**3**) is formed (symbiotic effect),[6] whereas, due to the electron-donating character of the pinacol ring in (**1**), exclusive generation of (**4**) proceeds via ring opening of the less stable glycol fragment. Addition of free 2,3-dimethylbutanediol-2,3 (pinacol) to (**1**) results in conversion to the more stable compound (**2**) with simultaneous release of glycol. This process, proceeding via the reactive isomer (**4**), can be regarded as a transesterification. Introduction of a six-membered ring in tetraoxaspirophosphoranes with a P—H bond results in a considerable decrease in stability. To our knowledge, only one example has been



X = O, NH, NR ; R'= stabilizing factors (substituents, unsaturation)

SCHEME 1 P(III)—P(V) equilibrium in P—H spirophosphoranes.



SCHEME 2 Illustration of the stability of asymmetrical spirophosphoranes.

reported and confirmed by ^{31}P NMR spectroscopy (Figure 1). However, despite the stabilizing carbonyl group and both phenyl substituents, this compound could not be isolated.[8] Remarkably, spirophosphoranes of the same type but with a P—OR bond are relatively stable[9–11] and show a high preference for an apical-equatorial alignment of the six-membered ring.[12] In our search for a possible P(III)—P(V) equilibrium inherent in tetraoxaspirophosphoranes with a six-membered ring, the ring closure and ring opening behaviour of the compounds depicted in Figure 2 was studied with the aid of NMR spectroscopic techniques.

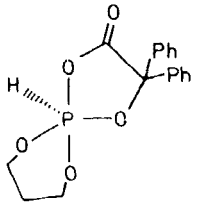


FIGURE 1 Tetraoxaspirophosphorane with six-membered ring, characterized by ^{31}P NMR.

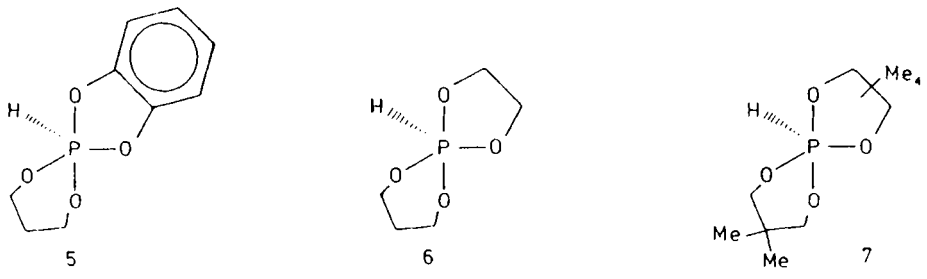


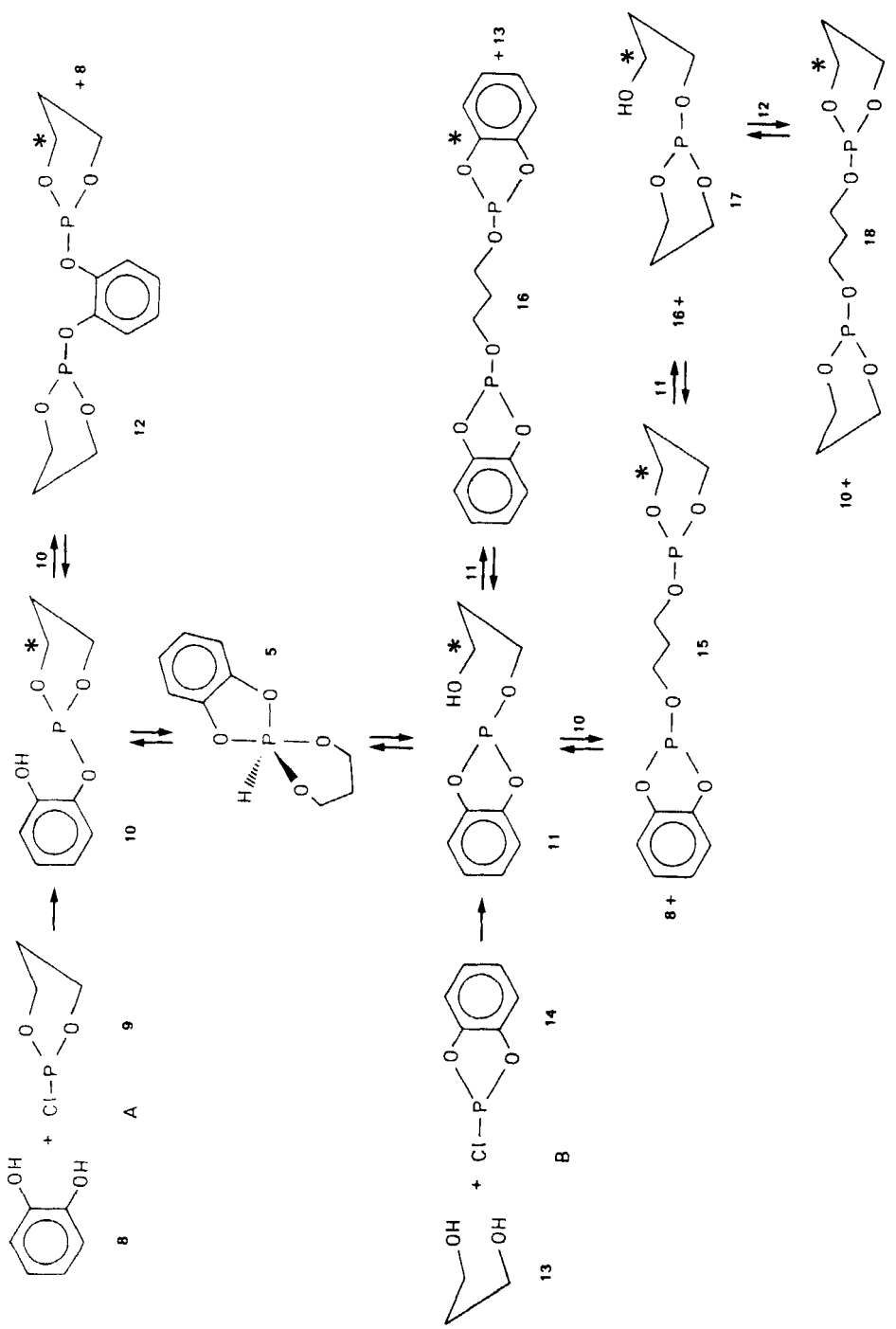
FIGURE 2 Spirophosphoranes studied in this work.

The obtained data are rationalized on the basis of Pearson's HASB (Hard Acid Soft Base) theory[13] and ring orientation effects.[14] The base-catalyzed proton transfer from the hydroxyl oxygen to the phosphorus atom during ring closure in one of these compounds is discussed. This behaviour is put into perspective with regard to the possible role of the bases Histidine 12 and Histidine 119 in the active site of RNase A in selective hydrolysis of ribonucleic acids.[15-17]

RESULTS AND DISCUSSION

In order to prepare 5-hydrido-2,3-benzo-1,4,6,10-tetraoxa-5-phosphaspiro(4,5)dec-2-ene (compound **5**) we took recourse to the synthetic routes *A* and *B* which are presented in Scheme 3.

By reacting equimolar amounts of 1,2-dihydroxybenzene (**8**) and 2-chloro-1,3,2-dioxaphosphorinane (**9**) in the presence of a base, the corresponding P(V) precursor **10** is obtained, while analogous reaction of propanediol-1,3 (**13**) with 2-chloro-4,5-benzo-1,3,2-dioxaphospholane (**14**) leads to the P(V) precursor **11**. The advantage of this procedure is that, upon generation of the isomeric precursors **10** and **11**, closure of the five- respectively six-membered ring can be determined independently with the aid of ^{31}P NMR spectroscopy at various temperatures. To our surprise, both synthetic routes gave rise to products with identical ^{31}P NMR spectra and nearly similar product distribution, indicative of a common intermediate structure. A typical ^{31}P NMR spectrum, obtained via route *A*, is given in Figure 3. Besides eight resonances in the P(III) domain (δ 130.0; 129.9; 129.7; 127.8; 127.5 (double); 124.0 and 123.7), no phosphate could be detected. Moreover, we found a broad multiplet ($\delta^{31}P = -21.8$ ppm) with extremely low intensity, which can be attributed to the symmetrical 5-hydrido-2,3,7,8-benzo-1,4,6,9-tetraoxa-5-phosphaspiro(4,4)non-2,7-diene (**24**, viz. Table I). In the absence of the spirophosphorane **5**, bimolecular reaction of **10** (Route *A*) can only lead to the formation of the diphosphite **12**, while bimolecular reaction of **11** (Route *B*) results in exclusive generation of diphosphite **16** (Scheme 3). Considering the obtained product distribution in both synthetic routes, it can therefore be concluded that the spirophosphorane **5** must be involved as an intermediate in the isomerization **10** $\rightleftarrows$ **11**. By studying the behaviour of 5-hydrido-2,3-benzo-1,4,6,9-tetraoxa-5-phosphaspiro(4,4)non-2-ene, Munoz et. al. established the formation of several diphosphites due to subsequent reactions.[18]



SCHEME 3 Various equilibria inherent in the synthesis of spirophosphorane **5**. Compounds which have been characterized by ^{31}P NMR are indicated with an asterisk.

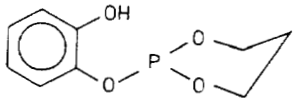
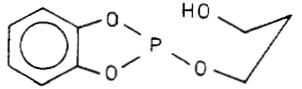
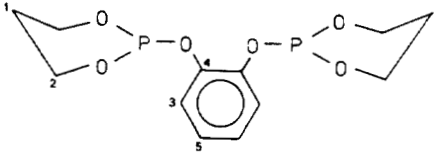
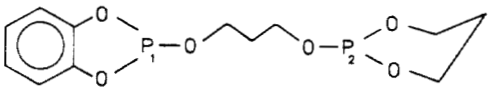
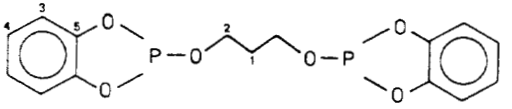
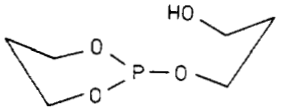
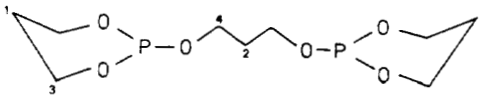
However, not all the proposed structures in their reaction scheme were characterized. In order to investigate the possible formation of diphosphites, the model compounds **21–23** were prepared and characterized by means of ^{1}H, ^{13}C and ^{31}P NMR spectroscopy (Table I). The close resemblance in ^{31}P chemical shifts of compounds **21–23** to those observed for the reaction mixture confirmed that these structural units were present in the products. Therefore compounds **12** and **15–20** were synthesized. The corresponding NMR parameters are listed in Table I. Subsequent addition of these various compounds to the reaction mixture established the presence of compounds **12** and **15–18** by comparative ^{31}P NMR measurements.

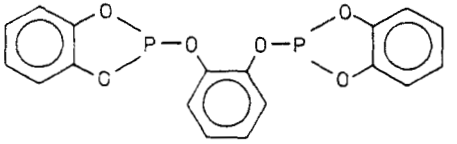
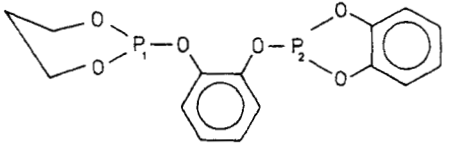
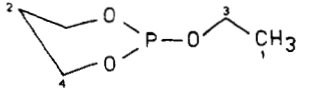
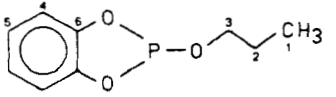
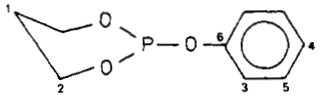
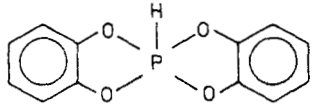
To elucidate the two remaining resonances in the ^{31}P NMR spectrum, 0.5 mmol of **8** was dissolved in 0.4 ml of $CDCl_3$ in an NMR sample tube. The solution was cooled at $-20°C$ while equimolar amounts of base and **9** were quickly added. This resulted in instantaneous formation of two products ($\delta^{31}P = 123.7$ main signal; 127.5) which can be ascribed to the equilibrium **10** ⇄ **11**. This equilibrium is in fact an example of a fast intramolecular transesterification process. Cooling of the solution to $-50°C$ resulted in a slight shift of the equilibrium in favour of compound **10**, but even at this temperature no ^{31}P resonance indicative of the intermediate **5** could be detected. The preferential formation of **10** at low temperature can be rationalized on the basis of its more rigid structure in comparison with compound **11**. Addition of a slight excess of base to the reaction mixture immediately results in enhanced conversion of **10** into **11**. This observation enables us to conclude that the interconversion **10** ⇄ **11**, presumably proceeding via the intermediate **5**, is a *base-catalyzed* process. Warming of the solution to room temperature leads to gradual appearance of the products as depicted in Scheme 3. Once the more stable diphosphites **12**, **15**, **16** and **18** are formed, the original **10** ⇄ **11** equilibrium cannot be obtained any more by cooling of the reaction mixture.

The high percentage of compound **18** in the reaction mixture (Figure 3) can be rationalized on basis of the higher stability of the P—O-alkyl bond in comparison with the P—O-arylbond. Formation of a small quantity of compound **24** due to the equilibrium **8** + **16** ⇄ **11** + **24** was confirmed by ^{31}P NMR measurements but is not presented in Scheme 3. The ^{31}P chemical shift of compound **10** was also determined via addition of **8** to a solution of compound **12** in $CDCl_3$. This leads to gradual appearance of **10** due to the equilibrium **8** + **12** ⇄ **10** + **10** and eventually results in formation of the other products (vide supra). In order to investigate the ring closure of compound **11**, 0.5 mmol of **13** was dissolved in 0.4 ml of $CDCl_3$ in an NMR sample tube. The solution was cooled at $-20°C$ and, after addition of equimolar amounts of base and **14**, two different ^{31}P chemical shifts appeared (δ 127.5 main signal; 123.7) which can be ascribed to the equilibrium **11** ⇄ **10**. At $-20°C$, a slow conversion of **11** into **10** was observed, which could be accelerated by addition of excess base. Hence, we conclude that closure of the six-membered ring in **11** is also a base-catalyzed process but proceeds more slowly than closure of the five-membered ring in the isomeric structure **10**. Apparently, the rigid character of the five-membered ring fragment in **10** results in orientation of the free hydroxyl group in close proximity to the phosphorus atom, while this effect is less pronounced in compound **11**, due to a gain in translational entropy.[14] Addition of **13** to a solution of compound **16** gave rise to formation of **11** with subsequent conversion into **10** and

TABLE I

NMR spectroscopic data ($CDCl_3$, 27°C) of the compounds shown in Scheme 3 and related model compounds[a]

No.	Compound	δ ^{31}P	δ ^{13}C	δ ^{1}H
10		123.7	[b]	—
11		127.5	[b]	—
12		124.0	29.25 (C_1, $^3J_{PC}$ = 3); 60.93 (C_2); 112.70 (C_3); 124.70 (C_4); 145.13 (C_5)	0.93–2.84 (m, 4 H, CH_2); 3.26–4.93 (m, 8 H, OCH_2); 6.68–7.12 (m, 4 H, ArH)[c]
15		127.8 (P_1) 129.9 (P_2)	[b]	—
16		127.5	32.35 (C_1); 60.80 (C_2); 112.84 (C_3); 123.62 (C_4); 146.68 (C_5, $^2J_{PC}$ = 9)	1.58 (m, 2 H, $^3J_{HH}$ = 6, CH_2); 3.53 (dt, 4 H, $^3J_{PH}$ = $^3J_{HH}$ = 6, OCH_2); 6.71–7.17 (m, 8 H, ArH)
17		129.7	[b]	—
18		130.0	29.52 (C_1, $^3J_{PC}$ = 6); 33.76 (C_2); 60.19 (C_3); 60.66 (C_4)	1.10–2.83 (m, 6 H, CH_2); 3.46–4.80 (m, 12 H, OCH_2)[c]

19		129.6	—	—
20		124.1 (P_1) 130.9 (P_2)	—	—
21		129.6	17.79 (C_1, $^3J_{PC}$ = 4); 29.55 (C_2, $^3J_{PC}$ = 4); 59.04 (C_3); 60.05 (C_4)	1.33 (t, 3 H, $^3J_{HH}$ = 7, CH_3); 1.00–2.87 (m, 2 H, CH_2); 3.39–4.73 (m, 6 H, OCH_2)[c]
22		127.8	11.11 (C_1); 24.80 (C_2, $^3J_{PC}$ = 3); 66.59 (C_3); 112.70 (C_4); 123.49 (C_5); 146.85 (C_6, $^2J_{PC}$ = 7)	0.83 (m, 3 H, CH_3); 1.17–1.87 (m, 2 H, CH_2); 3.50 (dt, 2 H, $^3J_{PH}$ = $^3J_{HH}$ = 6, OCH_2); 3.50 (dt, 2 H, $^3J_{PH}$ = $^3J_{HH}$ = 6, OCH_2); 7.00 (m, 4 H, ArH)
23		123.6	29.35 (C_1, $^3J_{PC}$ = 4); 60.86 (C_2); 120.83 (C_3, $^3J_{PC}$ = 7); 124.23 (C_4); 130.63 (C_5); 154.03 (C_6, $^2J_{PC}$ = 6)	1.42 en 1.89–2.79 (m, 2 H, CH_2); 3.43–4.77 (m, 4 H, OCH_2); 6.72–7.36 (m, 5 H, ArH)[d]
24		−21.8	—	6.27–6.84 (m, 10 H, ArH); 8.64 (d, 1 H, $^1J_{PH}$ = 895, PH)

[a] See also experimental part; δ ^{31}P in ppm vs. 85% H_3PO_4; δ ^{13}C and δ ^1H in ppm vs. TMS; coupling constants (J) in Hz.
[b] No unambiguous ^1H and ^{13}C assignments possible due to subsequent reactions as shown in Scheme 3.
[c] Due to complexity no J's resolvable.
[d] No J_{HH} resolvable.

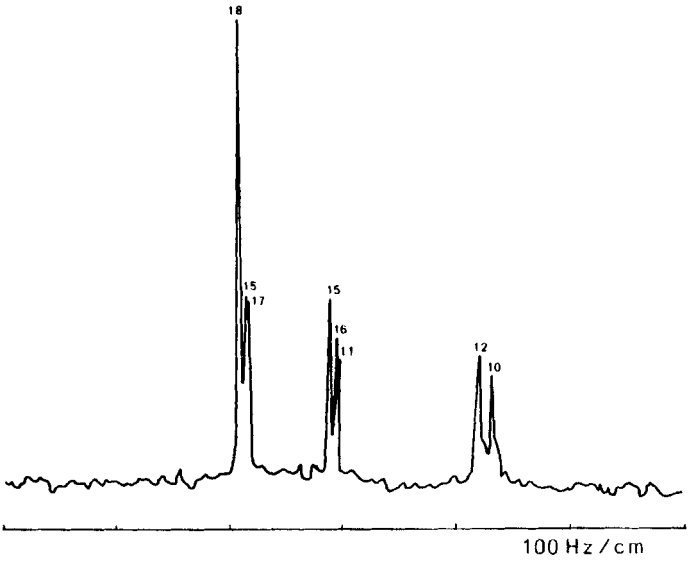
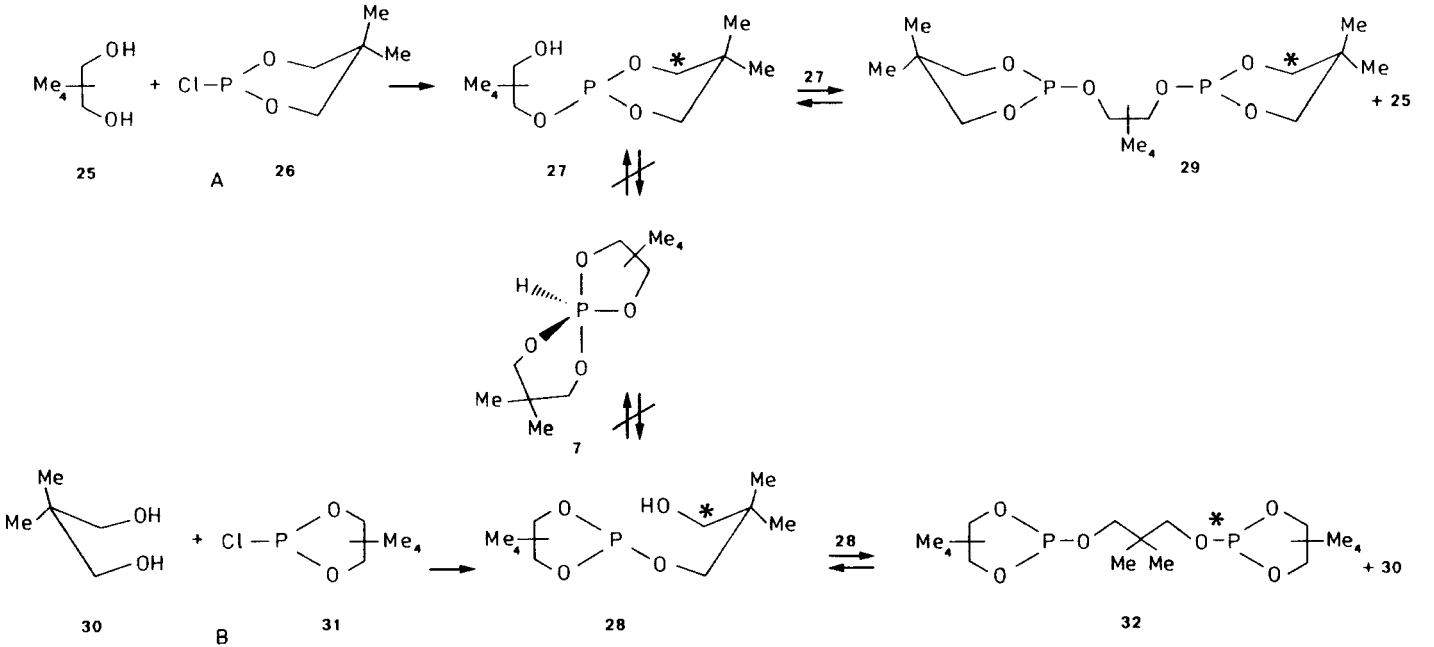


FIGURE 3 36.43 MHz ^{31}P NMR spectrum obtained via route *A*. The corresponding structures are given in Table I and Scheme 3.

15. Purification of the asymmetrical diphosphite **20** (Table I) was not possible due to its low intrinsic stability. Therefore, the presence of this compound during the reaction course could not be detected.

Despite the complexity of this system, the overall reaction Scheme 3 offers a good explanation for the various obtained products. A ^{31}P chemical shift indicative of spirophosphorane **5** could not be detected, even at a temperature of $-50°C$. Apparently, **5** is a high energy species in comparison with **10** and **11**.

Upon replacement of the 1,2-dihydroxybenzene fragment in compound **5** by glycol, one obtains the spirophosphorane **6** which is depicted in Figure 2. Due to the absence of an aromatic ring fragment, this spirophosphorane is less stable than compound **5** as a result of diminished delocalization.[8] Application of the synthetic routes *A* and *B* in a similar way as was described for compound **5** gave rise to identical ^{31}P NMR spectra. Elucidation of the various ^{31}P chemical shifts pointed to a complete analogy of this system with the one presented in Scheme 3. Therefore, the experimental details are not given here. Introduction of a pinacol ring instead of a glycol fragment results in a contribution to the intrinsic stability of the corresponding spirophosphorane **7** which is depicted in Scheme 4. On the basis of the known high stability of closed pinacol rings,[6] we expected the isomerization **28** → **27** to be restricted. Moreover, starting from the P(V) precursor **28**, generation of 5-hydrido-2,2,3,3,8,8-hexamethyl-1,4,6,10-tetraoxa-5-phosphaspiro(4,5)decane (**7**) by nucleophilic attack of the free hydroxyl oxygen atom will be retarded as a result of increased basicity of the phosphorus atom. For the reversed isomerization **27** → **28**, orientation effects as well as the high energy content of the intermediate compound **7** are of crucial significance. With respect to the pinacol fragment in **27**, the steric hindrance between the four methyl groups in the eclipsed conformation results in a



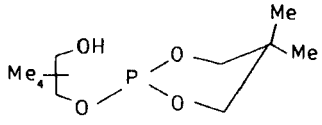
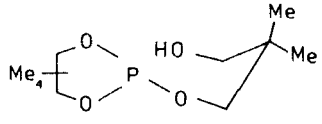
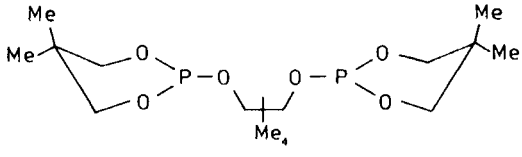
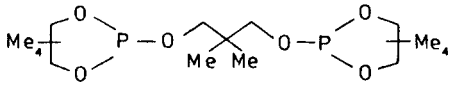
SCHEME 4 Various equilibria inherent in the synthesis of spirophosphorane **7**. Compounds which have been characterized by ^{31}P NMR are indicated with an asterisk.

more favourable trans orientation of the free hydroxyl group thus diminishing the possibility of ring closure.

In accordance with these predictions, reaction of equimolar amounts of pinacol (**25**) and 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (**26**) in the presence of one equivalent of base (Route *A*) gave rise to two resonances in the P(III) domain (δ 121.9 main signal; 121.7) which can be attributed to compounds **27** and **29**. No resonances indicative of compounds **33** and **2** could be detected (viz. Experimental). Moreover, we detected small amounts of products with $\delta^{31}P + 14/-21$ ppm and $J_{PH} = 690$ Hz, indicative of phosphonate structures.[19] No products with closed five-membered rings were found which excludes generation of the spirophosphorane **7** during the reaction course. The ^{31}P chemical shift of **27** was also confirmed via addition of excess **25** to a solution of compounds **25**, **27** and **29**. This leads to more intense appearance of compound **27** in the ^{31}P NMR spectrum due to the equilibrium **25** + **29** $\rightleftarrows$ **27** + **27**. Preparation of **27** at $-20°C$ in an NMR sample tube leads only to a minor amount of **29**. Addition of excess base and variable temperature conditions in the range $+30°C/-50°C$ failed to give the isomeric structure **28**. Application of route *B* by reacting equimolar amounts of 2,2-dimethylpropanediol-1,3 (**30**) and 2-chloro-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane (**31**) with one equivalent base resulted in exclusive formation of **28** (main product) and **32**. The corresponding ^{31}P NMR parameters are listed in Table II. Therefore, closure of the six-membered ring in compound **28** must be ruled out which was also confirmed by our low-temperature ^{31}P NMR measurements. Addition of excess **30** to a solution of **28**, **30** and **32** resulted in more intense appearance of **28** in the ^{31}P NMR spectrum due to the equilibrium **30** + **32** $\rightleftarrows$ **28** + **28**. In conclusion, the synthetic routes *A* and *B* are separated and lack the presence of the common intermediate **7**. This observation offers additional support for the proposed intermediacy of spirophosphorane **5** in Scheme 3. Apparently, in this case, conversion of products obtained via Route *A* into type *B* products proceeds uniquely via the isomerization **10** $\rightleftarrows$ **11** with intervention of the unstable phosphorane **5**. Due to the principle of microscopic reversibility[20] both ring opening and ring closure inherent in the interconversion **10** $\rightleftarrows$ **11** are catalyzed upon addition of base. The observed base-catalyzed proton transfer from the hydroxyl oxygen to the phosphorus atom during ring closure of compound **10** (Scheme 3) can be compared with the selective role of Histidine 12 in the active site of RNase A. Moreover, the base-catalyzed opening of the six-membered ring in **5** resulting in **11** (Scheme 3) may mimic the role of Histidine 119. In the first transphosphorylation step (Figure 4a) the enzyme binds the 3′-nucleotide in such a way that Histidine 12 lies in close proximity to the 2′-OH group.[15] Catalysis of the abstraction of the 2′-OH proton by Histidine 12 facilitates intramolecular nucleophilic attack on the phosphorus atom and generates the penta-coordinated intermediate. Stabilization of the intermediate structure is accomplished by hydrogen-bonding from protonated Lysine 41 to the anionic oxygen ligands. Subsequent activation of the leaving group by proton transfer from Histidine 119 to the 5′-nucleotide generates the 2′,3′-cyclic nucleotide. In the comparative situation (Figure 4b) the rigid character of the 1,2-dihydroxybenzene fragment, which results in a favoured orientation of the free hydroxyl group towards the phosphorus atom,[14] nicely accounts for the fixed orientation of the 2′-OH group in the 3′-nucleotide unit. The lone pair in Figure 4b replaces one of the equatorial

TABLE II

^{31}P NMR spectroscopic data ($CDCl_3$, 27°C) of the compounds depicted in Scheme 4[a]

No.	Compound	δ ^{31}P
27		121.7
28		147.7
29		121.9
32		147.5

[a]See also experimental part.

anionic oxygen ligands while the apically located oxygen atom in the six-membered ring[12] simulates the departing 5'-nucleotide unit.[21] The excess base in solution mimics the catalytic role of Histidine 12 and Histidine 119 in the active site of the enzyme. Hence, base-catalyzed proton transfer from the oxygen to the phosphorus atom results in the intermediate spirophosphorane **5** (Figure 4c). In the absence of base, Burgada et al. proposed an analogous intermediate state for the proton transfer.[7] The presence of the six-membered ring reduces the required activation energy to generate the intermediate **5** and therefore has a stabilizing effect. Subsequent base-catalyzed proton transfer from phosphorus to the apically located oxygen atom of the six-membered ring results in structure **11** (Figure 4d).

In conclusion, the combined NMR data point to spirophosphoranes with a P—H bond and a six-membered ring although, due to their instability, these compounds could not be detected with the aid of low-temperature ^{31}P NMR techniques. Application of both Route *A* and *B* in order to prepare the spirophosphorane offers a possibility to establish the formation of a common intermediate structure. Strong support in favour of the spirophosphorane intermediates comes from comparison of Scheme 3 and 4. Due to the absence of the intermediate **7** in Scheme 4, products obtained via Route *A* cannot be converted into phosphites obtained via Route *B* and vice versa, as was established with ^{31}P NMR techniques at various temperatures. The formation of the intermediate structure **5** (Scheme 3) readily accounts for the observed product distribution. This implies that possible other routes, which might

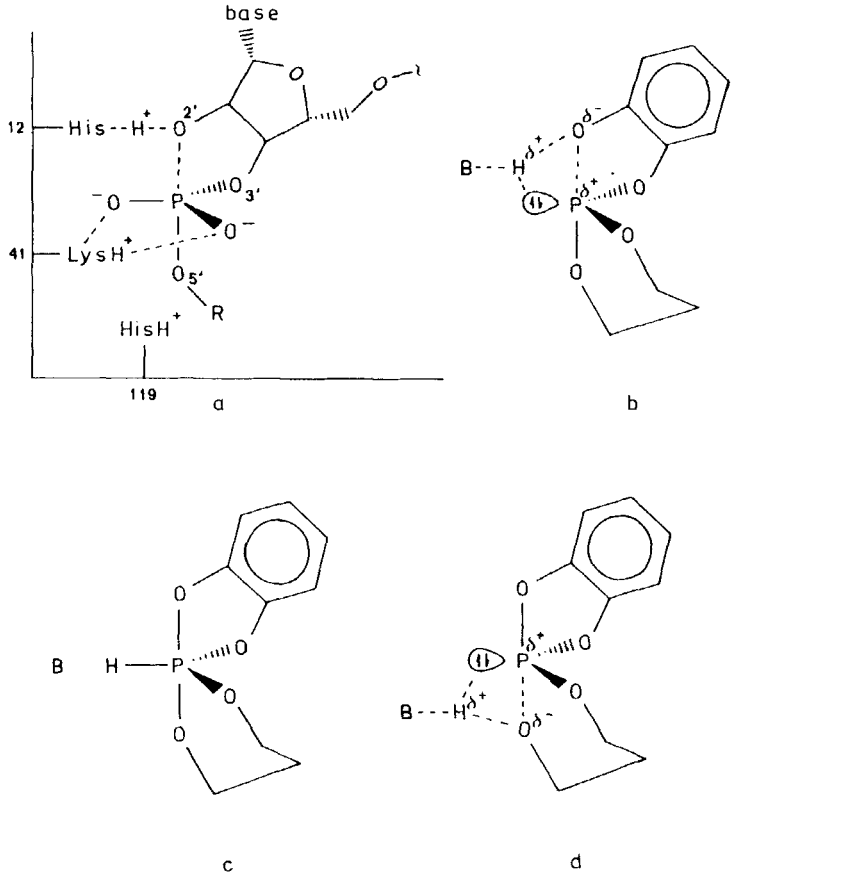


FIGURE 4 Analogy between the base-catalyzed proton transfer in RNase A (a) and in the equilibrium **10** ⇄ **11** which involves intermediate c.

explain the conversion of type *A* products into type *B* products and vice versa can be ruled out. Closure of the six-membered ring in **11** proceeds more slowly than closure of the five-membered ring in **10**. This can be explained on the basis of the decrease in translational entropy in five-membered ring fragments if compared with their six-membered analogues. Introduction of a six-membered ring in spirophosphoranes results in considerable destabilization if compared to analogous structures consisting of two five-membered rings. The latter structures have been detected as stable intermediates in the alcoholysis of phosphoramidites and in transesterification reactions. The rate of the interconversion **11** ⇄ **10** is enhanced upon addition of excess base and leads to various products through a series of equilibria. However, interconversion of both isomeric P(V) precursors **27** and **28** was not detected which can be rationalized on the basis of a high concomitant activation energy, electronic factors (vide supra) and orientation of the free hydroxyl group.

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian EM-360 A spectrometer. The ^{13}C (at 22.63 MHz) and ^{31}P (at 36.43 MHz) spectra were obtained using a Bruker HX-90 R spectrometer equipped with a Digilab-FT-NMR-3 computer. Standards were tetramethylsilane (TMS) for ^{13}C and ^1H NMR, and 85% H_3PO_4 for ^{31}P NMR. ^{31}P chemical shifts downfield from 85% H_3PO_4 are designated positive. 1,2-Dihydroxybenzene (**8**) was purchased from Merck and recrystallized from benzene solution after azeotropic removal of the water. Propanediol-1,3 (**13**) was purchased from Fluka, dried over K_2CO_3 and fractionally distilled under reduced pressure before use. 2,3-Dimethylbutanediol-2,3 (pinacol, **25**) and 2,2-dimethylpropanediol-1,3 (**30**) were purchased from Aldrich and recrystallized from dry benzene before use. Diethylaniline (BDH Laboratory Reagents), pyridine (Merck) and triethylamine (Fluka) were kept over KOH pellets and fractionally distilled before use.

Melting points were measured with a Mettler FP 1 apparatus. Special care was taken in handling the phosphorus compounds because of their moisture sensitivity. Therefore, all preparations were carried out in dry nitrogen atmosphere. After purification all compounds were stored at −20°C under dry nitrogen.

$CDCl_3$, used for NMR samples, was stored over molsieves (4 Å).

Route A (*Scheme 3*). 3.51 g (25 mmol) of **9** dissolved in 10 ml of dry ether was added dropwise over 30 min to a cooled (0°C) and stirred solution of 2.76 g (25 mmol) of **8** and 3.76 g (25 mmol) of diethylaniline in 40 ml of dry ether. The reaction mixture was then stirred for 15 min and warmed to room temperature over 30 min. The diethylanilinium salt was filtered off and washed twice with 10 ml portions of dry ether. The clear solution together with the combined washings, was evaporated in vacuo at room temperature. The resulting light oil was stored at −20°C under nitrogen. For NMR experiments an aliquot (0.2 ml) was dissolved in 0.3 ml of $CDCl_3$ and transferred to an NMR sample tube.

For low-temperature ^{31}P NMR measurements (−20°C), 55 mg (0.5 mmol) of **8** was dissolved in 0.4 ml of $CDCl_3$ in an NMR sample tube. The solution was kept at −20°C while 75 mg (0.5 mmol) of diethylaniline and 70 mg (0.5 mmol) of **9** were quickly added. ^{31}P NMR ($CDCl_3$): δ 123.7 (main signal) indicative of **10**.

Route B (*Scheme 3*). 8.73 g (50 mmol) of **14** dissolved in 15 ml of dry ether was added dropwise over 45 min to a cooled (0°C) and stirred solution of 3.81 g (50 mmol) of **13** and 7.52 g (50 mmol) of diethylaniline in 40 ml of dry ether. The reaction mixture was then stirred for 15 min and warmed to room temperature over 30 min. The diethylanilinium salt was filtered off and washed twice with 10 ml portions of dry ether. The clear solution, together with the combined washings, was evaporated in vacuo at room temperature. The resulting light oil was stored at −20°C under nitrogen. For NMR experiments an aliquot (0.2 ml) was dissolved in 0.3 ml of $CDCl_3$ and transferred to an NMR sample tube.

For low-temperature ^{31}P NMR measurements (−20°C), 38 mg (0.5 mmol) of **13** was dissolved in 0.4 ml of $CDCl_3$ in an NMR sample tube. The solution was kept at −20°C while 75 mg (0.5 mmol) of diethylaniline and 87 mg (0.5 mmol) of **14** were quickly added. ^{31}P NMR ($CDCl_3$): δ 127.5 (main signal) indicative of **11**.

2-Chloro-1,3,2-dioxaphosphorinane (**9**). Prepared according to the procedure described by Lucas et al.[22] B.p. 64–65°C/15 mm Hg; yield 54%. ^1H NMR ($CDCl_3$): δ 1.19–3.00 (m, 2 H, CH_2); 3.45–5.00 (m, 4 H, OCH_3). ^{31}P NMR ($CDCl_3$): δ 154.0.

2,2'-(o-Phenyldioxy)-1,3,2,-dioxaphosphorinane-1',3',2'-dioxaphosphorinane (**12**). 6.55 g (47 mmol) of **9** dissolved in 30 ml of dry ether was added dropwise over 45 min to a cooled (0°C) solution of 2.57 g (23.5 mmol) of **8** and 6.96 g (47 mmol) of diethylaniline in 20 ml of dry ether. The reaction mixture was then stirred for 15 min and maintained at 4°C for 16 h. The salt was filtered off and washed twice with 10 ml portions of dry ether. The clear solution, together with the combined washings, was evaporated in vacuo at room temperature, followed by fractional distillation. B.p. 153–160°C/0.003 mm Hg; yield 52%. The product contained 10% of **15**. For NMR data, see Table I.

2-Chloro-4,5-benzo-1,3,2-dioxaphospholane (**14**). Prepared according to the procedure described in Houben-Weyl.[23] B.p. 76°C/8.2 mm Hg; yield 85%. ^1H NMR ($CDCl_3$): δ 7.12 (m, 5 H, ArH). ^{31}P NMR ($CDCl_3$): δ 173.8.

2,2'-(1,3-Propanedioxy)-4,5-benzo-1,3,2-dioxaphospholane-1',3',2'-dioxaphosphorinane (**15**). 3.49 g (20 mmol) of **14** dissolved in 15 ml of dry ether was added dropwise over 30 min to a cooled (0°C) and stirred solution of 3.60 g (20 mmol) crude **17** and 2.98 g (20 mmol) diethylaniline in 15 ml dry ether. The reaction mixture was then stirred for 15 min, the diethylanilinium salt was filtered off and washed twice with 10 ml

portions of dry ether. The clear solution, together with the combined washings, was evaporated at room temperature. Several attempts to distill the crude product failed. For NMR data viz. Table I.

2,2'-(1,3-Propanedioxy)-4,5-benzo-1,3,2-dioxaphospholane-4',5'-benzo-1',3',2'-dioxaphospholane (**16**). 8.73 g (50 mmol) of **14** dissolved in 15 ml of dry ether was added dropwise over 45 min to a cooled (0°C) and vigorously stirred solution of 1.80 g (25 mmol) of **13** and 7.52 g (50 mmol) diethylaniline in 40 ml of dry ether. The reaction mixture was then stirred for 15 min and maintained at 4°C for 16 h. The diethylanilinium salt was filtered off and washed twice with 10 ml portions of dry ether. The clear solution, together with the combined washings, was evaporated in vacuo at room temperature and fractionally distilled. B.p. 174–176°C/0.04 mm Hg; yield 79%. For NMR data viz. Table I.

2-(3-Hydroxypropoxy)-1,3,2-dioxaphosphorinane (**17**). 7.03 g (50 mmol) of **9** dissolved in 15 ml of dry ether was added dropwise over 1 h to a cooled (10°C) and stirred solution of 6.06 g (50 mmol) of diethylaniline and 3.18 g (50 mmol) of **13** in 40 ml of dry ether. The reaction mixture was then cooled at 4°C for 16 h, the diethylanilinium salt was filtered off and washed twice with 10 ml portions of dry ether. The clear solution, together with the combined washings, was evaporated in vacuo at room temperature. Yield 8.6 g crude product which consisted of equimolar amounts **17** and **18**. Several attempts to distill the crude product failed due to the equilibrium **17** + **17** ⇄ **13** + **18**. For NMR data viz. Table I.

2,2'-(1,3-Propanedioxy)-1,3,2-dioxaphosphorinane-1',3',2'-dioxaphosphorinane (**18**). Preparation analogous to the one described for **16**. B.p. 132–136°C/0.005 mm Hg; yield 79%. For NMR data viz. Table I.

2,2'-(o-Phenyldioxy)-4,5-benzo-1,3,2-dioxaphospholane-4',5'-benzo-1',3',2'-dioxaphospholane (**19**). 0.55 g (5 mmol) of **8** and 1.01 g (10 mmol) of triethylamine dissolved in 20 ml of dry ether was added dropwise over 30 min at room temperature to a stirred solution of 1.75 g (10 mmol) of **14** dissolved in 30 ml of dry ether. The reaction mixture was then stirred for 15 min. The triethylammonium salt was filtered off and washed twice with 5 ml portions of dry ether. The clear solution, together with the combined washings, was evaporated in vacuo at room temperature. ^{31}P NMR ($CDCl_3$): δ 129.6 and −21.8 (5% compound **24**).

2,2'-(o-Phenyldioxy)-4,5-benzo-1,3,2-dioxaphospholane-1',3',2'-dioxaphosphorinane (**20**). This compound was prepared on NMR scale due to its instability. 50 Mg (0.2 mmol) of **24** was dissolved in 0.4 ml $CDCl_3$ in an NMR sample tube at room temperature. Quick addition of 20 mg (0.2 mmol) triethylamine and 28 mg (0.2 mmol) of **9** resulted in formation of **20** (main product), **16** and **12**. ^{31}P NMR ($CDCl_3$): δ 124.1 and 130.9 (equal intensity) indicative of **20**.

2-Ethoxy-1,3,2-dioxaphosphorinane (**21**). 14.05 g (100 mmol) of **9** dissolved in 10 ml of dry ether was added dropwise over 1 h to a cooled (10°C) and stirred solution of 4.60 g (100 mmol) of absolute ethanol and 10.12 g (100 mmol) of triethylamine in 40 ml of dry ether. The reaction mixture was warmed to room temperature and stirred for 30 min. The triethylammonium salt was filtered off and washed twice with 20 ml portions of dry ether. The clear solution, together with the combined washings, was evaporated in vacuo at room temperature followed by fractional distillation. B.p. 78°C/25 mm Hg; yield 50%. For NMR data viz. Table I.

2-Propoxy-4,5-benzo-1,3,2-dioxaphospholane (**22**). Prepared by a method analogous to that described by Crofts et al.[24] B.p. 108–109°C/10 mm Hg; yield 84%. For NMR data viz. Table I.

2-Phenoxy-1,3,2-dioxaphosphorinane (**23**). This compound was prepared in essentially the same way as **21**. B.p. 90–92°C/0.75 mm Hg; M.p. 41–44°C; yield 83%. For NMR data viz. Table I.

5-Hydrido-2,3,7,8-benzo-1,4,6,9-tetraoxa-5-phosphaspiro(4,4)non-2,7-diene (**24**). This compound was prepared according to the method described by Munoz et al.[5]; Yield 82%. ^{31}P NMR ($CDCl_3$): δ −21.8.

Route A and B (Scheme 4). For these routes the same procedure was followed as described for compound **5**, Scheme 3. The relevant ^{31}P NMR data of the various compounds are listed in Table II.

2-Chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (**26**). Prepared according to the procedure described in Houben-Weyl.[25] B.p. 83–84°C/25 mm Hg; yield 75%. ^{1}H NMR ($CDCl_3$): δ 0.84(s) and 1.26(s) (6 H, CH_3); 3.30–3.78 and 4.08–4.49 (m, 4 H, OCH_3). ^{31}P NMR ($CDCl_3$): δ 146.7.

2,2'-(1,1,2,2-Tetramethyl-1,2-ethanedioxy)-5,5-dimethyl-1,3,2-dioxaphosphorinane-5',5'-dimethyl-1',3',2'-dioxaphosphorinane (**29**). 3.37 g (20 mmol) of **26** dissolved in 20 ml of dry ether was added

dropwise over 20 min to a cooled (−78°C) and stirred solution of 1.18 g (10 mmol) of **25** and 2.02 g (20 mmol) of triethylamine in 30 ml of dry ether. The reaction mixture was then stirred for 15 min, warmed up and maintained at 4°C for 16 h. The triethylammonium salt was filtered off and washed twice with 10 ml portions of dry ether. The clear solution, together with the combined washings, was evaporated in vacuo at room temperature. Yield 3.8 g crude product, which could not be purified by fractional distillation. ^{31}P NMR ($CDCl_3$): δ 121.9 (main product **29**), 121.7 (**27**) and resonances between δ +14 and −21 (phosphonate structures).[19]

2-Chloro-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane (**31**). Prepared according to the procedure described in Houben-Weyl.[25] B.p. 69.5°C/6.5 mm Hg; yield 54%. ^{1}H NMR ($CDCl_3$): δ 1.32 and 1.50 (m, 12 H, CH_3), ^{31}P NMR ($CDCl_3$): δ 175.5.

2,2'-(2,2-Dimethyl-1,3-propanedioxy)-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane-4',4',5',5'-tetramethyl-1',3',2'-dioxaphospholane (**32**). Preparation analogous to that described for **29**. Nearly quantitative yield of crude **32** was obtained. This compound could not be purified by fractional destillation. ^{31}P NMR ($CDCl_3$): δ 147.7 (**28**), 147.5 (main product **32**) and resonances with δ +13 (phosphonate structures).

2,2'-(2,2-Dimethyl-1,3-propanedioxy)-5,5-dimethyl-1,3,2-dioxaphosphorinane-5',5'-dimethyl-1',3',2'-dioxaphosphorinane (**33**). Preparation analogous to that described for **29**. Nearly quantitative yield of **33** after evaporation of the dry ether in vacuo. M.p. 44–46°C. ^{1}H NMR ($CDCl_3$): δ 0.74(s), 0.99(s) and 1.25(s) (18 H, CH_3); 3.03–4.38 (m, 12 H, OCH_2). ^{13}C NMR ($CDCl_3$): δ 22.37 (s, ring CH_3); 23.51 (d, $^4J_{PC}$ = 6, CH_3); 33.59 (d, $^3J_{PC}$ = 4, ring C); 37.81 (t, $^3J_{PC}$ = 6, C); 68.38 (d, $^2J_{PC}$ = 16.7, CH_2); 69.58 (s, ring CH_2). ^{31}P NMR ($CDCl_3$): δ 121.9.

5-Hydrido-2,2,3,3,7,7,8,8-octamethyl-1,4,6,9-tetraoxa-5-phosphaspiro(4,4)nonane (**2**). Prepared according to the procedure described by Sanchez et al.[26] The crude product **2** was crystallized from petr. ether 60–80. Yield 90%. ^{1}H NMR ($CDCl_3$): δ 1.20 (m, 24 H, CH_3); 7.14 (d, 1 H, $^1J_{PH}$ = 799, P—H). ^{31}P NMR ($CDCl_3$): δ −40.6.

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