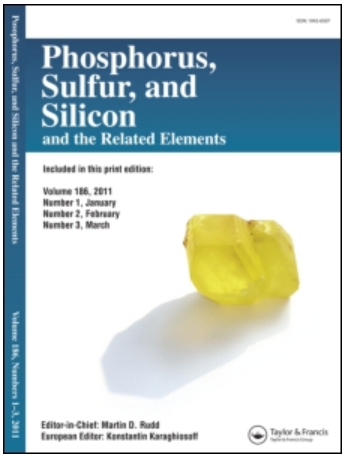

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND CONFORMATIONAL STUDIES OF A NUMBER OF SATURATED BICYCLIC SIX-MEMBERED RING PHOSPHITES

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To cite this Article Hermans, Rob. J. M. and Buck, Henk M.(1987) 'SYNTHESIS AND CONFORMATIONAL STUDIES OF A NUMBER OF SATURATED BICYCLIC SIX-MEMBERED RING PHOSPHITES', Phosphorus, Sulfur, and Silicon and the Related Elements, 31: 3, 255 — 265
To link to this Article: DOI: 10.1080/03086648708080644
URL: http://dx.doi.org/10.1080/03086648708080644

Phosphorus and Sulfur, 1987, Vol. 31, pp. 255–265
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SYNTHESIS AND CONFORMATIONAL STUDIES OF A NUMBER OF SATURATED BICYCLIC SIX-MEMBERED RING PHOSPHITES

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(Received July 10, 1986; in final form September 30, 1986)

An ^{1}H NMR study of the conformation of the dioxaphosphorinane ring of a number of diastereoisomeric bicyclic saturated six-membered ring phosphites (**3ab–10ab**) has been performed. The dioxaphosphorinane ring of these phosphites is transannelated with a tetrahydrofuran, cyclopentane, tetrahydropyran or cyclohexane ring. The substituent on the phosphorus atom is a methoxy or phenoxy group. It is shown that the cis isomers **3a–10a** prefer a chair conformation of the dioxaphosphorinane ring, independent of the substituent on the phosphorus atom and of the nature of the transannelated ring. In contrast, for the trans isomers **3b–10b** a twist rather than a chair conformation of the dioxaphosphorinane ring is preferred. The fraction of the twist conformer in the trans isomers is mainly determined by the substituent on phosphorus. The size and composition of the transannelated ring are relatively unimportant in this respect. For both cis and trans isomers, the preferred geometry is solvent-independent. The measured $^3J_{POCH}$ couplings of the cis isomers **3a–10a** are used to formulate an expression for the dependence of such couplings upon dihedral angles in bicyclic phosphites.

INTRODUCTION

The conformations of monocyclic six-membered ring phosphites, 1,3,2-dioxaphosphorinanes, have been studied thoroughly.[1,2] Little is known, however, about the conformational properties of saturated bicyclic six-membered ring phosphites. The only well investigated systems of this kind are the methyl and phenyl 3′,5′-cyclic phosphites of thymidine, **1ab–2ab**[3] (Figure 1).

It was demonstrated that the dioxaphosphorinane ring of the cis isomers **1a–2a** preferentially adopts a chair conformation with the OR group axial. The thermodynamically less stable trans isomers **1b** and **2b**, however, showed a preference for a twist conformation of the dioxaphosphorinane ring in which the OR group occupies a pseudoaxial position. It was suggested that the strong stereoelectronic preference of the OR group for an axial or pseudoaxial position was responsible for the rather unusual twist conformation. A low chair-twist free energy difference, however, could not be excluded. In order to establish whether these special conformational properties are only limited to the compounds **1ab–2ab** which contain a dioxaphosphorinane ring transannelated with a deoxyribosering, we have studied the conformation of the dioxaphosphorinane ring of the bicyclic phosphites **3ab–10ab**[4] (Figure 2) by NMR-spectroscopy. In these compounds the dioxaphosphorinane ring is transannelated with a tetrahydrofuran (**3ab–4ab**), cyclopentane (**5ab–6ab**), tetrahydropyran (**7ab–8ab**) and cyclohexane ring (**9ab–**

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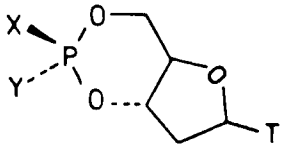
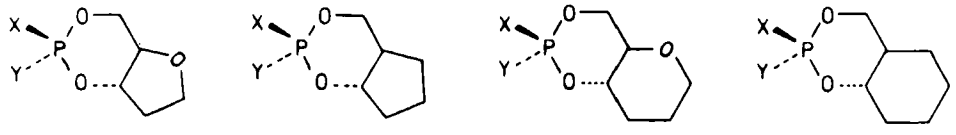


1a: cis, X = OCH_3, Y = lone pair
1b: trans, X = lone pair, Y = OCH_3
2a: cis, X = OPh, Y = lone pair
2b: trans, X = lone pair, Y = OPh
T = Thymine

FIGURE 1

10ab), respectively. The observations made on these phosphites can be used to determine the effect of the size and composition of the transannelated ring on the preferential conformation of the phosphorus containing ring.



3ab **5ab** **7ab** **9ab**

4ab **6ab** **8ab** **10ab**

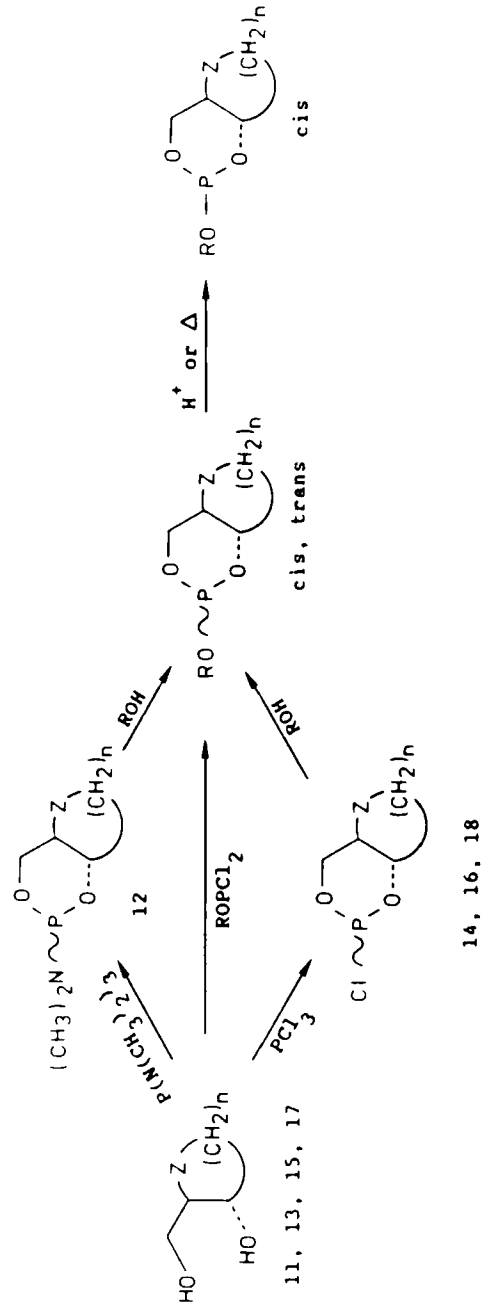
3a, **5a**, **7a**, **9a**: cis, X = OCH_3, Y = lone pair
3b, **5b**, **7b**, **9b**: trans, X = lone pair, Y = OCH_3
4a, **6a**, **8a**, **10a**: cis, X = OPh, Y = lone pair
4b, **6b**, **8b**, **10b**: trans, X = lone pair, Y = OPh

FIGURE 2

RESULTS AND DISCUSSION

Synthesis

The isomer **3b** (less than 20% of **3a** present as was established by ^{31}P NMR) was obtained by the reaction of methanol with the dimethylamino-derivative **12** (Scheme 1) at room temperature using 1H-tetrazole as catalyst. Phosphite **3a** was prepared by thermal isomerization of compound **3b**. Reaction of methoxydichlorophosphite with (1R,2S)-2-hydroxytetrahydrofuranmethanol **11** afforded a 40:60 mixture of the diastereoisomers **3a** and **3b**. This ratio, however, varied considerably with the reaction. The percentage trans was mostly less than 50%. The triester **4b** was synthesized from compound **12** by reaction with phenol at 70°C or at room temperature using 1H-tetrazole as a catalyst. Thermal isomerization of **4b** afforded **4a**. Compound **4a** could also be obtained by the reaction of phenoxydichlorophosphite with diol **11**. Compound **11** was prepared from 3,5-di-p-toluyl-2-deoxy-D-ribosylchloride.[7] Isomer **5b** was prepared from the corresponding chlorophosphite **14** according to the method of Verkade *et al.*[8] Thermal isomerization of **5b** gave compound **5a**. Reaction of chlorophosphite **14** with phenol afforded a mixture of **6a** and **6b** (approximately 70:30) suitable for NMR analysis. The starting diol **13** for the chlorophosphite **14** was obtained in several steps from cyclopentanone as described by Penney and Belleau.[9] The compounds **7b**–**10b** were obtained by reaction of the corresponding chlorophosphites **16** and **18** with methanol (**7b** and **9b**) and phenol (**8b** and **10b**). Isomer-



SCHEME 1. **11**, **12**: Z = O, n = 2; **13**, **14**: Z = CH_2, n = 2; **15**, **16**: Z = O, n = 3; **17**, **18**: Z = CH_2, n = 3; R = CH_3, Ph.

ization of these compounds by addition of traces of trifluoroacetic acid afforded the cis phosphites **7a–10a**. The starting diol (1RS,2SR)-2-hydroxytetrahydropyranmethanol **15** for the chlorophosphite **16** was prepared from dihydropyran according to a method described by Bouchu and Dreux.[10] Chlorophosphite **18** was synthesized from phosphorustrichloride and (1RS,2SR)-2-hydroxycyclohexanemethanol **17**. Compound **17** was prepared according to literature procedures.[11,12] The cis isomers **3a–10a** obtained by isomerization of the corresponding trans isomers all contained less than 1% trans as shown by ^{31}P NMR.

Characterization of Diastereoisomers

Assignment of cis and trans geometries to the diastereoisomers **3ab–10ab** was made by analogy to the compounds **1ab–2ab**[3] on the basis of the relative upfield ^{31}P NMR shifts of the cis isomers compared to those of the trans.

^{1}H NMR Studies

The ^{1}H NMR data of the dioxaphosphorinane part of the compounds **3ab–10ab** in benzene-d_6 are listed in Table I. The spectral parameters were obtained by iterative fitting of expansions of the H_{5a}, H_{5b}, H_6 and H_1 patterns of the 300 MHz ^{1}H NMR spectra using the PANIC program.[13] For comparison, the values of **1ab–2ab** in acetone-d_6[3] and of **9ab** in tetra[5] are also given.

The dioxaphosphorinane ring of the cis isomers **3a–10a** dominantly populates the chair conformer **19** (Figure 3) on the basis of the similarity of the $^3J_{HP}$ values for H_{5b} (ranging from 10.3–11.1 Hz) and H_{5a} (2.4–2.9 Hz) to those of **1a** and **2a** and other phosphites for which a chair conformation of the dioxaphosphorinane ring was established.[1,3,5] The small $^3J_{1P}$ couplings (1.6–2.5 Hz) and relatively large $^3J_{5a6}$ couplings (10.5–11.4 Hz) are in agreement with this assignment.

From the data in Table I it can be concluded that the conformation of the phosphorus containing ring in **3a–10a** is not altered by replacing the methoxy group on the phosphorus atom by the more electronegative phenoxy group. The somewhat larger $^3J_{5aP}$, $^3J_{5bP}$ and $^3J_{1P}$ couplings of the phenoxy phosphites compared to the methoxy phosphites can be explained by the dependene of these couplings on the nature of the substituent.[14] The data in Table I also reveal that the flexibility of the transannelated ring is unimportant with respect to the conformation of the dioxaphosphorinane ring in the cis isomers. Thus, the magnitude of the coupling constants of 3β-methoxy-trans-2,4,7-trioxa-3-phosphabicyclo(4.3.0)nonane **3a** and its phenoxy analog **4a**, both having a transannulated tetrahydrofuran ring is almost similar to those of 3β-methoxy- and 3β-phenoxy-trans-2,4,7-trioxa-3-phosphabicyclo(4.4.0)decane **7a** and **8a**, respectively, possessing a tetrahydropyran ring. The same applies to **5a** and **6a**, containing a cyclopentane ring, and the triesters **9a** and **10a**, possessing a cyclohexane ring. Finally, comparison of the coupling patterns of the trioxa compounds **3a–4a** and **7a–8a** with those of the dioxa analogs **5a–6a** and **9a–10a**, respectively, indicate that the nature of the atom on position 7 in the transannelated ring is of little influence on the preferential geometry of the dioxaphosphorinane ring. The differences in $^3J_{5a6}$, $^3J_{5b6}$ and $^3J_{16}$ between the trioxa and dioxa cis phosphites originate from the lower electronegativity of the carbon on position 7 in the

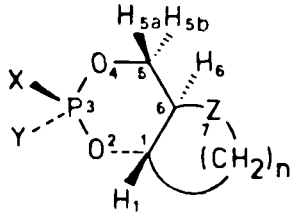
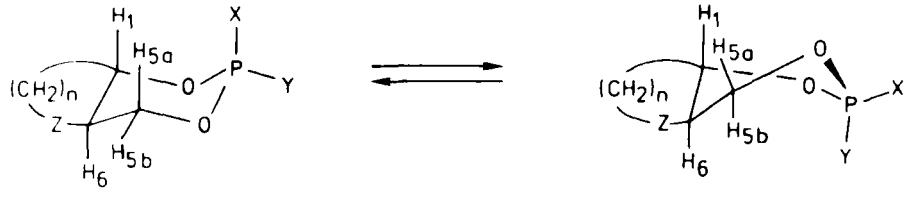


TABLE I

Selected ^{1}H NMR spectral parameters for **1ab–10ab** at 300 MHz and 300 K in benzene-d_6.[a]

	Chemical shift[b]				Coupling constants[c]							
Compound	H_{5a}	H_{5b}	H_6	H_1	J_{5a5b}	J_{5aP}	J_{5a6}	J_{5bP}	J_{5b6}	J_{16}	J_{1P}	J_{6P}
1a[d,e]					−9.1	2.4	10.8	10.6	4.3	9.5	1.8	<0.6
2a[d,e]					−9.2	2.6	10.7	10.8	4.4	9.1	~2	<0.6
3a	4.22	4.08	3.27	4.10	−9.1	2.4	10.6	10.5	4.4	9.0	1.6	<0.5
4a	4.36	4.15	3.25	4.23[e]	−9.1	2.6	10.7	10.8	4.4	9.0	2.0[e]	<0.5
5a	4.04	3.79	—[f]	3.96[e]	−10.0	2.4	11.4	10.3	4.2	10.5[e]	1.9[e]	—[f]
6a	4.18	3.85	—[f]	4.12[e]	−10.0	2.8	11.4	10.6	4.2	10.5[e]	2.2[e]	—[f]
7a	4.16	3.81	3.24	4.20	−10.0	2.4	10.5	10.8	4.7	9.2	2.0	<0.5
8a	4.35	3.87	3.22	4.38[e]	−10.0	2.7	10.6	11.1	4.7	9.3	2.2[e]	<0.5
9a	3.93	3.38	—[f]	4.08[e]	−10.5	2.6	11.4	10.5	4.2	10.0[e]	2.2[e]	—[f]
9a[g]	3.94	3.49			−10.6	2.5	11.4	10.8	4.2			
10a	4.07	3.43	—[f]	4.23[e]	−10.6	2.9	11.4	10.9	4.1	10.2[e]	2.5[e]	—[f]
1b[d]					−9.6	7.7	9.7	3.0	6.2	9.5	1.1	−0.8
2b[d]					−9.7	9.2	9.8	1.4	6.6	9.7	1.1	−1.0
3b	3.88	4.34	3.95	3.55	−9.5	7.8	9.8	3.0	6.2	9.3	1.4	−1.0
4b	3.94	4.48	4.21	3.57[e]	−9.6	9.3	9.7	1.4	6.5	9.5	1.1[e]	−1.0
5b	3.59	4.16	—[f]	3.52[e]	−10.1	6.3	11.4	3.9	6.2	10.4[e]	1.6[e]	—[f]
6b	3.61	4.29	—[f]	3.52[e]	−10.0	7.6	11.6	1.5	6.6	10.6[e]	1.6[e]	—[f]
7b	3.77	4.17	3.63	—[f]	−10.4	6.9	9.2	6.6	5.9	9.0[e]	—[f]	—[f]
8b	3.78	4.34	4.01	3.59[e]	−10.3	9.2	9.1	2.0	6.9	9.8	1.9[e]	−0.9
9b	3.44	3.77	—[f]	3.52[e]	−10.8	4.7	11.3	8.2	5.3	—[f]	—[f]	—[f]
9b[g]	3.59	3.91			−10.7	4.6	11.2	8.3	5.5			
10b	3.39	3.92	—[f]	3.54[e]	−10.3	6.6	11.5	2.2	5.9	—[f]	3.0[e]	—[f]

[a] Obtained by iterative fitting using the PANIC program,[13] unless stated otherwise.
[b] Proton chemical shifts in parts per million downfield from TMS as internal standard.
[c] Coupling constants in Hz.
[d] In acetone-d_6[3].
[e] First order analysis.
[f] Could not be determined.
[g] In chloroform-d_1[5].



cis: X = OCH_3 or OPh, Y = lone pair
trans: X = lone pair, Y = OCH_3 or OPh

FIGURE 3

dioxa phosphites. According to the generalized Karplus relation for three bond ^1H–^1H spin–spin coupling constants[15,16] the values of 10.6 and 11.4 Hz of $^3J_{5a6}$ for the trioxa and dioxa phosphites, respectively, both point to a dihedral angle $H_{5a}C_5C_6H_6$ of 180°. The values found for $^3J_{5b6}$ (4.2, 4.4 and 4.7 Hz) indicate that dihedral angle $H_{5b}C_5C_6H_6$ is about 60° (65°, 64° and 62°, respectively). Both dihedral angles are consistent with conformation **19**. With the dihedral angles $PO_4C_5H_{5a}$ and $PO_4C_5H_{5b}$ of the cis isomers being equal to 60° and 180° in the chair conformation **19**, the results obtained for the $^3J_{5aP}$ and $^3J_{5bP}$ couplings can be used to formulate a Karplus relation[17] for the dihedral dependence of $^3J_{POCH}$ in these bicyclic phosphites. Hence, taking the average values for $^3J_{5aP}$ (2.5 and 2.8 Hz for the methoxy and phenoxy cis phosphites, respectively) and $^3J_{5bP}$ (10.5 and 10.9 Hz, respectively) relation 1 is obtained with $c = 0$ for the methoxy compounds and $c = 0.3$ for the phenoxy compounds.

$$^3J_{POCH} = 10.4 \cos^2 \phi - 0.2 \cos \phi + c \quad (1)$$

As can be seen in Figure 4, this relation gives nearly the same results as the Kainosho relation[18] for the dihedral dependence of $^3J_{POCH}$ couplings in 2,7,8-trioxa-1-phosphabicyclo(3.2.1) octane **21**.

From the data given in Table I it is clear that the dioxaphosphorinane ring of the trans isomers **1b–10b** exists primarily in non-chair conformations. For **1b** and **2b** a predominance of the twist conformation **20** (Figure 3) was found.[3] Characteristic for the twist geometry is the combination of large couplings of H_{5a} to both phosphorus and H_6, which is not possible in the chair conformer **19**. Furthermore, the skewing of the dioxaphosphorinane ring in **20** is such that coupling $^3J_{5aP}$ is larger than $^3J_{5bP}$. The difference between both couplings is determined by the extent of twisting of the dioxaphosphorinane ring (dihedral angle $H_{5a}C_5O_4P$ can be as large as 180°, reducing that for H_{5b} C_5O_4P to as low as

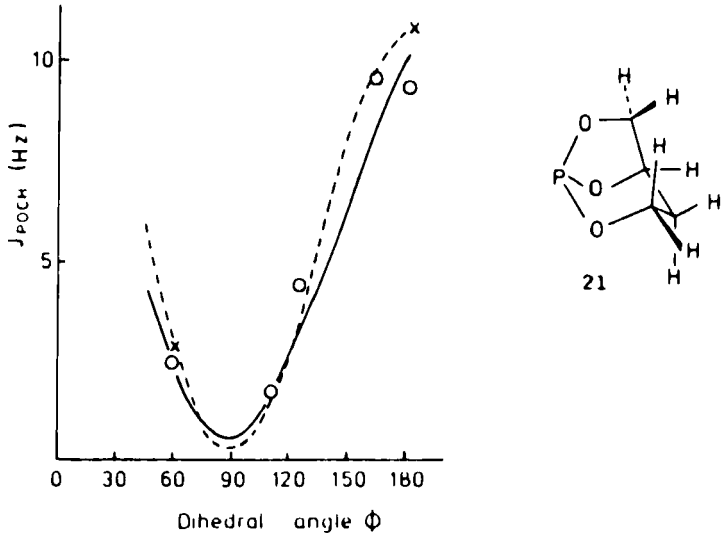


FIGURE 4 Plots of $^3J_{POCH}$ vs. POCH Dihedral angle. - - - = relation 1 for phenoxy cis isomers (×), —— = Kainosho relation for phosphite **21** (○).[18]

60°). The couplings of H_1 to H_6 and to phosphorus in **20** will be of the same order as in the chair **19** since the $C_6C_1O_2P$ side of the ring maintains the chairlike arrangement of **19**. The somewhat reduced $H_{5b}C_5C_6H_6$ dihedral angle increases $^3J_{5b6}$ in **20** as compared to **19**. The couplings of **3b** and **4b** are equal to those of **1b** and **2b**, respectively, indicating that the thyminegroup on position 8 of the transannelated ring has no influence on the preference of the dioxaphosphorinane ring for a twist conformation. The decreased $^3J_{5aP}$ and increased $^3J_{5bP}$ values of **3b** relative to **4b** are caused by a partial population of the chair conformer **19**. An exact quantification of the percentage of twist populated by **3b** and **4b** is difficult to give, since the couplings in case of 100% twist are unknown. Assuming, however, that **4b** is 100% in the twist conformation and the couplings to H_{5a} and H_{5b} being equal for the chair conformers of **3a** and **3b**, a 80% twist population for **3b** is calculated. The cyclopentane derivative **6b** exhibits coupling constants which also point to a major contribution of the twist conformer. The decreased $^3J_{5aP}$ coupling relative to **4b** can be the result of a greater population of the chair conformer **19** present in **6b**. A lesser extent of twist of the dioxaphosphorinane ring in **6b**, however, would also result in a smaller $^3J_{5aP}$ coupling. Substitution of the phenoxy group in **6b** by a methoxy group results in an increase of the fraction of conformer **19** as reflected in the decrease of $^3J_{5aP}$ and increase of $^3J_{5bP}$ for **5b**. The increase is comparable to the one observed going from **4b** to **3b**. Compound **8b** populates a twist conformer to a comparable extent as **4b** as can be deduced from the coupling pattern. The couplings of **10b** also indicate a dominant population of the twist conformer, although the percentage of chair conformer populated by **10b** will be greater than for the other trans phenoxy phosphites as can be concluded from the smaller difference between the $^3J_{5aP}$ and $^3J_{5bP}$ values. The methoxy phosphites **7b** and **9b** show quite different coupling patterns as compared with the other trans phosphites. Thus, **7b** shows nearly equal $^3J_{5aP}$ and $^3J_{5bP}$ couplings while the $^3J_{5bP}$ coupling of **9b** is almost twice the $^3J_{5aP}$ coupling. These values can be explained by assuming a considerable amount of chair conformer **19** (50–70% relative to their phenoxy analogs) present in these compounds. The spectral parameters for **3ab–10ab** in the more polar solvent acetone-d_6 did not differ significantly from the results given in Table I. This shows that the preferred conformations of these phosphites are solvent-independent which is in contrast with the results found for the fourcoordinated derivative of **10b**.[19]

CONCLUSIONS

^{1}H NMR analysis of the bicyclic phosphites **3ab–10ab** shows that the cis isomers **3a–10a** preferentially populate the chair conformer **19**, independent of the substituent on the phosphorus atom and of the nature of the transannelated ring. The dioxaphosphorinane ring of the trans isomers **3b–10b** shows a preference for a twist conformation. The fraction of the twist population mainly depends on the electronegativity of the substituent on the phosphorus atom. The size of the transannelated ring and the nature of the atom on position 7 in this ring have only a minor influence on the preferential conformation of the dioxaphos-

phorinane ring. Furthermore, the preferred conformation in both cis and trans phosphites is solvent-independent.

EXPERIMENTAL SECTION

All solvents and materials were reagent grade and were used as received or purified as required. All reactions involving trivalent phosphorus compounds were routinely run under an atmosphere of dry nitrogen. ^{1}H NMR spectra were run in the FT mode on a Bruker CXP-300 spectrometer at 300.1 MHz, 32K data base, 3000 Hz SW and 5.47 s acquisition time. Coupling constants were taken from expansions of the H_{5a}, H_{5b}, H_6 and H_1 patterns and iteratively analyzed with the PANIC program.[13] Chemical shifts in parts per million for ^{1}H are referenced to TMS. ^{31}P spectra were run on a Bruker HX-90R spectrometer at 36.4 MHz, using 85% H_3PO_4 as external standard.

(1R,2S)-2-hydroxytetrahydrofuranmethanol **11**. 53.8 gr (140 mmol) of 3,5-di-p-toluyl-2-deoxy-D-ribosyl-chloride[7] was added in portions in 2 hr to a well-stirred suspension of 32 gr of lithium aluminium hydride in 1400 ml of tetrahydrofuran with cooling in ice. The temperature varied between 10–15°C. After the addition was completed, the mixture was refluxed for 3 days. The excess of lithium aluminium hydride was decomposed by careful addition of 120 ml of ethylacetate followed by 1500 ml of water. The precipitated metal salts were removed by centrifugation. The resulting solution was concentrated to approximately 500 ml and washed with 3 portions of 100 ml of chloroform. Percolation of the strong basic solution through an Amberlite IR-120 (H^+) column afforded a strong acid effluent. This was rendered neutral by treatment with Amberlite IR-45. Evaporation of the water afforded 14.7 gr of a yellow viscous syrup. Destillation of this syrup to remove dissolved ionexchange particles gave 11.2 gr (95 mmol, 68%) of colourless **11**, bp. 104°C/0.03 mm. ^{1}H NMR (acetonitrile-d_3): δ 1.6–2.4 (m, 2H, CH_2), 3.2–4.3 (m, 8H, CH_2OH, CHOH, CH_2OH, OCH, CHOH, OCH_2).

3-dimethylamino-trans-2,4,7-trioxa-3-phosphabicyclo-(4.3.0)nonane **12**. 3.06 gr (25.9 mmol) of diol **11** and 0.05 eq of 1H-tetrazole were dissolved in 250 ml of dry dioxane. To this solution was added dropwise 4.23 gr (25.9 mmol) of tris-dimethylaminophosphite at room temperature. After the addition was completed, the mixture was stirred for 18 hr at 70°C. The dioxane was evaporated and the resulting crude product was fractionated to give 1.0 gr (5.2 mmol, 20%) of **12**, bp. 59–63°C/0.35 mm. ^{31}P NMR (benzene-d_6): δ 145.1. ^{1}H NMR (benzene-d_6): δ 1.6–1.9 (m, 2H, H_{9a}, H_{9b}), 2.6 (d, 6H, CH_3, J = 9 Hz), 3.5–4.4 (m, 6H, H_{5a}, H_{5b}, H_6, H_1, H_{8a}, H_{8b}).

3β- and 3α-methoxy-trans-2,4,7-trioxa-3-phosphabicyclo(4.3.0)nonanes **3a** *and* **3b**. a. from diol **11** and methoxydichlorophosphite. A solution containing the diol **11** (10.40 gr, 88 mmol) and triethylamine (17.81 gr, 176 mmol) in methylenechloride (130 ml) and a separate solution containing the methoxydichlorophosphite (11.70 gr, 88 mmol) in methylenechloride (150 ml) were added dropwise at equal rates to 225 ml of methylenechloride at −10°C over a 2.5 hr period. The mixture was stirred further at 0°C for 30 min and at 25°C for 2 hr. The solvent was removed at 25°C/30 mm and the residue was triturated with dry ether (150 ml) and filtered. The ether was evaporated. Destillation of the residue afforded 3.35 gr (18.8 mmol, 21%) product with bp. 53°C/0.7 mm which consisted of 40% **3a** and 60% of **3b** as shown by ^{31}P NMR. Pure **3a** (>99%) could be obtained by thermal isomerization of this mixture of diastereoisomers. b. from 3-dimethylamino-trans-2,4,7-trioxa-3-phosphabicyclo(4.3.0)nonane **12** and methanol. A solution of 0.25 gr (1.3 mmol) of **12**, 0.042 gr (1.3 mmol) of methanol and 4.5 mgr (0.065 mmol) of 1H-tetrazole in 50 ml of dry dioxane was stirred for 28 hr at room temperature. Evaporation of the dioxane and destillation afforded almost pure **3b**.
3a: ^{31}P NMR (benzene-d_6): δ 122.4 (lit[22]: δ 121.5). ^{1}H NMR (benzene-d_6): δ 1.5–1.7 (m, 2H, H_{9a}, H_{9b}), 3.2 (d, 3H, OCH_3, J = 12.2 Hz), 3.2–3.3 (m, 1H, H_6), 3.4–3.5 (m, 2H, H_{8a}, H_{8b}), 4.0–4.1 (m, 2H, H_1, H_{5b}), 4.2–4.3 (m, 1H, H_{5a}).
3b: ^{31}P NMR (benzene-d_6): δ 129.5. ^{1}H NMR (benzene-d_6): δ 1.5–1.8 (m, 2H, H_{9a}, H_{9b}), 3.2 (d, 3H, OCH_3, J = 11.9 Hz), 3.4–3.6 (m, 3H, H_{8a}, H_{8b}, H_1), 3.8–4.0 (m, 2H, H_6, H_{5a}), 4.3–4.4 (m, 1H, H_{5b}).

3β- and 3α-phenoxy-trans-2,4,7-trioxa-3-phosphabicyclo(4.3.0)nonanes **4a** *and* **4b**. A solution of 0.25 gr (1.3 mmol) of **12** and 0.123 gr (1.3 mmol) of phenol in 50 ml of dry dioxane was refluxed for 18 hr at 70°C. Evaporation of the dioxane afforded **4b**. Thermal isomerization of **4b** gave its cis isomer **4a**.
4a: ^{31}P NMR (benzene-d_6): δ 114.1. ^{1}H NMR (benzene-d_6): δ 1.5–1.8 (m, 2H, H_{9a}, H_{9b}), 3.2–3.3 (m, 1H, H_6), 3.4–3.5 (m, 2H, H_{8a}, H_{8b}), 4.1–4.2 (m, 1H, H_{5b}), 4.2–4.3 (m, 1H, H_{5a}), 6.7–7.3 (m, 5H, ArH).

4b: ^{31}P NMR (benzene-d_6): δ 120.3. ^{1}H NMR (benzene-d_6): δ 1.6–1.9 (m, 2H, H_{9a}, H_{9b}), 3.4–3.6 (m, 3H, H_1, H_{8a}, H_{8b}), 3.9–4.0 (m, 1H, H_{5a}), 4.2–4.3 (m, 1H, H_6), 4.4–4.5 (m, 1H, H_{5b}), 7.0–7.2 (m, 5H, ArH).

(1RS,2SR)-2-hydroxycyclopentanemethanol **13**. This compound was prepared in several steps from cyclopentanone as described by Penney and Belleau.[9] Bp. 97–100°C/1.0 mm (lit[9]: bp. 96–99°C/1 mm). ^{1}H NMR (chloroform-d_1): δ 0.8–2.2 (m, 7H, ring CH_2, CH), 3.2–4.2 (m, 5H, CH_2OH, CHOH, CH_2OH, CHOH). GC showed this compound to contain no cis diol.

3-chloro-trans-2,4-dioxa-3-phosphabicyclo(4.3.0)nonane **14**. This compound was prepared from diol 13 and phosphorustrichloride as described by Ramirez *et al.*[21] Yield 42%, bp. 68–70°C/0.85 mm (lit[21]: yield 53%, bp. 49–50°C/0.4 mm). ^{31}P NMR (benzene-d_6): δ 146.3 (lit[21]: δ 145.4). ^{1}H NMR (benzene-d_6): δ 0.3–1.7 (m, 7H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.6–3.8 (m, 1H, H_{5b}), 3.9–4.2 (m, 2H, H_1, H_{5a}).

3α-methoxy-trans-2,4-dioxa-3-phosphabicyclo(4.3.0)nonane **5b**. Phosphite **5b** was prepared from compound **14** and methanol by the general method of Verkade *et al.*[8] To a solution of the chlorophosphite **14** (0.72 gr, 4.0 mmol) in 10 ml of anhydrous ether maintained at 0°C was added dropwise with stirring a solution containing 0.9 eq of methanol (0.116 gr, 3.6 mmol) and 1 eq of triethylamine (0.404 gr, 4.0 mmol) in 5 ml of anhydrous ether. After removal of the triethylamine-HCl salt by filtration, the ether solution was evaporated and the residue distilled to give 0.41 gr (2.34 mmol, 65%) of **5b**, bp. 57–58°C/0.8 mm (lit[20]: bp. 54°C/0.7 mm). ^{31}P NMR (benzene-d_6): δ 130.8 (lit[20]: δ 130 4). ^{1}H NMR (benzene-d_6): δ 0.5–2.4 (m, 7H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.4 (d, 3H, OCH_3, J = 11.7 Hz), 3.5–3.6 (m, 1H, H_1), 3.6 (m, 1H, H_{5a}), 4.1–4.2 (m, 1H, H_{5b}).

3β-methoxy-trans-2,4-dioxa-3-phosphabicyclo(4.3.0)nonane **5a**. This compound was obtained by thermal isomerization of its trans isomer **5b**. ^{31}P NMR (benzene-d_6): δ 125.0. ^{1}H NMR (benzene-d_6): δ 0.5–1.9 (m, 7H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.3 (d, 3H, OCH_3, J = 12.1 Hz), 3.7–3.8 (m, 1H, H_{5b}), 3.9–4.1 (m, 2H, H_1, H_{5a}).

3β- and 3α-phenoxy-trans-2,4-dioxa-3-phosphabicyclo(4.3.0)nonanes **6a** *and* **6b**. A 70:30 mixture of **6a** and **6b**, suitable for NMR analysis, was obtained by the reaction of chlorophosphite **14** with phenol according to the procedure that was described for the preparation of **5b**. Yield 57%, bp. 93–99°C/0.55 mm. Addition of traces of trifluoracetic acid to this mixture afforded nearly pure (>99%) cis isomer **6a**.
6a: ^{31}P NMR (benzene-d_6): δ 117.0. ^{1}H NMR (benzene-d_6): δ 0.5–1.9 (m, 7H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.8–3.9 (m, 1H, H_{5b}), 4.1–4.2 (m, 2H, H_1, H_{5a}), 7.0–7.2 (m, 5H, ArH).
6b: ^{31}P NMR (benzene-d_6): δ 121.6. ^{1}H NMR (benzene-d_6): δ 0.5–2.8 (m, 7H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.5–3.6 (m, 1H, H_1), 3.6–3.7 (m, 1H, H_{5a}), 4.2–4.3 (m, 1H, H_{5b}), 7.0–7.2 (m, 5H, ArH).

(1RS, 2SR)-2-hydroxytetrahydropyranmethanol **15**. Compound **15** was prepared in several steps from dihydropyran according to the procedure described by Bouchu and Dreux.[10] Overall yield 11%, bp. 108–112°C/1.9 mm (lit[10]: bp. 130–135°C/2.0 mm). ^{1}H NMR (chloroform-d_1): δ 1.0–2.4 (m, 4H, ring CH_2), 2.8–4.2 (m, 7H, CH_2OH, CH_2OH, OCH_2, OCH, CHOH).

3-chloro-trans-2,4,7-trioxa-3-phosphabicyclo(4.4.0)decane **16**. This chlorophosphite is prepared from diol **15** and phosphorustrichloride by the method described for the preparation of compound **14**. Yield 32%, bp. 95°C/2.2 mm. ^{31}P NMR (benzene-d_6): δ 147.3. ^{1}H NMR (benzene-d_6): δ 0.9–1.7 (m, 4H, H_{9a}, H_{9b}, H_{10a}, H_{10b}), 2.8–3.0 (m, 2H, H_6, H_8), 3.4–3.5 (m, 1H, H_8), 3.6–3.9 (m, 1H, H_{5b}), 4.1–4.4 (m, 2H, H_1, H_{5a}).

3α-methoxy-trans-2,4,7-trioxa-3-phosphabicyclo(4.4.0)decane **7b**. Phosphite **7b** was prepared from chlorophosphite **16** and methanol according to the procedure described for the preparation of **5b**. Yield 74%, bp. 70–76°C/2.0 mm. ^{31}P NMR (benzene-d_6): δ 131.3. ^{1}H NMR (benzene-d_6): δ 1.0–1.9 (m, 4H, H_{9a}, H_{9b}, H_{10a}, H_{10b}), 2.9–3.0 (m, 1H, H_8), 3.3 (d, 3H, OCH_3, J = 11.2 Hz), 3.5–3.7 (m, 3H, H_1, H_6, H_8), 3.7–3.8 (m, 1H, H_{5a}), 4.1–4.2 (m, 1H, H_{5b}).

3β-methoxy-trans-2,4,7-trioxa-3-phosphabicyclo(4.4.0)decane **7a**. Addition of traces of trifluoroacetic acid to compound **7b** afforded nearly pure (>99%) **7a**. ^{31}P NMR (benzene-d_6): δ 125.8. ^{1}H NMR (benzene-d_6): δ 1.0–1.8 (m, 4H, H_{9a}, H_{9b}, H_{10a}, H_{10b}), 2.9–3.0 (m, 1H, H_8), 3.2 (d, 3H, OCH_3, J = 12.0 Hz), 3.2–3.3 (m, 1H, H_6), 3.5–3.6 (m, 1H, H_8), 3.8–3.9 (m, 1H, H_{5b}), 4.1–4.2 (m, 2H, H_1, H_{5a}).

3α-phenoxy-trans-2,4,7-trioxa-3-phosphabicyclo(4.4.0)decane **8b**. Reaction of the chlorophosphite **16** with phenol according to the procedure described for the preparation of **5b** furnished **8b**, bp. 113–114°C/0.5 mm. ^{31}P NMR (benzene-d_6): δ 122.2. ^{1}H NMR (benzene-d_6): 1.0–2.0 (m, 4H, H_{9a}, H_{9b}, H_{10a}, H_{10b}), 2.9–3.0 (m, 1H, H_8), 3.4–3.6 (m, 1H, H_8), 3.5–3.7 (m, 1H, H_1), 3.7–3.9 (m, 1H, H_{5a}), 4.0–4.1 (m, 1H, H_6), 4.3–4.5 (m, 1H, H_{5b}), 6.8–7.3 (m, 5H, ArH).

3β-phenoxy-trans-2,4,7-trioxa-3-phosphabicyclo(4.4.0)decane **8a**. Cis isomer **8a** was prepared from compound **8b** by isomerization caused by traces of trifluoroacetic acid. ^{31}P NMR (benzene-d_6): δ 117.6. ^{1}H NMR (benzene-d_6): δ 1.0–1.8 (m, 4H, H_{9a}, H_{9b}, H_{10a}, H_{10b}), 2.8–3.0 (m, 1H, H_8), 3.2–3.3 (m, 1H, H_6), 3.5 (m, 1H, H_8), 3.8–4.0 (m, 1H, H_{5b}), 4.3–4.5 (m, 2H, H_1, H_{5a}), 6.7–7.2 (m, 5H, ArH).

(1RS, 2SR)-2-hydroxycyclohexanemethanol **17**. Diol **17** was prepared from cyclohexene and paraformaldehyde according to literature procedures.[11,12] ^{1}H NMR (chloroform-d_1): δ 0.7–2.3 (m, 9H, ring CH_2, CH), 3.1–4.7 (m, 5H, CH_2OH, CHOH, CH_2OH, CHOH).

3-chloro-trans-2,4-dioxa-3-phosphabicyclo(4.4.0)decane **18**. This compound was prepared from diol **17** and phosphorustrichloride by the method described for the preparation of **14**. Bp. 92–94°C/2.2 mm (lit[22]: bp. 102°C/2.2 mm). ^{31}P NMR (benzene-d_6): δ 152.4 (lit[22]: δ 152.2). ^{1}H NMR (benzene-d_6): δ 0.5–1.8 (m, 9H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}, H_{10a}, H_{10b}), 3.3–3.4 (m, 1H, H_{5b}), 3.9–4.0 (m, 1H, H_{5a}), 4.1–4.3 (m, 1H, H_1).

3α-methoxy-trans-2,4-dioxa-3-phosphabicyclo(4.4.0)decane **9b**. The preparation of phosphite **9b** was analogous to that of compound **5b**. Yield 65%, bp. 70–71°C/0.59 mm (lit[22]: bp. 100–103°C/3.3 mm). ^{31}P NMR (benzene-d_6): δ 133.1 (lit[22]: δ 133.5). ^{1}H NMR (benzene-d_6): δ 0.8–2.2 (m, 9H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}, H_{10a}, H_{10b}), 3.4 (d, 3H, OCH_3, J = 10.9 Hz), 3.3–3.6 (m, 2H, H_{1b}, H_{5a}), 3.7–3.8 (m, 1H, H_{5b}).

3β-methoxy-trans-2,4-dioxa-3-phosphabicyclo(4.4.0)decane **9a**. Acidic isomerization of phosphite **9b** afforded isomer **9a**. ^{31}P NMR (benzene-d_6): δ 130.3 (lit[22]: δ 129.8). ^{1}H NMR (benzene-d_6): δ 0.8–1.9 (m, 9H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}, H_{10a}, H_{10b}), 3.3 (d, 3H, OCH_3, J = 12.0 Hz), 3.3–3.4 (m, 1H, H_{5b}), 3.9–4.0 (m, 1H, H_{5a}), 4.0–4.1 (m, 1H, H_1).

3α-phenoxy-trans-2,4-dioxa-3-phosphabicyclo(4.4.0)decane **10b**. Compound **10b** was prepared according to the method described for the preparation of phosphite **5b**. Yield 72%, bp. 118–120°C/0.4 mm. ^{31}P NMR (benzene-d_6): δ 124.3. ^{1}H NMR (benzene-d_6): δ 0.6–2.7 (m, 9H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}, H_{10a}, H_{10b}), 3.3–3.4 (m, 1H, H_{5a}), 3.5–3.6 (m, 1H, H_1), 3.9–4.0 (m, 1H, H_{5b}), 7.0–7.2 (m, 5H, ArH).

3β-phenoxy-trans-2,4-dioxa-3-phosphabicyclo(4.4.0)decane **10a**. Cis isomer **10a** was obtained by isomerization of compound **10b**. ^{31}P NMR (benzene-d_6): δ 122.5. ^{1}H NMR (benzene-d_6): δ 0.8–1.8 (m, 9H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}, H_{10a}, H_{10b}), 3.4–3.5 (m, 1H, H_{5b}), 4.0–4.1 (m, 1H, H_{5a}), 4.2–4.3 (m, 1H, H_1), 7.0–7.2 (m, 5H, ArH).

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$$^3J_{HH} = 13.22\cos^2\phi - 0.99\cos\phi + \sum \{0.87 - 2.46\cos^2(\xi_i\phi + 19.9\,|\Delta\chi_i|)\}\Delta\chi_i.$$

ϕ is the proton-proton torsion angle, $\Delta\chi_i$ is the difference in electronegativity between the substituent and hydrogen according to the electronegativity scale of Huggins, and ξ_i is a substituent orientation parameter.
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