Synthesis and Conformational Analysis of Six-Membered Cyclic Phenyl Phosphites

Barbara Gordillo,* Catalina Garduño, Gerardo Guadarrama, and Javier Hernández

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado Postal 14-740, México, D. F., México

Received July 27, 1994 (Revised Manuscript Received June 8, 1995®)

A procedure for synthesizing potentially anancomeric equatorial phenyl phosphites (*cis*-**1** and *eq-cis*-**2**) is reported. Spectral characteristics and low-temperature NMR studies on the phenyl phosphites suggest that *eq-cis*-**2** is a system with a predominant chair conformation in solution. On the contrary, *cis*-**1** is conformationally heterogeneous.

Introduction

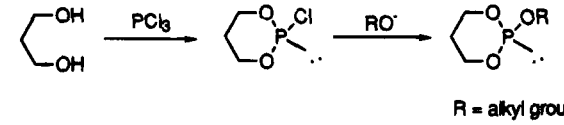
A long time ago, Lucas et al.[1] developed the synthesis of six-membered ring alkyl phosphites using glycols and phosphorus trichloride, followed by the addition of an alkoxy group as shown in Scheme 1.

Later, the application of the NMR techniques to the conformational analysis of heterocycles[2] prompted Denney and his group[3] to study the stereochemistry of these important phosphite intermediates. From these studies and those of others,[4] it was found that equatorial-substituted phosphites isomerized to the more stable axial diastereomers upon the addition of a catalytic amount of hydrogen chloride or during purification by preparative GC at high temperatures (Scheme 2).

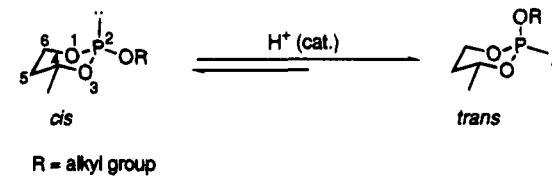
As part of our interest in the study of the mechanism and the stereochemistry of the hydrolysis of phenyl phosphates[5] and their *S*-analogs,[6] we attempted to synthesize the potentially anancomeric 4-methyl[7a] and *cis*-4,6-dimethyl axial and equatorial phenyl phosphites **1** and **2** (Scheme 3) by using a method based on the Lucas procedure.[4a,7b] However, under such conditions, the axial isomers were the unique products.

In this paper, we report a method for obtaining exclusively the equatorial diastereomers of **1** and **2**. The conformational analysis of axial and equatorial **1** and **2** was assessed by analysis of the spectral NMR characteristics at room and low temperature of the cited compounds. The decreased stability of the aromatic equatorial phosphites as compared with the stability of aliphatic series was manifested from the results of this work.

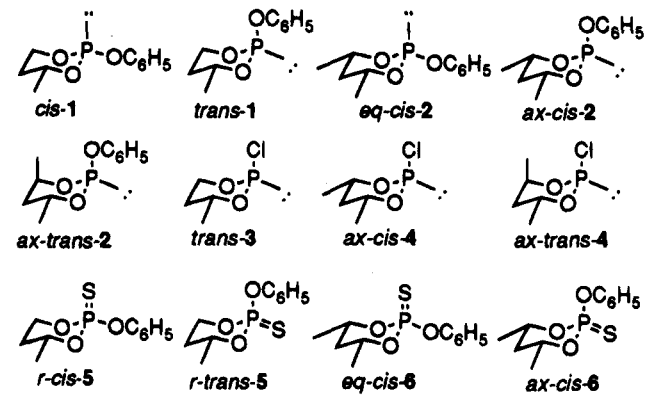
Scheme 1



Scheme 2



Scheme 3



Results and Discussion

The phosphorochloridite *trans*-**3** was produced from the reaction between (±)-1,3-butanediol and phosphorus trichloride. The geometrical isomer *trans*-**3** is thermodynamically more stable than *cis*-**3** because of the stabilizing (O–P–Cl) anomeric interaction[8] and the destabilizing four-electron antiperiplanar relationship[9] (Scheme 4).

The addition of phosphorochloridite *trans*-**3** to a solution of phenol and triethylamine at room temperature led exclusively to the phenyl phosphite *trans*-**1**. In spite

® Abstract published in *Advance ACS Abstracts*, July 15, 1995.

(1) Lucas, W. J.; Mitchell, F. W.; Scully, C. N. *J. Am. Chem. Soc.* **1950**, *72*, 5491.

(2) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison G. A. *Conformational Analysis*; Interscience Publishers, Wiley: New York, 1965; p 152.

(3) Denney, D. Z.; Denney, D. B. *J. Am. Chem. Soc.* **1966**, *88*, 1830.

(4) (a) Asknes, G.; Ericksen, R.; Melligen, K. *Acta Chem. Scand.* **1967**, *21*, 1028. (b) Gagnaire, D.; Robert, J. B.; Verrier, J. *Bull. Soc. Chim. Fr.* **1968**, 2392. (c) Hargis, J. H.; Bentrude, W. G. *Tetrahedron Lett.* **1968**, 5365. (d) Rodgers, J.; White, D. W.; Verkade, J. G. *Tetrahedron Lett.* **1968**, 5369. (e) Bodkin, C.; Simpson, P. *Chem. Commun.* **1969**, 829. (f) Albrand, J. P.; Gagnaire, D.; Robert, J. B.; Haemers, M. *Bull. Soc. Chim. Fr.* **1969**, 3496. (g) Bentrude, W. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 7136. (h) Bentrude, W.; Yee, K. C. *Tetrahedron Lett.* **1970**, 3999. (i) Cox, R. H.; Newton, G.; Campbell, B. S. *J. Am. Chem. Soc.* **1971**, *93*, 528. (j) Rodgers, J.; White, D. W.; Verkade, J. G. *J. Chem. Soc. A* **1971**, 77. (k) Haemers, M.; Ottinger, R.; Reisse, J.; Zimmerman, D. *Tetrahedron Lett.* **1971**, 461. (l) Bentrude, W. G.; Tan, H.-W.; Yee, K. C. *J. Am. Chem. Soc.* **1975**, *97*, 573.

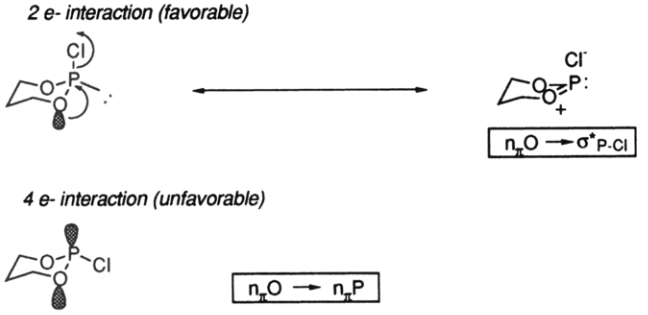
(5) Gordillo, B.; Eliel, E. L. *J. Am. Chem. Soc.* **1991**, *113*, 2172.

(6) Gordillo, B.; Garduño, C.; Guadarrama, G.; Eliel, E. L. Alkaline Hydrolysis of Six-Membered Cyclic Phenyl S-Phosphates. The Thiolo-Thiono Rearrangement. *Abstracts of Papers*, 207th ACS National Meeting of the American Chemical Society, San Diego, CA, March 13–17, 1994; American Chemical Society: Washington, DC, 1984; ORG 112.

(7) (a) The analog *cis*-2-methoxy-1,3,2λ^3-dioxaphosphorinane has been claimed on the basis of NMR to be 70% diequatorial chair and the rest diaxial chair or boat. See ref 7b. (b) Eliel, E. L.; Chandrasekaran, S.; Carpenter, L. E., II; Verkade, J. G. *J. Am. Chem. Soc.* **1986**, *108*, 6651 and references cited therein.

0022-3263/95/1960-5180$09.00/0

Scheme 4



of the fact that the *trans* configuration of the product **1** suggests a reaction with retention of configuration, the results were explained by proposing a S_N2P type of mechanism[10] as in the case of the alkyl phosphites, followed by isomerization of *cis*-**1** to *trans*-**1** provoked by the slight acidity of the triethylammonium chloride which is a byproduct of the reaction.

In order to avoid the acidic medium, the synthesis of *cis*-**1** was performed with sodium phenoxide (generated from phenol and sodium) in anhydrous ethyl ether at room temperature; however, the *trans*-**1** isomer was again obtained as a single product.

The reaction between phosphorochloridites and phenoxide ion is an exothermic reaction ($\Delta H_f°_{298}$ of P−Cl = 78.5 kcal/mol vs $\Delta H_f°_{298}$ of P−O = 142.3 kcal/mol).[11] At high temperatures, *cis* alkyl phosphites[12] and their thio analogs[13] epimerized at the phosphorus center to the more stable *trans* diastereomers. The phosphorochloridite *trans*-**3** was then reacted with phenol in triethylamine (TEA) at −78 °C under a modified Lucas procedure.[4a] Unfortunately, we were not able to detect the *cis*-**1** isomer even when using sodium phenoxide.

During several experiments in which we changed the concentration as well as the sequence of addition of the reactants and temperatures, we found that an excess of phenoxide also precluded formation of the *cis* phosphite. This result can be explained by postulating a second attack of the phenoxide ion on *cis*-**1** in an early transition state, following an antiperiplanar pathway,[14a] which produces the thermodynamically more stable *trans*-**1** diastereomer. The thermal equilibration of *cis*-**1** to *trans*-**1** led to a value of $\Delta G°$ (neat) = 2.1 kcal/mol at 80 °C[14c] (Scheme 5).

Scheme 5

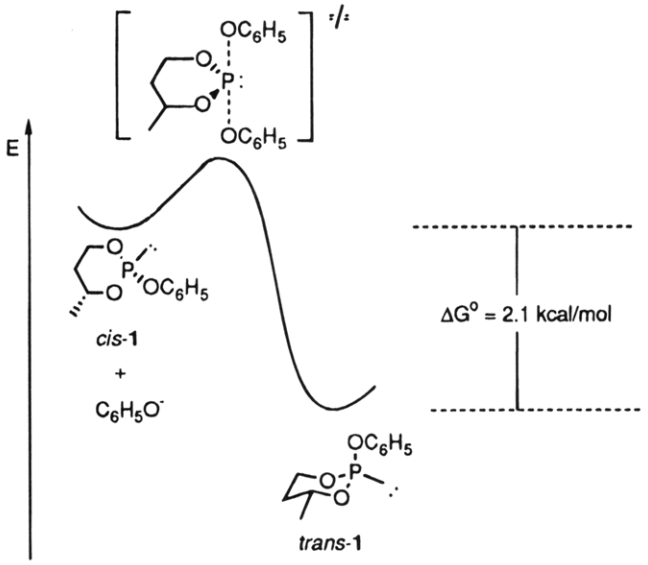


Table 1. ^{1}H NMR Chemical Shifts (in ppm) for Thionophosphates 5 and 6 in $CDCl_3$

chemical shifts	compound			
	r-cis-**5**	*r-trans*-**5**	*eq-cis*-**6**	*ax-cis*-**6**
$\delta_{H_{4a}}$	4.89	4.83	4.83	4.79
$\delta_{H_{5a}}$	1.98	2.19	1.70	1.82
$\delta_{H_{5e}}$	1.90	1.81	1.89	1.88
$\delta_{H_{6a}}$	4.61	4.59	4.83	4.79
$\delta_{H_{6e}}$	4.42	4.42	–	–

In summary, by avoiding the excess of the phenoxide ion during the reaction at low temperature,[15] we were able to obtain the *cis*-**1** isomer exclusively. The procedure for the synthesis of *cis*-**1** was successfully followed for the preparation of its analog, the equatorial 2-phenoxy-*cis*-4,6-dimethyl-1,3,2λ^3-dioxaphosphorinane (**2**). In the case of the 4,6-dimethyl phosphites, a mixture of *meso* and *d,l* diols (84:16) was used as starting material. Therefore, formation of a small amount of the *trans*-4,6-dimethyl isomer (less than 10% as indicated in the Experimental Section) was unavoidable in the final phosphites.

Stereochemistry and Conformational Analysis. In order to confirm the assigned configuration of the phosphites **1** and **2**, both were reacted with sulfur in a stereospecific manner[16] to produce the corresponding thionophosphates **5** and **6**,[17] as described in the Experimental Section. ^{1}H NMR chemical shifts of these thionophosphates are presented in Table 1.

^{1}H and ^{13}C NMR spectra of phosphites **1** and **2** are presented in Tables 2 and 3, respectively.

(8) (a) Mosbo, J. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4659. (b) Hodges, R. V.; Houle, F. A.; Beauchamp, J. L.; Montag, R. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1980**, *102*, 932. (c) Verkade, J. G. *Phosphorus Sulfur* **1976**, *2*, 251. (d) Hudson, R. F.; Verkade, J. G. *Tetrahedron Lett.* **1975**, 3231. See also the stereoelectronic effects in phosphates: Tatcher, G. R. J.; Kluger, R. In *Advances in Physical Organic Chemistry*; Bethell, D., Ed.; Academic Press: New York, 1989; Vol. 25, p 99. Van Nuffel, P.; Van Alsenoy, C.; Lenstra, A. T. H.; Geise, H. J. *J. Mol. Struct.* **1984**, *125*, 1. Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1047.

(9) In acyclic phosphites, a lone pair on oxygen antiperiplanar to the phosphite lone pair raises the energy of the molecule by 3.3 kcal/mol relative to a phosphite conformation with no antiperiplanar four-electron interaction: Taira, K.; Gorenstein, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 7825.

(10) For similar types of mechanisms, see: (a) Hudson, R. F.; Keay, L. *J. Chem. Soc.* **1956**, 2463. (b) White, D. W.; Bertrand, R. D.; McEwen, G. K.; Verkade, J. G. *J. Am. Chem. Soc.* **1970**, *92*, 7125.

(11) The ΔH_f values were taken from: Dean, J. A. *Handbook of Organic Chemistry*; McGraw Hill Book Co.: New York, 1987; pp 3−25.

(12) (a) Dutasta, J. P.; Grand, A.; Robert, J. B.; Taieb, M. *Tetrahedron Lett.* **1974**, 2659. (b) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187.

(13) (a) Hutchins, R. O.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1972**, *94*, 3266. (b) Ninfant'ev, E. E.; Borisenko, A. A.; Zavalishina, A. I.; Sorokina, S. F. *Dokl. Akad. Nauk SSSR* **1974**, *219*, 881; *Engl. Transl.* **1974**, *219*, 839.

(14) (a) See the stereoelectronic effects in transition states, for instance, in the glycoside hydrolysis: Deslongschamps, P. *Pure Appl. Chem.* **1993**, *65*, 1161. See it also in the α-effect (the enhanced nucleophilicity of a base possessing a heteroatom with an unshared electron pair[14b]) in ref 9. (b) The α-effect is defined: Hoz, S.; Buncel, E. *Isr. J. Chem.* **1985**, *24*, 313. (c) Gordillo, B.; Guadarrama, G. Kinetics of Isomerization of *cis* Cyclic Six Membered Phenyl Phosphite Esters. In *1st J. Organomet. Chem. Conference on Applied Organometallic Chemistry;* 1993; p 36.

(15) If the reaction is carried out at room temperature, a mixture with the *trans*-**1** isomer predominant is obtained. The concentration of phenoxide during the reaction is controlled by the slow addition of TEA to a mixture of both reactants as indicated in the Experimental Section.

(16) McEwen, W. E. *Top. Phosphorus Chem.* **1965**, *2*, 1. See also ref 12b.

(17) Because of the participation of stereoelectronic effects in 1,3-dioxaphosphorinanes, the conformation in the thionophosphates is expected to be different from that of the phosphites (see ref 12b).

Table 2. ^{1}H NMR Backbone Coupling Constants (in Hertz) for Phosphites 1 and 2[a]

coupling constants	compound			
	cis-**1**	*trans*-**1**	*eq-cis*-**2**	*ax-cis*-**2**
$^3J_{H_{4a}H_{5a}}$	4.6	11.2	11.9	9.8
$^3J_{H_{4a}H_{5e}}$	6.2	2.6	3.4	5.4
$^3J_{H_{6a}H_{5a}}$	4.6	11.2	11.9	9.8
$^3J_{H_{6a}H_{5e}}$	7.0	2.6	3.4	5.4
$^3J_{H_{6e}H_{5a}}$	8.3	4.6	–	–
$^3J_{H_{6e}H_{5e}}$	4.0	2.3	–	–
$^3J_{H_{4a}H_a}$	6.6	5.9	6.2	6.4
$^3J_{H_{6a}H_a}$	–	–	6.2	6.4
$^2J_{H_{5a5e}}$	14.2	13.9	14.5	13.5
$^2J_{H_{6a6e}}$	11.2	10.8	-	-
$^3J_{H_{4a}P}$	3.3	2.6	3.4	2.0
$^4J_{H_{5a}P}$	1.3	-	1.3	1.0
$^4J_{H_{5a}P}$	–	2.6	3.3	2.2
$^3J_{H_{6a}P}$	8.3	2.6	3.4	2.0
$^3J_{H_{6e}P}$	3.3	10.8	–	–

[a] First-order analysis in $CDCl_3$.

As expected,[18] axial OPh phosphites have smaller $^3J_{P\text{-ring}C5}$ coupling constants than do the equatorial ones; i.e., the constant for *cis*-**1** = 11.0 Hz, the constant for *trans*-**1** = 4.4 Hz, the constant for *eq-cis*-**2** = 16.6 Hz, and the constant for *ax-cis*-**2** = 3.3 Hz.

First-order analysis of the ^{1}H NMR spectra and homonuclear decoupling experiments of *trans*-**1**, *eq-cis*-**2**, and *ax-cis*-**2** indicated that in solution (27 °C, $CDCl_3$) the 1,3,2-dioxaphosphorinane ring is in a preferred chair conformation.[19a]

As shown in Scheme 6 for isomeric phosphites **2**, the methylene and methine protons of the ring comprise ABM_2 systems centered at δ 1.85, 2.45, and 4.38 ppm, respectively, for *eq-cis*-**2** and δ 1.66, 1.73, and 4.73 ppm, respectively, for *ax-cis*-**2**. Irradiation at 1.37 ppm (CH_3's at C_4 and C_6) for *eq-cis*-**2** led to decoupling of the methine multiplet to a double of triplets (dt) with $^3J_{HH}$ = 11.9 and 3.4 Hz and $^3J_{HP}$ = 3.4 Hz. On the other hand, irradiation at 1.24 ppm (CH_3's at C_4 and C_6) for *ax-cis*-**2** led to decoupling of the methine multiplet to a doublet of double doublets (ddd) with $^3J_{HH}$ = 9.8 and 5.4 Hz and $^3J_{HP}$ = 2.0 Hz.[19b] Some other coupling constants are shown in Table 2.

For *trans*-**1**, the methylene and methine protons comprise an ABMM'N system (Scheme 6) centered at δ 1.67, 2.13, 3.92, 4.63, and 4.76 ppm. The integrated spectrum indicated that each multiplet was attributable to a single proton. Signals at 1.67 and 2.13 ppm were assigned to methylene A and B protons and signals at 4.63 and 3.92 ppm to methylene M and N protons, and the signal at 4.76 ppm was assigned to the methine M' proton. In the homonuclear decoupling experiment, on irradiation at 1.27 ppm (CH_3 at C_4), the multiplet around 4.76 ppm was found to decouple to a doublet of triplets with $^3J_{HH}$ = 11.2 and 2.6 Hz and $^3J_{PH}$ = 2.6 Hz. By irradiation at the N proton at 3.92 ppm, the doublet of quintuplets at 1.67 ppm was collapsed to a doublet of quartets ($^3J_{HH}$ = 13.9, 2.6, and 2.6 Hz and $^4J_{PH}$ = 2.6 Hz); therefore, the signal was assigned to H_{5e}. The multiplet at 2.13 ppm was collapsed to a broad quartet (J = 13.9, 11.2, and 11.2 Hz), so the signal was assigned to H_{5a}. Selective irradiation of A and B signals led to the determination of the other coupling constants $^3J_{H_eP}$ = 10.8 Hz for H_{6e} and $^3J_{H_aP}$ = 2.6 Hz for H_{6a}, as shown in Table 2. The assignment and all coupling constants strongly support a chair conformation for *trans*-**1**.[19a]

On the other hand, first-order analysis of the ^{1}H NMR spectrum and a homonuclear decoupling experiment of *cis*-**1** suggest that the conformation of the six-membered ring is not a chair but a predominant twist conformation. As illustrated in Scheme 6, the methylene and methine protons of the ring of *cis*-**1** comprise an ABMM'N system with multiplets centered at δ 2.1, 2.28, 4.02, 4.39, and 4.54 ppm. The integrated spectrum of *cis*-**1** indicated that each multiplet was attributable to a single proton. Signals at 2.1 and 2.28 ppm were assigned to methylene A and B protons and signals at 4.02 and 4.54 ppm to methylene M and N protons, and the signal at 4.39 ppm was assigned to the methine M' proton. On irradiation at 1.51 ppm (CH_3 at C_4), the multiplet at 4.39 ppm was found to decouple. Irradiation at 4.54 ppm resulted in collapse of the multiplet at 2.28 ppm into an apparent dt with J = 14.2, 4.6, and 4.6 Hz, split by long-range coupling J = 1.3 Hz, and collapse of the multiplet at 2.1 ppm into a ddd with J = 14.2, 7.3, and 4.6 Hz. Irradiation at δ 2.28 ppm resulted in collapse of the multiplet at 4.54 ppm into an apparent dt with J = 11.2, 4.0, and 3.3 Hz, collapse of the multiplet at 4.39 ppm into another multiplet with J = 6.7, 6.2, and 3.3 Hz, and collapse of the multiplet at 4.02 ppm into a ddd with J = 11.2, 7.9, and 4.6 Hz.[20] The Altona calculated coupling constants[21] of *cis*-**1** suggested also that the conformation of the six-membered ring in this case is not a chair but a predominant twist conformation as shown in Scheme 7.[22,23]

In tricovalent P derivatives, the $^2J_{PC}$ coupling constant is dominated by the proximity of the phosphorus lone pair to the coupled carbon atom. In general, coupling is large when the lone pair is close and it is quite small when remote.[18a] The lack of a coupling constant $^2J_{PC_6}$ compared with the $^2J_{PC_4}$ = 5.5 Hz for *cis*-**1** (Table 3) supports a twist conformation, as that proposed in Scheme 7,[24] as the major component of an equilibrium of twist-boat conformations where the chair conformation is not likely.

(18) (a) Quin, L. D. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis;* Verkade, J. G., Quin, L. D., Eds.; VCH Publishers, Inc: Deerfield Beach FL, 1987; p 391. (b) Haemers, M.; Ottinger, R.; Zimmermann, D.; Reisse, J. *Tetrahedron Lett.* **1973**, 2241. (c) Haemers, M.; Ottinger, R.; Zimmermann, D.; Reisse, J. *Tetrahedron* **1973**, 29, 3539. (d) Arbuzov, B. A.; Arshinova, R. P.; Mareev, Y. M.; Vinogradova, V. S. *Dokl. Akad. Nauk SSSR* **1973**, *208*, 849; *Engl. Transl.* **1973**, *208*, 77. (e) Eliel, E. L.; Pietrusiewicz, K. M. ^{13}C NMR of Nonaromatic Heterocyclic Compounds. *Top. Carbon-13 NMR Spectrosc.* **1979**, *3*, 171.

(19) (a) The expected values for six-membered ring phosphites[12b] in chair conformations are $^3J_{H_aH_a}$ = 11.2–11.8 Hz, $^3J_{H_aH_e}$ = 2.2–5.5 Hz, $^3J_{H_aP}$ = 1.7–4.6 Hz, and $^3J_{H_eP}$ = 8–10 Hz. (b) The $^3J_{HH}$ values for *ax-cis*-**2** are slightly deviate from what is expected for a chair conformation. These differences are hard to explain in terms of another conformation because they are at odds with the chair conformation suggested by the ^{13}C NMR spectra: $J_{P(C_{4a})} = J_{P(C_{6a})}$ = 2.2 Hz (Table 3). (c) For a similar analysis in phosphites, see: Kainosho, M.; Nakamura, A. *Tetrahedron* **1969**, *25*, 4071. Bodkin, C. L.; Simpson, P. *J. Chem. Soc. B* **1971**, 1136. Bodkin, C.; Simpson, P. *J. Chem. Soc., Chem. Commun.* **1969**, 829. Bergensen, K.; Albriktensen, P. *Acta Chem. Scand.* **1971**, *25*, 2257.

(20) As noted, double irradiation experiments led to a coupling constant somewhat different (ΔJ < 2 Hz) from those calculated from the single irradiated spectrum (Table 2). This might be a result of a rapid interconversion between twist conformations.

(21) The conformation was calculated by using the Altona software: Cerda-García-Rojas, C. M.; Zepeda, L. G.; Joseph-Nathan, P. *Tetrahedron Comput. Methodol.* **1990**, *3*, 113.

(22) Bentrude et al.[4g] have calculated, by average ^{1}H NMR coupling constants, that the percentage of twist-boat form in *trans*-4-*tert*-butyl-2-methoxy-1,3,2λ^3-dioxaphosphorinane is around 58%.

(23) Despite numerous conformational studies, twist forms for analog phosphites are not unequivocally established: Nelson, K. A.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1983**, *105*, 7752. Other high-energy conformations such as diaxial chair or boat in similar phosphites are nevertheless less likely.[7]

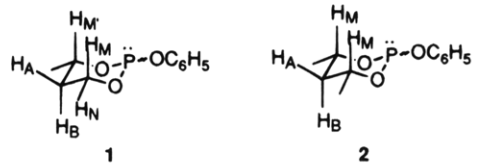
(24) A Dreiding model of the twist conformation of *cis*-**1** shown in Scheme 7 indicated that the distance between the $P_{\text{lone pair}}$ and C_6 is almost 20% longer than the distance between the $P_{\text{lone pair}}$ and C_4.

Table 3. Room-Temperature ^{13}C NMR Signal Assignments in Phosphites 1 and 2[a]

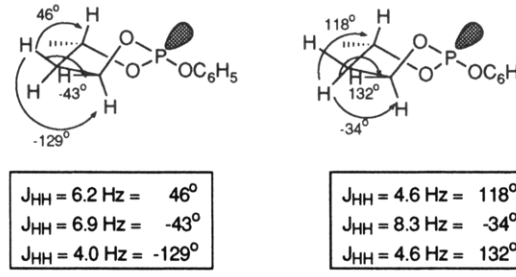
compound	C_4	C_5	C_6	$C_{4\alpha}$	$C_{6\alpha}$	$C_{1'}$	$C_{2',6'}$	$C_{3',5'}$	$C_{4'}$
cis-**1**	69.92	32.55	58.3	22.9	–	152.92	119.93	123.06	129.56
	(5.5)	(11.0)				(7.7)			
trans-**1**	66.38	35.47	60.25	22.85	–	*b*	119.64	129.59	123.07
	(2.2)	(4.4)	(2.2)	(3.3)			(7.7)		
eq-cis-**2**	71.09	40.1	71.09	23.84	23.84	153.03	120.2	129.5	122.94
	(6.6)	(16.6)	(6.6)			(6.6)	(7.7)		
ax-cis-**2**	66.78	42.67	66.78	22.71	22.71	152.92	119.62	129.56	122.98
	(3.3)	(3.3)	(3.3)	(2.2)	(2.2)	(7.7)	(7.7)		

[a] Chemical shift (δ) in ppm from TMS in $CDCl_3$. J_{PC} in parentheses in hertz. [b] The signal was not observed.

Scheme 6



Scheme 7



The undecoupled ^{31}P NMR spectrum of *cis*-**1** (δ 125.24 ppm, broad signal) also confirmed that *cis*-**1** was not in a single chair conformation as in the case of its isomer *trans*-**1** (δ 122.2 ppm, doublet with $^3J_{PH} = 11.1$ Hz). From Table 2, the sum $^3J_{H_{6e}P} + {}^3J_{H_{6a}P}$ is 13.4 Hz for *trans*-**1** and 11.6 Hz for *cis*-**1**, the latter value being lower than what was expected for a chair conformation (12.6–13.9 Hz).[25]

The analyses at low temperatures of *cis*-**1**, *trans*-**1**, *eq-cis*-**2**, and *ax-cis*-**2** were performed in toluene-d_8 by ^{31}P NMR. No decoalescence was observed in any case; however, the temperature dependance of the chemical shift and half-widths $\nu_{1/2}$ suggest that the *cis* OPh isomer in the 4-methyl series consists of a mixture of conformers in mobile equilibrium (Table 4). A broader and upfield-shifted signal for *cis*-**1** was observed, compared with the same in *trans*-**1** ($\nu_{1/2}$ at -90 °C $- \nu^\circ_{1/2}$ is equal to 14.1 Hz for *cis*-**1** and equal to 11.3 Hz for *trans*-**1**; $(\Delta\delta)_{27\rightarrow-90°C}$ is 1.23 ppm for *cis*-**1** and 0.48 ppm for *trans*-**1**). On the other hand, *eq-cis*-**2** presented a large upfield shift at low temperaures ($(\Delta\delta)_{27\rightarrow-90°C} = 1.94$ ppm); however the lack of a significant change in the half-widths $\nu_{1/2}$ of the signal (i.e., $\nu_{1/2}$ at -90 °C $- \nu^\circ_{1/2} = 2.8$ Hz) allows us to discard the contribution of more than one conformation for this molecule.

Conclusion

A method for the synthesis of six-membered ring phosphites with equatorial OPh was found. In these phenyl phosphites, a single methyl group on the equatorial position at C_4 is not enough to lock the conformation of the equatorial isomer because it has to compete with the axial preference of the OPh group on phosphorus in addition to the destabilizing four-electron $n_O - n_P$ stereoelectronic interaction.

The axial and equatorial OPh *cis*-4,6-dimethyl phosphites are, on the contrary, potentially conformational homogeneous systems with predominant chair conformations.

Table 4. The Dynamic Exchange Half-Width ($\nu_{1/2}$) in Hertz[a] and Chemical Shift[b,c] of ^{31}P NMR signals for Phosphites 1 and 2

	compound			
temp (°C)	*cis*-**1**	*trans*-**1**	*eq-cis*- **2**	*ax-cis*-**2**
27	5.4[d]	4.3[d]	5.3[d]	3.6[d]
	(125.41)	(122.59)	(124.46)	(120.5)
−20	14.3	12.5	–	–
	(124.88)	(122.39)		
−30	–	–	7.1	4.0
			(123.59)	(120.2)
−60	16.4	14.9	–	–
	(124.46)	(122.22)		
−80	16.7	15.4	–	–
	(124.28)	(122.15)		
−90	19.5	15.6	8.1	6.3
	(124.18)	(122.11)	(122.52)	(119.87)

[a] Estimated error in values is ±1.2 Hz. [b] Spectra in toluene-d_8. [c] Chemical shift (δ) in parentheses in ppm from external H_3PO_4. [d] These values could be considered as the line width due to spin–spin relaxation ($\nu^\circ_{1/2}$) for each compound because, at 27 °C, the signals are sharp, indicating that at this temperature the process is at the fast exchange limit: Macomber, R. S. *NMR Spectroscopy. Basic Principles and Applications*; Harcourt Brace Jovanovich Publishers: New York, 1988; p 174.

Experimental Section

Spectral Analyses. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 270 and 67.5 Hz, respectively, and are referenced to internal $(CH_3)_4Si$. ^{31}P NMR spectra were recorded at 109.25 MHz in $CDCl_3$ and are reported in ppm downfield (+) from external 85% H_3PO_4. Low-temperature NMR analyses of **1** and **2** were performed in toluene-d_8. The mass spectrometry analyses were obtained at 70 eV.

Syntheses. Cyclic phosphites *trans*-**1** and *ax-cis*-**2** were synthesized according to a literature procedure[4a] using phosphorus trichloride and the corresponding diols. The resulting phosphorochloridites *trans*-**3** and *ax-cis*-**4** were purified by distillation and reacted with phenol in triethylamine. The *cis* isomers **1** and **2** were obtained by careful addition of the triethylamine to a mixture of the corresponding phosphorochloridite *trans*-**3** and *trans*-**4**, respectively, and phenol. Moreover, compounds should be treated carefully since some are powerful phosphorylating agents.

Phosphites **1** and **2** were analyzed in crude form since the attempts at purification failed.[26a] Column chromatography of the *cis* isomers under nitrogen using mixtures of hexane and ethyl acetate as the eluent caused an isomerization to the *trans* diastereomer and decomposition. The distillation of the *trans*-**1** and *ax-cis*-**2** isomers, on the other hand, at ca. 80 °C/1.3 mmHg led to decomposition.

(25) (a) Bentrude, W. G.; Setzer, W. N. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH Publishers, Inc: Deerfield Beach FL, 1987; 365. (b) Bentrude, W. G.; Tan, H.-W. *J. Am. Chem. Soc.* **1973**, *95*, 4666.

***trans*-2-Chloro-4-methyl-1,3,2λ³-dioxaphosphorinane (3).** A racemic (±)-mixture of 1,3-butanediol (18.8 mL, 210 mmol) was added dropwise to a solution of 19.5 mL of phosphorus trichloride (223.5 mmol) in 50 mL of methylene chloride at room temperature under nitrogen. The product was distilled under vacuum (32 °C/2.8 mmHg) until the residue turned orange. The product was kept under nitrogen and refrigerated until it was used: yield 19.1 g, 59%; ^{1}H NMR δ 1.30 (d, J = 5.9 Hz, 3 H), 1.74 (dm, J = 13.9, 4.6, 4.0 Hz, J_{HP} = 2.0 Hz, 1 H), 2.15 (m, J = 13.9, 4.6 Hz, J_{HP} = 1.3 Hz, 1 H), 4.05 (tdd, J = 10.5, 4.0 Hz, J_{HP} = 10.5 Hz, 1 H), 4.65 (m, 1 H), 4.75 (m, 1 H); ^{13}C NMR δ 22.44 (d, J_{CP} = 2.2 Hz), 35.14 (d, J_{CP} = 4.4 Hz), 62.01 (d, J_{CP} = 3.3 Hz), 68.8 (d, J_{CP} = 3.3 Hz); ^{31}P NMR δ 151.9 (s).

***trans*-2-Phenoxy-4-methyl-1,3,2λ³-dioxaphosphorinane (1).** To a solution of 3.78 g (40.21 mmol) of phenol and 96 mL of anhydrous Et_2O, under nitrogen, was added dropwise 5.76 mL (41.33 mmol) of triethylamine. After 30 min, the phosphorochloridite *trans*-**3** (6 g, 38.83 mmol) was added dropwise to the mixture while it was stirred under nitrogen for an additional 30 min. The mixture was then filtered, and the solvent was removed (heated rotary evaporator) until no traces were found to afford 7.15 g (87%) of an oil containing 86–93% of the compound:[26] ^{1}H NMR δ 1.26 (d, 3 H), 1.67 (dm, 1 H), 2.13 (m, 1 H), 3.92 (tdd, 1 H), 4.63 (~tt, 1 H), 4.76 (~q, 1 H), 7.05–7.21 (d, 3 H), 7.14–7.41 (m, 2 H); ^{31}P NMR δ 122.2 (d, $^3J_{PH}$ = 11.1 Hz); MS m/z 212 (M^+), 159 (M^+ − 53), 140 (M^+ − 72), 119 (M^+ − 93), 94 (M^+ − 118), 77 (M^+ − 135), 55 (M^+ − 157).

***cis*-2-Phenoxy-4-methyl-1,3,2λ³-dioxaphosphorinane (1).** To a solution of 1 g (6.47 mmol) of the phosphorochloridite *trans*-**3**, 0.63 g (6.7 mmol) of phenol, and 16 mL of anhydrous ethyl ether under nitrogen at −78 °C was added slowly dropwise 0.96 mL (6.89 mmol) of triethylamine. When the addition was complete, the resultant triethylammonium chloride was filtered off, and the solvent was removed with a rotary evaporator without heating. Traces of solvent were removed under reduced pressure to afford 1.11 g (81%) of an oily product containing 86–90% of the compound:[26] ^{1}H NMR δ 1.51 (d, 3 H), 2.10 (m, 1 H), 2.28 (m, 1 H), 4.02 (m, 1 H), 4.39 (m, 1 H), 4.54 (m, 1 H), 7.08 (d, 3 H), 7.29 (m, 2 H); ^{31}P NMR δ 125.24 (broad signal).

***r*-2-Phenoxy-2-thio-*trans*-4-methyl-1,3,2λ⁵-dioxaphosphorinane (5).** To a solution of 1.03 g (4.86 mmol) of phosphite *trans*-**1** and 5 mL of carbon disulfide was added 0.16 g (5.0 mmol) of sulfur powder. After the suspension was stirred for 30 min, the excess of sulfur was filtered off, and the solvent was removed with a rotary evaporator to afford a solid 0.99 g (86%). Recrystallization from 80% hexanes/ethyl acetate solution yield 0.71 g (62%) of needles (mp 70–72 °C): ^{1}H NMR δ 1.47 (d, 3 H), 1.81 (dm, 1 H), 2.19 (m, 1 H), 4.42 (dddd, 1 H), 4.59 (~tt 1H), 4.83 (m, 1 H), 7.21 (m, 3 H), 7.35 (m, 2 H); ^{13}C NMR δ 22.01 (d, J_{CP} = 8.9 Hz), 32.61 (d, J_{CP} = 5.5 Hz), 68.04 (d, J_{CP} = 9.9 Hz), 77.11 (d, J_{CP} = 8.8 Hz), 119.87 (d, J_{CP} = 5.5 Hz), 124.84 (s), 129.43 (s), 150.38 (d, J_{CP} = 6.6 Hz); ^{31}P NMR δ 55.81 (d, J_{PH} = 24.7 Hz) (these data are consistent with previously reported values[28]); MS m/z 244 (M^+), 190 (M^+ − 54), 110 (M^+ − 134), 94 (M^+ − 150), 77 (M^+ − 167).

***r*-2-Phenoxy-2-thio-*cis*-4-methyl-1,3,2λ⁵-dioxaphosphorinane (5).** To a solution of 1.03 g (4.86 mmol) of the phosphite *cis*-**1** and 5 mL of carbon disulfide under nitrogen at −78 °C was added 0.16 g (5.0 mmol) of sulfur powder. After the mixture was stirred for 7 h at −78 °C, the excess of sulfur was filtered off, and the solvent was removed with a rotary evaporator. The oily residue was chromatographed on silica gel using a 90% hexanes/ethyl acetate solution to give 0.81 g of the corresponding thionophosphate (70%). A small amount of the sample was distilled under reduced pressure: bp 86 °C/3 mmHg; ^{1}H NMR δ 1.44 (dd, 3 H), 1.90 (m, 1 H), 1.98 (m, 1 H), 4.42 (qt, 1 H), 4.61 (m, 1 H), 4.89 (m, 1 H), 7.21 (d, 3 H), 7.35 (m, 2 H); ^{13}C NMR δ 22.0 (d, J_{CP} = 7.7 Hz), 33.0 (d, J_{CP} = 6.6 Hz), 66.8 (d, J_{CP} = 5.5 Hz), 76.4 (d, J_{CP} = 5.5 Hz), 117.2 (d, J_{CP} = 7.4 Hz), 125.5 (s), 129.6 (s), 150.5 (d, J_{CP} = 7.7 Hz); ^{31}P NMR δ 60.03 (d, J_{HP} = 22 Hz) (these data are consistent with previously reported values[28]); MS m/z 244 (M^+), 190 (M^+ − 54), 110 (M^+ − 134), 94 (M^+ − 150), 77 (M^+ − 167), 55 (M^+ − 189).

***meso*-2,4-Pentanediol.** A mixture of *meso*- and *d,l*-pentanediols (50:50) was obtained from acetyl acetone and sodium borohydride. A *meso*-enriched mixture (84%) was also obtained following the procedure in the literature.[29]

2-Chloro-4,6-dimethyl-1,3,2λ³-dioxaphosphorinane (4). This compound was prepared by reaction between a mixture of 5 g (48.0 mmol) of *meso*- and *d,l*-pentanediols (84:16) and 4.19 mL (48.02 mmol) of phosphorus trichloride in 20 mL of methylene chloride following the procedure described for *trans*-**3**. The product was distilled at 40 °C/4 mmHg, affording 5 g (62%) of a mixture of axial chloro-*cis*-4,6-dimethyl and axial chloro-*trans*-4,6-dimethyl **4** in a 92.4:7.6 ratio. The product was kept under nitrogen and refrigerated until it was used. *ax-cis*-**4**: ^{1}H NMR δ 1.29 (d, J = 5.9 Hz, 6H), 1.78 (m, J = 14.5 Hz, 1 H), 1.8 (m, 1 H), 4.76 (m, J = 5.9 Hz, 2 H); ^{13}C NMR δ 22.21 (d, J_{CP} = 2.2 Hz, 2 C), 42.28 (d, J_{CP} = 3.3 Hz), 69.36 (d, J_{CP} = 3.3 Hz); ^{31}P NMR δ 148.68 (s). *ax-trans*-**4**: ^{31}P NMR δ 150.37 (s).

***ax*-2-Phenoxy-*cis*-4,6-dimethyl-1,3,2λ³-dioxaphosphorinane (2).** This compound was prepared by reaction of 2.1 g (12.46 mmol) of a mixture of *ax-cis*- and *ax-trans*-**4** in a 92.4:7.6 ratio with 1.36 g (14.47 mmol) of phenol, 2.02 mL (14.49 mmol) of triethylamine, and 14.5 mL of anhydrous ethyl ether as described for *trans*-**1**. A crude yield of 2.2 g (78%) of an oily product contained 85–90%[26] of a mixture: 93.5% *ax-cis*-**2** and 6.5% *ax-trans*-**2**. *ax-cis*-**2**: ^{1}H NMR δ 1.24 (d, 6 H), 1.66 (m, 2 H), 4.73 (m, 2 H), 7.08 (d, 3 H), 7.3 (m, 2 H); ^{31}P NMR δ 120.3 (s). *ax-trans*-**2**: ^{31}P NMR δ 123.8 (d, J_{PH} = 11.0 Hz).

***eq*-2-Phenoxy-*cis*-4,6-dimethyl-1,3,2λ³-dioxaphosphorinane (2).** This compound was prepared by reaction of 1.03 g (6.11 mmol) of a mixture of *ax-cis*- and *ax-trans*-**4** in a 92.4:7.6 ratio with 0.58 g (6.17 mmol) of phenol, 0.87 mL (6.24 mmol) of triethylamine, and 14 mL of anhydrous ethyl ether as described for *cis*-**1**. A crude yield of 1.13 g (82%) of an oily product contained 89–92%[26] of a mixture of the *eq-cis*- and *ax-trans*-**2** (93:7). *eq-cis*-**2**: ^{1}H NMR δ 1.37 (d, 6 H), 1.85 (dq, 1 H), 2.45 (~q, 1 H), 4.38 (m, 2 H), 7.08 (d, 3 H), 7.3 (m, 2 H); ^{31}P NMR δ 124.66 (s).

***ax*-2-Phenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ⁵-dioxaphosphorinane (6).** This compound was prepared by reaction of 1.0 g (4.42 mmol) of a mixture of *ax-cis*- and *ax-trans*-**4** in a 92.7:7.3 ratio with 0.14 g (4.42 mmol) of sulfur powder in 4.7 mL of carbon disulfide as described for *r-trans*-**5**. A crude yield of 0.95 g (83%) was obtained. *ax-cis*-**6** was purified by recrystallization from 85% hexanes/ethyl acetate solution to give 0.69 g (60%): mp 120–122 °C; ^{1}H NMR δ 1.43 (d, 3 H), 1.82 (m, 1 H), 1.88 (m, 1 H), 4.79 (m, 2 H), 7.19 (m, 3 H), 7.35 (m, 2 H); ^{13}C NMR δ 21.88 (d, J_{CP} = 9.9 Hz), 39.92 (d, J_{CP} = 4.4 Hz), 76.19 (d, J_{CP} = 8.8 Hz), 119.79 (d, J_{CP} = 5.5 Hz), 124.71 (s), 129.38 (s), 150.46 (d, J_{CP} = 7.0 Hz); ^{31}P NMR δ 55.66; MS m/z 258 (M^+), 217 (M^+ − 41), 191 (M^+ − 67), 172 (M^+ − 86), 94 (M^+ − 164), 69 (M^+ − 189). Anal. Calcd for $C_{11}H_{15}O_3PS$: C, 51.16; H, 5.85. Found: C, 50.45; H, 5.92.

***eq*-2-Phenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ⁵-dioxaphosphorinane (6).** This compound was prepared by reaction of 0.4 g (1.76 mmol) of a mixture of *eq-cis*- and *ax-trans*-**4** in a 92.9:7.1 ratio with 0.057 g (1.78 mmol) of sulfur powder in 2.0 mL of carbon disulfide as described for *r-cis*-**5**; this reaction produced crude yield of 0.38 g (84%). The residue was chromatographed on silica gel using a 90% hexanes/ethyl acetate solution to give 0.34 g (75%) of *eq-cis*-**6**. A little amount of the sample was distilled under reduced pressure: bp = 91 °C/1.6 mmHg; ^{1}H NMR δ 1.39 (d, 3 H), 1.70 (~dt, 1 H), 1.89

(26) (a) Because 2-X-1,3,2λ³-dioxaphosphorinanes are sensitive to humidity, 2-hydro-2-oxo-1,3,2λ⁵-dioxaphosphorinanes[27] formed during workup were observed in crude oils as byproducts in percentages up to 10%; some other minor contaminants (less than 2%) were triethylammonium chloride or residual phenol. (b) Range values are the result of several experiments.

(27) Mosbo, J. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 204.

(28) Majoral, J.-P.; Navech, J. *Bull. Soc. Chim. Fr.* **1971**, *1*, 95.

(29) Pritchard, G. J.; Vollmer, R. J. *J. Org. Chem.* **1963**, *28*, 1545.

(~dq, 1 H), 4.83 (m, 2 H), 7.20 (m, 3 H), 7.35 (m, 2 H); ^{13}C NMR δ 22.1 (d, J_{CP} = 10.0 Hz), 41.03 (d, J_{CP} = 4.4 Hz), 75.37 (d, J_{CP} = 5.5 Hz), 121.32 (d, J_{CP} = 4.4 Hz), 125.5 (d, J_{CP} = 2.2 Hz), 129.46 (s); ^{31}P NMR δ 60.28; MS m/z 258 (M^+), 191 (M^+ − 67), 172 (M^+ − 86), 149 (M^+ − 109), 94 (M^+ − 164), 69 (M^+ − 189). Anal. Calcd for $C_{11}H_{15}O_3PS$: C, 51.16; H, 5.85. Found: C, 51.44; H, 5.98.

Acknowledgment. We are grateful to Prof. L. D. Quin as well as the reviewers for helpful comments. This work was supported by CONACYT (México) Grant D111-904288.

JO941296S