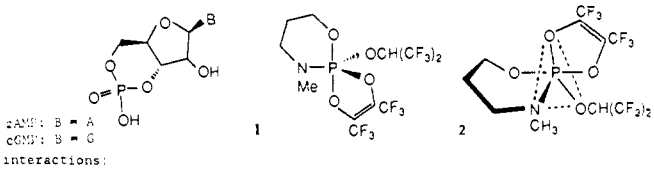
Pentacovalent Phosphorus-Containing Models of P(V) H_2O- or Enzyme-cAMP Adducts. Nonchair Conformations of the Phosphorus-Containing Rings As Determined by ^1H NMR Spectroscopy and X-ray Crystallography

Jaehoon H. Yu, Atta M. Arif, and Wesley G. Bentrude*

Contribution from the Department of Chemistry, University of Utah, Salt Lake City, Utah 84112.
Received February 20, 1990

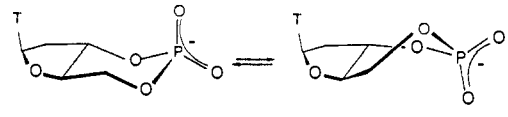
Abstract: A series of pentacovalent phosphorus-containing, P(V), molecules (**3–6**), designed as models of P(V) H_2O–cAMP or enzyme–cAMP adducts (or transition states) were prepared and studied by NMR (**3–6**) and X-ray crystallography (**6**). The preparation of **3–6** by reaction of the phosphite precursors with $(CF_3)_2CO$ or $(CF_3)_2COCO(CF_3)_2$ was shown to proceed with retention of configuration at phosphorus. The X-ray structure of **6** showed it to be close to trigonal bipyramidal with the six-membered, 1,3,2-dioxaphosphorinane ring attached equatorial/apical to phosphorus. The oxygen equivalent to the O5′ of cAMP is in the apical position. The ring is in a twist conformation in the crystal. ^1H NMR measurements show the 1,3,2-dioxaphosphorinane ring of **3–6** to be in a nonchair (probably twist) conformation in solution as well. It is concluded that in solution the 1,3,2-dioxaphosphorinane ring of **3–6** is almost certainly apical/equatorial. It is also postulated that for a 1,3,2-oxaza- or dioxaphosphorinane ring attached apical/equatorial to phosphorus a nonchair (boat or twist) conformation is intrinsically more stable than the chair form. It is suggested that a likely principle role of phosphodiesterase in the catalyzed hydrolysis of cAMP is to assure the formation of a cAMP–H_2O adduct with the water and P–O3′ bonds coapical. It is pointed out that if the O3′ apical twist form is formed enzymatically, the *p*-orbital lone pair on O5′ is lined up parallel to the apical bonding systems such that it could assist stereoelectronically in the formation of the P(V) adduct and in its rapid scission to form 5′-AMP. The *possibility* is suggested that cAMP may be bound in the twist form and the cAMP–H_2O adduct may be formed directly therefrom in the twist conformation.

The naturally occurring nucleoside cyclic 3′,5′-monophosphates, cAMP and cGMP, play a central role in the regulation of cell



metabolism.[1] The structural requirements for binding cAMP to the regulatory subunit of protein kinases I and II and also to various phosphodiesterases have been determined.[2] The stereochemistries of both enzymic[3] and nonenzymic (base-catalyzed) hydrolysis[4] of cAMP to 5′-AMP have been established. Although the phosphate ring of cAMP is normally in the chair form, as established by X-ray[5] and ^1H NMR[6] work, recently the possibility that a conformational change to a nonchair (boat or twist) conformation might accompany its binding within an enzyme active site has begun to receive attention.

Studies from this laboratory[7b-d] have emphasized the very low change (~2 kcal/mol)[7b] in free energy ($\Delta G°_{CT}$) required to effect the chair to twist interconversion of the phosphate ring of thymidine cyclic 3′,5′-monophosphate, an amount of energy that could be easily supplied by enzyme–substrate interactions:



For the phosphodiesterase-catalyzed hydrolysis of cAMP to its 5′-monophosphate, it has been proposed[8] that pentacovalent phosphorus adducts (or transition states) are formed in the enzyme active site involving cAMP and a water molecule and/or a nucleophilic moiety from the peptide chain of the enzyme itself. Pentacovalent enzyme–cAMP adduct formation following cAMP complexation to the regulatory subunit has also been speculatively suggested[2c,9] as a key step in the dissociation of protein kinase holoenzyme to free the catalytic subunit. No detailed consideration seems to have been given to the conformation of the phosphorus-containing ring of such a P(V) adduct, i.e., whether it would

(1) See, for example, the review series: *Advances in Cyclic Nucleotide Research*; Greengard, P., Robinson, G. A., Sr., Eds.; Raven Press: New York, 1970–1988; Vols. 1–18.

(2) For reviews, see: (a) Revenkar, G. R.; Robins, R. K. In *Handbook of Experimental Pharmacology*; Nathanson, J. A., Kebabian, J. W., Eds.; Springer Verlag: Berlin and Heidelberg, West Germany, 1982; Vol. 58/I, Chapter 2. (b) Miller, J. P. *Adv. Cyclic Nucleotide Res.* **1981**, *148*, 335. (c) Meyer, R. B., Jr. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley Interscience: New York, 1979; Chapter 34, Part II. (d) Miller, J. P. In *Cyclic Nucleotides: Mechanisms of Action*; Cramer, H., Schultz, J., Eds.; Wiley: London 1977; pp 77–105. For selected papers, see: (e) de Wit, R. J. W.; Hekstra, D.; Jastorff, B.; Stec, W. J.; Baraniak, J.; van Driel, R.; van Haastert, P. J. M. *Eur. J. Biochem.* **1984**, *142*, 255. (f) van Haastert, P. J. M.; Dijkgraaf, P. A. M.; Konijn, T. M.; Abbad, E. G.; Petridis, G.; Jastorff, B. *Eur. J. Biochem.* **1983**, *131*, 659. (g) Corbin, J. D.; Rannels, S. R.; Flockhart, D. A.; Robinson-Steiner, A. M.; Tigani, M. C.; Doskeland, S. O.; Suva, R. H.; Suva, R.; Miller, J. P. *Eur. J. Biochem.* **1982**, *125*, 259. (h) O'Brian, C. A.; Roczniak, S. O.; Bramson, H. N.; Baraniak, J.; Stec, W. J.; Kaiser, E. T. *Biochemistry* **1982**, *21*, 4371. (i) de Wit, R. J. W.; Hoppe, J.; Stec, W. J.; Baraniak, J.; Jastorff, B. *Eur. J. Biochem.* **1982**, *122*, 95. (j) Yagura, T. S.; Miller, J. P. *Biochemistry* **1981**, *20*, 879.

(3) For studies with PDE from bovine heart and Baker's yeast, see: (a) Burgers, P. M. J.; Eckstein, F.; Hunneman, D. H.; Baraniak, J.; Kinas, R. W.; Lesiak K.; Stec, W. J. *J. Biol. Chem.* **1979**, *254*, 9959. (b) Coderre, J. A.; Mehdi, S.; Gerlt, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 1872. (c) Cullis, P. M.; Jarvest, R. L.; Lowe, G.; Potter, B. V. L. *J. Chem. Soc., Chem. Commun.* **1981**, 245. (d) Jarvest, R. L.; Lowe, G.; Baraniak, J.; Stec, W. J. *Biochem. J.* **1982**, *203*, 461.

(4) Mehdi, S.; Coderre, J. A.; Gerlt, J. A. *Tetrahedron* **1983**, *39*, 3483.

(5) Varughese, K. I.; Lu, C. T.; Kartha, O. *J. Am. Chem. Soc.* **1982**, *104*, 3398.

(6) Blackburn, B. J.; Lapper, R. D.; Smith, I. C. P. *J. Am. Chem. Soc.* **1973**, *95*, 2873.

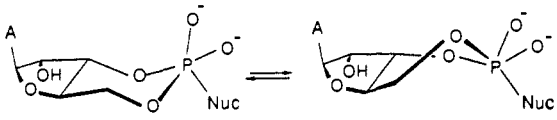
(7) (a) For use of $^3J_{HP}$ in conformational analysis, including chair–twist equilibria, see the review: Bentrude, W. G.; Setzer, W. N. In *^{31}P NMR Spectroscopy in Stereochemical Analysis: Organic Compounds and Metal Complexes*; Verkade, J. G., Quin, L., Eds.; VCH Publishers, Inc.: Deerfield Beach, FL, 1987; Chapter 11. (b) Nelson, K. A.; Bentrude, W. G; Setzer, W. N.; Hutchinson, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 4058. (c) Sopchik, A. E.; Bajwa, G. S.; Nelson, K. A.; Bentrude, W. G. In *Phosphorus Chemistry*; ACS Symposium Series 171; Quin, L. D., Verkade, J., Eds.; American Chemical Society: Washington, DC, 1981; pp 217–220. (d) Sopchik, A. E.; Bentrude, W. G. *Tetrahedron Lett.* **1980**, *21*, 4679.

(8) See e.g.: References 2f, 3a, 4, and 9.

(9) (a) van Ool, P. J. J. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 119. (b) van Ool, P. J. J. M.; Buck, H. M. *Eur. J. Biochem.* **1982**, *121*, 329. (c) van Ool, P. J. J. M.; Buck, H. M. *Recl. Trav. Chim Pays-Bas* **1981**, *100*, 79.

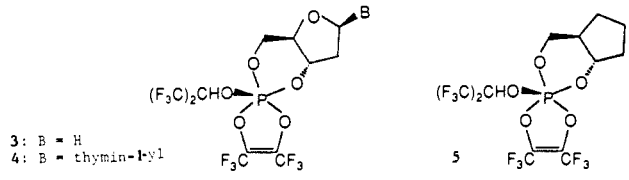
0002-7863/90/1512-7451$02.50/0

reasonably be a chair or a twist(boat) form:



Indeed, until recently, it was not certain that the sort of ^1H NMR studies applied successfully to the conformational analysis of three- and four-coordinate phosphorus rings in cyclic nucleotide like molecules derived from thymidine[7] would be valid with pentacovalent analogues. However, studies of a closely related pentacovalent phosphorus-containing six-membered-ring system, the 1,3,2-oxazaphosphorinanes (e.g., **1**), demonstrated the presence of three-bond coupling constants, J_{HCOP} and J_{HCNP}, which responded in a Karplus-like manner to changes in dihedral angles HCOP and HCNP.[10] In fact a nonchair conformation(s), approximated by **2**, was seen to be populated by **1**.

The work on the nonchair conformation of **1** was followed by *preliminary accounts*[11] *of the study of P(V) derivatives 3 and 4.*



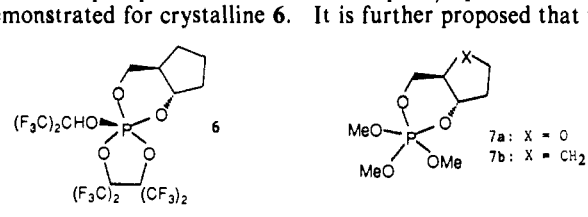
3: B = H
4: B = thymin-1-yl

5

which serve as models for cAMP–enzyme or cAMP-H_2O adducts (or transition states) in biological systems. The P(V)-containing rings of both diastereomers of **3** were clearly shown by ^1H NMR measurements to be largely if not completely in nonchair conformations.

In the present paper we report the results of NMR investigations of the thymidine-based P(V) model system, **4**, the carbocyclic analogues **5** and **6**, and a full account of the study of **3**, along with a single-crystal X-ray structure of **6**. These comparisons are of special interest because of the suggestion[9a] that the 2′-deoxyribose-like compound **7a** and its carbocyclic congener **7b** have intrinsically different preferences for the attachment of the six-membered ring to phosphorus, i.e., diequatorial vs apical/equatorial.

The inescapable finding for **3–6** is that *a nonchair (boat/twist) conformation is populated in every case.* It also is concluded that the most reasonable assignment for the attachment of the P(V) 1,3,2-dioxaphosphorinane for **3–6** is apical/equatorial, as is demonstrated for crystalline **6**. It is further proposed that the



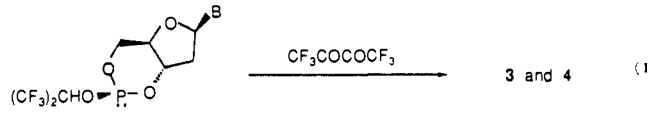
6

7a: X = O
7b: X = CH_2

nonchair conformation provides a potential stereoelectronic advantage in the phosphodiesterase-catalyzed hydrolysis of cAMP that could accelerate both the addition of water and the subsequent cleavage of the P–O3′ bond to yield 5′-AMP.

Results

Preparation of 3–6. Phosphoranes **3–6** were prepared by the low-temperature reaction[12] of the phosphite precursors **8–10** with $CF_3COCOCF_3$ (**3–5**) or with hexafluoroacetone (**6**), as illustrated for **3** and **4** by eq 1. Phosphoranes **3** and **5** were purified in 78

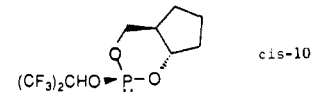


cis-8: B = H
cis-9: B = thymin-1-yl

(1)

and 80% yields, respectively. Product **5** was distilled to analytical purity, while distilled **3** was established by ^{31}P and ^1H NMR to be >90% pure and gave a correct M^+ HRMS peak. The thymidine-based phosphorane **4**, a foam, was seen to be >95% pure by ^1H and ^{31}P NMR and was analytically pure as prepared (C, H, N, within 0.4% of theory) in 92% yield. Analytically pure white crystalline **6** was obtained (97% yield).

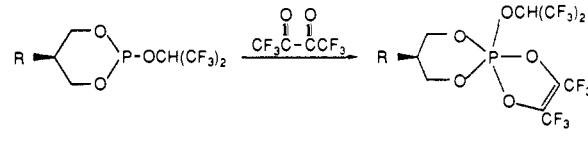
Configuration at Phosphorus for 3–6. Potentially two diastereomeric phosphoranes can result from reaction of phosphites **8–10**



cis-10

with the corresponding ketone. An example is phosphorane **4**. In one diastereomer the $(CF_3)_2CHO$ group is on the same side of the trans-fused ring system as the thymin-1-yl group. This is designated as the cis phosphorane. Phosphoranes **3**, **5**, and **6** are similarly designated cis or trans. The so-called cis diastereomer is depicted for **3–6**. For simplicity these phosphoranes will be treated as though a single enantiomer were present, as illustrated in the structures given, even though as prepared each diastereomer of **3**, **5**, and **6** exists as a racemic pair of enantiomers.

The starting phosphite in each case was prepared as an approximately 95/5 cis/trans mixture of diastereomers[13] and yielded diastereomers of the corresponding phosphorane in close to the same ratio. The high degree of *stereospecificity* of the reaction was more carefully verified for **10** and for two simplier phosphites, **11** (R = Ph) and **12** (R = *t*-Bu). Thus, as determined by



cis and trans 11: R = Ph
cis and trans 12: R = *t*-Bu

cis and trans 13: R = Ph
cis and trans 14: R = *t*-Bu

quantitative ^{31}P NMR, an initial cis/trans ratio of **11** of 35/65 reacted very cleanly with $CF_3COCOCF_3$ to give the diastereomeric product phosphoranes, **13**, in 25/75 ratio. Similarly, diastereomeric phosphoranes **14** in cis/trans ratio 96/4 were obtained on reaction of the same ketone with phosphite **12** featuring a 92/8 cis/trans ratio of diastereomers. Phosphite **10** (cis/trans = 96/4) gave phosphorane **5** in cis/trans ratio 92/8 in a third carefully monitored study.

It is reasonable that the reactions discussed above are not only highly *stereospecific*, as shown experimentally, but also occur with *retention* of configuration at phosphorus. That means that the cis structures shown for **3–6** resulted from the corresponding cis phosphites, **8–10**. The reasonableness of the retentive stereochemistry is demonstrated in eq 2. Initial formation of **15** clearly retains the configuration about phosphorus. Closure of **15** to pentacovalent derivative **16** will logically occur via apical introduction of the five-membered-ring oxygen during facial attack of the enolate opposite O2, O1, or $(CF_3)_2CHO$. In the case shown, attack is opposite O1. The retentive nature of this reaction was proven by the single-crystal X-ray structure of **6** formed from *cis*-**10** (see below).

Inversion of configuration at phosphorus (interconversion of cis and trans diastereomers), once the apical/equatorial attachment

(10) Yu, J. H.; Bentrude, W. G. *J. Am. Chem. Soc.* **1988**, *110*, 7897.
(11) Yu, J. H.; Bentrude, W. G. *Tetrahedron Lett.* **1989**, *30*, 2195. Bentrude, W. G.; Yu, J. H.; Sopchik, A. E. *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, *51/52*, 73.
(12) For an early example of the use of $CF_3COCOCF_3$, see: Ramirez, F.; Kugler, H. J. *Phosphorus Sulfur Relat. Elem.* **1972**, *2*, 203. A wide variety of phosphoranes have been made with $(CF_3)_2C{=}O$ as reactant by the group of G.-V. Roeschenthaler. See, for example: Bohlen, R.; Hacklin, H.; Heine, J.; Offermann, W.; Roeschenthaler, G.-V. *Phosphorus Sulfur Relat. Elem.* **1986**, *27*, 321.
(13) The assignment of diastereomer configuration at phosphorus is easily done on the basis of relative ^{31}P NMR chemical shifts. See data compiled in the following: Maryanoff, B. A.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187.

Table I. Crystal Data for **6** at −140 °C

mol formula	$C_{16}H_{14}O_5F_{16}P$
mol wt	659.23
space group	*Pbca* (No. 61)
cell dimensions	
a, Å	12.858 (2)
b, Å	16.920 (3)
c, Å	19.536 (3)
V, Å^3	4250.42
Z	8.0
D_{calcd}, g cm^{-3}	2.063
radiation, Å	λ (Cu) 1.5418
2θ range, deg	4.00–120.00
scan technique	θ/2θ
scan width, deg	0.6000 + 0.1400 tan θ
no. of reflections used	2859
absorption coeff, cm^{-1}	29.880
data to parameter ratio	8.099
shift in error ratio	0.006
R	0.0567
R_W	0.0656

Table II. Selected Bond Distances for **6**[a]

atoms	distance, Å	atoms	distance, Å
P–O1	1.655 (3)	P–O5	1.621 (3)
P–O2	1.719 (3)	C5–O5	1.468 (6)
P–O3	1.576 (3)	C3–O3	1.466 (6)
P–O4	1.602 (3)		

[a] Estimated standard deviations in parentheses.

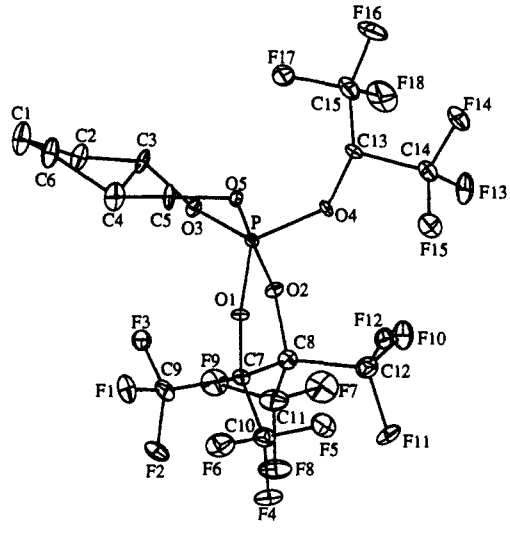


Figure 1. ORTEP perspective view of **6**.

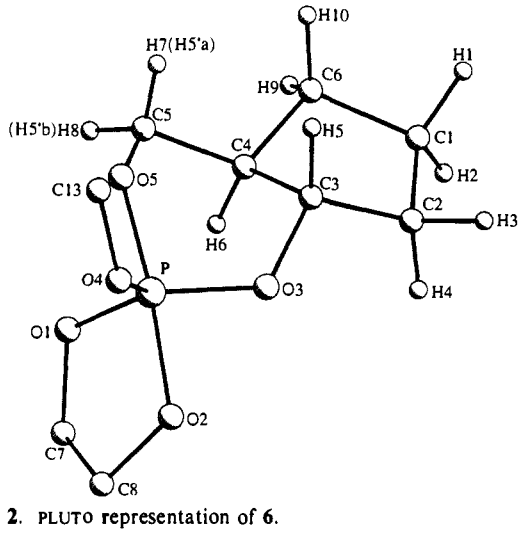
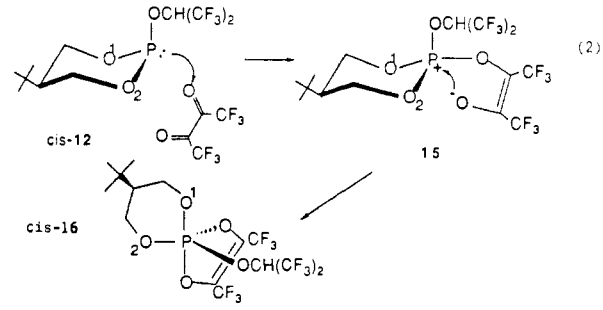


Figure 2. PLUTO representation of **6**.



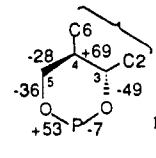
of the ring is established, is a relatively high energy process,[14] since it requires permutational exchange through a pentacovalent intermediate with the five-membered ring diequatorial. This only occurs at the higher temperatures required for distillation of these adducts. Thus, on distillation the percentage of the minor (trans) isomer of **3** and **5** increased. The resulting ratios (cis/trans: **3**, 78/22; **5**, 71/29) presumably are closer to the thermodynamic ratios, but there is no proof that they have been fully equilibrated.

Single-Crystal X-ray Structure of 6. Crystal data for **6**, recrystallized from benzene, are compiled in Table I. An ORTEP perspective view of the molecule, along with the labeling scheme, is given in Figure 1. Figure 2 is a PLUTO drawing with ring hydrogens attached but without the CF_3 substituents. In it the conformation of the five-membered carbocyclic ring, the torsional angles involving hydrogens 7(5a) and 8(5b) and the bonded atoms C5–O5–P, and the near-trigonal-bipyramidal geometry about phosphorus are represented optimally. A PLUTO drawing intended to clarify further the conformation of the 1,3,2-dioxaphosphorinane ring is given in Figure 3. Selected bond distances, bond angles, and torsional angles appear in Tables II–IV. (A preliminary report of this structure appeared earlier.[17b])

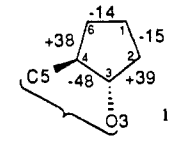
A most important feature of the structure is the position of the six-membered 1,3,2-dioxaphosphorinane ring, which is *attached apical–equatorial to phosphorus*. Moreover, O5′ is apical while O3′ is equatorial. Crystal structures of such a trans-fused five-ring/six-ring system containing P(V) are rare. (See Note Added in Proof.)

The geometry about phosphorus is near trigonal bipyramidal as shown by the O5–P–O2 bond angle, 174.5°, and the equatorial O–P–O angles, 118.2–120.7°. The O–P–O angles involving apical and equatorial oxygen pairs are within 3° of 90° with the exception of O5–P–O3, which is increased to 98.9°. For P–O bonds within the individual five- or six-membered ring, the apical bond is longer than the equatorial one, as expected. However, both P–O bonds in the five-membered ring are longer than the P–O5 (apical) bond in the six-membered ring.

As seen in Figures 1–3, the 1,3,2-dioxaphosphorinane ring of **6** is in the twist conformation, located on the pseudorotational pathway for such a flexible nonchair six-membered ring between the two boat structures with P and C4 or with O5 and C3 at the bow positions. This is seen from the torsional angles for that ring shown in structure **17**. Torsional angles for bonds on opposite



17



18

sides of a true boat-form ring are 0°. This is not observed for **6**. The C4–C5 and P–O3 bonds come closest (C3/O5 boat). The failure of those torsional angles to be more nearly equal as the ring has twisted away from the C3/O5 boat stems from variations in bond lengths and angles within this heteroatomic ring, especially

(14) (a) Holmes, R. R. *Pentacoordinated Phosphorus*; ACS Monographs 175 and 176; American Chemical Society: Washington, DC, 1980; Vols. 1 and 2. (b) Westheimer, F. H. In *Rearrangements in Ground and Excited States*; DeMayo, P., Ed.; Academic Press: New York, 1980; Vol. II, p 229. (c) Gillespe, P.; Ramirez, F.; Ugi, I.; Marquarding, D. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 91. (d) Holmes, R. R. *Acc. Chem. Res.* **1972**, *5*, 296. (e) Mislow, K. *Acc. Chem. Res.* **1970**, *3*, 321.

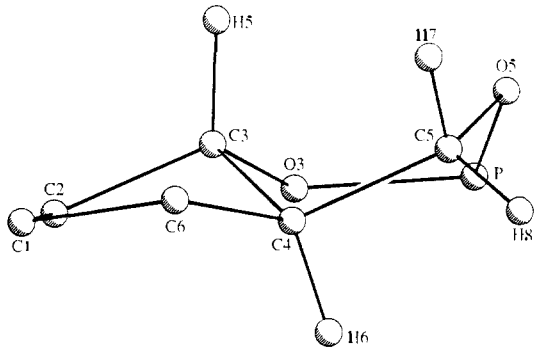


Figure 3. PLUTO drawing of fused rings of **6**.

Table III. Selected Bond Angles for **6**[a]

atoms	angle, deg	atoms	angle, deg
O1-P-O2	88.0 (2)	O3-P-O4	118.2 (2)
O1-P-O3	120.7 (2)	O3-P-O5	98.8 (2)
O1-P-O4	120.1 (2)	O4-P-O5	92.0 (2)
O1-P-O5	88.7 (2)	P-O3-C3	121.2 (3)
O2-P-O3	86.7 (2)	P-O4-C13	128.3 (3)
O2-P-O4	85.8 (2)	P-O5-C5	122.5 (3)
O2-P-O5	174.5 (2)		

[a] Estimated standard deviations in parentheses.

Table IV. Selected Torsional Angles for **6**[a]

atom 1	atom 2	atom 3	atom 4	angle, deg
O1	P	O3	C3	86.99 (0.36)
O2	P	O3	C3	172.62 (0.34)
O4	P	O3	C3	-103.92 (0.35)
O5	P	O3	C3	-6.82 (0.36)
O1	P	O4	C13	-103.40 (0.40)
O2	P	O4	C13	171.41 (0.40)
O3	P	O4	C13	87.44 (0.42)
O5	P	O4	C13	-13.70 (0.41)
O1	P	O5	C5	-67.80 (0.35)
O3	P	O5	C5	53.12 (0.36)
O4	P	O5	C5	172.09 (0.35)
P	O3	C3	C2	-160.22 (0.34)
P	O3	C3	C4	-48.57 (0.49)
P	O3	C3	H5	66.58 (0.53)
P	O5	C5	C4	-35.66 (0.53)
P	O5	C5	H7	-144.41 (0.34)
P	O5	C5	H8	95.60 (0.50)
C6	C1	C2	C3	-15.06 (0.58)
C2	C1	C6	C4	-14.12 (0.59)
C1	C2	C3	O3	153.53 (0.42)
C1	C2	C3	C4	38.49 (0.53)
O3	C3	C4	C5	68.78 (0.53)
O3	C3	C4	C6	-166.03 (0.40)
C2	C3	C4	C5	-173.17 (0.44)
C2	C3	C4	C6	-47.98 (0.50)
H5	C3	C4	H6	-163.56 (0.47)
C3	C4	C5	O5	-28.02 (0.58)
C6	C4	C5	O5	-143.46 (0.47)
H6	C4	C5	H7	-160.84 (0.46)
H6	C4	C5	H8	-37.01 (0.64)
C3	C4	C6	C1	37.73 (0.53)
C5	C4	C6	C1	157.29 (0.48)
O1	C7	C8	O2	-33.29 (0.44)

[a] Estimated standard deviations in parentheses.

the 98.9° O5-P-O3 angle. From inspection of Dreiding models, it is evident that the increased P-O3-C3 angle results in the small torsional angle about P-O3 (-6.8°), which in turn places the lone-pair-containing p orbital on O3 nearly in the equatorial plane where it is maximally stabilized.[15] (The O5-P-O4-C3 torsional angle, -13.4°, places the analogous lone pair on O4 in close to the same position.) *A twist rather than a boat conformation is*

(15) (a) Hoffmann, R.; Howell, J. M.; Muetterties, E. L. *J. Am. Chem. Soc.* **1972**, *94*, 3047. (b) Szobata, J. S.; Holmes, R. R. *Inorg. Chem.* **1977**, *16*, 2299, and references therein.

Table V. ^{31}P NMR Chemical Shifts for Phosphoranes **3-7**[a]

compd	$\delta^{31}P$	solvent	compd	$\delta^{31}P$	solvent
cis-**3**	-49.22	C_6D_6	*cis*-**5**	-50.04	C_6D_6
trans-**3**	-48.70	C_6D_6	*trans*-**5**	-49.56	C_6D_6
cis-**4**	-49.85	$CDCl_3$	*cis*-**6**	-52.20	C_6D_6
trans-**4**	-48.95	$CDCl_3$	*trans*-**6**	-51.66	C_6D_6

[a] Negative chemical shifts are upfield from external 85% H_3PO_4. At 121 MHz, 21-22 °C.

also seen from the H7-C5-O5-P (-144°) and H8-C5-O5-P (95.6°) angles and those for H7-C5-C4-H6 (-161°) and H8-C5-C4-H6 (-37.0°). These angles differ greatly from those expected for a boat with P and C4 (angle H7-C5-C4-C6, ≃180°) or O3 and C4 (angle H7-C5-C4-C6, ≃120°) bow position atoms. The values found in the crystal for these torsional angles are quite consistent with the small decrease in J_{HH} values in Table VII for the coupling of protons corresponding to H7 and H6 ($J_{4'5'a}$) and increase in J_{HH} for H8/H6 coupling ($J_{4'5'b}$), as noted below.

The transoid fusion of the five- and six-membered rings makes the nonchair form of the six-membered ring rather inflexible, as is evident from Dreiding models. Thus, the two boat forms identified above appear to be of higher energy than the twist conformation. Nonetheless, the ring system is able to accommodate the O3 lone pair nearly in the equatorial plane without moving to the C3/O5 bow position boat form. Even monocyclic analogues of **6**, however, can have twist-form rings.[16,17a]

The five-membered carbocyclic ring is in a $^3_4$T (C3 exo-C4 endo) conformation,[18] as indicated by the nearly equal torsional angles in structure **18** involving the C1-C2 and C1-C6 bonds. Interestingly, these angles are not far from those reported for the 2'-deoxyribose ring in X-ray crystal structures of derivatives of cTMP with the 1,3,2-dioxaphosphorinane ring in a chair conformation, *cis*-thymidine cyclic 3',5'-methylphosphonate,[19] or half-chair conformation, *trans*-thymidine phenyl cyclic 3',5'-monophosphate.[7b]

^{31}P,^{13}C NMR Spectroscopy of 3-6 and 8-10. NMR parameters for **3-6**, including both diastereomers if formed in measurable amounts, are listed in Tables V-IX. Where all parameters are not given, those most pertinent to the assignment of structure and the determination of the conformations of the phosphorus-containing ring are tabulated. (See Experimental Section for other parameters.)

In the ^{31}P NMR chemical shifts (Table V), a clearly discernable trend is seen in that in each case the chemical shift of the major, cis, diastereomer is *upfield* of that of the minor one. This same ordering of relative ^{31}P chemical shifts, interestingly, also is noted for diastereomeric 3'5'-cyclic three- and four-coordinate phosphorus-containing derivatives of thymidine[7,20,21] and closely related five-ring/six-ring trans-fused 1,3,2-dioxaphosphorinane systems.[22]

In Table VI are the ^{13}C parameters for the six-membered ring systems for **3-6**. The assignments of carbon resonances were straightforward except for C3' and C4' of **3** and **4**. These were

(16) Schomburg, D.; Hacklin, H.; Roeschenthaler, G. V. *Phosphorus Sulfur Relat. Elem.* **1988**, *35*, 241.

(17) (a) Yu, J. H.; Sopchik, A. E.; Arif, A. M., unpublished results from this laboratory. (b) Yu, J. H.; Sopchik, A. E. Arif, A. M.; Bentrude, W. G. *J. Org. Chem.* **1990**, *55*, 3444.

(18) For these designations, see the IUPAC recommendations: *Eur. J. Biochem.* **1983**, *131*, 9.

(19) Bentrude, W. G.; Sopchik, A. E.; Bajwa, G. S.; Setzer, W. N.; Sheldrick, W. S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1986**, *C42*, 1027.

(20) Nelson, K. A.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1983**, *105*, 7752.

(21) Nelson, K. A., unpublished results from this laboratory.

(22) For related transoid fused 2-oxo- and 2-thio-1,3,2-dioxaphosphorinanes, see: (a) Hermans, R. J. M.; Buck, H. M. *J. Org. Chem.* **1987**, *52*, 5150. (b) Hermans, R. J. M.; Buck, H. M. *Phosphorus Sulfur Relat. Elem.* **1987**, *31*, 255. (c) Taira, K.; Lai, K.; Gorenstein, D. G. *Tetrahedron* **1986**, *42*, 229. (d) Taira, K.; Gorenstein, D. G. *Tetrahedron* **1984**, *40*, 3215. (e) Bouchu, D. *Phosphorus Sulfur Relat. Elem.* **1983**, *15*, 33. (f) Rowell, R.; Gorenstein, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 5894. (g) Bouchu, D.; Dreux, J. *Tetrahedron Lett.* **1980**, *21*, 2513. (h) Gorenstein, D. G.; Rowell, R.; Findlay, J. *J. Am. Chem. Soc.* **1980**, *102*, 5077. (i) Gorenstein, D. G.; Rowell, R. *J. Am. Chem. Soc.* **1979**, *101*, 4925.

Table VI. Selected ^{13}C NMR Parameters for Phosphoranes **3–6** and Phosphites **8–10**[a]

		J_{CP}, Hz							δ ppm						
compd	solvent	Co[c]	C1′	C2′	C3′	C4′	C5′	C″[b]	Co[c]	C1′	C2′	C3′	C4′	C5′	C″[b]
cis-**3**[d]	$CDCl_3$		<0.5	10.5	6.5	8.1	9.8	11.0		68.3	28.8	79.1	73.9	69.4	73.8
trans-**3**[d]	$CDCl_3$		<0.5	10.5	6.4	9.1	9.1	12.6		68.0	28.8	79.4	73.0	68.6	72.4
cis-**4**[e]	acetone-d_6		<0.5	10.6	5.9	9.7	10.6	11.1		87.8	34.7	78.7	74.6	68.9	72.2
cis-**5**[f]	$CDCl_3$	<0.5	<0.5	10.4	8.1	7.9	9.1	11.0	24.6	20.3	29.0	83.3	41.9	71.6	73.5
									20.3	24.6					
trans-**5**[g]	$CDCl_3$	1.4	<0.5	11.8	7.8	8.5	8.4	12.0	24.9	20.2	28.9	83.8	40.5	70.8	72.7
		<0.5	1.4						20.2	24.9					
cis-**6**[e]	C_6D_6	<0.5	<0.5	10.5	7.8	8.4	9.5	11.1	25.0	20.2	28.5	83.1	40.9	71.1	73.9
									20.2	25.0					
cis-**8**[e]	$CDCl_3$		<0.5	<0.5	<0.5	7.5	5.3	21.1		64.3	29.6	71.3	73.8	68.7	69.8
cis-**9**[e]	acetone-d_6		<0.5	<0.5	<0.5	7.7	5.4	20.3		83.7	35.7	71.1	75.1	68.7	69.9
cis-**10**[f]	$CDCl_3$	1.6	<0.5	1.2	<0.5	4.9	4.8	21.3	23.4	16.7	29.8	73.7	43.5	69.8	69.5
		<0.5	1.6						16.7	23.4					

[a] At 75 MHz, 25 °C. See Experimental Section for other ^{13}C NMR parameters. [b] C″ is $CH(CF_3)_2$. [c] Carbon that replaces oxygen of tetrahydrofuranyl ring. [d] Acquisition time, 3.137 s. [e] Acquisition time, 1.871 s. [f] Acquisition time, 3.509 s.

Table VII. Selected ^1H NMR Parameters for the Six-Membered Phosphorus-Containing Rings of **3–6**

		J, Hz									δ ppm				
compd	solvent[c]	5′aP	5′bP	3′P	4′P	4′5′a	4′5b′	3′4′	5′a5′b	H″P[b]	3′	4′	5′a	5′b	H″[b]
cis-**3**	C_6D_6[d]	27.0	1.9	<0.2	<0.2	9.4	6.9	9.2	−10.0	13.7	3.78	3.30	3.47	4.04	5.17
cis-**3**	$CDCl_3$[d]	26.2	2.6	<0.2	<0.2	9.4	6.9	9.4	−10.1	13.9	4.33	3.76	4.05	4.57	5.38
trans-**3**	$CDCl_3$[d]	30.0	<0.2	<0.2	<0.2	9.1	7.1	9.2	−10.2	15.2	4.47	3.87	4.02	4.45	5.26
cis-**4**	$CDCl_3$[e]	26.5	2.6	<0.2	<0.2	9.5	7.0	9.1	−10.0	13.9	4.83	3.93	4.23	4.63	5.53
cis-**4**	acetone-d_6[e]	27.6	<0.2	<0.2	<0.2	9.7	6.9	9.3	−9.5	13.9	5.10	4.23	4.36	4.69	5.01
cis-**5**	C_6D_6[a]	26.4	2.7	<0.2	<0.2	10.6	7.6	10.3	−10.3	13.9	3.72	1.47	3.19	3.97	5.33
trans-**5**	C_6D_6[a]	28.9	2.0	<0.2	<0.2	10.5	7.1	10.3	−10.5	15.5	3.66	1.77	3.35	4.01	5.36
cis-**6**	C_6D_6[a]	29.4	<0.2	<0.2	<0.2	10.6	7.9	10.3	−10.2	13.4	3.71	1.89	3.10	3.97	5.30

[a] At 300 MHz, 25 °C. [b] See Table IV and Experimental Section for other ^1H NMR parameters. H″ is $CH(CF_3)_2$. [c] Parameters recorded for solvent that gave maximum resolution. [d] At 500 MHz. [e] At 400 MHz.

Table VIII. Selected ^1H NMR Parameters for the Six-Membered Rings of Phosphites **8–10** and **19**[a]

		J, Hz								δ, ppm					
compd	solvent	5′aP	5′bP	3′P	4′P	5′a5′b	4′5a	4′5′b	3′4′	C″P[b]	3′	4′	5′a	5′b	C″[b]
cis-**8**	C_6D_6[c]	2.4	11.3	1.7	<0.1	−9.3	10.8	4.5	9.0	8.4	4.04	3.36	4.14	3.96	4.01
cis-**9**	acetone-d_6[d]	2.7	11.1	1.8	<0.2	−9.2	10.6	4.5	9.2	8.8	4.81	3.79	4.56	4.46	5.61
cis-**10**	C_6D_6[d]	2.7	10.9	<0.2	<0.2	−10.3	11.4	4.3	9.3	8.4	3.91	1.65	3.95	3.67	4.42
cis-**19**[e]	acetone-d_6[d]	2.6	11.0	2.0	<0.2	−9.2	10.7	4.4	9.2		4.97	3.80	4.71	4.43	
trans-**19**[e]	acetone-d_6[d]	9.2	1.4	1.0	−1.0	−9.7	9.8	6.6	9.7		4.47	4.57	4.31	4.76	
cTMP[f]	D_2O	2.2	20.4	1.7	0.1	−9.5	10.6	4.7	9.2		4.70	3.91	4.29	4.45	

[a] Ambient probe temperatures. [b] $CH(CF_3)_2$. [c] 500 MHz. [d] 300 MHz. [e] References 20 and 21. *trans*-**19** spectrum iteratively refined by use of LAOCN3. [f] Reference 6.

Table IX. Pertinent ^1H NMR Parameters for the Five-Membered Saturated Rings of Phosphoranes **3** and **4** and for Phosphites **8**, **9**, and **19**[a]

		J_{HH}, Hz									δ, ppm					
compd	solvent	1′a2′a	1′a2′b	1′b2′a	1′b2′b	2′a3′	2′b3′	3′4′	1′a1′b	2′a2′b	1′a	1′b	2′a	2′b	3′	4′
cis-**8**	C_6D_6[b]	10.3	2.9	8.9	7.4	10.5	7.4	9.0	−8.8	−11.5	3.32	3.26	1.40	1.54	4.04	3.06
cis-**3**	$CDCl_3$[b,d,g]	10.3	3.2	8.7	7.6	10.2	7.6	9.4	−9.2	−12.0	4.17	4.10	2.09	2.32	4.33	3.76
cis-**3**	C_6D_6[b,d,h]	10.3	3.5	8.6	7.5	10.2	7.8	9.2	−9.2	−11.8	3.40	3.36	1.21	1.34	3.78	3.31
cis-**9**	acetone-d_6[f,d,j]	9.0	2.9			10.4	8.2	9.2		−13.1	6.22		2.52	2.60	4.81	3.79
cis-**4**	acetone-d_6[c,d,f]	9.4	3.2			9.6	8.0	9.3		−13.4	6.30		2.62	2.68	5.10	4.23
cis-**19**[d]	acetone-d_6[f,k,l]	9.1	2.6			10.6	8.3	9.2		−13.2	6.28		2.54	2.58	4.97	3.80
cTMP[e]	D_2O	8.9	2.4			10.8	8.0	9.2		−13.3	6.30		2.59	2.50	4.70	3.91

[a] At ambient probe temperatures. [b] 500 MHz. [c] 400 MHz. [d] All parameters for spectra simulated by LAOCN programs. [e] Reference 6. [f] 300 MHz. [g] RMS error, 0.2034. [h] RMS error, 0.0603. [i] RMS error, 0.1701. [j] RMS error, 0.0867. [k] References 20 and 21. [l] RMS error, 0.045.

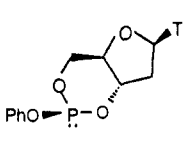
distinguished by a single-frequency decoupling experiment on **3** and assumed to have the same relative order in **4**. (For the sake of simplicity in listing the data, the designations C1′, C2′, etc. and H1′, H2′, etc., are used for all molecules in the tables even when the thymin-1-yl group is not present.) The data clearly are consistent with and support the structures assigned. Correlations useful in distinguishing the identities of individual diastereomers of **3** and **5** can be pointed out. There is a small effect of diastereomer identity on the C5′ chemical shift and on $J_{C5'P}$ as well as a systematic variation of the chemical shift and J_{CP} for the secondary carbon of the group $CH(CF_3)_2$. The overall consistency of the J_{CP} and $\delta^{13}C$ values for *cis*- and *trans*-**3**, as well as *cis*-**4**, and again for *cis*- and *trans*-**5** and **6** fits well with the conclusion to be drawn below from the ^1H NMR data, i.e., the invariancy of the conformation and apical/equatorial attachment to phosphorus of the six-membered ring in all these phosphoranes.

The ^{13}C data for *cis*-**8–10** also are included in Table VI for comparison. Of particular note are the perhaps surprising *downfield* shifts of the C3′ and C5′ resonances in the carbocycic five-membered-ring cases (**5**, **6**, and **10**) relative to those resonances for **3**, **4**, **8**, and **9**. Since this occurs in the phosphites as well as the phosphoranes, it seems to be intrinsic to the ring systems. Also notable are the relatively large J_{CP} values for the P(V) compounds for C2′, C3′, C4′, and C5′.

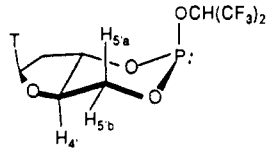
^{13}C parameters for the five-membered saturated and unsaturated ring attached to phosphorus may be found for **3–6** (and also

cis-**8**–**10**) in the Experimental Section. These signals are particularly weak. Invariably an accidental isochronicity of the potentially chemical-shift-nonequivalent alkene ring carbons as well as those for all attached CF_3 groups was seen. When the solvent was C_6D_6, the alkene peaks were obscured by solvent.

Conformations of Phosphorus-Containing Six-Membered Rings. Table VII displays the pertinent ^1H NMR data for the phosphoranes of interest. For comparison, analogous data for the phosphorus-containing rings of the phosphites from which the phosphoranes of this study were prepared, along with those for another phosphite, **19**, from earlier work,[20] are given in Table VIII.



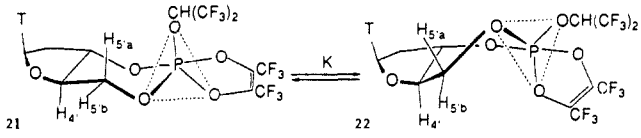
cis-19



cis-20

Coupling constants were generally derived by first-order inspection, as justified by the reasonably large separations in chemical shifts. For *cis*- and *trans*-**19**, however, the J_{HP} values had been obtained by computer-assisted spectral simulation. The assignment of H5a′ and H5b′ resonances in all these derivatives is easily made[6,7,20–22] on the basis of the expected large value of $J_{4'5a'}$, regardless of whether the ring is in the chair (**20**) or twist form. This is a result of the close to antiperiplanar relationship for these protons in *both* conformations, as demonstrated by Dreiding molecular models. For the cis phosphites, H5a′ has a small value of J_{HP} (2.4–2.7 Hz) while that for H5b′ is relatively large (10.9–11.3 Hz). This is as expected[20] for such rings *with an RO or PhO axial on a chair-form ring*, ***20***. (The cis and trans geometries of these phosphites are easily assigned on the basis of relative ^{31}P chemical shifts.)[3,20,22b]

By contrast for phosphoranes **3**–**6** (Table VII), the relative magnitudes of $J_{H5a'P}$ (26.4–30.0 Hz) and $J_{5b'P}$ (<0.2–2.7 Hz) are reversed compared to those parameters for the cis diastereomers of phosphites **8**, **9**, **10**, and **19**. As has been shown,[23] this situation is completely diagnostic, as illustrated below for the thymidine-based derivative **4**, for the *very predominant if not total population of a nonchair conformation*, ***22***, *rather than chair form* ***21***. (As



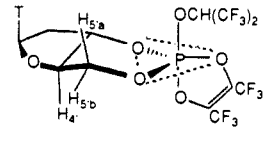
reported earlier,[20] phosphite *trans*-**19** (Table VIII) represents a case in which *both* some chair and a very predominant amount of twist conformation are occupied, as seen by comparing $J_{5'aP}$ and $J_{5'bP}$.) There is in all cases an increase in $J_{4'5b'}$ and a small decrease in $J_{4'5'a}$ as is consistent with the decreases in dihedral angles H4′–C–C–H5′b and H4′–C–C–H5′a demonstrated by Dreiding models when the chair conformation is converted to the twist. (See also above discussion of X-ray structure of **6**.) The very large $^3J_{HP}$ values seen for the pseudoequatorial H5a′ for **3**–**6** are similar in magnitude to those observed with six-membered-ring 1,3,2-oxazaphosphorinanes featuring pentacovalent phosphorus.[10] The large values for $J_{H5a'P}$ suggest a torsional angle H5′a–C5′–O5′–P for **3**–**6** that is reasonably large. As noted above, that angle for **6**, as determined by X-ray crystallography, is 144°, while that for the H5′b–C5′–O5′–P is 95.6°. If the degree of twisting of the ring is the same in solution as in the crystal, and a true Karplus relationship obtains for these three-bond couplings, larger values of $J_{5'aP}$ may be encountered in other cases. The X-ray of **6** also shows the six-membered ring to be in a twist conformation. As noted above, the $J_{4'5'a}$ and $J_{4'5'b}$ values for **3**–**6** are quite consistent with a twist conformation rather than either of the two potential boat structures that could be populated in solution. The evident lower energy of the twist form was discussed earlier in connection with the X-ray structure of **6**.

Interestingly, although in all cases $J_{5'aP}$ is much greater than $J_{5'bP}$, there are some variations in the magnitudes of $J_{5'aP}$ and $J_{5'bP}$ in Table VII. These differences could reflect small effects of structure on the chair–twist equilibrium. Alternatively, small differences in the degree of twist, i.e., in the dihedral angle C4′–C5′–O5–P, may occur between diastereomers and also between phosphoranes depending on whether the saturated (**6**) or unsaturated (**3**–**5**) five-membered ring is attached to phosphorus.

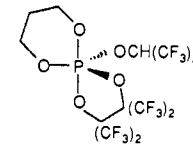
Conformations of the Five-Membered Rings. Listed in Table IX are the ^1H NMR parameters for the five-membered rings of the phosphoranes and phosphites discussed above along with those of thymidine cyclic 3′,5′-monophosphate (cTMP) for comparison. Several of these spectra required iterative computer simulation because of their closely coupled nature. The 2′-deoxyribose ring of cTMP has been assigned[25] a conformation in the very narrow range $_4E$–$_4T^3$, which designates its position in the psuedorotational circuit available to a five-membered ring.[18] The conformations of the saturated five-membered ring for cTMP and the compounds of this study are restricted by the transoid fusion of the six-membered rings. However, small variations in geometry can occur.

$J_{1'a2'a}$ and $J_{1'a2'b}$ depend on whether or not the 1′-position is thymin-1-yl substituted or not (Compare *cis*-**8** to *cis*-**9**). However, there is *little variation* in these coupling constants, which are the ones most diagnostic of change in conformation, between the phosphite precursor and the corresponding pentacovalent adduct. (Compare *cis*-**3** to *cis*-**8**, *cis*-**4** to *cis*-**9**.) Thus, the conformations of the relatively rigid 2′-deoxyribose ring are little if any affected by the coordination state of phosphorus or by the conversion of the phosphorus-containing ring to the twist conformation (**3**–**6**). The similarities in J_{HH} for *cis*-**4**, -**9**, and -**19** (small differences) and cTMP suggest that all the thymidine-based compounds have a deoxyribose ring conformation like that of cTMP.

Apical/Equatorial Position of Six-Membered Ring. In the chair–twist equilibrium for these pentacovalent phosphorus-containing rings illustrated for the thymidine case (*cis*-**4**) by **21** ⇄ **22**, the phosphorus-containing ring has been attached to phosphorus in *apical/equatorial fashion*. The only alternative would be to attach the six-membered ring diequatorial, as in **23**, since



23



24

a diequatorial five-membered ring would have an unreasonably high energy.[14] Unfortunately the NMR data do not allow **22** and **23**, were the latter in a twist conformation, to be distinguished. Several arguments, however, can be given to support structure **22**.

First, an earlier low-temperature ^{13}C NMR study at 22.6 MHz by Buck and co-workers of **7b**,[9a] the carbocyclic compound analogous to **7a**, unmistakably showed the ring to be attached apical/equatorial to phosphorus. The X-ray structure of **6** is completely consistent with that result and also at least suggests the location of O3′ and O5′ in solution. Very recent ^{13}C mea-

(23) For previous examples of the use of this combination of J_{HH} and J_{HP} to identify twist conformations, see: References 7, 20, 22, and 24.

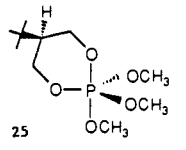
(24) (a) Bajwa, G. S.; Chandrasekaran, S.; Hargis, J. H.; Sopchik, A. E.; Blatter, D.; Bentrude, W. G. *J. Am. Chem. Soc.* **1982**, *104*, 6385. (b) Bentrude, W. G.; Day, R. O.; Holmes, J. M.; Quin, G. S.; Setzer, W. N.; Sopchik, A. E.; Holmes, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 106. (c) Bentrude, W. G.; Setzer, W. N.; Sopchik, A. E.; Bajwa, G. S.; Burright, D. D.; Hutchinson, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 6669. (d) Bentrude, W. G.; Setzer, W. N.; Sopchik, A. E.; Chandrasekaran, S.; Ashby, M. T.; *J. Am. Chem. Soc.* **1988**, *110*, 7119.

(25) Robins, M. J.; MacCoss, M.; Wilson, J. S. *J. Am. Chem. Soc.* **1977**, *99*, 4660.

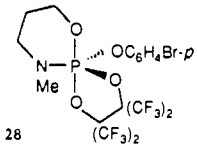
surements at 121 MHz in this laboratory have demonstrated for **7a** a decoalescence of the methoxy ^{13}C chemical shifts at low temperatures which is completely parallel to that reported for **7b**.[17b,26] This means there is *no major intrinsic difference* in the stereochemical properties of the two ring systems; and the ring is attached apical/equatorial in both. This is contrary to the suggestions of Buck et al., who were unable at lower fields[9a] to slow down the MeO exchange in **7a** and suggested a diequatorial ring preference for **7a**. Furthermore, the essentially identical values of J_{HP} for the 5'a and 5'b protons of *cis*-**3** and to those of *cis*-**5** are totally consistent with their having the same structures stereochemically, including the position of attachment and the conformation of the ring in question.

Second, the alternative structure for *cis*-**3** and *cis*-**5** with the ring attached diequatorial, **23**, might result if the $(CF_3)_2CHO$ group is so apicophilic that it overcomes the propensities of the six-membered ring to be equatorial/apical in **7a** and **7b**. However, Roeschenthaler et al.[16] have shown by X-ray crystallography the $(CF_3)_2CHO$ to be *equatorial* in phosphorane **24**, which features the P(V) ring apical/equatorial on phosphorus and *in a boat/twist conformation.*

Third, there is increasing evidence for the *general* apical/equatorial preference of 1,3,2-dioxaphosphorinane rings attached to P(V),[27] although its magnitude is not known. For example, we have unpublished low-temperature ^{13}C NMR evidence for the structure **25** based on nonequivalent CH_2 resonances.[17a] The position of the ring attachment found for **7a** and **7b** also is consistent with this principle.

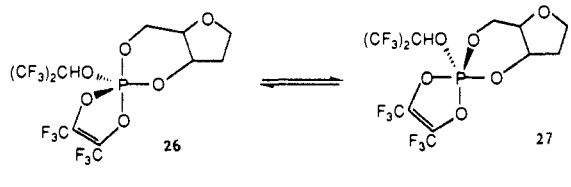


25



28

In the equilibrium **21** ⇄ **22**, the six-membered ring is shown attached to phosphorus *with the O3' apical.* This is done arbitrarily so as to place the O3'–P bond in the required position for its cleavage to the 5'-monophosphate, as occurs in the phosphodiesterase-catalyzed hydrolysis of cAMP. The potential equilibrium resulting from Berry pseudorotational interconversion of structures with apical O5'–P (**26**) and O3'–P (**27**) bonds is shown by **26** ⇄ **27**. There is no evidence concerning the position of this



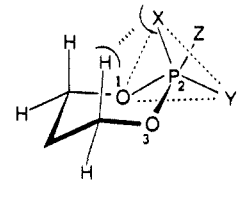
equilibrium in *solution*, although it has been suggested that less highly substituted alkyloxy groups may be more electronegative and hence more apicophilic.[28] This reasoning would mean that **26** is more stable than **27**. (The low-temperature spectra for **7b** did not resolve the C3' and C5' resonances into more than one peak,[17b] which may mean that a *single* apical/equatorial form is dominant.) The X-ray structure of **6** supports these ideas in that the $H_2C5'O5'$ group is in fact apical in the crystal and with reasonable probability, by inference, also in solution.

Discussion

Conformations of 1,3,2-Dioxaphosphorinane Rings. From the above results it can be concluded that the six-membered rings of the phosphoranes **3–6** exist in solution in nonchair (boat/twist) conformations with the ring almost certainly attached to phosphorus apical/equatorial. This result, our recent report that the P(V) 1,3,2-oxazaphosphorinane **1** has a nonchair conformation in solution,[10] the crystal structures for **6**[17b] and **24**,[16] earlier solution NMR work on 1,3,2-dioxaphosphorinanes,[27c,e] the series of X-ray structures of Holmes et al.,[27b] and the X-ray structure of **28**,[29] all showing that ring to be in a nonchair conformation, give strong support to the postulation that *1,3,2-dioxa- and 1,3,2-oxazaphosphorinane rings are attached apical/equatorial to pentacovalent phosphorus*[27c,e] *and that a nonchair (boat or twist) conformation is intrinsically more stable than the chair form.*[10,27] These examples are not sterically loaded with substituents with unusual steric bulk or stereoelectronic requirements, as is needed with the corresponding rings containing four-coordinate phosphorus (oxides and sulfides) to convert the more stable chair conformation to the twist, even though that free energy requirement is very low.[7,30]

It also is significant that on the basis of the X-ray structure of **6** and the J_{HH} values involving H4', H5'a, and H5'b for **3–6** that a *twist structure* rather than a true boat is present. This likely results at least in part from the restrictions on the flexibility of the ring imposed by the strained, transoid fusion of the five- and six-membered rings. The p-orbital lone pair on O3 of **6** (X-ray, Figures 1–3, and Table III) is nonetheless able to be optimally[16] located in the equatorial plane.

It appears that the preference of these P(V)-containing rings to be in nonchair conformations was first suggested by Trippett et al.[27f,28,29] They reasoned that the primary driving force for the chair or boat interconversion was the fact that the conformationally mobile boat-form ring allows the p-hybridized lone pair on oxygen or nitrogen to move into the equatorial plane where it is most stable.[15] We agree that once in the nonchair conformation, the ring will pseudorotate, within the restraints imposed on it by the system of which it is a part, until interactions such as the above are optimized, as was shown for **1**. Nonetheless, we tentatively suggest that an *important driving force* for the chair → nonchair (boat or twist) interconversion is the instability of the chair conformation arising from the 90° O–P–O or O–P–N bond angle within the six-membered ring. As a result, the phosphorus end of the ring becomes strongly puckered. This brings the group on phosphorus, which is much like an axial ring substituent, in close proximity to the axial hydrogen on carbon 3 or carbon 5. (See structure **29**). This synaxial-like repulsion destabilizes the chair



29

conformation. Although only one of the axial ring carbon hydrogens is involved at one time in such a repulsion, the internuclear distance, O···H, is very short, of the order 1.5–2.0 Å for **21**(**27**)

(26) Indeed at −80 °C in CD_2Cl_2 at 121 MHz the methoxy doublet had decoalesced into three individual doublets in relative chemical shift order consistent with the presence of two *equatorial* methoxy groups. The ring must be, therefore, apical/equatorial.[17b]

(27) For recent papers, see: (a) Reference 16. (b) Since this paper was accepted, the following publications have appeared: Kumara Swamy, K. C.; Holmes, J. M.; Day, R. O.; Holmes, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6092. Kumara Swamy, K. C.; Day, R. O.; Holmes, J. M.; Holmes, R. R. *Ibid.* **1990**, *112*, 6095. Burton, S. D.; Kumara Swamy, K. C.; Holmes, J. M.; Holmes, R. R. *Ibid.* **1990**, *112*, 6104. (c) van Ool, P. J. J. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 215. Earlier evidence is found in: (d) Bone, S. A.; Trippett, S.; Whittle, P. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 80. (e) Chang, B. C.; Conrad, W. E.; Denney, D. B.; Denney, D. Z.; Edelman, R.; Powell, R. L.; White, D. W. *J. Am. Chem. Soc.* **1971**, *93*, 4004. (f) Trippett, S. *Pure Appl. Chem.* **1974**, *40*, 595. That nonchair P(V) 1,3,2-dioxaphosphorinanes might be invoked to explain the stereochemistry of certain cyclization reactions was suggested in 1980: Hall, C. R.; Inch, T. D. *Tetrahedron* **1980**, *36*, 2059. (g) Day, R. O.; Kumara Swamy, K. C.; Fairchild, L.; Holmes, J. M.; Holmes, R. R., submitted for publication.

(28) Trippett, S. *Phorphorus Sulfur Relat. Elem.* **1976**, *1*, 89.

(29) Barlow, J. H.; Bone, S. A.; Russell, D. R.; Trippett, S.; Whittle, P. J. *J. Chem. Soc., Chem. Commun.* **1976**, 1031.

(30) For some examples in monocyclic systems, see: (a) Day, R. O.; Bentrude, W. G.; Yee, K. C.; Setzer, W. N.; Deiters, J. A.; Holmes, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 103. (b) Gerlt, J. A.; Gutterson, N. I.; Drews, R. E.; Sokolow, J. A. *Ibid.* **1980**, *102*, 1665. (c) Mosbo, J. A. *Org. Magn. Reson.* **1978**, *11*, 281. (d) Bentrude, W. G.; Tan, H. W. *J. Am. Chem. Soc.* **1973**, *95*, 4666. (e) Bentrude, W. G.; Yee, K. C. *J. Chem. Soc., Chem. Commun.* **1972**, 169. (f) Bentrude, W. G.; Hargis, J. H. *J. Chem. Soc., Chem. Commun.* **1969**, 1114.

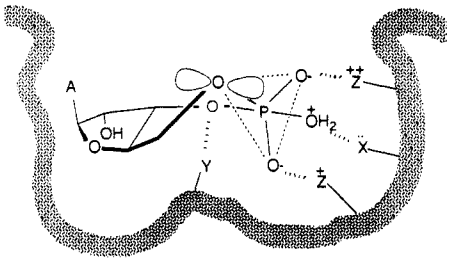


Figure 4. Speculative representation of enzyme-bound P(V) cAMP–H_2O adduct.

according to estimates based on Dreiding models. In the nonchair conformation, there is sufficient flexibility to allow similar interactions to be relieved. For O3′-apical structure **21**, it is H5′b that is in close proximity to the oxygen of the $OCH(CF_3)_2$ group. However, the idea that the free energy differences between chair and boat(twist) structures may be relatively small is indicated by recent findings of both chair and twist boat structures in the same unit cell for a P(V) 1,3,2-dioxaphosphorinane ring system studied by X-ray crystallography.[27g]

Possible Implications for Phosphodiesterase-Catalyzed Hydrolysis of cAMP. Special note should be made of the apical position of O5′ in the crystal structure of **6**. The likelihood[28] that C5′O5′ is more apicophilic than C3′O3′ and the fact that only in the C5′O5′ nonchair form can a lone pair on oxygen (O3′) be in the energetically favored equatorial plane means that *nonchair forms corresponding to* ***26*** *are most probably thermodynamically more favorable than those similar to* ***27***. However, under the usually assumed rule of apical entry and departure of substituents on P(V), cAMP–H_2O adducts analogous to **26** would yield 3′- rather than 5′-AMP. *An essential role of phosphodiesterase most probably is to assure that enzyme-bound cAMP forms a cAMP-H_2O adduct (or transition state) with C3′O3′ apical.* Pictured diagramatically in Figure 4 is such an species. The water molecule and departing O3′ are coapical, as required for an intermediate or transition state in a so-called inline displacement. Such a structure, as has been widely recognized,[8] most simply accounts for the inversion of stereochemistry at phosphorus known to accompany the PDE-catalyzed hydrolysis of cAMP to adenosine 5′-monophosphate.[3]

The same stereochemistry would result, as pointed out by Gerlt,[4] if a residue attached to the active site of the enzyme were to attack phosphorus to give an intermediate or transition state like that shown in Figure 2, but with an amino acid moiety in place of water. The latter would be subsequently removed from phosphorus by displacement *on the enzyme rather than at phosphorus*. (An acyl-bound phosphorus intermediate giving 5′-phosphate on attack at acyl carbon has been proposed as a possible example.[4]) However, in the absence of clear evidence for such an intermediate, Figure 4 most economically depicts the enzyme-catalyzed hydrolysis of cAMP.

Another stereochemically consistent two-step possibility that has been be considered[2f,3a,4,9] involves a cAMP–enzyme adduct with the six-membered ring diequatorial. After Berry pseudorotation, the ring opens (O3′–P apical scission) with retention of configuration at phosphorus to an intermediate, which then yields inverted 5′-monophosphate on subsequent hydrolysis via an in-line mechanism. There seems no need in view of the apical/equatorial preference for the six-membered ring in question to involve such a more complicated mechanism, especially in the absence of evidence for an enzyme–cAMP intermediate.

Since we have noted that the chair–twist interconversion of the nucleoside 3′,5′-monophosphates themselves occurs with relative energetic ease,[7] the possibility may be suggested that a chair to twist conformational change takes place on bonding of cAMP to the active site of the phosphodiesterase *prior to formation of a pentacovalent adduct*. The H_2O–cAMP adduct would then be formed directly in the twist conformation pictured diagramatically in Figure 4. This idea is *completely speculative*. No experimental evidence on this point is available.

A potential chemical advantage to the structure depicted in Figure 4 is the fact that the p-hybridized electron lone pair on O5′, as shown, is lined up so as to weaken the apical bonding system in the adduct and to lower the energies of the transition states for both its *formation* and the subsequent *scission* of the P–O3′ bond.[31] *Thus, it appears that both adduct formation and 5′-monophosphate formation may be favored kinetically by the formation of the pentacovalent adduct (or transition state) in the twist conformation shown in Figure 2.*

Nonenzymic Hydrolysis. The nonenzymic base-catalyzed hydrolysis of cAMP also proceeds with inversion of configuration at phosphorus.[4] By contrast to the enzymic reaction, the cleavage of the O5′–P bond, rather than the O3′–P bond, is favored by approximately 4/1. Presuming that the 3′- and 5′-monophosphates result from P–O scissions involving apical O5′–P and O3′–P bonds, respectively, this result is quite consistent with the idea proposed above for the role of phosphodiesterase in assuring the formation of the sort of structure (O3′ apical) depicted in Figure 4. One possible explanation[17b] for the preferential cleavage of the P–O5′ bond by base in the absence of enzyme would involve a kinetic as well as thermodynamic preference for formation of **30**

30

(analogous to **26**), which undergoes rapid P–O5′ scission to 3′-AMP more rapidly than (or in competition with) pseudorotation to the form with C3′O3′ apical which cleaves to 5′-AMP. These possibilities have been considered in more detail elsewhere.[17b]

Experimental Section

General Procedures and Materials. All glassware was dried in an oven for at least 3 h at 120 °C before use. Air-sensitive materials were transferred by syringe or glovebox. A syringe pump was used for simultaneous addition of two solutions. Commercial solvents and reagents were used as received unless otherwise noted. Ethyl ether, tetrahydrofuran, and *n*-pentane were dried over sodium and freshly distilled before use. Acetonitrile was dried over phosphorus pentoxide. Ethyl acetate was dried over calcium hydride. Both were freshly distilled before use. Triethylamine was dried over potassium hydroxide and distilled. Hexafluoroacetone, diethyl phenylmalonate, and hexamethylphosphorous triamide (HMPT) were purchased from Aldrich Chemical Co. 2,3-Dichloro-1,1,1,4,4,4-hexafluoro-2-butene was purchased from SCM Chemicals. Thymidine and 2-deoxy-D-ribose from Aldrich or Sigma were used as received. Pyridine hydrochloride was sublimed before use.

Spectral and Physical Data. Fourier-transformed ^1H NMR spectra were recorded on Varian XL-300, XL-400, and VXR-500 spectrometers. Coupling constants were measured on 100-MHz expansions with 3.752-s acquisition times and approximately ±0.3-Hz accuracy at 300 MHz, 5.201-s acquisition times and approximately ±0.2-Hz accuracy at 400 MHz, and 8.001-s acquisition times and approximately ±0.1-Hz accuracy at 500 MHz. Splittings involving closely coupled, geminal protons were analyzed with the aid of the LAOCN3 program. ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer at 75 MHz operated with full proton decoupling, acquisition time ≥1.871 s. ^1H and ^{13}C NMR chemical shifts are recorded in δ parts per million (ppm) relative to internal tetramethylsilane or deuterated solvent peaks. When more than one nucleus is responsible for a splitting pattern, the individual coupling constants are designated J_{CP}, J_{CF}, etc. ^{31}P NMR spectra were taken on a Varian XL-300 spectrometer at 121 MHz under proton decoupling conditions. ^{31}P chemical shifts are reported in δ ppm downfield (+) or upfield (−) from external 85% H_3PO_4. NMR parameters not given in Tables VI–IX are recorded in the Experimental Section. The carbon NMR signals for the five-membered phosphorus-containing rings of **3–6** and **8–10** were characteristically weak. When the signal/noise ratio was great enough, individual doublet splittings (J_{PC}) were assigned as such. Weaker, unresolved signals that were clearly not singlets are designated as multiplets.

Infrared spectra were recorded on a Perkin-Elmer Model 298-A IR spectrophotometer. The spectra were calibrated on the 1602-cm^{-1} band

(31) For an extensive coverage of such ideas, see: Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1047. Transition-state effects are normally greater than ground-state effects.

of polystyrene. Mass spectra were recorded on a VG Micro Mass 7050E double-focusing high-resolution instrument with a VG Data System 2000 operated in the electron ionization (EI) mode using a direct sample inlet. Gas chromatography and GS/MS spectra employed flame ionization detection and a Hewlett-Packard Model 5830A gas chromatograph equipped with a Heliflex RSL-150 capillary column (30 m × 0.32 mm). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Melting points are uncorrected.

General Procedure for the Reactions of Phosphites with Hexafluoroacetone. A 25-mL two-necked flask was fitted with a three-way stopcock and a dry ice condenser. The phosphite (1 equiv) was placed in the flask under an argon atmosphere. To the three-way stopcock were connected a cylinder of hexafluoroacetone and a thick-walled glass tube. The thick-walled glass tube was cooled by liquid nitrogen. The tap of the cylinder was slowly opened, and the hexafluoroacetone was condensed into the thick-walled glass tube as a white solid. (Approximately 5 equiv). The dry ice–acetone condenser was charged, and the reaction flask was cooled to −78 °C by using a dry ice–acetone bath. The thick-walled glass tube was slowly warmed so that the melting hexafluoroacetone was vaporized and completely transferred to the reaction vessel. (The thawing must be extremely slow to avoid a buildup of gas pressure.) The argon flow was shut off, and the continuously stirred reaction mixture was slowly thawed to −26 °C, the boiling point of hexafluoroacetone. The resulting mixture was refluxed for 5 h. The dry ice was removed from the condenser. The product began to appear as a white solid. Unreacted hexafluoroacetone was recondensed into the liquid nitrogen cooled thick-walled glass tube. The product remained on the walls of the reaction vessel.

General Procedure for the Reactions of Phosphites with Hexafluorobiacetyl. A 25-mL one-necked flask was fitted with a pressure-equalized dropping funnel. The phosphite (1 equiv) was placed in the round-bottomed flask under an argon atmosphere. By use of a cannula, an excess amount of hexafluorobiacetyl was transferred to the rubber septum fitted dropping funnel and was then slowly added, dropwise, to the phosphite at 0 °C over a 30-min period. The resulting yellow mixture was stirred for 1 h at 0 °C, warmed to room temperature, and stirred for an additional 3 h. The remaining hexafluorobiacetyl was removed by a vacuum pump, and the residue was distilled under high vacuum (<0.01 mmHg). Except for the higher boiling phosphoranes, a 15-cm Vigreux column was used.

Hexafluorobiacetyl. The procedure was a modification of the literature method.[32] A mixture of chromium trioxide (39.0 g, 390 mmol), fuming sulfuric acid (120 mL), and concentrated sulfuric acid (45 mL) was placed under argon in a flask connected through a Vigreux column to two traps in series cooled by a dry ice–acetone bath. 2,3-Dichloro-1,1,1,4,4,4-hexafluoro-2-butene (39.0 g, 129 mmol) was added dropwise over a 2-h period to the stirred slurry maintained at 40 °C under an argon atmosphere. The resulting slurry was stirred for an additional hour at 45–50 °C. Argon gas was allowed to flow through the reaction vessel for approximately 1 h until all the products were condensed in the two traps. The contents of the two (approximately 15 mL of a yellow liquid) were distilled at room temperature through a Vigreux column (15 cm) to give approximately 10 mL of product. The temperature of the oil bath was maintained below 40 °C. The receiving flask was cooled to 0 °C.

(2*R*,3*S*)-2-(Hydroxymethyl)-3-hydroxyfuran was prepared from 2-deoxy-D-ribose as described in the literature[33] [62.9% yield; bp 113–115 °C (0.01 mmHg)].

***trans*-(2-Hydroxymethyl)cyclopentanol** was prepared from cyclopentene and paraformaldehyde as described in the literature:[34,35] 40.0% yield; bp 80–85 °C (0.3 mmHg) (lit.[35] bp 80–86 °C (0.3 mmHg)). ^1H NMR and GLC indicated that the diol was contaminated by approximately 30% of the *cis*-diol.

2-Phenyl-1,3-propanediol. The procedure was essentially that described in the literature.[24b]

Stereochemistry of Reaction of Phosphite 11 with Hexafluorobiacetyl. The cis/trans ratio was monitored by ^{31}P NMR immediately before the start of the reaction; cis/trans = 35/65. To the neat **11** (0.10 g, 0.29 mmol) was added dropwise excess hexafluorobiacetyl at −10 °C under an argon atmosphere with continuous stirring. The addition took 1 min. The resulting solution was stirred for an additional 5 min. Excess hexafluorobiacetyl was removed at −10 °C by a vacuum pump. The cis/trans ratio of the products was measured by ^{31}P NMR immediately after the completion of the reaction: ^{31}P NMR (121 MHz, C_6D_6) δ major isomer (cis) −50.39 (s), minor isomer (trans) −49.70 (s); cis/trans = 25/75.

Stereochemistry of Reaction of Phosphite 12 with Hexafluorobiacetyl. By a procedure identical with that used for **11**, phosphite **12** (0.10 g, 0.30 mmol), initial cis/trans ratio of 93/7, was converted to phosphorane **13**: ^{31}P NMR (121 MHz, C_6D_6) δ major isomer (cis) −49.36 (s), minor isomer (trans) −49.08 (s); cis/trans = 91/9.

Stereochemistry of Reaction of Phosphite 10 with Hexafluorobiacetyl. In a fashion identical with the above, neat phoshite **10** (0.10 g, 0.20 mmol), initial cis/trans ratio of 96/4, gave phosphorane **5**: ^{31}P NMR (121 MHz, C_6D_6) δ major isomer (cis) −50.04 (s), minor isomer (trans) −49.56 (s); cis/trans = 92/8. The product was approximately 30% contaminated by the geometrical isomer from *cis*-(2-hydroxymethyl)-cyclopentanol: ^{31}P NMR (121 MHz, C_6D_6) δ −49.04 (s).

2-(Hexafluoroisopropoxy)-5-phenyl-1,3,2-dioxaphosphorinane (11). To a solution of 2-chloro-5-phenyl-1,3,2-dioxaphosphorinane (8.09 g, 37.3 mmol) in 100 mL of dry ether was added dropwise at room temperature under an argon atmosphere a solution of 1,1,1,3,3,3-hexafluoropropan-2-ol (6.27 g, 3.93 mL, 37.3 mmol) and triethylamine (3.77 g, 5.19 mL, 37.3 mmol) in 20 mL of dry ether. The resulting solution was stirred for 5 h. The salts were filtered off under argon. The solvent was removed by rotary evaporation. The residue was distilled to give a colorless oil: 7.60 g, 21.8 mmol, 58.5%; bp 88–90 °C (0.03 mmHg); ^{31}P NMR (121 MHz, $CDCl_3$) δ major isomer (trans) 131.86 (septet, J = 7.7 Hz), minor isomer (cis) 125.49 (septet, J = 8.0 Hz), cis/trans = 40/60; ^{13}C NMR (75 MHz, $CDCl_3$) δ major isomer 136.93 (d, C_1 phenyl, J = 1.7 Hz), 128.74, 127.80, 127.28 (three s, C_2, C_3, C_4, phenyl), 121.23 (q of m, $(CF_3)_2CH$, J = 283.5 Hz), 69.87 (septet of d, $(CF_3)_2CH$, J_{CF} = 33.9 Hz, J_{CP} = 21.8 Hz), 64.35 (d, CH_2O, J = 2.8 Hz), 41.07 (d, PhC, J = 7.7 Hz), minor isomer (cis) 139.79 (s, C_1, phenyl), 129.01, 128.02, 127.07 (three s, C_2, C_3, C_4 phenyl), 121.23 (q of m, $(CF_3)_2CH$, J = 283.5 Hz), 69.94 (septet of d, $(CF_3)_2CH$, J_{CF} = 33.9 Hz, J_{CP} = 21.1 Hz), 64.60 (d, CH_2O, J_{PC} = 1.9 Hz), 43.31 (d, PhC, J = 6.0 Hz); ^1H NMR (300 MHz, C_6D_6) δ major isomer 7.15–6.68 (m, 5 H, phenyl Hs), 4.32 (ddd, 2 H, $H_1/H_{1'}$ CH_2, $J_{11'}$ = 1.1 Hz, J_{13} = 3.5 Hz, J_{1P} = 3.5 Hz, J_{12} = −11.4 Hz), 4.07 (septet of d, 1 H, $(CF_3)_2CH$, J_{FP} = 5.9 Hz, J_{HP} = 7.8 Hz), 3.62 (dddd, 2 H, $H_2/H_{2'}$, CH_2, $J_{22'}$ = 1.1 Hz, CH, J_{23} = 3.2 Hz, J_{2P} = 10.0 Hz, J_{12} = −11.4 Hz), 2.25 (tt, 1 H, H_3, J_{23} = 3.2 Hz, J_{13} = 3.5 Hz), minor isomer 7.15–6.68 (m, 5 H, phenyl Hs), 4.33 (dddd, 2 H, $H_1/H_{1'}$, CH_2, $J_{11'}$ = 1.4 Hz, J_{1P} = 2.7 Hz, J_{12} = −11.7 Hz, J_{13} = 12.0 Hz), 4.10 (septet of d, 1 H, $(CF_3)_2CH$, J_{FP} = 5.9 Hz, J_{HP} = 8.0 Hz), 3.55 (tdd, 2 H, $H_2/H_{2'}$, CH_2, $J_{22'}$ = 1.2 Hz, J_{23} = 4.4 Hz, J_{12} = −11.2 Hz, J_{2P} = 11.2 Hz), 3.01 (tt, 1 H, H_3, CH, J_{23} = 4.4 Hz, J_{13} = 12.0 Hz); IR (neat) 3090, 3065, 2980, 2960, 2945, 2900, 1605, 1585, 1510, 1495, 1475, 1465, 1455, 1373, 1288, 1263, 1228, 1218, 1193, 1165, 1125, 1105, 1090, 1072, 1030, 1020, 1000, 965, 950, 905, 898, 875, 867, 853, 795, 752, 718, 698, 685, 670, 650, 630 cm^{-1}. Anal. Calcd for $C_{12}H_{11}O_3F_6P$: C, 41.40; H, 3.18; P, 8.89. Found: C, 41.45; H, 3.18; P, 9.04.

2-Chloro-5-phenyl-1,3,2-dioxaphosphorinane was prepared as described in the literature:[36] 51% yield; bp 99–99.5 °C (0.01 mmHg) (lit.[36] bp 122 °C (2 mmHg).

Thymidine 3′,5′-Cyclic-1,1,1,3,3,3-hexafluoroisopropyl Phosphite (9). To a solution of thymidine 3′,5′-cyclic *N*,*N*-dimethylphosphoramidite[37] (2.00 g, 6.34 mmol) of 50 mL in dry methylene chloride was added dropwise at room temperature under an argon atmosphere 1,1,1,3,3,3-hexafluoropropan-2-ol (1.07 g, 0.670 mL, 6.34 mmol) in 20 mL of dry methylene chloride. The addition took 1 h. The resulting solution was stirred for 5 h and flash column chromatographed under argon (2 × 10 cm, SiO_2, 60–230 mesh; eluting solvent, ethyl acetate). The solvent was removed by vacuum pump, giving 2.49 g of a foamy white solid: 5.68 mmol, 89.6%; ^{31}P NMR (121 MHz, $CDCl_3$) δ major isomer (cis) 123.73 (septet, J = 6.9 Hz), minor isomer (trans) 131.43 (septet, J = 6.9 Hz), cis/trans = 96/4; ^{13}C NMR (75 MHz, acetone-d_6) δ major isomer (cis) 164.42 (s, C_2), 151.13 (s, C_4), 137.51 (s, C_6), 122.37 (q of d, $(CF_3)_2CH$, J_{CF} = 283.5 Hz, J_{CP} = 3.5 Hz), 111.42 (s, C_5), 69.90 (septet of d, $(CF_3)_2CH$, J_{FP} = 33.7 Hz, J_{HP} = 20.3 Hz), 12.28 (s, CH_3C_5); ^1H NMR (300 MHz, acetone-d_6) δ major isomer (cis) 10.29 (s, 1 H, NH), 7.44 (q, 1 H, H_6, J = 1.2 Hz), 6.22 (dd, 1 H, $H_{1'}$), 5.61 (septet of d, 1 H, $(CF_3)_2CH$, J_{FH} = 6.0 Hz, J_{HP} = 8.8 Hz), 4.81 (dddd, 1 H, $H_{3'}$), 4.56 (ddd, 1 H, $H_{5'a}$), 4.46 (ddd, 1 H, $H_{5'b}$), 3.79 (ddd, 1 H, $H_{4'}$), 2.61 (ddd, 1 H, $H_{2'b}$), 2.51 (ddd, 1 H, $H_{2'a}$), 1.83 (d, 3 H, CH_3C_5, J = 1.2 Hz). Anal. Calcd for $C_{13}H_{13}O_6N_2F_6P$: C, 35.63; H, 2.99; N, 6.39; P, 7.07. Found: C, 35.60; H, 3.37; N, 6.68; P, 7.29.

5-*tert*-Butyl-2-(1,1,1,3,3,3-hexafluoroisopropoxy)-1,3,2-dioxaphosphorinane (12). To a solution of 5-*tert*-butyl-2-chloro-1,3,2-dioxaphosphorinane (7.00 g, 35.6 mmol) in 50 mL of dry ether was added dropwise

(32) Moore, L. O.; Clark, J. W. *J. Org. Chem.* **1965**, *50*, 2472.
(33) Eritja, R.; Walker, P. A.; Randall, S. K.; Goodman, M. F.; Karplan, B. E. *Nucleosides Nucleotides* **1987**, *6*, 803.
(34) Ramirez, F.; Marecek, J. F.; Ugi, I.; Lemmen, P.; Marquarding, D. *Phosphorus Sulfur Relat. Elem.* **1978**, *5*, 73.
(35) Penney, C. L.; Belleau, B. *Can. J. Chem.* **1978**, *56*, 2396.
(36) Bergesen, K.; Albriktsen, P. *Acta Chem Scand.* **1972**, *26*, 1680.
(37) Bentrude, W. G.; Khan, M. H.; Saadein, M. R.; Sopchik, A. E. *Nucleosides Nucleotides* **1989**, *8*, 1359.

a solution of 1,1,1,3,3,3-hexafluoropropan-2-ol (5.98 g, 3.75 mL, 35.6 mmol) and triethylamine (3.60 g, 4.96 mL, 35.6 mmol) in 50 mL of dry ether at 0 °C under argon. The addition took 1 h. The resulting solution was then stirred for an additional 1 h. The salts were filtered off under argon. The solvent was removed from the filtrate by rotary evaporation. The residue was distilled to give a colorless liquid: 10.5 g, 32.0 mmol, 89.9%; bp 46–47 °C (0.3 mmHg); ^{31}P NMR (121 MHz, C_6D_6 δ major isomer (cis) 127.13 (septet, J = 7.8 Hz), minor isomer (trans) 134.28 (septet, J = 7.9 Hz). cis/trans = 93/7; ^{13}C NMR (75 MHz, C_6D_6) δ major isomer (cis) 121.89 (q, CF_3)$_2$CH, J = 282.0 Hz), 69.95 (septet of d, (CF$_3$)$_2$*C*H, J_{FC} = 33.5 Hz, J_{PC} = 20.5 Hz), 62.74 (d, *C*H$_2$O, J = 1.7 Hz), 45.89 (d, *t*-Bu*C*H, J = 5.5 Hz), 31.14 (s, (CH$_3$)$_3$*C*), 26.87 (s, (*C*H$_3$)$_3$C); ^{1}H NMR (300 MHz, C_6D_6) δ major isomer (cis) 4.24 (septet of d, 1 H, (CF$_3$)$_2$C*H*, J_{FH} = 5.9 Hz, J_{PH} = 8.0 Hz), 4.10 (dddd, 2 H, *H*1/*H*$_{1'}$, CH$_2$, $J_{11'}$ = 1.5 Hz, J_{1P} = 2.9 Hz, J_{12} = −11.2 Hz, J_{13} = 11.8 Hz), 3.66 (dddd, *H*$_2$/*H*$_{2'}$, CH$_2$, $J_{22'}$ = 1.3 Hz, J_{23} = 4.0 Hz, J_{2P} = 11.5 Hz, J_{12} = −11.2 Hz), 1.74 (tt, 1 H, *H*$_3$, J_{13} = 11.8 Hz, J_{23} = 4.0 Hz); IR (CCl_4) 2990, 2970, 2950, 2910, 2880, 2850, 1415, 1468, 1450, 1403, 1370, 1290, 1265, 1228, 1198, 1165, 1140, 1120, 1105, 1045, 1005, 965, 950, 925, 898, 870, 845, 685, 618 cm^{-1}. Anal. Calcd for $C_{10}H_{15}O_3F_6P$: C, 36.60; H, 4.61; F, 34.73; P, 9.44. Found: C, 36.59; H, 4.47; F, 34.87; P, 9.49.

(1*R*,6*S*)-3β-(1,1,1,3,3,3-Hexafluoroisopropoxy)-2,4,7-trioxa-3-phosphabicyclo[4.3.0]nonane (8). To a solution of (1*R*,6*S*)-3α-(dimethylamino)-2,4,7-trioxa-5-phosphabicyclo[4.3.0]nonane (2.12 g, 11.1 mmol) in 50 mL of dry methylene chloride was added dropwise a solution of 1,1,1,3,3,3-hexafluoropropan-2-ol (1.86 g, 1.17 mL, 11.1 mmol) in 20 mL of dry methylene chloride at room temperature under argon. The addition took 30 min. The resulting solution was stirred for an additional 5 h at room temperature. The solvent was removed by a vacuum pump, and the residue was distilled to give a colorless oil: 2.30 g, 7.32 mmol, 66.1%; bp 56–56.5 °C (0.6 mmHg); ^{31}P NMR (121 MHz) δ major isomer (cis) 123.32 (septet, J = 7.4 Hz), minor isomer (trans) 129.23 (septet, J = 7.8 Hz), cis/trans = 94/6; ^{13}C NMR (75 MHz, $CDCl_3$) δ major isomer (cis) 121.03 (q, (*C*F$_3$)$_2$CH, J = 282.8 Hz), 69.79 (septet of d, (CF$_3$)$_2$*C*H, J_{FC} = 34.1 Hz, J_{CP} = 21.1 Hz); ^{1}H NMR (500 MHz, C_6D_6) δ 4.14 (ddd, 1 H, *H*$_{5'a}$), 4.04 (dddd, 1 H, *H*$_{3'}$), 4.01 (septet of d, 1 H, (CF$_3$)$_2$C*H*, J_{FH} = 5.9 Hz, J_{PH} = 8.4 Hz), 3.96 (ddd, 1 H, *H*$_{5'b}$), 3.32 (ddd, 1 H, *H*$_{1'a}$), 3.26 (ddd, 1 H, *H*$_{1'b}$), 3.06 (ddd, 1 H, H$_{4'}$), 1.54 (dddd, 1 H, *H*$_{2'b}$), 1.40 (dddd, 1 H, *H*$_{2'a}$); IR ($CDCl_3$) 2995, 2970, 2940, 2908, 2880, 1478, 1458, 1370, 1292, 1265, 1228, 1220, 1200, 1180, 1165, 1120, 1105, 1185, 1055, 990, 965, 862, 830, 775, 700, 685, 645 cm^{-1}. Anal. Calcd for $C_8H_9O_4F_6P$: C, 30.59; H, 2.89. Found: C, 30.53; H, 2.99.

(1*R*,6*S*)-3α-(Dimethylamino)-2,4,7-trioxa-3-phosphabicyclo[4.3.0]nonane. A solution of HMPT (5.74 g, 6.40 mL, 35.2 mmol) in 50 mL of dry acetonitrile and a solution of (2*R*,3*S*)-3-hydroxy-2-(hydroxymethyl)furan (4.16 g, 35.2 mmol) in 50 mL of dry acetonitrile were simultaneously added to 200 mL of acetonitrile in a 500-mL flask at room temperature under argon. The addition employed a syringe pump and took 1 h. The resulting solution was then warmed to 65 °C and stirred overnight under argon. The solvent was removed by a vacuum pump. The residue was distilled to give 2.50 g of a colorless oil: 13.1 mmol, 37.2%; bp 82–85 °C (1.5 mmHg) ((lit.[38] bp 59–63 °C (0.35 mmHg)); ^{31}P NMR (121 MHz, $CDCl_3$) δ major isomer (trans) 144.79 (s), minor isomer (cis) 136.33 (s), cis/trans = 82/18; ^{1}H NMR (300 MHz, $CDCl_3$) δ major isomer (trans) 4.31 (ddd, 1 H, *H*$_{5'b}$), 3.98 (ddd, 1 H, *H*$_{5'a}$). 3.77 (dddd, 1 H, *H*$_{3'}$), 3.61–3.45 (m, 2 H, *H*$_{1'a}$, *H*$_{1'b}$), 3.26 (ddd, 1 H, H$_{4'}$), 2.52 (d, 6 H, (*C*H$_3$)$_2$N, J_{PH} = 9.0 Hz). 1.75–1.66 (m, 2 H, *H*$_{2'a}$, *H*$_{2'b}$).

(1*R*,6*S*)-3β-(1,1,1,3,3,3-Hexafluoroisopropoxy)-2,4,dioxa-3-phosphabicyclo[4.3.0]nonane (10). To a solution of (1*R*,6*S*)-3α-(dimethylamino)-2,4-dioxa-5-phosphabicyclo[4.3.0]nonane (2.43 g, 12.8 mmol) in 50 mL of dry ether was added dropwise a solution of 1,1,1,3,3,3-hexafluoropropan-2-ol (2.16 g, 1.35 mL, 12.8 mmol) in 20 mL of dry ether at room temperature under argon. The addition took 1 h. The resulting solution was stirred for an additional 5 h at room temperature. The solvent was removed by a vacuum pump, and the residue was distilled to give a colorless oil: 2.70 g, 8.65 mmol, 67.6%; bp 58–59 °C (0.4 mmHg); ^{31}P NMR (121 MHz, C_6D_6) δ major isomer (cis) 126.37 (septet, J = 7.9 Hz), minor isomer (trans) 131.40 (septet, J = 7.9 Hz), cis/trans = 96/4; ^{13}C NMR (75 MHz, $CDCl_3$) δ major isomer (cis) 121.26 (q of m, (*C*F$_3$)$_2$CH, J = 283.0 Hz), 69.47 (septet of d, (CF$_3$)$_2$*C*H, J_{CF} = 33.9 Hz, J_{PC} = 21.3 Hz); ^{1}H NMR (300 MHz, C_6D_6) δ major isomer (cis) 4.42 (septet of d, 1 H, (CF$_3$)$_2$C*H*, J_{FH} = 5.9 Hz, J_{PH} = 8.0 Hz), 3.95 (ddd, (H, *H*$_{5'a}$), 3.91 (ddd, 1 H, *H*$_{3'}$), 3.67 (ddd, 1 H, H$_{5'b}$), 1.65 (m, 1 H, *H*$_4$), 1.33–0.31 (m, 6 H, C*H*$_2$C*H*$_2$C*H*$_2$); IR ($CDCl_3$) 3160, 3015, 2985, 2970, 2960, 2908, 1815, 1795, 1640, 1475, 1398, 1375, 1293, 1263. 1228, 1215, 1200, 1125, 1105, 1095, 1040, 998, 935, 905, 770, 735, 705, 685, 675, 665, 650, 622 cm^{-1}. Anal. Cacld for $C_9H_{11}O_3F_6P$: C, 34.63; H, 3.55; P, 9.92. Found: C, 34.58; H, 3.58; P, 9.80.

(1*R*,6*S*)-3β-(Dimethylamino)-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane. A solution of HMPT (5.11 g, 31.3 mmol) in 50 mL of dry acetonitrile and a solution of *trans*-(2-hydroxymethyl)cyclopentanol (3.63 g, 31.3 mmol) in 50 mL of dry acetonitrile were simultaneously added to 200 mL of acetonitrile contained in a flask at room temperature under argon by means of a syringe pump over a 2-h period. The resulting solution was then warmed to 55 °C and stirred overnight under argon. The solvent was removed by a vacuum pump. The residue was distilled to give 2.42 g of a colorless oil: 12.8 mmol, 40.9%; bp 70–72 °C (0.01 mmHg) (lit.[39] bp 60–62 °C (0.34 mmHg)).

(1*R*,6*S*)-3β-(1,1,1,3,3,3-Hexafluoroisopropoxy)-2,4,7-trioxa-3-phosphabicyclo[4.3.0]nonane Hexafluorobiacetyl Adduct (3). Hexfluorobiacetyl (5 mL) was added dropwise to (1*R*,6*S*)-3β-(1,1,1,3,3,3-hexafluoroisopropoxy)-2,4-7-trioxa-3-phosphabicyclo[4.3.0]nonane (1.50 g, 4.78 mmol) at 0 °C under an argon atmosphere. The addition took 30 min. The resulting mixture was stirred for 2 h at 0 °C, warmed to room temperature, and stirred for an additional 5 h. Excess hexafluorobiacetyl was removed by a vacuum pump, and the residue was distilled to give a yellowish oil: 1.89 g, 3.72 mmol, 77.8%; bp 62–63 °C (0.05 mmHg). The oil showed >90% purity by ^{31}P and ^{1}H NMR: ^{31}P NMR (121 MHz, C_6D_6) δ major isomer (cis) −49.22 (s), minor isomer (trans) −48.70 (s), cis/trans = 78/22; ^{13}C NMR (75 MHz, $CDCl_3$) δ major isomer 128.90 (m, CF_3C=), 120.37 (q of m, (*C*F$_3$)$_2$CH, J = 281.9 Hz), 118.35 (q of d, *C*F$_3$C=, J_{CF} = 269.5 Hz, J_{CP} = 19.5 Hz), 73.82 (septet of d, (CF$_3$)$_2$*C*H, J_{CF} = 35.0 Hz, J_{CP} = 11.0 Hz), minor isomer 128.91 (m, CF_3C=), 120.37 (q of m, (*C*F$_3$)$_2$CH, J = 281.9 Hz), 118.35 (q of d, *C*F$_3$C=, J_{FC} = 269.5 Hz, J_{CP} = 19.5 Hz), 72.39 (septet of d, (CF$_3$)$_2$*C*H, J_{CF} = 35.0 Hz, J_{CP} = 12.6 Hz); ^{1}H NMR (400 MHz, C_6D_6) δ major isomer (cis) 5.82 (septet of d, 1 H, (CF$_3$)$_2$C*H*, J_{FH} = 5.8 Hz, J_{HP} = 13.7 Hz), 4.04 (ddd, 1 H, *H*$_{5'b}$), 3.78 (ddd, 1 H, *H*$_{3'}$), 3.48 (ddd, 1 H, *H*$_{5'a}$), 3.40 (m, 1 H, *H*$_{1'a}$), 3.38 (m, 1 H, H$_{1'b}$), 3.31 (ddd, 1 H, *H*$_{4'}$), 1.34 (dddd, 1 H, *H*$_{2'b}$), 1.21 (dddd, 1 H, *H*$_{2'a}$); ^{1}H NMR (300 MHz, $CDCl_3$) δ major isomer 5.45 (septet of d, 1 H, (CF$_3$)$_2$C*H*, J_{FP} = 5.8 Hz, J_{HP} = 13.9 Hz), 4.63 (ddd, 1 H, *H*$_{5'b}$), 4.38 (ddd, 1 H, *H*$_{3'}$), 4.19 (m, 2 H, *H*$_{1'a}$, *H*$_{1'b}$), 4.13 (ddd, 1 H, *H*$_{5'a}$), 3.81 (ddd, 1 H, *H*$_{4'}$), 2.36 (apparent dddd, 1 H, *H*$_{2'b}$), 2.11 (apparent dddd, 1 H, *H*$_{2'a}$), minor isomer (trans) 5.34 (septet of d, 1 H, (CF$_3$)$_2$C*H*, J_{FP} = 5.8 Hz, J_{HP} = 15.2 Hz), 4.52 (ddd, 1 H, *H*$_{5'b}$), 4.51 (ddd, 1 H, *H*$_{3'}$), 4.18 (m, 2 H, *H*$_{1'a}$, *H*$_{1'b}$), 4.09 (ddd, 1 H, *H*$_{5'a}$), 3.94 (ddd, 1 H, *H*$_{4'}$), 2.36 (m, 1 H, *H*$_{2'b}$), 2.11 (m, 1 H, *H*$_{2'a}$); IR (neat) 3000, 2970, 2950, 2910, 2870, 1712, 1460, 1383, 1295, 1268, 1230, 1205, 1160, 1110, 1070, 1030, 995, 980, 960, 915, 908, 880, 860, 790, 758, 750, 735, 688 cm^{-1}; HRMS calcd for $C_{12}H_9O_6F_{12}P$ (M^+) 507.9945, found 507.9925; GC/MS, M^+ = 508.0, both diastereomers.

***cis*-Thymidine 3′,5′-Cyclic 1,1,1,3,3,3-Hexafluoroisopropyl Phosphite Hexafluorobiacetyl Adduct (4).** Hexafluorobiacetyl (3 mL) was added dropwise to *cis*-thymidine 3′,5′-cyclic 1,1,1,3,3,3-hexafluoroisopropyl phosphite (1.00 g, 2.28 mmol) at 0 °C under an argon atmosphere. The addition took 30 min. The resulting mixture was stirred for 2 h at 0 °C, warmed to room temperature, and stirred for an additional 5 h. Excess hexafluorobiacetyl was removed by a vacuum pump to give 1.32 g of a white, foamy solid (2.09 mmol, 91.6%) ≥95% pure by ^{1}H and ^{31}P NMR: ^{31}P NMR (121 MHz, $CDCl_3$) δ −49.85 (s), a minor peak, likely for *trans*-**4** was noted at −48.95; ^{13}C NMR (75 MHz, acetone-d_6) δ 164.07 (s, C_2), 151.01 (s, C_4), 138.12 (s, C_6), 124.08 (q of m, (*C*F$_3$)$_2$CH, J = 286.9 Hz), 121.48 (q of m, *C*F$_3$C=, J = 280.0 Hz), 111.35 (s, C_5), 72.23 (septet of d, (CF$_3$)$_2$*C*H, J_{CF} = 33.5 Hz, J_{CP} = 11.1 Hz), 12.31 (s, CH$_3$C$_5$), *C*5 and CF$_3$*C*= resonances not observed; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (q, 1 H, H_6, J = 1.1 Hz), 6.02 (dd, 1 H, $H_{1'}$), 5.53 (septet of d, 1 H, (CF$_3$)$_2$C*H*, J_{FP} = 5.7 Hz, J_{HP} = 13.9 Hz), 4.83 (ddd, 1 H, *H*$_{3'}$), 4.63 (ddd, 1 H, *H*$_{5'b}$), 4.23 (ddd, 1 H, *H*$_{5'a}$), 3.93 (ddd, 1 H, *H*$_{4'}$), 2.56 (m, 1 H, *H*$_{2'b}$), 2.54 (m, 1 H, *H*$_{2'a}$), 1.93 (d, 3 H, C*H*$_3$C$_5$, J = 1.1 Hz); IR ($CDCl_3$) 3150, 2985, 2940, 2905, 2250, 1820, 1795, 1700, 1690, 1640, 1563, 1475, 1468, 1380, 1293, 1230, 1215, 1193, 1175, 1100, 1095, 985, 935, 870, 770, 670, 660, 635, 620 cm^{-1}; MS, m/z (M^+) 632.7. Anal. Calcd for $C_{17}H_{13}O_8N_2F_{12}P$: C, 32.30; H, 2.07; N, 4.43; P, 4.90. Found: C, 31.89; H, 2.42; N, 4.03; P, 4.24.

(1*R*,6*S*)-3β-(1,1,1,3,3,3-Hexafluoroisopropoxy)-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane Hexafluorobiacetyl Adduct (5). Hexafluorobiacetyl (5 mL) was added dropwise to (1*R*,6*S*)-(1,1,1,3,3,3-hexafluoroisopropoxy)-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (1.80 g, 5.77 mmol) at −10 °C under an argon atmosphere. The addition took 30 min. The resulting mixture was stirred for 1 h at −10 °C, warmed to room temperature, and stirred for an additional 3 h. Excess hexafluorobiacetyl was removed by a vacuum pump, and the residue was distilled, to give an oil: 2.34 g, 4.64 mmol, 80.4%; bp 82–84 °C (0.005 mmHg); ^{31}P

(38) Hermans, R. J. M.; Buck, H. M. *Phorphorus Sulfur Relat. Elem.* **1987**, *31*, 255.

(39) Hermans, R. J. M.; Buck, H. M. *J. Org. Chem.* **1987**, *52*, 5150.

NMR (121 MHz, C_6D_6) δ major isomer (*cis*) −50.04 (s), minor isomer −49.56 (s), *cis*/*trans* = 92/8 (before distillation), cis/trans = 71/29 (after distillation); ^{13}C NMR (75 MHz, $CDCl_3$) δ major isomer (cis) 129.0 (s, CF_3C=), 120.47 (q of m, $(CF_3)_2CH$, J = 282.0 Hz), 118.57 (q of d, CF_3C=, J_{CF} = 270.0 Hz, J_{PC} = 19.9 Hz), 73.47 (septet of d, $(CF_3)_2CH$, J_{FC} = 34.8 Hz, J_{PC} = 11.0 Hz), minor isomer (trans) 129.0 (s, CF_3C=), 120.47 (q of m. $(CF_3)_2CH$, J = 282.0 Hz), 118.57 (q of d, $(CF_3C$=, J_{CF} = 270.0 Hz, J_{PC} = 19.9 Hz), 72.69 (septet of d, $(CF_3)_2CH$, J_{FC} = 34.8 Hz, J_{PC} = 12.0 Hz); ^1H NMR (300 MHz, C_6D_6) δ major isomer (cis) 5.33 (septet of d, 1 H, $(CF_3)_2CH$, J_{FH} = 5.9 Hz, J_{PH} = 13.9 Hz), 3.97 (ddd, 1 H, $H_{5'b}$), 3.72 (ddd, 1 H, $H_{3'}$), 3.19 (ddd, 1 H, $H_{5'a}$), 1.47 (m, 1 H, $H_{4'}$), 1.45–0.38 (m, 6 H, $CH_2CH_2CH_2$), minor isomer 5.34 (septet of d, 1 H, $(CF_3)_2CH$, J_{FH} = 5.9 Hz, J_{PH} = 15.5 Hz), 4.01 (ddd, 1 H, $H_{5'b}$), 3.66 (ddd, 1 H, $H_{3'}$), 3.35 (ddd, 1 H, $H_{5'a}$), 1.77 (m, 1 H, $H_{4'}$), 1.45–0.38 (m, 6 H, $CH_2CH_2CH_2$); IR (neat) 3000, 2970, 2960, 2880, 1710, 1410, 1348, 1295, 1265, 1228, 1203, 1175, 1160, 1110, 1060, 1045, 1025, 995, 880, 740, 730, 710, 685 cm^{-1}. Anal. Calcd for $C_{13}H_{11}O_5F_{12}P$: C, 30.85; H, 2.19; P, 6.12. Found: C, 30.54; H, 2.03; P, 5.65.

(1*R*,6*S*)-(1,1,1,3,3,3-Hexafluoroisopropoxy)-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane Hexafluoroacetone Adduct (6). Hexafluoroacetone (5 mL) was added to (1*R*,6*S*)-(1,1,1,3,3,3-hexafluoroisopropoxy)-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (1.34 g, 4.29 mmol) at −78 °C under an argon atmosphere. The resulting mixture was then warmed to −26 °C and allowed to reflux for 6 h. Excess hexafluoroacetone was removed at room temperature, leaving a white crystalline solid: 2.34 g, 4.64 mmol, 96.6%; mp 73–76 °C; ^{31}P NMR (121 MHz, C_6D_6) δ major isomer (cis) −52.20 (s), minor isomer (trans) −51.66; cis/trans = 97/3; ^{13}C NMR (75 MHz, C_6D_6) δ major isomer (cis) 120.41 (q of m, CF_3s, J = 303.1 Hz), 73.88 (septet of d, $(CF_3)_2CH$, J_{FC} = 34.8 Hz, J_{PC} = 11.1 Hz), a separate resonance for $(CF_3)_2CC(CF_3)$ was not seen; ^1H NMR (300 MHz, C_6D_6) δ major isomer (cis) 5.30 (septet of d, 1 H, $(CF_3)_2CH$, J_{HF} = 5.9 Hz, J_{PH} = 13.4 Hz), 3.97 (dd, 1 H, $H_{5'b}$), 3.71 (ddd, 1 H, $H_{3'}$), 3.10 (ddd, 1 H, $H_{5'a}$), 1.89 (m, 1 H, $H_{4'}$), 1.58–0.44 (m, 6 H, $CH_2CH_2CH_2$); IR ($CDCl_3$) 3160, 3000, 2985, 2980, 2908, 2885, 2250, 1825, 1795, 1645, 1560, 1468, 1378, 1348, 1298, 1270, 1245, 1218, 1203, 1168, 1110, 1098, 1050, 1000, 985, 965, 930, 905, 870, 775, 740, 635, 620 cm^{-1}. Anal. Calcd for $C_{15}H_{11}O_5F_{18}P$: C, 27.97; H, 1.72; P, 4.81. Found: C, 27.81; H, 1.95; P, 4.62.

Collection of X-ray Data and Solution of Structure. A crystal of **6**, $C_{16}H_{14}PO_5F_{18}$, of approximate dimensions of 0.21 × 0.18 × 0.15 mm was mounted on a fiber glass fiber with its long axis roughly parallel to the ϕ axis of the goniometer. Preliminary examinations and data collection were performed with Cu Kα radiation g = 1.5418 Å on an Enraf-Nonius CAD_4 diffractometer. Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range of 28.0° < 2θ < 36.0°, measuring by the computer-controlled method of centering. The data were collected at a temperature of −140 °C by using a variable-scan rate. A total of 3549 reflections were collected. Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 29.88 cm^{-1} for Cu Kα radiation. An empirical absorption correction band on a series of ψ scans was applied to the data. Relative transmission coefficients ranged from 0.7958 to 1.4977 with an average value of 0.9792.

The structure was solved by the direct methods, which revealed the position of all non-hydrogen atoms. Hydrogen atoms were located from final difference Fourier synthesis and added to the structure factor calculations. Their positions were refined with fixed thermal parameters. The structure was refined in full-matrix least squares where the function minimized was $\sum w(|F_o| - |F_c|)^2$ and the weight w is defined as 1.0 for all observed reflections.

Scattering factors were taken from Cromer and Wabe.[40] Anomalous dispersion effects were included in F_c;[41] the values for Δ' and Δ'' were those of Cromer.[42] All calculations were performed on a VAX 3100 computer using SDP/VAX.[43] Only the 2859 reflections having intensities greater than 3.0 times their standard deviations were used in the refinements. The final cycle of refinement included 353 variable parameters and converged with unweighted and weighted agreement factors of $R = \sum(|F_o| - |F_c|)/\sum|F_o| = 0.0567$ and $R_w = [(\sum w(|F_o| - |F_c|)^2)/\sum w(F_o)^2]^{1/2} = 0.0656$. The standard deviation of an observation of unit weight was 3.71.

Acknowledgment. Support of this work by a grant (CA11045) from the National Cancer Institute of the Public Health Service is gratefully acknowledged. We also thank Dr. Alan E. Sopchik for the 500-MHz ^1H NMR spectra and help with simulation of certain of the ^1H NMR spectra of **3–6**.

Note Added in Proof. According to R. R. Holmes, University of Massachusetts, a structure closely related to **6**, but with the five-membered ring included as part of a phenanthrene structure, has been determined by X-ray crystallography: Holmes, R. R.; Kumara Swamy, K. C.; Holmes, J. M.; Day, R. O., submitted for publication.

Supplementary Material Available: Tables of hydrogen atom parameters, bond distances, torsional angles, and thermal positional parameters (16 pages); observed and calculated structure factors for X-ray structure of *cis*-**6** (10 pages). Ordering information is given on any current masthead page.

(40) Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IX, Table 2.2B.
(41) Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781.
(42) Cromer, D. T. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.3.1.
(43) Frenz, B. A. The Enraf–Nonius CAD 4 SDP–A Real-time System for Concurrent X-ray Data Collection and Crystal Structure Determination. In *Computing in Crystallography*; Schenk, H., Olthof-Hazelkamp, R., van-Konigsveld, H., Baasi, G. C., Eds.; Delft University Press: Delft, Holland, 1978; pp 64–71.