dried over Na_2SO_4 to afford a toluene solution of **22**. **Reduction.** To a mechanically stirred, heated (50 °C) solution of 234 mL (3.4 M in toluene, 0.796 mol) of sodium bis(2-methoxyethoxy)aluminum hydride in 375 mL of dry toluene was added the solution of **22** over a 1-h period. The solution was then heated for 1 h at 80 °C. The reaction mixture was cooled to 20 °C and the excess hydride quenched by the cautious addition of 1.3 L of 1.3 M aqueous NaOH. Following the addition of 3.1 g (11 mmol) of n-Bu_4NCl, the mixture was stirred rapidly for 4 h at 20 °C. The mixture was partitioned and the organic layer washed with 1.3 M aqueous NaOH (2 × 860 mL), H_2O (860 mL), and brine (860 mL), dried over Na_2SO_4, and concentrated in vacuo to afford **23** free base as an oil. The oil was dissolved in 2.1 L of 9:1 Et_2O/EtOH and then treated with 90 mL of 7 M HCl in EtOH. The mixture was cooled to 0 °C and stirred for 1 h. The mixture was filtered and the cake washed with 860 mL of 9:1 Et_2O/EtOH and 860 mL of Et_2O. The product was dried in vacuo to afford 149 g (94%) of **23**·HCl as a white solid. An analytical sample was recrystallized from MeCN: mp 230–232 °C [lit.[1a] mp 231–233 °C]; ^1H NMR (DMSO-d_6) [as free base] δ 6.98 (d, 1, J = 8.5 Hz, H-7), 6.92 (d, 1, J = 2.5 Hz, H-10), 6.73 (dd, 1, J = 2.5, 8.5 Hz, H-8), 4.15 (d, 1, J = 9.0 Hz, H-10b), 3.97 (dd, 1, J = 2.5, 11.5 Hz, H-2), 3.74 (dt, 1, J = 2.3, 11.5 Hz, H-2), 3.69 (s, 3, OCH_3), 2.68–2.85 (m, 4, H-1′, H-3, 2 H-6), 2.02–2.31 (m, 4, H-1′, H-3, H-4a, H-5), 1.33–1.52 (m, 3, 2 H-2′, H-5), 0.85 (t, 3, J = 7.8 Hz, 3 H-3′); ^{13}C NMR (DMSO-d_6) [as free base] δ 157.3 (s, C-9), 137.4 (s, C-10a), 128.8 (d, C-7), 126.7 (s, C-6a), 113.2 (d, C-8), 109.2 (d, C-10), 78.2 (d, C-10b), 66.6 (t, C-2), 62.1 (d, C-4a), 54.8 (q, OCH_3), 54.2 (t, C-3), 51.8 (t, C-1′), 26.5 (t, C-6), 23.8 (t, C-5), 18.6 (t, C-2′), 11.7 (q, C-3′); $[\alpha]_{589}$ +49.0° (c 1.09, EtOH) [lit.[1a] $[\alpha]_{589}$ +47.3° (c 0.103, EtOH)]. Anal. Calcd for $C_{16}H_{24}NO_2Cl$: C, 64.53; H, 8.11; N, 4.70. Found: C, 64.55; H, 8.11; N, 4.81.

(4a*R*,10b*R*)-3,4,4a,5,6,10b-Hexahydro-4-propyl-2*H*-naphth[1,2-*b*]-1,4-oxazin-9-ol Hydrochloride (1). Caution: 1 is a potent CNS agent. Do not allow solutions of 1 or solid 1 to come in contact with the skin, eyes, nose, or mouth! To a mechanically stirred suspension of 226 g (1.51 mol) of (±)-methionine in 1.5 L of $MeSO_3H$ at 20 °C was added 148 g (0.497 mol) of **23** portionwise over a 10-min period. The mixture was stirred for 40 h at 20 °C. The mixture was cooled to 5 °C and diluted with 1.5 L of H_2O and the pH adjusted to 13.5 with 3.6 L of 6.1 M aqueous NaOH while the temperature was maintained at <10 °C. Following the addition of 30 g of charcoal (Darco KB, prewashed with aqueous NaOH), the mixture was stirred for 1.5 h at 20 °C. The mixture was filtered through a pad of Super-Cel and the cake washed with 1.0 L of H_2O. The pH of the combined filtrates was adjusted to 9.0 with 300 mL of 12 M aqueous HCl and the mixture cooled to 0 °C and stirred for 1 h. The mixture was filtered and the cake washed with 3.1 L of cold H_2O. The free base was dried in vacuo and then dissolved in 1.6 L of EtOH at 40 °C. Following the addition of 12 g of charcoal (Darco G-60), the solution was filtered through a pad of Super-Cel. The solution was cooled to 20 °C, treated with 122 mL of 7 M HCl in EtOH over a 0.5-h period, and diluted with 1.6 L of Et_2O and the mixture stirred 1 h at 0 °C. The mixture was filtered and the cake washed with 1.5 L of cold 1:1 Et_2O/EtOH. The product was dried in vacuo at 30 °C to afford 127 g (90%) of **1**·HCl as a white crystalline solid: mp 303–305 °C [lit.[1b] mp >260 °C]; ^1H NMR (DMSO-d_6) [as the free base] δ 9.07 (s, 1, OH), 6.8–6.9 (m, 2, H-7, H-10), 6.57 (dd, 1, J = 1.9, 7.8 Hz, H-8), 4.11 (d, 1, J = 8.3 Hz, H-10b), 3.95 (br d, 1, J = 10.8 Hz, H-2), 3.74 (br t, 1, J = 11.2 Hz, H-2), 2.63–2.86 (m, 4, H-1′, H-3, 2 H-6), 2.00–2.35 (m, 4, H-1′, H-3, H-4a, H-5), 1.30–1.55 (m, 3, 2 H-2′, H-5), 0.90 (t, 3, J = 7.3 Hz, 3 H-3′); ^{13}C NMR (DMSO-d_6) [as the free base] δ 155.2 (s, C-9), 137.2 (s, C-10a), 128.6 (d, C-7), 124.8 (s, C-6a), 114.0 (d, C-8), 111.3 (d, C-10), 78.4 (d, C-10b), 66.6 (t, C-2), 62.2 (d, C-4a), 54.2 (t, C-3), 51.9 (t, C-1′), 26.5 (t, C-6), 24.0 (t, C-5), 18.6 (t, C-2′), 11.7 (q, C-3′); $[\alpha]_{589}$ +55.9° (c 1.0, 0.10 M HCl in MeOH).

A ^{31}P and ^1H NMR Study of the Conformations of a Series of Diastereomeric 3-Substituted *trans*-2,4-Dioxa-3-oxo- and *trans*-2,4-Dioxa-3-thioxo-3-phosphabicyclo[4.3.0]nonanes as Model Compounds for Cyclic Nucleotides

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A number of epimeric pairs of 3-X-*trans*-2,4-dioxa-3-Y-3-phosphabicyclo[4.3.0]nonanes (**1**, X = OCH_3, Y = O; **2**, X = OCH_3, Y = S; **3**, X = OPh, Y = O; **4**, X = OPh, Y = S; **5**, X = Cl, Y = O; **6**, X = Cl, Y = S; **7**, X = $N(CH_3)_2$, Y = O; **8**, X = $N(CH_3)_2$, Y = S; **9**, X = S, Y = O; **10**, X = O, Y = O) have been prepared and their configuration and conformation studied by ^{31}P and ^1H NMR. The cis isomers **1a–6a** and the trans isomers **7b** and **8b** are shown to populate exclusively chair conformation **18**. Their diastereomers **1b–6b**, **7a**, and **8a**, however, exist as an equilibrium between chair conformation **18** and twist conformation **19**. The mole fraction of twist is found to vary with the nature of the exocyclic substituents on the phosphorus atom, being maximal for the chloro compounds **5b** and **6b**. In addition, it is shown that the chair ⇄ twist equilibrium is solvent-sensitive. The charged compounds **9a**, **9b**, and **10** are in a chair conformation. The position of the negatively charged sulfur atom has no influence on the preferred conformation of the phosphorothioates **9a** and **9b**. The results for **9a** and **9b** are discussed in relation to the difference in biological activity of (S_P)- and (R_P)-cAMPS.

Introduction

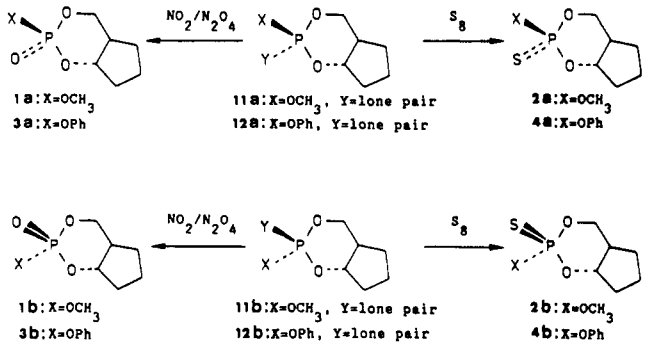
3′,5′-Cyclic nucleotides, e.g., cAMP and cGMP, play a central role in hormone action and cell communication.[1] Recently, it was shown that the biological activity of cyclic nucleotide analogues, derivatized at phosphorus, is governed by the configuration on the phosphorus atom (S_P or R_P).[2] Furthermore, it was established that the conformation of the dioxaphosphorinane ring of comparable cyclic nucleotides is determined by the phosphorus configuration.[3] In this paper we present a detailed configu-

(1) See, e.g.: Miller, J. P. *Cyclic 3′,5′-Nucleotides: Mechanism of Action*; Cramer, H., Schultz, J., Eds.; Wiley: London, 1977; p 77.

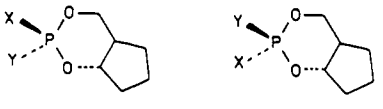
(2) (a) van Haastert, P. J. M.; van Driel, R.; Jastorff, B.; Baraniak, J.; Stec, W. J.; de Wit, R. J. W. *J. Biol. Chem.* **1984**, *259*, 10020. (b) de Wit, R. J. W.; Hekstra, D.; Jastorff, B.; Stec, W. J.; Baraniak, J.; van Driel, R.; van Haastert, P. J. M. *Eur. J. Biochem.* **1984**, *142*, 255. (c) Erneux, C.; van Sande, J.; Jastorff B.; Dumont, J. E. *Biochem. J.* **1986**, *234*, 193. (d) van Ool, P. J. J. M.; Buck, H. M. *Eur. J. Biochem.* **1982**, *121*, 329. (e) van Ool, P. J. J. M.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 119. (f) van Ool, P. J. J. M. Ph.D. Thesis, Eindhoven University of Technology, 1983.

0022-3263/87/1952-5150$01.50/0

Scheme I



rational and conformational analysis of a number of epimeric *trans*-2,4-dioxa-3-oxo- and *trans*-2,4-dioxa-3-thioxo-3-phosphabicyclo[4.3.0]nonanes **1a–9a**, **1b–9b**, and **10**.



	X	Y		X	Y
1	OCH_3	O	6	Cl	S
2	OCH_3	S	7	$N(CH_3)_2$	O
3	OPh	O	8	$N(CH_3)_2$	S
4	OPh	S	9	S	O
5	Cl	O	10	O	O

These compounds contain a dioxaphosphorinane ring trans fused to a cyclopentane ring and can be considered as simple model compounds for cyclic nuceotides. Other bicyclic model compounds in which the phosphorus containing ring was transannelated with a six-membered tetrahydropyran or cyclohexane ring have been already studied.[4,5] It seems, however, likely that conclusions drawn from model compounds possessing a five-membered ring adjacent to the dioxaphosphorinane ring are more directly applicable to cyclic nucleotides.

Results and Discussion

Synthesis. The cis compounds **1a** and **3a** (singly bonded substituent on phosphorus cis to H_1) were prepared from the corresponding cis methyl and phenyl phosphites **11a** and **12a**,[6] respectively, by stereochemically retentive[7] NO_2/N_2O_4 oxidation (Scheme I). The trans diastereoisomers **1b** and **3b** were obtained in an analogous way from the trans phosphites **11b** and **12b**, respectively. Since these phosphites were never completely free of their thermodynamically favored cis isomers, the trans phosphates **1b** and **3b** were always obtained as mixtures with their cis epimers **1a** and **3a**. The phenyl phosphates **3a** and **3b**, however, could be separated by column chromatography. Reaction of the phosphites **11a** and **12a** with elemental sulfur, which is known to proceed with retention of configuration at the phosphorus atom,[8] yielded the cis thiooxophosphorinanes **2a** and **4a**, respectively. The trans isomers **2b** and **4b** were obtained by separation of the cis/trans mixtures which resulted from the reaction of sulfur with the mixture of **11a** and **11b** and of **12a** and **12b** (Scheme I). Stereospecific removal of the methyl group of the phosphates **1a,b** and **2a,b** by *tert*-butylamine[9] led almost quantitatively to the charged compounds **10** and **9b,a**, respectively.

The chlorophosphonates **5a** and **5b** were prepared in two steps from the thiophosphates **9a** and **9b** via the intermediate sulfenyl chlorides **13a** and **13b** according to a method described by Michalski et al.[10] Both steps proceeded with predominant retention of configuration at phosphorus. Compound **5a** was also obtained as major product by the oxidation of the cis chlorophosphonite **14**[11] with NO_2/N_2O_4 (Scheme II).

Independent confirmation of the configurational assignment of the chlorophosphonates **5a** and **5b** was obtained by their transformation into the methyl phosphates **1b** and **1a**, respectively. In addition, nucleophilic substitution of the chlorine atoms in **5a** and **5b** by dimethylamine yielded the phosphoramidates **7b** and **7a**, respectively, with complete inversion of configuration at phosphorus. Reaction of thiophosphoryl chloride **15** with (1*RS*,2*SR*)-2-hydroxycyclopentanemethanol (**16**)[13] afforded a mixture of the thiophosphonates **6a** and **6b** (22/78 as judged by ^{31}P NMR), which could not be separated by column chromatography. Methanolysis of this mixture at room temperature yielded a mixture of **2b** and **2a** (22/78) (Scheme III). On the basis of this result, **6a** could be assigned the cis configuration and **6b** the trans configuration. This assignment was confirmed by the formation of the phosphoramidates **8b** and **8a** (18/82) in the reaction of a mixture of **6a** and **6b** (19/81) with dimethylamine. Equilibration of the initial mixture of **6a** and **6b** with a catalytic amount of tetraethylammonium chloride in acetone at room temperature resulted in the formation of a mixture containing **6a** and **6b** in the ratio 76/24.

Oxidation of a mixture of (dimethylamino)phosphonites **17a** (20%, dimethylamino group cis) and **17b** (80%, dimethylamino group trans) furnished a mixture of phosphoramidates **7a** and **7b** (20/80). A mixture of **7a** and **7b** (23/77) was also obtained by the reaction of dimethylchloroamine with a mixture of methyl phosphites **11a** and **11b** (40% of **11a**) (Scheme IV).[3] The spectral parameters of the phosphoramidates thus obtained were identical with those of the compounds obtained by the reaction of the chlorophosphonates **5a** and **5b** with dimethylamine.

A mixture of the isomeric thiophosphoramidates **8a** and **8b** (20/80) was obtained by the reaction of elemental sulfur with a mixture of **17a** and **17b** (20/80) (Scheme V). Chromatographic separation of this mixture yielded the single diastereomers which were identical with the ones obtained by the reaction of the chloro compounds **6a** and **6b** with dimethylamine (Schemes III and V).

Assignment of Configuration at Phosphorus. The assignment of the cis and trans configurations to the diastereomers **1a–9a** and **1b–9b** was made on the basis of

(3) Sopchik, A. E.; Bentrude, W. G. *Tetrahedron Lett.* **1980**, *21*, 4679.
(4) (a) Bouchu, D.; Dreux, J. *Tetrahedron Lett.* **1980**, *21*, 2513. (b) Bouchu, D. *Phosphorus Sulfur*, **1983**, *15*, 33.
(5) (a) Haemers, M.; Ottinger, R.; Reisse, J.; Zimmermann, D. *Tetrahedron Lett.* **1971**, 461. (b) Gorenstein D. G.; Rowell, R. *J. Am. Chem. Soc.* **1979**, *101*, 4925. (c) Gorenstein, D. G.; Rowell, R.; Findlay, J. *J. Am. Chem. Soc.* **1980**, *102*, 5077. (d) Taira, K.; Lai, K.; Gorenstein, D. G. *Tetrahedron* **1986**, *42*, 229.
(6) Hermans, R. J. M.; Buck, H. M. *Phosphorus Sulfur* **1987**, *31*, 255.
(7) (a) Denney, D. Z.; Chen, G. Y.; Denney, D. B. *J. Am. Chem. Soc.* **1969**, *91*, 6838. (b) Michalski, J.; Okruszek, A.; Stec, W. J. *J. Chem. Soc. D* **1970**, 1495. (c) Mosbo, J. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4659.
(8) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187.
(9) (a) Smith, D. J.; Ogilvie, K. K.; Gillen, M. F. *Tetrahedron Lett.* **1980**, *21*, 861. (b) Sopchik, A. E.; Bentrude, W. G. *Tetrahedron Lett.* **1981**, *22*, 307.
(10) Bouchu, D.; Tardy, F.; Moreau, M.; Dreux, J.; Skowronska, A.; Michalski, *J. Tetrahedron Lett.* **1985**, *26*, 443.
(11) The chloro substituent in **14**[6,12] is cis according to the large $J_{5b,P}$ (10.6 Hz) and small $J_{5a,P}$ coupling (5.3 Hz).
(12) Ramirez, F.; Marecek, J. F.; Ugi, I.; Lemmen, P.; Marquarding, D. *Phosphorus* **1975**, *5*, 73.
(13) Penney, C. L.; Belleau, B. *Can. J. Chem.* **1978**, *56*, 2396.

Scheme II

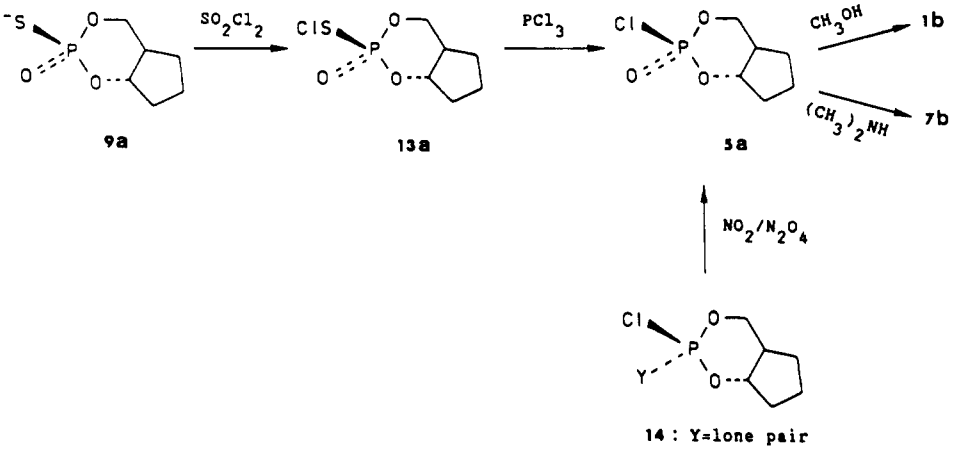
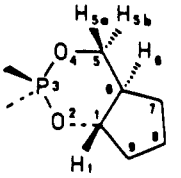


Table I. Selected ^{1}H NMR Spectral Parameters for 1a–9a, 1b–9b, and 10 at 300 MHz and 300 K[a]



	chem shift[b]			coupling constants[c]					
compd	H_{5a}	H_{5b}	H_1[d]	$J_{5a,5b}$	$J_{5a,P}$	$J_{5a,6}$	$J_{5b,P}$	$J_{5b,6}$	$J_{1,P}$[d]
1a[e]	4.20	4.46	4.32	−10.4	0.5	11.4	22.2	4.5	<0.6
2a[e]	4.26	4.42	4.32	−10.2	1.0	11.5	22.7	4.5	1.1
3a[e]	4.39	4.54	4.56	−10.3	0.5	11.5	22.9	4.6	<0.6
4a[e]	4.49	4.56	4.59	−10.2	1.2	11.5	23.5	4.5	1.4
5a[e]	4.42	4.67	4.52	−10.6	1.5	11.5	27.6	4.5	2.2
6a[e]	4.47	4.66	4.52	−10.6	2.8	11.6	28.2	4.4	3.6
7a[e]	4.03	4.39	4.22	−10.0	7.1	11.4	13.5	5.3	0.8
8a[e]	4.16	4.37	4.30	−10.1	3.6	11.4	19.2	4.8	1.3
9a[f]	4.12	4.27	4.31	−10.3	2.5	11.4	24.4	4.5	3.0
10[f]	4.01	4.25	4.17	−10.5	1.3	11.4	21.2	4.6	0.8
1b[e]	4.27	4.51	4.43	−10.2	5.7	11.6	15.6	5.3	<0.6
2b[e]	4.29	4.46	4.44	−10.1	4.6	11.5	20.8	4.9	2.3
3b[e]	4.32	4.59	4.56	−10.2	10.2	11.7	10.2	5.9	<0.6
4b[e]	4.39	4.60	4.55	−10.3	7.3	11.6	17.2	5.3	1.8
5b[e]	4.49	4.79	4.57	−10.1	17.5	11.9	5.4	6.5	1.6
6b[e]	4.52	4.81	4.69	−10.2	18.5	11.8	6.5	6.6	1.6
7b[e]	4.18	4.33	4.30	−10.4	0.9	11.5	21.7	4.6	1.2
8b[e]	4.25	4.31	4.41	−10.4	2.0	11.5	24.7	4.5	2.6
9b[f]	4.14	4.27	4.24	−10.5	2.4	11.5	21.4	4.5	1.8
dcAMP[g]	1.10	1.27	1.73	−9.7	2.2	10.7	20.6	4.6	2.0

[a] Obtained by iterative fitting using the PANIC program,[14] unless stated otherwise. [b] Proton chemical shift in parts per million downfield from TMS as internal standard. [c] Coupling constants in Hz. [d] Noniterated value. [e] In acetone-d_6. [f] In D_2O. [g] In D_2O with proton chemical shifts in parts per million downfield from TMA as internal standard.[15]

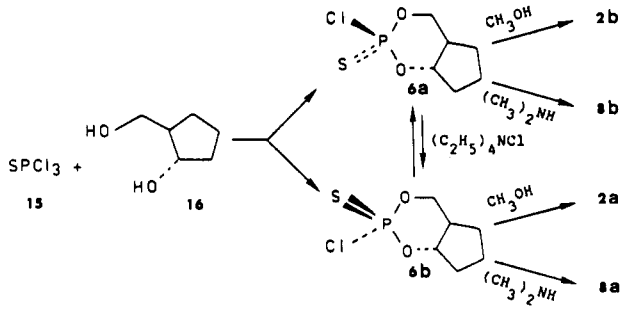
their stereospecific way of synthesis (vide supra). As was noted previously for other isomeric pairs of monocyclic and bicyclic 1,3,2-dioxaphosphorinanes,[4,5,8] the ^{31}P chemical shifts of the cis isomers of **1–9** (Table III) are upfield of those for the trans isomers except for the chlorophosphates **5a** and **5b** and the dimethylamino compounds **8a** and **8b**.

^{1}H NMR Conformational Analysis. The ^{1}H NMR data of the dioxaphosphorinane part of the compounds **1a–8a** and **1b–8b** (in acetone-d_6) and of **9a, 9b**; and **10** (in D_2O) are listed in Table I. The spectral parameters for H_{5a} and H_{5b} were obtained by iterative fitting of expansions of the H_{5a} and H_{5b} patterns of the 300-MHz ^{1}H NMR spectra using the PANIC program.[14] The chemical shift and $J_{1,P}$ coupling of H_1 are noniterated values. For comparison, the relevant parameters of 2′-deoxy-3′,5′-cyclic AMP (dcAMP) are also given.[15]

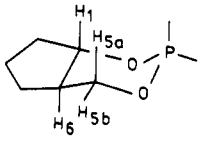
Neutral Phosphorinanes 1a–8a and 1b–8b. The di-

(14) PANIC program: Copyright, Bruker Spectrospin AG, Switzerland.
(15) Lee, C.-H.; Sarma, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 3541.

Scheme III

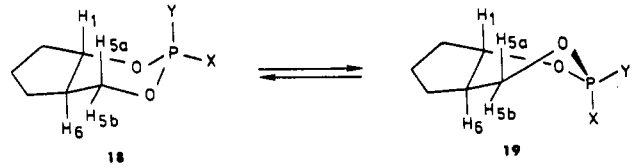


oxaphosphorinane ring of the compounds **1a–6a**, **7b**, and **8b** is readily assigned the chair conformation **18** on the basis of the similarity of its coupling constants to those for underivatized cyclic nucleotides, for instance dcAMP, which unquestionably possess chair form phosphate rings.



18

Most diagnostic is the combination of a large $J_{5b,P}$ coupling constant (21.7–28.2 Hz) with small $J_{5a,P}$ and $J_{1,P}$ coupling constants (0.5–3.6 Hz). The variations in $J_{5a,P}$ and particularly $J_{5b,P}$ values for the compounds **1a–6a**, **7b**, and **8b**, result from the dependence of these couplings on the nature of the substituents on the phosphorus atom.[16] A significant change in the conformation of the dioxaphosphorinane ring, resulting also in differences in the $J_{5a,P}$ and $J_{5b,P}$ couplings, can be excluded since $J_{5a,6}$ and $J_{5b,6}$ are almost equal for the compounds **1a–6a**, **7b**, and **8b**. The population of a chair conformation by the cis isomers **1a–6a** is consistent with the strong predilection of the electronegative methoxy (**1a**, **2a**), phenoxy (**3a**, **4a**), and chloro (**5a**, **6a**) substituents for an axial position in 2-oxo- and 2-thioxo-1,3,2-dioxaphosphorinanes.[8,16] The relatively large size of the dimethylamino group and its consequent preference for an equatorial position explains the chair conformation of **7b** and **8b**. The coupling constants of **1b–6b**, **7a**, and **8a** are inconsistent with chair conformation **18**. Due to the trans fusion of the dioxaphosphorinane ring with the cyclopentane ring, the only nonchair conformation energetically accessible to these isomers is the twist conformation **19**. In conformation **19**, dihedral angle $H_{5a}C_5O_4P$ can be as large as 180°, leading to a large $J_{5a,P}$ coupling (>22 Hz) and a small $J_{5b,P}$ coupling (~1 Hz). The $J_{5a,6}$ coupling in **19** will remain relatively unchanged compared to that in the chair conformation **18**. This leads to the combination of large couplings of H_{5a} to both phosphorus and H_6, which is not possible in a chair conformation. The somewhat reduced dihedral angle $H_6C_6H_5H_{5b}$ in **19** results in an increased $J_{5b,6}$ coupling in **19** relative to the chair conformation **18**.



1b–6b: Y=O or S, X=OCH_3, OPh, Cl
7a–8a: Y=$N(CH_3)_2$, X=O or S

(16) Bentrude, W. G.; Tan, H.-W. *J. Am. Chem. Soc.* **1973**, *95*, 4666.

Table II. Mole Fraction of Twist Conformation x(T) of Compounds 1b–6b, 7a, and 8a at 300 K

	acetone-d_6		benzene-d_6	
compd	$x(T)^a$	$x(T)^b$	$x(T)^a$	$x(T)^b$
1b	0.24	0.30	0.21	0.28
2b	0.17	0.09	0.13	0.03
3b	0.43	0.57	0.35	0.44
4b	0.27	0.28	0.17	0.12
5b	0.62	0.85	0.61	0.82
6b	0.62	0.85	0.60	0.82
7a	0.30	0.40	0.46	0.59
8a	0.07	0.24	0.15	0.30

[a] Calculated from eq 1 and 2. [b] Calculated from eq 1 and 3.

From the intermediate $J_{5a,P}$ and $J_{5b,P}$ couplings of the compounds **1b–6b**, **7a**, and **8a**, it is obvious that these compounds do not entirely exist in a twist conformation. An equilibrium between chair conformation **18** and twist conformation **19**, however, can explain the observed couplings of H_{5a} and H_{5b} to phosphorus. The mole fraction of **19** can be calculated by using eq 1–3, where $J_{5a,P}$(obsd)

$$x(T) + x(C) = 1 \quad (1)$$

$$J_{5a,P}(\text{obsd}) = x(T)J_{5a,P}(T) + x(C)J_{5a,P}(C) \quad (2)$$

$$J_{5b,P}(\text{obsd}) = x(T)J_{5b,P}(T) + x(C)J_{5b,P}(C) \quad (3)$$

and $J_{5b,P}$(obsd) are the observed coupling constants for H_{5a} and H_{5b} and phosphorus in Table I. $J_{5a,P}(T)$ and $J_{5b,P}(T)$ are the phosphorus–proton coupling constants to H_{5a} and H_{5b} in the twist conformation **19**, respectively. $J_{5a,P}(C)$ and $J_{5b,P}(C)$ are the $J_{5a,P}$ and $J_{5b,P}$ couplings in the chair conformation **18**. $x(T)$ and $x(C)$ are mole fractions of twist and chair conformation, respectively. The $J_{5a,P}(C)$ and $J_{5b,P}(C)$ couplings of the chair conformation of **1b–6b**, **7a**, and **8a** are given the values of $J_{5a,P}$ and $J_{5b,P}$ found for their epimers **1a–6a**, **7b**, **8b**, which are also in a chair conformation (the phosphorus configuration has little effect on these couplings in 2-oxo- and 2-thioxo-1,3,2-dioxaphosphorinanes[8]). The $J_{5a,P}(T)$ and $J_{5b,P}(T)$ couplings of the twist conformations of **1b–6b**, **7a**, and **8a** are assumed to be equal to the respective $J_{5b,P}$ and $J_{5a,P}$ couplings of their diastereomeric counterparts. The assumption seems reasonable since dihedral angles $H_{5a}C_5O_4P$ and $H_{5b}C_5O_4P$ in the twist conformation **19** are about 180° and 60°, respectively. (Compare the values of 60° and 180° for dihedral angles $H_{5a}C_5O_4P$ and $H_{5b}C_5O_4P$, respectively, in the chair conformation of **1a–6a**, **7b**, and **8b**). The results of the calculations are listed in Table II.

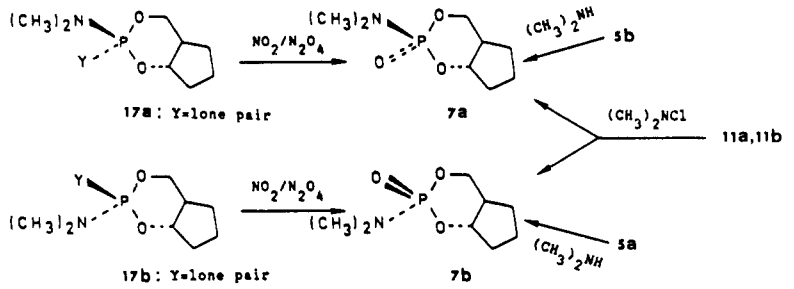
As can be seen, the mole fractions calculated from $J_{5a,P}$(obsd) (using eq 1 and 2) and from $J_{5b,P}$(obsd) (using eq 1 and 3) show for several compounds a large difference. This results from the fact that the sum of the $J_{5a,P}$ and $J_{5b,P}$ couplings is different for the cis and trans isomers in these cases. Although an exact analysis of the results in Table II is hampered by the noted differences several conclusions can be drawn. Thus, the mole fraction of twist increases upon going from the methoxy to the phenoxy to the chloro derivatives in the oxo and thioxo compounds. This increase is consistent with the increasing electronegativity and consequent increasing preference of these substituents for the pseudo-axial position in the twist conformation. Furthermore, replacement of the doubly bonded oxygen atom by sulfur results in a considerable decrease in the twist population for the compounds **1b–4b**, **7a**, and **8a**. In case of the chloro compounds **5b** and **6b**, however, substitution of oxygen by sulfur has no effect. The mole fraction of twist populated by **7a** is substantially smaller

Table III. ^{31}P NMR Chemical Shifts for 1a–9a, 1b–9b, and 10 at 81.0 MHz and 300 K[a]

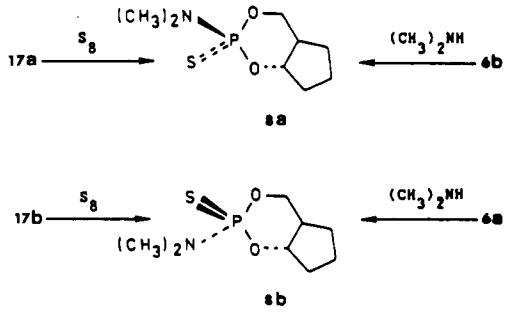
	b			c		
	isomer			isomer		
compd	a	b	Δ(a − b)	a	b	Δ(a − b)
1	−0.1	1.6	−1.7	−5.0	−2.8	−2.2
2	69.1	72.1	−3.0	63.8	68.0	−4.2
3	−7.2	−5.5	−1.7	−12.6	−10.0	−2.6
4	61.0	65.1	−4.1	55.4	61.2	−5.8
5	2.7	2.0	0.7	−2.0	−2.5	0.5
6	64.9	65.9	−1.0	58.2	60.3	−2.1
7	11.4	12.9	−1.5	6.0	8.2	−2.2
8	79.6	79.0	0.6	74.2	74.5	−0.3
9	54.1[d]	56.9[d]	−2.8			
10	0.8[d]					

[a] In parts per million with 85% H_3PO_4 as external standard. [b] In acetone-d_6. [c] In benzene-d_6. [d] In D_2O.

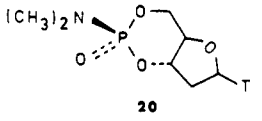
Scheme IV



Scheme V



than the value of 0.64 reported for the cyclic nucleotide analogue **20** in acetone-d_6.[3]



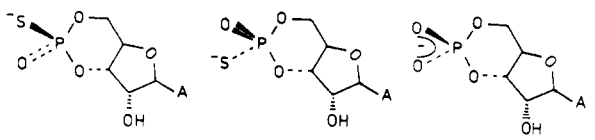
20

The difference in twist population between **7a** and **20** may be the result of the replacement of thymidine in **20** by a cyclopentane ring in **7a**. However, further information on the twist populations of the thymidine analogues of **1b–6b** is necessary in order to support this conclusion. In order to obtain information about a solvent dependence of the conformations of the phosphorus containing ring, the compounds **1a–8a** and **1b–8b** were also measured in the apolar benzene-d_6.[17] For the cis compounds **1a–6a** and the trans compounds **7b** and **8b**, no differences are observed between the couplings in both solvents. In contrast, the $J_{5a,P}$ and $J_{5b,P}$ couplings of some of their diastereomers change significantly. The mole fractions of twist calculated from these couplings are given in Table II. As can be seen, the compounds **1b–6b** populate the twist form to a lesser extent in benzene-d_6. By contrast, the mole fraction of the dimethylamino derivatives **7a** and **8a** is strongly increased.

(17) Hermans, R. J. M.; Buck, H. M., unpublished results.

Both observations are consistent with twist **19** being the more polar form in case of **1b–6b** and chair **18** being the more polar form for **7a** and **8a**.[8] In addition, the noted effect of solvent change upon the chair ⇄ twist equilibrium is parallel to what is reported for compound **20** (mole fraction in toluene-d_8 is 0.75)[3] and other bicyclic dioxaphosphorinanes.[5c]

Charged Compounds 9a, 9b, and 10. Natural cyclic nucleotides bear a negative charge on the phosphate group. In order to assess the effect of a negatively charged phosphate group on the dioxaphosphorinane ring conformation, the compounds **9a**, **9b**, and **10** were synthesized and measured in D_2O. In phosphate **10** the negative charge is delocalized between the two exocyclic oxygen atoms. In the compounds **9a** and **9b**, however, the negative charge is localized on the axial (**9a**) or equatorial sulfur atom (**9b**) as can be inferred from recent ^{31}P NMR investigations on *O,O*-dialkyl phosphorothioates.[18] The couplings of **9a**, **9b**, and **10** (Table I) are clearly indicative of a chair conformation. The preference for this conformation results from the introduction of the negative charge and is independent of the exact position of this charge. The diastereomeric forms of adenosine 3′,5′-cyclic monophosphorothioate, (S_P)-cAMPS and (R_P)-cAMPS, have been shown respectively to mimic and to inhibit activation of protein kinase type I and II by cAMP.[2a,b]



Sp-cAMPS Rp-cAMPS cAMP

Regarding the results obtained for the compounds **9a**, **9b**, and **10**, which closely resemble (S_P)-cAMPS, (R_P)-

(18) (a) Iyengar, R.; Eckstein, F.; Frey, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 8309. (b) Frey, P. A.; Sammons, R. D. *Science (Washington, D.C.)* **1985**, *228*, 541. (c) Frey, P. A.; Reimschüssel, W.; Paneth, P. *J. Am. Chem. Soc.* **1986**, *108*, 1720.

cAMPS, and cAMP, respectively, it seems likely that the difference in biological activity is not due to a different conformation of the phosphate rings of these nucleotides if bound to the enzyme.

^{31}P Measurements. The ^{31}P chemical shifts of the compounds **1a–8a** and **1b–8b** in acetone-d_6 and in benzene-d_6 and of **9a**, **9b**, and **10** in D_2O are listed in Table III. In addition, the difference in chemical shift for each pair of epimers **1a–8a** and **1b–8b** in acetone-d_6 and in benzene-d_6 is given.

Findlay et al.,[5c] used the ^{31}P chemical shift difference between the epimers of a number of 3-(aryloxy)-*trans*-2,4-dioxa-3-oxo-3-phosphabicyclo[4.4.0]decanes to calculate the percentage of twist conformation populated by the trans isomers in several solvents. According to his results, a greater chemical shift difference corresponded with a smaller percentage of twist population. The results in Tables II and III show that the increased chemical shift differences for the compounds **1a–4a** and **1b–4b** in benzene-d_6 relative to acetone-d_6 are in agreement with a decreased twist population in benzene-d_6. Furthermore, the almost identical shift differences of the chlorophosphonates **5a** and **5b** in acetone-d_6 and benzene-d_6 are consistent with the equal twist populations in both solvents. According to Table II, one would expect the same difference in chemical shift for **6a** and **6b** as was found for **5a** and **5b**. In this case, however, a quite large chemical difference is observed in benzene-d_6. The results for **7a** and **7b** are contrary to what is expected, since an increase in twist population is accompanied with a larger chemical shift difference. In addition, the chemical shift difference between **8a** and **8b** in both solvents is very small, although the twist population of **8a** is very low. These observations clearly show that one must be cautious in assessment of twist populations solely from the observed chemical shift differences.

Conclusions

It is shown that the conformation of the dioxaphosphorinane ring of the bicyclic phosphates **1a,–9a**, **1b–9b**, and **10**, which are simple model compounds for cyclic nucleotides, is determined by the nature and the spatial arrangement of the exocyclic substituents on the phosphorus atom. Thus, the cis isomers **1a–6a** and the trans isomers **7b** and **8b** populate a chair conformation. Their epimers **1b–6b** and **7a** and **8a**, however, exist as an equilibrium between a chair and twist conformation. The percentage of twist is solvent-sensitive. Introduction of a negatively charged phosphate group (compounds **9a**, **9b**, and **10**) results in a preference for a chair conformation.

Note Added in Proof. The results of a recent ^{1}H NMR investigation[19] on the conformation of the phosphate ring of the diastereomeric cis and trans forms of thymidine phenyl cyclic 3′,5′-monophosphate triesters closely resemble those found in the present study for **3a,b**.

Experimental Section

All solvents and materials were reagent grade and were used as received or purified as required. All reactions involving phosphorus compounds were routinely run under an atmosphere of dry nitrogen. ^{1}H NMR spectra were run in the FT mode on a Bruker CXP-300 spectrometer at 300.1 MHz, 32K data base, 3000 Hz SW, and a 5.47-s acquisition time. Coupling constants were taken from expansions of the H_{5a} and H_{5b} patterns and iteratively analyzed with the PANIC program.[14] ^{13}C NMR spectra were recorded on a Bruker AC-200 at 50.3 MHz. Chemical shifts in parts per million for ^{1}H and ^{13}C are referenced to TMS for acetone-d_6 and benzene-d_6 and the sodium salt of 3-(trimethylsilyl)propanesulfonic acid (DSS) for D_2O. ^{31}P spectra were run on a Bruker AC-200 spectrometer at 81.0 MHz. Positive ^{31}P chemical shifts are in δ (parts per million) downfield from external 85% H_3PO_4. Melting points are uncorrected. Column chromatography was performed by using silica gel (type 60 Merck) as the stationary phase. TLC was performed on silica gel 60 F-254 (Merck). Detection was effected by exposure to iodine vapor.

The syntheses of the diol **16** and compounds **11a,b**, **12a,b**, and **14** have been described before.[6]

3β-Methoxy-*trans*-2,4-dioxa-3α-oxo-3-phosphabicyclo[4.3.0]nonane (1a). A solution of NO_2/N_2O_4 in CH_2Cl_2 (1 g/40 mL) was added dropwise to a stirred solution of methyl phosphite **11a** (200 mg, 1.14 mmol) in 15 mL of methylene chloride at −78 °C until a faint greenish blue color appeared in the solution (TLC (hexane/ether, 5/4) indicated that no starting material remained). The mixture was allowed to come to room temperature. Evaporation of the methylene chloride yielded 220 mg (1.14 mmol, 100%) of **1a** as a colorless oil: ^{31}P NMR (acetone-d_6) δ −0.1; ^{1}H NMR (acetone-d_6) δ 1.18–2.36 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.78 (d, 3 H, OCH_3), J = 11.1 Hz), 4.17–4.25 (m, 1 H, H_{5a}), 4.28–4.39 (m, 1 H, H_1), 4.42–4.54 (m, 1 H, H_{5b}); ^{13}C NMR (benzene-d_6) δ 19.3 (C_7, J = 1.0 Hz), 21.0 (C_8, J = 1.0 Hz), 29.2 (C_9, J = 8.1 Hz), 42.4 (C_6, J = 5.6 Hz), 53.7 (OCH_3, J = 5.8 Hz), 73.3 (C_5, J = 7.2 Hz), 84.7 (C_1, J = 6.0 Hz).

3β-Methoxy-*trans*-2,4-dioxa-3α-oxo- and 3α-Methoxy-*trans*-2,4-dioxa-3β-oxo-3-phosphabicyclo[4.3.0]nonanes (1a and 1b). NO_2/N_2O_4 oxidation of a mixture of **11a** and **11b** (60/40) according to the procedure described for the synthesis of **1a** afforded a mixture of **1a** and **1b** (60/40) as a yellowish oil. Separation of the epimers by column chromatography was not successful. **1b**: ^{31}P NMR (acetone-d_6) δ 1.6; ^{1}H NMR (acetone-d_6) δ 1.10–2.42 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.74 (d, 3 H, OCH_3, J = 11.5 Hz), 4.23–4.31 (m, 1 H, H_{5a}), 4.48–4.56 (m, 2 H, H_1, H_{5b}); ^{13}C NMR (benzene-d_6) δ 19.5 (C_7, J = 1.0 Hz), 21.8 (C_8, J = 0.8 Hz), 29.4 (C_9, J = 7.7 Hz), 42.1 (C_6, J = 6.7 Hz), 55.1 (OCH_3, J = 6.6 Hz), 73.5 (C_5, J = 6.3 Hz), 83.9 (C_1, J = 4.9 Hz).

3β-Methoxy-*trans*-2,4-dioxa-3α-thioxo-3-phosphabicyclo[4.3.0]nonane (2a). A solution of 500 mg (2.84 mmol) of phosphite **11a** and 91 mg (2.84 mmol) of elemental sulfur in 5 mL of benzene was heated under reflux until TLC (hexane/ether, 5/4) indicated that the reaction was completed. The solvent was removed under reduced pressure. Column chromatography of the resulting crude product with hexane/ether (5/4) as eluent afforded 220 mg (1.1 mmol, 37%) of **2a**, which solidified upon standing: mp 53.2–54.2 °C. Anal. Calcd for $C_7H_{13}O_3PS$: C, 40.38; H, 6.29. Found: C, 40.49; H, 5.99. ^{31}P NMR (acetone-d_6) δ 69.1; ^{1}H NMR (acetone-d_6) δ 1.19–2.29 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.72 (d, 3 H, OCH_3, J = 13.4 Hz), 4.21–4.49 (m, 3 H, H_1, H_{5a}, H_{5b}); ^{13}C NMR (benzene-d_6) δ 18.7 (C_7, J = 0.8 Hz), 21.5 (C_8, J = 1.4 Hz), 29.3 (C_9, J = 7.5 Hz), 42.0 (C_6, J = 6.0 Hz), 53.5 (OCH_3, J = 4.8 Hz), 72.8 (C_5, J = 10.3 Hz), 82.6 (C_1, J = 8.3 Hz).

3β-Methoxy-*trans*-2,4-dioxa-3α-thioxo- and 3α-Methoxy-*trans*-2,4-dioxa-3β-thioxo-3-phosphabicyclo[4.3.0]nonanes (2a and 2b). (a) Reaction of Sulfur with Phosphites 11a and 11b. A mixture of **11a** and **11b** (60/40, 500 mg, 2.84 mmol) was dissolved in 5 mL of dry benzene. To this solution was added 91 mg (2.84 mmol) of elemental sulfur. The resulting mixture was heated under reflux until TLC (hexane/ether, 5/4) indicated that all starting material had been converted. Evaporation of the solvent afforded 630 mg of crude product containing **2a** and **2b** (58/42), which was separated over silica gel with hexane/ether (5/4) as eluent. In order of elution, **2b** (250 mg, 1.20 mmol, 42%) and **2a** (180 mg, 0.86 mmol, 31%) were obtained. **2b**: colorless liquid. Anal. Calcd for $C_7H_{13}O_3PS$: C, 40.38; H, 6.29. Found: C, 40.64; H, 6.29. ^{31}P NMR (acetone-d_6) δ 72.1; ^{1}H NMR (acetone-d_6) δ 1.21–2.35 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.80 (d, 3 H, OCH_3, J = 13.6 Hz), 4.24–4.33 (m, 1 H, H_{5a}), 4.32–4.51 (m, 2 H, H_1, H_{5b}). ^{13}C NMR (benzene-d_6) δ 19.1 (C_7, J < 0.8 Hz), 21.5 (C_8, J < 0.8 Hz), 29.1 (C_9, J = 8.2 Hz), 42.9 (C_6, J = 5.8 Hz), 54.6 (OCH_3, J = 5.6 Hz), 72.0 (C_5, J = 6.2 Hz), 82.4 (C_1, J = 4.7 Hz).

(b) Reaction of Methanol with 6a and 6b. A mixture of **6a** and **6b** (22/78, 250 mg, 1.2 mmol) was dissolved in 15 mL of

(19) Nelson, K. A.; Bentrude, W. G.; Setzer, W. N.; Hutchinson, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 4058.

anhydrous methanol and stirred for 1 day at 25 °C. Methanol was then evaporated. The residue was dissolved in 25 mL of benzene. After washing with sodium carbonate, drying (Na_2SO_4), and evaporation of the solvent, a mixture of **2a** and **2b** (78/22) (220 mg, 1.06 mmol, 89%) was obtained.

3β-Phenoxy-*trans*-2,4-dioxa-3α-oxo-3-phosphabicyclo[4.3.0]nonane (3a). This compound was prepared by oxidation of the phenyl phosphite **12a** with NO_2/N_2O_4 at 0 °C analogous to the procedure described for the preparation of **1a**. The crude product was purified by column chromatography using hexane/ether (1/1) as eluent. The solid product thus obtained was recrystallized from ether: mp 104.8–105.2 °C. Anal. Calcd for $C_{12}H_{15}O_4P$: C, 56.70; H, 5.95. Found: C, 56.88; H, 5.70. ^{31}P NMR (acetone-d_6) δ −7.2; ^1H NMR (acetone-d_6) δ 1.27–2.39 (m, 7 H, H_9, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 4.35–4.42 (m, 1 H, H_{5a}), 4.47–4.61 (m, 2 H, H_1, H_{5b}), 7.28–7.32 (m, 5 H, Ar H); ^{13}C NMR (benzene-d_6) δ 19.3 (C_7, J = 1.0 Hz), 21.0 (C_8, J = 1.1 Hz), 29.1 (C_9, J = 8.2 Hz), 42.4 (C_6, J = 5.5 Hz), 73.0 (C_5, J = 8.1 Hz), 84.5 (C_1, J = 6.8 Hz), 120.1 (Ar C, J = 5.3 Hz), 124.9 (Ar C, J = 0.9 Hz), 130.0 (Ar C, J = 0.5 Hz), 151.5 (Ar C, J = 6.3 Hz).

3β-Phenoxy-*trans*-2,4-dioxa-3α-oxo- and 3α-Phenoxy-*trans*-2,4-dioxa-3β-oxo-3-phosphabicyclo[4.3.0]nonanes (3a and 3b). A mixture of **12a** and **12b** (50/50, 450 mg, 1.88 mmol) was dissolved in 30 mL of methylene chloride and oxidized by NO_2/N_2O_4 at 0 °C. Purification of the crude product by column chromatography (eluent, chloroform) afforded 360 mg (1.42 mmol, 76%) of a mixture of **3a** and **3b** (55/45). This mixture melted at 84.6–88.6 °C. Column chromatography of this mixture with ether as eluent afforded the single diastereomers **3a** and **3b**. Anal. Calcd for $C_{12}H_{15}O_4P$: C, 56.70; H, 5.95. Found for mixture: C, 56.64; H, 5.83. **3b**: mp 89.2–90.2 °C; ^{31}P NMR (acetone-d_6) δ −5.5; ^1H NMR (acetone-d_6) δ 1.13–2.56 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 4.27–4.38 (m, 1 H, H_{5a}), 4.52–4.65 (m, 2 H, H_1, H_{5b}), 7.19–7.54 (m, 5 H, Ar H); ^{13}C NMR (benzene-d_6) δ 19.5 (C_7, J = 1.0 Hz), 22.2 (C_8, J = 1.0 Hz), 29.5 (C_9, J = 7.4 Hz), 41.5 (C_6, J = 8.1 Hz), 72.7 (C_5, J = 7.0 Hz), 83.4 (C_1, J = 5.2 Hz), 120.7 (Ar C, J = 4.9 Hz), 125.1 (Ar C, J = 1.3 Hz), 129.9 (Ar C, J = 0.9 Hz), 151.6 (Ar C, J = 7.0 Hz). Penney and Belleau[13] reported a melting point of 83–85 °C for the product obtained by the reaction of phenyl dichlorophosphinate with diol **16**. This product was probably a mixture of **3a** and **3b**.

3β-Phenoxy-*trans*-2,4-dioxa-3α-thioxo-3-phosphabicyclo[4.3.0]nonane (4a). Thiophosphate **4a** was prepared by the reaction of phenyl phosphite **12a** with elemental sulfur according to the procedure described for the preparation of **2a**. It was recrystallized from ether: mp 90.0–90.6 °C. Anal. Calcd for $C_{12}H_{15}O_3PS$: C, 53.33; H, 5.59. Found: C, 53.55; H, 5.73. ^{31}P NMR (acetone-d_6) δ 61.0; ^1H NMR (acetone-d_6) δ 1.22–2.39 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 4.44–4.64 (m, 3 H, H_1, H_{5a}, H_{5b}), 7.15–7.30 (m, 5 H, Ar H); ^{13}C NMR (benzene-d_6) δ 18.7 (C_7, J = 0.7 Hz), 21.5 (C_8, J = 1.4 Hz), 29.2 (C_9, J = 7.5 Hz), 42.0 (C_6, J = 6.1 Hz), 73.7 (C_5, J = 10.7 Hz), 83.4 (C_1, J = 8.6 Hz), 120.8 (Ar C, J = 5.3 Hz), 125.1 (Ar C, J = 1.5 Hz), 129.9 (Ar C, J = 1.0 Hz), 151.6 (Ar C, J = 6.6 Hz).

3α-Phenoxy-*trans*-2,4-dioxa-3β-thioxo-3-phosphabicyclo[4.3.0]nonane (4b). This compound was obtained by chromatographic separation (eluent, hexane/ether, 3/1) of the reaction product of the reaction of 400 mg (1.68 mmol) of a mixture of **12a** and **12b** (50/50) with 50 mg of elemental sulfur in benzene at 10 °C. In order of elution, **4a** (140 mg, 0.52 mmol, 30%) and **4b** (150 mg, 0.56 mmol, 33%) were obtained. **4b**: mp 96.6–97.6 °C. Anal. Calcd for $C_{12}H_{15}O_3PS$: C, 53.33; H, 5.59. Found: C, 53.68; H, 5.70. ^{31}P NMR (acetone-d_6) δ 65.1; ^1H NMR (acetone-d_6) δ 1.24–2.48 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 4.34–4.44 (m, 1 H, H_{5a}), 4.49–4.66 (m, 2 H, H_1, H_{5b}), 7.12–7.48 (m, 5 H, Ar H); ^{13}C NMR (benzene-d_6) δ 19.0 (C_7, J = 0.9 Hz), 21.7 (C_8, J = 1.1 Hz), 29.2 (C_9, J = 8.0 Hz), 42.5 (C_6, J = 6.7 Hz), 72.6 (C_5, J = 6.9 Hz), 82.7 (C_1, J = 5.2 Hz), 121.7 (Ar C, J = 4.9 Hz), 125.5 (Ar C, J = 2.0 Hz), 129.8 (Ar C, J = 1.6 Hz), 151.3 (Ar C, J = 7.8 Hz).

3β-Chloro-*trans*-2,4-dioxa-3α-oxo-3-phosphabicyclo[4.3.0]nonane (5a). (a) From Thiophosphate 9a according to the Procedure Described by Michalski et al.[10] Sulfuryl chloride (94.5 mg, 0.70 mmol) in 2 mL of deuteriated methylene chloride was added to a stirred suspension of 198 mg (0.70 mmol) of **9a** in 3 mL of CD_2Cl_2 at −20 °C. After the addition was completed, the solution was clear. ^{31}P NMR showed that all phosphate **9a** had been converted to a mixture of two compounds with $\delta_{^{31}P}$ signals at 12.7 and 15.4 ppm in the ratio 69/31. This mixture was cooled to −78 °C, and 89.6 mg (0.70 mmol) of phosphorus trichloride in 2 mL of CD_2Cl_2 was added dropwise. After the addition was finished, the solution was brought to room temperature and filtered. The methylene chloride was evaporated and the residue triturated with ether and then filtered. The ether was evaporated to give 90 mg of a brown, viscous liquid. ^{31}P NMR of this liquid indicated the presence of chlorophosphonate **5a** (major compound) and minor amounts of **5b** and **6a** and other phosphates. **5a**: ^{31}P NMR (acetone-d_6) δ 2.7; ^1H NMR (acetone-d_6) δ 1.15–2.50 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 4.35–4.78 (m, 3 H, H_1, H_{5a}, H_{5b}); ^{13}C NMR (acetone-d_6) δ 19.7 (C_7, J = 1.1 Hz), 21.4 (C_8, J = 1.2 Hz), 29.3 (C_9, J = 9.0 Hz), 43.2 (C_6, J = 5.7 Hz), 75.5 (C_5, J = 8.8 Hz), 86.4 (C_1, J = 7.3 Hz).

(b) By Oxidation of Chlorophosphonite 14. Oxidation of chlorophosphonite **14** with NO_2/N_2O_4 according to the method described by Ramirez et al.[12] furnished an oil consisting of **5a** and varying amounts of **5b** (up to 30%) and acyclic compounds.

3α-Chloro-*trans*-2,4-dioxa-3β-oxo-3-phosphabicyclo[4.3.0]nonane (5b). The preparation of this compound from **9b** is analogous to that described for its stereomer **5a**. In this case reaction of sulfuryl chloride with **9b** yielded two compounds with $\delta_{^{31}P}$ signals at 18.1 and 17.2 ppm in the ratio 70/30. Chlorophosphonate **5b** was obtained as a very viscous oil contaminated with small amounts of **5a** and **6b** and other phosphates. **5b**: ^{31}P NMR (acetone-d_6) δ 2.0; ^1H NMR (acetone-d_6) δ 1.18–2.94 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 4.41–4.62 (m, 2 H, H_1, H_{5a}), 4.75–7.83 (m, 1 H, H_{5b}); ^{13}C NMR (acetone-d_6) δ 20.2 (C_7, J = 1.0 Hz), 23.8 (C_8, J = 1.3 Hz), 30.2 (C_9, J = 6.6 Hz), 40.3 (C_6, J = 13.5 Hz), 76.1 (C_5, J = 8.9 Hz), 86.9 (C_1, J = 7.1 Hz).

3β-Chloro-*trans*-2,4-dioxa-3α-thioxo- and 3α-Chloro-*trans*-2,4-dioxa-3β-thioxo-3-phosphabicyclo[4.3.0]nonanes (6a and 6b). A solution of 2.55 g (22.0 mmol) of diol **16** and 3.48 g (44.0 mmol) of dry pyridine in 50 mL of dry toluene was added dropwise to a stirred solution of 3.73 g (22.0 mmol) of thiophosphoryl chloride in 100 mL of toluene held at 40 °C. After the addition was completed, the mixture was stirred for 2.5 h at 40 °C. The pyridine–HCl salt was filtered off and the organic phase washed twice with 15 mL of water. After drying on calcium chloride, toluene was evaporated to give a viscous oil. ^{31}P NMR showed the presence of three compounds: **6a** (13%), **6b** (47%), and a compound with $\delta_{^{31}P}$ 63.9 (40%). The isomers **6a** and **6b** were obtained as a mixture (22/78) by column chromatography using hexane/ether (5/4) as eluent. Stirring a solution of this mixture in acetone in the presence of a catalytic amount of tetraethylammonium chloride resulted in the formation of a 76/24 mixture of **6a** and **6b** and a compound with $\delta_{^{31}P}$ 67.6. The latter could be removed by column chromatography using hexane/ether (5/4) as eluent. **6a**: ^{31}P NMR (acetone-d_6) δ 64.9; ^1H NMR (acetone-d_6) δ 1.32–2.45 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 4.43–4.58 (m, 2 H, H_1, H_{5a}), 4.59–4.74 (m, 1 H, H_{5b}); ^{13}C NMR (acetone-d_6) δ 19.1 (C_7, J = 1.0 Hz), 22.0 (C_8, J = 1.5 Hz), 29.5 (C_9, J = 8.4 Hz), 43.1 (C_6, J = 6.1 Hz), 76.3 (C_5 , J = 11.5 Hz), 85.7 (C_1, J = 9.0 Hz). **6b**: ^{31}P NMR (acetone-d_6) δ 65.9; ^1H NMR (acetone-d_6) δ 1.00–2.36 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 4.44–4.58 (m, 1 H, H_{5a}), 4.63–4.74 (m, 1 H, H_1), 4.76–4.85 (m, 1 H, H_{5b}); ^{13}C NMR (acetone-d_6) δ 19.7 (C_7, J = 0.7 Hz), 24.4 (C_8, J = 1.4 Hz), 30.2 (C_9, J = 5.7 Hz), 40.3 (C_6, J = 14.6 Hz), 77.0 (C_5, J = 11.3 Hz), 85.8 (C_1, J = 8.6 Hz).

3β- and 3α-(Dimethylamino)-*trans*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonanes (17a and 17b). Diol **16** (3.48 g, 30 mmol) and 0.05 equiv of 1*H*-tetrazole were dissolved in 200 mL of dry dioxane. To this solution was added dropwise 4.90 g (30 mmol) of tris(dimethylamino)phosphine at room temperature. After the addition was completed, the mixture was stirred for 2 h at 70 °C. The dioxane was evaporated, and the resulting crude mixture was fractionated to give 3.34 g (17.1 mmol, 57%) of a mixture of **17a** and **17b** (20/80): bp 60–62 °C (0.34 mm) [lit.[12] bp 51–52 °C (0.1 mm)]; ^{31}P NMR (acetone-d_6) δ 137.3 (**17a**) and 144.7 (**17b**).

3β-(Dimethylamino)-*trans*-2,4-dioxa-3α-oxo- and 3α-(Dimethylamino)-*trans*-2,4-dioxa-3β-oxo-3-phosphabicyclo[4.3.0]nonanes (7a and 7b). (a) Oxidation of a Mixture of 17a and 17b with NO_2/N_2O_4. A solution of NO_2/N_2O_4 in methylene chloride (1 g/40 mL) was added to a stirred solution

of 350 mg of **17a** and **17b** (20/80) in 15 mL of methylene chloride at −78 °C until a blue color appeared in the solution. Evaporation of the solvent furnished a mixture of **7a** and **7b** (20/80). Attempts to separate this mixture by column chromatography were not successful. **7a**: ^{31}P NMR (acetone-d_6) δ 11.4; ^{1}H NMR (acetone-d_6) δ 1.10–2.40 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.60 (d, 6 H, $N(CH_3)_2$, J = 10.8 Hz), 3.98–4.08 (m, 1 H, H_{5a}), 4.21–4.44 (m, 2 H, H_1, H_{5b}); ^{13}C NMR (benzene-d_6) δ 19.8 (C_7, J = 0.7 Hz), 23.0 (C_8, J < 0.7 Hz), 30.0 (C_9, J = 6.3 Hz), 36.3 ($N(CH_3)_2$, J = 3.3 Hz), 41.8 (C_6, J = 10.1 Hz), 71.6 (C_5, J = 7.2 Hz), 83.4 (C_1, J = 6.0 Hz). **7b**: ^{31}P NMR (acetone-d_6) δ 12.9; ^{1}H NMR (acetone-d_6) δ 1.10–2.19 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.66 (d, 6 H, $N(CH_3)_2$, J = 10.1 Hz), 4.14–4.22 (m, 1 H, H_{5a}), 4.25–4.39 (m, 2 H, H_1, H_{5b}); ^{13}C NMR (benzene-d_6) δ 19.5 (C_7, J = 0.8 Hz), 21.5 (C_8, J = 0.9 Hz), 29.6 Hz (C_9, J =8.2 Hz), 36.1 ($N(CH_3)_2$, J = 4.7 Hz), 43.0 (C_6, J = 4.0 Hz), 71.1 (C_5, J = 6.2 Hz), 81.6 (C_1, J = 4.5 Hz).

(b) Reaction of Dimethylchloroamine with 11a and 11b. Addition of 230 mg (2.8 mmol) of dimethylchloroamine to a stirred solution of 500 mg (2.8 mmol) of **11a** and **11b** (40/60) in 5 mL of CD_2Cl_2 at −78 °C resulted in the formation of a mixture of **7a** and **7b** (23/77).

(c) Reaction of Dimethylamine with Chlorophosphonates 5a and 5b. Dimethylamine was bubbled through a solution of **5a** and **5b** (73/27) in CD_2Cl_2 held at 0 °C. After 1 h ^{31}P NMR showed that all chlorophosphonate had been converted to a mixture of **7a** and **7b** in the ratio 25/75. The methylene chloride was then evaporated and the residue triturated with ether then filtered. The filtrate was evaporated to yield a viscous oil.

3β-(Dimethylamino)-*trans*-2,4-dioxa-3α-thioxo- and 3α-(Dimethylamino)-*trans*-2,4-dioxa-3β-thioxo-3-phosphabicyclo[4.3.0]nonanes (8a and 8b). (a) By Reaction of Aminophosphonites 17a and 17b with Sulfur. Elemental sulfur (59.0 mg, 1.85 mmol) was added in portions to a stirred solution of 350 mg (1.85 mmol) of **17a** and **17b** (20/80) in 2 mL of benzene at 5–10 °C. After the addition was completed, the mixture was stirred for 24 h at room temperature. Evaporation of the solvent yielded 360 mg of a mixture of **8a** and **8b**. Chromatographic separation of this mixture afforded in order of elution 290 mg (1.31 mmol, 71%) of **8b** and 70 mg (0.32 mmol, 17%) of **8a**. **8a**: mp 77.8–79.0 °C. Anal. Calcd for $C_8H_{16}NO_2PS$: C, 43.43; H, 7.29; N, 6.33. Found: C, 43.41; H, 6.94; N, 6.12. ^{31}P NMR (acetone-d_6) δ 79.6; ^{1}H NMR (acetone-d_6) δ 1.12–2.34 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.51 (d, 6 H, $N(CH_3)_2$, J = 13.3 Hz), 4.12–4.21 (m, 1 H, H_{5a}), 4.24–4.42 (m, 2 H, H_1, H_{5b}); ^{13}C NMR (benzene-d_6) δ 18.9 (C_7, J < 0.8 Hz), 22.2 (C_8, J = 1.3 Hz), 29.5 (C_9, J = 6.7 Hz), 36.6 ($N(CH_3)_2$, J = 2.5 Hz), 41.8 (C_6, J = 7.6 Hz), 72.0 (C_5, J = 9.6 Hz), 82.5 (C_1, J = 8.1 Hz). **8b**: mp 79.4–81.0 °C. Found: C, 43.69; H, 6.87; N, 6.38. ^{31}P NMR (acetone-d_6) δ 79.0; ^{1}H NMR (acetone-d_6) δ 1.18–2.19 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.80 (d, 6 H, $N(CH_3)_2$, J = 11.5 Hz), 4.20–4.46 (m, 3 H, H_1, H_{5a}, H_{5b}); ^{13}C NMR (benzene-d_6) δ 19.1 (C_7, J = 0.8 Hz), 21.3 (C_8, J = 0.9 Hz), 29.2 (C_9, J = 8.5 Hz), 36.5 ($N(CH_3)_2$, J = 5.7 Hz), 43.2 (C_6, J = 4.3 Hz), 70.8 (C_5, J = 6.0 Hz), 81.5 (C_1, J = 4.7 Hz).

(b) By Reaction of Dimethylamine with Chlorophosphonates 6a and 6b. Dimethylamine (45 mg) in 1 mL of C_6D_6 was added to a solution of 210 mg (0.98 mmol) of **6a** and **6b** (19/81) in 1 mL of benzene at 10 °C. After the addition was completed, the dimethylamine–HCl salt was removed by filtration. ^{31}P NMR of the filtrate showed the presence of **8a** and **8b** (82/18).

3β-Thioxo-*trans*-2,4-dioxa-3α-oxo-3-phosphabicyclo[4.3.0]nonane *N*-Methyl-*tert*-butylammonium Salt (9a). A solution of 110 mg (0.53 mmol) of **2b** in 5 mL of *tert*-butylamine was refluxed for 48 h. The excess *tert*-butylamine was removed by evaporation and the resulting white solid recrystallized from methanol/ether: yield, 147 mg (0.52 mmol, 98%); mp 213–216 °C dec. Anal. Calcd for $C_{11}H_{24}NO_3PS$: C, 46.96; H, 8.60; N, 4.98. Found: C, 46.28; H, 8.56; N, 4.72. ^{31}P NMR (D_2O) δ 54.1; ^{1}H NMR (D_2O) δ 1.10–2.14 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 1.34 (s, 12 H, CH_3), 4.07–4.16 (m, 1 H, H_{5a}), 4.20–4.37 (m, 2 H, H_1, H_{5b}); ^{13}C NMR (D_2O) δ 21.5 (C_7, J < 0.7 Hz), 23.7 (C_8, J = 0.7 Hz), 29.4 ($(CH_3)_3C$), 31.3 (C_9, J = 8.0 Hz), 45.7 (C_6, J = 4.5 Hz), 54.7 ($(CH_3)_3C$, CH_3N), 74.0 (C_5, J = 6.3 Hz), 85.5 (C_1, J = 5.1 Hz).

3α-Thioxo-*trans*-2,4-dioxa-3β-oxo-3-phosphabicyclo[4.3.0]nonane *N*-Methyl-*tert*-butylammonium Salt (9b). This compound was prepared from **2a** according to the procedure described for the preparation of **9a**. It was recrystallized from methanol/ether: mp 139–142 °C dec. Anal. Calcd for $C_{11}H_{24}NO_3PS$: C, 46.96; H, 8.60; N, 4.98. Found: C, 46.36; H, 8.44; N, 5.23. ^{31}P NMR (D_2O) δ 56.9; ^{1}H NMR (D_2O) δ 1.10–2.20 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 1.35 (s, 12 H, CH_3), 4.09–4.17 (m, 1 H, H_{5a}), 4.18–4.34 (m, 2 H, H_1, H_{5b}); ^{13}C NMR (D_2O) δ 21.1 (C_7, J < 0.7 Hz), 24.1 (C_8, J = 1.1 Hz), 29.4 ($(CH_3)_3C$), 31.8 (C_9, J = 7.0 Hz), 45.1 (C_6, J = 4.7 Hz), 54.7 ($(CH_3)_3C$, CH_3N), 74.0 (C_5, J = 8.4 Hz), 84.0 (C_1, J = 6.6 Hz).

3β-Oxo-*trans*-2,4-dioxa-3α-oxo-3-phosphabicyclo[4.3.0]nonane *N*-Methyl-*tert*-butylammonium Salt (10). This compound was synthesized from **1a** and **1b** by refluxing with *tert*-butylamine. It was recrystallized from methanol/ether: mp 226–228 °C dec. Anal. Calcd for $C_{11}H_{24}NO_4P$: C, 49.80; H, 9.12; N, 5.28. Found: C, 49.21; H, 8.84; N, 5.67. ^{31}P NMR (D_2O) δ 0.8; ^{1}H NMR (D_2O) δ 1.00–2.18 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 1.36 (s, 12 H, CH_3), 3.96–4.08 (m, 1 H, H_{5a}), 4.12–4.36 (m, 2 H, H_1, H_{5b}); ^{13}C NMR (D_2O) δ 21.6 (C_7, J = 0.8 Hz), 23.6 (C_8, J = 0.9 Hz), 29.3 ($(CH_3)_3C$), 31.6 (C_9, J = 7.7 Hz), 45.6 (C_6, J = 4.4 Hz), 54.6 ($(CH_3)_3C$, CH_3N), 73.7 (C_5, J = 6.1 Hz), 85.6 (C_1, J = 5.1 Hz).

Registry No. **1a**, 109717-99-9; **1b**, 109718-01-6; **2a**, 109669-77-4; **2b**, 109718-02-7; **3a**, 109718-04-9; **3b**, 109718-06-1; **4a**, 109669-80-9; **4b**, 109718-07-2; **5a**, 109718-08-3; **5b**, 109718-11-8; **6a**, 109669-78-5; **6b**, 109718-03-8; **7a**, 109669-82-1; **7b**, 109718-14-1; **8a**, 109669-83-2; **8b**, 109718-15-2; **9a**, 109669-81-0; **9a** (*N*-methyl-*tert*-butylammonium salt), 109718-16-3; **9b**, 109718-10-7; **9b** (*N*-methyl-*tert*-butylammonium salt), 109784-31-8; **10** (*N*-methyl-*tert*-butylammonium salt), 109718-18-5; **11a**, 109717-98-8; **11b**, 109718-00-5; **12a**, 109669-79-6; **12b**, 109718-05-0; **14**, 109718-09-4; **16**, 53229-68-8; **17a**, 109718-12-9; **17b**, 109718-13-0; (S_p)-cAMPS, 71774-13-5; (R_p)-cAMPS, 73208-40-9.