Synthesis and Conformational Analysis of Torsionally Constrained 1,3,2-Dioxaphosphepanes[1]

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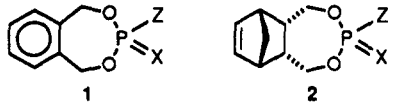
A series of benzo-fused and norbornene-fused 1,3,2-dioxaphosphepanes have been synthesized and conformationally studied by proton and phosphorus-31 NMR, infrared spectroscopy, and X-ray crystallography. The NMR data are best interpreted in terms of chair–chair equilibria in which substituents on phosphorus (phenoxy, dimethylamino, and phenyl) show a remarkable preference for axial positions. Twist conformations cannot be completely ruled out, however. X-ray crystal structures have been determined for two of the norbornene-fused compounds, *trans*-5,6-(*endo*,*endo*-2′,3′-bicyclo[2.2.1]hept-5′-eno)-2-oxo-2-phenoxy-1,3,2-dioxaphosphepane (*trans*-**2a**) and *trans*-5,6-(*endo*,*endo*-2′,3′-bicyclo[2.2.1]hept-5′-eno)-2-oxo-2-phenyl-1,3,2-dioxaphosphepane (*trans*-**2b**), and one of the benzo-fused compounds, 5,6-benzo-2-oxo-2-phenyl-1,3,2-dioxaphosphepane (**1b**). The X-ray structures of the two norbornene-fused dioxaphosphepanes confirm the stereochemical assignments for these materials and show the seven-membered ring to adopt a chair conformation. A twist conformation is seen in the structure of the benzo-fused dioxaphosphepane, on the other hand.

This paper presents the synthesis and conformational properties of several medium-sized ring phosphorus heterocycles. Thus, the seven-membered ring phosphorus heterocycles (1,3,2-dioxaphosphepanes), **1** and **2**, have been prepared, purified by liquid chromatography, and studied by phosphorus-31 and proton NMR spectroscopy, infrared spectroscopy, and X-ray crystallography.



1 **2**

a: X = O, Z = OPh
b: X = O, Z = Ph
c: X = O, Z = NMe_2

Introduction

Conformational analyses using NMR techniques, particularly vicinal proton–phosphorus coupling constants, have been widely utilized in the study of six-membered-ring phosphorus heterocycles.[3] Our research group has been interested in extending conformational studies to include five-membered-ring phosphorus heterocycles[4] and medium-sized-ring phosphorus heterocycles.

Conformational and stereochemical analysis of phosphorus heterocycles having more than six members is still relatively unexplored. Some work of note has appeared in the literature[5] but the studies to date are very complex and there is little in the way of useful correlations.[6] The seven-membered-ring system, 1,3,2-dioxaphosphepane, has received some attention in terms of its conformational properties, and vicinal proton–phosphorus couplings have been used to some degree in the conformational analysis of a number of these heterocycles.[7-12] There are many conformational possibilities in these medium-sized rings, and interpretation of $^3J_{POCH}$ data in terms of specific individual conformations is often very difficult.

Cyclic 2′,5′-nucleotides have been examined conformationally,[13-15] and in these compounds the conformational possibilities and mobility are reduced due to the fused bicyclo[4.2.1]nonane ring system.[16] The $^3J_{POCH}$ data for these compounds have led to conclusions regarding the specific conformational preferences. It has been noted that strain inherent in the seven-membered rings leads to greatly enlarged P–O–C bond angles and increased $^3J_{POCH}$ values. A modified Karplus curve has been proposed to accommodate these data.[14,15]

Unsaturation, benzo ring fusion, or cis ring fusion at C(5)–C(6) would serve to impart planarity in that part of the ring, favoring the chair conformation over the twist-chair. In addition to the chair, two other conformations, the twist and twist-boat, have been suggested to be energetically feasible.[5] Arbuzov and co-workers have concluded, based upon ^1H NMR, dipole moment, and Kerr effect data, that flexible twist forms are important if not predominant conformations in the equilibria of these compounds.[10-12] Note that nonchair conformations have been observed in benzo-fused 1,4-dioxapanes[17] and MM2 calculations show a nonchair (twist-boat) to be favored in 2,3-dihydro-1,4-dioxepine.[18]

The conformational equilibria of **1** (Z = Cl, OMe, OPh) have been examined by Sato and Goto[7] who concluded chair–chair equilibration with the phosphoryl oxygen pseudoequatorial in the dominant conformer. Note that

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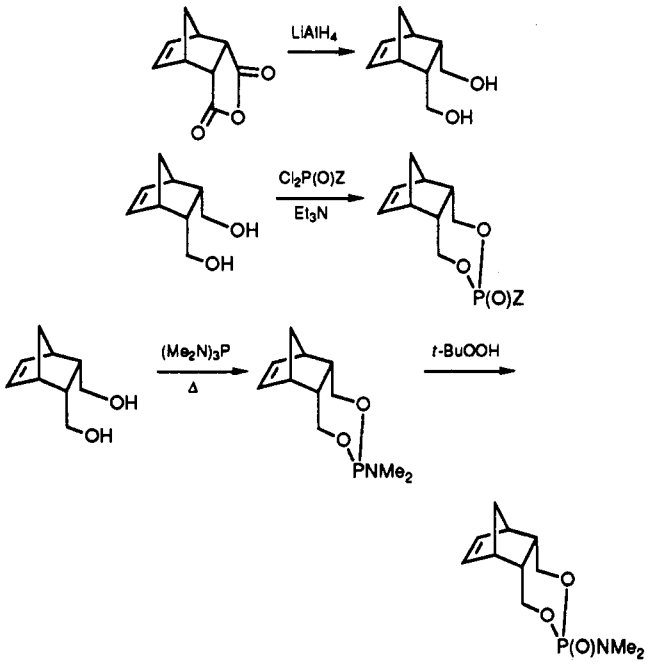
(2) American Chemical Society Petroleum Research Fund Undergraduate Student Summer Research Fellow (from Oakwood College, Huntsville, AL), 1987.
(3) Bentrude, W. G.; Setzer, W. N. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH Publishers: Deerfield Beach, FL, 1987; Chapter 11.
(4) Setzer, W. N.; Black, B. G.; Hovanes, B. A.; Hubbard, J. H. *J. Org. Chem.* **1989**, *54*, 1709.
(5) Quin, L. D. In *Conformational Analysis of Medium-Sized Heterocycles*; Glass, R. S., Ed.; VCH: Deerfield Beach, FL, 1988; Chapter 5.
(6) Gallagher, M. J. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH: Deerfield Beach, FL, 1987; Chapter 9.
(7) Sato, T.; Goto, K. *J. Chem. Soc., Chem. Commun.* **1973**, 494.
(8) Guimaraes, A. C.; Robert, J. B. *Tetrahedron Lett.* **1976**, 473.
(9) Guimaraes, A. C.; Robert, J. B.; Taieb, C.; Tabony, J. *Org. Magn. Reson.* **1978**, *11*, 411.
(10) Arbuzov, B. A.; Kadyrov, R. A.; Arshinova, R. P.; Sharikov, I. K.; Shagidullin, R. R. *Zhur. Obshch. Khim.* **1985**, *55*, 1975.
(11) Arbuzov, B. A.; Kadyrov, R. A.; Klochkov, V. V.; Arshinova, R. P.; Aganov, A. V. *Izv. Akad. Nauk, SSSR, Ser. Khim.* **1982**, 588.
(12) Arbuzov, B. A.; Aganov, A. V.; Klochkov, V. V.; Kladyrov, R. A.; Arshinova, R. P. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1982**, 1195.
(13) Kainosho, M.; Ajisaka, K. *J. Am. Chem. Soc.* **1975**, *97*, 6839.
(14) Kung, W.; Marsh, R. E.; Kainosho, M. *J. Am. Chem. Soc.* **1977**, *99*, 5471.
(15) MacCoss, M.; Ainsworth, C. F.; Leo, G.; Ezra, F. S.; Danyluk, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7353.
(16) The structurally similar 1,5:2,3-bis-*O*-[(*N*,*N*-diethylamino)-thionophosphato]-*β*-ribofuranosides have also been examined: Nabiullin, V. N.; Musina, A. A.; Chernov, P. P.; Mukmenev, E. T. *Izv. Akad. Naus SSSR, Ser. Khim.* **1981**, 1036.
(17) Lachapelle, A.; St-Jacques, M. *Tetrahedron* **1988**, *44*, 5033.
(18) Entrena, A.; Gallo, M. A.; Espinosa, A.; Jaime, C.; Campos, J.; Dominguez, J. F. *J. Org. Chem.* **1989**, *54*, 6034.

0022-3263/92/1957-2812$03.00/0

Cl, OMe, and OPh are strongly axial seeking in the six-membered ring 1,3,2-dioxaphosphorinanes.[3] In a more recent analysis using ^{1}H NMR, dipole moment, and Kerr effect data, Arbuzov and co-workers[19] have concluded that 1 (X = O, Z = OPh) exists in a three-component equilibrium which includes a flexible twist conformation as well as the two chair forms. It has been concluded that the methoxy analogue (1, X = O, Z = OMe) may also involve a twist conformation in equilibrium with the two chair forms.[20] In 1 (X = S, Z = Me or NMe_2), X-ray crystallographic analysis indicates a chair conformation with axial P=S and equatorial P—Z,[21] and ^{1}H NMR analysis is consistent with this conformation in solution.[9] It has been concluded, however, that for 1 (X = O, S, Z = NMe_2), dipole moment and Kerr effect data indicate some (20–30%) population of twist form.[22] Note that $-NMe_2$ has been found to be equatorially seeking in 1,3,2-dioxaphosphorinanes.[23–26]

Results and Discussion

Synthesis. The 1,3,2-dioxaphosphepanes 1 and 2 (Z = OPh or Ph) are conveniently prepared by reaction of 1,2-benzenedimethanol and 5-norbornene-*endo*,*endo*-2,3-dimethanol, respectively, withe the appropriate $ZP(O)Cl_2$ reagent. Preparation of **1c** and **2c** was accomplished by heating the appropriate diol with hexamethylphosphorus triamide followed by oxidation with *tert*-butyl hydroperoxide. The two diastereomers which resulted from the cyclizations using norbornenedimethanol were separated by preparative HPLC on silica gel. The dialcohols were prepared by lithium aluminum hydride reduction of the corresponding anhydride.



(19) Arbuzov, B. A.; Kadyrov, R. A.; Arshinova, R. P.; Klochkov, V. V.; Aganov, A. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 1762.
(20) Gnevashev, S. G.; Arshinova, R. P.; Arbuzov, B. A. *Izv. Akad Nauk SSSR, Ser. Khim.* **1988**, 2022.
(21) Grand, A.; Robert, J. B. *Acta Crystallogr., Sect. B* **1978**, *B34*, 199.
(22) Kadyrov, R. A.; Arshinova, R. P.; Klochkov, V. V.; Aganov, A. V.; Arbuzov, B. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 799.
(23) Dale, A. J. *Acta Chem. Scand.* **1972**, *26*, 2985; **1976**, *B30*, 255.
(24) Majoral, J.-P.; Bergounhou, C.; Navech, J.; Maria, P. C.; Elegant, L.; Azzaro, M. *Bull. Soc. Chim. Fr.* **1973**, 3142.
(25) Bentrude, W. G.; Hargis, J. H. *J. Chem. Soc., Chem. Commun.* **1969**, 1113.
(26) Bentrude, W. G.; Tan, H.-W. *J. Chem. Soc.* **1973**, *95*, 4666.

Table I. NMR and IR Spectroscopic Data for 1,3,2-Dioxaphosphepanes[a]

compd	δ_P	δ_A	δ_B	J_{AB}	J_{AP}	J_{BP}	J_{AX}	J_{BX}	$\nu_{P=O}$
1a	−8.14	5.65	5.18	−13.2	9.1	23.1			1290
1b	23.38	5.68	5.09	−13.7	12.7	17.5			1250
1c	13.68	5.46	5.09	−13.2	9.5	20.6			1239
cis-**2a**	−9.34	3.96	4.26	−12.0	7.0	26.5	12.2	3.7	1300
trans-**2a**	−1.29	3.98	4.27	−12.3	8.2	23.3	11.7	4.1	1264
cis-**2b**	18.08	4.06	4.27	−11.9	7.1	25.2	11.8	2.5	1255
trans-**2b**	22.90	4.25	3.70	−12.3	8.4	20.5	12.3	3.8	1230
cis-**2c**	13.79	3.60	4.13	−11.9	3.1	23.7	11.4	2.7	1245
trans-**2c**	18.61	3.83	3.97	−12.3	10.0	21.5	10.0	4.1	1228

[a] The NMR spectra were obtained in acetone-d_6 at ambient temperatures at 200 MHz. J values are given in Hz, ν in cm^{-1}.

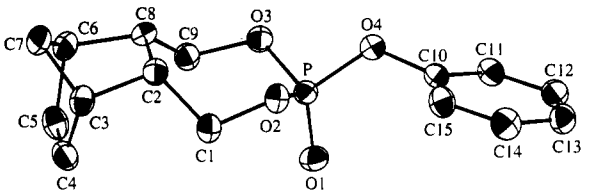


Figure 1. ORTEP perspective view of *trans*-**2a**.[28]

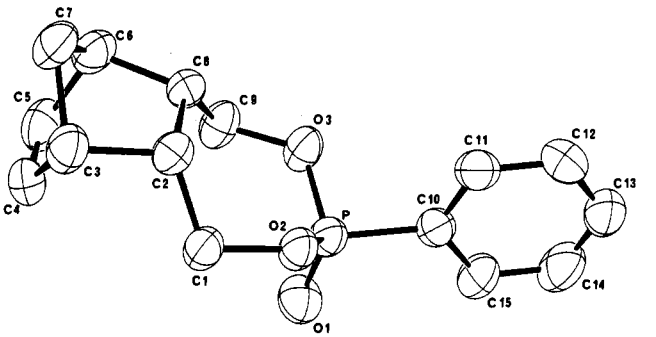
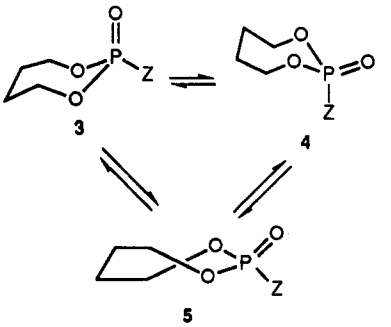


Figure 2. ORTEP perspective view of *trans*-**2b**.[28]

NMR Parameters, Stereochemical Assignments, and Conformations. The ^{1}H and ^{31}P NMR parameters (coupling constants and chemical shifts) for the 1,3,2-dioxaphosphepanes are listed in Table I. These NMR parameters were obtained at 200 MHz and, except for *trans*-**2b**, are first order. (The ^{1}H NMR spectrum for *trans*-**2b** was subsequently obtained at 500 MHz.[27]) These NMR data may be interpreted in terms of chair ⇌ chair equilibria of the type **3** ⇌ **4**, although population to some extent of a flexible twist form, **5**, cannot be precluded.



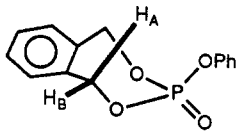
The stereochemistry of the diastereomers (cis and trans) of **2a** and **2b** were assigned based upon single-crystal X-ray structural determinations (Figures 1 and 2).[28] In the chromatographic separations of **2a** and **2b** the trans dia-

(27) The 500-MHz ^{1}H NMR spectrum was kindly obtained by Dr. Alan E. Sopchik, Department of Chemistry, The University of Utah.
(28) The crystallographic details of these studies have been published elsewhere: Setzer, W. N.; Brown, M. L.; Arif, A.; VanDerveer, D. G. *Phosphorus, Sulfur Silicon Relat. Elem.* **1990**, *54*, 187.

stereomer (substituent Z and the alkene group trans) was the later diastereomer to elute from the column. In addition, the ^{31}P chemical shifts of the trans diastereomers for **2a** and **2b** are at lower field than the respective cis diastereomers. The cis and trans diastereomers of **2c** were then assigned on the basis of chromatographic retention time and relative ^{31}P chemical shifts.

The X-ray crystal structures of trans-**2a** and trans-**2b** (Figures 1 and 2, respectively) show these materials to adopt chair conformations with substituent Z in an *equatorial disposition*. The geometrical parameters of these compounds[28] indicate little, if any, manifestation of the anomeric effect[29] in these compounds.

Sato and Goto[7] have concluded from NMR studies that **1a** adopts predominantly a chair conformation with the phenoxy group axial, **6**, rather than equatorial, **7**. Arbuzov



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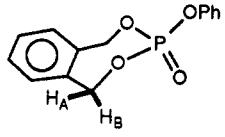

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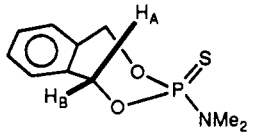
and co-workers[19] conclude that some twist conformation is important in the equilibria of this compound in polar solvent (e.g., acetone). Compound **1** (X = S, Z = NMe_2), on the other hand, was concluded to adopt an analogous chair conformation with the dimethylamino group equatorial, **8**. Our NMR data for **1a** are consistent with chair–chair–twist equilibria but it is curious that H_A (the proton with the smaller $^3J_{HP}$ and thus, predominantly axial) has a chemical shift, δ_A, at *lower* field than that of H_B (that is, $^3J_{BP} > {}^3J_{AP}$ and $\delta_A > \delta_B$). It is generally observed in 1,3,2-dioxaphosphorinanes that the proton cis to the phosphoryl oxygen is found at lower field than the proton trans due to the deshielding effects of the P=O group.[3,30-33] It may be that the preferred conformation for **1a** is actually the chair conformation with the phenoxy substituent *equatorial*, **7**, rather than axial. If the anomeric effect is relatively unimportant in 1,3,2-dioxaphosphepanes, then steric effects should predominate and the phenoxy group would *not* be axial-seeking in these seven-membered-ring phosphorus heterocycles; an unexpected result. An alternative explanation may be that the preferred conformation is the chair with the phenoxy axial but that the relative chemical shifts show anomalous behavior in this compound due to deshielding effects of the aryl ring.



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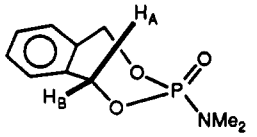

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The ^1H NMR data for **1c** are consistent with the predominance of a chair conformation with the dimethylamino group equatorial, **9**. This interpretation is in agreement with Kadyrov and co-workers[22] for **1c** (in $CHCl_3$) and with Guimaraes and co-workers[9] for the analogous 2-thio compound, **1** (X = S, Z = NMe_2). Note

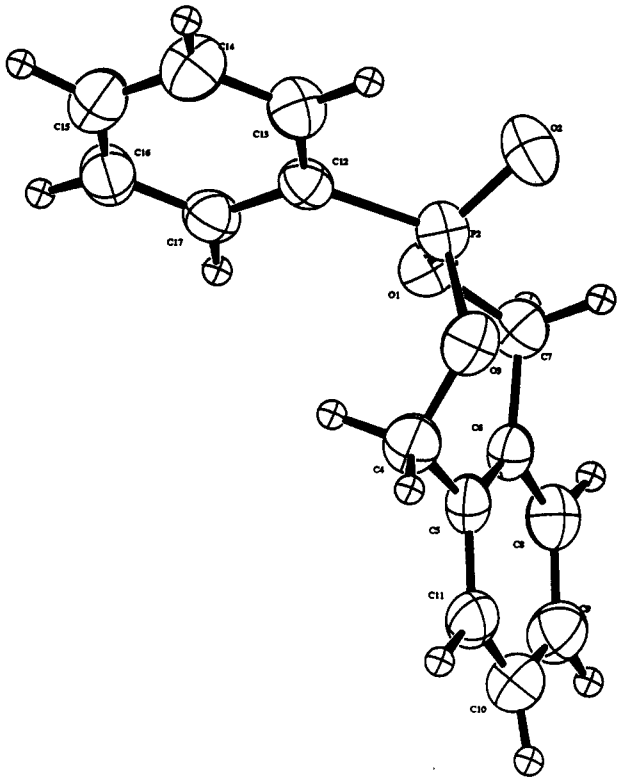


Figure 3. ORTEP perspective view of **1b**.[35]

that the dimethylamino group is presumed to be equatorial based upon steric arguments, but the ^1H NMR data do not necessarily rule out the alternative chair with dimethylamino axial (see below).

The NMR coupling data for **1b** may be interpreted in terms of an equilibrium mixture of the two chair forms as evidenced by the larger J_{AP} and smaller J_{BP} values than those observed in either **1a** or **1c**. Clearly an equilibrium of this type cannot be due to steric effects alone. The phenyl group is a significantly more sterically demanding substituent than is oxygen. Steric effects would dictate that phenyl should be very largely equatorial in this equilibrium.[34] Apparently, then, the conformational equilibrium in **1b** is governed by a combination of steric and electronic effects. In 2-substituted 1,3,2-dioxaphosphorinanes dimethylamino has been found to be more sterically demanding than phenyl.[24]

It is very likely that a twist conformation predominates in solution for **1b**, as suggested by Arbuzov and Arshinova and their co-workers.[10-12] A single-crystal X-ray structural determination has been carried out on **1b** (Figure 3),[35] and this compound adopts a twist conformation in the solid state. Thus, the coupling data for **1b** can also accommodate an equilibrium involving twist forms (as well as chair forms).

Variable-temperature ^1H NMR data (Table II) indicate **1a** to adopt largely conformation **6** although some conformational mobility is evident. That is, J_{AP} gets somewhat smaller as the temperature is lowered while J_{BP} gets correspondingly larger. Compounds **1b** and **1c**, on the other hand, show very little change upon cooling. This may reflect a predominance of the twist form for **1b** at the three temperatures investigated (25, 0, and −25 °C); there is very

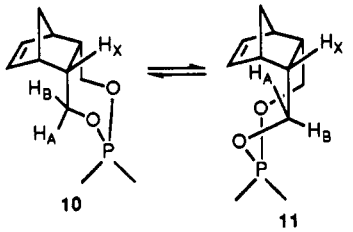
(29) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983.
(30) Bentrude, W. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 7136.
(31) Warrent, R. W.; Caughlan, C. N.; Hargis, J. H.; Yee, K. C.; Bentrude, W. G. *J. Org. Chem.* **1978**, *43*, 4266.
(32) Eto, M.; Fukuhara, N.; Kuwano, E.; Koyama, H. *Agric. Biol. Chem.* **1981**, *45*, 915.
(33) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187.
(34) The conformational energy in cyclohexane equilibria for a phenyl group is about 3.0 kcal/mol and about 2.1 kcal/mol for a dimethylamino group: Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.
(35) The crystallographic details of this study have been published elsewhere: Setzer, W. N.; Brown, M. L.; Wu, C.-K.; Meehan, E. J. *Heteroatom Chem.* **1991**, *2*, 533.

Table II. Variable-Temperature ^{1}H NMR Coupling Data

compd	temp (°C)	J_{AP} (Hz)	J_{BP} (Hz)
1a	25	9.1	23.1
	0	8.4	24.0
	-25	7.5	24.9
1b	25	12.7	17.5
	0	13.2	17.7
	-25	13.3	17.9
1c	25	9.5	20.6
	0	9.1	20.9
	-25	9.1	21.1
cis-**2a**	25	7.0	26.5
	0	7.1	26.4
	-25	7.1	26.9
trans-**2a**	25	8.2	23.3
	0	8.3	23.6
	-25	8.2	23.7
cis-**2b**	25	7.1	25.2
	0	7.3	25.9
	-25	7.2	26.6
cis-**2c**	25	3.1	23.7
	0	2.7	23.8
	-25	2.1	23.1
trans-**2c**	25	10.0	21.5
	0	10.2	21.4
	-25	9.8	21.6

little increase in population of either chair form upon cooling. Although **1c** shows little change in coupling (J_{AP} and J_{BP}) upon cooling, the somewhat large value of J_{AP} (9.1 Hz) and small value of J_{BP} (21.1 Hz), compared to those of **1a**, would argue against population of exclusively one chair form (either **6** or **7**).

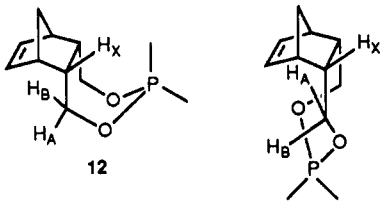
The norbornene-fused dioxaphosphepanes **2** show some evidence of equilibria but seem to adopt predominantly chair conformation **10**. The ^{1}H NMR data do *not* support population of alternative chair **11** to a large extent. Note



10 **11**

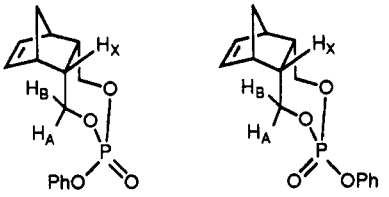
that the norbornene-fused dioxaphosphepanes **2** show very little "equilibrium shift" upon cooling (Table II) indicating essentially complete population of chair **10** for these compounds. The chair conformation **10** for each of these compounds is indicated by the relatively large J_{BP} and small J_{AP} values and correspondingly small J_{BX} and large J_{AX} values. Note the anti dihedral arrangement of H_B–C–O–P, the gauche H_A–C–O–P, the anti H_A–C–C–H_X, and gauche H_B–C–C–H_X.

Molecular models indicate boat conformation **12** to have H_B–C–O–P ≃ 180° and H_A–C–O–P ≃ 60°, whereas chair **10** has H_B–C–O–P ≃ 140° and H_A–C–O–P ≃ 20°. Thus, population of boat **12** should *increase* J_{BP} and *decrease* J_{AP}, while J_{AX} and J_{BX} values should remain about the same. A twist-type conformation, **13**, would serve to increase J_{AP} and decrease J_{BP} with concommitant decrease in J_{AX} but J_{BX} should remain small (i.e., H_X–C–C–H_B is always gauche). Note that interconversion between boat **12** and twist **13** is possible through a pseudorotational pathway. Note also that the twist conformation, according to molecular models, may suffer from repulsive steric interactions between H_A and C(5′) of the norbornene ring [H_A···C(5′) ≃ 2.0 Å] as well as steric interactions between O(1) and C(5′) [O(1)···C(5′) ≃ 2.5 Å]. Thus, a flexible-twist conformation for the norbornene-fused 1,3,2-dioxaphosphepane ring may be less accessible, due to steric interactions, than in the benzo-fused system.



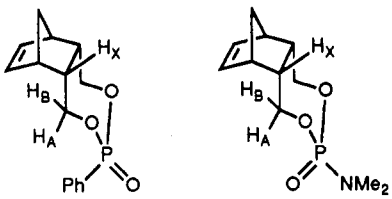
12 **13**

In **2a**, whether or not the phenoxy group is cis or trans, the compound apparently adopts predominantly chair conformation **10**. That is, the conformation of *cis*-**2a** is a chair with an axial phenoxy group while *trans*-**2a** adopts an analogous chair with the phenoxy group equatorial. Apparently the phenoxy group is *not* axial seeking enough to cause population of the alternative chair to much extent in *trans*-**2a** (see the X-ray structure, Figure 1). Note that for *trans*-**2a**, J_{BP} and J_{AX} are slightly smaller than those in *cis*-**2a** and J_{AP} and J_{BX} are somewhat larger. This would indicate some chair–chair equilibration, **10** ⇌ **11** (to the extent of about 7% chair form **11**, assuming *cis*-**2a** to be conformationally locked in chair form **10**). There does not seem to be any evidence of boat or twist conformation population in *trans*-**2a** (J_{AP} is larger in *trans*-**2a** than in *cis*-**2a** rather than smaller).



cis-**2a** *trans*-**2a**

The ^{1}H NMR coupling data for *cis*-**2b** are similar to those for *cis*-**2a** and indicate *cis*-**2b** is largely one chair conformation with the phenyl group axial. The axial-seeking nature of the phenyl group on phosphorus in cyclic phosphonates is evident in *trans*-**2b**: J_{BP} is smaller in *trans*-**2b** than in *cis*-**2b** (20.5 vs 25.2 Hz, respectively), and J_{AP} is correspondingly larger in *trans*-**2b** than in *cis*-**2b** (8.4 vs 7.1 Hz). Apparently *trans*-**2b** adopts, to a small extent (about 15%), alternative chair **10**.[36]



cis-**2b** *trans*-**2c**

The sterically demanding dimethylamino group should prefer to be equatorial and would be expected to conformationally lock *trans*-**2c** in a chair. Although largely a chair conformation, the $^3J_{HP}$ couplings do not support a conformationally locked, single-chair conformation. While J_{BP} is large and J_{AP} relatively small (21.5 and 10.0 Hz, respectively), they are not the extremes seen in *cis*-**2a** (26.5 and 7.0 Hz). Not only that, but the values of J_{BP} and J_{AP}

(36) Note that the sums of J_{AP} + J_{BP} for these compounds are not constant. They range from a high of 33.5 Hz (*cis*-**2a**) to a low of 26.8 Hz (*cis*-**2c**). Caution should therefore be used when comparing coupling data for these heterocyclic systems.

for *cis*-**2c** do not show the expected trend. That is, J_{BP} for *cis*-**2c** is *larger* than J_{BP} for *trans*-**2c** and J_{AP} is smaller for *cis*-**2c** than for *trans*-**2c**. The J_{AX} and J_{BX} couplings show analogous unexpected trends: J_{AX}(*cis*-**2c**) > J_{AX}(*trans*-**2c**); J_{BX}(*cis*-**2c**) < J_{BX}(*trans*-**2c**).[37] These results would suggest that the dimethylamino substituent on phosphorus in 1,3,2-dioxaphosphepanes is actually axial seeking rather than equatorial seeking as observed in 1,3,2-dioxaphosphorinanes.

The relative chemical shifts for the norbornene-fused 1,3,2-dioxaphosphepanes do not behave as expected. Both *cis*-**2a** and *trans*-**2a** show $\delta_B > \delta_A$ (very nearly the same chemical shifts in these two compounds). Although $\delta_B > \delta_A$ for *cis*- and *trans*-**2c**, the resonances of H_A and H_B are shifted in the expected directions. Thus, *cis*-**2c** has P=O and H_B cis, and H_B is, therefore, deshielded with respect to H_A (4.13 vs 3.60 ppm, respectively). In *trans*-**2c** (P=O and H_B trans), H_B is shifted to higher field (3.97 ppm) and H_A is shifted to lower field (3.83 ppm) than those observed in the cis diastereomer. The chemical shifts for **2b** behave as expected: *cis*-**2b** (P=O and H_B cis, $\delta_B > \delta_A$); *trans*-**2b** (P=O and H_B trans, $\delta_B < \delta_A$).

Infrared Studies. Correlations between P=O stretching frequencies and phosphoryl orientations have been used in studying 1,3,2-dioxaphosphorinanes.[33] Compounds with axial P=O generally have $\nu_{P=O}$ at *lower* frequency than analogous compounds with equatorial P=O. We have examined the P=O stretching region of the compounds, and we have found some interesting comparisons. Compound **1a** presumably has the P=O equatorial (and $\nu_{P=O}$ = 1290 cm^{-1} for this compound). Compound *cis*-**2a** presumably also has P=O equatorial (and has $\nu_{P=O}$ = 1300 cm^{-1}). The trans diastereomer *trans*-**2a** has P=O axial (as determined by X-ray crystal structure, Figure 1) and has a lower P=O stretching frequency (1264 cm^{-1}), as expected.[38]

The phenyl-substituted compounds show similar trends in P=O stretching frequencies: **1b** ($\nu_{P=O}$ = 1250 cm^{-1}), *cis*-**2b** ($\nu_{P=O}$ = 1255 cm^{-1}), and *trans*-**2b** ($\nu_{P=O}$ = 1230 cm^{-1}). Note that *trans*-**2b** is shown (X-ray crystal structure, Figure 2) to adopt a chair conformation with axial P=O, and the lower P=O stretching frequency reflects this. Of interest is the P=O stretching frequency of **1b**, very close to that found for *cis*-**2b**. Thus, the IR data suggest that the phosphoryl group of **1b** is equatorial in the solid state. This point is moot, however, since the X-ray crystal structure of **1b** shows the compound to adopt a twist conformation with isoclinal P=O and P—Ph. Note, however, that the IR spectrum of **1b** in solution (5% $CHCl_3$) shows a broad P=O stretch (1190–1260 cm^{-1}) indicating, perhaps, conformational equilibrium.

The IR data for the dimethylamino compounds **1c** and **2c** are perhaps less clear. As in the other compounds investigated the cis diastereomer shows a P=O stretch at higher frequency (*cis*-**2c**, $\nu_{P=O}$ = 1245 cm^{-1}) that that of the trans (*trans*-**2c**, $\nu_{P=O}$ = 1228 cm^{-1}), consistent with equatorial P=O in *cis*-**2c** and axial P=O in *trans*-**2c**. (Unfortunately we have been unable, so far, to get X-ray-quality crystals of *trans*-**2c**). Compound **1c**, which we have presumed to adopt conformation **8** (axial P=O), has a P=O stretching frequency of 1239 cm^{-1}; close to that observed for *cis*-**2c**, but not too far from that of *trans*-**2c**. It may be that the preferred conformation of **1c** is the alternative chair conformation with the P=O equatorial and the P–NMe_2 axial. Although dimethylamino is sterically demanding, and thus prefers to be equatorial, in 1,3,2-dioxaphosphorinanes, it is seen to be somewhat axial seeking in 1,3,2-oxazaphosphorinanes.[39,40] Perhaps it is also axial seeking in 1,3,2-dioxaphosphepanes. An axial-seeking dimethylamino group would help to explain the otherwise anomalous ^{1}H NMR results for **2c**. That is, if dimethylamino is axial seeking in these compounds, then chair conformation **10** would be somewhat depopulated in favor of conformation **11** for *trans*-**2c**. The ^{1}H NMR data do, in fact, support just such an equilibrium for this compound.

Phosphorus-31 Chemical Shifts. Phosphorus-31 chemical shifts have been used in conformational studies of 1,3,2-dioxaphosphorinanes.[33] By comparing the ^{31}P chemical shifts for two highly biased model compounds epimeric at phosphorus with the values for conformationally nonbiased analogues, an estimation of the amount of each conformer in the nonbiased system can be made (this rule is not without exception, however).[33] As we have seen, the norbornene-fused 1,3,2-dioxaphosphepanes are generally biased systems while the benzo-fused 1,3,2-dioxaphosphepanes are potentially conformationally mobile.

A comparison of ^{31}P chemical shift data for these compounds shows some trends analogous to those observed in the IR P=O stretching comparisons. The ^{31}P chemical shift for **1a** (−8.14 ppm) is comparable to that for *cis*-**2a** (−9.34 ppm) but not so close to that for *trans*-**2a** (−1.29 ppm). Thus, the ^{31}P chemical shift data indicate **1a** to adopt, predominantly, conformation **6** (P–OPh axial), as expected and in agreement with the IR results. The ^{31}P chemical shift data for **1b** and **2b** are not in complete agreement with the IR P=O frequency results: δ_P(**1b**) = 23.38 ppm, δ_P(*cis*-**2b**) = 18.08 ppm, and δ_P(*trans*-**2b**) = 22.90 ppm. Thus, the ^{31}P NMR data would imply the predominant conformer for **1b**, *in solution*, to be the chair with *equatorial* P–Ph while the X-ray structure shows **1b** to adopt a twist conformation with P–Ph isoclinal, *in the solid state*. The solution IR spectrum of **1b** (see above) does not rule out a predominance of the chair form with equatorial P–Ph.

Compound **1c** shows a ^{31}P shift similar to that for *cis*-**2c** (13.68 and 13.79 ppm, respectively), while the chemical shift for *trans*-**2c** is at lower field (18.61 ppm). These ^{31}P NMR data suggest that **1c** adopts a chair conformation with the dimethylamino group axial as does, presumably, *cis*-**2c**. These results are in agreement with the P=O stretching frequency results and again suggest that a dimethylamino substituent on phosphorus is axial seeking in the 1,3,2-dioxaphosphepane ring system.

Conclusions

The ^{1}H NMR data ($^3J_{HH}$ and $^3J_{HP}$ coupling constants), in conjunction with IR data (P=O stretching frequencies) and ^{31}P NMR data (chemical shifts), indicate that substituents on phosphorus (phenoxy, phenyl, or dimethylamino) are axial seeking in the 1,3,2-dioxaphosphepane ring system. The degree of axial preference seems to follow the order OPh > NMe_2 > Ph, paralleling conformational energies from cyclohexane equilibria rather than from 1,3,2-dioxaphosphorinane equilibria; a completely unex-

(37) It may be that ring strain, transannular steric effects, and bond angle distortions result in the variations in the sums of $^3J_{HP}$ for these compounds. Such effects may even be responsible for the anomalous coupling behavior in *cis*- and *trans*-**2c**.

(38) It has been pointed out that caution should be exercised when using P=O stretching frequencies for assigning conformations; some results can be misleading: White, D. W.; Gibbs, D. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1979**, *101*, 1937.

(39) Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1985**, *107*, 2083.

(40) Holmes, R. R.; Day, R. O.; Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1984**, *106*, 2353.

pected result. The axial-seeking nature of these substituents in this heterocyclic system is clearly not due to steric effects alone but must also include electronic effects, i.e., the anomeric effect. It is very likely that twist conformations are also important in the benzo-fused 1,3,2-dioxaphosphepanes, and this possibility complicates the equilibrium picture for these compounds.

Experimental Section

Methods and Materials. All reagents were obtained from Aldrich Chemical Co., Milwaukee, WI. Solvents were dried using standard techniques. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. Melting points are uncorrected. NMR coupling constants were measured at 200 MHz on 100-Hz SW expansions, 32K data base, 9.044-s acquisition times, and are probably accurate to ±0.2 Hz. Phosphorus-31 NMR spectra were collected at 81.015 MHz with proton decoupling.

2-Phenoxy-2-oxo-5,6-benzo-1,3,2-dioxaphosphepane, 1a.[7] A solution of 1,2-benzenedimethanol (2.00 g, 14.5 mmol), anhydrous triethylamine (4.0 mL, 29 mmol), and sufficient anhydrous ethyl acetate to dilute to 80 mL and a solution of phenyl dichlorophosphate (1.85 mL, 14.5 mmol) and sufficient anhydrous ethyl acetate to dilute to 80 mL were added simultaneously by dropwise addition to a three-necked flask containing 150 mL of anhydrous ethyl acetate. The reaction mixture was allowed to stir for 48 h, the triethylamine hydrochloride filtered off, the solid washed with ethyl acetate, and the solvent removed from the filtrate under reduced pressure to give a colorless crystalline solid which was recrystallized from ethyl acetate/hexane to give 2.71 g (99.5% yield) of pure **1a** as a colorless crystalline solid.

2-Phenyl-2-oxo-5,6-benzo-1,3,2-dioxaphosphepane, 1b. A solution of 1,2-benzenedimethanol (2.04g, 14.78 mmol), anhydrous triethylamine (4.0 mL, 29 mmol), and sufficient anhydrous ethyl acetate to dilute to 80 mL and a solution of phenylphosphonic dichloride (1.85 mL, 14.78 mmol) and sufficient anhydrous ethyl acetate to dilute to 80 mL were added simultaneously by dropwise addition to a three-necked flask containing 150 mL of anhydrous ethyl acetate. The reaction mixture was allowed to sir for 48 h, the triethylamine hydrochloride filtered off, the solid washed with ethyl acetate, and the solvent removed from the filtrate under reduced pressure to give a yellow oil which crystallized overnight. The solid residue was recrystallized from toluene to give 1.96 g (50.7% yield) of pure **1b** as a colorless crystalline solid: mp 128.5 °C; ^{1}H NMR (acetone-d_6) δ 5.09 (dd, 2 H, $-CH_2O-$, J_{HH} = 13.7 Hz, J_{PH} = 17.5 Hz), 5.68 (dd, 2 H, $-CH_2O-$, J_{HH} = 13.7 Hz, J_{PH} = 12.7 Hz), 7.22–7.88 (m, 9 H, aromatic); ^{31}P NMR (acetone-d_6) δ 23.38; IR (KBr) 3060, 3030, 2880, 1500, 1448, 1439, 1380, 1292, 1275, 1250 (s, P=O), 1206, 1129 (s), 1062 (s), 1024 (s), 1014 (s), 1004 (s), 986 (s), 946, 867, 842 (s), 809 (s), 754 (s), 693 (s), 626, 615, 560, 530, 500, 479, 429, 394, 313 cm^{-1}. Anal. Calcd for $C_{14}H_{13}PO_3$: C, 64.62: H, 5.03; P, 11.90. Found: C, 64.23; H, 5.17; P, 11.66.

2-(Dimethylamino)-2-oxo-5,6-benzo-1,3,2-dioxaphosphepane, 1c. Hexamethylphosphorous triamide (11.4 mL, 54.6 mmol) was slowly added to a stirred solution of 1,2-benzenedimethanol (8.1 g, 54.6 mmol) in anhydrous toluene (200 mL) under dry nitrogen atmosphere. The reaction mixture was allowed to reflux overnight and then cooled to 0 °C. A solution of *tert*-butyl hydroperoxide (18.2 mL of a 3 M solution in 2,2,4-trimethylpentane, 54.6 mmol) was slowly added and the reaction mixture allowed to stir at 0 °C for 15 min. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solvents were removed from the reaction mixture by rotary evaporation to leave 16.7 g of a yellow mushy solid. A 1.93-g sample of the crude product was chromatographed on a gravity column (2.5 × 60 cm) of silica gel, eluting with ethanol/ethyl acetate (1:9), and the product recrystallized from ethyl acetate/hexane to give 895 mg (62.4% yield) of pure **1c** as a colorless crystalline solid: mp 149–152 °C; ^{1}H NMR (acetone-d_6) δ 2.60 (d, 6 H, NMe_2, J_{PH} = 10.0 Hz), 4.91 (dd, 2 H, $-CH_2O-$, J_{HH} = 13.2 Hz, J_{PH} = 20.6 Hz), 5.46 (dd, 2 H, $-CH_2O-$, J_{HH} = 13.2 Hz, J_{PH} = 9.5 Hz), 7.38–7.49 (m, 4 H, aromatic); ^{31}P NMR (acetone-d_6) δ 13.68 ppm; IR (KBr) 2985, 2940, 2910, 2845, 2810, 1721, 1471, 1449, 1322, 1290 (s), 1239 (s, P=O), 1218, 1175, 1116, 1065, 1049 (s), 1017 (s), 999 (s), 977 (s), 955 (s), 839, 800, 784 (s), 743, 621, 602, 478, 455, 410, 364, 337, 317, 293 cm^{-1}. Anal. Calcd for $C_{10}H_{14}NO_3P$: C, 52.86; H, 6.21; P, 13.63. Found: C, 52.13; H, 6.02; P, 13.71.

5-Norbornene-*endo*,*endo*-2,3-dimethanol. A solution of 5-norbornene-*endo*,*endo*-2,3-dicarboxylic anhydride[41] (16.5 g; 100 mmol) in anhydrous tetrahydrofuran (100 mL) was added slowly to a stirred suspension of lithium aluminum hydride (4.0 g, 105 mmol) in tetrahydrofuran (200 mL). The reaction mixture was heated to gentle reflux for 48 h, allowed to cool to room temperature, quenched with a solution of tetrahydrofuran (100 mL) and water (6.0 mL), and stirred for an additional 1 h. Anhydrous magnesium sulfate was added and stirring continued for 20 min. The reaction mixture was filtered, and the solids were washed with tetrahydrofuran (4×). The solvent was removed from the filtrate under reduced pressure leaving a crystalline solid residue which was recrystallized from ether/pentane to give 6.7 g (39.4% yield) norbornenedimethanol as a colorless crystalline solid.

5,6-(*endo*,*endo*-2′,3′-Bicyclo[2.2.1]hept-5′-eno)-2-oxo-2-phenoxy-1,3,2-dioxaphosphepane, 2a. A solution of 5-norbornene-*endo*,*endo*-2,3-dimethanol (2.00 g, 13.0 mmol), triethylamine (3.10 mL, 22.4 mmol), and sufficient ethyl acetate to dilute to 100 mL and a solution of 1.66 mL of phenyl dichlorophosphate (1.66 mL, 11.1 mmol) and sufficient ethyl acetate to dilute to 100 mL were added simultanously by dropwise addition to 200 mL of ethyl acetate under anhydrous conditions. The reaction mixture was stirred for 48 h, the triethylamine hydrochloride filtered off, the solid washed with ethyl acetate, and the solvent removed from the filtrate under reduced pressure to give 4.04 g of a pale yellow oil which solidified upon standing. A 2.00-g sample of the crude product was chromatographed by a gravity column (2.5 × 60 cm) on silica gel, eluting with ethyl acetate/hexane (60:40) to give 1.67 g (88.7% yield) of pure **2a** as a mixture of diastereomers. Anal. Calcd for $C_{15}H_{17}O_4P$: C, 61.64; H, 5.87; P, 10.59. Found: C, 61.81; H, 5.87; P, 10.14. The diastereomers were separated by preparative HPLC on silica gel, eluting with ethyl acetate/hexane (60:40) to give pure *cis*-**2a** as a colorless crystalline solid [mp 134.5 °C; ^{1}H NMR (acetone-d_6) δ 1.44–1.57 (m, 2 H, norbornyl), 2.78–2.91 (m, 4 H, norbornyl), 3.96 (ddd, 2 H, $-CH_2O-$, J_{HH} = 12.0 Hz, J_{HH} = 12.2 Hz, J_{PH} = 7.0 Hz), 4.26 (ddd, 2 H, $-CH_2O-$, J_{HH} = 12.0, J_{HH} = 3.7 Hz, J_{PH} = 26.5 Hz), 6.21 (m, 2 H, vinyl), 7.21–7.44 (m, 5 H, aryl); ^{31}P NMR (acetone-d_6) δ −9.34; IR (KBr) 3160, 2972 (s), 2940 (s), 2870, 1735, 1598, 1580, 1487 (s), 1450, 1352, 1335, 1313, 1300 (s, P=O), 1290 (s), 1260, 1249, 1210 (s), 1169 (s), 1139, 1090, 1050 (s), 1020, 1010, 995, 979, 930 (s), 903, 870, 845, 827, 800, 758, 738, 722, 690, 614, 582, 563, 498, 439 cm^{-1}] and pure *trans*-**2a** as a colorless crystalline solid: mp 125 °C; ^{1}H NMR (acetone-d_6) δ 1.43–1.55 (m, 2 H, norbornyl), 2.78–2.91 (m, 4 H, norbornyl), 3.98 (ddd, 2 H, $-CH_2O-$, J_{HH} = 12.3 Hz, J_{HH} = 11.7 Hz, J_{PH} = 8.2 Hz), 4.27 (ddd, 2 H, $-CH_2O-$, J_{HH} = 12.3 Hz, J_{HH} = 4.1 Hz, J_{PH} = 23.3 Hz), 6.20 (m, 2 H, vinyl), 7.20–7.44 (m, 5 H, aryl); ^{31}P NMR (acetone-d_6) δ −1.29; IR (KBr) 3070, 2980 (s), 2965 (s), 2935, 2920, 2900, 1586, 1486 (s), 1459, 1377, 1348, 1337, 1290, 1264 (s, P=O), 1250, 1200 (s), 1172, 1164, 1137, 1120, 1073, 1041 (s), 1025, 1015, 993, 970, 964 (s), 935, 922, 900, 875 (s), 845, 835, 806, 780, 746, 730, 696, 577, 547, 510, 472 cm^{-1}.

5,6-(*endo*,*endo*-2′,3′-Bicyclo[2.2.1]hept-5′-eno)-2-oxo-2-phenyl-1,3,2-dioxaphosphepane, 2b. A solution of 5-norbornene-*endo*,*endo*-2,3-dimethanol (2.00 g, 13.0 mmol), triethylamine (3.10 mL, 30.0 mmol), and sufficient ethyl acetate to dilute to 100 mL and a solution of phenylphosphonic dichloride (1.95 mL, 13.0 mmol) and sufficient ethyl acetate to dilute to 100 mL were added simultanously by dropwise addition to 200 mL of ethanol acetate under anhydrous conditions. The reaction mixture was stirred for 24 h, the triethylamine hydrochloride filtered off, the solid washed with ethyl acetate, and the solvent removed from the filtrate under reduced pressure to give 5.27 g of a yellow solid residue. A 2.00-g sample of the crude product was chromatographed by a gravity column (2.5 × 60 cm) on silica gel, eluting with ethyl acetate/hexane (90:10), to give 1.56 g (58.6% yield) pure **2b** as a mixture of diastereomers. Anal. Calcd for $C_{15}H_{17}O_3P$: C, 65.22; H, 6.20; P, 11.20. Found: C, 65.37; H, 6.40; P, 11.05. The diastereomers were separated by preparative HPLC

(41) Roberts, R. M.; Gilbert, J. C.; Rodewald, L. B.; Wingrove, A. S. *Modern Experimental Organic Chemistry*, 4th ed.; Saunders: Philadelphia, 1985; pp 388–389.

on silica gel, eluting with ethyl acetate/hexane (90:10) to give pure *cis*-**2b** as a thick paste [^{1}H NMR (acetone-d_6) δ 1.08–1.55 (m, 2 H, norbornyl), 3.30–3.61 (m, 4 H, norbornyl), 4.06 (ddd, 2 H, $-CH_2O-$, J_{HH} = 11.9 Hz, J_{HH} = 11.8 Hz, J_{PH} = 7.1 Hz), 4.27 (ddd, 2 H, $-CH_2O-$, J_{HH} = 11.9 Hz, J_{HH} = 2.5 Hz, J_{PH} = 25.2 Hz), 6.23 (t, 2 H, vinyl, J_{HH} = 1.6 Hz), 7.47–7.87 (m, 9 H, aryl); ^{31}P NMR (acetone-d_6) δ 18.08; IR (thin film) 2960–2850, 1400, 1255 (s, P=O), 1100–1020, 795, 700–660 cm^{-1}] and pure *trans*-**2b** as a colorless crystalline solid: mp 131–136 °C; ^{1}H NMR (C_6D_6) δ 1.00 (dt, 1 H, norbornyl bridge, J_{HH} = 8.3 Hz, J_{HH} = 1.4 Hz), 1.20 (dt, 1 H, norbornyl bridge, J_{HH} = 8.3 Hz, J_{HH} = 1.9 Hz), 2.18 (m, 2 H, norbornyl), 2.42 (m, 2 H, norbornyl), 3.70 (ddd, 2 H, $-CH_2O-$, J_{HH} = 12.3 Hz, J_{HH} = 3.8 Hz, J_{PH} = 20.5 Hz), 4.25 (ddd, 2 H, $-CH_2O-$, J_{HH} = 12.3 Hz, J_{HH} = 12.3 Hz, J_{PH} = 8.4 Hz), 5.59 (t, 2 H, vinyl), 6.69–7.07 (m, 3 H, aryl), 8.04–8.09 (m, 2 H, aryl); ^{31}P NMR (acetone-d_6) δ 22.90; IR (KBr) 3050, 2990, 2965 (s), 2940, 2900, 2870, 1595, 1568, 1494, 1475, 1453, 1439, 1382, 1339, 1268, 1254, 1230 (s, P=O), 1177, 1137 (s), 1057 (s), 1020, 1000, 982, 968, 906, 860 (s), 840, 825, 806 (s), 746, 730, 711, 693 (s), 593, 546, 498, 457, 430 cm^{-1}.

5,6-(*endo*,*endo*-2',3'-Bicyclo[2.2.1]hept-5'-eno)-2-oxo-2-(*N*,*N*-dimethylamino)-1,3,2-dioxaphosphepane, 2c. Hexamethylphosphorous triamide (10.0 mL, 42.8 mmol) was slowly added to a stirred solution of 5-norbornene-*endo*,*endo*-2,3-dimethanol (6.72 mg, 42.8 mmol) in anhydrous ethyl acetate (200 mL) under dry nitrogen atmosphere. The reaction mixture was allowed to reflux overnight and then cooled to 0 °C. A solution of *tert*-butyl hydroperoxide (14.3 mL of a 3 M solution in 2,2,4-trimethylpentane, 42.8 mmol) was slowly added and the reaction mixture allowed to stir at 0 °C for 15 min. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solvents were removed from the reaction mixture by rotary evaporation to leave 14.9 g of a yellow solid. A 2.00-g sample of the crude product was chromatographed by a gravity column (2.5 × 60 cm) on silica gel, eluting with ethyl acetate, to give 580 mg (41.5% yield) **2c** as a mixture of diastereomers. Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.27; H, 7.46; N. 5.76; P, 12.73. Found: C, 54.15; H, 7.56; P, 12.01. The diastereomers were separated by preparative HPLC on silica gel eluting with ethyl acetate to give pure *cis*-**2c** as a colorless oil [^{1}H NMR (acetone-d_6) δ 1.41–1.50 (m, 2 H, norbornyl), 2.59 (d, 6 H, NMe_2, J_{PH} = 7.0 Hz), 2.75–2.85 (m, 4 H, norbornyl), 3.60 (ddd, 2 H, $-CH_2O-$, J_{HH} = 11.9 Hz, J_{HH} = 11.4 Hz, J_{PH} = 3.1 Hz), 41.3 (ddd, 2 H, $-CH_2O-$, J_{HH} = 11.9 Hz, J_{HH} = 2.7 Hz, J_{PH} = 23.7 Hz), 6.15 (t, 2 H, vinyl); ^{31}P NMR (acetone-d_6) δ 13.79 ppm; IR (thin film) 2960–2860, 1455, 1376, 1245 (s, P=O), 1175, 1090, 1040 (s), 1015, 1000, 940 (s), 817, 789, 740, 717 cm^{-1}] and pure *trans*-**2c** as a colorless crystalline solid: mp 137.5 °C; ^{1}H NMR (acetone-d_6) δ 1.41–1.53 (m, 2 H, norbornyl), 2.60 (d, 6 H, NMe_2, J_{PH} = 10.0 Hz), 2.71–2.87 (m, 4 H, norbornyl), 3.83 (ddd, 2 H, $-CH_2O-$, J_{HH} = 12.3 Hz, J_{HH} = 10.0 Hz, J_{PH} = 10.0 Hz), 3.97 (ddd, 2 H, $-CH_2O-$, J_{HH} = 12.3 Hz, J_{HH} = 4.1 Hz, J_{PH} = 21.5 Hz), 6.15 (t, 2 H, vinyl); ^{31}P NMR (acetone-d_6) δ 18.61 ppm; IR (KBr) 2970, 2935, 2900, 1474, 1456, 1386, 1333, 1302, 1276, 1228 (s, P=O), 1172, 1050 (s), 985 (s), 963 (s), 857, 839, 812, 750, 736, 710, 555, 476 cm^{-1}.

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Redox Glycosidation: Stereoselective Syntheses of 1 → 6 Linked Disaccharides via Thionoester Intermediates

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Perbenzyl derivatives of the disaccharides benzyl 6-*O*-(α(and β)-D-glucopyranosyl)-α-D-galactopyranoside and benzyl 6-*O*-(α(and β)-D-mannopyranosyl)-α-D-galactopyranoside were each prepared in a stereoselective manner by acylation, thionation, and reductive desulfurization. The use of 2,4-bis(4-phenoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (**4b**) as a mild thionation reagent for esters and lactones is also described.

Introduction

The efficient synthesis of oligosaccharides is a highly desirable objective, the key to which relies upon the efficient stereoselective formation of the glycosidic bond. Virtually all oligosaccharide syntheses rely heavily upon the Koenigs–Knorr alkylation chemistry or modern variations of this theme.[1] Recently, our laboratory[2] presented a novel approach for assembling glycosidic bonds using redox glycosidation. This strategy establishes the anomeric C–O bond by acylation, not alkylation as in the Koenigs–Knorr reaction. Tebbe methylenylation, desilylation, and iodoetherification reveals the glycosidic linkage. The application of redox glycosidation was recently demonstrated in a highly stereoselective synthesis of sucrose.[3] While this method is of potential use for the synthesis of ketose-based oligosaccharides, it is totally inappropriate for the more common aldose-based systems. We have reported a potential solution to this problem by way of thionoester intermediates.[4] In this case, aldonic ester thionation using Lawesson's reagent **4a**,[5] reductive *S*-methylation, and cyclization of the resultant monothioacetal gave the corresponding glycoside. The process is exemplified by the transformation in Scheme I.

As an extension of this methodology, we report in this paper the syntheses of several 1→6 linked disaccharides by the stereoselective acylation of a protected D-galactose derivative, thionation, and reductive desulfurization. Furthermore, we report the use of 2,4-bis(4-phenoxy-

(1) Schmidt, R. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 33–64.
(2) Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Gasiecki, A. F.; Howell, A. R.; Russell, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 1392.
(3) Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Melcher, L. M. *J. Org. Chem.* **1990**, *55*, 5196.
(4) Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Howell, A. R.; Lee, A. C.; Russell, M. A. *J. Org. Chem.* **1989**, *54*, 2275.
(5) Pedersen, B. S.; Scheibye, S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 293.

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