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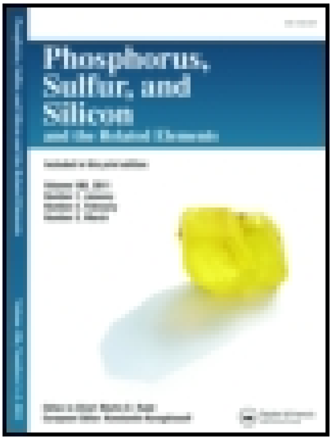

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PREPARATIONS AND TRANSFORMATIONS OF BIFUNCTIONAL EXO-2-PHOSPHORUS SUBSTITUTED BICYCLO[2.2.1]HEPTANES

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PREPARATIONS AND TRANSFORMATIONS OF BIFUNCTIONAL EXO-2-PHOSPHORUS SUBSTITUTED BICYCLO[2.2.1]HEPTANES

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Dedicated to John Verkade on the occasion of his 60th birthday

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The secondary phosphonate ester *exo*-2-(dimethoxyphosphoryl)bicyclo[2.2.1]heptane **1** was prepared by literature methods on a mole scale. This synthetic method was extended to include the stereoselective preparation of the *exo*-diethyl phosphonate analog **3** in 71% yield. Derivatization of these *exo*-phosphonates **1** and **3** required vigorous conditions, but proceeded in moderate to high yields. The configuration about carbon-2 was retained in all but one case. Isomerization about carbon-2 was observed during the desulfurization of *exo*-thiophosphonic dichloride **15** with triphenylphosphine at 240°C. A 3:2 ratio of *exo*- to *endo*-phosphonous dichlorides **16** resulted. When the reaction was conducted at 100°C, *exo*-phosphonous dichloride **16** was formed without epimerization at carbon-2 (97% exo isomer). The *exo*-dichloride **16** isomerized to the endo-isomer upon treatment with triphenylphosphine at 240–260°C. The intermediate phosphaalkene **17** was implicated to precede this isomerization. Moreover, intentional isomerization of the parent compound **3** could be readily effected by treatment with LDA at −78°C. Attempts were also made to stereoselectively displace a benzyl group from the prochiral phosphorus center in *exo*-dibenzylphosphonium salt **21**. However, alkaline hydrolysis of *exo*-methyldibenzylphosphonium bromide **21** under a variety of conditions gave a 1:1 mixture of *exo*-2-(benzylmethylphosphoryl)bicyclo[2.2.1]heptane **22**.

Key words: Bicyclo[2.2.1]heptane, norbornyl, phosphaalkene, phosphonate, epimerization, isomerization.

INTRODUCTION

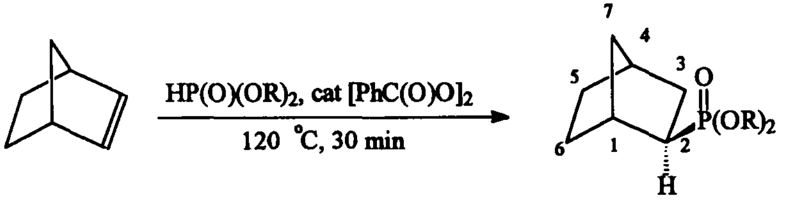
Organophosphorus systems have been utilized in a wide array of important applications.[1] Within the last thirty years versatile methods have been developed to prepare phosphorus compounds which contain chiral centers.[2] As a result, these developments have extended the utility of organophosphorus systems into several important areas.[3] For instance, optically active phosphorus compounds display important biological activity.[4] The use of phosphonates as nonhydrolyzable bioisosteres of biologically important phosphates is another application which has received much attention.[5] Phosphorus compounds which contain chiral centers have been employed as ligands in conjunction with asymmetric transition metal catalysis.[6] In addition, chiral phosphorus centers have been utilized to induce asymmetry into nearby prochiral carbon centers.[7]

The stereoselective synthesis of organophosphorus compounds has attracted much attention; many of these preparations have been discussed in several excellent reviews.[8] Investigations of the stereochemical aspects of nucleophilic displacement at phosphorus have been conducted in this laboratory for several years. Most of the substrates were 4–6 membered rings or bicyclic systems.[9] As an extension of this earlier work, a program to investigate the stereochemical aspects of nucleophilic displacement at bifunctional exocyclic, prochiral phosphorus centers was initiated.

The bicyclo[2.2.1]heptyl (norbornyl) group was initially chosen both as an inexpensive source of asymmetry[10] and as a model for the popular bornyl chiral auxiliary.[11] A variety of synthetic methods for preparation of phosphorus substituted norbornanes have been developed.[12] However, few reports describe the derivatization of hindered phosphorus groups which are attached to chiral carbon centers. This paper describes initial synthetic efforts for preparation and stereoselective transformations of bifunctional *exo*-2-phosphorus substituted bicyclo[2.2.1]heptanes.

RESULTS AND DISCUSSION

Stereoselective synthesis of the *exo*-2-phosphorus substituted bicyclo[2.2.1]heptane system was accomplished using the method of Callot and Benezra.[12a] The addition of dimethylphosphite to norbornene was conducted under free radical conditions (catalytic benzoyl peroxide) to give *exo*-2-(dimethoxyphosphoryl)bicyclo[2.2.1]-heptane **1** in 85% yield (Equation 1).

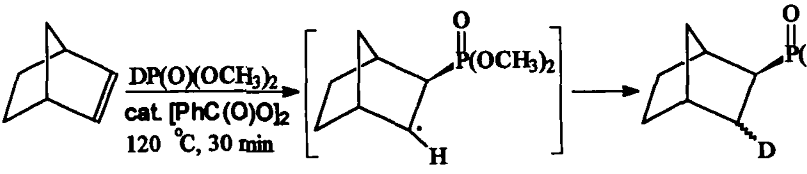


(1)

1 $R = CH_3$ (85%)
3 $R = CH_2CH_3$ (71%)

Benzene was preferable to CCl_4 as a solvent[12a] since it was stable under the free radical conditions. This preparation could be carried out on a large scale. Only traces of the *endo* isomer were observed by ^1H, ^{13}C or ^{31}P NMR spectroscopy. Quin and coworkers have determined that stereospecific J_{PC} coupling constants can be used to determine the *exo* or endocyclic orientation of the phosphorus substituent in **1** and related compounds.[12j] Additions to bicyclo[2.2.1]heptanes usually occur preferentially at the *exo* face.[13]

It was of interest to determine whether the hydrogen of dimethylphosphite was delivered from the *exo* or *endo* face of the intermediate radical **2**. Dimethylphosphite-d_1 was prepared in 33% yield (98% deuterated, determined via ^1H NMR spectroscopy) by deuterium exchange of dimethylphosphite with methanol-d_1.[14] Treatment of norbornene with dimethylphosphite-d_1 under the free radical conditions furnished deuterated *exo*-phosphonate **1-d** in 56% yield (Equation 2).



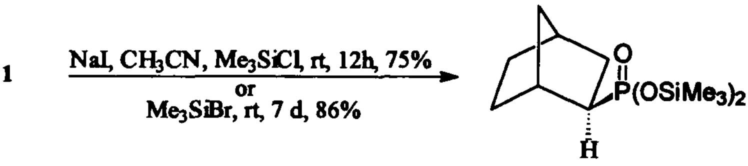
(2)

2 **1-d**

The ^{13}C NMR spectrum of **1-d** was identical to that of phosphonate **1** except for the collapse of the doublet at δ 31.4 into six lines (J_{CD} = 20.3 Hz and J_{PC} = 5.4 Hz). A 2:1 mixture of *endo*- to *exo*-deuterated phosphonates **1-d** was estimated by ^{31}P and ^{2}H NMR spectroscopy. The ^{2}H NMR spectrum (61 MHz, $CDCl_3$) of phosphonate **1-d** showed two incompletely resolved signals at δ 1.68 (66% $^{3}J_{PD}$ = 4.4 Hz, *exo* isomer) and δ 1.42 (33% $^{3}J_{PD}$ = 1.3 Hz, *endo* isomer). The *exo*-deuterio isomer **1-d** is expected to have a larger $^{3}J_{PCCD}$ coupling constant due to the approximate 0° torsional angle between the phosphorus and deuterium atoms. The PCCD torsional angle in the *endo*-isomer **1-d** is approximately 120° and should result in a coupling constant which approaches 0 Hz by analogy to the known Karplus relationships between phosphorus and hydrogen.[12b,15]

It was further found that the treatment of diethylphosphite with norbornene under conditions similar to the preparation of phosphonate **1** gave a 71% yield of the purified *exo*-diethyl analog **3** (Equation 1). Again, only traces of the *endo* isomer of **3** were observed.

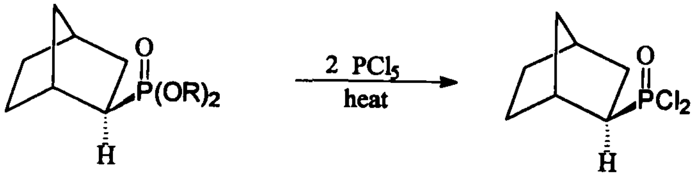
Since dialkyl phosphonates are relatively unreactive,[16] conversion of phosphonates **1** and **3** into a more reactive substrate was desired. This was accomplished by treating **1** with two equivalents each of anhydrous NaI and chlorotrimethylsilane in CH_3CN[17] which furnished **4** in 75% yield after distillation (Equation 3).



4

(3)

It was later found that treatment of neat *exo*-phosphonate **1** with two equivalents of bromotrimethylsilane[18] for 7 days at rt also gave **4**, but in 86% yield. Compound **4** hydrolyzed readily and was used immediately or stored in a sealed ampule. Alternative derivatization was accomplished directly by treatment of **1** with two equivalents of phosphorus pentachloride at 90°C for 1 h (Equation 4).



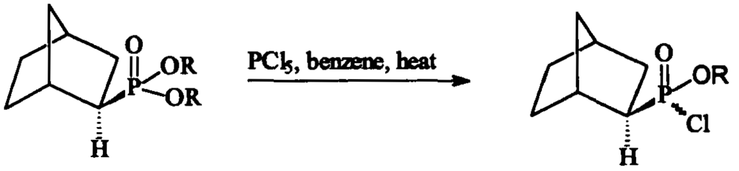
1 R = CH_3
3 R = CH_2CH_3
4 R = $SiMe_3$

5

(4)

This procedure furnished **5** in 75% yield after distillation. This procedure[19] proved a superior preparation of **5** in terms of convenience, scale and ease of product purification. Tebby and coworkers had previously synthesized **5** by the treatment of norbornane with trichlorophosphine and molecular oxygen.[20] More vigorous conditions (105°C, 16 h) were necessary to convert **3** into **5** with two equivalents of PCl_5; however, the yield increased to 82%. Treatment of **4** with two equivalents of PCl_5 in CCl_4 gave **5** in 53% yield. Confirmation of the identity of the dichloride **5** was obtained by treatment with a 10% solution of NaOMe in MeOH at rt for 1 h. This procedure furnished **1** in 60% yield and established that the dichlorination had proceeded with the preservation of the stereochemistry at carbon-2.

It was anticipated that diastereoselective monodisplacement of the alkoxy group in *exo*-phosphonates **1** and **3** may occur if only one equivalent of PCl_5 were used.[21] When **1** was treated with one equiv. of PCl_5 in anhydrous benzene at 15–16°C, a 1:1 mixture of diastereomeric *exo*-methylphosphonochloridates **6** was formed in 86% yield (Equation 5).



(5)

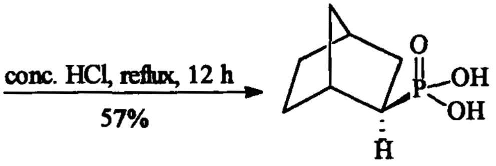
1 R = CH_3
3 R = CH_2CH_3

6 R = CH_3 (86%)
7 R = CH_2CH_3 (70%)

Purification of **6** by distillation produced only glassy, "polymeric" material. This behavior of alkoxyphosphonochloridates has been noted.[22] The same procedure was then employed with **3** as the substrate; the crude product contained a small amount of **5**. Careful distillation gave a 70% yield of **7**, contaminated with a minor amount of polymeric material (determined via ^{31}P NMR spectroscopy). Compound **7** was not as prone to polymerize as **6** under the conditions for purification.

Standard conditions[16] (conc. HCl, reflux 12 h) for the hydrolysis of *exo*-phosphonate **1** produced *exo*-phosphonic acid **8** in 57% yield after crystallization (Equation 6).

1

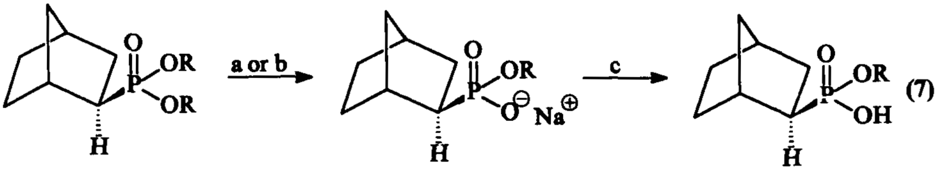


(6)

8

No endo isomer was observed (via NMR spectroscopy).

Conditions for the conversion of *exo*-phosphonates **1** and **3** into their half-acid esters **10** and **11** were developed (Equation 7).



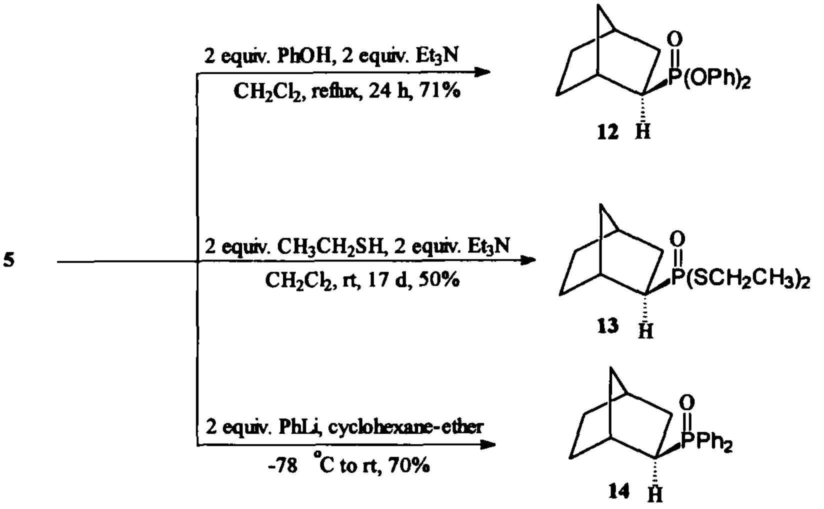
(7)

1 R = CH_3
3 R = CH_2CH_3

9a R = CH_3 (97%)
9b R = CH_2CH_3

10 R = CH_3 (98%)
11 R = CH_2CH_3 (75% from **3**)

a) **1**, 2.7M NaOMe, reflux, 26 h b) **3**, 5% NaOH, THF, 0°C, 10 min; 2 d, rt c) **9a**, 10% aq. HCl



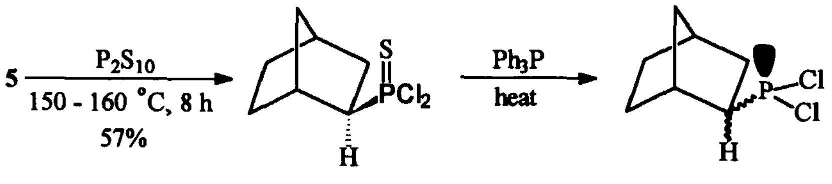
SCHEME 1

When **1** was stirred with a 2.7 M solution of sodium methoxide in methanol at reflux, **9a** was produced in 97% yield. The sodium salt **9a** was then acidified to give the *exo*-isomer of the half acid **10** in 98% yield (96% overall yield from **1**). These transformations (**1** to **9a** to **10**) occurred with complete preservation of stereochemistry at carbon-2 to furnish only the *exo*-isomers. Preparation of **11** from **3** using analogous conditions (sodium ethoxide, ethanol, reflux) failed; however, when **3** was treated first with a 5% aq. NaOH solution in THF at rt for 2 days and then neutralized with a 10% aq. HCl solution, **11** was produced in 75% yield. The latter procedure represents a direct and mild method for the conversion of phosphonates into half-acids without isomerization about the α-carbon center.

The *exo*-phosphonic dichloride **5** was also converted into several bifunctional phosphonic acid derivatives (Scheme 1). The *exo*-dichloride **5** was converted into **12** in 71% purified yield by treatment with two equivalents each of triethylamine and phenol at reflux for 24 h. This represents a slight improvement in the reported yield of an earlier synthesis of **12** from **5** (NaOPh, ether, 61%).[20] Similarly, **13** was produced in 50% yield on treatment of **5** with two equivalents each of ethanethiol and Et_3N in CH_2Cl_2 at rt for 17 days. This reaction was extremely sluggish and **5** was susceptible to aqueous hydrolysis. However, reproducible yields of pure **13** were obtained. It was also found that double displacement reactions on **5** gave higher yields in CH_2Cl_2 than in diethyl ether. Products, such as **13**, demonstrated improved tolerance to the workup conditions when the reaction was conducted in CH_2Cl_2.

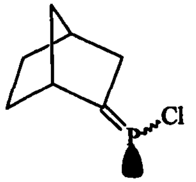
The reaction of organometallic reagents with phosphonic acid derivatives has been reported to generally give unsatisfactory results.[16] However, when **5** was treated with exactly two equivalents of phenyllithium in cyclohexane-ether at −78°C and then warmed to rt, **14** was formed in 70% yield; none of the *endo*-isomer of **14** was observed. The strongly basic lithium reagent did not appear to remove the α-phosphoryl proton in this case. It was consumed more rapidly in the substitution process. Deprotonation of **14** did occur when an excess of phenyllithium was used.

The conversion of **5** to thiophosphoryl and phosphonite derivatives was also investigated (Equation 8).

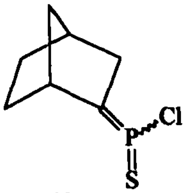


15 **16** (8)

It was found that **5** was smoothly converted to **15** in 57% yield upon treatment with phosphorus pentasulfide at 150–160°C over an 8 h period. Despite the relatively high temperatures involved, none of the *endo*-isomer of **15** was identifiable by NMR spectroscopy. The *exo*-thiophosphonic dichloride **15** was then treated with triphenylphosphine following literature conditions[16] (240–260°C, neat). Under these vigorous conditions trivalent phosphonous dichloride **16** was produced in 61% yield as a 3:2 mixture of *exo*:*endo*-isomers. In an attempt to clarify the mechanism of this isomerization, **16** was heated at 240–260°C in a nitrogen atmosphere for 24 h. No isomerization of **16** was evident by ^{31}P NMR spectroscopy nor was intermediate **18** detected. In separate experiments **15** was heated with half of an equivalent of PPh_3 from 150°C to 240°C and heated with half an equivalent of PPh_3 at 240°C for 8 h. In both of these experiments no isomerization of **15** was observed. When **16** was heated with one equivalent of triphenylphosphine at 240–260°C, a final 3:2 ratio of *exo*- to *endo*-phosphonous dichlorides **16** was observed. Therefore, the isomerization likely occurs via reversible deprotonation of **16** by triphenylphosphine under these vigorous reaction conditions to give the phosphaalkene intermediate **17**.



17

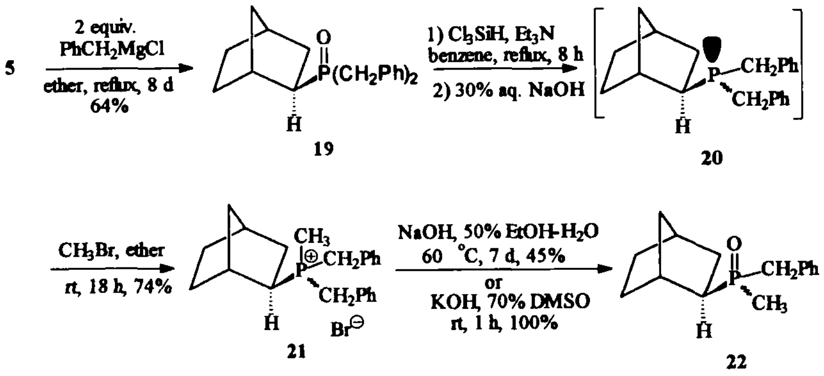


18

(9)

The intermediate **17** is then protonated at either the *exo* or *endo* face with triphenylphosphine hydrochloride to give the observed mixture of isomers. However, when **15** was treated with Ph_3P at 100°C (note: control of the reaction temperature and distillation temperature is critical) for 2 h, *exo*-phosphonous dichloride **16** was produced (84%) without epimerization at carbon-2 (97% *exo*-isomer by ^{1}H and ^{31}P NMR spectroscopy). This result strongly suggests that the desulfurization step should precede the deprotonation step under the previously described conditions (240–260°C) which promoted isomerization to give a mixture of *endo*- and *exo*-dichlorides **16**; thus, phosphaalkene **17** is the logical intermediate in the isomerization.

After ascertaining that **5** reacts without isomerization with organolithium reagents, a solution of **5** in ether was treated with two equivalents of a solution of benzylmagnesium chloride in ether (Scheme 2) and heated at reflux for 8 days to give **19** in 64% yield. This yield was surprising in view of the notorious resistance of phosphonic acid derivatives towards Grignard reagents.[16] In addition, none of the *endo*-



SCHEME 2

isomer of **19** was observed. The *exo*-dibenzyl oxide **19** was then converted to **20** in 74% yield by a two-step sequence[23] using trichlorosilane and Et_3N in benzene at reflux for 8 h, followed by quaternization with bromomethane. In one run the intermediate **20** was isolated for spectroscopic characterization. None of the *endo*-isomer of **20** was formed. Isolation of the intermediate **20** is not recommended in routine work, since it rapidly oxidizes in the presence of air. It was of interest to see if the benzyl groups attached to the prochiral phosphorus atom in **21** could be diastereoselectively hydrolyzed under alkaline conditions. When **21** was treated with one equivalent of NaOH in 50% EtOH-H_2O at 60°C for 7 days, methylbenzylphosphine oxide **22** was produced as a 1:1 mixture of diastereomers (by ^{31}P NMR) in 45% yield and unreacted **21**. Neither the *endo*-isomer of salt **21** or oxide **22** were observed by NMR spectroscopy. It was also found that the treatment of **21** with one equivalent of KOH in 70% DMSO-H_2O at rt for 1 h gave a 1:1 diastereomeric mixture of only the *exo*-phosphine oxides **22** in quantitative yield. The dramatic rate increase for hydrolysis of phosphonium salts in DMSO has been noted.[24]

^{13}C NMR spectral data were used to establish the exocyclic versus endocyclic nature of the phosphorus substituent of all compounds isolated in this study using the method of Quin and coworkers.[12j,25] It was found that this method could be extended with confidence to include the orientation of the phosphorus substituent for the classes of norbornyl phosphorus compounds which are reported for the first time. For instance, only small differences in the chemical shifts and coupling constants were noted in all of the tetravalent phosphorus compounds subject to this investigation. Quin[12j,25] and others[12f,12h] have found that the magnitudes of ^{31}P and ^{13}C coupling constants are sensitive to the number of bonds between the coupled nuclei. In this regard, the magnitude of the $^{3}J_{PCCC}$ coupling constants for trivalent phosphorus compounds are a function of the torsional angle between the bond connecting the carbon atoms in the coupling pathway and the orientation of the phosphorus lone pair.[12j,25] On the other hand, the magnitude of the $^{3}J_{PCCC}$ coupling constants of tetracovalent and quin-covalent phosphorus compounds are a function of the torsional angle relating the phosphorus to α-carbon bond and the bond between the terminal carbons of the coupling pathway. This Karplus relationship is sensitive to the nature of the phosphorus substituents and provides a reliable method to determine the exocyclic nature of the compounds prepared for this study as well as for the complete assignment of carbon resonances. At least one X-ray crystallographic determination of a phosphorus-substituted bicyclo[2.2.1]heptane has been done.[26] Although the assignment of the exocyclic versus endocyclic orientation of the phosphorus substituent in the norbornyl system is on solid NMR spectroscopic grounds,[12j] work is in progress in this laboratory to provide X-ray crystallographic support for these assignments.

EXPERIMENTAL

Proton NMR spectra were recorded on a Varian 360L or GE Omega 300NB spectrometer. Chemical shifts are reported on the delta scale from internal TMS. Both ^{13}C and ^{31}P NMR spectra were recorded with proton decoupling on a Jeol JNM-FX60Q or a GE OMEGA 300NB spectrometer. Chemical shifts for ^{13}C NMR spectra are reported from internal TMS, or the upfield resonance of internal $(CH_3)_3Si(CH_2)_3SO_3NaH_2O$ (TSP) when D_2O was the solvent. Coupling constants (J_{PC}) are reported in Hz in parentheses. Chemical shifts for ^{31}P NMR spectra are reported in parts per million downfield from external 85% H_3PO_4. Isomer ratios were obtained with pulse delays which were 5 times the typical T_1 value[27] for the analogous family of compounds. GC-MS results were obtained from a Hewlett-Packard model 5970 spectrometer at 70 eV using a 0.25 mm × 30 m DB-1 capillary column. IR spectra were recorded on an Analect Instruments FX 6200 FTIR spectrometer. Elemental Analyses were performed by Midwest Microlab, LTD., Indianapolis, Indiana. High Resolution mass spectrometry (EI and FAB) were conducted by the Midwest Center for Mass Spectrometry [partial support by the National Science Foundation, Biology Division (Grant No. DIR9017262)]. All boiling and melting points (Thomas-Hoover apparatus) were uncorrected. Reactions, unless otherwise noted, were conducted under a nitrogen atmosphere. Moisture sensitive compounds and reagents were handled in a Labconco glovebox. Diethyl ether and THF were distilled from sodium or potassium/benzophenone ketyl. Cyclohexane, CH_2Cl_2 and CH_3CN were distilled from P_2O_5. All reagents were obtained from Aldrich Chemical Co and used as received unless otherwise noted. Diethyl phosphite was obtained from Eastman Kodak. Triethylamine was distilled from KOH under nitrogen.

The ^{31}P NMR spectra were utilized primarily to insure the purity of the products. In addition, the sensitivity of ^{31}P NMR greatly assisted in the observance of traces of the *endo* isomers. All product ratios were determined by integration of the ^{31}P NMR spectral resonances obtained from experiments conducted with predelay values five times the expected relaxation time.[27] A ^{31}P NMR spectrum was also taken of the crude reaction mixtures to insure that no isomerization occurred during the workup or purification procedures.

(±)-exo-2-(Dimethoxyphosphoryl)bicyclo[2.2.1]heptane **1**.[12a] A solution of benzoyl peroxide (0.5 g) in benzene (5 mL) was added in one portion to a mixture of bicyclo[2.2.1]hept-2-ene (50 g, 0.53 mol) and dimethylphosphite (117 g, 1.1 mol). The reaction temperature quickly rose. The reaction temperature was promptly arrested at 170°C by lowering the reaction mixture into an ice-H_2O bath. After the reaction temperature cooled to 120°C, the reaction mixture was heated at 110–120°C with an oil bath for 15 min. The excess starting materials were removed by distillation (42°C, 2.5 mm). The product was then distilled to give 92.1 g (85%) of phosphonate **1**: bp 76°C (0.1 mm), lit.[12a] bp 127–132°C (10 mm). ^{1}H, ^{13}C, ^{31}P NMR are in agreement with lit.[12a]

Dimethyl phosphite-d. Prepared by the method of Emmick and Letsinger.[14] A mixture of dimethyl phosphite (10.1 g, 91 mmol) and methyl alcohol-d (9.2 g, 0.28 mol) was stirred at rt for 2 d. The methyl alcohol was removed by distillation (15°C, 20 mm) through a silver-jacketed column. This procedure was repeated twice. The residue that remained in the distillation flask was 98% phosphite-d **3** by ^{1}H NMR spectroscopy: 3.34 g (33%, based on starting dimethyl phosphite); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.81 (d, J = 11.5 Hz).

(±)-exo-2-(Dimethoxyphosphoryl)-[3-$^{2}H_1$]-bicyclo[2.2.1]heptane **1-d**. A mixture of bicyclo[2.2.1]hept-2-ene (1.3 g, 14 mmol), dimethyl phosphite-d (3.0 g, 27 mmol) and benzoyl peroxide (0.5 g) in a thick-walled pressure tube sealed with a Teflon screw cap was partially immersed into a 110–130°C oil bath for 9 h. After the reaction mixture cooled to room temperature, the excess starting materials were removed by distillation (45–50°C, 20 mm). The residue which remained was distilled to give 1.54 g (56%) of phosphonate-d **1-d**: bp 62–68°C (0.05 mm); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.76 (d, J = 10.2 Hz, 3 H, OCH_3), 3.74 (d, J = 10.2 Hz, 3 H), 2.63 (m, 1 H), 2.47 (m, 1 H), 2.37 (m, 1 H), 2.20–1.00 (m, 7 H). The ^{13}C NMR spectrum (15 MHz, $CDCl_3$) was identical to the spectrum of the nondeuterated

4 except that the signal at δ 31.4 collapsed to six lines (J_{CD} = 20.3 Hz, J_{PC} = 5.4 Hz); ^{31}P NMR (101 MHz, $CDCl_3$) δ 36.43, 36.38. ^{2}H NMR (61 MHz, $CDCl_3$) δ 1.68 (J = 4.36 Hz, *endo*-**2-d**) and 1.42 (J = 1.34 Hz, *exo*-**2-d**) in an approximate 2:1 ratio, not completely resolved; GC-MS: m/e (%); 205 (M^+, 6), 190 (3), 176 (37), 175 (13), 164 (5), 163 (3), 138 (100), 137 (24), 124 (7), 110 (30), 96 (16), 95 (15), 79 (32).

(±)-exo-2-(Diethoxyphosphoryl)bicyclo[2.2.1]heptane **3**. Approximately half of a solution of benzoyl peroxide (0.25 g) in benzene (3 mL) was added at once to a 100°C mixture of bicyclo[2.2.1]hept-2-ene (5.0 g, 53 mmol) and diethyl phosphite (14.7 g, 0.11 mmol). The reaction temperature immediately rose to 128°C. The heat was removed and the temperature cooled to 100°C. Then, the remainder of the benzoyl peroxide solution was added, and the heat was reapplied. The temperature rose to 128°C. The heat was removed and the reaction mixture was stirred until the mixture reached ambient temperature. The excess starting materials were removed by distillation (28°C, 0.1 mm). The crude phosphonate **2** was obtained upon distillation: 8.78 g (71%); bp 84°C (0.15 mm); ^{1}H NMR (60 MHz, $CDCl_3$) δ 4.07 (2 overlapped pentets, J = 7.1 Hz, 4 H, OCH_2), 2.70–2.20 (m, 2 H), 2.20–1.0 (m, 9 H), 1.33 (t, J = 7.1 Hz, 6 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.40 (6.8, OCH_2), 38.31 (2.5, C-1), 37.50 (148.9, C-2), 36.39 (C-7), 33.65 (3.7, C-4), 31.29 (6.1, C-3), 31.20 (19.5, C-6), 27.94 (1.5, C-5), 16.60 (5.9, Me); ^{31}P NMR (121 MHz, $CDCl_3$) δ 33.9. Anal. Calcd. for $C_{11}H_{21}O_3P$: C, 56.89; H, 9.11. Found: C, 56.77; H, 9.30.

LDA treatment of **3**. To dry 100 mL flask was added **3** (2.0 g, 8.6 mmol) in 50 mL dry THF. LDA (9.0 mmol) was added dropwise at −78°C maintaining a temperature below −70°C. After stirring at −78°C for 1.5 h the mixture was quenched with 10% aq. HCl. The *exo/endo* ratio of isomers was determined to be 50:50 by ^{31}P NMR spectroscopy.

(±)-exo-2-[Bis(trimethylsiloxy)phosphoryl]bicyclo[2.2.1]heptane **4**. A solution of anhydrous NaI (48.6 g, 0.32 mmol) in CH_3CN (500 mL) was added to a mixture of **1** (30.0 g, 0.15 mol) and trimethylchlorosilane (41.9 mL, 0.33 mol) in CH_3CN (500 mL) at room temperature dropwise over a 1 h period. The reaction mixture was stirred at room temperature overnight. The liquid was carefully poured from the white precipitate, and the volatile materials were distilled (25°C, 20 mm) to leave a dark red liquid. The red liquid was distilled to give **4** as a light yellow solid: yield 35.5 g (75%); bp 100°C (0.3 mm); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.67 (m, 1 H), 2.23 (m, 2 H), 2.14–0.98 (m, 8 H), 0.36 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.52 (149.9, C-2), 39.15 (1.5, C-1), 37.68 (C-7), 37.24 (3.9, C-4), 32.90 (3.9, C-3), 32.41 (20.9, C-6), 29.09 (1.5, C-5), 1.79 (Me); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.7.

Alternate Procedure: Bromotrimethylsilane (5.0 g, 33 mmol) was added slowly to **1** (3.3 g, 16 mmol). The resultant mixture was stirred at room temperature for 7 days. The reaction mixture was concentrated *in vacuo*. The crude product was distilled to give **4** as a clear, light yellow liquid: yield 9.1 g (86%), bp 62.5°C (0.03 mm). HRMS Calcd. for $C_{13}H_{29}O_3PSi_2$: 320.1393. Found: 320.1389.

(±)-exo-2-(Dichlorophosphoryl)bicyclo[2.2.1]heptane **5**. Phosphorus pentachloride (12.8 g, 61 mmol) was added to **1** (5.0 g, 25 mmol) at 0°C over a 20 min period. The resultant heterogeneous mixture was heated at 90°C for 1 h. After the reaction mixture cooled to room temperature, phosphorus oxychloride was removed by distillation (bp 34°C, 20 mm). The crude product was then distilled to give **5** as a clear, colorless liquid: yield 3.9 g (75%); bp 66°C (0.1 mm), lit.[21] bp 115–116°C (1 mm); ^{1}H, ^{13}C, ^{31}P NMR in agreement with lit.[20] IR (neat) 1269 cm^{-1}, P=O. Anal. Calcd. for $C_7H_{11}Cl_2OP$: C, 39.46; H, 5.20. Found: C; 39.65; H, 5.31.

Alternate Procedure: Phosphorus pentachloride (19.91 g, 96 mmol) was added to **2** (10.6 g, 45 mmol) in portions over a 15 min period. The resultant heterogeneous mixture was heated at 105°C for 16 h. After the reaction mixture cooled to room temperature, phosphorus oxychloride and the excess PCl_5 were distilled (bp 25–60°C, 20 mm). Distillation of the crude product gave **5**: yield 7.9 g (82%).

Alternate Procedure: A solution of **4** (35.5 g, 0.11 mol) in CCl_4 (100 mL) was added dropwise over a 40 min period to a heterogeneous mixture of phosphorus pentachloride (53.3 g, 0.25 mol) and CCl_4 (100 mL) at room temperature. The resultant mixture was stirred at room temperature for 13 h and then heated at reflux for 1 h. The volatile materials were removed *in vacuo* to leave a dark red liquid. Molecular distillation (25°C, 0.5–1.0 mm) provided **5** (12.6 g, 53%) as a red liquid. The color was removed by stirring the product over activated zinc powder[18c] and then decanting the clear liquid from the zinc metal. Further purification was accomplished by distillation: bp 53°C (0.1 mm).

Reaction of exo-dichloride **5** *with sodium methoxide to give (±)-exo-dimethylphosphonate* **1**. The dichloride **5** (1.0 g, 4.7 mmol) was added dropwise to a 10% solution of sodium methoxide in methanol (10.3 mmol NaOMe) at room temperature. A white solid precipitated, and the reaction mixture was stirred at rt for 1 h. Ether (30 mL) was added to the reaction mixture. The mixture was washed with

0.5 N HCl (20 mL) and H_2O (2 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 0.58 g (60%) of **1**.

(±)-exo-2-(Methoxychlorophosphoryl)bicyclo[2.2.1]heptane **6**. A solution of **1** (4.6 g, 23 mmol) in benzene (20 mL) was added to a mixture of phosphorus pentachloride (5.0 g, 24 mmol) in benzene (40 mL) (which was cooled in an ice-H_2O bath) dropwise at a rate to keep the reaction mixture at 15–16°C. The solid PCl_5 gradually dissolved. The reaction mixture was warmed to rt and stirred for 6 h. Phosphorus oxychloride and benzene were distilled under a 1 mm vacuum. The residue contained crude **7** as a 1:1 mixture of diastereomers: yield 4.0 g (86%); ^1H NMR (60 MHz, $CDCl_3$) δ 3.78 (d, J = 12 Hz, 1.5 H, OMe), 3.76 (d, J = 12 Hz, 1.5 H), 2.95–0.80 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 52.80 (8.8, OMe) and 52.60 q (8.8, OMe), 45.79 (120.6, C-2) and 45.23 (10.7, C-3), 31.43 (20.5, C-6), 28.31 37.04 (C-7), 36.33 (3.9, C-4) 2), 38.65 (2.4, C-1) and 38.37 (1.0, C-1), (2.0, C-5); ^{31}P NMR (121 MHz, $CDCl_3$) δ 50.6 and 50.3 in 1:1 ratio. Upon distillation of the crude chloride **6**, a glassy polymeric material resulted.

(±)-exo-2-(Ethoxychlorophosphoryl)bicyclo[2.2.1]heptane **7**. Phosphorus pentachloride (9.3 g, 44.8 mmol) was added to a solution of **3** (10.4 g, 45 mmol) in benzene (50 mL) cooled with an ice-H_2O bath in portions at a rate to keep the reaction temperature at 10–15°C. The reaction mixture was warmed to rt over a 30 min period and stirred overnight. The reaction mixture was then concentrated, and the crude phosphonochlorodate **7** was distilled: 6.9 g (70%), contaminated with polymeric material; ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 62.62 and 62.43 (8.6, OCH_2), 45.53 (120.9, C-2) and 45.30 (120.9, C-2), 38.22 (2.4, C-1) and 37.88 (1.2, C-1), 36.59 and 36.54 (C-7), 35.91 (4.3, C-4) and 35.78 (4.3, C-4), 31.94 (6.7, C-3) and 31.57 (5.5, C-3), 31.04 (21.4, C-6) and 31.00 (20.8, C-6), 27.90 and 27.88 (C-5), 15.57 (7.3, Me) and 15.54 (6.7, Me); ^{31}P NMR $CDCl_3$, (crude reaction mixture) δ 41.2 and 41.0 in a 1:1 ratio.

(±)-exo-2-(Dihydroxyphosphoryl)bicyclo[2.2.1]heptane **8**. A mixture of **1** (10.0 g, 49 mmol) and concentrated HCl was heated at reflux for 12 h. The concentrated HCl was removed by distillation at atmospheric pressure. Upon cooling, **8** crystallized as a white solid: yield 4.9 g (57%); mp 174–175°C; ^1H NMR (60 MHz, DMSO-d_6) δ 8.40–7.40 (br s, 2 H, OH), 2.70–2.10 (m, 2 H), 2.10–1.85 (m, 9 H); ^{13}C NMR (15 MHz, D_2O) δ 41.2 (136.7, C-2), 40.5 (1.5, C-1), 39.1 (C-7), 38.6 (4.4, C-4), 34.3 (5.4, C-3), 33.9 (18.6, C-6), 30.3 (1.5, C-5); ^{31}P NMR (24.6 MHz, D_2O) δ 33.8. Anal. Calcd. for $C_7H_{13}O_3P$: C, 47.73; H, 7.44. Found: C, 47.51; H, 7.45.

(±)-exo-2-(Methoxyhydroxyphosphoryl)bicyclo[2.2.1]heptane **10**. A mixture of **1** (2.0 g, 9.8 mmol) and sodium methoxide (2.74 M in CH_3OH, 4.0 mL, 11 mmol) was heated at reflux for 26 h. Methanol was removed *in vacuo* to leave a white solid. The solid was washed with several portions of pentane and then dried *in vacuo* to give **9** as a white solid: yield 2.02 g (97%); mp, did not melt to 270°C; ^1H NMR (300 MHz, D_2O) δ 3.54 (d, J = 10.1 Hz, 3 H, OMe), 2.37–2.13 (m, 2 H), 163–1.14 (m, 9 H); ^{13}C NMR (75 MHz, D_2O) δ 53.61 (6.1, OMe), 40.75 (137.95, C-2), 40.66 (C-1), 39.23 (C-7), 38.65 (3.7, C-4). 34.81 (6.1, C-3), 34.14 (17.1, C-6), 30.54 (C-5); ^{31}P NMR (121 MHz, D_2O) δ 33.1; HRMS (FAB) Calcd. for $C_8H_{14}O_3P$: 189.0681. Found: 189.0686.

The sodium salt of **9** (1.62 g, 7.6 mmol) was dissolved in 10% HCl (20 mL). The aqueous solution was extracted with $CHCl_3$ (3 × 25 mL), dried with Na_2SO_4 and concentrated *in vacuo* to give **10** as a colorless oil: yield 1.59 g (98%); ^1H NMR (300 MHz, $CDCl_3$) δ 11.60 (br s, 1 H, OH), 3.69 (d, J = 10.7, 3 H, OMe), 2.54 (d, J = 9.3 Hz, 2.31 (s, 1 H), 1.77–1.15 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.26 (7.3, OMe), 37.98 (C-1), 37.84 (145.0, C-2), 36.88 (C-7), 36.26 (3.9, C-4), 31.73 (18.1, C-6), 31.72 (5.9, C-3), 28.47 (C-5); ^{31}P NMR (121 MHz, $CDCl_3$) δ 37.7; HRMS m/e (%) 190 (M^+, 13), 175 (31), 161 (48), 137 (58), 123 (100), 95 (36); HRMS Calcd. for $C_8H_{15}O_3P$: 190.0759. Found: 190.0757.

(±)-exo-2-(Ethoxyhydroxyphosphoryl)bicyclo[2.2.1]heptane **11**. An aqueous NaOH solution (5%, 7 mL) was added to a solution of **3** (1.7 g, 7.8 mmol) in THF (35 mL) at 0°C (ice-H_2O bath) in one portion. The resultant two-layer mixture was warmed to rt and stirred for two days until the H_2O layer became acidic. The crude reaction mixture was extracted with ether (3 × 30 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was molecularly distilled (90°C, 0.1 mm) to give purified **11**: 1.2 g (75%), ^1H NMR (300 MHz, $CDCl_3$) δ 12.39 (s, 1 H, OH), 4.06 (q, J = 7.0 Hz, 1 H, OCH_2), 4.03 (q, J = 7.0 Hz, 1 H, OCH_2), 2.55–2.48 (m, 1 H, H-1), 2.32–2.25 (m, 1 H, H-4), 1.84–1.09 (m, 9 H), 1.29 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.75 (7.3, OCH_2), 37.90 (145.3, C-2), 37.84 (C-1), 36.73 (C-7), 36.14 (3.7, C-4), 31.63 (18.9, C-6), 31.58 (5.5, C-3), 28.37 (C-5), 16.29 (Me). ^{31}P NMR (121 MHz, $CDCl_3$) δ 36.9. Anal. Calcd. for $C_9H_{17}O_3P$: C: 52.94; H, 8.39. Found: C, 53.07; H, 8.43.

(±)-exo-2-(Diphenoxyphosphoryl)bicyclo[2.2.1]heptane **12**. A solution of **5** (5.6 g, 26 mmol) in CH_2Cl_2 (25 mL) was added dropwise over a 15 min period to a solution of phenol (4.9 g, 53 mmol) and triethylamine (8.1 mL, 58 mmol) in CH_2Cl_2 (100 mL) at rt. The mixture was heated at reflux for 24 h, cooled to rt and added to ether (50 mL). The resultant mixture was washed with sat'd $NaHCO_3$ (50 mL), brine (50 mL) and H_2O (50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give crude **12** which was further purified by molecular distillation (140–150°C, 0.1 mm) and then recrystallized three times from petroleum ether (30–60°C): yield 6.14 g (71%); mp 65–67°C; ^{1}H, ^{13}C, ^{31}P NMR are in agreement with lit.[20] GC-MS: m/e (%); 328 (M^+, 81), 299 (73), 261 (100), 235 (3), 95 (67), 94 (79), 77 (55), 67 (55). Anal. Calcd. for $C_{19}H_{21}O_3P$: C, 69.50; H, 6.45. Found: C, 69.56; H, 6.35.

(±)-exo-2-(S,S-Diethoxyphosphoryl)bicyclo[2.2.1]heptane **13**. A solution of **5** (4.9 g, 23 mmol) in CH_2Cl_2 (35 mL) was added dropwise over a 15 min period to a solution of ethanethiol (2.9 g, 46 mmol) and triethylamine (7.0 mL, 50 mmol) in CH_2Cl_2 (100 mL) at rt. The resultant mixture was stirred at rt for 17 days and then added to ether (100 mL). The ethereal solution was washed with sat'd $NaHSO_3$ (100 mL), H_2O (50 mL), and brine (50 mL) and then was dried over Na_2SO_4 and concentrated *in vacuo* to give crude **13** as a light yellow liquid. The crude **12** was purified by molecular distillation (90°C, 0.05 mm): yield 3.0 g (50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96–2.80 (m, 4 H, SCH_2), 2.75–2.67 (m, 1 H), 2.49–2.31 (m, 1 H), 2.07–1.80 (m, 2 H), 1.77–1.67 (m, 1 H), 1.66–1.43 (m, 3 H), 1.34 (t, J = 7.3 Hz, 3 H), 1.32 (t, J = 7.3 Hz, CH_3), 1.28–1.10 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.92 (70.8, C-2), 38.94 (1.8, C-1), 37.29 (C-7), 36.46 (3.6, C-4), 32.48 (5.5, C-3), 31.66 (18.3, C-6), 28.40 (1.2, C-5), 25.19 (3.1, SCH_2) and 25.09 (3.1, SCH_2), 16.40 (4.8, Me); ^{31}P NMR (121 MHz, $CDCl_3$) δ 74.6; GC-MS: m/e (%); 264 (M^+, 8), 235 (8), 204 (16), 176 (10), 142 (11), 113 (11), 95 (100), 67 (37). Anal. Calcd. for $C_{11}H_{21}OPS_2$: C, 49.97; H, 8.01. Found: C, 50.29; H, 8.20.

(±)-exo-2-(Diphenylphosphoryl)bicyclo[2.2.1]heptane **14**. Phenyllithium (0.2 M in 20:80 cyclohexane-ether, 2.0 mL, 3.9 mmol) was added to a solution of **5** (0.40 g, 1.9 mmol) in ether (15 mL) dropwise at −78°C over a 15 min period. The reaction mixture was warmed to rt, slowly turning orange with formation of a large amount of white precipitate. An aqueous NaOH solution (15%, 10 mL) and ether (15 mL) were then added. The ethereal solution was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give solid **14** which was recrystallized twice from benzene-cyclohexane: 0.39 g (70%); mp 164–165°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.68 (m, 4 H), 7.52–7.35 (m, 6 H), 2.66–2.23 (m, 3 H), 2.04–1.10 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.9 (95.2, arom. C-1′) and 133.6 (arom. 95.2, arom. C-1′), 131.3 (2.4, arom. C-4′) and 131.2 (2.4, arom. C-4′), 131.0 (9.8, arom. C-2′) and 130.9 (8.5, arom. C-2′), 128.5 (11.0, arom. C-3′) and 128.4 (11.0, arom. C-3′), 39.78 (73.3, C-2), 37.95 (1.2, C-1), 37.06 (C-7), 36.21 (3.1, C-4), 31.86 (14.7, C-6), 31.21 (4.3, C-3), 28.47 (C-5); ^{31}P NMR (121 MHz, $CDCl_3$) δ 34.2. Anal. Calcd. for $C_{19}H_{21}OP$: C, 77.01; H, 7.14. Found: C, 77.19; H, 7.19.

(±)-exo-2-[(Dichloro)thiophosphoryl]bicyclo[2.2.1]heptane **15**. A mixture of **5** (6.7 g, 32 mmol) and phosphorus pentasulfide (5.6 g, 13 mmol) was heated with an oil bath (oil bath temperature at 150–160°C for 8 h. The dark red liquid which resulted was distilled to give **15**: 4.15 g (57%); bp 91°C (0.9 mm); ^{1}H NMR (300 MHz, C_6D_6) δ 2.69–2.58 (m, 1 H), 2.40–2.27 (m, 1 H), 2.13–2.05 (m, 1 H), 1.98–1.87 (m, 2 H), 1.45–1.20 (m, 3 H), 1.03–0.81 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.88 (64.6, C-2), 40.91 (C-1), 37.27 (4.9, C-4), 37.11 (C-7), 34.80 (6.8, C-3), 32.03 (23.0, C-6), 28.63 (2.0, C-5); ^{31}P NMR (121 MHz, $CHCl_3$) δ 99.8. Anal. Calcd. for $C_7H_{11}Cl_2PS$: C, 36.70; H, 4.84. Found: C, 36.20; H, 4.63.

(±)-exo-2-Bicyclo[2.2.1]heptyl phosphonous dichloride **16**. A mixture of **15** (20.0 g, 87 mmol) and triphenylphosphine (46 g, 0.18 mmol) was heated at 100°C for 2 h. The phosphinous dichloride **16** was distilled directly from the reaction mixture (Note: the distillation flask must be kept below 100°C or racemization will occur to give a mixture of *exo-* and *endo-***16**): 97% *exo*-isomer by NMR spectroscopy; 14.4 g (84%); bp 44°C (0.4 mm); ^{1}H NMR (300 MHz, C_6D_6) δ 2.22–2.13 (m, 1 H), 2.09–2.00 (m, 1 H), 1.97–1.88 (m, 1 H), 1.32–1.05 (m, 5 H), 1.00–0.68 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, in agreement with lit.[12j]) δ 54.61 (45.8, C-2), 38.60 (17.7, C-1), 37.07 (C-7), 36.99 (3.2, C-4), 33.18 (14.7, C-3), 31.31 (7.9, C-6), 28.57 (1.8, C-5); ^{31}P NMR (121 MHz, $CDCl_3$) δ 186.9 (lit.[12j] δ 187.5).

In a separate experiment, a mixture of **15** (5.15 g, 23 mmol) and triphenylphosphine (8.3 g, 32 mmol) was heated to 240°C under a flow of nitrogen. The product **16** was carried through a U-shaped tube and collected in a flask cooled with dry ice-acetone. This procedure produced 14.4 g (84%) of a 3:2 mixture of *exo-* and *endo*-phosphonous dichlorides **16**.

In separate experiments a mixture of **15** (1.5 g, 9.5 mmol) and PPh_3 (1.24 g, 4.5 mmol) was heated and the reaction monitored by ^{31}P NMR. In the first, the mixture was heated from 150°C to 240°C over 1.5 h. The reaction was complete. In the second, the mixture was plunged into a 240°C oil bath for 8 h. No isomerization of unreacted **15** was observed in either case.

Attempted thermal isomerization of exo-phosphonous dichloride **16**. The *exo*-phosphonous dichloride **16** (1.5 g, 7.6 mmol) was heated to 240–250°C for 4 days. No isomerization occurred as indicated by the ^{31}P NMR spectrum.

Isomerization of exo-phosphonous dichloride **16** *with triphenylphosphine*. A mixture of **16** (1.5 g, 7.6 mmol) and triphenylphosphine (2.0 g, 7.6 mmol) was heated at 240–260°C for 24 h. The ^{31}P NMR spectrum (24 MHz, C_6D_6) of this mixture showed signals at δ 195.5 (39%, *endo*-**16**) and δ 186.7 (61%, *exo*-**16**).

(±)-exo-2-(Dibenzylphosphoryl)bicyclo[2.2.1]heptane **19**. One half of a solution of benzylchloride (4.4 g, 35 mmol) in ether (25 mL) was added to magnesium turnings (0.84 g, 35 mmol) in one portion at rt. After 5 min the mixture began to reflux. The remainder of the benzylchloride solution was added, and the reaction mixture was stirred for 15 min without additional heating. A solution of **5** (3.3 g, 16 mmol) in ether (20 mL) was added dropwise over a 1 h period at rt. Gradually, a white solid precipitated. The reaction mixture was then heated at reflux for 8 days, cooled to rt and added to sat'd NH_4Cl (75 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give **19** which was recrystallized from 2:1 benzene-cyclohexane and dried *in vacuo* (80°C, 0.1 mm): 3.26 g (64%); mp 166–167°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.20 (m, 10 H), 3.25–2.85 (m, 4 H), 2.52–2.44 (m, 1 H), 2.34–2.27 (m, 1 H), 1.91–1.68 (m, 2 H), 1.61–1.48 (m, 2 H), 1.48–1.40 (m, 1 H), 1.38–1.25 (m, 1 H), 1.24–1.18 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.66 (6.7, arom. C-1′) and 132.23 (7.3, arom. C-1′), 129.83 (4.9, arom. C-2′) and 129.73 (4.9, arom. C-2′), 128.72 (1.8, arom. C-3′) and 128.63 (2.4, arom. C-3′), 126.75 (3.1, arom. C-4′) and 126.71 (2.4, arom. C-4′), 38.69 (66.5, C-2), 37.98 (1.8, C-1), 37.34 (C-7), 36.11 (3.1, C-4), 35.16 (59.2, Bn—CH_2), 34.19 (59.2, Bn—CH_2), 31.56 (14.0, C-6), 31.40 (4.9, C-3), 28.26 (C-5); ^{31}P NMR (121 MHz, $CDCl_3$) δ 48.5. Anal. Calcd. for $C_{21}H_{25}OPS$: C, 77.75; H, 7.77. Found: C, 77.81; H, 7.70.

(±)-exo-2-(Methyldibenzylphosphonio)bicyclol[2.2.1]heptane bromide **21**. Trichlorosilane (2.8 mL, 28 mmol) was added to a mixture of **19** (1.8 g, 5.4 mmol) and triethylamine (3.8 g, 27 mmol) in benzene (25 mL) in one portion at rt. The resultant mixture was heated at reflux for 8 h, cooled to rt and added to benzene (95 mL). To the diluted reaction mixture which was cooled in an ice-H_2O bath was slowly added an aqueous 30% solution of NaOH (18 mL) over a 2 h period. The resultant mixture was stirred until two layers were evident (1.5 days). The layers were separated. The organic layer was washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), dried with $MgSO_4$ and concentrated *in vacuo* to a 15 mL volume. A solution of bromomethane (3 mL) in ether (8 mL) was added to the concentrate. The resultant mixture was stirred at rt for 18 h. The white solid **21** which had precipitated was filtered and washed. The crude salt **21** was recrystallized from CH_3CN—EtOAc and dried *in vacuo*: 1.6 g (74%); mp 207–208°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (m, 4 H), 7.30–7.12 (m, 6 H), 4.32 (t, *J* = 14.8 Hz, 1 H), 4.20 (t, *J* = 14.6 Hz, 1 H), 3.97 (t, *J* = 14.8 Hz, 1 H), 3.81 (t, *J* = 14.7 Hz, 1 H), 2.53–2.42 (m, 1 H), 2.27–2.21 (m, 1 H), 2.19–2.12 (m, 1 H), 1.92–1.72 (m, 1 H), 1.82 (d, *J* = 12.8 Hz, 3 H), 1.60–1.46 (m, 1 H), 1.46–1.26 (m, 2 H), 1.26–1.10 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.87 (5.2, arom. C-2′) and 129.76 (5.2, arom. C-2′), 128.74 (arom. C-3′) and 128.70 (arom. C-3′), 127.94 (8.9, arom C-1′), 127.80 (3.7, arom. C-4′) and 127.74 (4.4, C-4′), 37.99 (C-7), 37.94 (C-1), 35.83 (3.7, C-4), 33.10 (44.0, C-2), 32.66 (4.9, C-3), 31.60 (14.0, C-6), 27.52 (44.6, Bn—CH_2), 27.05 (C-5), 26.93 (44.6, Bn—CH_2), 2.81 (50.1, Me); ^{31}P NMR (121 MHz, $CDCl_3$) δ 31.2. Anal. Calcd. for $C_{22}H_{28}BrP$: C, 65.51; H, 7.00. Found: C, 65.61; H, 7.09.

In one experiment the intermediate **20** was collected by concentration of the benzene solution. The crude **20** was slowly, molecularly distilled (200°C, 0.8 mm) to give an oil which solidified on standing in a nitrogen atmosphere. The phosphine **20** rapidly oxidized in air and was used immediately: ^{1}H NMR (300 MHz, C_6D_6) δ 7.23–7.02 (m, 10 H), 2.72 (m, 2 H), 2.61 (m, 2 H), 2.14–2.06 (m, 1 H), 1.95–1.88 (m, 1 H), 1.69–1.62 (m, 1 H), 1.52–0.91 (m, 8 H); ^{13}C NMR (75 MHz, C_6D_6) δ 139.63 (5.5), 139.06 (3.7), 130.16 (3.7), 130.08 (2.4), 128.98 (3.7), 126.34 (1.8), 41.15 (15.9), 40.23 (14.0), 37.82 (2.4), 37.59 (4.3), 35.95 (10.4), 35.06 (21.4) and 32.87 (20.1), 32.15 (6.1), 29.74; ^{31}P NMR (121 MHz, C_6D_6) δ −7.9.

Alkaline hydrolysis of exo-dibenzylmethylphosphonium bromide **21**: *exo-2-Benzylmethylphosphoryl)bicyclo[2.2.1]heptane* **22**. The *exo*-dibenzylmethylphosphonium bromide **21** (2.0 g, 5.0 mmol) was added to a solution of KOH (306 mg, 5.5 mmol) in 70% DMSO-H_2O (8 mL) in one portion at room temperature. All of the phosphonium salt reacted within 15 min (as indicated by NMR spectroscopy). The reaction mixture was stirred at rt for an additional 45 min. The mixture was concentrated *in vacuo* (0.1 mm). The crude product was chromatographed (60–200 mesh silica) on a 13 × 2.5 cm column with 99.5% CH_2Cl_2—MeOH as the eluent. After concentration and drying *in vacuo*, **22** was obtained as a 1:1 mixture of diastereomers: 1.23 g (100%); mp 89.5–91°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.08 (m, 5 H), 3.39–2.97 (m, 2 H), 2.70–2.59 (m, 0.5 H), 2.48–2.32 (m, 1.5 H), 2.04–1.10 (m, 9 H), 1.35 (d, *J* = 11.9 Hz, 1.5 H), 1.21 (d, *J* = 11.9 Hz, 1.5 H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 132.66 (6.1, arom. C-1′) and 132.39 (6.7, arom. C-1′), 129.23 (4.9, arom. C-2′), 128.49 (2.4, C-3′) and 128.46 (2.4, C-3′); 126.49 (3.1, C-4′) and 126.46 (3.7, arom. C-4′), 40.18 (69.0, C-2) and 39.52 (69.0, C-2), 40.11 (69.0, Bn—CH_2) and 39.40 (69.6, Bn—CH_2), 37.70 (1.2, C-1) and 37.34 (1.8, C-1), 37.07 (C-7) and 37.03 (C-7), 36.00 (3.1, C-4) and 35.88 (3.1, C-

4), 31.59 (14.6, C-6) and 31.44 (14.0, C-6), 30.98 (4.3, C-3) and 30.77 (4.9, C-3), 28.24 (C-5) and 28.05 (C-5), 12.45 (66.5, Me) and 11.49 (66.5, Me); ^{31}P NMR (121 MHz, $CDCl_3$) δ 47.2 and 46.4 in a 1:1 ratio. Anal. Calcd. for $C_{15}H_{21}OP$: C, 72.56; H, 8.52. Found: C, 72.65; H, 8.53.

In a separate experiment, a solution of NaOH (60 mg, 1.5 mmol) in 1:1 EtOH—H_2O (1.5 mL) was added to **21** in one portion. The mixture which resulted was heated at 60°C for 7 days, cooled to rt and then extracted with benzene (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give 0.14 g (45%) of a 1:1 mixture of diastereomeric *exo*-phosphine oxides **22**. This was determined by ^{31}P NMR spectroscopy. The ^{31}P NMR spectrum (24 MHz, $CDCl_3$) of the crude reaction mixture showed 59% hydrolysis (41% unreacted **21**) and a 1:1 ratio of signals at δ 47.2 and 46.4 (*exo*-phosphine oxide diastereomers **22**).

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REFERENCES

1. (a) M. Eto, "Organophosphorus Pesticides: Organic and Biological Chemistry," CRC Press: Cleveland, OH, 1974; (b) W. M. Loffredo, R. T. Jiang and M. D. Tsai, *Biochemistry*, **29**, 10912 (1990); (c) G. M. Blackburn, P. R. Ashton, M. J. Guo, M. Rogers, G. Taylor, A. Guranowski and D. Watts, *Hereroatom Chem.*, **2**, 163 (1991); (d) J. D. Smith, "Role Phosphonates Living Syst.," R. L. Hilderbrand, ed., 1983; (e) G. M. Blackburn, *Chem. Ind.*, **5**, 134 (1981); (f) T. Klenner, P. Valenzuela-Paz, K. B. Keppler, G. Angres, H. R. Scherf, F. Wingen, F. Amelung and D. Schmaehl, *Cancer Treat. Rev.*, **17**, 253 (1990); (g) E. Uhlmann and A. Peyman, *Chem. Rev.*, **90**, 543 (1990).
2. (a) H. B. Kagan, in "Asymmetric Synthesis," J. D. Morrison, ed., Academic: Orlando, FL, 1985, Vol. 5, Chap. 1; (b) K. Pacheco-Panhans, Masters Thesis, Marquette University, May 1988; (c) J. Neuffer and W. J. Richter, *J. Organomet. Chem.*, **301**, 289 (1986); (d) S. Ryu, J. A. Jackson and C. M. Thompson, *J. Org. Chem.*, **56**, 4999 (1991); (h) C. R. Hall and T. D. Inch, *Phosphorus and Sulfur*, **7**, 171 (1979); (i) J. M. Harrison and T. D. Inch, *J. Chem. Soc., Perkin Trans I*, 1104 (1979); (j) T. Takahashi, M. Matsui, N. Maeno and T. Koizumi, *Heterocycles*, **30**, 353 (1990); (k) C. M. Thompson, J. A. Frick and D. L. Green, *J. Org. Chem.*, **55**, 111 (1990).
3. (a) C. M. Thompson, J. A. Frick, B. C. Natke and L. K. Hansen, *Chem. Res. Tox.*, **2**, 386 (1989); (b) V. Solodenko, T. Kasheva and V. Kukhar, *Synth. Commun.*, **21**, 1631 (1991); (c) R. M. Valerio, J. W. Perich, P. F. Alewood, G. Tong and R. B. John, *Aust. J. Chem.*, **45**, 777 (1992).
4. (a) J. P. Whitten, R. V. Muench, P. L. Cube, P. L. Nyce, B. M. Baren and I. A. McDonald, *Biorg. Med. Chem. Lett.*, **1**, 441 (1991); (b) D. A. McLeod, R. I. Brinkworth, J. A. Ashley, K. D. Janda and P. Wirsching, *Biorg. Med. Chem. Lett.*, **1**, 653 (1991); (c) P. Kafarski and B. Lejczak, *Phosphorus, Sulfur and Silicon*, **63**, 193 (1991); (d) J. A. Robl, L. A. Duncan, J. Pluscec, D. S. Karanowsky, E. M. Gordon, C. P. Ciosek, L. C. Rich, D. A. Dehmel, D. A. Slusarchyk, T. H. Harrity and K. A. O'Brien, *J. Med. Chem.*, **34**, 2804 (1991); (e) D. Howson, J. M. Hills, G. M. Blackburn and M. Brockman, *Biorg. Med. Chem. Lett.*, **1**, 501 (1991).
5. (a) J. Balzarini and E. De Clercq, *Adv. Exp. Med. Biol.*, **309A**, 29 (1991); (b) E. De Clercq, *Int. J. Immunopharm.*, **13**, 93 (1992); (c) E. DeClercq, *Biochem. Pharmacol.*, **42**, 963 (1991); (d) P. Miller, *Mol. Cell. Biol.*, **1**, 83 (1992).
6. J. Halpern, in "Asymmetric Synthesis," J. D. Morrison, ed., Academic: Orlando, FL, 1985, Vol. 5, Chap. 2.
7. (a) W. Schrader and W. Steglich, *Synthesis*, **96** (1989); (b) N. J. S. Harmat and W. Stuart, *Tetrahedron Lett.*, **31**, 2743 (1990); (c) S. C. Welch, J. A. Levine, I. Bemal and J. Cetrullo, *J. Org. Chem.*, **55**, 5991 (1990); (d) T. Takahashi, M. Matsui, N. Maeno, T. Koizumi and M. Shiro, *Heterocycles*, **30**, 353 (1990); (e) J. M. Brown, J. V. Carey and M. J. H. Russell, *Tetrahedron*, **46**, 4877 (1990); (f) S. E. Denmark, H. Stadler, R. L. Dorow and J. H. Kim, *J. Org. Chem.*, **56**, 5063 (1991); (g) A. Alexakis, S. Mutti and J. F. Normant, *J. Am. Chem. Soc.*, **113**, 6332 (1991); (h) S. E. Denmark and C. Chen, *J. Org. Chem.*, **59**, 2922–4 (1994).
8. For example see: (a) R. Engel, "Synthesis of Carbon-Phosphorus Bonds," CRC: Boca Raton, FL, 1988; (b) "Organic Phosphorus Compounds," G. M. Kosolapoff and L. Maier, eds., Wiley-Interscience: New York, 1972; 7 Vols; (c) K. M. Pietrusiewicz and M. Zablocka, *Chem. Rev.*, **94**, 1375 (1994).
9. (a) S. E. Cremer, R. J. Chorvat and B. C. Trivedi, *Chem. Commun.*, 769 (1969); (b) S. E. Cremer

and C. H. Chang, *Chem. Commun.*, 1456 (1969); (c) S. E. Cremer, B. C. Trivedi and F. L. Weitl, *J. Org. Chem.*, **36,** 3226 (1971); (d) S. E. Cremer, F. L. Weitl, F. A. Farr, P. W. Kremer, G. A. Gray and H. O. Hwang, *J. Org. Chem.*, **38,** 3199 (1973); (e) S. E. Cremer, F. A. Farr, P. W. Kremer, H. O. Hwang, G. A. Gray and M. G. Newton, *J. Chem. Soc. Chem. Commun.*, **374** (1975); (f) S. E. Cremer, J. M. Cowles, F. R. Farr, H. O. Hwang, P. W. Kremer, A. C. Peterson and G. A. Gray, *J. Org. Chem.*, **57,** 511 (1992); (g) M. K. Tasz, A. Gamliel, O. P. Rodriguez, T. M. Lane and S. E. Cremer, *J. Org. Chem.*, **60,** 6281 (1995) and references therein.

10. These investigations could be carried out using racemic compounds, since the displacement of diastereotopic leaving groups from prochiral phosphorus centers would produce diastereomeric products which could then be spectroscopically characterized.
11. W. Oppolzer, *Tetrahedron*, **43,** 1969 (1987) and references cited therein.
12. (a) H. J. Callot and C. Benezra, *Can. J. Chem.*, **48,** 3382 (1970); (b) C. Benezra, *J. Am. Chem. Soc.*, **95,** 6890 (1973); (c) N. K. Zyk, M. Y. Krysin, A. A. Borisenko, T. G. Shestakova and N. S. Zefirov, *Doklady Chemistry (Engl. Transl.)*, **265,** 241 (1982); (d) C. C. Hanstock and J. C. Tebby, *Phosphorus and Sulfur*, 15 (1983); (e) C. Benezra and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2270 (1966); (f) G. Adiwidjaja, B. Meyer and J. Z. Thiem, *Naturforsch., B: Anorg. Chem., Org. Chem.*, **34B,** 1547 (1979); (g) J. Thiem and B. Meyer, *Org. Magn. Reson.*, **11,** 50 (1978); (h) G. W. Buchanon and F. G. Morin, *Can. J. Chem.*, **58,** 530 (1980); (i) R. Bonjouklian and R. A. Ruden, *J. Org. Chem.*, **42,** 4095 (1977); (j) L. D. Quin, M. J. Gallagher, G. T. Cunkle and D. B. Chesnut, *J. Am. Chem. Soc.*, **102,** 3136 (1980); (k) P. Sampson, G. H. Hammond and D. F. Wiemer, *J. Org. Chem.*, **51,** 4342 (1986); (l) G. B. Hammond, T. Calogeropoulou and D. F. Wiemer, *Tetrahedron Lett.*, 4265 (1986); (m) T. Calogeropoulou, G. B. Hammond and D. F. Wiemer, *J. Org. Chem.*, **52,** 4185 (1987); (n) K. Lee and D. F. Wiemer, *J. Org. Chem.*, **56,** 5556 (1991).
13. For example see: (a) S. J. Cristol, G. D. Brindell and J. A. Reeder, *J. Am. Chem. Soc.*, **80,** 635 (1958); (b) S. J. Cristol and J. A. Reeder, *J. Org. Chem.*, **26,** 2182 (1961); (c) E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4,** 382 (1958).
14. T. L. Emmick and R. L. Letsinger, *J. Am. Chem. Soc.*, **90,** 3459 (1968).
15. (a) A. P. Marchand, "Stereochemical Applications of NMR Studies in Rigid Bicyclic Systems," Verlag Chemie International: Deerfield Beach, FL, 1982.
16. K. D. Berlin, T. H. Austin, M. Peterson and M. Nagabhushanam, "Topics in Phosphorus Chemistry," M. Grayson and E. J. Griffith, eds., Wiley-Interscience: New York, 1964, Vol. 1, pp. 43–48 and references cited therein.
17. T. Morita, Y. Okamoto and H. Sakurai, *Chem. Lett.*, **435** (1980).
18. (a) T. Morita, Y. Okamato and H. Sakurai, *Bull. Chem. Soc. Jpn.*, **51,** 2169 (1978); (b) M. Sekine, T. Futsuaki, Z. Yamada and T. Hata, *J. Chem. Soc., Perkin Trans 1*, 2509 (1982); (c) D. J. Burton and L. G. Sprague, *J. Org. Chem.*, **53,** 1523 (1988).
19. W. C. Still and C. Gennari, *Tetrahedron Lett.*, 4405 (1983).
20. C. C. Hanstock, J. C. Tebby and H. Coates, *J. Chem. Res. (S)*, **110** (1982).
21. (a) C. M. Welch, E. J. Gonzales and J. D. Guthrie, *J. Org. Chem.*, **26,** 3270 (1961); (b) Z. Pelchowicz, *J. Chem. Soc.*, **238** (1961).
22. L. Maier, *Phosphorus and Sulfur*, **10,** 47 (1981).
23. S. E. Cremer and R. J. Chorvat, *J. Org. Chem.*, **32,** 4066 (1967).
24. F. Y. Khalil and G. Aknes, *Phosphorus and Sulfur*, **3,** 27 (1977).
25. L. D. Quin, in "Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis," J. G. Verkade and L. D. Quin, eds., VCH: New York, 1987, Chap. 8.
26. *Exo*-2-(Diphenoxyphosphoryl)bicyclo[2.2.1]heptan-2-ol. Manuscript in preparation. S. E. Cremer, S. M. Levsen, A. C. Peterson, T. M. Lane and M. U. Haque.
27. J. C. Tebby, in "Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis, Methods in Stereochemical Analysis," J. G. Verkade and L. D. Quin, eds., VCH: Deerfield Beach, FL, 1987, Vol. 8, Chap. 1.