Diastereoselective Vinyl Phosphate/β-Keto Phosphonate Rearrangements

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Several nonracemic diols and amino alcohols have been tested for their utility as chiral auxiliaries in vinyl phosphate/β-keto phosphonate rearrangements. When (2*R*,4*R*)- or (2*S*,4*S*)-pentane-2,4-diol were employed, the diastereomeric β-keto phosphonates obtained from three prochiral cyclohexanones gave separate resonances in their respective ^{31}P NMR spectra, allowing estimation of diastereomeric excess (de) via straightforward integration. A crystalline enol form of the β-keto phosphonate was obtained from one ketone (4-(1,1-(ethylenedioxy)ethyl)-4-methylcyclohexanone, **10**), which allowed determination of its absolute stereochemistry by X-ray diffraction analysis. When LTMP was used to induce rearrangement of vinyl phosphates derived from ketone **10** and (2*R*,4*R*)- or (2*S*,4*S*)-pentane-2,4-diol, a de of 2.5:1 was obtained. In addition, de values of 2.0:1 and 1.4:1 were obtained with parallel rearrangements of 4-isopropyl- and 4-methylcyclohexanone, suggesting that this sequence may be more generally applicable to preparation of nonracemic materials from prochiral cyclohexanones.

For some years we have studied the base-induced rearrangements of vinyl phosphates to the corresponding β-keto phosphonates.[1] The earliest of these investigations established the viability of this reaction for five- and six-membered ring ketones, as well as specific bicyclic bridged and fused-ring systems,[1−3] and delineated some aspects of the reaction sequence involved. These findings have allowed application of this rearrangement in natural product synthesis[4] and have provided convenient access to a variety of novel compounds that have found use in other studies of β-keto phosphonate reactivity.[5−7] Still broader application of this methodology would be encouraged by procedures establishing stereocontrolled rearrangements.

As shown in Figure 1, the vinyl phosphate rearrangement offers an intriguing possibility for diastereoselection when prochiral ketones are paired with phosphoryl substituents containing stereogenic centers. For example, the reaction of LDA with a cyclohexanone bearing two different substituents at the C-4 position affords a racemic mixture of enolates. Subsequent reaction of these enolates with a nonracemic dialkyl phosphorochloridate provides a mixture of diastereomeric vinyl phosphates. Upon reaction with additional LDA, both vinyl phosphate diastereomers converge to a single intermediate in cases where the rearrangement involves a delocalized anion. When carbon−phosphorus bond formation takes place, it must occur at either the *pro-R* or the *pro-S* position of the allyl system, again affording a mixture of diastereomers. Because the transition states

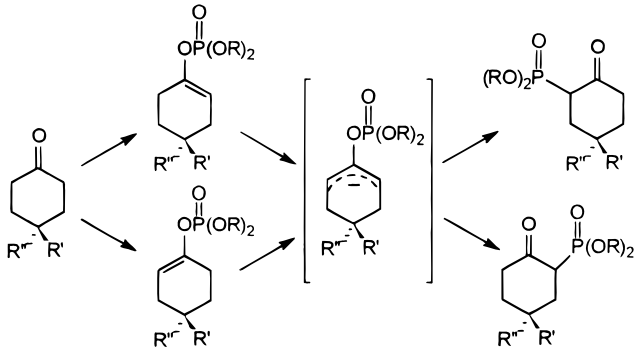

Figure 1. Stereochemistry of the vinyl phosphate/β-keto phosphonate rearrangement.(a) Rearrangement induced by treatment with LDA. (b) Crystalline material obtained from reaction a. (c) Rearrangement induced by treatment with LTMP.

leading to the two rearrangement products are themselves diastereomeric, some level of diastereoselectivity may be attainable under properly chosen conditions.

In an earlier paper,[8] we reported examination of a series of nonracemic phosphate esters in the vinyl phosphate rearrangement. Of the chiral auxiliaries surveyed at that time, the best results were observed with rearrangement of vinyl phosphates incorporating (*S*)-2-methylbutyl esters. However, while that investigation established the viability of the general idea, only a modest diastereomeric excess (de) was observed with 4-methylcyclohexanone and more highly substituted cyclohexanones gave mixtures wherein the de and absolute stereochemistry could not be readily established. In this report, studies of a new series of chiral auxiliaries are described, along with new strategies for establishing both the de and the absolute stereochemistry of some rearrangement products.

For this study, the phosphorochloridates shown in Table 1 were examined. In each case, the phosphorus atom was incorporated in a cyclic system, based on the premise that stricter control of the conformations avail-

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(1) (a) Hammond, G. B.; Calogeropoulou, T.; Wiemer, D. F. *Tetrahedron Lett.* **1986**, 4265−4268. (b) Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185−4190.

(2) Gloer, K. B.; Calogeropoulou, T.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 2842−2846.

(3) An, Y. Z.; Wiemer, D. F. *J. Org. Chem.* **1992**, *57*, 317−321.

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(5) Ruder, S. M.; Kulkarni, V. R. *J. Org. Chem.* **1995**, 60, 3084−3091.

(6) Vedejs, E.; Garcia-Rivas, J. A. *J. Org. Chem.* **1994**, *59*, 6517−6518.

(7) Clarke, R.; Gahagan, M.; Mackie, R. K.; Foster, D. F.; Cole-Hamilton, D. J.; Nicol, M.; Montford, A. W. *J. Chem. Soc., Dalton Trans.* **1995**, 1221−1226.

(8) An, Y. Z.; An, J. G.; Wiemer, D. F. *J. Org. Chem.* **1994**, *59*, 8197−8202.

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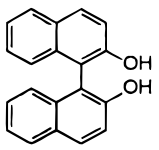
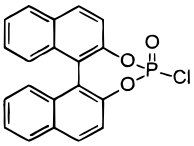
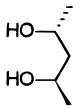
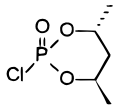
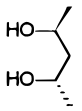
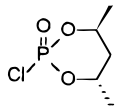
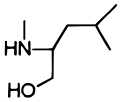
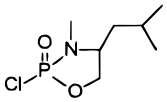
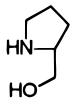
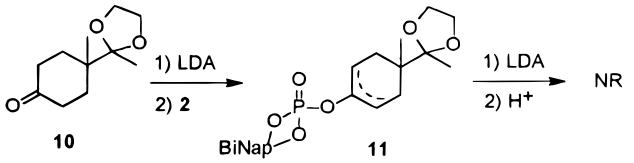
Table 1. Chiral Auxiliaries for the Vinyl Phosphate/ β-Keto Phosphonate Rearrangement

		Yield
 **1**	 **2**	78%
 **3**	 **4**	96%
 **5**	 **6**	96%
 **7**	 **8**	62%
 **9**		---

able to the chiral auxiliary might be reflected in a more diastereoselective rearrangement. The three phosphate esters (**2**, **4**, and **6**) were prepared through reaction of $POCl_3$ with commercially available binaphthol (**1**)[9] or (2*R*,4*R*)- (**3**) or 2*S*,4*S*-pentane-2,4-diol (**5**).[10] One phosphoramide (**8**) was prepared from $POCl_3$ and the amino alcohol *N*-methylleucenol (**7**),[11] but attempted preparation of a bicyclic reagent from the related amino alcohol (*S*)-(+)-2-pyrrolidinemethanol (**9**) was not successful under the same reaction conditions, perhaps due to a higher degree of strain.

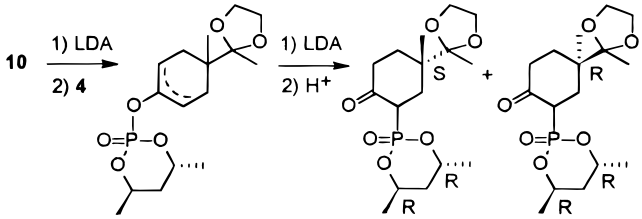
The prochiral ketone selected for initial study was the cyclohexanone **10**, available via a short sequence from acrylonitrile.[12] On the one hand, this ketone presents a well-defined conformation if the assumption is made that the steric demands of the acetal moiety approximate those of a *tert*-butyl group. At the same time, the acetal functionality was likely to be compatible with the conditions required for formation of the vinyl phosphate and for the subsequent rearrangement[3] and yet allow further modification of this substituent to obtain more varied C-4 groups once a rearrangement had been achieved.[13]

Reaction of ketone **10** with LDA cleanly gave the expected racemic enolate, and that enolate reacted smoothly with the phosphoryl chlorides **2**, **4**, **6**, and **8** to afford the desired vinyl phosphates. Attempted rearrangement of the binaphthol-derived vinyl phosphate **11** was not successful under the standard rearrangement conditions.[1] At this time it is not clear whether the difficulty lies in formation of the requisite anion or whether the anion was formed and simply failed to proceed to C−P bond formation under these conditions. In any event, only the parent vinyl phosphate **11** was recovered after the usual acidic workup.



10 **11**

The vinyl phosphates derived from ketone **10** and the pentanediol phosphorochloridates **4** and **6** proved much more interesting than those from binaphthol. Vinyl phosphate **12** was formed in about 80% yield from reaction of ketone **10** with LDA and the phosphorochloridate **4**. When treated with LDA, this vinyl phosphate rearranged as expected, forming the diastereomeric β-keto phosphonates **13** and **14** in yields of 40−50%. Analysis of the de of this reaction was possible, albeit not immediately obvious, by direct inspection of the ^{31}P NMR spectrum of the reaction mixture. The spectrum contains six resonances, three (23.3, 19.4, and 18.9 ppm) representing the 5*R* series (corresponding to C-4 of the original ketone) with the phosphoryl group in enolic, 1*S*, and 1*R* positions and three (23.4, 19.2, and 19.1 ppm) attributable to the 5*S* series in the enol, 1*R*, and 1*S* forms. If the spectrum is obtained under basic conditions, such that only the anions of the β-keto phosphonates are present, only two resonances are observed (30.1 and 29.9 ppm). Although integration of these resonances did not show appreciable de from this rearrangement with LDA, the pentanediol auxiliary was the first we have observed to result in distinguishable ^{31}P resonances for the rearrangement products (Figure 2) and thus the first to allow an approximate determination of de by ^{31}P NMR.



12 **13** **14**

A second advantage of the pentane-2,4-diol auxiliary became apparent when it proved possible to separate the diastereomeric series by a simple crystallization. When the product was crystallized from a mixture of ether and methanol, the crystalline material obtained showed only a single resonance in its ^{31}P NMR spectrum, if the spectrum was recorded immediately after dissolution of the crystals. The single peak corresponds in chemical

(9) Both binaphthol enantiomers are commercially available from Aldrich Chemical Co. Previous applications of binaphthyl phosphorochloridates include ref 7 and the following: (a) Gong, B.; Chen, W.; Hu, B. *J. Org. Chem.* **1991**, *56*, 423−425. (b) Kato, N. *J. Am. Chem. Soc.* **1990**, *112*, 254−257. (c) Kyba, E. P.; Gokel, G. W.; de Jong, F.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Kaplan, L.; Sogah, G. D. Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173−4184. (d) Jacques, J.; Fouquey, C.; Vitterbo, R. *Tetrahedron Lett.* **1971**, 4617−4620.

(10) Gordillo, B.; Eliel, E. L. *J. Am. Chem. Soc.* **1991**, *113*, 2172−2177 and references therein.

(11) Hiroshi, T.; Suzuki, Y. *Chem. Pharm. Bull.* **1983**, *31*, 4295−4299.

(12) Vig, O. P.; Sharma, S. D.; Bari, S. S.; Lal, M. *Indian J. Chem.* **1976**, *14B*, 932−933.

(13) The further elaboration of phosphonates **14** and **16** will be the subject of a later report.

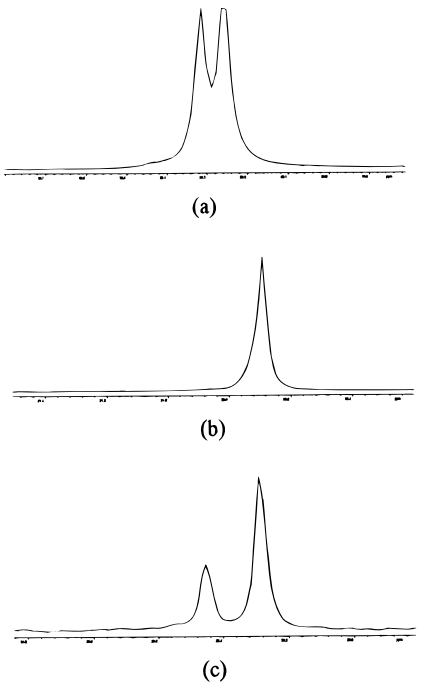
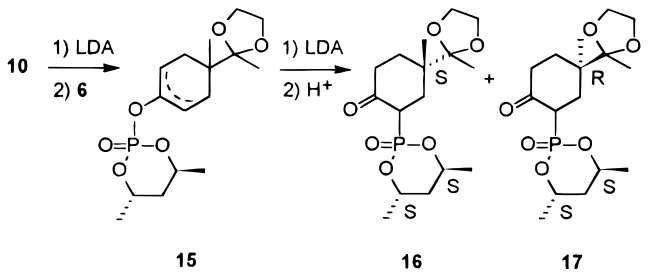


Figure 2. ^{31}P NMR resonances for the enol isomers obtained from rearrangements of vinyl phosphate **15**. (a) Rearrangement induced by treatment with LDA. (b) Crystalline material obtained from reaction a. (c) Rearrangement induced by treatment with LTMP.

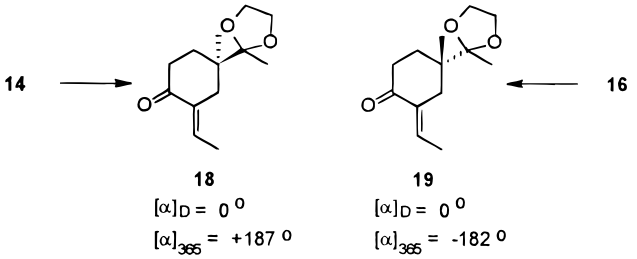
shift to one of the enol resonances observed in the initial product mixture. On allowing the product to stand in $CDCl_3$, equilibration occurs such that a mixture of the 1*R* and 1*S* isomers accompanies the enol form.

The fortuitous formation of crystalline material allowed determination of absolute stereochemistry by single-crystal diffraction analysis.[14] The known absolute stereochemistry of the starting pentanediol allowed facile determination of the C-5 stereochemistry of the enol. Thus it was established that use of (2*R*,4*R*)-pentane-2,4-diol resulted in formation of a crystalline enol with *R*,*R*,*R* stereochemistry (**14**).

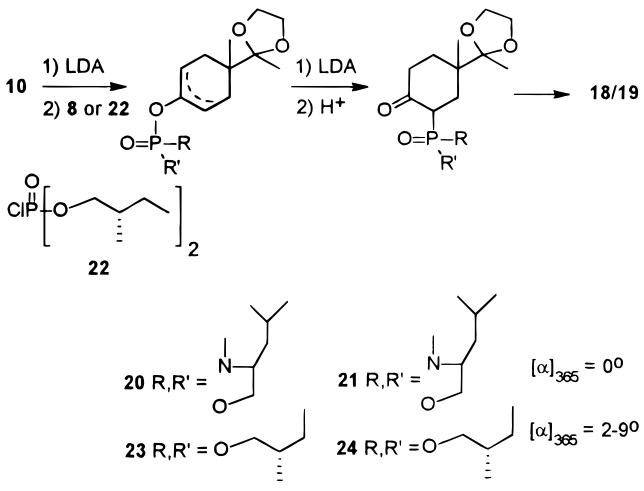
In a series of parallel experiments, the phosphorochloridate **6** derived from (2*S*,4*S*)-pentane-2,4-diol was allowed to react with the enolate of ketone **10**, and the resulting vinyl phosphate **15** was treated with LDA to induce rearrangement to the *β*-keto phosphonates **16** and **17**. Once again, six resonances were observed in the initial product mixture, and crystallization gave only the enol form of the *S*,*S*,*S* isomer **16**. With access to both C-5 stereoisomers, it was possible to probe various aspects of this rearrangement in ways hitherto not possible.



The immediate goal was to establish the de values of the rearrangements conducted with ketone **10** and other chiral auxiliaries, which would be possible through comparisons of optical rotations if all the varied phosphonates could be converted to a common derivative in which C-5 was the only stereogenic center. One obvious embodiment of this strategy is to employ a Horner−Wadsworth−Emmons condensation for removal of the chiral auxiliaries and conversion of C-2 to an sp^2 center. Condensation of the *R*,*R*,*R* phosphonate **14** with acetaldehyde gave the enone **18** as a single olefin isomer, but surprisingly the product had $[\alpha]_D = 0°$. Because it was extremely unlikely that racemization had occurred under the condensation conditions and the starting phosphonate was known to have the 5*R* stereochemistry from the diffraction analysis, other wavelengths were examined. When an $[\alpha]_{365} = +187°$ was observed, it became clear that the D-line rotation for compound **18** simply happens to be near 0°. For confirmation of this conclusion, crystalline *S*,*S*,*S* diastereomer **16** also was treated with acetaldehyde under typical Horner−Wadsworth−Emmons conditions to obtain the enantiomeric enone **19**. This enone also has $[\alpha]_D = 0°$ and $[\alpha]_{365} = -182°$.



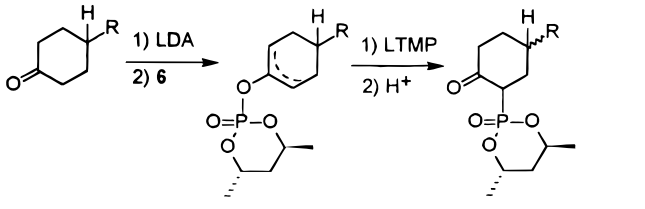
The enolate of ketone **10** was then treated with phosphorochloridate **8**, and the resulting vinyl phosphate **20** was treated with LDA to obtain the *β*-keto phosphonate **21**. In contrast to phosphonates **13/14** and **16**/**17**, compound **21** showed only two resonances in its ^{31}P NMR spectrum. Furthermore, while condensation with acetaldehyde proceeded under standard conditions, the resulting enone (**18/19**) was clearly racemic ($[\alpha]_{365} = 0°$). A similar situation prevailed with the vinyl phosphate **23** prepared from ketone **10** and bis((*S*)-2-methylbutyl) phosphorochloridate (**22**).[8] In this series, the overall yield for formation of the vinyl phosphate and its subsequent rearrangement to *β*-keto phosphonate was quite good (54%) and condensation with acetaldehyde also was smooth. Unfortunately, an $[\alpha]_{365} = +2-9°$ for the product indicated minimal diastereoselectivity for the rearrangement.



(14) Capron, M. A.; An, J.; Swenson, D. C.; Wiemer, D. F. *Acta Crystallogr.* **1995**, *C51*, 479−482.

Because use of these different auxiliaries did not materially improve the diastereoselectivity, and because it was now possible to establish de through ^{31}P NMR data in the pentane-2,4-diol series, we examined the impact of other conditions on the diastereoselectivity of the rearrangement of vinyl phosphate **12**. To induce rearrangement, the vinyl phosphates usually have been treated with excess LDA but because these conditions gave no de with compound **12**, other bases were examined. When a mixture of LDA and lithium 2,6-dimethylpiperidide (LDMP), or when 2 equiv of LDMP, was used to effect rearrangement, the *S*,*S*,*S* and *S*,*S*,*R* diastereomer series were obtained in essentially a 1:1 ratio. However, when the more hindered base lithium 2,2,6,6-tetramethylpiperidide (LTMP) was employed, analysis of the ^{31}P NMR spectrum of the mixture indicated that the *S*,*S*,*S* series was formed in a 2.5:1 preference over the *S*,*S*,*R* series (Figure 2). Given that crystallization can be employed to obtain the enol form of the *S*,*S*,*S* diastereomer, this was an important step in making diastereoselective rearrangements a more attractive process.

Our final goal was to begin testing other ketones for the generality of diastereoselective rearrangements with the 2,4-pentane-2,4-diol auxiliary. Reaction of 4-isopropylcyclohexanone (**25**) with LDA and phosphorochloridate **6** gave the expected vinyl phosphate **26**, and subsequent reaction of **26** with LTMP resulted in rearrangement to corresponding β-keto phosphonates **27**. In the ^{31}P NMR spectrum of the reaction mixture, six resonances representing the three isomers of each C-5 diastereomeric series were observed in a ratio indicating that this rearrangement had proceeded with a de of about 2:1. Another example of this diastereoselective rearrangement was observed with 4-methylcyclohexanone (**28**). Again in this series, six resonances were observed in the ^{31}P NMR spectrum of the final product mixture when LTMP was employed to induce rearrangement, corresponding to the 1*R*, 1*S*, and enol isomers of each C-5 stereochemistry. Integration of these resonances indicated that this rearrangement proceeded with a de of ca. 1.4:1. Unfortunately, the products of the latter two reactions were obtained as oils, precluding direct use of crystallography for determination of the C-5 stereochemistry in these cases.



25 R = $CH(CH_3)_2$ **26** R = $CH(CH_3)_2$ **27** R = $CH(CH_3)_2$ (2:1)
28 R = CH_3 **29** R = CH_3 **30** R = CH_3 (1.4:1)

In conclusion, examination of several additional chiral auxiliaries in the vinyl phosphate/β-keto phosphonate rearrangement has led to recognition of the special utility of 2,4-pentane-2,4-diol derivatives. The β-keto phosphonates that include this auxiliary have given rise to distinct signals in their ^{31}P NMR spectra, allowing ready estimates of de. In one case, a rearrangement product crystallized readily in the enol form, allowing determination of absolute stereochemistry via single-crystal diffraction analysis. Finally, this information has allowed the discovery of rearrangement conditions that produce de values that range from 1.4:1 to 2.5:1. While further work will be necessary to establish the range of this process and to allow prediction of the major diastereomer, it seems clear that diastereoselective vinyl phosphate/β-keto phosphonate rearrangements have potential for preparation of nonracemic synthetic intermediates from prochiral ketones.

Experimental Section

All reaction solvents were distilled immediately prior to use. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, while benzene, triethylamine, and diisopropylamine were distilled from CaH_2. All reactions were conducted in oven-dried glassware, under an atmosphere of nitrogen, and with magnetic stirring. Flash chromatography was carried out on Baker silica gel with 40 μm average particle diameter. Melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 141 automatic polarimeter. NMR spectra (^1H at 300 MHz and ^{13}C at 75 MHz) were recorded with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^1H) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards. ^{31}P NMR chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). Both low- and high-resolution mass spectra were obtained at an ionization potential of 70 eV. High-resolution mass spectra were obtained at the University of Iowa Mass Spectrometry Facility or at the Midwest Center for Mass Spectrometry, Lincoln, NB. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

1,1′-Binaphthyl-2,2′-diyl Phosphorochloridate (2).[7,9] Phosphorus oxychloride (766 mg, 5.0 mmol in 10 mL benzene) was added slowly to a solution of 1,1′-bi-2-naphthol (143 mg, 5.0 mmol) and triethylamine (2.0 g, 20 mmol) in benzene (40 mL) at rt, and a white precipitate was formed immediately. After 15 h, the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography (90% hexanes, 10% ethyl acetate) gave compound **2** (1.43 g, 78%): ^1H NMR δ 8.08 (d, J = 8.9 Hz, 1), 8.07 (d, J = 8.9 Hz, 1), 7.99 (d, J = 8.2 Hz, 1), 7.97 (d, J = 8.2 Hz, 1), 7.63 (dd, J = 8.9, 0.9 Hz, 1), 7.56−7.50 (m, 3), 7.42−7.30 (m, 4); ^{31}P NMR 11.5; ^{13}C NMR δ 132.1, 131.8, 131.6, 128.6, 127.2, 127.1, 127.0, 126.3, 120.3, 119.9 (d, J_{CP} = 4.1 Hz).

(4*R*,6*R*)- or (4*S*,6*S*)-(+)-2-Chloro-4,6-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (4 or 6). According to the procedure described for the preparation of compound **2**, (2*R*,4*R*)- or (2*S*,4*S*)-pentane-2,4-diol (5.0 g, 50 mmol), triethylamine (20.2 g, 200 mmol), benzene (250 mL), and phosphorus oxychloride (7.7 g, 50 mmol) were added sequentially to a reaction flask. After filtration of the reaction mixture and concentration of the filtrate in vacuo, compound **4** (8.5 g, 96%), or compound **6**, was obtained through flash column chromatography (hexanes 35%, ethyl acetate 65%). For compound **4**: $[\alpha]_D$ = +43° ($CHCl_3$, c = 3.7); ^1H NMR δ 5.03−4.86 (m, 2), 2.24−2.14 (m, 1), 2.00 (dd, J = 14.9, 2.9 Hz, 1), 1.61 (d, J = 6.8 Hz, 3), 1.50 (dd, J = 6.3, 2.6 Hz, 3); ^{31}P NMR −4.2; ^{13}C NMR δ 78.5 (d, J_{CP} = 8.7 Hz), 74.5 (d, J_{CP} = 7.4 Hz), 36.7 (d, J_{CP} = 8.0 Hz), 21.5 (d, J_{CP} = 9.3 Hz), 20.0; EIMS m/z (rel intensity) 187 (M^+ + 2, 1), 185 (M^+, 3), 147 (30), 145 (90), 119 (23), 117 (70), 68 (100), 45 (48). For compound **6** $[\alpha]_D$ = −45° ($CHCl_3$, c = 1.0), but all other spectral data were identical to that for compound **4**.

(4*S*)-*N*-methyl-4-isobutyl-2-chloro-1,3,2-oxazaphospholidin-2-one (8). According to the procedure described for compound **2**, compound **7**[11] (4.01 g, 30.6 mmol), triethylamine (15.5 g, 153 mmol), benzene (100 mL), and phosphorus oxychloride (4.7 g, 31 mmol) were added sequentially to a reaction flask. After standard workup, compound **8** (4.01 g, 62%) was obtained through flash column chromatography (hexanes 10%, ethyl acetate 90%): $[\alpha]_D$ = +61° ($CHCl_3$, c = 2.3); ^1H NMR δ 4.50−4.41 (m, 1), 4.09−4.00 (m, 1), 3.41−3.31 (m, 1), 2.65 (d, J_{HP} = 14.4 Hz, 3), 1.70−1.53 (m, 2), 1.48−1.36 (m, 1), 0.97 (d, J = 6.4 Hz, 3), 0.94 (d, J = 6.0 Hz, 3); ^{31}P NMR 27.3; ^{13}C NMR δ 70.5, 55.8 (d, J_{CP} = 14.0 Hz), 40.3 (d, J_{CP} = 10.0 Hz), 28.6 (d, J_{CP} = 4 Hz), 23.9, 23.3, 21.5; EIMS m/z (rel intensity) 213 (M^+ +2, 0.8), 211 (M^+, 2.4), 196 (0.3), 156 (61),

154 (100), 118 (14), 42 (16); HRMS calcd for $C_7H_{15}NO_2P^{35}Cl$ 211.0529, found 211.0514; calcd for $C_7H_{15}NO_2P^{37}Cl$ 213.0499, found 213.0497.

4-(1,1′-(Ethylenedioxy)ethyl)-4-methylcyclohexanone (10). Ketone **10** was prepared from acrylonitrile according to a literature procedure.[12] For **10**: ^{1}H NMR δ 4.03−3.86 (m, 4), 2.45−2.27 (m, 4), 2.05−1.94 (m, 2), 1.75−1.66 (m, 2), 1.28 (s, 3), 1.21 (s, 3); ^{13}C NMR δ 212.3, 113.4, 64.7 (2), 40.4, 36.9 (2), 30.7 (2), 18.9, 18.8.

1,1′-Bi-2-naphthyl 4-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)-1-cyclohexenyl Phosphate (11). According to the procedure described below for compound **12**, ketone **10** (0.48 g, 2.5 mmol in 4 mL THF) was added to an LDA solution (0.33 mmol in 30 mL THF) and phosphorochloridate **2** (0.93 g, 2.54 mmol in 6 mL THF) was then added. Standard workup as described below and purification by flash column chromatography (50% hexanes, 50% ethyl acetate) gave vinyl phosphates **11** (0.28 g, 21%) as an oil: ^{1}H NMR δ 8.08 (d, J = 8.9 Hz, 1), 8.07 (d, J = 8.9 Hz, 1), 8.0 (d, J = 8.2 Hz, 1), 7.9 (d, J = 8.2 Hz, 1), 7.6 (d, J = 8.9 Hz, 1), 7.5−7.2 (m, 7), 5.6 (br, 1), 3.98−3.82 (m, 4), 2.42−2.20 (br, 3), 1.92−1.70 (br, 2), 1.65−1.55 (br, 1), 1.31 (s, 3), 1.05 (s, 3); ^{31}P NMR −2.2, −2.4; ^{13}C NMR δ 147.5 (d, J_{CP} = 5.0 Hz), 147.3, 146.5, 146.3 (d, J_{CP} = 5.0 Hz), 146.2, 146.1, 132.1, 131.8, 131.6, 131.4, 131.0, 128.4, 128.3, 128.2, 127.1, 126.9, 126.7, 125.7, 121.4, 120.6, 120.1, 113.7, 110.4, 65.0, 64.8, 39.8, 31.5, 30.4, 27.3, 18.9, 18.2; HRMS calcd for $C_{31}H_{29}O_6P$ 528.1702, found 528.1677.

Cyclic (1*R*,3*R*)-1,3-Dimethyltrimethylene 4-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)-1-cyclohexenyl Phosphate (12). Compound **10** (1.00 g, 5.0 mmol) in THF (5 mL) was added slowly to an LDA solution (5.0 mmol in 20 mL THF) at −78 °C. After 1 h, phosphorochloridate **4** (0.70 g, 3.8 mmol in 5 mL THF) was added, and the reaction was allowed to warm to rt slowly. After 4 h at rt, the reaction was quenched by addition of saturated aqueous NH_4Cl. The aqueous layer was extracted twice with ether (50 mL), and the combined organic extracts were dried over Na_2SO_4 and then concentrated in vacuo. Final purification of the residue by flash column chromatography (100% ethyl acetate) gave the vinyl phosphate **12** as a mixture of diastereomers (3.06 g, 80%): ^{1}H NMR δ 5.40 (br, 1), 4.87−4.74 (m, 2), 4.00−3.82 (m, 4), 2.34−2.24 (br, 3), 2.11−2.02 (br, 1), 1.88−1.69 (m, 3), 1.49 (d, J = 6.7 Hz, 3), 1.44 (dd, J = 6.3, 2.1 Hz, 3), 1.25 (s, 3), 1.00 (s, 3); ^{31}P NMR −12.33, −12.43; ^{13}C NMR δ 146.0 (d, J_{CP} = 8.0 Hz), 113.2, 108.56 (d, J_{CP} = 5.7 Hz) and 108.33 (d, J_{CP} = 5.3 Hz) (two diastereomers), 74.8 (d, J_{CP} = 7.3 Hz), 72.6 (d, J_{CP} = 6.5 Hz), 64.8, 64.6, 39.6, 37.2 (d, J_{CP} = 7.2 Hz), 30.2, 27.1, 24.6, 21.6 (d, J_{CP} = 8.2 Hz), 20.3, 18.7, 17.9; EIMS m/z (rel intensity) 346 (M^+, 1), 331 (1.6), 302 (1), 284 (1), 259 (4), 215 (3), 99 (13), 87 (100), 43 (19); HRMS calcd for $C_{16}H_{27}O_6P$ 346.1545, found 346.1568.

Cyclic (1*R*,3*R*)-1,3-Dimethyltrimethylene [(5*R*)-5-Methyl-5-(2-methyl-1,3-dioxolan-2-yl)-2-oxocyclohexyl] phosphonate (14) and the 5*S* Diastereomer 13. Compound **12** (2.59 g, 7.5 mmol in 10 mL THF) was added dropwise to an LDA solution (16.4 mmol in 80 mL THF) at −78 °C. The reaction mixture then was allowed to warm to rt, and after 5 h at rt, the reaction was quenched by addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with ether (3 × 40 mL), the combined organic extracts were dried over Na_2SO_4, and this solution was concentrated in vacuo. Final purification by flash column chromatography (95% ethyl acetate, 5% methanol) gave equal amounts of two diastereomers, the *R*,*R*,*R* and *R*,*R*,*S* isomers (1.05 g, 41%). Crystallization from ether/methanol (9:1) afforded compound **14** as white crystalline needles: mp = 163 °C; $[\alpha]_D$ = +17.3° ($CHCl_3$, c = 1.0); ^{1}H NMR δ 10.91 (s, 1), 4.90−4.85 (m, 1), 4.70−4.60 (m, 1), 4.03−3.84 (m, 4), 2.28−2.22 (m, 3), 1.94−1.87 (m, 2), 1.82−1.68 (m, 2), 1.62−1.48 (m, 1), 1.57 (d, J = 6.7 Hz, 3), 1.38 (dd, J = 6.2, 1.5 Hz, 3), 1.28 (s, 3), 0.99 (s, 3); ^{31}P NMR ($CDCl_3$) 23.3, 19.4, 18.9 (enol form, trans, and cis); (CH_3OH/NaOMe) 30.1; EIMS m/z (rel intensity) 346 (M^+, 1), 331 (1), 301 (8), 259 (10), 233 (8), 113 (9), 87 (100); HRMS calcd for $C_{16}H_{27}O_6P$ 346.1545, found 346.1552. Anal. Calcd for $C_{16}H_{27}O_6P$: C, 55.48; H, 7.86. Found: C, 55.49; H, 7.90.

The mother liquors from the crystallization were enriched in the 5*S* diastereomer: ^{31}P NMR ($CDCl_3$) 23.4, 19.2, 19.1; (CH_3OH/NaOMe) 29.9.

Cyclic (1*S*,3*S*)-1,3-Dimethyltrimethylene 4-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)-1-cyclohexenyl Phosphate (15). Vinyl phosphates **15** were prepared from ketone **10** (9.11 g, 46 mmol) and phosphorochloridate **6** (8.49 g, 46 mmol) in a fashion exactly parallel to preparation of vinyl phosphates **12** (87% yield).

Cyclic (1*S*,3*S*)-1,3-Dimethyltrimethylene [(5*S*)-5-Methyl-5-(2-methyl-1,3-dioxolan-2-yl)-2-oxocyclohexyl] phosphonate (16) and the 5*R* Diastereomer 17. In a manner parallel to preparation of compounds **13** and **14**, vinyl phosphates **15** (0.80 g, 2.3 mmol in 10 mL THF) were added slowly to a solution of LDA (2.5 mmol) and LTMP (2.5 mmol) in 40 mL THF. Standard workup and final purification by flash column chromatography (95% ethyl acetate, 5% methanol) gave equal amounts of the expected products, the *S*,*S*,*S* and *S*,*S*,*R* diastereomers (0.38 g, 47%). Crystallization from ether/methanol (9:1) afforded compound **16** as white crystalline needles: mp = 163 °C, $[\alpha]_D$ = −19.2° ($CHCl_3$, c = 0.96). Both NMR (^{1}H,^{31}P, and ^{13}C) and mass spectral data were identical to that obtained for the opposite enantiomer, compound **14**. The mother liquors were enriched in the *S*,*S*,*R* diastereomer **17**, as seen previously with compounds **13** and **14**.

(4*R*)-2(*E*)-Ethylidene-4-methyl-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexanone (18). A mixture of β-keto phosphonate **14** (0.13 g, 0.38 mmol), potassium carbonate (51 mg, 0.45 mmol), and acetaldehyde (167 mg, 3.8 mmol) in 1,4-dioxane (10 mL) and water (2 drops) was stirred at rt for 15 h.[15] The resulting solution was concentrated in vacuo, and the residue was purified by flash column chromatography (80% hexanes, 20% ethyl acetate) to give enone **18** (33 mg, 40%) as a light oil: $[\alpha]_{365}$ = +187° ($CHCl_3$, c = 0.8); ^{1}H NMR δ 6.78−6.71 (m, 1), 4.03−3.78 (m, 4), 2.58−2.32 (m, 4), 2.08−1.98 (m, 1), 1.74 (d, J = 8.7 Hz, 3), 1.70−1.61 (m, 1), 1.31 (s, 3), 1.05 (s, 3); ^{13}C NMR δ 200.9, 135.7, 134.7, 113.7, 65.0, 64.8, 41.0, 35.7, 32.3, 28.8, 20.8, 19.0, 13.4; EIMS m/z (rel intensity) 224 (M^+, 0.1), 209 (2.3), 179 (0.4), 87 (100), 67 (4), 53 (6), 43 (35); HRMS calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1424.

(4*S*)-2(*E*)-Ethylidene-4-methyl-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexanone (19). In a manner identical to that described for preparation of compound **18**, phosphonate **16** (106 mg, 0.31 mmol) was treated with potassium carbonate (51 mg, 3.1 mmol) and acetaldehyde in wet dioxane to afford compound **19** (40 mg, 58%) as a light oil: $[\alpha]_{365}$ = −182° ($CHCl_3$, c = 0.7). ^{1}H and ^{13}C NMR and mass spectral data were identical to those found for the corresponding (+)-enantiomer **18**. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.43; H, 9.07.

2-[(4-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexenyl)oxy]-*N*-methyl-4-(4*S*)-isobutyl-1,3,2-oxazaphospholidin-2-one (20). According to the procedure described for compound **12**, ketone **10** (1.0 g, 5.0 mmol in 5 mL THF) was added to an LDA solution (5.0 mmol in 30 mL THF), followed by addition of phosphorochloridate **8** (0.85 g, 4.0 mmol). Standard workup and purification by flash column chromatography (100% ethyl acetate) afforded vinyl phosphates **20** (1.02 g, 68%) as a mixture of diastereomers: ^{1}H NMR δ 5.34 (br, 1), 4.37−4.28 (m, 1), 4.00−3.85 (m, 5), 3.42−3.37 (m, 1), 2.65 (d, J_{HP} = 10.5 Hz, 3), 2.35−2.20 (m, 3), 1.83−1.53 (m, 5), 1.41−1.28 (m, 1), 1.25 (s, 3), 1.00 (s, 3), 0.95 (d, J = 6.3 Hz, 3), 0.91 (d, J = 6.3, 3); ^{31}P NMR 17.6, 17.4; ^{13}C NMR δ 146.6 (d, J_{CP} = 5.0 Hz) and 146.5 (d, J_{CP} = 5.0 Hz) (for two diastereomers), 113.4, 109.2 (d, J_{CP} = 5.7 Hz), 69.7, 64.9, 64.7, 56.6 (d, J_{CP} = 13.6 Hz), 40.6 (d, J_{CP} = 6.9 Hz), 39.8, 30.4, 28.7, 24.8 (d, J_{CP} = 6.4 Hz), 24.3, 23.6, 21.7, 18.8, 18.1; EIMS m/z (rel intensity) 373 (M^+, 0.6), 358 (0.8), 311 (2), 286 (2.1), 254 (0.5), 194 (13), 136 (11), 87 (100), 43 (19); HRMS calcd for $C_{18}H_{32}NO_5P$ 373.2018, found 373.2011.

2-[5-Methyl-5-(2-methyl-1,3-dioxolan-2-yl)-2-oxocyclohexyl]-*N*-methyl-4(*S*)-isobutyl-1,3,2-oxazaphospholidin-2-one (21). According to the procedure described for phos-

(15) Mouloungui, Z.; Delmas, M.; Gaset, A. *Synth. Commun.* **1984**, *14*, 701−705.

phonate **14**, compound **20** (0.93 g, 2.5 mmol in 5 mL THF) was added to an LDA solution (5.5 mmol in 30 mL THF). Standard workup and final purification by flash column chromatography (100% ethyl acetate) gave phosphonates **21** (0.35 g, 37%) as a mixture of diastereomers: ^{1}H NMR δ 11.17 (d, J_{HP} = 1.3 Hz, 1) and 11.13 (d, J_{HP} = 1.3 Hz, 1) (for two diastereomers), 4.07−3.84 (m, 5), 3.41−3.37 (m, 1), 2.61(d, J_{HP} = 9.9 Hz, 3) and 2.58 (d, J_{HP} = 9.7 Hz, 3) (for two diastereomers), 2.34−2.20 (m, 2), 2.05−2.03 (br, 1), 1.76−1.56 (m, 5), 1.45−1.36 (m, 1), 1.26 (s, 3), 1.01 (s, 3) and 1.00 (s, 3) (for two diastereomers), 0.95 (d, J = 6.3 Hz, 3), 0.92 (d, J = 6.3 Hz, 3) and 0.91 (d, J = 6.3 Hz, 3) (for two diastereomers); ^{31}P NMR 45.9, 45.6; ^{13}C NMR δ 170.4 (d, J_{CP} = 4.9 Hz) and 170.3 (d, J_{CP} = 4.9 Hz) (for two isomers), 113.2 and 113.1 (for two isomers), 85.7 (d, J_{CP} = 163.7 Hz), 71.1 and 70.8 (two isomers), 58.4 (d, J_{CP} = 11.5 Hz) and 58.22 (d, J_{CP} = 11.2 Hz) (for two isomers), 40.90 (d, J_{CP} = 11.3 Hz) and 40.2 (d, J_{CP} = 9.7 Hz) (for two isomers), 37.0, 28.9 (d, J_{CP} = 6.1 Hz) and 28.8 (d, J_{CP} = 8.0 Hz) (for two isomers), 27.8 (d, J_{CP} = 8.4 Hz) and 27.6 (d, J_{CP} = 7.7 Hz) (for two isomers), 26.44, 26.3 and 26.1 (for two isomers), 24.7, 23.6, 21.7, 18.7, 17.9 and 17.7 (for two isomers); EIMS *m*/*z* (rel intensity) 373 (M^+, 3), 358 (1), 330 (6), 328 (16), 286 (8), 254 (3), 188 (4), 87 (100), 43 (31); HRMS calcd for $C_{18}H_{32}NO_5P$ 373.2018, found 373.2016.

Condensation with acetaldehyde, as described for phosphonate **14**, gave a mixture of compounds **18** and **19** in 40% yield; a measured $[\alpha]_{365} = 0°$ indicated that no de was obtained in this rearrangement.

Bis[(*S*)-2-methylbutyl] 4-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)-1-cyclohexenyl Phosphate (23). According to the procedure described for compounds **12**, ketone **10** (2.18 g, 11 mmol in 10 mL THF) was added to an LDA solution (13 mmol in 50 mL THF) at −78 °C, followed by addition of bis-[(*S*)-(−)-2-methylbutyl] phosphorochloridate (2.80 g, 11 mmol).[8] Flash column chromatography (hexanes 80%, ethyl acetate 20%) gave vinyl phosphates **23** (3.61 g, 78%) as a mixture of two diastereomers: ^{1}H NMR δ 5.41−5.38 (m, 1), 3.99−3.83 (m, 8), 2.36−2.06 (m, 3), 1.89−1.64 (m, 4), 1.62−1.40 (m, 3), 1.29−1.12 (m, 2), 1.25 (s, 3), 1.00 (s, 3), 0.95 (d, J = 6.6 Hz, 6), 0.91 (t, J = 7.3 Hz, 6); ^{31}P NMR −4.6; ^{13}C NMR δ 146.2 (d, J_{CP} = 8.7 Hz), 113.4, 108.9 (d, J_{CP} = 5.3 Hz), 72.3, 72.2, 64.9 (d, J_{CP} = 11.6 Hz), 39.8, 35.3 (d, J_{CP} = 7.1 Hz), 30.4, 27.3, 25.3, 24.5, 18.8, 18.1, 15.8, 11.0; EIMS *m*/*z* (rel intensity) 418 (M^+, 1), 403 (1), 331 (1), 261 (1), 234 (2), 216 (11), 180 (5), 135 (7), 118 (10), 99 (29), 87 (100), 77 (6), 55 (12); HRMS calcd for $C_{21}H_{39}O_6P$ 418.2484, found 418.2481.

Bis[(*S*)-2-methylbutyl] [5-Methyl-5-(2-methyl-1,3-dioxolan-2-yl)-2-oxocyclohexyl] phosphonate (24). According to the procedure described for **14**, compound **23** (1.4 g, 3.3 mmol in 10 mL THF) was added to an LDA solution (7 mmol in 40 mL THF). Flash column chromatography (80% hexanes, 20% ethyl acetate) gave phosphonate **24** (0.97 g, 69%): $[\alpha]_D$ = 2.40° ($CHCl_3$, c = 3.5); ^{1}H NMR δ 10.76 (enol tautomer), 4.40−3.62 (m, 8), 3.35 (ddd, J_{HP} = 24.5 Hz, J = 12.5, 5.7 Hz), 3.01 (ddd, J_{HP} = 23.0 Hz, J = 13.9, 5.7 Hz), 2.50−2.01 (m, 4), 1.84−1.48 (m, 6), 1.24−1.13 (m, 2), 1.26 (m, 3), 1.00 (m, 3), 0.97−0.88 (m, 12); ^{31}P NMR 27.9, 25.1, 24.7; ^{13}C NMR δ 207.4 (d, J_{CP} = 6.2 Hz), 206.7 (d, J_{CP} = 6.9 Hz), 168.5 (d, J_{CP} = 6.6 Hz), 146.9 (d, J_{CP} = 8.9 Hz), 113.4, 113.3, 113.2, 108.7, 108,7, 72.4, 72.3, 70.7, 70.6, 69.9, 69.8, 65.0 (d, J_{CP} = 4.8 Hz), 65.0 (d, J_{CP} = 5.6 Hz), 64.9 (d, J_{CP} = 4.0 Hz), 46.6 (d, J_{CP} = 139.3 Hz), 45.5 (d, J_{CP} = 143.8 Hz), 41.9, 41.0, 40.9, 40.2, 40.1, 35.6 (d, J_{CP} = 7.5 Hz), 35.4 (d, J_{CP} = 6.8 Hz), 34.4 (d, J_{CP} = 4.0 Hz), 32.1, 30.9, 29.2, 29.1, 26.7, 26.6, 26.1, 25.9, 25.6, 25.5, 25.4, 25.2, 20.5, 19.1, 19.0, 18.9, 18.8, 18.4, 18.0, 16.1, 16.0, 15.9, 11.1; EIMS *m*/*z* (rel intensity) 418 (M^+, 1), 403 (1), 373 (1), 233 (9), 217 (5), 191 (15), 180 (4), 135 (12), 113 (7), 87 (100), 71 (7), 55 (14); HRMS calcd for $C_{21}H_{39}O_6P$ 418.2484, found 418.2480. Condensation with acetaldehyde, as described for compound **14**, gave a mixture of compounds **18** and **19** in 67% yield; a measured $[\alpha]_{365} = +2-9°$ ($CHCl_3$, c = 1.0) indicated a slight diastereoselectivity for the 5*R* isomer in this rearrangement.

Cyclic (1*S*,3*S*)-1,3-Dimethyltrimethylene (5-Isopropyl-2-oxocyclohexyl)phosphonate (27). 4-Isopropylcyclohexanone (**25**) (700 mg, 5.0 mmol) was added slowly to an LDA solution (5 mmol in 10 mL THF) at 0 °C. After 15 min, phosphorochloridate **6** (923 mg, 5.0 mmol) was added, and the reaction was allowed to warm slowly to rt. After 4 h at rt, the reaction was quenched by addition of saturated aqueous NH_4Cl. The aqueous layer was extracted three times with ether (30 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Vinyl phosphates **26** were utilized for rearrangement without further purification: ^{31}P NMR −13.1, −13.1.

Compound **26** (1.44 g, 5.0 mmol) was added dropwise to an LTMP solution (12.5 mmol in 50 mL of THF) at −78 °C. The reaction mixture was then allowed to warm slowly to rt. After 1 h at rt, the reaction was quenched by addition of saturated aqueous NH_4Cl. The aqueous layer was extracted three times with ether (30 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Final purification of the residue by flash column chromatography (90% ethyl acetate, 10% methanol) gave an oil identified as a mixture of diastereomers **27** (533 mg, 37% overall from ketone **25**): ^{1}H NMR δ 10.87 (s, enol tautomer), 4.93−4.73 (m, 1), 4.72−4.51 (m, 1), 3.12−2.98 (m, 1), 2.97−2.67 (m, ketone tautomer), 2.53−2.30 (m, 2), 2.28−2.21 (m, 1), 2.20−1.70 (m, 5), 1.69−1.23 (m, 9), 0.97−0.84 (m, 7); ^{31}P NMR 23.1, 23.1, 18.7, 18.5, 18.4, 17.6. Anal. Calcd for $C_{14}H_{25}O_4P$: C, 58.32; H, 8.74. Found: C, 58.46; H, 8.76.

Cyclic (1*S*,3*S*)-1,3-Dimethyltrimethylene (5-Methyl-2-oxocyclohexyl)phosphonate (30). According to the procedure described for compound **12**, ketone **28** (0.23 g, 2.0 mmol in 2 mL THF) was added to an LDA solution (2 mmol in 8 mL THF) at −78 °C, followed by addition of compound **22** (0.37 g, 2 mmol in 2 mL THF). After standard workup, purification by flash column chromatography (20% hexanes, 80% ethyl acetate) gave compound **29** (0.39 g, 75%): ^{1}H NMR δ 5.44 (br, 1), 4.86−4.70 (m, 2), 2.35−2.01 (m, 5), 1.85−1.61 (m, 4), 1.49 (d, J = 6.7 Hz, 3), 1.44 (dd, J = 6.3, 2.2 Hz, 3), 0.96 (d, J = 6.6 Hz, 3); ^{13}C NMR δ 147.4 (d, J_{CP} = 10.6 Hz), 109.6 (d, J_{CP} = 6.1 Hz), 74.8 (d, J_{CP} = 7.4 Hz), 72.6 (d, J_{CP} = 6.9 Hz), 37.5 (d, J_{CP} = 7.0 Hz), 32.9, 31.8, 30.6, 27.6 (d, J_{CP} = 9.1 Hz), 21.9 (d, J_{CP} = 8.4 Hz), 21.0, 20.6; ^{31}P NMR −12.3.

Vinyl phosphate **29** (0.39 g, 1.5 mmol in 3 mL THF) then was added to an LTMP solution (3.75 mmol in 20 mL THF) at −78 °C, according to the procedure described for compound **23**. After standard workup, purification by flash column chromatography (100% ethyl acetate) gave compound **30** as a mixture of diastereomers (0.22 g, 56%): ^{1}H NMR δ 10.87 (enol tautomer), 4.87−4.83 (m, 1), 4.68−4.55 (m, 1), 3.07−2.91 (m, 1), 2.82−2.71 (m, ketone tautomer), 2.45−2.31 (m, 2), 2.24−2.10 (m, 1), 2.06−1.89 (m, 3), 1.77−1.60 (m, 1), 1.55−1.30 (m, 1), 1.50−1.40 (m, 6), 1.05−0.95 (m, 3); ^{31}P NMR 23.1 and 22.8 (two isomers of enol forms), 18.5, 18.4, 18.2, and 17.6 (four isomers of ketone forms); EIMS *m*/*z* (rel intensity) 260 (M^+, 19), 232 (12), 192 (26), 177 (33), 165 (39), 150 (89), 109 (83), 69 (91), 41 (100); HRMS calcd for $C_{12}H_{21}O_4P$ 260.1177, found 260.1150.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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