# Rearrangements of Nonracemic Vinyl Phosphates to β-Keto Phosphonates

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A series of chiral auxiliaries has been tested for viability in the vinyl phosphate/β-keto phosphonate rearrangement. While dienyl phosphates derived from ephedrine, pseudoephedrine, and isopinocampheol succumbed to competing elimination reactions, ones derived from menthol and (*S*)-2-methylbutanol were found to undergo rearrangement to the desired β-keto phosphonates. The bis((*S*)-2-methylbutyl) phosphorochloridate then was used to prepare the vinyl phosphates of the prochiral ketone 4-methylcyclohexanone, and modest diastereoselectivity was observed upon rearrangement of these phosphates to the corresponding β-keto phosphonates. The de of this rearrangement was established by degradation of the β-keto phosphonate to 3-methyladipic acid and determination of the optical rotation. This sequence allowed identification of the major rearrangement product as the 4*R*-diastereomer of β-keto phosphonate **13**. Finally, two other prochiral cyclohexanones were found to be suitable substrates for the vinyl phosphate/β-keto phosphonate rearrangement.

Some years ago we first reported the rearrangement of vinyl phosphates to β-keto phosphonates.[1] Since then, we have attempted to probe the limits of this reaction and found that it is applicable to a variety of cyclic ketones (e.g., **1** to **3**),[1] lactones,[2] and esters.[2] Much of our subsequent effort has been focused on applying this rearrangement in ever more complex systems.[3–5] In this paper we report the synthesis of some nonracemic vinyl phosphates and studies on their rearrangements to the corresponding β-keto phosphonates.[6]

A detailed mechanism for the vinyl phosphate/β-keto phosphonate rearrangement is not yet available, but some of the more salient features have been established. The failure of attempted crossover experiments suggests that the rearrangement is intramolecular.[1b] Studies of rearrangements in unsymmetrical vinyl phosphates generated regiospecifically via conjugate addition reactions have suggested that the reaction proceeds via formation of an allyl anion if the vinyl phosphate contains an acidic allylic hydrogen. However, rearrangement can proceed through formation of a vinyl anion when formation of an allyl anion is precluded (e.g., with the vinyl phosphate derived from camphor).[1]

As shown in Figure 1, the vinyl phosphate rearrangement offers an intriguing possibility for diastereoselection if rearrangement of vinyl phosphates bearing stereogenic center(s) in the phosphoryl group can be accomplished. Reaction of LDA with a cyclohexanone (**1**) bearing two different substituents at the C-4 position affords a racemic mixture of enolates, and subsequent reaction of these enolates with a dialkyl phosphorochloridate fixes the cyclohexyl stereochemistry (**2**). If the dialkyl phosphorochloridate is achiral, a mixture of enantiomeric vinyl phosphates results. However, if the dialkyl phosphorochloridate itself contains one, or more, stereogenic center(s), then a mixture of diastereomers results. In either case, if treatment of the resulting vinyl phosphates with strong base results in formation of a delocalized allyl anion, symmetry is reestablished within the cyclohexyl system. Upon rearrangement, carbon–phosphorus bond formation must occur at either the *pro-R* or the *pro-S* position of the allyl system. Because the transition states leading to the two rearrangement products (**3**) are themselves diastereomeric, some level of diastereoselectivity might be accomplished if rearrangements involving nonracemic phosphoryl groups are viable.

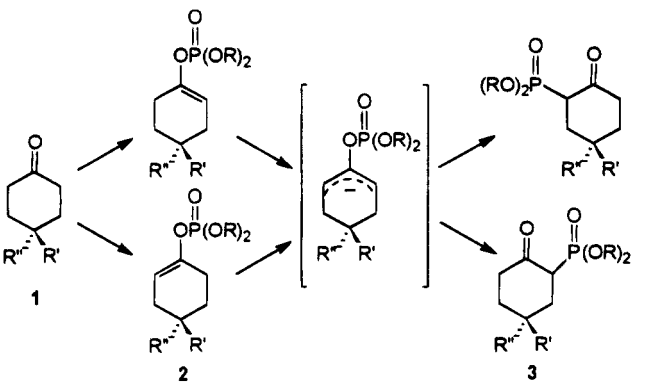


**Figure 1.** Stereo- and regiochemistry of the vinyl phosphate/β-keto phosphonate rearrangement.

At this time there are no direct reports on the impact of chirality on the vinyl phosphate/β-keto phosphonate rearrangement. However, the literature is not without stereochemical information on the rearrangement of aryl phosphates to aryl phosphonates, a process that may be closely related in mechanism. Welch and co-workers[7] prepared aryl phosphate derivatives of pseudoephedrine (**4**) and ephedrine. Base-induced rearrangement to the corresponding phosphonates (e.g., phosphonate **5** from phosphate **4**) was complicated in one ephedrine derivative

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

(2) Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750.

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

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(6) Taken in part from the PhD thesis of Yi-Zhong An, University of Iowa, 1992.

(7) Welch, S. C.; Levine, J. A.; Bernal, I.; Cetrullo, *J. Org. Chem.* **1990**, *55*, 5991.

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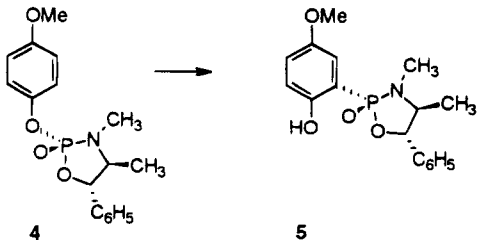
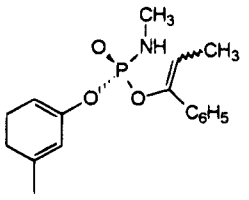


4 5

by a competing ring opening reaction involving formation of the benzyl anion, but it was possible to conclude that the aryl phosphonates were formed with retention of phosphorus stereochemistry in both series.[7] While vinyl phosphate to β-keto phosphonate rearrangements are inherently more complicated, because they also include formation of an additional stereogenic center at the α-carbon, the known aryl phosphate rearrangements encouraged exploration of the vinyl phosphate rearrangements.

To explore the viability of different chiral auxiliaries in a vinyl phosphate/β-keto phosphonate rearrangement, while initially minimizing the issues of stereochemistry, we examined rearrangement of a series of vinyl phosphate derivatives of 3-methylcyclohexenone (Table 1). The first vinyl phosphates in this series were derived from ephedrine[8a] and pseudoephedrine[8b] since these had demonstrated viability in the aryl phosphate rearrangements.[7] Treatment of enone **6** with LDA, followed by reaction of the enolate with the ephedrine chlorophosphate **7a**, gave the desired dienyl phosphate **8a** in good yield (69%). However, subsequent reaction of this dienyl phosphate with LDA did not lead to the desired β-keto phosphonate. Instead, opening of the ephedrine ring was observed, leading to an unstable product (**10**) isolated in



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low yield. In the pseudoephedrine series, formation of the dienyl phosphate **8b** also proceeded smoothly, but only a minor product resulting from opening of the pseudoephedrine ring was observed upon attempted rearrangement. These results suggest that the acidity of the benzylic position of these chiral auxiliaries was too high to permit formation of an intermediate cyclohexadienyl anion. This is in marked contrast to the earlier rearrangements of aryl phosphates derived from ephedrine and pseudoephedrine, where competing ring-opening reactions were usually minor.[7]

Somewhat more encouraging results were observed when (1*R*,2*S*,5*R*)-(−)-menthol was employed to prepare the vinyl phosphate. Reaction of 2 equiv of menthol with $POCl_3$ gave the dialkyl phosphorochloridate **7c** as a somewhat unstable oil. This phosphorochloridate reacted with the enolate of 3-methylcyclohexenone in modest

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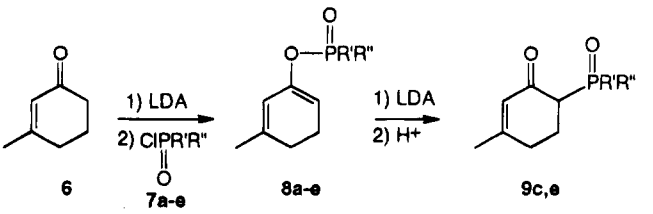
**Table 1. Preparation of β-keto phosphonates with nonracemic auxiliaries**



6 7a-e 8a-e 9c,e

| Entry | R',R" | % Yield | % Yield |
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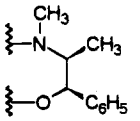
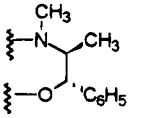
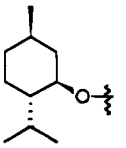
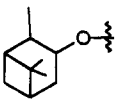
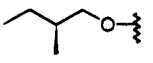
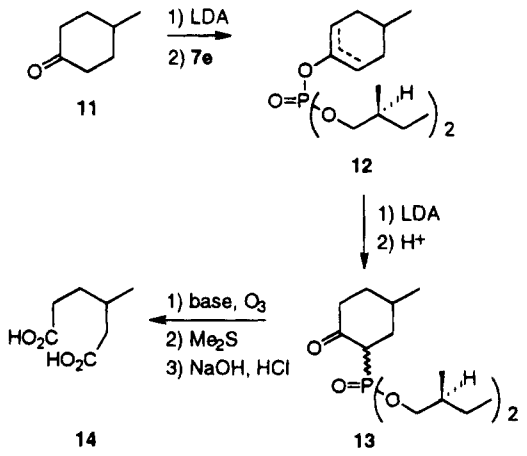
| a |  | 69 | --- |
| b |  | 77 | --- |
| c |  | 24 | 15 |
| d |  | --- | |
| e |  | 66 | 39 |

yield, affording the desired dienyl phosphate **8c**. Subsequent reaction of this dienyl phosphate with LDA gave the desired phosphonate (**9c**), but the low overall yield of this sequence (ca. 4%) made the dimenthol series unattractive. The nonracemic terpene alcohol, (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheol, also reacted with $POCl_3$ to give a dialkyl phosphorochloridate (**7d**), but this compound gave only the parent monoterpene via phosphate elimination upon attempted reaction with the enolate of compound **6**.

The most attractive sequence was observed when (*S*)-(−)-2-methylbutanol was employed as the chiral auxiliary. Reaction of this alcohol with $POCl_3$ gave dialkyl phosphorochloridate **7e** in 90% yield, and subsequent reaction with the lithium enolate of enone **6** gave the dienyl phosphate **8e** in good yield (66%). Upon reaction with LDA under standard rearrangement conditions, this dienyl phosphate gave the desired β-keto phosphonate **9e** in approximately 40% yield. Because the chemical yields were acceptable throughout the three-step sequence, this chiral auxiliary was then employed in the first study of the diastereoselectivity of the vinyl phosphate/β-keto phosphonate rearrangement.

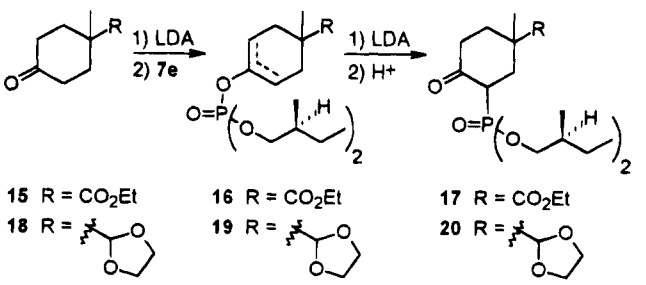
Reaction of the prochiral 4-methylcyclohexanone (**11**) with LDA and the dialkyl phosphorochloridate **7e** gave the desired vinyl phosphate (**12**) in 81% yield. This material proved stable to column chromatography and was readily isolated. Furthermore, upon reaction with LDA vinyl phosphate **12** rearranged smoothly to the corresponding phosphonate **13** (73%).




The $^1$H NMR spectrum of compound **13** indicated unequal amounts of diastereomers, but cannot of itself establish the stereochemistry of the predominant isomer. In fact, determination of the diastereomeric excess via analysis of the $^1$H NMR spectrum is not straightforward, because the product mixture is epimeric at C-2 as well as C-4. In the $^1$H NMR spectrum taken at 600 MHz, four complex resonances are observed between $\delta$ 2.6 and 3.0 corresponding to the α-hydrogens of the β-keto phosphonates, and small peaks are observed for the corresponding enol forms as well. While the mixed stereochemistry at C-2 would be unimportant to subsequent transformations such as the Horner–Wadsworth–Emmons condensation, it does complicate analysis of de with respect to C-4.

In a study of deprotonation of 4-methylcyclohexanone by nonracemic amide bases, Koga *et al.* solved a similar problem by devising an oxidative degradation to 3-methyladipic acid.[9] Because phosphoranes can be cleaved by ozonolysis,[10] a brief model study with the diethyl phosphonate of 4-methylcyclohexanone was conducted. This phosphonate reacted with excess ozone to give racemic 3-methyladipic acid in low yield. In the nonracemic case, sequential treatment of phosphonate **13** with ozone under basic conditions, addition of dimethyl sulfide to reduce intermediate ozonides, and saponification also gave 3-methyladipic acid. The resulting material had a rotation of +1.54°. If one assumes that reaction of the phosphonate with ozone is not diastereoselective, this rotation indicates a 57*R*:43*S* ratio.[11]

To broaden the range of targets that might be derived via these rearrangements, it would be useful to incorporate additional functionality within the C-4 substituents. Accordingly, the two prochiral ketones **15** and **18** were examined. In each case, reaction of the ketone with LDA and phosphorochloridate **7e** gave the desired vinyl phosphates (**16** and **19**), and subsequent rearrangement to the β-keto phosphonates (**17** and **20**) was observed upon reaction of the vinyl phosphates with additional LDA. In both cases, unequal amounts of diastereomeric rearrangement products were indicated by analysis of the 600




MHz $^1$H NMR spectra, but in both cases the presence of C-2 epimers along with the enol tautomers complicated analysis of the C-4 stereochemistry. Furthermore, oxidative degradations are not attractive in these series because the corresponding adipic acids are apparently still unknown. While these results encourage further studies of the diastereoselective vinyl phosphate to β-keto phosphonate rearrangement, they also make clear that new strategies for determination of the product stereochemistry and de will be required.

In conclusion, these studies have demonstrated that some chiral auxiliaries are compatible with conditions employed in the vinyl phosphate/β-keto phosphonate rearrangement. While the extent of diastereoselection is not yet large in the rearrangement of the bis((*S*)-2-methylbutyl) phosphate derivative of 4-methylcyclohexanone, this is not unexpected given the minimal facial differentiation brought about by the relatively small steric difference between the hydrogen and methyl substituents at C-4. With more varied C-4 substituents or still other chiral auxiliaries, it may be possible to achieve better diastereoselectivity. Because this process may ultimately allow synthesis of nonracemic natural products from prochiral ketones, further studies in this vein will be pursued.

## Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use, and all reactions in this solvent were conducted under a positive pressure of nitrogen. Column chromatography was done on Merck grade 62A silica gel (100–200 mesh), while radial chromatography was performed with a Chromatotron apparatus and Merck PF254 silica gel with $CaSO_4 \cdot 0.5H_2O$. Both $^1$H (300 MHz) and $^{13}$C NMR spectra were recorded with $CDCl_3$ as solvent and residual $CHCl_3$ as internal standard unless otherwise noted; $^{31}$P chemical shifts are reported in ppm relative to 85% $H_3PO_4$ (external standard). Low-resolution electron impact (EI) mass spectra were recorded on Hewlett-Packard 5985B or VG Trio-1 instruments operating at 70 eV. High-resolution mass spectra were obtained at the Midwest Center for Mass Spectrometry or the University of Iowa Mass Spectrometry Facility.

**(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-((3-methyl-1,5-cyclohexenyl-1-oxy)-5-phenyl-1,3,2-oxazaphospholidin-2-one (8a).** 3-Methyl-2-cyclohexenone (0.165 g, 1.5 mmol) was added dropwise to an LDA solution (1.5 mmol in 8 mL THF, prepared in situ from freshly distilled diisopropylamine and *n*-BuLi) at −78 °C. After 2 h, the phosphorochloridate **7a**[8a] (0.368 g, 1.5 mmol in 4 mL THF) was added to the reaction mixture. One h later the reaction was allowed to warm to rt slowly, and then it was monitored periodically by $^{31}$P NMR. Once the reaction was complete, the reaction mixture was quenched with 1 M $CH_3CO_2H$ in ether, filtered through Celite, and concentrated *in vacuo*. Purification by radial chromatography (70% hexane, 30% ethyl acetate) afforded compound **8a** (0.328 g, 69%): $^1$H NMR $\delta$ 7.39–7.08 (m, 5), 5.69 (d, $J$ = 6.3 Hz, 1), 5.68 (s, 1), 5.32 (br, 1), 3.69 (dm, $J_{HP}$ = 18.0 Hz, 1), 2.78 (d, $J_{HP}$ = 10.0 Hz, 3), 2.36–2.25 (m, 2), 2.15–2.05 (m, 2), 1.83 (s, 3), 0.75 (d,

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(10) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371.

(11) The maximum rotation reported for 3-methyladipic acid is +11.5° (*c* 9.38, $CHCl_3$): Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556.

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$J$ = 6.6 Hz, 3); $^{13}$C NMR $\delta$ 145.7 (d, $J_{CP}$ = 10.6 Hz), 139.6, 135.4 (d, $J_{CP}$ = 8.9 Hz), 127.9, 127.7, 125.2, 118.0 (d, $J_{CP}$ = 3.8 Hz), 105.0 (d, $J_{CP}$ = 6.2 Hz), 80.3 (d, $J_{CP}$ = 3.0 Hz), 59.3 (d, $J_{CP}$ = 13.3 Hz), 29.0 (d, $J_{CP}$ = 5.6 Hz), 27.4, 22.5, 21.4, 13.0; $^{31}$P NMR +15.1; EIMS $m/z$ (rel intensity) 319 ($M^+$, 42), 304 (13), 228 (38), 202 (49), 138 (51), 119 (41), 117 (50), 104 (45), 91 (100); HRMS calcd for $C_{17}H_{22}NO_3P$ 319.1337, found 319.1335.

**Phosphate Amide 10.** Dienyl phosphate **8a** (0.2 g, 0.63 mmol in 2 mL THF) was added to an LDA solution (2.3 equiv in 8 mL THF) at −78 °C. After 1 h, the reaction was allowed to warm to rt and monitored by $^{31}$P NMR. Five hours later, the reaction mixture was quenched by addition of saturated $NH_4Cl$, extracted with ether, filtered, and concentrated *in vacuo*. Final purification by radial chromatography (60% hexane, 40% ethyl acetate) gave compound **10** (34 mg, 19%): $^1$H NMR $\delta$ 7.47−7.45 (m, 2), 7.37−7.25 (m, 3), 5.80 (qd, $J$ = 7.3 Hz, $J_{HP}$ = 2.7 Hz, 1), 5.56 (br, 1), 5.30 (br, 1), 2.69 (br, 1), 2.54 (dd, $J_{HP}$ = 12.5 Hz, $J$ = 6.8 Hz, 3), 2.28−2.20 (m, 2), 2.10−2.02 (m, 2), 1.78 (s, 3), 1.75 (dd, $J$ = 7.3 Hz, $J_{HP}$ = 2.5 Hz, 3); $^{13}$C NMR $\delta$ 146.5 (d, $J_{CP}$ = 8.4 Hz), 145.8 (d, $J_{CP}$ = 8.2 Hz), 139.7, 134.6 (d, $J_{CP}$ = 4.2 Hz), 128.6, 128.2, 127.9, 118.2 (d, $J_{CP}$ = 5.7 Hz), 111.4, 104.4 (d, $J_{CP}$ = 5.9 Hz), 28.0, 27.7, 22.8, 22.0, 12.9; $^{31}$P NMR +2.2; EIMS $m/z$ (rel intensity) 320 ($M^+$ + 1, 2), 319 ($M^+$, 0.2), 227 (37), 202 (52), 117 (57), 115 (100), 110 (89), 91 (86), 77 (55); HRMS calcd for $C_{17}H_{22}NO_3P$ 319.1337, found 319.1338.

**(2*S*,4*S*,5*S*)-3,4-Dimethyl-2-((3-methyl-1,5-cyclohexenyl)-1-oxy)-5-phenyl-1,3,2-oxazaphospholidin-2-one (8b).** According to the procedure described for compound **8a**, LDA (1.5 mmol in 8 mL THF), 3-methylcyclohexenone (0.165 g, 1.5 mmol), and phosphorochloridate **7b**[8b] (0.368 g, 1.5 mmol in 4 mL THF) were allowed to react. Purification of the resulting oil by radial chromatography (70% hexane, 30% ethyl acetate) afforded compound **8b** as a colorless oil (0.366 g, 77%): $^1$H NMR $\delta$ 7.38 (br, 5), 5.66 (br, 1), 5.31 (m, 1), 4.89 (dd, $J$ = 9.1 Hz, $J_{HP}$ = 2.1 Hz, 1), 3.35 (dq, $J$ = 9.1, 6.1 Hz, 1), 2.69 (d, $J_{HP}$ = 10.9 Hz, 3), 2.34−2.26 (m, 2), 2.15−2.04 (m, 2), 1.82 (s, 3), 1.19 (d, $J$ = 6.1 Hz, 3); $^{13}$C NMR $\delta$ 146.1 (d, $J_{CP}$ = 10.5 Hz), 140.1, 136.6 (d, $J_{CP}$ = 6.6 Hz), 128.9, 128.5, 126.9, 105.0, 104.9, 85.3, 61.6 (d, $J_{CP}$ = 11.8 Hz), 28.3 (d, $J_{CP}$ = 3.5 Hz), 27.7, 22.8, 21.7, 15.3 (d, $J_{CP}$ = 9.8 Hz); $^{31}$P NMR +15.2 (d, $J_{HP}$ = 10.9 Hz); EIMS $m/z$ (rel intensity) 319 ($M^+$, 38), 304 (10), 239 (28), 228 (64), 202 (40), 138 (65), 119 (80), 104 (38), 91 (100), 77 (47), 56 (66); HRMS calcd for $C_{17}H_{22}NO_3P$ 319.1337, found 319.1335.

**Bis[(1*R*,2*S*,5*R*)-(−)-menthyl] Phosphorochloridate (7c).** In a fashion analogous to procedures described for compounds **7a** and **7b**,[8] (1*R*,2*S*,5*R*)-(−)-menthol (3.13 g, 20 mmol), triethylamine (5.06 g, 6.97 mL, 50 mmol), benzene (50 mL), and phosphorus oxychloride (1.687 g, 1.03 mL, 11 mmol) were added to a reaction flask. The resulting mixture was heated at reflux for 72 h. A similar workup and flash column chromatography (100% hexane, then 100% ethyl acetate) afforded compound **7c** (2.04 g, 52%): $^1$H NMR $\delta$ 4.44−4.30 (m, 2), 2.36−2.30 (m, 2), 2.15−2.11 (m, 2), 1.70−1.67 (m, 4), 1.44−1.37 (m, 4), 1.28−1.17 (m, 2), 1.09−0.92 (m, 4), 0.95−0.92 (m, 12), 0.83 (d, $J$ = 4.1 Hz, 6); $^{13}$C NMR $\delta$ 82.0 (d, $J_{CP}$ = 8.6 Hz), 81.8 (d, $J_{CP}$ = 7.8 Hz), 48.2, 48.1, 42.2, 41.8, 33.7, 31.4, 25.7, 22.7, 21.8, 21.7, 20.1, 15.6; $^{31}$P NMR +4.1; EIMS $m/z$ (rel intensity) 139 (44), 138 (56), 123 (28), 95 (100), 83 (52), 81 (87), 67 (35), 55 (30).

**Dimenthyl 5-Methyl-1,5-cyclohexenyl Phosphate (8c).** According to the procedure described for compound **8a**, 3-methylcyclohexenone (0.165 g, 1.5 mmol) was added to an LDA solution (1.5 mmol in 10 mL THF) at −78 °C. After 2 h, the temperature was allowed to increase to −40 °C, and phosphorochloridate **7c** (0.589 g, 1.5 mmol in 2 mL THF) was added. A similar workup and flash column chromatography (80% hexane, 20% ethyl acetate) gave an impure product, which was finally purified by radial chromatography (93% hexane, 7% ethyl acetate) to afford compound **8c** (0.17 g, 24%): $^1$H NMR $\delta$ 5.60 (br, 1), 5.34 (m, 1), 4.33−4.15 (m, 2), 2.42−2.15 (m, 7), 1.80 (s, 3), 1.68−1.64 (m, 6), 1.45−1.30 (m, 5), 1.23−0.88 (m, 5), 0.81 (d, $J$ = 7.0 Hz, 6), 0.91 (d, $J$ = 6.7 Hz, 6), 0.90 (d, $J$ = 7.0 Hz, 6), 0.81 (d, $J$ = 7.1 Hz, 3), 0.79 (d, $J$ = 7.1 Hz, 3); $^{13}$C NMR $\delta$ 145.8 (d, $J_{CP}$ = 8.1 Hz), 139.4, 118.1 (d, $J_{CP}$ = 6.2 Hz), 103.9 (d, $J_{CP}$ = 5.2 Hz), 79.4 (d, $J_{CP}$ = 6.9 Hz), 48.4 (d, $J_{CP}$ = 4.9 Hz), 48.3 (d, $J_{CP}$ = 4.8 Hz), 42.6, 42.3, 33.9, 31.4, 27.8, 25.2 (d, $J_{CP}$ = 3.0 Hz), 22.8 (d, $J_{CP}$ = 9.5 Hz), 22.6 (d, $J_{CP}$ = 5.9 Hz), 21.8 (d, $J_{CP}$ = 4.7 Hz, 21.7 (d, $J_{CP}$ = 3.2 Hz), 20.8, 15.6; $^{31}$P NMR −6.4; EIMS $m/z$ (rel intensity) 467 ($M^+$ + 1, 1), 328 (10), 191 (53), 190 (100), 189 (74), 95 (38), 92 (54); HRMS calcd for $C_{27}H_{45}O_4P$ 364.3055 ($M^+$ − 2), found 364.3049.

**β-Keto Phosphonate 9c.** According to the procedure described for compound **10**, dienyl phosphate **8c** (0.17 g, 0.365 mmol in 1.5 mL THF) was added to an LDA solution (2.3 equiv in 10 mL of THF). Flash column chromatography (70% hexane, 30% ethyl acetate) afforded phosphonate **9c** (23 mg, 15%): $^1$H NMR $\delta$ 5.88 (d, $J$ = 7.2 Hz, 1), 4.32−4.13 (m, 2), 2.85 (dt, $J_{HP}$ = 25.4 Hz, $J$ = 5.4 Hz, 1), 2.65−2.50 (m, 1), 2.49−2.01 (m, 7), 1.95 (s, 3), 1.72−1.58 (m, 4), 1.54−0.90 (m, 10), 0.95−0.73 (m, 18); $^{13}$C NMR $\delta$ 193.1 (d, $J_{CP}$ = 5.0 Hz), 192.8 (d, $J_{CP}$ = 5.7 Hz), 162.1 (d, $J_{CP}$ = 4.8 Hz), 126.5, 78.1 (d, $J_{CP}$ = 7.6 Hz), 77.7 (d, $J_{CP}$ = 8.6 Hz), 48.8 (d, $J_{CP}$ = 6.7 Hz), 48.5 (d, $J_{CP}$ = 6.2 Hz), 47.5 (d, $J_{CP}$ = 52.7 Hz), 45.7 (d, $J_{CP}$ = 52.6 Hz), 43.7, 43.2, 43.1, 42.8, 34.1, 31.6, 31.5, 29.2, 29.1, 25.5, 25.3, 25.1, 24.9, 24.2, 24.1, 24.0, 23.9, 22.8, 22.7, 22.0, 21.2, 21.1, 21.0, 15.8, 15.7, 15.5; $^{31}$P NMR +21.6, 21.5; EIMS $m/z$ (rel intensity) 467 ($M^+$ + 1, 0.1), 330 (2), 207 (2), 191 (100), 190 (63), 173 (13), 109 (21), 108 (39); HRMS calcd for $C_{27}H_{47}O_4P$ 366.3211, found 366.3197.

**Bis[(1*S*,2*S*,3*S*,5*R*)-(+)-isopinocamphyl] Phosphorochloridate (7d).** Through procedures analogous to those used for preparation of the ephedrine compounds,[8] (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheol (3.085 g, 20 mmol), triethylamine (5.06 g, 50 mmol), benzene (50 mL), and phosphorus oxychloride (1.533 g, 10 mmol) were added to a reaction flask in sequence, and the reaction mixture was maintained at 60 °C for 24 h. Compound **7d** (0.634 g, 16%) was obtained through flash column chromatography (95% hexane, 5% ethyl acetate): $^1$H NMR $\delta$ 4.89 (ddd, $J_{HP}$ = 19.5 Hz, $J$ = 9.7, 5.2 Hz, 2), 2.70−2.58 (m, 2), 2.44−2.37 (m, 2), 2.31−2.26 (m, 2), 1.24 (s, 6), 1.20 (d, $J$ = 7.4 Hz, 6), 1.12 (d, $J$ = 10.0 Hz, 2), 0.94 (d, $J$ = 1.2 Hz, 6); $^{13}$C NMR $\delta$ 81.5 (d, $J_{CP}$ = 7.6 Hz), 81.4 (d, $J_{CP}$ = 7.6 Hz), 47.5, 45.0 (d, $J_{CP}$ = 6.3 Hz), 44.9 (d, $J_{CP}$ = 6.8 Hz), 41.3 (d, $J_{CP}$ = 3.5 Hz), 38.1, 36.6, 36.2, 33.7, 33.6, 27.2, 23.8, 20.0, 19.8; $^{31}$P NMR +4.2 (dd, $J_{HP}$ = 9.9, 9.9 Hz); EIMS $m/z$ (rel intensity) 137 (46), 136 (80), 121 (66), 107 (36), 93 (100), 92 (66), 91 (48), 81 (84), 80 (58), 79 (45).

**Bis[(*S*)-(−)-2-methylbutyl] Phosphorochloridate (7e).** Through procedures analogous to those used for preparation of the ephedrine compounds,[8] (*S*)-(−)-2-methylbutanol (22.04 g, 250 mmol), triethylamine (63.25 g, 625 mmol), benzene (250 mL) and phosphorus oxychloride (19.2 g, 125 mmol) were added in sequence to a reaction flask. The reaction was maintained at rt for 24 h and monitored by $^{31}$P NMR. Standard workup, concentration *in vacuo*, and flash column chromatography (70% hexane, 30% ethyl acetate) gave compound **7e** (28.8 g, 90%): $^1$H NMR $\delta$ 4.14−3.93 (m, 4), 1.85−1.74 (m, 2), 1.53−1.44 (m, 2), 0.97 (d, $J$ = 6.8 Hz, 6), 0.93 (t, $J$ = 7.5 Hz, 6); $^{13}$C NMR $\delta$ 73.8 (d, $J_{CP}$ = 6.8 Hz, 6), 35.0 (d, $J_{CP}$ = 8.3 Hz), 25.3, 15.8, 10.9; $^{31}$P NMR +5.6 (t, $J_{HP}$ = 7.3 Hz); EIMS $m/z$ (rel intensity) 199 (11), 197 (31), 130 (34), 119 (26), 117 (77), 71 (100), 70 (53).

**Dienyl Phosphate 8e.** According to the procedure described for compound **8a**, 3-methylcyclohexenone (0.33 g, 3.0 mmol) was added to an LDA solution (3.0 mmol in 10 mL THF), followed by dropwise addition of bis(2-methylbutyl) phosphorochloridate (0.77 g, 3.0 mmol in 2 mL of THF). Flash column chromatography (80% hexane, 20% ethyl acetate) afforded product **8e** (0.65 g, 66%): $^1$H NMR $\delta$ 5.60 (br, 1), 5.31 (br, 1), 4.01−3.85 (m, 4), 2.34−2.24 (m, 2), 1.21−2.05 (m, 2), 1.81 (s, 3), 1.83−1.68 (m, 2), 1.59−1.43 (m, 2), 1.27−1.12 (m, 2), 0.94 (d, $J$ = 6.7 Hz, 6), 0.91 (t, $J$ = 7.2 Hz, 6); $^{13}$C NMR $\delta$ 145.7 (d, $J_{CP}$ = 8.5 Hz), 140.1, 117.7 (d, $J_{CP}$ = 5.9 Hz), 104.4 (d, $J_{CP}$ = 5.7 Hz), 72.5 (d, $J_{CP}$ = 6.6 Hz), 35.4 (d, $J_{CP}$ = 7.2 Hz), 27.8, 25.4, 22.9, 21.8, 15.9, 11.1; $^{31}$P NMR −5.0; EIMS $m/z$ (rel intensity) 330 ($M^+$, 17), 261 (32), 191 (100), 190 (61), 189 (100), 175 (45), 99 (57), 92 (100), 91 (100), 77 (31), 55 (30); HRMS calcd for $C_{17}H_{29}O_4P$ 328.1803 ($M^+$ − 2), found 328.1800.

**β-Keto Phosphonate 9e.** According to the procedure described for compound **10**, dienyl phosphate **8e** (0.33 g, 1.0

mmol in 1 mL of THF) was added to an LDA solution (2.3 equiv in 10 mL of THF). After flash column chromatography (60% hexane, 40% ethyl acetate), 130 mg (39%) of phosphonate **9e** was obtained: $[\alpha]^{25}_D = 2.79°$ ($CDCl_3$, $c = 3.9$); $^1H$ NMR $\delta$ 5.92 (br, 1), 3.99–3.80 (m, 4), 2.96 (dt, $J_{HP} = 20.7$ Hz, $J = 5.5$ Hz, 1), 2.71–2.62 (m, 1), 2.47–2.16 (m, 3), 1.97 (s, 3), 1.80–1.57 (m, 2), 1.56–1.35 (m, 2), 1.26–1.08 (m, 2), 0.95 (d, $J = 6.7$ Hz, 3), 0.91 (t, $J = 7.1$ Hz, 3), 0.90 (d, $J = 6.7$ Hz, 3), 0.88 (d, $J = 7.1$ Hz, 3); $^{13}C$ NMR $\delta$ 192.8 (d, $J_{CP} = 4.9$ Hz), 162.9, 126.3, 70.6 (d, $J_{CP} = 7.2$ Hz), 45.0 (d, $J_{CP} = 131.1$ Hz), 35.5 (d, $J_{CP} = 6.5$ Hz), 28.9 (d, $J_{CP} = 5.1$ Hz), 25.5 (d, $J_{CP} = 4.4$ Hz), 24.3, 23.6, 15.9, 11.0; $^{31}P$ NMR 23.8; EIMS $m/z$ (rel intensity) 330 ($M^+$, 1), 191 (21), 109 (23), 108 (100); HRMS calcd for $C_{17}H_{31}O_4P$ 330.1960, found 330.1948.

**Racemic 3-Methyladipic Acid (14).** Excess ozone was bubbled through a solution of the diethylphosphono derivative of ketone **11** (0.248 g, 1.0 mmol) and sodium (0.069 g, 3.0 mmol) in ethanol (15 mL) at −78 °C. After 2.5 h, dimethyl sulfide (1 mL) was added, and the reaction mixture was allowed to warm to rt. The reaction mixture was concentrated in vacuo, and 1 N HCl was added to adjust the pH to 1–2. After addition of water (2 mL), the aqueous solution was extracted with $CH_2Cl_2$ (10 mL, five times), and the combined organic layer was dried over $MgSO_4$. Flash column chromatography (70% hexane, 30% ethyl acetate) gave two fractions with the first containing a mixture of 3-methyladipic acid mono ethyl esters (35 mg, 19%).

These esters (35 mg, 0.186 mmol) were added to aqueous NaOH (10 mL, 2 M). The mixture was heated at reflux for 2.5 h. After the reaction mixture had cooled to rt, it was acidified with 1 N HCl and concentrated. After the solution was nearly dried, the residue was washed with $CH_2Cl_2$ several times, and the combined $CH_2Cl_2$ solution was dried over $MgSO_4$ and concentrated *in vacuo* to give 3-methyladipic acid (12 mg, 40%). The $^1H$ NMR spectrum was identical with an authentic sample.[12]

**Bis[2(*S*)-Methylbutyl] 4-Methyl-1-cyclohexenyl Phosphate (12).** 4-Methylcyclohexanone (0.965 g, 8.6 mmol in 5 mL THF) was added dropwise to an LDA solution (8.6 mmol in 40 mL THF) at −78 °C. After 40 min, phosphorochloridate **7e** (2.200 g, 8.6 mmol in 5 mL THF) was added, and the reaction mixture was allowed to warm to rt over 6 h. The reaction was quenched by addition of saturated $NH_4Cl$, and the aqueous layer was extracted with ether. The combined organic layer was dried ($Na_2SO_4$) and then concentrated *in vacuo*. Flash column chromatography (80% hexanes, 20% ethyl acetate) provided compound **12** (2.34 g, 7.0 mmol, 81%): $[\alpha]^{25}_D = 3.0°$ ($CDCl_3$, $c = 3.7$); $^1H$ NMR $\delta$ 5.44–5.42 (m, 1), 3.98–3.82 (m, 4), 2.36–2.08 (m, 3), 1.81–1.59 (m, 5), 1.58–1.31 (m, 3), 1.30–1.13 (m, 2), 0.96 (d, $J = 6.3$ Hz, 3), 0.95 (d, $J = 6.6$ Hz, 6), 0.91 (t, $J = 7.2$ Hz, 6); $^{13}C$ NMR $\delta$ 147.4 (d, $J_{CP} = 8.7$ Hz), 109.9 (d, $J_{CP} = 5.6$ Hz), 72.3 (d, $J_{CP} = 6.3$ Hz), 35.4 (d, $J_{CP} = 7.3$ Hz), 31.8, 30.7, 27.7, 27.4 (d, $J_{CP} = 4.1$ Hz), 25.4, 21.0, 15.9, 11.0; $^{31}P$ NMR −5.3; EIMS $m/z$ (rel intensity) 332 ($M^+$, 2), 193 (10), 192 (85), 99 (35), 94 (100), 79 (39), 55 (22), 43 (42); HRMS calcd for $C_{17}H_{33}O_4P$ 332.2116, found 332.2122.

**β-Keto Phosphonate 13.** Vinyl phosphate **12** (2.34 g, 7.0 mmol in 10 mL THF) was added to an LDA solution (2.2 equiv in 70 mL of THF) at −70 °C. After 2 h at that temperature, the reaction mixture was allowed to warm to rt over 9 h and then kept at rt for 1 h. The reaction was quenched by addition of saturated $NH_4Cl$ and extracted with ether. After the combined organic layers were dried over $Na_2SO_4$ and concentrated in *vacuo*, final purification by flash column chromatography (75% hexanes, 25% ethyl acetate) gave compound **13** (1.70 g, 73%) as a mixture of diastereomers: $[\alpha]^{25}_D = 4.07°$ ($CDCl_3$, $c = 3.0$); $^1H$ NMR $\delta$ 10.74 (enol), 4.04–3.77 (m, 4), 3.11–2.91 (m, 0.7), 2.79 (ddd, $J_{HP} = 14.3$ Hz, $J = 14.2$, 6.1 Hz, 0.3), 2.50–1.86 (m, 4), 1.78–1.60 (m, 3), 1.59–1.37 (m, 2), 1.26–1.08 (m, 2), 1.05–0.88 (m, 15); $^{13}C$ NMR $\delta$ 206.3 (d, $J_{CP} = 8.3$ Hz), 203.2 (d, $J_{CP} = 6.8$ Hz), 193.6, 156.0, 109.0, 106.5, 70.9 (d, $J_{CP} = 6.4$ Hz), 70.6 (d, $J_{CP} = 12.3$ Hz), 70.3 (d, $J_{CP} = 6.9$ Hz), 50.4 (d, $J_{CP} = 4.5$ Hz), 48.5, 48.4, 48.4, 46.4, 41.6 (d, $J_{CP} = 6.7$ Hz), 40.5, 36.2, 36.1, 35.6, 35.4, 35.3, 34.6, 34.4, 32.0, 31.7, 31.5, 31.0, 30.5, 30.2, 27.4, 25.6, 25.5, 21.1, 20.9, 16.0, 11.1; $^{31}P$ NMR ($CDCl_3$) 27.6; 24.2; 23.5; 23.2; EIMS $m/z$ (rel intensity) 333 ($M^+ + 1$, 1), 264 (5), 193 (100), 192 (63), 165 (22), 150 (42), 110 (45), 109 (29), 93 (20), 55 (78); HRMS calcd for $C_{17}H_{33}O_4P$ 332.2116, found 332.2125. Anal. Calcd for $C_{17}H_{33}O_4P$: C, 61.42; H, 10.01. Found: C, 61.17; H, 10.04.

**Ozonolysis of β-Keto Phosphonate 13.** β-Keto phosphonate **13** (0.332 g, 1.0 mmol) was added to a solution of sodium (0.115 g, 5.0 mmol) and ethanol (15 mL). After the reaction temperature had reached −78 °C, ozone was bubbled into the solution for 7 h. $Me_2S$ (4.0 mL) was added, and the reaction mixture was allowed to warm to rt slowly and the solution was stirred overnight. After concentration *in vacuo*, NaOH (20 mL, 0.5 M) was added to the residue, and the mixture was then heated at reflux overnight. The reaction mixture was acidified with 1 N HCl to pH ≈ 1 and then was concentrated to near dryness. The residue was washed with $CH_2Cl_2$ several times, and the combined $CH_2Cl_2$ solution was dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (60% hexane, 40% ethyl acetate) afforded (+)-3-methyladipic acid (8.5 mg, 5%): $[\alpha]^{25}_D = 1.54°$ ($CH_3OH$, $c = 0.8$). On the basis of the highest literature value for this rotation,[11] the measured value indicates ca. 14% ee.

**Vinyl Phosphate 16.** According to the procedure described for compound **12**, ketone **15**[6] (0.51 g, 3.0 mmol in 2 mL of THF) was added to an LDA solution (3.0 mmol in 8 mL of THF), followed by addition of bis(2-methylbutyl) phosphorochloridate (1.10 g, 4.3 mmol). Flash column chromatography (75% hexane, 25% ethyl acetate) afforded product **16** (1.00 g, 85%): $^1H$ NMR $\delta$ 5.43–5.41 (m, 1), 3.98–3.82 (m, 4), 3.68 (s, 3), 2.64–2.58 (m, 1), 2.32–1.96 (m, 4), 1.78–1.65 (m, 3), 1.52–1.34 (m, 2), 1.29–1.12 (m, 2), 1.23 (s, 3), 0.94 (d, $J = 6.7$ Hz, 6), 0.93 (t, $J = 7.4$ Hz, 3), 0.92 (t, $J = 7.4$ Hz, 3); $^{13}C$ NMR $\delta$ 177.4, 146.6 (d, $J_{CP} = 9.2$ Hz), 108.4 (d, $J_{CP} = 5.2$ Hz), 72.5 (d, $J_{CP} = 6.1$ Hz), 51.9, 40.6, 35.4 (d, $J_{CP} = 7.2$ Hz), 32.8, 31.1, 25.5, 25.1, 23.7, 16.0, 11.1; $^{31}P$ NMR −5.4; EIMS $m/z$ (rel intensity) 390 ($M^+$, 2), 250 (27), 190 (100), 189 (25), 99 (36), 92 (33), 55 (24), 43 (50); HRMS calcd for $C_{19}H_{35}O_6P$ 390.2171, found 390.2163.

**β-Keto Phosphonate 17.** According to the procedure described for compound **13**, vinyl phosphate **16** (0.86 g, 2.2 mmol in 3 mL of THF) was added to an LDA solution (2.2 equiv in 40 mL of THF). Flash column chromatography (70% hexane, 30% ethyl acetate) gave compound **17** as a mixture of C-2 and C-4 diastereomers and their respective enol tautomers (0.288 g, 34%): $[\alpha]^{25}_D = 2.76°$ ($CHCl_3$, $c = 3.4$); $^1H$ NMR $\delta$ 10.80 (enol tautomer), 4.14–3.63 (m, 7), 3.14 (ddd, $J_{HP} = 21.6$ Hz, $J = 13.3$, 5.4 Hz, 1), 2.73–1.12 (m, 15), 0.97–0.89 (m, 12); $^{31}P$ NMR ($CDCl_3$) 26.8, 23.7; $^{31}P$ NMR ($CD_3OD$/Na) 33.4; EIMS $m/z$ (rel intensity) 331 (3), 351 (54), 250 (31), 191 (100), 190 (45), 150 (42), 109 (50), 91 (26), 79 (22), 55 (51); HRMS calc for $C_{19}H_{35}O_6P$ 390.2171, found 390.2165. In the $^1H$ NMR at 600 MHz, the α-hydrogens of four stereoisomers were observed: $\delta$ 3.13 (ddd, $J_{HP} = 20.6$ Hz, $J = 13.3$, 5.6 Hz), 3.03 (ddd, $J_{HP} = 23.9$ Hz, $J = 11.1$, 6.1 Hz), 2.76 (m), 2.71 (ddd, $J_{HP} = 13.5$ Hz, $J = 9.0$, 4.5 Hz).

**Vinyl Phosphate 19.** According to the procedure described for compound **12**, keto ketal **18**[6] (0.184 g, 1.0 mmol in 1 mL of THF) was added to an LDA solution (1.0 mmol in 10 mL of THF), followed by addition of bis(2(S)-methylbutyl) phosphorochloridate (0.301 g, 1.2 mmol). Flash column chromatography (80% hexane, 20% ethyl acetate) afforded compound **19** (0.278 g, 69%): $[\alpha]^{25}_D = 2.44°$ ($CHCl_3$, $c = 2.7$); $^1H$ NMR $\delta$ 5.41–5.40 (m, 1), 4.95 (s, 1), 3.98–3.83 (m, 8), 2.28–2.17 (m, 3), 1.84–1.40 (m, 7), 1.27–1.12 (m, 2), 0.95 (d, $J = 6.4$ Hz, 6), 0.93 (s, 3), 0.91 (t, $J = 7.3$ Hz, 6); $^{13}C$ NMR $\delta$ 146.5 (d, $J_{CP} = 8.6$ Hz), 109.0, 108.5 (d, $J_{CP} = 5.6$ Hz), 72.4 (d, $J_{CP} = 6.6$ Hz), 65.3 (d, $J_{CP} = 5.2$ Hz), 35.5, 35.4 (d, $J_{CP} = 7.3$ Hz), 30.7, 28.8, 25.4, 24.3 (d, $J_{CP} = 3.6$ Hz), 17.7, 15.9, 11.1; $^{31}P$ NMR −5.3; EIMS $m/z$ (rel intensity) 404 ($M^+$, 0.2), 166 (25), 99 (21), 94 (17), 79 (11), 73 (100), 55 (12); HRMS calcd for $C_{20}H_{37}O_6P$ 404.2328, found 404.2319.

**β-Keto Phosphonate 20.** According to the procedure described for compound **13**, vinyl phosphate **19** (0.173 g, 0.428 mmol in 1 mL of THF) was added to an LDA solution (2.3 equiv in 10 mL of THF). Compound **20** (90 mg, 52%) was obtained, as a mixture of C-2 and C-4 diastereomers and their enol tautomers, through flash column chromatography (70% hex-

ane, 30% ethyl acetate): $[\alpha]^{25}_D = 4.0°$ ($CHCl_3$, $c = 1.8$); $^1H$ NMR $\delta$ 10.80 (enol tautomer), 10.19 (enol tautomer), 4.61 (s, 1), 4.13–3.68 (m, 8), 2.69 (d, $J_{HP} = 14.5$ Hz), 2.55 (dd, $J_{HP} = 17.2$ Hz, $J = 6.0$ Hz), 2.42 (dd, $J_{HP} = 16.6$ Hz, $J = 1.2$ Hz), 2.27–2.05 (m), 2.69–2.05 (total 4 H), 1.83–1.61 (m, 2), 1.58–1.40 (m, 2), 1.26–1.06 (m, 4), 0.97–0.88 (m, 15); $^{31}P$ NMR 27.7, 24.8, 23.7; EIMS $m/z$ (rel intensity) 278 (2), 251 (10), 178 (10), 113 (27), 96 (11), 73 (100); HRMS calcd for $C_{20}H_{37}O_6P$ 404.2328, found 404.2324.

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