Regiochemistry of Vinyl Phosphate/β-Keto Phosphonate Rearrangements in Functionalized Cyclohexanones and Decalones

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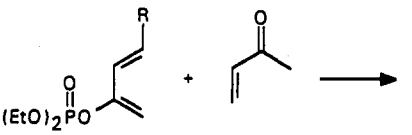
Diethyl vinyl phosphates derived from simple alkyl-substituted cyclohexanones and cyclohexenones are known to rearrange to β-keto phosphonates upon treatment with excess LDA. To establish the effect of oxygen-containing functional groups on this transformation, vinyl phosphates containing remote carbonyl groups or acetals have been studied. The rearrangement fails in the presence of unprotected carbonyl groups but proceeds in the presence of acetals. To establish the regiochemistry of this rearrangement in fused-ring systems, representative decalins were studied. Through use of various ketones and enones, the 2- and 4-phosphono 3-keto compounds have been prepared in both cis- and trans-fused decalin series.

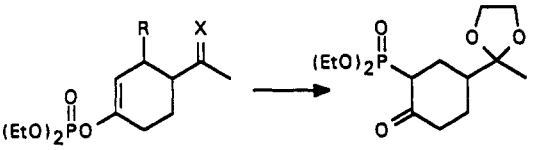
We recently introduced a convenient route to β-keto phosphonate derivatives of medium-ring ketones[1] and lactones,[2] a route based on rearrangement of vinyl phosphate anions. Many cyclic vinyl phosphates appropriate for this transformation should be readily available through reaction of dialkyl phosphorochloridates with ketone enolates; others should be accessible through cycloadditions of phosphate dienes.[3,4] The rearrangement itself proceeds in attractive yield, but with substituted cyclohexanones where rearrangement proceeds through an unsymmetrical allyl anion, the regiochemistry can be difficult to predict or control. One solution to this problem was discovered through examination of a series of cyclohexenone derivatives.[5] In this series, treatment of the enone with LDA under conditions of kinetic control, trapping the enolate with diethyl phosphorochloridate, and rearrangement to the β-keto phosphonate consistently results in C–P bond formation at the α′-position of the α,β-unsaturated systems, apparently due to selective formation of the corresponding vinyl anion. With the problem of regiocontrol resolved for simple cyclohexenones, we began to explore functionalized systems more representative of intermediates required for natural products synthesis. In particular, because complexation between a lithium base and the vinyl phosphate appears to be involved in the rearrangement, it was necessary to establish experimentally a sequence that would be compatible with the presence of oxygen-containing functional groups.

The first substrate was prepared by cycloaddition of diethyl butadienyl phosphate (1) and methyl vinyl ketone (2).[3,4] Vinyl phosphate 3 was then treated with LDA, both under standard rearrangement conditions and with LDA in large excess, but no phosphonates could be detected by ^{31}P NMR. Based on the reasonable premise that formation of a ketone enolate prevented formation of the vinyl phosphate anion required for rearrangement, protection of the carbonyl group was pursued. Upon treatment of compound 3 with ethylene glycol and PPTS, the ketal 4 was obtained in virtually quantitative yield. Treatment of compound 4 with LDA under standard conditions gave β-keto phosphonate 5 in 67% yield after column chromatography.



1 R = H
6 R = OMe

2



3 R = H, X = O
4 R = H, X = OCH_2CH_2O
7 R = OMe, X = O

5

The example described above suggested that vinyl phosphates could survive the minimal acidic conditions required for ketalization of remote carbonyl groups, and that rearrangement to the β-keto phosphonate was viable in the presence of remote oxygen as long as acidic positions were protected. However, because rearrangement of compound 4 presumably proceeds through a symmetrical allyl anion,[1] an analogous cyclohexenone was sought to test regiocontrol. Cycloaddition of diethyl 4-methoxy-2-butadienyl phosphate (6)[3] and methyl vinyl ketone gave the vinyl phosphate 7 in good yield. However, when compound 7 was treated with ethylene glycol under the same reaction conditions, a complex mixture was obtained. As an alternative model, the known keto aldehyde 10 was prepared through cycloaddition of Danishefsky's diene (8) with methacrolein (9), followed by treatment with dilute HCl.[6] After formation of the acetal (11), reaction of the enone with LDA and diethyl phosphorochloridate gave the phosphate diene 12. Subsequent treatment of dienyl phosphate 12 with LDA gave only β-keto phosphonate 13 (as a 56:44 mixture of diastereomers), demonstrating a regiocontrol analogous to that observed with simple cyclohexenones.[5]

Because of the importance of decalin intermediates in syntheses of terpenoids and steroids, we have explored the course of this rearrangement in representative fused-ring systems. Efforts to obtain vinyl phosphate cycloadducts from phosphate diene 1 and 2-methylcyclohexenone (14),

(1) 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) Calogeropoulou, T.; Wiemer, D. F. *J. Org. Chem.* **1988**, *53*, 2295.
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(5) Gloer, K. B.; Calogeropoulou, T.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 2842.
(6) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.

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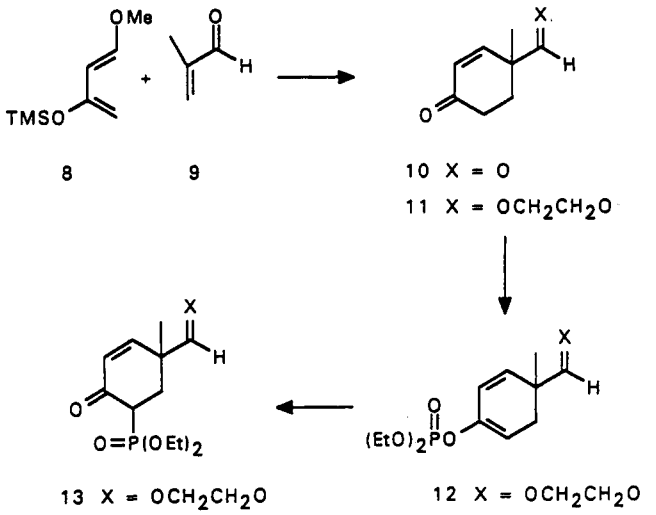
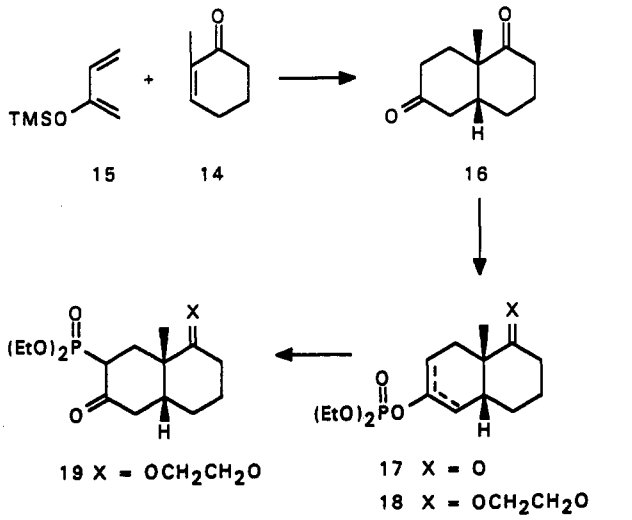
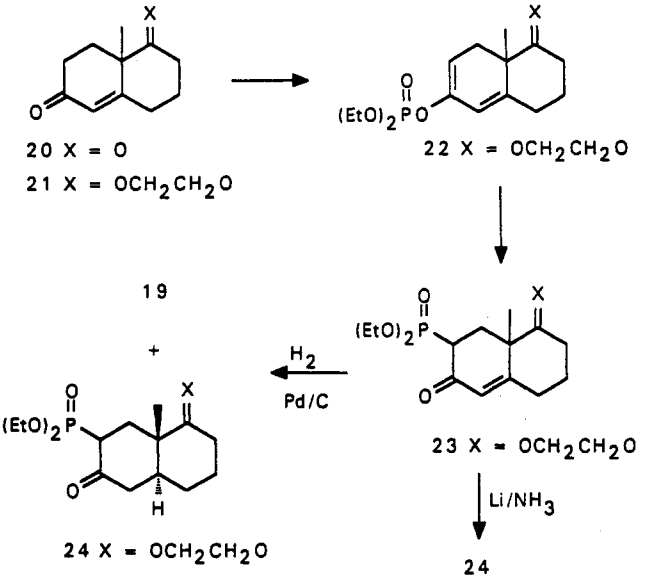


a relatively unreactive dienophile,[6,7] were frustrated by low yields, but the known dione **16** was prepared in modest yield through cycloaddition of enone **14** and siloxy diene **15**.[6-8] Treatment of this dione with LDA and diethyl



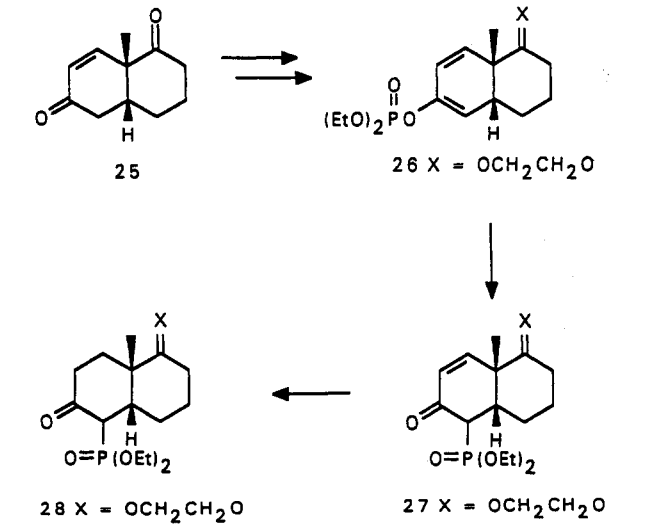
phosphorochloridate favored formation of the A-ring phosphates **17**, but no rearrangement was detected upon subsequent treatment of these vinyl phosphates with excess LDA. However, the corresponding ketals (**18**) were obtained in good yield by reaction with ethylene glycol and PPTS, with no appreciable hydrolysis of the vinyl phosphate. Treatment of these ketals with LDA gave the 2-phosphono compound **19** as a mixture of diastereomers, although the predominant product was isolated in only 27% yield.

To verify the regiochemical assignment of compound **19**, parallel sequences were explored with the regioisomeric enones **20**[9] and **25**,[6] where formation of vinyl anions from the dienyl phosphates would be expected to result in regiocontrolled rearrangements.[5] After preparation of an acetal derivative (**21**) of Wieland–Miescher ketone (**20**),[10] this enone was converted to dienyl phosphate **22**. As expected, rearrangement of the dienyl phosphate proved more facile and gave the single regioisomer **23**. Reduction



of phosphono enone **23** with H_2–Pd/C gave a mixture of two phosphonates in a 2:1 ratio and virtually quantitative yield. The major isomer was identical to compound **19**, and so must be the C-2 phosphonate (steroid numbering) with a cis-fused decalin system. The minor isomer was assigned trans-fused structure **24**.

The regioisomeric enone **25**[6] was converted to dienyl phosphate **26** by an analogous series of reactions. When phosphate **26** was treated with LDA, β-keto phosphonate **27** was obtained as a single regioisomer in 80% yield (ca. 6:4 ratio of diastereomers). Upon catalytic hydrogenation, this enone was reduced to the corresponding β-keto phosphonate **28** in quantitative yield. This sequence provides facile access to the cis-fused 4-phosphonodecalin series.



To complete the obvious set, we explored preparation of phosphonate derivatives of the analogous trans-fused decalins. Reduction of Wieland–Miescher ketone and some protected derivatives with Li/NH_3 is known to provide the trans-fused ring systems.[11] With enone **21**, this reduction, followed by trapping the intermediate enolate with diethyl phosphorochloridate, proved to be an expeditious route to vinyl phosphate **29**. Treatment of compound **29** with LDA under the standard rearrangement

(7) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056.
(8) Danishefsky, S.; Kitahara, T. *J. Org. Chem.* **1975**, *40*, 538.
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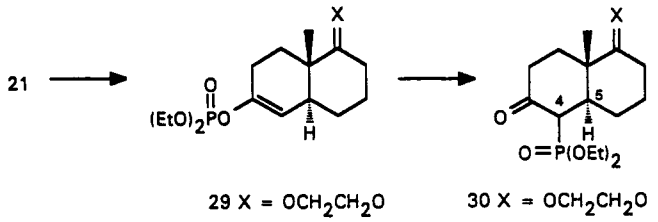
(10) Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 478.
(11) Dutcher, J. S.; Macmillan, J. G.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2663. Gopalakrishnan, G.; Jayaraman, S.; Rajagopalan, K.; Swaminathan, S. *Synthesis* **1983**, 797.

conditions gave a surprising 58% yield of phosphonate **30**.



29 X = OCH_2CH_2O 30 X = OCH_2CH_2O

Initially, this regiochemistry was assigned on the basis of ^1H NMR data, because a clean doublet of doublets (J_{HP} = 17.7 Hz, J = 12.6 Hz) was observed for the C-4 hydrogen. Upon irradiation of the ^{31}P resonance, this signal collapsed to a simple doublet, reflecting only diaxial coupling with the C-5 hydrogen. This assignment was confirmed when comparison of ^1H NMR data clearly indicated that this compound was *not* identical to compound **24**, the minor, trans-fused product obtained from catalytic hydrogenation of phosphono enone **23**. Specifically, the C-2 hydrogen in compound **24** shows discrete coupling to both the axial and equatorial hydrogens at C-1 (J_{PH} = 27.9 Hz, J = 13.7, 6.0 Hz). Ultimately, compound **24** proved to be more readily available by treatment of phosphonate **23** with Li/NH_3, because the only phosphonate produced by this reaction has the trans-fused skeleton.

Even though the isolated yield for the rearrangement leading to phosphonate **30** is modest, this short sequence provides facile access to the trans-fused 4-phosphonodecalin series. Thus, 4-phosphono derivatives of decalindiones now are readily available in both the cis- and trans-fused systems; 2-phosphono compounds now are accessible in the cis-fused series and are readily prepared in the isomeric trans-fused series.

These studies have shown that the vinyl phosphate/β-keto phosphonate rearrangement can be used to prepare specific phosphonate regioisomers in functionalized cyclohexanones and common decalin systems. While rearrangement was not observed in the presence of unprotected carbonyl groups, the stability of vinyl phosphates to mild ketalization conditions allows selective protection of remote ketones or aldehydes. Because the vinyl phosphate itself can be viewed as a protected carbonyl group, and because β-keto phosphonates can be transformed into α,β-unsaturated systems and other common functionality, it is possible to envision application of this rearrangement in preparation of a variety of natural products.

Experimental Section

THF was distilled from sodium/benzophenone immediately prior to use, and all reactions in this solvent were conducted under a positive pressure of an inert gas. For standard workup, reaction mixtures were diluted with ether, quenched by addition of brine, aqueous NH_4Cl, or acetic acid, the aqueous layer was extracted with ether, and the combined organic extracts were dried over Na_2SO_4 or $MgSO_4$. All of the following compounds were isolated as oils. Unless otherwise noted, NMR spectra were recorded with $CDCl_3$ as solvent. For ^1H and ^{13}C spectra, TMS and/or $CDCl_3$ were used as internal standard; ^{31}P chemical shifts are reported in ppm relative to H_3PO_4 as an external standard. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV; only selected ions are reported here. High-resolution mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. Microanalyses were conducted by Galbraith Laboratories, Knoxville, TN.

Ketal 4. Vinyl phosphate **3**[3,4] (2.07 g, 7.5 mmol) was added to a solution of PPTS (0.38 g, 1.5 mmol) and ethylene glycol (1.86 g, 30 mmol) in benzene (15 mL). The reaction mixture was heated at reflux for 6 h with a Dean–Stark trap, allowed to cool to rt, and then concentrated in vacuo. After addition of ether (100 mL), this solution was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL) and dried ($MgSO_4$). Concentration in vacuo and purification by flash column chromatography gave ketal **4** (2.28 g, 95%): ^1H NMR δ 5.49 (br, 1), 4.14 (m, 4), 3.91 (s, 4), 2.37–1.55 (m, 7), 1.34 (t, J = 7.0 Hz, 6), 1.25 (s, 3); ^{13}C NMR 146.9 (d, J_{CP} = 8.8 Hz), 110.5, 109.3 (d, J_{CP} = 5.8 Hz), 64.2, 63.5 (d, J_{CP} = 5.9 Hz), 41.4, 24.3, 23.0, 20.5, 15.5 (d, J_{CP} = 7.3 Hz), 13.5; ^{31}P NMR −7.47; EIMS m/z (rel intensity) 321 (M^+ + 1, 2), 320 (M^+, 3), 305 (9), 258 (47), 233 (29), 230 (16), 229 (18), 99 (66), 87 (100), 43(88). Anal. Calcd for $C_{14}H_{25}O_6P·0.25H_2O$: C, 51.77; H, 7.91. Found: C, 51.87; H, 7.87.

Phosphonate 5. A solution of ketal **4** (0.80 g, 2.5 mmol) in 1 mL of THF was added to a solution of LDA (2.3 equiv, in 3 mL THF) at −78 °C. After being stirred for 2 h, the reaction was allowed to warm to −60 °C and stirred for another 2 h. The reaction was then quenched by addition of glacial acetic acid (1 M in ethyl ether), and the resulting solution was filtered and dried ($MgSO_4$). After concentration in vacuo, the crude product was purifed by flash column chromatography (60% heptane, 30% ether, 10% acetone) to give compound **5** (0.54 g, 67%) as a mixture of phosphonate epimers and the enol tautomer: ^1H NMR δ 8.90 (br, enol tautomer), 4.25–3.93 (m, 8), 3.08–1.55 (m, 8), 1.37–1.26 (m, 9); ^{13}C NMR δ 205.9 (br), 205.8 (d, J_{CP} = 6.8 Hz), 169.4 (d, J_{CP} = 5.7 Hz), 110.4 (d, J_{CP} = 23.3 Hz), 88.5, 86.6, 65.0, 62.6 (d, J_{CP} = 6.4 Hz), 62.5 (d, J_{CP} = 6.1 Hz), 62.2 (d, J_{CP} = 6.8 Hz), 61.8 (d, J_{CP} = 6.1 Hz), 61.5 (d, J_{CP} = 4.5 Hz), 49.5 (d, J_{CP} = 124.9 Hz), 49.2 (d, J_{CP} = 146.4 Hz), 44.7 (d, J_{CP} = 13.4 Hz), 42.5 (d, J_{CP} = 9.9 Hz), 40.9 (d, J_{CP} = 7 Hz), 40.3, 40.0, 29.3 (d, J_{CP} = 14.7 Hz), 28.5 (br), 27.7 (d, J_{CP} = 5.7 Hz), 26.8, 26.6, 24.0, 23.1, 22.8, 21.1, 21.0, 16.3 (m); ^{31}P NMR ($CDCl_3$) +26.99 (enol tautomer), +23.55, +22.87 (cis, trans isomers), ($NaOCD_3$–CD_3OD) +33.5 ppm; EIMS m/z (rel intensity) 320 (M^+, 2), 305 (2), 233 (2), 87 (100). Anal. Calcd for $C_{14}H_{25}O_6P$: C, 52.50; H, 7.87. Found: C, 52.39; H, 7.56.

Phosphate 12. Compound **11**[12] (0.364 g, 2 mmol, in 1 mL of THF) was added to an LDA solution (1 equiv in 10 mL of THF) at −75 °C. Over a 2-h period, the temperature was allowed to warm to 0 °C, and the reaction mixture was kept at this temperature for an additional hour. The reaction mixture then was cooled to −75 °C, diethyl phosphorochloridate (360 mg, 2.10 mmol) was added, and the temperature was maintained at −75 °C for 4 h. After it had warmed to rt, the reaction mixture was quenched by addition of brine (75 mL). Standard workup and purification by column chromatography (60% hexane, 30% ether, 10% acetone) afforded compound **12** (0.53 g, 83%): ^1H NMR δ 5.84 (dd, J = 10.1, 2.0 Hz, 1), 5.73 (d, J = 10.1 Hz, 1), 5.42–5.38 (m, 1), 4.71 (s, 1), 4.17 (dq, J_{HP} = 15.1 Hz, J = 7.1 Hz, 4), 3.98–3.85 (m, 4), 2.58 (ddd, J = 17.5, 3.7, 3.7 Hz, 1), 2.10 (ddd, J = 17.5, 5.9, 2.2 Hz, 1), 1.35 (t, J = 7.1 Hz, 6), 1.03 (s, 3); ^{13}C NMR 143.9 (d, J_{CP} = 8.5 Hz), 134.2, 121.9 (d, J_{CP} = 6.0 Hz), 107.6, 105.8 (d, J_{CP} = 5.0 Hz), 65.2, 64.1 (d, J_{CP} = 6.0 Hz), 38.5, 29.6, 19.0, 15.9 (d, J_{CP} = 6.4 Hz); ^{31}P NMR −5.46; EIMS m/z (rel intensity) 318 (M^+, 2), 245 (2), 108 (3), 91 (13), 73 (100). Anal. Calcd for $C_{14}H_{23}O_6P·0.5H_2O$: C, 51.37; H, 7.39. Found: C, 51.44; H, 7.21.

Phosphonate 13. Compound **12** (0.318 g, 1.0 mmol) was treated with LDA as described for compound **5**, but the reaction temperature was allowed to warm to −5 °C over 3 h. After an additional 2 h at −5 °C, the mixture was allowed to warm to rt and quenched by addition of brine. Standard workup and purification by column chromatography (50% ether, 50% chloroform) gave compound **13** (0.20 g, 63%) as a mixture of diastereomers (56:44) and the enol tautomer (^{31}P NMR 26.9); EIMS m/z (rel intensity) 318 (M^+, 0.7), 246 (5), 108 (14), 91 (10), 74 (5), 73 (100), 45 (28). Anal. Calcd for $C_{14}H_{23}O_6P$: C, 52.83; H, 7.28. Found: C, 52.44; H, 7.32.

Major diastereomer: ^1H NMR δ 6.85 (dd, J = 10.3, 1.8 Hz, 1), 6.40 (dd, J = 10.3, 1.6 Hz, 1), 4.80 (s, 1), 4.30–4.12 (m, 4), 4.10–3.81 (m, 4), 3.47 (ddd, J_{HP} = 22.7 Hz, J = 11.5, 6.0 Hz, 1), 2.44–2.34 (m, 2), 1.34 (t, J = 7.1 Hz, 6), 1.20 (s, 3); ^{31}P NMR +24.72; ^{13}C NMR δ 192.8 (d, J_{CP} = 6.9 Hz), 152.0, 130.2 (d, J_{CP} = 5.2 Hz), 107.4, 65.5, 65.1, 62.3, 43.6 (d, J_{CP} = 72.3 Hz), 40.2, 29.5 (d, J_{CP} = 6.3 Hz), 18.3, 16.2. Minor diastereomer: ^1H NMR δ 6.06 (dd, J = 10.2, 2.9 Hz, 1), 5.98 (dd, J = 10.2, 3.4 Hz, 1), 4.70 (s, 1), 4.30–4.12 (m, 4), 4.10–3.81 (m, 4), 3.08 (ddd, J_{HP} = 25.5 Hz, J =

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14.4, 5.1 Hz, 1), 2.14–2.02 (m, 2), 1.34 (t, J = 7.1 Hz, 6), 1.22 (s, 3); ^{31}P NMR +24.44; (minor) ^{13}C NMR 193.3 (d, J_{CP} = 6.7 Hz), 152.5, 128.6 (d, J_{CP} = 4.2 Hz), 108.2, 65.4, 64.7, 61.7 (d, J_{CP} = 7.0 Hz), 41.7 (d, J_{CP} = 75.7 Hz), 39.1 (d, J_{CP} = 11.5 Hz), 32.0 (d, J_{CP} = 3.7 Hz), 23.5, 16.2.

Vinyl Phosphates 17. 9-Methyloctalin-1,6-dione[7] (0.36 g, 2.0 mmol, in 5 mL of THF) was added dropwise to an LDA solution (1 equiv, 30 mL THF) at −75 °C. The reaction mixture was allowed to warm to −45 °C and to stand at this temperature for 2 h. Diethyl phosphorochloridate (0.345 g, 2.0 mmol, in 5 mL of THF) was added, the reaction was allowed to stir for 6 h, and then was warmed to rt. After the reaction was quenched by addition of saturated NH_4Cl, standard workup and purification by column chromatography gave vinyl phosphate **17** (0.29 g, 46%): ^{1}H NMR δ 5.28 (br, 1), 4.18–4.07 (m, 4), 2.70–1.64 (m, 11), 1.34 (t, J = 7.0 Hz), 1.19 (s, 3); ^{31}P NMR −5.47, −5.62; ^{13}C NMR δ 213.8, 148.1 (d, J_{CP} = 8.8 Hz), 113.3 (d, J_{CP} = 5.1 Hz), 106.4 (d, J_{CP} = 5.4 Hz), 63.8 (d, J_{CP} = 6.0 Hz), 63.2 (d, J_{CP} = 5.8 Hz), 46.2, 42.2, 41.6, 38.2, 36.7, 30.5, 27.2, 24.7, 24.6, 23.8, 22.5, 15.7 (d, J_{CP} = 6.9 Hz); EIMS m/z (rel intensity) 317 (M^+ + 1, 8), 316 (M^+, 47), 301 (8), 245 (32), 189 (39), 162 (100), 147 (57), 134 (50), 127 (73), 119 (63), 106 (30), 105 (55), 99 (95), 91 (100), 81 (61); HRMS calcd for $C_{15}H_{25}O_5P$ 316.1441, found 316.1422.

Ketal 18. According to the procedure described for preparation of compound **4**, vinyl phosphate **17** (0.21 g, 0.67 mmol) was treated with PPTS (0.05 g, 0.20 mmol) and ethylene glycol (0.21 g, 3.33 mmol) in benzene (10 mL). After 6 h at reflux, standard workup gave ketal **18** (0.17 g, 71%), which was used for the subsequent reaction without further purification: ^{1}H NMR δ 5.47 (br, 1), 4.14 (m, 4), 3.94 (s, 4), 1.34 (t, J = 7.1 Hz, 6), 0.94 (s, 3); ^{13}C NMR 146.1 (d, J_{CP} = 7.3 Hz), 114.5, 112.2, 64.7, 63.9, 40.2, 30.6, 30.0, 25.1, 24.0, 22.3, 16.0; ^{31}P NMR −5.96; EIMS m/z (rel intensity) 360 (M^+, 2), 345 (2), 315 (17), 287 (6), 206 (43), 189 (24), 163 (52), 155 (41), 144 (50), 113 (41), 105 (23), 100 (13), 99 (100), 91 (49), 86 (97), 81 (32); HRMS calcd for $C_{17}H_{29}O_6P$ 360.1703, found 360.1685.

Phosphonate 19. Ketal **18** (150 mg, 0.42 mmol, in 1 mL of THF) was added to a solution of LDA (2.3 equiv, 5 mL of THF) at −60 °C. After 19 h, the reaction mixture was allowed to warm to rt and then quenched by addition of glacial acetic acid (1 M in ether). Purification by column chromatography (60% hexane, 30% ether, 10% acetone) gave phosphonate **19** as a mixture of epimers and the enol tautomer (total 40.5 mg, 27%): ^{1}H NMR δ 10.85 (s, enol tautomer), 4.25–3.90 (m, 4), 3.97 (s, 2), 3.96 (s, 2), 3.02 (ddd, J_{HP} = 21.6, J = 13.3, 6.3 Hz, 1), 2.76–1.40 (m, 11), 1.34 (t, J = 7.1 Hz, 6), 0.93 (s, 3); ^{31}P NMR +27.92, +25.49; ^{13}C NMR δ 206.2, 167.5 (d, J_{CP} = 5.7 Hz), 112.1 (d, J_{CP} = 22.7 Hz), 84.6, 84.0, 65.2, 64.9, 61.5 (d, J_{CP} = 4.3 Hz), 44.9 (d, J_{CP} = 31.1 Hz), 41.9 (d, J_{CP} = 62.2 Hz), 40.6, 40.5, 37.7, 32.8, 32.6, 30.2, 29.5, 28.8, 28.1, 27.3, 27.2, 22.6, 22.4, 17.8, 17.2, 16.5, 16.4, 16.3, 16.2; EIMS m/z (rel intensity) 361 (M^+ + 1, 9), 360 (M^+, 62), 345 (16), 315 (100), 234 (35), 245 (68), 189 (62), 161 (31), 111 (41), 109 (42), 107 (31), 99 (63), 86 (78), 55 (45); HRMS calcd for $C_{17}H_{29}O_6P$ 360.1703, found 360.1716.

Vinyl Phosphate 22. Compound **21**[10] (0.666 g, 3.0 mmol, in 2 mL of THF) was treated with LDA and diethyl phosphorochloridate (0.535 g, 3.1 mmol) as described for compound **12** and then quenched by addition of brine. Standard workup and purification by column chromatography gave compound **22** (0.84 g, 78%): ^{1}H NMR δ 5.55 (br, 1), 5.35 (ddd, J_{HP} = 6.7 Hz, J = 2.8, 1.1 Hz, 1), 4.15 (dq, J_{HP} = 14.6 Hz, J = 7.3 Hz, 4), 4.03–3.87 (m, 4), 2.84 (dm, J = 17.4, 1), 2.37–2.17 (m, 2), 1.92 (ddd, J = 17.4, 6.8, 1.5 Hz, 1), 1.81–1.53 (m, 4), 1.34 (t, J = 7.1 Hz, 6), 1.15 (s, 3); ^{13}C NMR 146.4, 142.8 (d, J_{CP} = 7.7 Hz), 116.7 (d, J_{CP} = 6.1 Hz), 112.0, 104.3 (d, J_{CP} = 5.1 Hz), 64.8, 64.5, 64.0 (d, J_{CP} = 6.0 Hz), 43.7, 29.8, 29.5, 28.0, 21.7, 19.6, 15.9 (d, J_{CP} = 6.0 Hz); ^{31}P NMR −5.45; EIMS m/z (rel intensity) 358 (M^+, 6), 357 (15), 281 (3), 267 (5), 239 (17), 207 (5), 177 (3), 115 (7), 99 (100), 91 (14); HRMS calcd for $C_{17}H_{27}O_6P$ 358.1546, found 358.1557.

Phosphonate 23. Vinyl phosphate **22** (358 mg, 1.0 mmol) in THF (2 mL) was added to an LDA solution (2.3 equiv, in 10 mL of THF) at −75 °C. The reaction was allowed to warm to −15 °C over 1 h and to stand at this temperature for 3 h and then was quenched by addition of brine. After standard workup and purification by column chromatography (50% ether, 50% chloroform), compound **23** (250 mg, 70%) was obtained as a 4:1 mixture of diastereomers along with the enol tautomer (^{31}P NMR 27.5): EIMS m/z (rel intensity) 359 (M^+ + 1, 1), 358 (M^+, 5), 100 (16), 99 (100), 91 (27), 55 (41). Anal. Calcd for $C_{17}H_{27}O_6P \cdot 0.5H_2O$: C, 55.58; H, 7.68. Found: C, 55.65; H, 7.50.

Major diastereomer: ^{1}H NMR δ 5.81 (dd, J = 3.5, 1.7 Hz, 1), 4.30–4.09 (m, 4), 4.08–3.92 (m, 4), 2.96 (ddd, J_{HP} = 19.5 Hz, J = 10.8, 4.4 Hz, 1), 2.64–2.18 (m, 4), 2.05–1.75 (m, 4), 1.37 (s, 3), 1.34 (t, J = 7.1 Hz, 6); ^{31}P NMR +24.44; ^{13}C NMR δ 192.4 (d, J_{CP} = 6.6 Hz), 167.4, 125.4 (d, J_{CP} = 6.5 Hz), 111.5, 65.1, 64.7, 62.1 (d, J_{CP} = 6.8 Hz), 44.5 (d, J_{CP} = 35.6 Hz), 30.8, 29.6, 27.9, 21.1, 19.7, 16.2.

Minor diastereomer: ^{1}H NMR δ 5.88 (dd, J = 2.9, 1.4 Hz, 1), 4.30–4.09 (m, 4), 4.08–3.92 (m, 4), 3.47 (ddd, J_{HP} = 22.0 Hz, J = 12.7, 5.7 Hz, 1), 2.64–2.18 (m, 4), 2.05–1.75 (m, 4), 1.35 (s, 3), 1.33 (t, J = 7.1 Hz, 6); ^{31}P NMR +25.93; ^{13}C NMR 193.5 (d, J_{CP} = 4.1 Hz), 166.4, 124.7 (d, J_{CP} =6.4 Hz), 114.2, 65.3, 64.5, 61.7 (d, J_{CP} = 6.5 Hz), 44.7 (d, J_{CP} = 39.2 Hz), 43.4, 31.3, 29.7, 23.3, 16.2, 15.0.

Hydrogenation of Phosphonate 23. Compound **23** (100 mg, 0.280 mmol) in ethanol (10 mL) was hydrogenated over Pd/C (ca. 50 mg, 5%, 40 psi of H_2) at rt for 1.5 h. After filtration and concentration, a mixture of compounds **19** and **24** was obtained in an approximate ratio of 2:1 (100 mg, ca. 100%).

Phosphonate 24. Compound **23** (ca. 150 mg, prepared in situ, in 2 mL of THF) was added to a solution of lithium (21 mg, 3.0 mmol) in 30 mL of NH_3 at reflux. The reaction was maintained at this temperature for 1 h, and then THF (10 mL) was added. The NH_3 was allowed to evaporate, and saturated NH_4Cl (10 mL) was added. Standard workup and purification by radial chromatography (70% hexane, 30% ethyl acetate) gave phosphonate **24** (57 mg, 38% overall yield from **22**; approximately 54% for the Li/NH_3 reduction) and the C-1 ketal of *trans*-9-methyloctalin-1,6-dione[13] (10 mg, 11%). Compound **24**: ^{1}H NMR δ 10.73 (br enol tautomer), 4.30–4.02 (m, 4), 4.00–3.85 (m, 4), 2.97 (ddd, J_{HP} = 27.9 Hz, J = 13.7, 6.0 Hz, 1), 2.30–1.40 (m, 11), 1.34 (t, J = 6.8 Hz, 6), 0.98 (s, 3); ^{31}P NMR +28.7, +25.8; ^{13}C NMR δ 205.2 (d, J_{CP} = 7.5 Hz), 167.9 (d, J_{CP} = 5.6 Hz), 111.9 (d, J_{CP} = 10.5 Hz), 87.8, 85.4, 65.1, 64.6, 62.1 (d, J_{CP} = 35.7 Hz), 61.6 (d, J_{CP} = 4.5 Hz), 47.3, 45.4, 44.5, 42.7, 41.9, 41.7, 41.3, 40.8, 40.7, 36.6, 33.2, 33.0, 30.3, 28.5, 28.4, 27.8, 27.4, 22.6, 22.3, 16.5 (d, J_{CP} = 6.2 Hz), 16.3 (d, J_{CP} = 6.8 Hz), 13.6, 13.3; EIMS m/z (rel intensity) 360 (M^+, 8), 345 (6), 315 (18), 299 (27), 245 (20), 189 (33), 109 (40), 99 (90), 86 (100), 43 (92); HRMS calcd for $C_{17}H_{29}O_6P$ 360.1703, found 360.1698.

Dienyl Phosphate 26. Compound **25** (356 mg, 2.0 mmol) was treated with ethylene glycol (136 mg, 2.2 mmol) and PPTS (0.15 g, 0.6 mmol) in benzene (15 mL), as described for compound **4**, to obtain the B-ring ketal (300 mg, 68%). Without further purification, this ketal (300 mg, 1.35 mmol, in 1 mL of THF) was treated with LDA and diethyl phosphorochloridate (236 mg, 1.37 mmol), and the reaction mixture was then quenched by addition of saturated NH_4Cl. Standard workup and purification by column chromatography (50% ethyl ether, 50% chloroform) gave **26** (340 mg, 70%): ^{1}H NMR δ 5.99 (d, J = 10.1 Hz, 1), 5.82 (dd, J = 10.1, 0.8 Hz, 1), 5.51 (br d, J = 6.8 Hz, 1), 4.25–4.05 (m, 4), 4.00–3.90 (m, 4), 2.26 (ddd, J = 12.4, 6.8, 5.6 Hz, 1), 1.80–1.40 (m, 6), 1.35 (t, J = 5.5 Hz, 6), 1.00 (s, 3); ^{13}C NMR 144.3 (d, J_{CP} = 5.9 Hz), 135.7, 120.9 (d, J_{CP} = 5.9 Hz), 112.5 (d, J_{CP} = 5.9 Hz), 110.8, 65.2, 64.8, 64.3 (d, J_{CP} = 7.5 Hz), 44.4, 40.1, 32.8, 27.3, 20.4, 16.7, 16.0 (d, J_{CP} = 7.5 Hz); ^{31}P NMR −6.04; EIMS m/z (rel intensity) 358 (M^+, 0.8), 343 (1.6), 270 (10), 244 (19), 114 (40), 91 (20), 87 (29), 86 (100); HRMS calcd for $C_{17}H_{27}O_6P$ 358.1546, found 358.1530.

Phosphonate 27. Compound **26** (55 mg, 0.154 mmol, in 1 mL of THF) was treated with LDA (2.3 equiv in 5 mL of THF) as described for compound **23**. Standard workup and purification by column chromatography (silica gel, 50% ethyl ether, 50% chloroform) provided compound **27** (45 mg, 80%) as a mixture of diastereomers in a ratio of 62:38 as measured by ^{1}H NMR: ^{13}C NMR δ 193.5 (d, J_{CP} = 5.5 Hz), 163.5 (d, J_{CP} = 7.4 Hz), 153.7, 153.1, 142.5, (d, J_{CP} = 24.6 Hz), 130.1, 127.9 (d, J_{CP} = 6.5 Hz), 122.2, 122.0, 112.0, 110.8, 110.4, 90.1, 88.6, 65.4, 65.1 (d, J_{CP} = 39.3 Hz), 65.0, 62.7 (d, J_{CP} = 7.3 Hz), 62.2 (d, J_{CP} = 6.7 Hz), 61.9 (d, J_{CP} = 6.7 Hz), 61.6, 56.2, 50.2, 48.2, 46.3, 46.1, 45.3, 45.2, 42.8, 40.7, 39.5, 39.5, 32.8, 32.7, 30.8, 27.8, 24.5, 22.6, 21.7, 20.7, 19.4, 18.8, 17.1, 16.5 (d, J_{CP} = 6.4 Hz), 16.3 (d, J_{CP} = 6.4 Hz); EIMS m/z

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(rel intensity) 358 (M^+, 0.5), 313 (0.2), 244 (5), 221 (7), 114 (19), 87 (8), 86 (100); HRMS calcd for $C_{17}H_{27}O_6P$ 358.1546, found 358.1549.

Major diastereomer: ^1H NMR δ 6.93 (dd, J = 10.3, 2.1 Hz, 1), 5.94 (dd, J = 10.3, 4.2 Hz, 1), 4.35–4.10 (m, 4), 4.03–3.97 (m, 4), 3.40 (dd, J_{HP} = 27.2 Hz, J = 3.7 Hz, 1), 2.59 (m, 1), 1.80–1.54 (m, 6), 1.33 (t, J = 7.0 Hz, 6), 1.23 (s, 3); ^{31}P NMR +24.9.

Minor diastereomer: ^1H NMR δ 6.31 (br d, J = 9.9 Hz, 1), 5.89 (dd, J = 9.9, 5.9 Hz, 1), 4.20–4.03 (m, 4), 4.03–3.97 (m, 4), 3.10 (dd, J_{HP} = 28.4 Hz, J = 9.8 Hz, 1), 2.27 (dddd, J_{HP} = 12.2 Hz, J = 10.7, 4.5, 1.6 Hz, 1), 1.80–1.54 (m, 6), 1.34 (t, J = 7.5 Hz, 6), 1.05 (s, 3); ^{31}P NMR +24.7.

Enol tautomer: ^1H NMR δ 10.55 (s), 6.65 (d, J = 10.2 Hz), 6.10 (d, J = 9.8 Hz), 2.04 (br d, J = 10.5 Hz); ^{31}P NMR +27.6.

Phosphonate 28. Under conditions analogous to those described for hydrogenation of compound **23**, compound **27** (13 mg, 0.0363 mmol) was hydrogenated to obtain compound **28** (13 mg, ca. 100%): ^1H NMR δ 10.94 (br, enol tautomer), 4.25–4.00 (m, 4), 3.98–3.90 (m, 4), 3.32 (dd, J_{HP} = 13.0, J = 4.2 Hz, 1), 2.80–1.60 (m, 11), 1.34 (t, J = 7.0 Hz, 6), 0.91 (s, 3); ^{31}P NMR +28.7 (enol tautomer), +25.0, +24.8; ^{13}C NMR δ 206.4 (d, J_{CP} = 6.2 Hz), 169.6 (d, J_{CP} = 6.3 Hz), 112.5, 93.7, 91.4, 65.0, 64.9, 62.0 (d, J_{CP} = 6.4 Hz), 61.6 (d, J_{CP} = 4.6 Hz), 61.5 (d, J_{CP} = 5.5 Hz), 54.1, 52.1, 45.0, 40.9, 40.8, 39.9, 39.8, 38.7, 37.0, 30.6, 30.4, 29.8, 29.7, 29.5, 28.9, 28.6, 26.4, 26.2, 23.7, 23.4, 23.0, 22.7, 16.5 (d, J_{CP} = 6.0 Hz), 16.4 (d, J_{CP} = 6.8 Hz), 16.2 (d, J_{CP} = 7.2 Hz), 14.1, 14.0; EIMS m/z (rel intensity) 360 (M^+, 9), 342 (3), 315 (9), 223 (23), 222 (41), 113 (24), 99 (48), 86 (100); HRMS calcd for $C_{17}H_{29}O_6P$ 360.1703, found 360.1714.

Phosphate 29. To a solution of lithium (87 mg, 12.5 mmol) in liquid ammonia (40 mL) was added a solution of ketal **21** (0.506 g, 2.25 mmol, in 10 mL of THF) via syringe pump. Once the addition was complete, the reaction mixture was stirred for 30 min, THF (15 mL) was added, and the reaction mixture was heated at reflux for 2 h. The reaction mixture was allowed to cooled to rt, diethyl phosphorochloridate (4.58 g, 26 mmol) was added as quickly as possible, and the resulting mixture was heated at reflux for 1 h. Purification of the crude product by flash chromatography (60% hexane, 40% EtOAc) gave 0.37 g (53%) of phosphate **29**: ^1H NMR δ 5.16 (br, 1), 4.15 (m, 4), 3.92 (m, 4), 2.47 (m, 1), 2.22 (m 2), 1.84–1.46 (m, 8), 1.35 (t, J = 6.8 Hz, 6), 0.96 (s, 3); ^{13}C NMR 146.0 (d, J_{CP} = 9.3 Hz), 113.7 (d, J_{CP} = 6.1 Hz), 112.0, 64.8, 63.8 (d, J_{CP} = 6.0 Hz), 40.5, 39.2, 30.2, 26.7, 26.2, 25.1, 22.8, 15.8 (d, J_{CP} = 6.1 Hz), 13.2; ^{31}P NMR −5.55; EIMS m/z (rel intensity) 360 (M^+, 5.8), 345 (6.9), 260 (23), 163 (36), 144 (33), 127 (18), 113 (28), 99 (100), 86 (66), 81 (27), 69 (15), 55 (28); HRMS calcd for $C_{17}H_{29}O_6P$ 360.1703, found 360.1727.

Phosphonate 30. Vinyl phosphate **29** (216 mg, 0.60 mmol) was added to a solution of LDA (2.3 equiv) in THF (20 mL) at −20 °C, and the reaction mixture was stirred at −20 °C for 3 h. After the reaction was quenched by addition of brine, standard workup and purification by flash column chromatography (50% hexane, 50% EtOAc) gave compound **30** (137 mg, 58%): ^1H NMR δ 10.72 (enol tautomer), 4.36–4.08 (m, 4), 4.03–3.80 (m, 4), 3.04 (dd, J_{HP} = 17.7 Hz, J = 12.6 Hz, 1), 2.73–1.48 (m, 11), 1.35 (t, J = 7.6 Hz, 6), 0.97 (s, 3); ^{31}P NMR +25.4, +24.0; ^{13}C NMR δ 208.9, 208.0 (d, J_{CP} = 6.2 Hz), 174.0, 120.0, 112.2, 65.2, 64.9, 62.8 (d, J_{CP} = 7.2 Hz), 62.3 (d, J_{CP} = 7.0 Hz), 61.5, 54.1, 52.4, 42.0, 41.9, 41.4, 36.3, 29.9, 28.0, 27.6, 27.0, 24.0, 23.1, 22.6, 22.4, 20.6, 16.4 (d, J_{CP} = 8.7 Hz), 16.3 (d, J_{CP} = 6.1 Hz), 15.3, 14.9, 11.9; EIMS m/z (rel intensity) 360 (M^+, 2), 315 (4), 250 (24), 222 (20), 189 (13), 113 (39), 99 (100), 86 (65); HRMS calcd for $C_{17}H_{29}O_6P$ 360.1703, found 360.1721.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **17–19**, **22**, **24**, and **26–30** and ^{13}C NMR spectra of compounds **5**, **13**, and **23** as mixtures of diastereomers at the α-carbon and the respective enol forms (23 pages). Ordering information is given on any current masthead page.