Notes

Regiocontrolled Synthetic Approach to α,α′-Disubstituted Unsymmetrical Ketones

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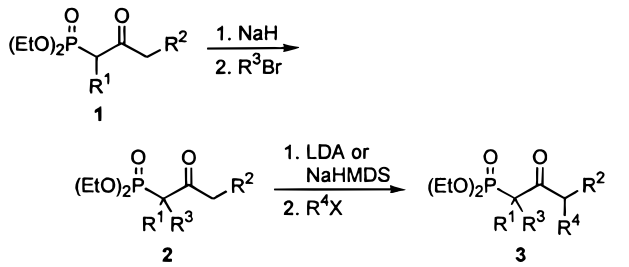
The regiospecific alkylation of ketones is a time-honored thesis in organosynthetic chemistry as a result of its difficulty arising from polyalkylation, nonregioselectivity, self-condensation, etc.[1] Many efforts have been made to seek efficient methods for the alkylation, many of which involve the introduction of a blocking group,[1a,b] the use of regioselective enol ethers as intermediates,[2−4] the employment of nitrogen derivatives of ketones,[5] or the utilization of a temporary activating group.[1a,6] Our research has focused on a potential procedure for the regiospecific α-alkylation of unsymmetrical ketones that relies upon phosphonate as an activating group.[7] We herein report the first synthetic approach to α,α′-disubstituted unsymmetrical ketones, whose four α-substituents are different from each other, via sequential alkylations and dephosphonylation of *β*-keto phosphonates as outlined in Scheme 1.

First, for preparation of the precursors to our desired ketone products, two consecutive alkylations[8] of *β*-keto phosphonates[9] were carried out step by step. Although it is possible to selectively alkylate the *γ*-carbon of the *β*-keto phosphonate first via the dianion with the active α-carbon left just as it is,[10] we selected the sequence of alkylating the α-carbon prior to the *γ*-carbon for higher yields. As a base, NaH was used for the α-alkylation, and NaHMDS (sodium hexamethyldisilazane) or LDA was used for the *γ*-alkylation. The α- and *γ*-alkylation reactions under the conditions of THF, room temperature, and 2−5 h gave **2** and **3**, respectively, in good yields (Table 1).[11] Products of O-alkylation were not obtained in any case.

Use of excess alkyl halides with equivalent bases resulted in shortening of the reaction times and heightening of the yields without formation of side products resulting from dialkylation. The *γ*-phenyl group of substrate **1d** activates the *γ*-carbon as well, and therefore the formation of α-enolate competes with that of *γ*-enolate on treatment with base. Actually, the first alkylation

Table 1. Preparation of the Precursors 3 by Two Successive Alkylations of *β*-Keto Phosphonates 1



entry	substrate: R^1, R^2, (R^3)	R^3Br/R^4X	product: yield (%)[a]
1	**1a**: *n*-Bu, Me	$Me_2C{=}CHCH_2Br$	**2a**: 88
2	**1b**: allyl, Et	$PhCH{=}CHCH_2Br$	**2b**: 91
3	**1c**: Me, Et	$PhCH_2Br$	**2c**: 74
4	**1d**: *n*-Pr, Ph	$CH_2{=}CHCH_2Br$	**2d**[b]: 66
5	**1e**: $-(CH_2)_3-$	$PhCH{=}CHCH_2Br$	**2e**: 83[c]
6	**2a**: *n*-Bu, Me, prenyl	$PhCH_2Br$	**3a**: 95[d]
7	**2a**	EtI	**3b**: 86[d]
8	**2b**: allyl, Et, cinnamyl	$Me_2C{=}CHCH_2Br$	**3c**: 87[e]
9	**2b**	4-$MePhCH_2Br$	**3d**: 89[e]
10	**2c**: Me, Et, Bn	$MeCH{=}CHCH_2Br$	**3e**: 80[e]
11	**2d**[b]: *n*-Pr, Ph, allyl (R^4)	$PhCH{=}CHCH_2Br$	**3f**[f]: 94[d]
12	**2e**: $-(CH_2)_3-$, cinnamyl	MeI	**3g**: 68[d]

[a] Yield of isolated product after chromatography. [b] The unusual product has the allyl group at the *γ*-position. [c] NaHMDS was used instead of NaH as a base. [d] NaHMDS was used as a base. [e] LDA was used as a base. [f] The unusual product has the cinnamyl group at the α-position.

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(11) With phenylselenenyl bromide as an alkylating agent, the α-phenylselenenyl *β*-keto phosphonate was successfully obtained as a product of the first α-alkylation in 68% yield. However, treatment of this product with base for the second alkylation resulted in decomposition of it, yielding a complicated mixture.

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Scheme 1

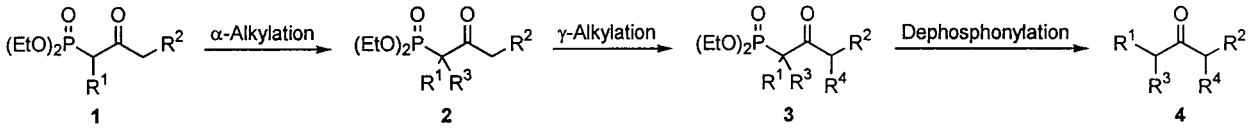
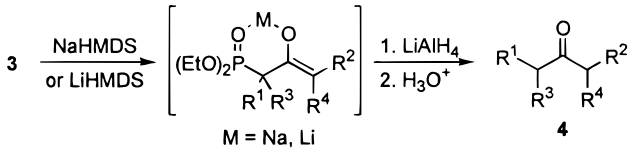


Table 2. Dephosphonylation of 3 into Ketones 4



substrate	R^1	R^2	R^3	R^4	product: yield (%)[a]
3a	*n*-Bu	Me	prenyl	Bn	**4a**: 71[b]
3b	*n*-Bu	Me	prenyl	Et	**4b**: 43[b]
3c	allyl	Et	cinnamyl	prenyl	**4c**: 53[c]
3d	allyl	Et	cinnamyl	4-MeBn	**4d**: 62[c]
3e	Me	Et	Bn	crotyl	**4e**: 45[c]
3f	*n*-Pr	Ph	cinnamyl	allyl	**4f**: 73[b]
3g	$-(CH_2)_3-$		cinnamyl	Me	**4g**: 55[b]

[a] Yield of isolated product after chromatography. [b] NaHMDS was used as a base. [c] LiHMDS was used as a base.

occurred at the γ-carbon unusually (entry 4). Furthermore, on being treated with base for the second alkylation (entry 11), **2d** underwent α-deprotonation although a γ-hydrogen remained, leading to α-alkylation against our expectation.

Dephosphonylation of the resultant precursors **3** affording the corresponding ketones **4** was accomplished by treatment of their sodium or lithium enolates with LAH (lithium aluminum hydride) followed by acidic quenching (Table 2). Compared with our previous results,[7] not only were the yields somewhat low but also the choice of the base was important. NaHMDS or LiHMDS was successfully employed as a base, but use of more common bases such as *n*-BuLi and LDA led to decomposition of **3** to give a complicated mixture. All of the ketone products except **4g**[2c] have four α-substituents that are different from each other. These substituents can be readily varied to the extent that β-keto phosphonates[9,10] and alkylating agents are available.

In conclusion, we have developed a regiocontrollable synthetic route to α,α′-disubstituted unsymmetrical ketones involving temporary use of phosphonate as an activating group. The procedure, containing two successive alkylations and dephosphonylation of β-keto phosphonates, is a complement of existing methods for the regiospecific alkylation of unsymmetrical ketones and furnishes ready access to structures not previously available in ketones.

Experimental Section

General. All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. THF was dried over and distilled from sodium metal with benzophenone as the indicator. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS (0 ppm), residual $CHCl_3$ (7.24 ppm), or solvent (77.0 ppm) as an internal standard. The starting β-keto phosphonates were prepared as described in the literature with minor modification.

General Procedure for the α-Alkylation of β-Keto Phosphonates. To a suspension of sodium hydride (0.060 g, 80%, 2.0 mmol) in dry THF (5 mL) under N_2 at room temperature was added β-keto phosphonate **1** (2.0 mmol) in dry THF (5 mL) slowly. The mixture was stirred until hydrogen evolution had ceased and the solution was homogeneous (ca. 1 h). Addition of the proper alkyl bromide (4.0 mmol) was followed by stirring of the reaction mixture for 2−4 h. An aqueous ammonium chloride solution (2 mL) was added, and the resulting solution was extracted with diethyl ether (30 mL × 3). The combined organic extracts were washed with water (5 mL × 2) and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on a silica gel column using an EtOAc/hexane mixture as eluent to give the pure product **2** as a colorless oil.

Phosphonate 2a. Using the general procedure described above and a reaction time of 4 h, **2a** was obtained (0.585 g, 88%) from **1a** (0.529 g, 2.0 mmol) and prenyl bromide (0.48 mL, 4.0 mmol) after chromatography (EtOAc/hexane, 35/65): ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H), 1.06−1.15 (m, 1H), 1.20−1.39 (several peaks, 9H), 1.61 (s, 3H), 1.65 (s, 3H), 1.80−1.90 (m, 2H), 2.57−2.68 (several peaks, 4H), 4.01−4.12 (m, 4H), 5.05 (br t, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.1, 13.8, 16.4 (d, J = 5.9 Hz), 17.9, 23.3, 26.0, 26.5 (d, J = 7.8 Hz), 29.2, 30.7 (d, J = 3.9 Hz), 33.0, 58.3 (d, J = 126.6 Hz), 62.3 (dd, J = 3.7, 7.3 Hz), 118.9 (d, J = 35.7 Hz), 133.9, 208.8.

Phosphonate 2b. Using the general procedure described above and a reaction time of 2 h, **2b** was obtained (0.689 g, 91%) from **1b** (0.525 g, 2.0 mmol) and cinnamyl bromide (0.813 g, 4.0 mmol) after chromatography (EtOAc/hexane, 35/65): ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.28 (t, J = 7.0 Hz, 6H), 1.59 (sextet, J = 7.3 Hz, 2H), 2.64−2.88 (several peaks, 6H), 4.05−4.15 (m, 4H), 5.07−5.14 (m, 2H), 5.72−5.85 (m, 1H), 6.13−6.24 (m, 1H), 6.43 (d, J = 15.8 Hz, 1H), 7.15−7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 16.4 (d, J = 5.8 Hz), 17.1, 34.4, 35.5, 42.0, 58.3 (d, J = 127.3 Hz), 62.5 (d, J = 7.2 Hz), 118.7, 125.1 (d, J = 8.6 Hz), 126.0, 127.1, 128.4, 132.9 (d, J = 9.8 Hz), 133.4, 137.3, 206.9.

Phosphonate 2c. Using the general procedure described above and a reaction time of 3 h, **2c** was obtained (0.483 g, 74%) from **1c** (0.473 g, 2.0 mmol) and benzyl bromide (0.48 mL, 4.0 mmol) after chromatography (EtOAc/hexane, 50/50): ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 7.3 Hz, 3H), 1.27−1.37 (several peaks, 9H), 1.52 (sextet, J = 7.3 Hz, 2H), 2.25−2.36 (m, 1H), 2.60−2.71 (m, 1H), 2.83 (dd, J = 10.4, 13.4 Hz, 1H), 3.67 (dd, J = 7.8, 13.5 Hz, 1H), 4.06−4.19 (m, 4H), 7.03−7.06 (m, 2H), 7.16−7.24 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 16.4 (d, J = 5.6 Hz), 16.5 (d, J = 5.2 Hz), 16.9, 38.5 (d, J = 4.7 Hz), 42.4, 55.0 (d, J = 125.6 Hz), 62.8 (dd, J = 7.4, 19.2 Hz), 126.7, 128.1, 130.4, 136.3 (d, J = 15.4 Hz), 208.4.

Phosphonate 2d. Using the general procedure described above and a reaction time of 4 h, unusually γ-alkylated **2d** was obtained (0.465 g, 66%) from **1d** (0.625 g, 2.0 mmol) and allyl bromide (0.35 mL, 4.0 mmol) after chromatography (EtOAc/hexane, 35/65): ^1H NMR (300 MHz, $CDCl_3$) δ 0.46−0.49 (m, 3H), 0.77−0.90 (m, 1H), 1.13−1.35 (several peaks, 7H), 1.39−1.50 (m, 1H), 1.84−1.95 (m, 1H), 2.42−2.52 (m, 1H), 2.73−2.83 (m, 1H), 3.22 (ddd, J = 3.1, 10.9, 25.4 Hz, 1H), 4.01−4.15 (m, 5H), 4.87−5.01 (m, 2H), 5.55−5.68 (m, 1H), 7.15−7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 16.4 (d, J = 6.2 Hz), 20.6 (d, J = 15.1 Hz), 27.7, 35.9, 50.6 (d, J = 122.0 Hz), 59.8, 62.6 (t, J = 7.0 Hz), 116.4, 127.6, 128.9, 128.9, 135.7, 136.9, 203.6.

Phosphonate 2e.[7c] To a stirred solution of diethyl 2-oxocyclohexylphosphonate (**1e**; 0.468 g, 2.0 mmol) in dry THF (8 mL) under N_2 at 0 °C was added NaHMDS (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) dropwise. After being stirred for 1 h, the mixture was allowed to warm slowly to room temperature. Cinnamyl bromide (0.813 g, 4.0 mmol) was added, and the reaction mixture was stirred for 4 h. Hereafter, the same workup and purification by chromatography (EtOAc/hexane, 50/50) as for the general procedure gave pure **2e** (0.582 g, 83%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.27−1.34 (m, 6H), 1.52−1.71 (m, 2H), 1.80−

2.02 (m, 2H), 2.07−2.34 (m, 2H), 2.38−2.53 (m, 2H), 2.78−2.89 (m, 1H), 2.94−3.05 (m, 1H), 4.04−4.20 (m, 4H), 6.04−6.15 (m, 1H), 6.37 (d, J = 15.8 Hz, 1H), 7.15−7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4 (t, J = 6.1 Hz), 21.5 (d, J = 2.4 Hz), 25.8, 31.9 (d, J = 4.4 Hz), 36.6 (d, J = 3.7 Hz), 41.2, 55.7 (d, J = 124.8 Hz), 62.7 (d, J = 7.1 Hz), 125.4 (d, J = 9.8 Hz), 126.1, 127.2, 128.4, 133.6, 137.2, 208.4.

General Procedure for the γ-Alkylation of β-Keto Phosphonates. To a stirred solution of phosphonate **2** (1.0 mmol) in dry THF (8 mL) under N_2 at −78 °C was added NaHMDS (1.0 mL of a 1.0 M solution in THF, 1.0 mmol) or LDA (0.50 mL of a 2.0 M solution in heptane/THF/ethylbenzene, 1.0 mmol) dropwise. The mixture was allowed to warm slowly for about 1 h to −40 °C, and then alkyl halide (2.0 mmol) was added. The cooling bath was removed, and the mixture was stirred at room temperature for 2−5 h. An aqueous ammonium chloride solution (2 mL) was added, and the resulting solution was extracted with diethyl ether (20 mL × 3). The combined organic extracts were washed with water (5 mL × 2), dried over magnesium sulfate, and concentrated. The residue was chromatographed on a silica gel column using an EtOAc/hexane mixture as eluent to give the pure product **3** as a colorless oil.

Phosphonate 3a. Using the general procedure described above, with a reaction time of 5 h and NaHMDS as a base, **3a** was obtained (0.313 g, 95%) from **2a** (0.259 g, 0.78 mmol) and benzyl bromide (0.19 mL, 1.6 mmol) after chromatography (EtOAc/hexane, 30/70): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (dt, J = 2.0, 7.1 Hz, 3H), 0.96 (dd, J = 2.4, 6.6 Hz, 3H), 1.03−1.16 (m, 1H), 1.19−1.40 (several peaks, 9H), 1.60 (s, 3H), 1.66 (s, 3H), 1.79−1.95 (m, 2H), 2.43−2.66 (several peaks, 3H), 2.90−2.98 (m, 1H), 3.43−3.53 (m, 1H), 4.06−4.16 (m, 4H), 5.03 (br dt, J = 26.0, 6.5 Hz, 1H), 7.15−7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 16.4, 17.5 (d, J = 10.0 Hz), 18.0, 23.3 (d, J = 4.6 Hz), 25.9, 26.4 (d, J = 6.5 Hz), 28.6 (d, J = 14.3 Hz), 30.1, 40.2 (d, J = 7.0 Hz), 43.8, 58.9 (d, J = 126.8 Hz), 62.3 (d, J = 6.9 Hz), 118.9 (d, J = 9.2 Hz), 126.1, 128.3, 129.3, 133.7 (d, J = 14.6 Hz), 139.9 (d, J = 3.2 Hz), 211.9.

Phosphonate 3b. Using the general procedure described above, with a reaction time of 5 h and NaHMDS as a base, **3b** was obtained (0.233 g, 86%) from **2a** (0.249 g, 0.75 mmol) and ethyl iodide (0.12 mL, 1.5 mmol) after chromatography (EtOAc/hexane, 25/75): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 6H), 1.01 (d, J = 6.6 Hz, 3H), 1.07−1.18 (m, 1H), 1.19−1.43 (several peaks, 10H), 1.54−1.61 (m, 1H), 1.61 (s, 3H), 1.65 (s, 3H), 1.76−1.94 (m, 2H), 2.58−2.65 (m, 2H), 3.01−3.09 (m, 1H), 4.03−4.13 (m, 4H), 5.03−5.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5 (d, J = 4.4 Hz), 13.9, 16.4 (d, J = 5.7 Hz), 17.0, 18.0, 23.3, 26.0, 26.5, 27.0, 28.7, 30.1, 43.2, 58.7 (d, J = 126.6 Hz), 62.2, 119.1 (d, J = 9.3 Hz), 133.6 (d, J = 4.0 Hz), 212.5.

Phosphonate 3c. Using the general procedure described above, with a reaction time of 5 h and LDA as a base, **3c** was obtained (0.276 g, 87%) from **2b** (0.269 g, 0.71 mmol) and prenyl bromide (0.18 mL, 1.4 mmol) after chromatography (EtOAc/hexane, 25/75): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (dt, J = 3.5, 7.4 Hz, 3H), 1.21−1.30 (m, 6H), 1.40−1.52 (m, 1H), 1.56−1.74 (several peaks, 7H), 2.09−2.31 (several peaks, 2H), 2.69−2.90 (several peaks, 4H), 3.02−3.11 (m, 1H), 4.05−4.15 (m, 4H), 5.03−5.13 (several peaks, 3H), 5.74−5.86 (m, 1H), 6.12−6.24 (m, 1H), 6.43 (d, J = 15.8 Hz, 1H), 7.17−7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5 (d, J = 2.7 Hz), 16.4 (d, J = 5.9 Hz), 17.8, 24.7 (d, J = 2.6 Hz), 25.7 (d, J = 4.9 Hz), 30.1, 34.2, 35.2, 49.0, 58.5 (d, J = 127.0 Hz), 62.4 (d, J = 7.2 Hz), 118.5, 122.0 (d, J = 8.1 Hz), 125.1 (d, J = 7.7 Hz), 126.1, 127.1 (d, J = 3.3 Hz), 128.4 (d, J = 1.9 Hz), 133.0, 133.1 (d, J = 10.3 Hz), 133.3, 137.3, 210.2.

Phosphonate 3d. Using the general procedure described above, with a reaction time of 5 h and LDA as a base, **3d** was obtained (0.339 g, 89%) from **2b** (0.299 g, 0.79 mmol) and 4-methylbenzyl bromide (0.30 g, 1.6 mmol) after chromatography (EtOAc/hexane, 25/75): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80−0.88 (m, 3H), 1.24−1.31 (m, 6H), 1.40−1.50 (m, 1H), 1.60−1.69 (m, 1H), 2.23−2.28 (m, 3H), 2.43−2.85 (several peaks, 5H), 2.90−2.98 (m, 1H), 3.32−3.41 (m, 1H), 4.08−4.15 (m, 4H), 4.97−5.11 (m, 2H), 5.67−5.80 (m, 1H), 6.04−6.15 (m, 1H), 6.37 (dd, J = 15.8, 23.8 Hz, 1H), 6.95−7.07 (m, 4H), 7.15−7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 16.3 (d, J = 5.9 Hz), 20.9 (d, J = 3.7 Hz), 24.5, 34.0 (dd, J = 3.1, 8.5 Hz), 35.2, 37.3 (d, J = 10.1 Hz), 50.7, 58.4 (d, J = 127.5 Hz), 62.4 (d, J = 7.4 Hz), 118.4, 125.0 (d, J = 8.0 Hz), 126.0 (d, J = 1.4 Hz), 127.1, 128.4, 128.9 (d, J = 2.7 Hz), 129.1 (d, J = 1.5 Hz), 133.1 (d, J = 8.6 Hz), 133.3 (d, J = 5.3 Hz), 135.6 (d, J = 2.8 Hz), 136.7 (d, J = 5.9 Hz), 137.3 (d, J = 8.0 Hz), 209.9 (d, J = 2.5 Hz).

Phosphonate 3e. Using the general procedure described above, with a reaction time of 3 h and LDA as a base, **3e** was obtained (0.304 g, 80%) from **2c** (0.326 g, 1.0 mmol) and crotyl bromide (0.24 mL, 2.0 mmol) after chromatography (EtOAc/hexane, 35/65): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53−0.59 (m, 3H), 1.00−1.23 (m, 2H), 1.28−1.34 (m, 6H), 1,46 (d, J = 17.9 Hz, 3H), 1.59 (d, J = 6.1 Hz, 3H), 2.05−1.13 (m, 1H), 2.23−2,31 (m, 1H), 2.80 (dd, J = 10.3, 13.3 Hz, 2H), 3.70 (dd, J = 8.1, 13.2 Hz, 1H), 4.05−4.19 (m, 4H), 5.27−5.46 (m, 2H), 7.10−7.23 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 16.4 (d, J = 5.2 Hz), 16.5, 17.9, 23.4, 33.9, 37.7 (d, J = 4.4 Hz), 48.3, 55.6 (d, J = 123.1 Hz), 62.8 (d, J = 7.5 Hz), 126.5, 126.6, 127.8, 128.8, 131.1, 136.6 (d, J = 14.6 Hz), 210.7.

Phosphonate 3f. Using the general procedure described above, with a reaction time of 2 h and NaHMDS as a base, unusually α-alkylated **3f** was obtained (0.440 g, 94%) as a mixture of diastereomeric isomers (de 20% determined by NMR analysis) from **2d** (0.352 g, 1.0 mmol) and cinnamyl bromide (0.406 g, 2.0 mmol) after chromatography (EtOAc/hexane, 25/75): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48 (t, J = 6.4 Hz, 3 × 2/5H), 0.82 (t, J = 7.2 Hz, 3 × 3/5H), 1.12−1.34 (several peaks, 8H), 1.12−1.41 (m, 2H), 2.52−2.93 (several peaks, 4H), 3.97−4.18 (m, 4H), 4.43−4.52 (m, 1H), 4.84−4.95 (m, 2H), 5.49−5.61 (m, 1H), 5.80−5.90 (m, 3/5H), 6.08−6.18 (m, 2/5H), 6.17 (d, J = 15.9 Hz, 3/5H), 6.39 (d, J = 15.9 Hz, 2/5H), 7.12−7.30 (several peaks, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.6, 16.3 (d, J = 5.7 Hz), 17.4 (d, J = 8.3 Hz), 32.6, 33.0, 33.7, 34.3, 39.9, 40.0, 54.7, 59.7 (d, J = 126.7 Hz), 59.7 (d, J = 126.7 Hz), 60.1 (d, J = 127.2 Hz), 62.4 (d, J = 7.3 Hz), 116.5, 116.6, 124.8 (d, J = 8.3 Hz), 126.0, (d, J = 2.3 Hz), 126.9, 127.0 (d, J = 4.9 Hz), 128.3 (d, J = 7.4 Hz), 128.5 (d, J = 14.3 Hz), 132.6, 132.8, 135.6 (d, J = 7.0 Hz), 137.1, 137.5, 138.2, 206.8 (d, J = 21.1 Hz).

Phosphonate 3g. Using the general procedure described above, with a reaction time of 5 h and NaHMDS as a base, **3g** was obtained (0.247 g, 68%) as a mixture of diastereomeric isomers (de 25% determined by NMR analysis) from **2e** (0.350 g, 1.0 mmol) and methyl iodide (0.25 mL, 4.0 mmol) after chromatography (EtOAc/hexane, 40/60): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02−1.06 (m, 3H), 1.20−1.37 (several peaks, 7H), 1.53−2.09 (several peaks, 4H), 2.20−2.38 (m, 2H), 2.42−2.54 (m, 1H), 3.00−3.12 (m, 1H), 4.00−4.19 (m, 4H), 5.95−6.15 (m, 1H), 6.37 (dd, J = 15.8, 6.3 Hz, 1H), 7.15−7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.1, 16.4 (d, J = 5.7 Hz), 18.4, 21.8, 27.6, 30.0 (d, J = 3.7 Hz), 32.8 (d, J = 4.3 Hz), 35.0, 36.9, 37.8, 39.4 (d, J = 4.5 Hz), 44.4, 45.1, 55.8 (d, J = 123.3 Hz), 62.6 (d, J = 6.8 Hz), 125.0, 126.0, 126.1, 127.1, 127.3, 128.4, 128.5, 133.5, 134.0, 137.1, 137.4, 209.4.

General Procedure for the Dephosphonylation of Tetrasubstituted β-Keto Phosphonates. NaHMDS (0.50 mL of a 1.0 M solution in THF, 0.50 mmol) or LiHMDS (0.50 mL of a 1.0 M solution in THF, 0.50 mmol) was added dropwise to a stirred solution of phosphonate **3** (0.50 mmol) in dry THF (3 mL) under N_2 at −78 °C. The mixture was allowed to warm slowly to 0 °C, and then $LiAlH_4$ (1.5 mL of a 1.0 M solution in THF, 1.5 mmol) was added. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. An aqueous H_2SO_4 solution (5 N, 2 mL) was added, and the resulting solution was extracted with diethyl ether (20 mL × 3). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 mL) and water (3 mL × 2), dried over magnesium sulfate, and concentrated. Purification of the residue by flash silica gel chromatography furnished the ketone **5** as a colorless oil.

Ketone 4a. Using the general procedure described above and NaHMDS as a base, **4a** was obtained (0.102 g, 71%) as a mixture of diastereomeric isomers (1:1 determined by NMR analysis) from **3a** (0.211 g, 0.50 mmol) after chromatography (EtOAc/hexane, 1/40): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (t, J = 7.2 Hz, 3 × 1/2H), 0.84 (t, J = 7.1 Hz, 3 × 1/2H), 0.93−1.03 (several peaks, 4H), 1.08−1.33 (several peaks, 5H), 1.50 (s, 3 × 1/2H), 1.56 (s, 3 × 1/2H), 1.63 (d, J = 3.2 Hz, 3H), 1.85−1.95 (m, 1H), 2.02 (sextet, J = 7.2 Hz, 2H), 2.18−2.29 (m, 1H), 2.43−2.55 (m, 2H), 2.82−2.91 (m, 1H), 2.91−3.00 (m, 1H), 4.87 (tt, J = 7.3,

1.2 Hz, 1/2H), 4.98 (tt, J = 7.3, 1.3 Hz, 1/2H), 7.13−7.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 13.9, 16.2, 16.3, 17.7, 22.8, 22.9, 25.7, 29.3, 29.7, 29.8, 30.5, 30.7, 38.4, 38.6, 48.2, 48.3, 51.6, 121.7, 121.9, 126.1, 128.3, 129.1, 133.1, 133.2, 140.1, 217.0; HRMS m/z (M^+) calcd for $C_{20}H_{30}O$ 286.2297, found 286.2296.

Ketone 4b. Using the general procedure described above and NaHMDS as a base, **4b** was obtained (0.048 g, 43%) as a mixture of diastereomeric isomers (1:1 determined by NMR analysis) from **3b** (0.180 g, 0.50 mmol) after chromatography (EtOAc/hexane, 1/50): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80−0.88 (several peaks, 6H), 0.99 (t, J = 7.1 Hz, 3H), 1.17−1.34 (several peaks, 7H), 1.53−1.69 (several peaks, 7H), 1.96−2.08 (m, 1H), 2.16−2.27 (m, 1H), 2.43−2.50 (m, 1H), 2.53−2.61 (m, 1H), 4.98−5.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 11.8, 13.9, 15.4, 15.6, 17.7, 22.9, 25.3, 25.7, 29.7, 30.0, 30.1, 30.7, 30.9, 47.6, 51.1, 121.9, 133.0. 208.7; HRMS m/z (M^+) calcd for $C_{15}H_{28}O$ 224.2140, found 224.2136.

Ketone 4c. Using the general procedure described above and LiHMDS as a base, **4c** was obtained (0.082 g, 53%) as a mixture of diastereomeric isomers (1:1 determined by NMR analysis) from **3c** (0.223 g, 0.50 mmol) after chromatography (EtOAc/hexane, 1/40): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78−0.86 (m, 3H), 1.34−1.46 (m, 1H), 1.52−1.65 (several peaks, 7H), 2.00−2.07 (m, 1H), 2.11−2.56 (several peaks, 6H), 2.70−2.79 (m, 1H), 4.96−5.08 (several peaks, 3H), 5.63−5.77 (m, 1H), 6.01−6.13 (m, 1H), 6.38 (d, J = 15.8 Hz, 1H), 7.12−7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 17.7, 23.4, 23.5, 25.7, 29.0, 33.9, 34.9, 51.2, 51.3, 53.4, 117.0, 117.1, 121.7, 121.9, 126.0, 127.1, 127.4, 128.4, 128.5, 132.1, 132.2, 133.2, 133.3, 135.6, 137.4, 215.2; HRMS m/z (M^+) calcd for $C_{22}H_{30}O$ 310.2297, found 310.2265.

Ketone 4d. Using the general procedure described above and LiHMDS as a base, **4d** was obtained (0.107 g, 62%) as a mixture of diastereomeric isomers (de 23% determined by NMR analysis) from **3d** (0.241 g, 0.50 mmol) after chromatography (EtOAc/hexane, 1/40): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81−0.90 (m, 3H), 1.37−1.50 (m, 1H), 1.56−1.70 (m, 1H), 1.93−2.21 (m, 2H), 2.23−2.63 (several peaks, 7H), 2.78−2.92 (m, 2H), 4.87−4.94 (m, 1H), 4.98−5.06 (m, 1H), 5.43−5.55 (m, 5/13H), 5.61−5.73 (m, 1H), 6.00−6.12 (m, 8/13H), 6.22 (d, J = 15.8 Hz, 5/13H), 6.36 (d, J = 15.8 Hz, 8/13H), 6.97−7.06 (m, 4H), 7.14−7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 21.0, 23.8, 23.9, 33.7, 34.4, 34.7, 36.0, 36.1, 51.5, 55.1, 117.0, 117.1, 126.0, 127.1, 127.4, 128.4, 128.5, 129.0, 132.0, 132.2, 135.4, 135.6, 135.7, 136.9, 137.3, 214.8; HRMS m/z (M^+) calcd for $C_{25}H_{30}O$ 346.2297, found 346.2293.

Ketone 4e. Using the general procedure described above and LiHMDS as a base, **4e** was obtained (0.055 g, 45%) as a mixture of diastereomeric isomers (1:1 determined by NMR analysis) from **3e** (0.190 g, 0.50 mmol) after chromatography (EtOAc/hexane, 1/40): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (t, J = 7.4 Hz, 3 × 1/2H), 0.79 (t, J = 7.4 Hz, 3 × 1/2H), 0.99−1.04 (m, 3H), 1.36−1.65 (several peaks, 5H), 1.85−1.96 (m, 1/2H), 1.97−2.11 (m, 1H), 2.17−2.28 (m, 1/2H), 2.46 (dd, J = 7.4, 13.3 Hz, 2H), 2.78−2.90 (m, 1H), 2.91−3.02 (m, 1H), 4.98−5.52 (several peaks, 2H), 7.12−7.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 11.9, 16.2, 17.9, 23.6, 23.7, 33.8, 34.2, 38.7, 48.1, 48.2, 53.0, 126.1, 127.1, 128.3, 128.4, 129.1, 140.0, 216.6; HRMS m/z (M^+) calcd for $C_{17}H_{24}O$ 244.1827, found 244.1828.

Ketone 4f. Using the general procedure described above and NaHMDS as a base, **4f** was obtained (0.121 g, 73%) as a mixture of diastereomeric isomers (1:1 determined by NMR analysis) from **3f** (0.234 g, 0.50 mmol) after chromatography (EtOAc/hexane, 1/50): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.57 (t, J = 7.1 Hz, 3 × 1/2H), 0.89 (t, J = 7.1 Hz, 3 × 1/2H), 1.17−1.64 (several peaks, 4H), 2.05−2.15 (m, 1/2 H), 2.20−2.46 (several peaks, 2 + 1/2H), 2.65−2.84 (several peaks, 2H), 3.74 (dt, J = 2.1, 7.5 Hz, 1H), 4.84−5.03 (m, 2H), 5.51−5.71 (several peaks, 1 + 1/2H), 6.03−6.14 (several peaks, 1H), 6.36 (d, J = 15.7 Hz, 1/2H), 7.06−7.31 (several peaks, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 14.2, 20.0, 20.4, 32.6, 34.1, 35.9, 36.5, 50.6, 50.8, 59.0, 59.2, 116.6, 126.0, 126.8, 127.2, 127.3, 127.6, 128.2, 128.5, 128.7, 128.8, 131.3, 132.1, 135.9, 137.2, 137.4, 137.5, 211.4; HRMS m/z (M^+) calcd for $C_{24}H_{28}O$ 332.2140, found 332.2148.

Ketone 4g.[2c] Using the general procedure described above and NaHMDS as a base, **4g** was obtained (0.063 g, 55%) from **3g** (0.182 g, 0.50 mmol) after chromatography (EtOAc/hexane, 1/40): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, J = 6.4 Hz, 3H), 1.27−1.41 (m, 2H), 1.65−1.87 (m, 2H), 2.03−2.24 (several peaks, 3H), 2.35−2.47 (several peaks, 2H), 2.61−2.71 (m, 1H), 6.15−6.25 (m, 1H), 6.37 (d, J = 15.8 Hz, 1H), 7.15−7.19 (m, 1H), 7.24−7.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 25.5, 33.0, 34.8, 37.3, 45.7, 50.9, 126.0, 126.9, 128.5, 128.8, 131.4, 137.6, 213.6; HRMS m/z (M^+) calcd for $C_{16}H_{20}O$ 228.1514, found 228.1519.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of all compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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