Acid-Catalyzed Transformation of α-Hydroxy-γ-oxo Acetals to γ-Oxo Esters. A Novel Deconjugation of 4-Oxo-2-alkenal Acetals

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Under acid catalysis, α-hydroxy-γ-oxo acetals which are readily available from the nitrile oxide cycloaddition route are smoothly converted into γ-oxo esters. This unusual and high-yield transformation involves rare acid-catalyzed deconjugation of the intermediary 4-oxo-2-alkenal acetals and is influenced by a substituent at the 5-position.

A sequence of cycloadditions of (diethoxyphosphinyl)acetonitrile oxide with olefins or acetylenes and reductive N–O bond cleavage of the cycloadducts provides 4-hydroxy-2-oxoalkylphosphonates.[1] The resulting functionalities are synthetically important when they are utilized in organic synthesis either separately, all together, or together with an additional function introduced from dipolarophiles.[2]

We were investigating a possibility of acid-catalyzed one-step transformation of 2-hydroxy-4-oxo-5-alkenal acetals into 5-alkylidene-2(3*H*)-furanones which are important heterocycles often seen in natural products.[3] During this investigation we came across an unusual and high-yield transformation of the acetals to γ-oxo esters. All the results with respect to this novel transformation and its reaction mechanism are discussed in the present article.

Results and Discussion

Acid-catalyzed ring closure of 2-hydroxy-4-oxo-5-alkenal acetals must be useful as a direct synthetic way to 5-alkylidene-2(3*H*)-furanones[4] when the starting acetals are easily available. Since we previously tested the synthetic value of Horner–Emmons olefination of 4-hydroxy-2-oxoalkylphosphonates,[5] its applications to the synthesis of 5-alkylidene-2(3*H*)-furanones were aimed.

(*E*)-6,6-Diethoxy-5-hydroxy-1-phenyl-1-hexen-3-one (**3**) as a starting compound, can be prepared by Horner–Emmons olefination of diethyl 5,5-diethoxy-4-hydroxy-2-oxopentylphosphonate (**2**) which is available by a sequence of 1,3-dipolar cycloaddition of (diethoxyphosphinyl)acetonitrile oxide with 3,3-diethoxypropene and Raney Ni reduction of the cycloadduct, 5-(diethoxymethyl)-3-[(diethoxyphosphinyl)-methyl]-2-isoxazoline (**1**).[1,5]

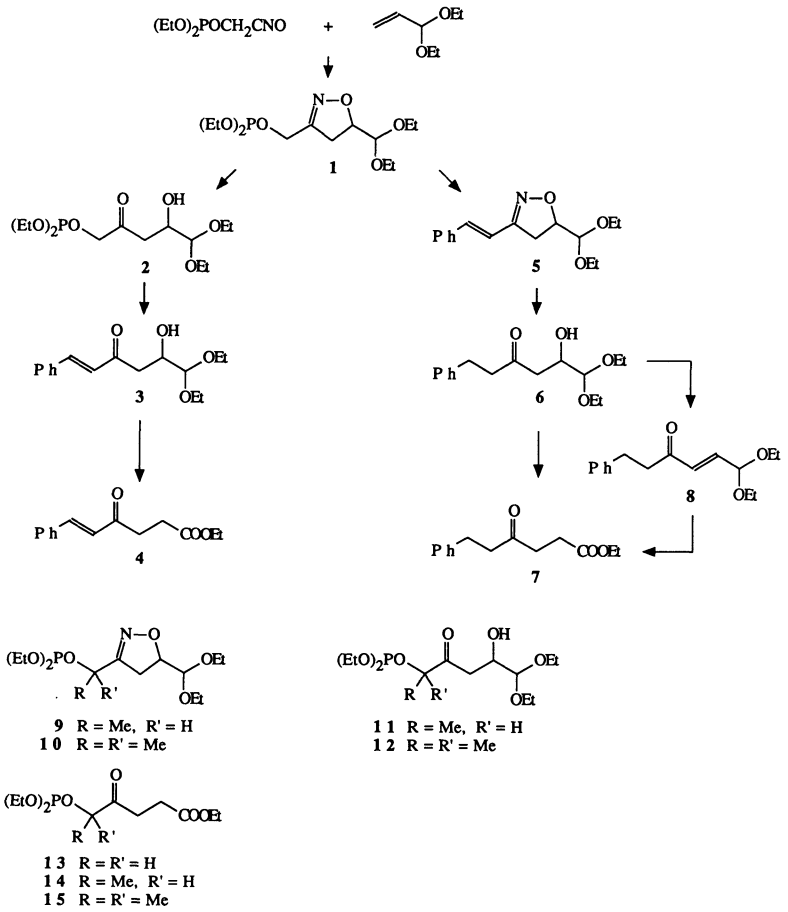
Treatment of **3** with hydrogen chloride in chloroform at room temperature unexpectedly led to quantitative formation of ethyl (*E*)-4-oxo-5-hexenoate (**4**) (Scheme 1). This reaction can be complete in 20 min at 0 °C and the same product **4** was obtained in 89% yield. Ester **4** showed quite high stability against acid. For example, **4** stayed unchanged even when heated under reflux in chloroform together with hydrogen chloride for a long time (18 h). This quantitative ester formation contrasts with the reported example[4] where an analogous acetal, 6-hydroxy-2,6-dimethyl-7,7-dimethoxy-2-hepten-4-one, gives 3-methyl-5-(2-methylpropylidene)-2(3*H*)-furanone in 72% yield under the comparable conditions. Although there are known several ring-closure reactions of γ-oxo esters or acids leading to 2-furanone derivatives,[1,6] the high stability of ester **4** indicates that the furanone synthesis cited in Ref. 4 has proceeded not via the corresponding γ-oxo ester intermediate.[7]

To see whether the double bond of **3** is requisite or not for this novel transformation, the saturated ketone **6** was prepared from **1**. The Horner–Emmons olefination of 2-isoxazoline **1** with benzaldehyde gave 5-(diethoxymethyl)-3-[(*E*)-2-phenylethenyl]-2-isoxazoline (**5**) in 82% yield, which was reductively cleaved on Raney Ni to provide 6,6-diethoxy-5-hydroxy-1-phenyl-3-hexanone (**6**) in 69% yield.

Similar treatment of **6** with hydrogen chloride in chloroform gave γ-oxo ester **7** albeit in a moderate yield (58%), indicating that the essential skeleton for the γ-oxo ester formation is an α-hydroxy-γ-oxo acetal framework. However, it should be emphasized that the double bond at the 5-position of **3** has certainly contributed to some stabilization of the corresponding intermediate. This will be discussed later.

As the reaction for α-hydroxy-γ-oxo acetal **6** most likely to undergo under acid catalysis would be dehydration, treatment of the dehydrated derivative, (*E*)-6,6-diethoxy-1-phenyl-4-hexen-3-one (**8**), with an acid was next examined. Compound **8** is readily obtained in 85% yield through a sequence of *O*-mesylation and triethylamine-mediated β-elimination. When **8** was allowed to react with hydrochloric acid, the expected γ-oxo ester **7** was obtained in 57% yield, confirming the intermediacy of 4-oxo-2-alkenal acetal **8**.

It was disappointing that phosphonate **2** as a pre-

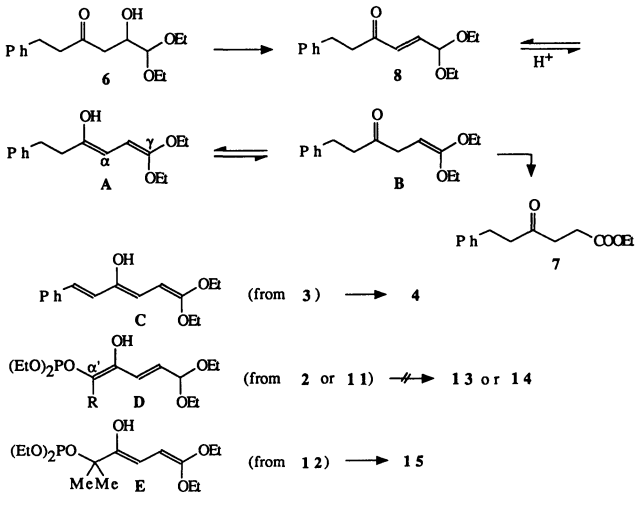


Scheme 1.

cursor of **3** underwent no such transformation into the corresponding γ-oxo ester **13** under similar conditions or even at −78 °C. The introduction of an alkyl moiety adjacent to the phosphinyl group (5-position) was of no use either. Thus phosphonate **2** as well as the methylated derivative **11** led to mixture of complex products.

Two methyl moieties were introduced adjacent to the phosphinyl moiety of **2** via 3-(1-phosphinyl-1-methylethyl)-2-isoxazoline **10** to give 2-(diethoxyphosphinyl)-6,6-diethoxy-5-hydroxy-2-methyl-3-hexanone (**12**). It was our delight to find that the dimethylated ketone **12** was smoothly converted into the corresponding γ-oxo ester **15** in 78% yield.

On the basis of the above results and observations, a possible reaction mechanism is illustrated in Scheme 2. Under acidic conditions the initial acid-catalyzed dehydration of **6** leads to enone **8** which then reversibly isomerizes into dienol intermediate **A**. Formation of **A** is facilitated by stabilization effect from the two ethoxyl groups attached at one end of the dienol conjugation. Since protonation occurs at the less congested α-position rather than the hindered γ-position, the isomerization equilibrates in favor for deconjugation leading to **B**. Under the reaction conditions, intermediate **B** is irreversibly hydrolyzed into γ-oxo ester **7**.



Scheme 2.

Although many synthetically useful examples are known for deconjugation processes under base catalyst[8] and under irradiation,[9] acid-catalyzed deconjugation was less important. As acid-catalyzed deconjugation is always a reversible reaction and often leads to a mixture of conjugated and deconjugated carbonyl compounds,[10] an irreversible step has to be involved for the process to be a useful synthetic reaction. In the

present case, the equilibrating intermediate **B** is irreversibly hydrolyzed by the water formed in the step of **6** to **8** under the applied conditions so that the equilibrium moves in favor for deconjugation.

The preexisting double bond of **3** provides some additional stabilization of the enolized intermediate **C** as a trienol. This is a reason why quantitative conversion of **3** into **4** has been achieved.

Since both the phosphonates **2** and **11** bear at least one highly acidic hydrogen at the α'- position, their enolization occurs exclusively at this position to form phosphorus-stabilized dienol intermediates **D** (R=H or Me) so that there is little chance for deconjugation. Only α',α'-dialkylated phosphonate **12** can undergo smooth conversion into γ-oxo ester **15** via dienol intermediate **E**.

In conclusion, 4-oxo-2-alkenal acetals are converted under acidic conditions into γ-oxo esters through a sequence of dehydration, enolization, deconjugation, and hydrolysis. Since both 3-(phosphinylmethyl)-2-isoxazoline **1** and 2-oxoalkylphosphonate **2** can be successfully employed for the introduction of a wide pattern of substituents by the aid of the phosphinyl moiety,[1] this transformation offers a general synthetic method of γ-oxo esters.

Experimental

General. Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with a JASCO IRA-1 or a JASCO A-702 spectrometer. ^{1}H NMR spectra were recorded on a JEOL FX-100 (100 MHz) or a JEOL GSX-270 instrument (270 MHz), and ^{13}C NMR on a JEOL FX-100 (25.05 MHz) or a JEOL GSX-270 spectrometer (67.94 MHz). Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL-01SG-2 spectrometer at 70 eV of ionization energy. High resolution mass spectra were obtained on the same instrument. Elemental analyses were performed on a Hitachi 026 CHN analyzer. Thin-layer chromatography (TLC) was accomplished on 0.2 mm precoated plates of silica gel 60 F-254 (Merck). For preparative column chromatography, Wakogel C-200, C-300 (Wako), and Silicagel 60 (Merck) were employed. Flash chromatography was carried out on an EYELA EF-10 apparatus using a column (20×180 mm) packed with Silicagel 60 (Merck, size: 0.04—0.063 mm). Micro vacuum distillation was carried out on a Sibata GTO-250R Kugelrohr distilling apparatus. Solvents were evaporated with a Tokyo Rikakikai rotary evaporator type-V at about 50 °C unless otherwise stated.

Materials and Solvents. 2-Oxoalkylphosphonate **2** and enone **3** were prepared according to the reported method starting from 2-isoxazoline **1**.[1,5] Tetrahydrofuran (THF) was distilled from lithium aluminum hydride under nitrogen immediately prior to its use.

Ethyl (*E*)-4-Oxo-6-phenyl-5-hexenoate (4): To a saturated solution of hydrogen chloride in chloroform (20 ml) was added dropwise a solution of **3** (0.067 g, 0.24 mmol) in chloroform (5 ml). The resulting solution was stirred at room temperature for 4 h, poured into ice water, and then extracted with chloroform (15 ml×2). The combined chloroform was washed with saturated aqueous sodium hydrogencarbonate, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was chromatographed over silica gel by using hexane–ethyl acetate (5:1 v/v) to give **4** (0.055 g, 98%). Similar reaction at 0 °C for 20 min afforded 89% of **4** and under reflux for 18 h 97%: Pale yellow liquid; IR (neat) 1730, 1680, 1660, 1610, 1575, 1490, 1445, 1360, 1200, 1160, 1100, 750, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.24 (3H, t, J=7.0 Hz, COOEt), 2.68, 3.01 (each 2H, t, J=6.5 Hz, 2- and 3-H), 4.14 (2H, q, J=7.0 Hz, COOEt), 6.73 (1H, d, J_{5-6}=16.0 Hz, 5-H), 7.1—7.8 (5H, m, Ph), and 7.57 (1H, d, J_{6-5}=16.0 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ=14.20 (COOEt), 28.24 (2-C), 35.26 (3-C), 60.62 (COOEt), 125.90, 128.32, 128.95 (each Ph), 130.52 (5-C), 134.44 (Ph), 142.86 (6-C), 172.87 (COOEt), and 198.04 (CO); MS m/z (rel intensity, %) 232 (M^+, 11), 131 (base peak), 103 (40), and 77 (30). HRMS Found: m/z 232.1107. Calcd for $C_{14}H_{16}O_3$: M, 232.1099.

5-(Diethoxymethyl)-3-(*E*)-2-phenylethenyl-2-isoxazoline (5): To a solution of **1** (0.522 g, 1.61 mmol) in dry THF (4 ml) was added, at −78 °C under nitrogen, butyllithium (15% in hexane, 1.14 ml, 1.78 mmol). After 1 h, benzaldehyde (0.343 g, 3.23 mmol) was added and the mixture was stirred at room temperature for 18 h. Saturated aqueous ammonium chloride was added to the mixture which was then extracted with dichloromethane (25 ml×2). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was subjected to column chromatography over silica gel with hexane–ethyl acetate (5:1 v/v) to give **5** (0.363 g, 82%): Pale yellow liquid; IR (neat) 1630, 1495, 1450, 1370, 1060, 960, 900, 750, and 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.20, 1.25 (each 3H, t, J=7.0 Hz, OEt), 3.18 (1H, dd, J_{gem}=16.2 and J_{4-5}=10.6 Hz, one of 4-H), 3.28 (1H, dd, J_{gem}=16.2 and J_{4-5}=7.0 Hz, the other of 4-H), 3.5—3.9 (4H, m, OEt), 4.52 (1H, d, J_{CH-5}=4.8 Hz, $CH(OEt)_2$), 4.71 (1H, ddd, J_{5-4}=10.6, 7.0, and J_{5-CH}=4.8 Hz, 5-H), 6.76 (1H, d, J=16.5 Hz, -CH=), 7.06 (1H, d, J=16.5 Hz, PhCH=), and 7.2—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=15.28, 15.36 (each OEt), 34.46 (4-C), 63.45, 64.43 (each OEt), 81.45 (5-C), 102.23 ($CH(OEt)_2$), 117.69 (-CH=), 126.97, 128.84, 128.89 (each Ph), 135.82 (Ph), 136.60 (PhCH=), and 157.85 (3-C); MS m/z (rel intensity, %) 275 (M^+, 4), 230 (10), 103 (base peak), 75 (47), and 47 (22). Found: C, 69.79; H, 7.69; N, 5.09%. Calcd for $C_{16}H_{21}NO_3$: C, 69.97; H, 7.93; N, 4.98%.

6,6-Diethoxy-5-hydroxy-1-phenyl-3-hexanone (6): To a solution of **5** (0.363 g, 1.32 mmol) in aqueous ethanol (17%, 7.2 ml) were added Raney Ni (W-2, suspension in ethanol, 0.5 ml) and boric acid (0.326 g, 5.27 mmol). The mixture was stirred at room temperature under hydrogen (1 atm) for 12 h. All insoluble materials were filtered off by the aid of Celite 545. The filtrate was diluted with water and extracted with dichloromethane (25 ml×2). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed over silica gel by using hexane–ethyl acetate (5:1 v/v) to give **6** (0.256 g, 69%): Colorless liquid; IR (neat) 3430, 1705, 1600, 1490, 1445, 1370, 1060, 745, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.20, 1.22 (each 3H, t, J=7.3 Hz, OEt), 2.6—3.0 (7H, m, 1-, 2-, 4-H, and OH), 3.4—3.9 (4H, m, OEt), 4.09 (1H, dt, J_{5-4}=7.7, 4.8, and J_{5-6}=4.8 Hz, 5-H), 4.38 (1H, d, J_{6-5}=4.8 Hz, 6-H), and 7.1—7.3 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=15.32, 15.35 (each OEt), 29.47 (2-C), 44.15 (1-C), 45.18 (4-C), 63.51, 63.93 (each OEt), 68.74 (5-C), 104.03 (6-C), 126.07, 128.30, 128.46 (each

Ph), 140.97 (Ph), and 209.63 (3-C); Ms *m/z* (rel intensity, %) 235 (M^+—OEt, 4), 105 (37), 104 (27), 103 (base peak), 91 (63), 74 (56), 47 (58), and 43 (35). Found: C, 68.29; H, 8.94%. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63%.

Ethyl 4-Oxo-6-phenylhexanoate (7): A procedure similar to that employed for the formation of **4** from **3** was applied to **6** (0.093 g, 0.33 mmol). The reaction at room temperature for 2 h and the followed workup (silica-gel chromatography with hexane–ethyl acetate (7:1 v/v)) gave **7** (0.045 g, 58%). Compound **7** was also obtained by a similar procedure on **8** (room temperature for 1 h, in 57% yield): Pale yellow liquid; IR (neat) 1725, 1495, 1450, 1410, 1370, 1185, 1100, 1030, 750, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.24 (3H, t, J=7.3 Hz, COOEt), 2.57, 2.69, 2.78, 2.91 (each 2H, t, $J_{2-3}=J_{5-6}$=7.0 Hz, 2-, 3-, 5-, and 6-H), 4.12 (2H, q, J=7.3 Hz, COOEt), and 7.1—7.3 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.17 (COOEt), 27.99 (2-C), 29.69 (3-C), 37.23 (5-C), 44.26 (6-C), 66.65 (COOEt), 126.13, 128.29, 128.51 (each Ph), 140.96 (Ph), 172.79 (COOEt), and 208.00 (CO); MS *m/z* (rel intensity, %) 234 (M^+, 16), 105 (48), 101 (29), 91 (base peak), 76 (22), and 30 (30). HRMS Found: *m/z* 234.1254. Calcd for $C_{14}H_{18}O_3$: M, 234.1255.

(*E*)-6,6-Diethoxy-5-hydroxy-1-phenyl-4-hexen-3-one (8): To a solution of **6** (0.1 g, 0.36 mmol) in dry dichloromethane (1 ml) were added, at −15 °C under nitrogen, triethylamine (0.108 g, 1.07 mmol) and methanesulfonyl chloride (0.049 g, 0.43 mmol). After stirring at −15 °C for 1 h and then at room temperature for 4 h, the reaction mixture was poured into ice water and then extracted with dichloromethane (20 ml×2). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed over silica gel with hexane–ethyl acetate (7:1 v/v) to provide **8** (0.08 g, 85%): Colorless liquid; IR (neat) 1680, 1640, 1605, 1500, 1450, 1370, 1330, 1130, 1060, 750, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.22 (6H, t, J=7.0 Hz, OEt), 2.9—3.0 (4H, m, 1- and 2-H), 3.4—3.8 (4H, m, OEt), 5.03 (1H, d, J_{6-5}=4.4 Hz, 6-H), 6.35 (1H, d, J_{4-5}=16.1 Hz, 4-H), 6.63 (1H, dd, J_{5-4}=16.1 and J_{5-6}=4.4 Hz, 5-H), and 7.1—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=15.19 (OEt), 29.83 (2-C), 41.96 (1-C), 61.50 (OEt), 99.54 (6-C), 126.12, 128.35, 128.48 (each Ph), 131.49 (Ph), 141.00, 141.35 (4- and 5-C), and 199.30 (CO); MS *m/z* (rel intensity, %) 262 (M^+, 1), 105 (24), 103 (base peak), 91 (93), 84 (30), 83 (21), 77 (22), 75 (33), 55 (34), and 47 (26). Found: C, 73.21; H, 8.83%. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%.

5-(Diethoxymethyl)-3-[1-(diethoxyphosphinyl)ethyl]-2-isoxazoline (9): To a solution of **1** (0.53 g, 1.64 mmol) in dry THF (4 ml) was added, at −78 °C under nitrogen, butyllithium (15% in hexane, 1.15 ml, 1.8 mmol). After 30 min at −78 °C, methyl iodide (0.465 g, 3.28 mmol) was added and the mixture was stirred at room temperature for 18 h. It was then poured into saturated ammonium chloride and extracted with dichloromethane (20 ml×2). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was subjected to column chromatography over silica gel by using hexane–ethyl acetate (5:1 v/v) to give **9** (0.388 g, 70%) as a 1:1 mixture (by ^{13}C NMR) of two diastereomers: Pale yellow liquid; IR (neat) 1610, 1440, 1390, 1375, 1250, 1160, 1120, 1060, 1020, 960, 885, and 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.20, 1.23 (each 3H, t, J=7.0 Hz, OEt), 1.34 (6H, t, J=7.0 Hz, OEt), 1.42, 1.49 (3H, each d, J=7.3 Hz, Me), 3.0—3.3 (3H, m, PCH and 4-H), 3.5—3.8 (4H, m, OEt), 4.15 (4H, dq, J=7.3 (HP) and 7.0 Hz, OEt), 4.44 (1H, d, J=5.1 Hz, $CH(OEt)_2$), and 4.5—4.7 (1H, m, 5-H); ^{13}C NMR ($CDCl_3$) δ=15.29 (Me), 15.33, 15.36 (each OEt), 16.46 (J=5.9 (CP) Hz, OEt), 32.09, 32.24 (each J=140.9 (CP) Hz, PCH), 36.47, 37.16 (each 4-C), 62.45, 62.50 (each J=6.9 (CP) Hz, OEt), 63.25, 63.37, 64.15, 64.33 (each OEt), 80.86, 80.89 (each 5-C), 102.17, 102.32 (each $CH(OEt)_2$), and 156.66 (J=6.9 (CP) Hz, 3-C); MS *m/z* (rel intensity, %) 292 (M^+—OEt, 26), 103 (base peak), 75 (50), and 47 (37). No satisfactory analytical result was obtained due to the hygroscopic nature of **9**.

5-(Diethoxymethyl)-3-[1-(diethoxyphosphinyl)-1-methylethyl]-2-isoxazoline (10): A similar procedure was employed under the following conditions: **1** (1.402 g, 4.34 mmol) in THF (9 ml), butyllithium (15% in hexane, 5.96 ml, 9.54 mmol) at −78 °C for 30 min, methyl iodide (2.462 g, 17.3 mmol), at room temperature for 17 h, silica-gel column chromatography with hexane–ethyl acetate (5:1 v/v). The dialkylated product **10** was obtained in 40% (0.61 g) yield: Pale yellow liquid; IR (neat) 1610, 1460, 1440, 1390, 1320, 1250, 1050, 1025, 960, 890, and 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.19, 1.23 (each 3H, t, J=7.0 Hz, OEt), 1.33 (6H, t, J=7.0 Hz, OEt), 1.44, 1.50 (each 3H, Me), 3.0—3.3 (2H, m, 4-H), 3.5—3.8 (4H, m, OEt), 4.14 (4H, dq, J=7.3 (HP) and 7.0 Hz, OEt), 4.43 (1H, d, J=5.5 Hz, $CH(OEt)_2$), and 4.5—4.7 (1H, m, 5-H); ^{13}C NMR ($CDCl_3$) δ=15.32 (OEt), 16.49 (J=4.9 (CP) Hz, OEt), 21.47, 21.69 (each Me), 36.72 (4-C), 37.64 (J=158.5 (CP) Hz, PC), 62.72 (J=7.8 (CP) Hz, OEt), 63.37, 64.16 (each OEt), 81.22 (5-C), 102.32 ($CH(OEt)_2$), and 160.32 (J=5.9 (CP) Hz, 3-C); MS *m/z* (rel intensity, %) 306 (M^+—OEt, 7), 103 (base peak), 75 (37), and 47 (24). No satisfactory analytical result was obtained due to the hygroscopic nature of **10**.

6,6-Diethoxy-2-(diethoxyphosphinyl)-5-hydroxy-3-hexanone (11): A procedure similar to that used to prepare **6** from **5** was employed to **9** under the following conditions: **9** (0.388 g, 1.15 mmol) in aqueous ethanol (17%, 9 ml), Raney Ni (W-2, suspension in ethanol, 0.5 ml), boric acid (0.284 g, 4.6 mmol), under hydrogen (1 atm) at room temperature for 12 h, silica-gel column chromatography with ethyl acetate. A 1:1 mixture (by ^{13}C NMR) of two diastereomers of **11** (0.271 g, 69%) was given: Colorless liquid; IR (neat) 3400, 1710, 1440, 1390, 1370, 1240, 1060, 1020, and 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.1—1.3 (6H, m, OEt), 1.33 (6H, t, J=7.0 Hz, OEt), 1.3—1.5 (3H, m, 1-H), 2.8—3.1 (3H, m, 2- and 4-H), 3.5—3.8 (4H, m, OEt), 4.13 (4H, dq, J=7.3 (CP) and 7.0 Hz, OEt), 4.0—4.2 (2H, m, 5-H), and 4.3—4.5 (1H, m, 6H); ^{13}C NMR ($CDCl_3$) δ=15.38 (1-C and OEt), 16.39 (J=5.9 (CP) Hz, OEt), 44.88 (4-C), 47.48, 47.57 (each J=126.2 (CP) Hz, 2-C), 62.55, 62.58 (each J=6.8 (CP) Hz, OEt), 63.44, 63.47, 63.97, 64.06 (each OEt), 68.78, 69.10 (each 5-C), 104.,04, 104.10 (each 6-C), 205.41, and 206.05 (each J=3.9 (CP) Hz, CO); MS *m/z* (rel intensity, %) 295 (M^+—OEt, 1), 236 (15), 103 (base peak), 74 (35), and 47 (23). No satisfactory analytical result was obtained due to the hygroscopic nature of **11**.

6,6-Diethoxy-2-(diethoxyphosphinyl)-5-hydroxy-2-methyl-3-hexanone (12): A procedure similar to that used to prepare **6** from **5** was employed to **10** under the following conditions: **10** (0.6 g, 1.71 mmol) in aqueous ethanol (17%, 10 ml), Raney Ni (W-2, suspension in ethanol, 2 ml), boric acid (0.422 g, 6.83 mmol), under hydrogen (1 atom) at room temperature for 22 h, silica-gel column chromatography with hexane–ethyl acetate (1:5 v/v). A 49% yield of **12** (0.298 g) was obtained and then the unreacted **10** was recov-

ered (0.132 g, 22%). **12**: Colorless liquid; IR (neat) 3400, 1710, 1460, 1450, 1395, 1370, 1240, 1025, 960, and 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.1—1.4 (6H, m, OEt), 1.32 (6H, t, J=7.0 Hz, OEt), 1.41, 1.47 (each 3H, 1-H and 2-Me), 2.8—3.1 (2H, m, 4-H), 3.5—3.9 (4H, m, OEt), 4.14 (4H, dq, J=7.3 (HP) and 7.0 Hz, OEt), 4.0—4.3 (2H, m, 5-H), and 4.42 (1H, d, J_{6-5}=4.8 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ=15.38 (OEt), 16.43 (J=5.9 (CP) Hz, OEt), 20.12, 20.19 (each 1-C and 2-Me), 40.92 (4-C), 50.79 (J=130.1 (CP) Hz, 2-C); 62.77 (J=6.8 (CP) Hz, OEt), 63.35, 63.84 (each OEt), 68.82 (5-C), 104.00 (6-C), and 208.73 (CO); MS m/z (rel intensity, %) 309 (M^+—OEt, 5), 251 (21), 180 (11), 123 (11), 103 (base peak), 76 (32), and 47 (22). No satisfactory analytical result was obtained due to the hygroscopic nature of **12**.

Ethyl 5-(Diethoxyphosphinyl)-2-methyl-4-oxohexanoate (15): A procedure similar to that used for the preparation of **4** from **3** was employed under the following conditions: **12** (0.092 g, 0.26 mmol) in chloroform (15 ml) saturated with hydrogen chloride, at room temperature for 5 h, silica-gel column chromatography with ethyl acetate. A 78% yield of **15** (0.062 g) was obtained: Colorless liquid; IR (neat) 1730, 1700, 1460, 1380, 1370, 1240, 1170, 1050, 1020, 960, and 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.25 (6H, t, J=7.0 Hz, OEt), 1.32 (6H, t, J=7.0 Hz, COOEt), 1.43, 1.49 (each 3H, s, 5-Me), 2.56, 3.05 (each 2H, t, J_{2-3}=6.6 Hz, 2- and 3-H), 4.12 (4H, q, J=7.0 Hz, COOEt), and 4.14 (4H, dq, J=7.3 (HP) and 7.0 Hz, OEt); ^{13}C NMR ($CDCl_3$) δ=14.20 (COOEt), 16.44 (J=5.9 (CP) Hz, OEt), 20.37, 20.45 (each 5-Me), 28.42 (2-C), 34.31 (3-C), 50.11 (J=131.1 (CP) Hz, 5-C), 60.55 (COOEt), 62.81 (OEt), 172.78 (COOEt), and 207.13 (CO); MS m/z (rel intensity, %) 308 (M^+, 5), 263 (20), 180 (base peak), 138 (41), 124 (21), 123 (43), 111 (20), 109 (45), 101 (36), 81 (46), 70 (25), 65 (23), and 55 (24). HRMS Found: m/z 308.1400. Calcd for $C_{13}H_{25}O_6P$: M, 308.1387.

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