  Bull. Chem. Soc. Jpn., 60, 4091—4098 (1987)

Horner-Emmons Olefination of 4-Hydroxy-2-oxoalkylphosphonates and Related Compounds: Applications to the Syntheses of (±)-Gingerol, (±)-Yashabushiketol, and (±)-Dihydroyashabushiketol

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(Received June 19, 1987)

Horner–Emmons olefination of 4-hydroxy-2-oxoalkylphosphonates, readily available by hydrogenation of 5-substituted 3-phosphinylmethyl-2-isoxazolines, gives mainly E-isomers of 1-hydroxy-4-alken-3-ones bearing a variety of substituents at the 1-position. Use of the combination of triethylamine (or DBU)+lithium bromide as a weak base on the *O*-unprotected phosphonates is favored. Similar olefinations on the isoxazolines, 2-oxo-3-alkenylphosphonates, and 4-alkoxy-2-oxoalkylphosphonates have been also examined. Their synthetic applications to (±)-Gingerol, (±)-Yashabushiketol, and (±)-Dihydroyashabushiketol are described.

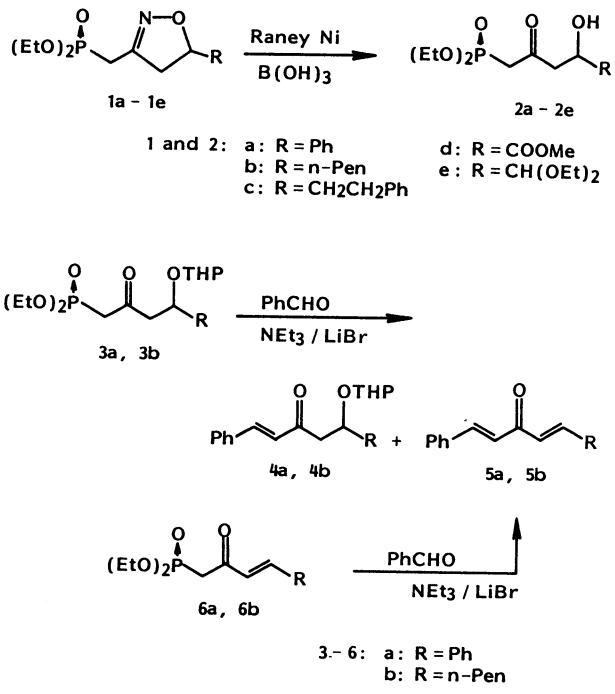
Regioselective 1,3-dipolar cycloaddition reactions of α-(diethoxyphosphinyl)acetonitrile oxide, a phosphorus-functionalized nitrile oxide, with unsymmetrically substituted olefins lead to 5-substituted 3-[(diethoxyphosphinyl)methyl]-2-isoxazolines (**1**).[1] Deprotonation occurs regioselectively at the side chain of **1** to form phosphorus-stabilized carbanions, which can be effectively utilized for the subsequent olefination, alkylation, or acylation to produce 3-substituted 2-isoxazolines. Hydrogenation of **1** on Raney Ni provides 4-hydroxy-2-oxoalkylphosphonates which are further dehydrated into 2-oxo-3-alkenylphosphonates.[1b]

The 4-hydroxy-2-oxoalkylphosphonates must be important as synthetic building blocks since they correspond to phosphorus-functionalized aldols. Their Horner–Emmons olefination leading to 1-hydroxy-4-alken-3-ones is therefore attractive. However 4-hydroxy-2-oxoalkylphosphonates and their *O*-protected derivatives are both base-sensitive so that the olefination may be only achieved under extremely mild and less basic conditions.[2]

With an aim of examining the synthetic utility of our phosphorus-functionalized nitrile oxide, α-(diethoxyphosphinyl)acetonitrile oxide,[1a] Horner–Emmons olefinations have been applied to 4-hydroxy-2-oxoalkylphosphonates and the related derivatives. The present article describes the details of these intractable olefinations which finally succeeded by the use of triethylamine (or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) + lithium bromide. Furthermore it should be noted that protection of the hydroxyl group has to be avoided. These olefination conditions were applied to the syntheses of some natural products such as (±)-Gingerol, (±)-Yashabushiketol, and (±)-Dihydroyashabushiketol.

Results and Discussion

4-Hydroxy-2-oxoalkylphosphonates **2a—e** are readily prepared by the cycloadditions of α-(diethoxyphosphinyl)acetonitrile oxide with monosubstituted olefins followed by hydrogenation of the cycloadducts **1a—e** on Raney Ni (Scheme 1).[1b] Initially two derivatives **2a,b** were protected as tetrahydropyranyl ethers **3a,b** and then subjected to the olefination reactions with benzaldehyde under various conditions. Deprotonation of **3a,b** with butyllithium or lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C and subsequent trapping with benzaldehyde, the usual reaction conditions frequently employed for the olefination of phosphoryl-stabilized carbanions,[3] resulted in the complex mixture of many products. After some efforts had been made to improve the reaction, a satisfactory result was obtained when a mixture of triethylamine (1.2 equiv) and lithium bromide (1.5 equiv) was used for the carbanion



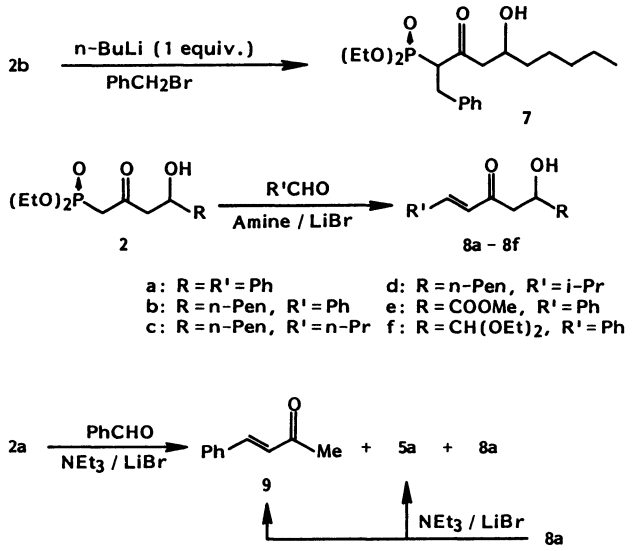
Scheme 1.

generation[4] and when the condensation with benzaldehyde was carried out at 0 °C in THF. However the desired olefins **4a,b** (**4a**: 64%, E only; **4b**: 54%, E only)[5] were accompanied by dienones **5a,b** (**5a**: 20%, E,E:E,Z=6:1; **5b**: 13%, 1E,4E:1Z,4E=8:1) as the elimination products of **4**. Several attempts to exclude the formation of dienones **5a,b** were not successful.

The dienones **5a,b** could be prepared, but in unsatisfactory yields (**5a**: 54%, E,E only; **5b**: 31%, 1E,4E:1Z,4E=9:1 as our best results[6]), by olefinations of 2-oxo-3-alkenylphosphonates **6a,b** (both E isomers) with benzaldehyde in the presence of lithium bromide and triethylamine, which were quantitatively and stereoselectively available by dehydration of **2a,b**.[1b]

Thus olefinations of either 4-alkoxy-2-oxoalkylphosphonates **3** or 2-oxo-3-alkenylphosphonates **6** could not provide a fruitful synthetic conversion.

To our surprise, not *O*-benzylated but *C*-benzylated product **7** was obtained (73% as a mixture of two diastereomers) when 4-hydroxy-2-oxononylphosphonate (**2b**) was treated with one equivalent of butyllithium followed by benzyl bromide (Scheme 2). In this reaction no elimination product **6b** was detected. The selective deprotonation adjacent to the phosphinyl moiety, not at the hydroxyl moiety, would be a result from high stabilization of the anionic center by the lithium chelation. These results indicate that *O*-unprotected 4-hydroxy-2-oxoalkylphosphonates **2** may undergo a successful olefination by the use of one equivalent of base and that the elimination as a major side reaction may be sufficiently suppressed when *O*-unprotected **2** is employed.[7]



Scheme 2.

O-Unprotected 4-hydroxy-2-oxoalkylphosphonates **2** underwent smooth and E-selective olefinations with both aromatic and aliphatic aldehydes to give 1-hydroxy-4-alken-3-ones **8** (Scheme 2 and Table 1). Olefination of **2b** bearing an alkyl substituent (R= *n*-Pen) was effected by NEt_3+LiBr producing high yields of **8b—d** (Entries 3—5), while phenyl-substituted **2a** gave only very poor yield (21%) of **8a** under identical conditions (Entry 1). Beside the elimination reaction leading to **5a** (9%), the major side reaction in this case was retro aldol condensation giving **9** (31%). Formation of both **5a** and **9** was apparently due to the instability of **8a** under the reaction conditions: A 1:2 mixture of **5a** and **9** was yielded on treatment of **8a** with NEt_3+LiBr in THF at room temperature, while **8a** was inert without LiBr.

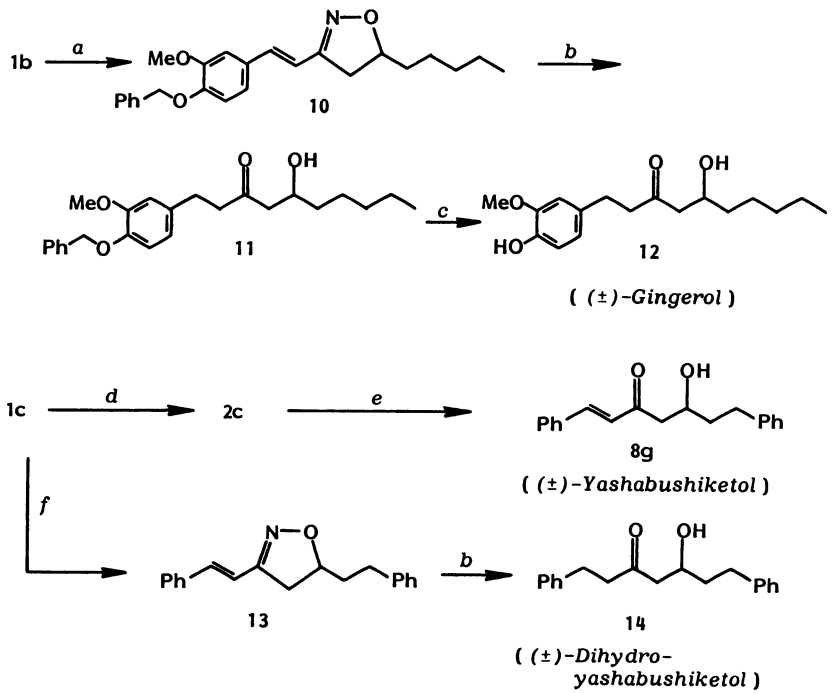
When DBU was used instead of triethylamine, the olefination reaction was significantly accelerated. The olefination reaction could be carried out at a lower temperature (0 °C) so that the side reactions were relatively suppressed. Thus the reaction of **2a** with benzaldehyde in the presence of DBU+LiBr (both 1 equiv) was very clean to give **8a** in 56% yield.[8,9] The unsatisfactory yield of **8a** was fully complemented by the recovery of the starting phosphonate **2a** (29%) and no formation of the side products **5a** and **9** (Entry 2).

It should be emphasized that 1-hydroxy-4-alken-3-ones **8e,f** bearing an ester or an acetal functionality

Table 1. Horner-Emmons Olefination of 4-Hydroxy-2-oxoalkylphosphonates **2a—e** Leading to 1-Hydroxy-4-alken-3-ones **8a—g**[a]

Entry		Aldehyde	Amine (equiv)	Temp/°C	Time/h	Product (yield/%)[b]
1	**2a** (R=Ph)	PhCHO	NEt_3 (1.2)	rt	24	**5a** (9), **8a** (21), **9** (31)
2	**2a**	PhCHO	DBU (1)[c]	0	24	**8a** (56)[d]
3	**2b** (R=*n*-Pen)	PhCHO	NEt_3 (1.2)	rt	24	**8b** (91)
4	**2b**	*n*-PrCHO	NEt_3 (1.2)	rt	24	**8c** (74)
5	**2b**	*i*-PrCHO	NEt_3 (1.2)	rt	24	**8d** (85)
6	**2d** (R=COOMe)	PhCHO	NEt_3 (1)	rt	15	**8e** (39)
7	**2d**	PhCHO	DBU (1)[c]	0	24	**8e** (52)[e]
8	**2e** (R=$CH(OEt)_2$)	PhCHO	NEt_3 (1.2)	rt	24	**8f** (64)[f]
9	**2c** (R=CH_2CH_2Ph)	PhCHO	DBU (1)[c]	0	24	**8g** (60)[g]

a) All reactions were carried out in dry THF in the presence of LiBr (1.5 equivalent). b) Yield of isolated products. c) One equivalent of LiBr was used. d) Recovered **2a**: 29%. e) Recovered **2d**: 21%. f) Recovered **2e**: 13%. g) Recovered **2c**: 18%.



a: 1) *n*-BuLi in THF, −78 °C, 2) 4-benzyloxy-3-methoxybenzaldehyde, rt. *b*: Raney Ni/$B(OH)_3$ in aqueous EtOH/dichloromethane, rt. *c*: H_2/5% Pd-C in MeOH, rt. *d*: Raney Ni/$B(OH)_3$ in aqueous EtOH, rt. *e*: 1) DBU/LiBr in THF, 0 °C, 2) benzaldehyde, 0 °C. *f*: 1) *n*-BuLi in THF, −78 °C, 2) benzaldehyde, rt.

Scheme 3.

could be available by these olefinations (Entries 6—8).

Synthetic applications of the diethoxyphosphinyl moieties of **1** and **2** were next examined (Scheme 3). 3-[(Diethoxyphosphinyl)-methyl]-5-pentyl-2-isoxazoline (**1b**) was condensed with 4-benzyloxy-3-methoxybenzaldehyde (*n*-BuLi, in THF at −78 °C) giving **10** (only E-isomer) in 79% yield. The N–O bond cleavage as well as the C–C double bond hydrogenation was carried out with Raney Ni (W-2) producing **11** (68%). Dichloromethane was employed as a co-solvent which increased the solubility of **10** in ethanol.[10] Debenzylation of **11** with palladium on charcoal gave a quantitative yield of (±)-Gingerol (**12**).

The Raney Ni reduction of 3-[(diethoxyphosphinyl)methyl]-5-(2-phenylethyl)-2-isoxazoline (**1c**) gave diethyl 4-hydroxy-2-oxo-6-phenylhexylphosphonate (**2c**) in 74% yield. The Horner–Emmons olefination of **2c** with benzaldehyde in the presence of DBU-LiBr at 0 °C led to (±)-Yashabushiketol (**8g**) as a single E-isomer. Reverse operation of the above procedure on **1c** gave (±)-Dihydroyashabushiketol (**14**) via 3-styryl-2-isoxazoline **13** (only E-isomer).

Experimental

General. Melting points were determined on a Yanagimoto melting point apparatus and are not corrected. IR spectra were taken with a JASCO IRA-1 or a JASCO A-702 spectrometer. ^1H NMR spectra were recorded on a Hitachi R-40 (90 MHz) or a JEOL FX-100 instrument (100 MHz) and ^{13}C NMR on a JEOL FX-100 spectrometer at 25.05 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra as well as high resolution mass spectra were measured with a JEOL-01SG-2 spectrometer at 70 eV of ionization energy. 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 60F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm), iodine, molybdophosphoric acid (5% in ethanol), or *p*-anisaldehyde (5% in ethanol containing 5% of sulfuric acid). For preparative column chromatography, Wakogel C-200, C-300 (Wako), and Silicagel 60 (Merck) were employed. Micro vacuum distillation was carried out on a Sibata GTO-250R Kugelrohr distilling apparatus. Solvents were evaporated at about 50 °C unless otherwise stated.

Materials. 3-[(Diethoxyphosphinyl)methyl]-2-isoxazolines **1a,b** and **1d,e** were prepared by the cycloaddition reactions of α-(diethoxyphosphinyl)acetonitrile oxide to the corresponding olefins.[1b] Diethyl 4-hydroxy-2-oxoalkylphosphonates **2a,b** and **2d,e** were obtained by the Raney Ni reduction of **1** in the presence of boric acid.[1b] The preparation of **1c** and **2c** is presented in the synthetic procedure of Yashabushiketol **8g** and Dihydroyashabushiketol **14**.

Diethyl 2-Oxo-4-phenyl-4-(2-tetrahydropyranyloxy)butylphosphonate (3a). To a solution of **1a** (0.977 g, 3.25 mmol) in dry dichloromethane (10 ml) was added 3,4-dihydro-2*H*-

pyran (0.821 g, 9.76 mmol) and then pyridinium *p*-toluenesulfonate (PPTS, 0.245 g, 0.976 mmol). The mixture was stirred under nitrogen at room temperature for 17 h and poured into water. The products were extracted with diethyl ether (15 ml×2). The combined ether was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was chromatographed over silica gel by using ethyl acetate to give **3a** (1.092 g, 87%): Colorless liquid (a mixture of two diastereomers); IR (neat) 1710, 1240, 1020, and 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.28, 1.30 (6H, each t, J=7.0 Hz, OEt), 1.1—1.9 (6H, m, THP), 2.8—3.4 (2H, m, $COCH_2$), 3.0—4.0 (2H, m, THP), 3.04, 3.18 (2H, each d, $^2J_{HP}$=22.0 Hz, PCH_2), 4.07, 4.09 (4H, each dq, $^3J_{HP}$=9.0 and J=7.0 Hz, OEt), 4.36, 4.85 (1H, each br, THP), 5.04, 5.20 (1H, each dd, J=8.5 and 4.5 Hz, CHOTHP), and 7.1—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=16.32 (qd, $^3J_{CP}$=7.4 Hz, OEt), 19.18, 19.35, 25.35, 30.59 (each t, THP), 43.34 (td, $^1J_{CP}$=126,5 Hz, PCH_2), 51.95 (t, $COCH_2$), 62.12 (t, THP), 62.62 (td, $^2J_{CP}$=7.4 Hz, OEt), 73.42, 75.42 (each d, CHOTHP), 95.30, 99.18 (each d, THP), 126.60, 127.13, 127.66, 128.18, 128.48, 128.77 (each d), 140.89, 142.60 (each s), and 200.19 (d, $^2J_{CP}$=5.9 Hz, CO); MS m/z (rel intensity, %) 299 (8, M^+ − 85), 283 (11), 194 (18), 179 (50), 167 (15), 152 (50), 151 (42), 131 (36), 125 (39), 123 (89), 109 (75), 105 (61), 104 (base peak), 103 (70), 97 (35), 91 (41), 85 (84), 81 (76), 78 (51), and 77 (90). This compound **3a** was used for the following reaction without further purification.

Diethyl 2-Oxo-4-(2-tetrahydropyranyloxy)nonylphosphonate (3b). A similar procedure using **2b** (0.806 g, 2.74 mmol), 3,4-dihydro-2*H*-pyran (0.691 g, 0.75 mmol), and PPTS (0.206 g, 0.82 mmol) in dichloromethane (15 ml) for 15 h at room temperature gave **3b** (0.869 g, 84%) after column chromatography over silica gel with diethyl ether: Colorless liquid (a mixture of two diastereomers); IR (neat) 1710, 1250, 1020, and 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.7—1.8 (17H, m, *n*-Pen and THP), 1.32 (6H, t, J=7.0 Hz, OEt), 2.6—3.0 (2H, m, $COCH_2$), 3.10, 3.16 (2H, each d, $^2J_{HP}$=22.5 Hz PCH_2), 3.3—4.3 (3H, m, THP), 4.12 (4H, dq, $^3J_{HP}$=8.0 and J=7.0 Hz, OEt), and 4.4—4.7 (1H, m, CHOTHP); ^{13}C NMR ($CDCl_3$) δ=13.65 (q, *n*-Pen), 16.00 (qd, $^3J_{CP}$=5.9 Hz, OEt), 19.59, 20.06, 22.24, 24.47, 24.71, 25.18, 30.77, 30.88, 31.47, 34.12, 35.30 (each t, THP and *n*-Pen), 42.83, 43.00 (each td, $^1J_{CP}$=126.5 Hz, PCH_2), 48.30, 49.59 (each t, $COCH_2$), 62.18 (td, $^2J_{CP}$=5.9 Hz, OEt), 62.42, 63.00 (each t, THP), 73.36, 73.71 (each d, CHOTHP), 98.30, 98.89 (each d, THP), 200.72, and 200.84 (each d, $^2J_{CP}$=5.9 Hz, CO); MS m/z (rel intensity, %) 293 (M^+ −85, 16), 278 (39), 277 (base peak), 223 (77), 195 (27), 194 (45), 179 (26), and 85 (27). This compound **3b** was used for the following reaction without further purification.

General Procedure for the Horner–Emmons Olefinations of 3 Leading to 4 and 5. As a typical procedure the olefination of **4a** with benzaldehyde is described as follows: To a solution of lithium bromide (0.109 g, 1.25 mmol) in dry THF (1 ml) was added **3a** (0.402 g, 1.05 mmol in THF (4 ml)). The mixture was stirred under nitrogen at room temperature for 10 min and triethylamine (0.16 ml, 1.15 mmol) was added at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. Addition of benzaldehyde (0.133 g, 1.25 mmol) was followed by the stirring at 0 °C for 18 h. The mixture was poured into ice water and 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 by using hexane–ethyl acetate (7:1 vol/vol) to give **4a** (0.226 g, 64%) and **5a** (0.049 g, 20%).

A similar procedure employing lithium bromide (0.102 g, 1.18 mmol) in dry THF (1 ml), **3b** (0.372 g, 0.983 mmol) in THF (4 ml), triethylamine (0.109g, 1.08 mmol), and benzaldehyde (0.125 g, 1.18 mmol) at 0 °C for 20 h gave **4b** (0.174 g, 54%) and **5b** (0.029 g, 13%) after the same chromatographic separation as shown above.

4a: (only E-isomer by ^1H NMR): Pale yellow liquid; IR (neat) 1660, 1610, 1580, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.2—1.9 (6H, m, THP), 2.83 (1H, dd, J=16.0 and 4.5 Hz, one of $COCH_2$), 3.1—4.0 (2H, m, THP), 3.32 (1H, dd, J=16.0 and 9.5 Hz, the other of $COCH_2$), 4.3—4.4, 4.8—5.0 (1H, each m, THP), 5.16, 5.28 (1H, each dd, J=9.5 and 4.5 Hz, CHOTHP), 6.67, 6.76 (1H, each d, J=16.0 Hz, COCH=), 7.0—7.7 (10H, m, Ph), and 7.48, 7.52 (1H, each d, J=16.0 Hz, PhCH=); ^{13}C NMR ($CDCl_3$) δ=19.18, 25.35, 30.53 (each t, THP), 49.12 (t, $COCH_2$), 61.71, 62.06 (each t, THP), 73.48, 76.01 (each d, CHOTHP), 94.71, 99.24 (each d, THP), 126.48, 126.83, 127.07, 127.48, 128.01, 128.42, 128.72, 129.07 (each d), 130.65, 134.60 (each s), 141.42, 143.19 (each d), and 197.95 (s, CO); MS m/z (rel intensity, %) 336 (M^+, 3), 252 (15), 251 (24), 131 (base peak), 104 (16), 103 (23), and 85 (92). HRMS Found: m/z 336.1722. Calcd for $C_{22}H_{24}O_3$: M, 336.1724.

4b: (only E-isomer by ^1H NMR): Pale yellow liquid; IR (neat) 1650, 1610, 1580, and 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.7—2.0 (17H, m, *n*-Pen and THP), 2.65, 2.71 (1H, each dd, J=15.5, 5.2 and J=15.5, 5.8 Hz, one of $COCH_2$), 2.97, 3.13 (1H, each dd, J=15.5, 7.3 and J=15.5, 6.2 Hz, the other of $COCH_2$), 3.3—4.3 (3H, m, THP and CHOTHP), 4.5—4.7 (1H, m, THP), 6.72, 6.74 (1H, each d, J=16.4 Hz, COCH=), and 7.2—7.6 (6H, Ph and =CH); ^{13}C NMR ($CDCl_3$) δ=14.06 (q, *n*-Pen), 20.00, 20.24, 22.59, 24.94, 25.18, 25.41, 31.24, 31.88, 34.65, 36.06, 45.89, 47.18, 62.95, 63.12 (each t, THP and *n*-Pen), 74.65, 76.01 (each d, CHOTHP), 98.83, 99.24 (each d, THP), 127.01, 127.24, 128.42, 129.07, 130.48, 130.65 (each d), 134.77, 134.95 (each s), 142.66, 143.01 (each d), 199.01, and 199.24 (each s, CO); MS m/z (rel intensity, %) 330 (M^+, 5), 131 (73), 103 (17), and 85 (base peak). HRMS Found: m/z 330.2171. Calcd for $C_{21}H_{30}O_3$: M, 330.2193.

5a: (a 6:1 mixture of E,E- and E,Z-isomers by ^1H NMR): Colorless solid; ^1H NMR ($CDCl_3$) E,E-isomer δ=7.00 (2H, d, J=15.6 Hz, COCH=), 7.1—7.7 (10H, m, Ph), and 7.65 (2H, d, J=15.6 Hz, PhCH=). E,Z-isomer δ=6.28 (1H, d, J=12.0 Hz, COCH=(Z)), 6.61 (1H, d, J=15.6 Hz, COCH=(E)), 6.90 (1H, d, J=12.0 Hz, PhCH=(Z)), and 7.1—7.7 (11H, m, Ph and PhCH= (E)). The major isomer of **5a** was identified to be (*E,E*)-1,5-diphenyl-1,4-pentadien-3-one by comparison with the authentic sample prepared from acetone and benzaldehyde.[11]

5b: (an 8:1 mixture of 1E,4E- and 1Z,4E-isomers by ^1H NMR): Pale yellow liquid; IR (neat) 1670, 1630, 1610, 1580, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) 1E,4E-isomer δ= 0.90 (3H, t, *n*-Pen), 1.0—1.8 (6H, m, *n*-Pen), 2.26 (2H, q, J=7.0 Hz, =CHCH$_2$), 6.40 (1H, dt, J=16.0 and 1.3 Hz, COCH=CHCH$_2$), 6.97 (1H, dt, J=16.0 and 7.0 Hz, =CHCH$_2$), 7.2—7.7 (5H, m, Ph), and 7.62 (1H, d, J=16.0 Hz, =CHPh); 1Z,4E-isomer δ=2.09 (2H, qd, J=7.0 and 1.5 Hz, =CHCH$_2$), 6.05 (1H, dt, J=16.0 and 1.5 Hz, COCH=CHCH$_2$), 6.20 (1H, d, J=12.8 Hz, PhCH=), 6.84 (1H, dt, J=16.0 and 7.0 Hz, =CHCH$_2$), 6.86 (1H, d, J=16.0 Hz, COCH=CHPh), and

7.2—7.7 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.00 (q, *n*-Pen), 22.53, 27.65, 27.94, 31.30, 31.47, 32.47, 32.77 (each t, *n*-Pen), 125.07, 128.48, 129.13, 129.54, 129.71, 130.54, 130.89 (each d), 135.13, 135.71 (each s), 138.89, 143.13, 148.60, 149.95 (each d), and 222.72 (s, CO); MS *m/z* (rel intensity, %) 228 (M^+, 20), 227 (34), 131 (25), 128 (37), 127 (20), 103 (59), 102 (22), 91 (22), 76 (66), 57 (32), 55 (37), 53 (22), 51 (27), 42 (25), and 40 (base peak). Found: C, 83.93; H, 8.76%. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83%.

A 2:1 mixture of 1E,4E- and 1Z,4E-isomers of **5b** was obtained in 30% yield when the reaction of **6b** with benzaldehyde was carried out at room temperature for 16 h in the presence of LiBr +NEt_3 (See Ref. 6). Their structures were clearly assigned on the basis of the ^{1}H NMR of this mixture, which was shown above.

General Procedure for the Olefination of 6 Leading to 5. As a typical procedure the olefination of **6b** with benzaldehyde is described below: To a solution of E-isomer of **6b** (0.197 g, 0.713 mmol) in dry THF (2 ml) was added lithium bromide (0.074 g, 0.856 mmol) under nitrogen. After 10 min at room temperature, the mixture was cooled to −20 °C. Benzaldehyde (0.076 g, 0.713 mmol) and then triethylamine (0.081 g, 0.11 ml, 0.799 mmol) were added. The resulting mixture was stirred for 2 h at −20 °C and then for 3 h at room temperature, poured into ice water, and extracted with diethyl ether (20 ml). The extract was washed with aqueous HCl, saturated aqueous sodium carbonate, and finally water. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed over silica gel to give **5b** (0.052 g, 31%, a 9:1 mixture of E- and Z-isomers by ^{1}H NMR) and recovered **6b** (13%).

A similar procedure using **6a** (0.223 g, 0.79 mmol), lithium bromide (0.082 g, 0.948 mmol), triethylamine (0.088 g, 0.12 ml, 0.869 mmol), and benzaldehyde (0.168 g, 1.58 mmol) at room temperature for 21 h gave **5a** (0.097 g, 52%, a 6:1 mixture of E- and Z-isomers by ^{1}H NMR).

Diethyl 1-Benzyl-4-hydroxy-2-oxononylphosphonate (7). To a solution of **2b** (0.326 g, 1.11 mmol) in dry THF (2 ml) was added dropwise, at −78 °C under nitrogen, butyllithium (15% solution in hexane, 0.69 ml, 1.11 mmol). After 10 min, benzyl bromide (0.379 g, 2.22 mmol) and then dry hexamethylphosphoric triamide (HMPA, 2 ml) were added slowly. The resulting mixture was warmed to room temperature, stirred for 6 h, and then poured into ice water. The products were extracted in diethyl ether (20 ml×3), the combined extracts were washed with water (50 ml×5), dried over magnesium sulfate, and finally evaporated in vacuo. The residue was chromatographed over silica gel by using hexane-ethyl acetate (3:2 vol/vol) to give **7** (0.312 g, 73%): Pale yellow liquid; IR (neat) 3400, 1700, 1600, 1490, 1240, 1020, and 790 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.7—1.6 (11H, m, *n*-Pen), 1.32 (6H, t, J=7.0 Hz, OEt), 2.2—3.5 (6H, m, CH_2, PCH, and OH), 3.5—4.3 (1H, m, CHOH), 4.12 (4H, dq, $^3J_{HP}$=8.0 and J=7.0 Hz, OEt), and 7.0—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.06 (q, *n*-Pen), 16.41 (qd, $^3J_{CP}$=5.9 Hz, OEt), 22.65, 25.12, 31.77 (each t, *n*-Pen), 32.48 (td, $^2J_{CP}$=3.0 Hz, $PhCH_2$), 36.59 (t, *n*-Pen), 52.18, 52.30 (each t, $COCH_2$), 55.00, 55.42 (each dd, $^1J_{CP}$=123.5 Hz, PCH), 62.77 (td, $^2J_{CP}$=5.9 Hz, OEt), 63.12, 63.42 (each d, CHOH), 126.95, 128.83 (each d), and 206.22 (d, $^2J_{CP}$=4.4 Hz, CO); MS *m/z* (rel intensity, %) 384 (M^+, 8), 313 (28), 241 (base peak), and 91 (25). HRMS Found: *m/z* 384.2066. Calcd for $C_{20}H_{33}O_5P$: M, 384.2064.

General Procedure for the Horner-Emmons Olefination of 2a—e Leading to 8a—g. As a typical procedure the reaction of **2a** with benzaldehyde leading to **8a** is described as follows: To a solution of lithium bromide (0.044 g, 0.503 mmol) in dry THF was added **2a** (0.151 g, 0.503 mmol). This mixture was stirred at room temperature under nitrogen for 10 min and cooled down to 0 °C. After DBU (0.076 g, 0.503 mmol) was added the stirring was continued for 30 min. Benzaldehyde (0.107 g, 1.01 mmol) was added dropwise. The mixture was stirred at 0 °C for 24 h, 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 (5:1 vol/vol) to give **8a** (0.071 g, 56%). The continued elution with ethyl acetate afforded **2a** (0.044 g, 29%).

The reactions of other phosphonates **2** with aldehydes were similarly carried out under the reaction conditions shown in Table 1 which also summarizes the results of the reactions.

8a: (a 20:1 mixture of E- and Z-isomers by ^{1}H NMR): Pale yellow liquid; IR (neat) 3400, 1650, 1600, 1580, and 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.01, (1H, d, J=5.0 Hz, one of $COCH_2$), 3.02 (1H, d, J=7.0 Hz, the other of $COCH_2$), 3.74 (1H, br s, OH), 5.21 (1H, dd, J=7.0 and 5.5 Hz, CHOH), 6.65, 7.49 (each 1H, d, J=16.5 Hz, PhC<u>H</u>=C<u>H</u>), and 7.0—7.6 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=49.12 (t, $COCH_2$), 70.18 (d, CHOH), 125.89, 126.48, 127.71, 128.60, 129.13, 130.89 (each d), 134.36, 143.42 (each s), 143.95 (d), and 200.18 (s, CO); MS *m/z* (rel intensity, %) 252 (M^+, 59), 146 (31), 145 (34), 131 (95), 120 (68), 106 (23), 105 (base peak), 104 (33), 103 (77), 91 (21), 79 (33), and 78 (21). HRMS Found: *m/z* 252.1143. Calcd for $C_{17}H_{16}O_2$: M, 252.1149. Z-Isomer of **8a**: ^{1}H NMR ($CDCl_3$) δ=6.10 (d, J=12.7 Hz, COCH=(Z)).

8b: (a 23:1 mixture of E- and Z-isomers by ^{1}H NMR): Colorless prisms (hexane); mp 38—39 °C; IR (KBr) 3350 and 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.6—1.7 (11H, m, *n*-Pen), 2.77 (2H, d, J=8.0 Hz, one of $COCH_2$), 2.80 (1H, d, J=4.0 Hz, the other of $COCH_2$), 3.24 (1H, br s, OH), 3.8—4.3 (1H, m, CHOH), 6.68, 7.53 (each 1H, d, J=16.0 Hz, PhC<u>H</u>=C<u>H</u>), and 7.0—7.6 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.06 (q, *n*-Pen), 22.65, 25.30, 31.83, 36.77 (each t, *n*-Pen), 47.24 (t, $COCH_2$), 68.01 (d, CHOH), 126.65, 128.60, 129.13, 130.83 (each d), 134.48 (s), 143.54 (d), and 201.01 (s, CO); MS *m/z* (rel intensity, %) 246 (M^+, 7), 146 (22), 131 (base peak), and 103 (29). Found: C, 78.10; H, 8.99%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%. Z-Isomer of **8b**: ^{1}H NMR ($CDCl_3$) δ=6.14 (d, J=12.6 Hz, COCH=(Z)).

8c: (Only E-isomer by ^{1}H NMR): Colorless liquid; IR (neat) 3400, 1650, and 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.7—1.8 (16H, m, *n*-Pen and *n*-Pr), 2.20 (2H, dt, J=8.0 and 7.0 Hz, *n*-Pr), 2.64 (1H, d, J=8.0 Hz, one of $COCH_2$), 2.68 (1H, d, J=4.0 Hz, the other of $COCH_2$), 3.20 (1H, br s, OH), 3.8—4.2 (1H, m, CHOH), 6.04 (1H, dt, J=16.0 and 1.5 Hz, COCH=), and 6.84 (1H, dt, J=16.0 and 7.0 Hz, CH_2C<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ=13.71, 14.06 (each q, *n*-Pen and *n*-Pr), 21.41, 22.71, 25.35, 31.94, 34.59, 36.77 (each t, *n*-Pen and *n*-Pr), 46.42 (t, $COCH_2$), 68.01 (d, CHOH), 131.13, 148.66 (each d, CH=CH), and 201.36 (s, CO); MS *m/z* (rel intensity, %) 212 (M^+, 1), 141 (55), 97 (base peak), 55 (89), 43 (35), and 41 (59). HRMS Found: *m/z* 212.1750. Calcd for $C_{13}H_{24}O_2$: M, 212.1775.

8d: (Only E-isomer by ^{1}H NMR): Colorless liquid; IR (neat) 3400, 1660, and 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.7—1.8 (11H, m, *n*-Pen), 1.07 (6H, d, J=7.0 Hz, *i*-Pr), 2.1—2.7 (1H, m, *i*-Pr), 2.66 (1H, d, J=8.0 Hz, one of $COCH_2$), 2.70 (1H, d, J=4.0 Hz, $COCH_2$), 3.28 (1H, br s, OH), 3.9—4.2 (1H, m, CHOH), 6.03 (1H, dd, J=16.0 and 1.0 Hz, COCH=), and 6.83 (1H, dd, J=16.0 and 6.5 Hz, *i*-PrCH=); ^{13}C NMR ($CDCl_3$) δ=14.06 (q, *n*-Pen), 21.30 (q, *i*-Pr), 22.65, 25.30 (each t, *n*-Pen), 31.24 (d, *i*-Pr), 31.88, 36.71 (each t, *n*-Pen), 46.42 (t, $COCH_2$), 67.89 (d, CHOH), 128.13, 154.84 (each d), and 201.72 (s, CO); MS *m/z* (rel intensity, %) 212 (M^+, 3), 141 (31), 97 (base peak), 69 (21), 56 (24), 43 (44), and 41 (80). HRMS Found: *m/z* 212.1765. Calcd for $C_{13}H_{24}O_2$: M, 212.1775.

8e: (only E-isomer by ^{1}H NMR): Pale yellow liquid; IR (neat) 3500, 1730, 1660, and 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.20 (2H, d, J=5.0 Hz, $COCH_2$), 3.5—3.8 (1H, m, OH), 3.76 (3H, s, COOMe), 4.64 (1H, q, J=5.5 Hz, CHOH), 6.71, 7.56 (each 1H, d, J=16.0 Hz, PhCH=CH), and 7.2—7.7 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=43.94 (t, $COCH_2$), 52.59 (q, COOMe), 67.30 (d, CHOH), 126.07, 128.60, 129.13, 130.95 (each d), 134.36 (s), 144.13 (d), 174.37 (s, COOMe), and 197.72 (s, CO); MS *m/z* (rel intensity, %) 234 (M^+, 11), 131 (base peak), 103 (76), 102 (21), 77 (63), and 52 (23); HRMS Found: *m/z* 234.0886. Calcd for $C_{13}H_{14}O_4$: M, 234.0891.

8f: (only E-isomer by ^{1}H NMR): Pale yellow liquid; IR (neat) 3450, 1650, 1610, 1580, and 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.22 (6H, t, J=7.0 Hz, OEt), 2.8—3.0 (3H, m, $COCH_2$ and OH), 3.4—3.9 (4H, m, OEt), 4.20 (1H, ddd, J=9.0, 7.0, and 4.5 Hz, CHOH), 6.72, 7.57 (each 1H, d, J=16.5 Hz, PhCH=CH), and 7.2—7.7 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=15.06 (q, OEt), 41.77 (t, $COCH_2$), 63.12, 63.65 (each t, OEt), 68.71 (d, CHOH), 104.01 (d, $CH(OEt)_2$), 126.54, 128.18, 128.77, 130.36 (each d), 134.30 (s), 142.95 (d), and 199.60 (s, CO); MS *m/z* (rel intensity, %) 233 (M^+—45, 4), 131 (42), 103 (base peak), 77 (30), 75 (40), and 48 (45). Found: C, 68.88; H, 7.95%. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97%.

8g: All data will be presented below (in the synthesis of Yashabushiketol **8g**).

Synthesis of (±)-Gingerol 12. Butyllithium (15% in hexane, 3.69 ml, 6 mmol) was added at −78 °C to a solution of **1b** (1.748 g, 6 mmol) in dry THF (12 ml) and stirred under nitrogen for 30 min. After 4-benzyloxy-3-methoxybenzaldehyde (1.599 g, 6.6 mmol) was added, the resulting mixture was stirred at −78 °C for 1 h, at room temperature for 4 h, poured into cold aqueous ammonium chloride solution, and extracted with diethyl ether (30 ml×2). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed over silica gel by using dichloromethane to give **10** (1.802 g, 79%) as a single E-isomer (^{1}H NMR): Colorless prisms (diethyl ether-hexane); mp 112—113 °C; IR (KBr) 1600, 1580, and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.8—2.0 (11H, m, *n*-Pen), 2.74 (1H, d, J=16.0 and 8.5 Hz, one of 4-H), 3.19 (1H, d, J=16.0 and 10.0 Hz, the other of 4-H), 3.86 (3H, s, OMe), 4.4—4.8 (1H, m, 5-H), 5.12 (2H, s, CH_2Ph), 6.59, 6.94 (each 1H, J=16.0 Hz, ArCH=CH), 6.8—7.1 (3H, m, Ar), and 7.2—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=13.98 (q, *n*-Pen), 22.52, 25.18, 31.60, 35.23 (each t, *n*-Pen), 38.50 (t, 4-C), 55.90 (q, OMe), 70.92 (t, OCH_2Ph), 81.49 (d, 5-C), 109.49, 113.79, 116.47, 120.63, 127.24, 127.89, 128.51 (each d), 129.46 (s), 135.72 (d), 136.81, 149.04, 149.87 (each s), and 157.66 (s, 3-C); MS *m/z* (rel intensity, %) 379 (M^+, 3), 288 (7), 92 (8), 91 (base peak), and 66 (14). Found: C, 75.96; H, 7.67; N, 3.74%. Calcd for $C_{24}H_{29}NO_3$: C, 75.96; H, 7.70; N, 3.69%. The mixture of **10** (0.38 g, 1 mmol), Raney Ni (W-2, suspension in ethanol, 0.14 ml), and boric acid (0.135 g, 2.1 mmol) in ethanol (5 ml, containing dichloromethane (2 ml) and water (1 ml)) was stirred at room temperature at an ordinary atmospheric pressure of hydrogen for 48 h. Insoluble materials were filtered off by the aid of celite. The filtrate was mixed with dichloromethane (30 ml), the dichloromethane was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed over silica gel with hexane–ethyl acetate (3:1 vol/vol) to give **11** (0.261 g, 68%): Colorless prisms (diethyl ether–hexane); mp 52—53 °C (lit,[12] mp 53—54 °C); IR (KBr) 3400, 1700, and 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.9—1.6 (11H, m, *n*-Pen), 2.4—2.6, 2.6—3.0 (2H+5H, m, CH_2 and OH), 3.84 (3H, s, OMe), 3.8—4.1 (1H, m, CHOH), 5.08 (2H, s, CH_2Ph), 6.5—6.9 (3H, m, Ar), and 7.1—7.5 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=14.06 (q, *n*-Pr), 22.59, 25.18, 29.18, 31.77, 36.65, 45.24, 49.53 (each t, CH_2), 56.00 (q, OMe), 62.77 (d, CHOH), 71.30 (t, OCH_2Ph), 112.60, 114.65, 120.30, 127.48, 127.89, 128.65 (each d), 134.36, 137.54, 146.83, 149.95 (each s), and 211.31 (s, CO); MS *m/z* (rel intensity, %) 384 (M^+, 14), 151 (15), 149 (19), 137 (19), and 91 (base peak). Found: C, 75.15; H, 8.43%. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39%. A mixture of **11** (0.038 g, 0.1 mmol) and palladium on charcoal (5%, 0.07 g) in methanol (3 ml) was stirred at room temperature at an ordinary atmospheric pressure of hydrogen for 7 h and then filtered by the aid of celite. The filtrate was evaporated in vacuo. The residue was purified through column chromatography over silica gel with hexane–ethyl acetate (3:1 vol/vol) to give (±)-Gingerol **12** (0.029 g, 100%): Colorless liquid; IR (neat) 3420, 1710, and 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.88 (3H, t, J=5.5 Hz, *n*-Pen), 1.0—1.8 (8H, m, *n*-Pen), 2.4—2.6, 2.6—3.2 (2H+5H, m, CH_2), 3.83 (3H, s, OMe), 3.7—4.2 (2H, m, CHOH and OH), and 6.4—6.9 (3H, m, Ar); MS *m/z* (rel intensity, %) 294 (M^+), 151 (16), 150 (55), 138 (13), and 137 (base peak). HRMS Found: *m/z* 294.1835. Calcd for $C_{17}H_{26}O_4$: M, 294.1830.

Synthesis of (±)-Yashabushiketol 8g. To a solution of *N*-2-(diethoxyphosphinyl)ethylidene hydroxylamine (0.625 g, 3.2 mmol) in dry *N,N*-dimethylformamide (DMF, 7 ml) was added at −20 °C *N*-bromosuccinimide (NBS, 1.139 g, 6.4 mmol in DMF (6.4 ml)). After 1 h at −20 °C and 30 min at 0 °C, dry diethyl ether (7 ml) was added. A mixture of triethylamine (0.324 g, 0.45 ml, 3.2 mmol) and 4-phenyl-1-butene (0.846 g, 6.4 mmol) in diethyl ether (7 ml) was added dropwise. The mixture was stirred at room temperaure for 18 h, poured into ice water, and extracted with dichloromethane (20 ml×2). The combined extracts were washed with water three times, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed over silica gel by using ethyl acetate to give **1c** (0.6 g, 58%): Pale yellow liquid; IR (neat) 1620, 1600, 1500, 1260, and 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.32 (6H, t, J=7.0 Hz, OEt), 1.7—2.2, 2.4—3.3 (2H+4H, m, CH_2 and 4-H), 2.93 (2H, d, $^2J_{HP}$=22.0 Hz, PCH_2), 4.11 (4H, qd, J=7.0 and $^3J_{HP}$=8.0 Hz, OEt), 4.4—4.8 (1H, m, 5-H), and 7.0—7.4 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=16.00 (q, $^3J_{CP}$=5.9 Hz, OEt), 26.00 (td, $^1J_{CP}$=141.2 Hz, PCH_2), 31.30, 36.53 (each t, CH_2), 42.00 (t, 4-C), 62.27 (td, $^2J_{CP}$=7.4 Hz, OEt), 80.01 (d, 5-C), 125.83, 128.25, 141.01 (each d), and 151.16 (d, $^2J_{CP}$=10.3 Hz, 3-C); MS *m/z* (rel intensity, %) 325 (M^+, 21), 220 (base peak), 192 (22),

164 (39), and 91 (40). HRMS Found: *m/z* 325.1443. Calcd for $C_{16}H_{24}NO_4P$: M, 325.1442. The mixture of **1c** (0.461 g, 1.42 mmol), boric acid (0.191 g, 2.976 mmol), and Raney Ni (W-2, 0.2 ml) in ethanol (7.8 ml, containing water (1.3 ml) was stirred at room temperature at an ordinary pressure of hydrogen for 13 h. The reaction mixture was filtered through celite and the filtrate was treated with dichloromethane (25 ml). The dichloromethane was dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed over silica gel by using ethyl acetate to give **2c** (0.343 g, 74%): Colorless liquid; IR (neat) 3400, 1700, 1600, 1490, 1240, 1020, and 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.30 (6H, t, J=7.0 Hz, OEt), 1.6—2.0, 2.5—3.2 (2H+6H, m, CH_2), 3.52 (1H, br s, OH), 4.12 (4H, qd, J=7.0 and $^3J_{HP}$=8.0 Hz, OEt), and 3.9—4.2 (1H, m, CHOH); ^{13}C NMR ($CDCl_3$) δ=16.29 (qd, $^3J_{CP}$=5.9 Hz, OEt), 31.83, 38.59 (CH_2), 43.03 (td, $^1J_{CP}$=128.0 Hz, PCH_2), 51.36 (CH_2), 62.77 (td, $^2J_{CP}$=5.9 Hz, OEt), 67.01 (d, CHOH), 125.95, 128.54, 128.65 (each d), 142.13 (s), and 202.72 (d, $^2J_{CP}$=5.9 Hz, CO); MS *m/z* (rel intensity, %) 328 (M^+, 16), 310(43), 277 (22), 223 (47), 220 (29), 195 (34), 194 (23), 179 (34), 172 (20), 167 (26), 152 (50), 151 (25), 139 (39), 125 (37), 123 (45), 109 (21), 105 (21), 97 (30), and 91 (base peak). HRMS Found: *m/z* 328.1446. Calcd for $C_{16}H_{25}O_5P$: M, 328.1438. To a solution of lithium bromide (0.065 g, 0.75 mmol) in dry THF (0.5 ml) was added **2c** (0.165 g, 0.5 mmol, in THF (1.5 ml)) and stirred at room temperature for 10 min. After addition of DBU (0.076 g, 0.5 mmol, in THF (0.5 ml)) at 0 °C the stirring was continued for 1 h. Benzaldehyde (0.107 g, 1 mmol) was added and the mixture was stirred at 0 °C for 24 h. It was then poured into ice water and 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 (5:1 vol/vol) to give (±)-Yashabushiketol **8g** (0.084 g, 60%) as a single E-isomer (^1H NMR). Further eluent with ethyl acetate gave **2c** (0.029 g, 18%). **8g**: Colorless needles (hexane); mp 82—83 °C (lit,[13] mp 59.5—60.5 °C); IR (KBr) 3300, 1650, 1610, 1580, and 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.6—1.9 (2H, m, $C\underline{H}_2CH_2Ph$), 2.4—2.9 (4H, m, $COCH_2$ and $CH_2C\underline{H}_2Ph$), 3.45 (1H, br s, OH), 3.9—4.3 (1H, m, CHOH), 6.65, 7.50 (each 1H, J=16.5 Hz, PhC$\underline{H}$=C$\underline{H}$), and 6.9—7.6 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=31.83, 38.30 (each t, CH_2CH_2Ph), 47.00 (t, $COCH_2$), 67.30 (d, CHOH), 126.01, 126.48, 128.54, 129.13, 130.89 (each d), 134.36, 142.13 (each s), 143.71 (d), and 200.89 (s, CO); MS *m/z* (rel intensity, %) 280 (M^+, 32), 175 (22), 131 (base peak), 103(38), 91 (41), 77 (20), and 32 (21). Found: C, 81.52; H, 7.12%. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19%.

Synthesis of (±)-Dihydroyashabushiketol 14. To a solution of **1c** (0.16 g, 0.492 mmol) in dry THF (1 ml) was added at −78 °C butyllithium (15% in hexane, 0.37 ml, 0.59 mmol) and stirred for 1 h under nitrogen. Benzaldehyde (0.104 g, 0.984 mmol) was added, the mixture was stirred at room temperature for 24 h, poured into aqueous ammonium chloride, and finally extracted with dichloromethane (20 ml×2). The combined extracts were washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed over silica gel by using hexane–ethyl acetate (5:1 vol/vol) to give **13** (0.102 g, 75%) as a single E-isomer (^1H NMR): Colorless needles (diethyl ether–hexane); mp 104—105 °C; IR (KBr) 1600 and 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.6—2.3, 2.6—3.4 (2H+4H, m, CH_2 and 4-H), 4.5—4.9 (1H, m, 5-H), 6.64, 7.07 (each 1H, d, J=17.0 Hz, PhC$\underline{H}$=C$\underline{H}$), and 7.0—7.6 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=31.77, 37.00, 38.53 (each t, CH_2 and 4-C), 80.65 (d, 5-C), 118.36, 126.18, 127.07, 128.69, 129.01 (each d), 136.01 (s), 136.25 (d), 141.30 (s), and 157.77 (s, 3-C); MS *m/z* (rel intensity, %) 277 (M^+, 65), 276 (base peak), 143 (26), 115 (23), 103 (39), 91 (72), and 77 (44). Found: C, 82.35; H, 6.91; N, 5.05%. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05%. The mixture of **13** (0.166 g, 0.6 mmol) and Raney Ni (W-2, suspension in ethanol, 0.16 ml) in ethanol (6 ml, containing dichloromethane (2.4 ml) and water (1.2 ml)) was stirred at room temperature under hydrogen for 14 h. All insoluble materials were filtered off and the filtrate was treated with dichloromethane (30 ml). The mixture was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed over silica gel with hexane–ethyl acetate (5:1 vol/vol) to give (±)-Dihydroyashabushiketol **14** (0.136 g, 80%): Colorless needles (hexane); mp 71—72 °C (lit,[14] mp 69—70.5 °C); IR (KBr) 3350, 1700, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.4—1.9, 2.3—3.0 (2H+9H, m, CH_2 and OH), 3.8—4.2 (1H, m, CHOH), and 6.9—7.2 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=29.41, 31.71, 38.24, 44.89, 49.42 (each t), 66.89 (d, CHOH), 125.95, 126.24, 128.54 (each d), 140.95, 142.01 (each s), and 210.77 (s, CO); MS *m/z* (rel intensity, %) 282 (M^+, 6), 264 (19), 133 (19), 105 (48), 104 (base peak), 92 (15), 91 (base peak), and 77 (19). Found: C, 81.02; H, 7.95%. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85%.

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2) Under basic conditions, they suffer from ready elimination of the hydroxyl moiety, a carbon–carbon bond cleavage through the retro aldol reaction, or some other decompositions. See Ref. 4a.

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5) The isomer ratio was determined on the basis of ^1H NMR spectra of the crude reaction mixture unless otherwise stated.

6) The olefination of **6b** with benzaldehyde was investigated under a variety of conditions: 1) NaH in 1,2-dimethoxyethane (DME), 0 °C, 1 h; benzaldehyde, room temp, 0.5 h: complex mixture×recovered **6b** (9%). 2) *n*-BuLi in THF, −78 °C, 0.5 h; benzaldehyde, −78 °C room temp, 44 h: **5b** (6%, 1E,4E:1Z,4E=7:1). 3) LDA in THF, −78 °C, 0.5 h; benzaldehyde, −78 °C room temp, 16 h: **5b** (12%, 1E,4E:1Z,4E=6:1)+recovered **6b** (12%). 4) $MgBr_2 \cdot OEt_2$+NEt_3+benzaldehyde in acetonitrile, room temp, 19 h: complex mixture. 5) LiCl+*N*,*N*-diisopropylethylamine+benzaldehyde in acetonitrile, room temp, 19 h: **5b** (5%, 1E,4E:1Z,4E=3:1). 6) LiBr+NEt_3+benzaldehyde in THF, room temp, 16 h: **5b** (30%, 1E,4E:1Z,4E=2:1).

7) From the viewpoint of pK_a value, the leaving ability of a hydroxyl group is slightly inferior to that of an alkoxy

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8) When this reaction was performed at 0 °C for 24 h in the presence of NEt_3 (1.2 equiv)+LiBr (1.5 equiv), no trace of **5a** was formed (**8a**: 38%; **9**: 3%; recovered **2a**: 36%).

9) DBU and LiBr were used both in one equivalent in order to avoid the retro aldol condensation.

10) Raney Ni reduction of **10** in aqueous ethanol was too slow because of its poor solubility.

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