A New Aldol Condensation of α-Allenic Esters with Aldehydes, Including a One-Pot Synthesis of Enyne Compounds[1]

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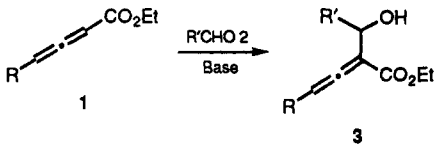
DABCO-catalyzed condensations of ethyl 2,3-butadienoate (**1a**) with aldehydes at −6 to 25 °C gave 3-hydroxy-2-vinylidenealkanoates **3** in 41–54% yields. Butyllithium-promoted condensations of **1a** with aldehydes at −105 to −70 °C afforded **3** in 56–67% yields. Reaction of ethyl 2,3-hexadienoate (**1k**) with 1-heptanal in the presence of butyllithium gave ethyl 3-hydroxy-2-(1-butenylidene)nonanoate (**3k**) in 64% yield; however, when the butyllithium-promoted condensation of **1k** with aldehydes was carried out at −90 to −70 °C and then treated in the same pot with wet THF for 11–27 h at room temperature, ethyl (*E*)-2-(1-alkynyl)-2-alkenoates **7** (12–36% yields) were obtained along with **3** (14-26% yields).

The aldol condensation is one of the most important reactions in organic synthesis. Since the first report by Wurtz in 1872,[2] a great number of papers have been published.[3] The aldol condensation is a useful and versatile method for the formation of carbon–carbon bonds as well as for the synthesis of chiral compounds. Although numerous papers concerning the condensation of aldehydes with the α-carbon of saturated ketones and esters have been published, the base-catalyzed condensations of α,β-unsaturated carbonyl compounds with aldehydes are less common. Some examples of this type of reaction, such as 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed condensations of aldehydes with acrylic esters and methyl vinyl ketone, have been reported.[4] In connection with our continuing interest in the chemistry of β-allenic esters,[5] we carried out the reaction of α-allenic esters **1** with aldehydes **2** in the presence of base. This paper describes the first aldol condensations of **1** with aldehydes **2** in the presence of either butyllithium or DABCO,[1] including a one-pot synthesis of enyne compounds, which have recently attracted the attention of organic chemists.

A number of years ago, a new series of highly active anticancer antibiotics, such as neocarzinostatin chromophore,[6] esperamicine A,[7] calicheamicin-γ,[8] and dynemicin A,[9] was isolated. These antibiotics contain a characteristic, cyclic 1,5-diyn-3-ene unit. The biological activity of these compounds has been ascribed to DNA cleavage resulting from H-atom abstraction from the sugar chain by a benzenoid biradical generated by Bergman cyclization[10] of the enediyne. In recent years, the design and synthesis of these natural products and their analogues have been extensively investigated, and many enediyne compounds have been synthesized.[11]

The reactions of α-allenic esters **1** with aldehydes **2** in the presence of DABCO at −6 to 25 °C or butyllithium at −105 to −70 °C provided moderate yields of aldol adducts **3**, substituted at the α position of **1**. The results of these



1 3

reactions are tabulated in Table I. DABCO-catalyzed condensations gave adducts **3** in 41– 54% yield, and the butyllithium-promoted condensations afforded adducts **3** in 56–67% yields. γ-Substituted allenes gave a ca. 1:1 mixture of two diastereomers, whose structures are de-

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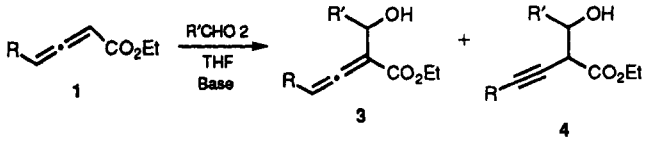
Table I. Reactions of 1 with Aldehydes 2 in the Presence of Base

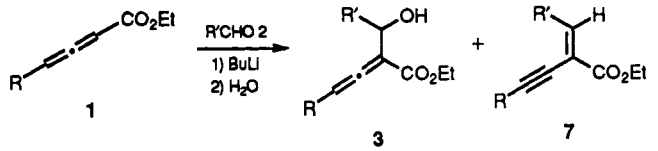


1 3 4

no.	R	R′	base	reactn condns temp (°C)	reactn condns time (h)	yield[a] (%) of products 3	yield[a] (%) of products 4
a	H	C_2H_5	DABCO	−6 to +23	16	41	
b	H	C_2H_5	*n*-BuLi	−105 to −99	5	58	
c	H	*n*-C_6H_{13}	DABCO	0–25	34	54	
d	H	*n*-C_6H_{13}	*n*-BuLi	−92	5	60[b]	
e	H	C_6H_5	*n*-BuLi	−93 to −70	5	56[c]	
f	H	*n*-$C_9H_{19}C{\equiv}C$	*n*-BuLi	−78	1	66	
g	H	$Me_2C{=}CH(CH_2)_2CHMeCH_2$	n-BuLi	−92	9	67	
h	CH_3	*n*-C_3H_7	*n*-BuLi	−90	2		73
i	CH_3	*n*-C_4H_9	*n*-BuLi	−100 to −90	7.5		61
j	CH_3	*n*-C_6H_{13}	*n*-BuLi	−83 to −78	2		59
k	C_2H_5	*n*-C_6H_{13}	*n*-BuLi	−85 to −70	2	64	

[a] Isolated yield. [b] Accompanied by disubstituted product **5d** (9.3%). [c] Accompanied by disubstituted product **5e** (18%).

Table II. Preparation of 3 and 7 by the Aldol Condensations of 1 with Aldehydes 2 and Subsequent Treatment with Water

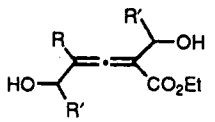


1 3 7

no.	R	R′	reactn time[a] (h)	temp (°C)	dehydration time[b] (h)	yield[c] (%) 3	yield[c] (%) 7
k	C_2H_5	n-C_6H_{13}	1.5	−85 to −70	17	22	28
			1.8	−85 to −70	27	26	36
l	C_2H_5	*n*-C_3H_7	4.5	−90 to −80	11		26
m	C_2H_5	(*E*)-*n*-$C_3H_7CH{=}CH$	6	−85 to −70	13		20
n	C_2H_5	C_6H_5	6	−85 to −75	16	14	12
o	C_2H_5	*n*-$C_9H_{19}C{\equiv}C$	2	−85 to −70	13		28
p	C_6H_5	$C_6H_5C{\equiv}C$	2.5	−85 to −75	12		15

[a] The reaction time under the anhydrous condition. [b] The time when the mixture was stirred with wet THF. [c] Isolated yield.

scribed below (structures A and B in Scheme II). In some of the reactions of ethyl 2,3-butadienoate with aldehydes in the presence of butyllithium, the products **5**, disubstituted at the α- and γ-positions of 1, were obtained in low yields.



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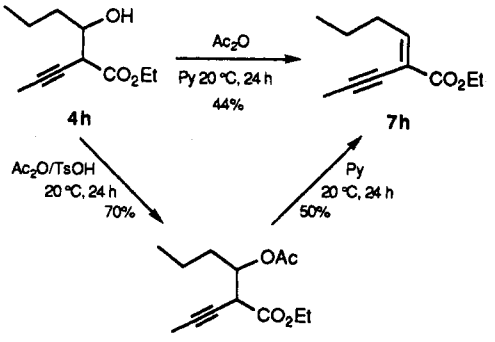
The reactions of ethyl 2,3-pentadienoate with aldehydes gave 2-(1-propynyl)-3-hydroxyalkanoates **4**, which were produced by migration of the allenic double bond. Ethyl 3-hydroxy-2-(1-propynyl)hexanoate (**4h**) was converted to enyne **7h** via acetoxylation with Ac_2O–*p*-TsOH (70% yields) and deacetoxylation (50% yield) of the resulting acetate **6**. Compound **7h** was also obtained directly by the treatment of **4h** with Ac_2O–pyridine in 44% yield. Enyne **7h** was determined to have the *E*-configuration by comparing the ^1H NMR data with those of an authentic sample.[12] The chemical shift of the olefinic proton of **7h** (7.06 ppm) was similar to that of ethyl (*E*)-2-ethynyl-2-heptenoate (7.22 ppm).[12] In contrast, it has been reported that the signal of the *Z*-isomer appears at 6.60 ppm.[12]



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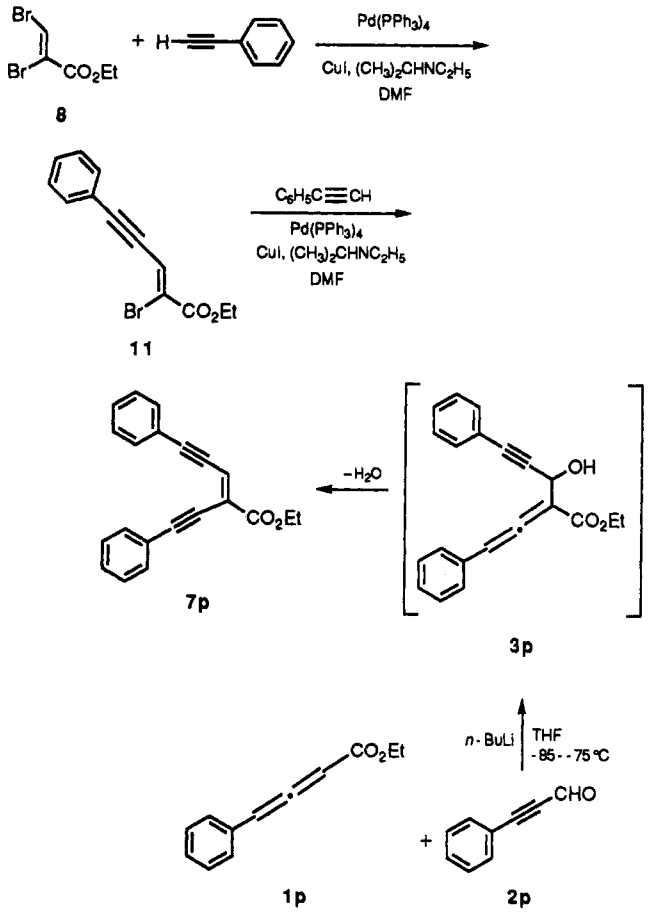
The outcome of the aldol condensation changed dramatically when the reaction was worked up in a manner different from that described in Table I. In the alternate workup, after the reaction was carried out at −70 to −90 °C, it was quenched with wet THF, and the mixture was stirred overnight at room temperature. The reaction gave enyne compound **7** (12–36% yield), the product of dehydration of **3** or **4**, in addition to adduct **3**, as shown in Table II.

In some cases, compound **7** was obtained as the sole product, while the reaction for 27 h gave **7k** in 36% yield along with **3k** (26%). Usually, the dehydration was carried out for 11–17 h. Prolonged dehydration did not improve the yield of **7** and afforded polymers as byproducts. Other efforts to obtain **7** by dehydration resulted in the formation of polymerized products. All of the reactions gave a single

(12) Kleijin, H.; Tigchelaar, M. T.; Meijer, J.; Vermeer, P. *J. Neth. Chem. Soc.* **1981**, *100*, 337.

Scheme I

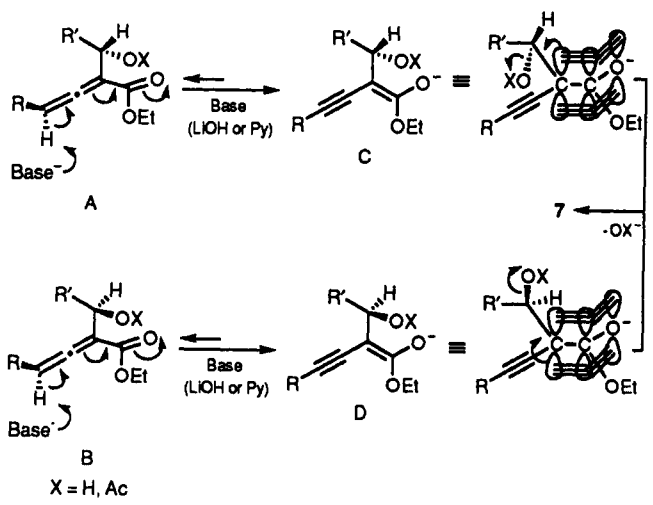


isomer of the enyne compound predominantly. No geometrical isomers were detected by ^{1}H-NMR or by ^{13}C NMR. The geometry was determined to be the (*E*)-configuration by comparison with similar known compounds.[12]

Furthermore, the structure of ethyl (*E*)-2-(phenylethynyl)-5-phenyl-2-penten-4-ynoate (**7p**) was unequivocally determined by independent synthesis as shown in Scheme I. The highly stereoselective coupling of ethyl (*Z*)-2,3-dibromopropenoate (**8**) with phenylacetylene in the presence of $Pd(PPh_3)_4$ as a catalyst[13] gave **7p** as the sole product via monosubstituted product **11**. The NMR data of **7p** were identical with those of the sample prepared by the present aldol condensation.

The reason that aldol adduct **3** affords enyne **7** exclusively is illustrated in Scheme II. The aldol reaction gives two diastereomers (A and B) as racemates. Lithium hydroxide is present in the reaction mixture when the reaction is treated with wet THF,[14] and the deacetoxylation of acetate **6** is carried out in pyridine. Under these basic conditions, alcohols A and B isomerize to enolates C and D, respectively. The alkyl groups of both enolates are situated far from the ester groups because of the conformational stability and the electronic push–pull effect[15] between the alkyl and ester groups. The π-orbitals of the

Scheme II



enolates and the LUMO of the leaving groups (OH and OAc) are anti-periplanar, and their overlap results in the formation of (*E*)-alkenoate **7** stereoconvergently.

This reaction is the first aldol condensation of α-allenic esters with aldehydes, and it provides a highly stereoselective and convenient one-pot synthesis of enyne and enediyne compounds, which may be useful for the Bergman cyclization.[16]

Experimental Section

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Eiichiro Amano in our laboratory. Infrared (IR) spectra were obtained with a JASCO Model A-102 infrared spectrophotometer. NMR spectra were recorded with JEOL JNM-FX100 apparatus (60 MHz), Varian VXR-200 (200 MHz for ^{1}H, 50 MHz for ^{13}C), and Varian VXR-500 (500 MHz for ^{1}H, 125 MHz for ^{13}C) spectrometers with $CDCl_3$ as a solvent. All chemical shifts are reported in δ units downfield from internal Me_4Si, and J values are given in hertz. Column chromatography was accomplished with 100–200-mesh Wakogel C-200. HPLC analyses were carried out with a Yanagimoto L-2000 fitted with a Yanapak SA-I column (6-mm o.d. × 250 mm).

All reactions were carried out under an atmosphere of nitrogen. All solvents were purified by distillation from the indicated drying agents: dichloromethane (CaH_2), triethylamine (CaH_2), THF (sodium benzophenone ketyl), HMPA (BaO), and methanol (Mg).

Ethyl 2,3-dienoates **1** were prepared by the method described in the literature.[17] 2-Dodecynal (**2f**) was prepared from tetrahydropyranyl propargyl ether in three steps as described below. Other reagents were commercially available and, if necessary, were purified by usual methods.

Tetrahydropyranyl 2-Dodecynyl Ether (9). To a solution of tetrahydropyranyl propargyl ether (3.00 g, 21.4 mmol) in THF (15 mL) at 0 °C was added butyllithum (1.55 M in hexane, 13.8 mL, 21.4 mmol) by syringe. After 30 min, a solution of nonyl bromide (4.44 g, 21.4 mmol) in HMPA (15 mL) was added by syringe at 0 °C, and then the mixture was stirred for 2 h at rt. The mixture was poured into ice–water, and the organic layer was extracted with ether, washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel to yield 5.34 g (93.8%) of **9**: R_f = 0.66 (hexane/ethyl acetate = 4/1); IR (neat) 2930, 2850, 2220, 1740 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.90 (t, J = 7 Hz, 3 H), 1.10–2.50 (m, 24 H), 3.20–4.00 (m, 2 H), 4.10 (d, J = 3 Hz, 2 H), 4.72 (bs, 1 H).

2-Dodecynol (10). A 50-mL dry, round-bottomed flask, charged with ion-exchange resin (Dowx-50w, 1.20 g, Muro-

(13) Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M. *Tetrahedron Lett.* **1989**, *30*, 6997.

(14) Independently, it was shown that the dehydration of aldol adducts **3** with aqueous LiOH solution gives enyne **7**. For example, treatment of **3k** (25 mg, 0.1 mmol) with LiOH (7 mg, 0.3 mmol) in H_2O/THF (0.2 mL/1 mL) at rt gave 11 mg (47%) of **7k** and 9 mg of unidentified mixtures.

(15) (a) Manatt, S. L.; Roberts, J. D. *J. Org. Chem.* **1959**, *24*, 1336. (b) Breslow, R.; Kivelevich, D.; Mitchell, M. J.; Fabian, W.; Wendel, K. *J. Am. Chem. Soc.* **1965**, *87*, 5132.

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(17) Bestmann, H. J.; Hartung, H. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 214.

machikagaku kogyo Ltd.), was flushed with nitrogen. Methanol (20 mL) and **9** (1.63 g, 6.13 mmol) were injected into the flask by syringe. The mixture was stirred for 12 h at rt and then filtered. After filtration, the filtrate was concentrated in vacuo, and the residue was purified by bulb-to-bulb distillation (150 °C/3 mmHg) to yield 809 mg (72.5%) of **10**: IR (neat) 3330, 2920, 2850, 2300, 2220 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.90 (t, J = 7 Hz, 3 H), 1.10–1.80 (m, 14 H), 1.90–2.40 (m, 2 H), 4.10 (t, J = 2 Hz, 2 H).

2-Dodecynal (2f). To a mixture of manganese dioxide (p-EMD,[18] 6.41 g, 73.4 mmol) and hexane (20 mL) was added **10** (670 mg, 3.68 mmol). The mixture was stirred for 2.3 h at rt and then filtered. After filtration, the filtrate was concentrated in vacuo, and the residue was purified by bulb-to-bulb distillation (150–160 °C/7 mmHg) to yield 497 mg (75.0%) of **2f**: IR (neat) 2930, 2850, 2280, 2200, 1670 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.90 (t, J = 7 Hz, 3H), 1.10–1.80 (m, 14 H), 2.20 (m, 2 H), 9.06 (s, 1 H).

Aldol Condensation of Allene 1 with Aldehyde 2. Some representative examples are given below.

Ethyl 3-Hydroxy-2-vinylidenepentanoate (3a). To a solution of DABCO (44 mg, 0.39 mmol) in 1 mL of dry ether at −6 °C was added ethyl 2,3-butadienoate (**1a**) (0.316 g, 2.82 mmol) under an atmosphere of argon. To the stirred mixture was added propionaldehyde (0.16 g, 2.76 mmol), and then the ice bath was removed. The mixture was stirred for 16 h at rt and poured into water. The organic materials were extracted with ether, and the combined extracts were washed with dilute HCl and water and dried over $MgSO_4$. Concentration of the extract gave 194 mg (42%) of **3a**: R_f = 0.39 (hexane/ethyl acetate = 2/1); IR (neat) 3500, 1965, 1941, 1710, 1260 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.93 (t, J = 7 Hz, 3 H), 2.78 (s, 1 H), 4.16 (m, 3 H), 5.08 (s, 1 H), 5.11 (s, 1 H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 10.1, 14.1, 28.3, 61.1, 70.7, 80.5, 102.9, 167.0, 212.3. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.25; H, 8.16.

Ethyl 3-Hydroxy-2-vinylidenenonanoate (3d) and Ethyl 2-(1-Hydroxyheptyl)-5-hydroxy-2,3-undecadienoate (5d). To a solution of ethyl 2,3-butadienoate (0.123 g, 1.10 mmol) in dry THF (8 mL) at −92 °C was added butyllithium (1.59 M in hexane, 0.63 mmol, 1.00 mL) under an atmosphere of nitrogen. After 1 h, 1-heptanal (0.114 g, 1.00 mmol) was added, and the mixture was stirred for 5 h at −92 °C. Wet THF was added, and the mixture was poured into ice–water and neutralized with 10% HCl. Organic materials were extracted with ethyl acetate, and the combined extracts were washed with water and dried over $MgSO_4$. After evaporation of the solvent, the products were separated by column chromatography (eluent: hexane/ethyl acetate = 10/1–1/1) on silica gel to give 0.136 g (60%) of **3d** as the first fraction: IR (neat) 3520 (OH), 1970, 1945, 1715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, J = 7 Hz, 3 H), 1.27 (m, 1 H), 1.42 (m, 1 H), 1.60 (m, 2 H), 4.20 (q, J = 7 Hz, 2 H), 4.37 (m, 1 H), 5.13 (s, 1 H), 5.21 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 22.6, 25.8, 29.1, 31.8, 35.5, 61.2, 69.3, 80.6, 103.4, 167.0, 212.5. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.79; H, 9.58. The second fraction gave 36 mg of a clean oil. HPLC analysis [Unisil Q (10.7-mm i.d. × 250 mm), eluent: hexane/ethyl acetate/ethanol = 80/1/1, 2.0 mL/min] showed four peaks at t_R = 40.5, 46.8, 59.8, and 82.4 min in a 8.1/11.8/31.6/35.3 ratio of peak areas due to the diastereomers of **5d** and three unidentified peaks at 32.5, 50.0, and 79.5 min. All of the components were collected and identified. First fraction: t_R = 40.5 min; 0.9% yield: ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, J = 6.06 Hz, 3 H), 0.88 (t, J = 7.58 Hz, 3 H), 1.27 (m, 16 H), 1.63 (m, 4 H), 4.21 (q, J = 7.16 Hz, 2 H), 4.28 (q, J = 6.51 Hz, 1 H), 4.43 (dt, J = 1.61 and 6.51 Hz, 1 H), 5.72 (dd, J = 1.74 and 6.41 Hz, 1 H). Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.65. Found: C, 70.72; H, 10.69. Second fraction: t_R = 46.8 min; 1.3% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 6.86 Hz, 3 H), 0.86 (t, J = 6.86 Hz, 3 H), 1.27 (m, 16 H), 1.60 (m, 4 H), 4.20 (q, J = 7.13 Hz, 2 H), 4.28 (q, J = 6.57 Hz, 1 H), 4.40 (dt, J = 2.16 and 6.97 Hz, 1 H), 5.75 (dd, J = 1.92 and 6.13 Hz, 1 H). Third fraction: t_R = 59.8 min; 3.4% yield; ^1H NMR (500 Hz, $CDCl_3$) δ 0.87 (t, J = 6.88 Hz, 3 H), 0.88 (t, J = 6.88 Hz, 3 H), 1.27 (m, 16 H), 1.54–1.70 (m, 4 H), 4.20 (q, J = 7.11 Hz, 2 H), 4.28 (q, J = 6.60 Hz, 1 H), 4.42 (dt, J = 1.71 and 6.35 Hz, 1 H), 5.70 (dd, J = 1.74 and 6.78 Hz, 1 H). Fourth fraction: t_R = 82.4 min; 3.7% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.05 Hz, 3 H), 0.86 (t, J = 6.68 Hz, 3 H), 1.27 (m, 16 H), 1.54–1.71 (m, 4 H), 4.20 (q, J = 7.13 Hz, 2 H), 4.27 (q, J = 6.35 Hz, 1 H), 4.39 (dt, J = 1.75 and 6.75 Hz, 1 H), 5.73 (dd, J = 1.68 and 6.35 Hz, 1 H). Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.54; H, 10.65. Found: C, 70.65; H, 10.78.

Ethyl 2-(1-Butenylidene)-3-hydroxynonanoate (3k). To a stirred solution of ethyl 2,3-hexadienoate (1.00 g, 7.14 mmol) in 15 mL of dry THF at −85 °C was added butyllithium (1.66 M in hexane, 4.3 mL, 7.14 mmol) under an atmosphere of nitrogen. After 30 min, 1-heptanal (813 mg, 7.14 mmol) was added, and the mixture was stirred for 1.5 h at −85 to −70 °C. Water (2 mL) was added, and the ice bath was removed. After the mixture was neutralized with 10% HCl, the organic materials were extracted with ethyl acetate. The combined extracts were washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 30/1), giving 1.16 g (64%) of **3k** as a mixture of two diastereomers (55/45 ratio by ^{13}C NMR analysis). The two diastereomers were separated by repeated column chromatography on silica gel (hexane/ethyl acetate = 30/1). First fraction: R_f = 0.43 on TLC (hexane/ethyl acetate = 4/1); IR (neat) 3500, 1960, 1710, 1465, 1255 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (t, J = 6.84 Hz, 3 H), 1.06 (t, J = 7.38 Hz, 3 H), 1.27 (t, J = 7.22 Hz, 3 H), 1.10–1.70 (m, 10 H), 2.16 (m, 2 H), 4.05–4.35 (m, 1 H), 4.20 (q, J = 7.34 Hz, 2 H), 4.36 (dq, J = 1.74 and 7.36 Hz, 1 H), 5.63 (dt, J = 1.74 and 7.36 H, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.29, 14.04, 14.17, 21.23, 22.58, 22.78, 29.10, 31.78, 35.44, 60.95, 69.78, 98.40, 104.01, 167.64, 208.12. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.72; H, 10.10. Second fraction: R_f = 0.39 on TLC (hexane/ethyl acetate = 4/1); IR (neat) 3500, 1960, 1710, 1465, 1255 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (bt, J = 6.84 Hz, 3 H), 1.07 (t, J = 7.32 Hz, 3 H), 1.28 (t, J = 7.22 Hz, 3 H), 1.10–1.70 (m, 10 H), 2.16 (m, 2 H), 4.05-4.35 (m, 1 H), 4.21 (q, J = 7.32 Hz, 2 H), 4.40 (dq, J = 1.56 and 4.88 Hz, 1 H), 5.70 (dt, J = 1.56 and 4.88 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.28, 14.06, 14.19, 21.27, 22.59, 25.80, 29.15, 31.81, 35.54, 60.96, 69.52, 98.51, 104.15, 163.85, 208.11. Anal. Calcd for $C_{15}H_{26}O_3$; C, 70.83; H, 10.30. Found: C, 70.94; H, 10.31.

Other enoates **3** and **5** were prepared as described above, and their physical and analytical data are shown below.

Ethyl 3-hydroxy-3-phenyl-2-vinylidenepropanoate (3e): R_f = 0.43 on TLC (hexane/ethyl acetate = 2/1); IR (neat) 3500, 1970, 1715, 1260, 1040 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.27 (t, J = 7 Hz, 3 H), 3.20 (br s, 1 H), 4.12 (q, J = 7 Hz, 2 H), 4.98 (d, J = 2 Hz, 2 H), 5.40 (m, 1 H), 7.18 (m, 5 H). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.47; H, 6.59.

Ethyl 5-hydroxy-2-((hydroxyphenyl)methyl)-5-phenyl-2,3-pentadienoate (5e) was obtained as a mixture of three diastereomers. The compounds were separated by preparative HPLC (Unisil Q (10.7-mm i.d. × 250 mm), eluent; hexane/ethyl acetate/ethanol = 20/1/1, 2.0 mL/min). Diastereomer 1 of **5e**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.32 Hz, 2 H), 2.54 (br s, 1 H), 3.77 (br s, 1 H), 4.19 (m, 2 H), 5.28 (d, J = 6.29 Hz, 1 H), 5.60 (s, 1 H), 5.72 (dd, J = 1.95 and 6.35 Hz, 1 H), 7.2–7.4 (m, 10 H). Diastereomer 2 of **5e**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.22 Hz, 3 H), 2.56 (s, 1 H), 3.48 (d, J = 4.88 Hz, 1 H), 4.16 (m, 2 H), 5.25 (d, 1 H), 5.54 (d, J = 2 Hz, 1 H), 5.81 (dd, J = 1.75 and 5.75 Hz, 1 H), 7.15–7.32 (m, 10 H). Diastereomer 3 of **5e**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, J = 7.22 Hz, 3 H), 2.10 (br s, 1 H), 3.29 (br s, 1 H), 4.21 (m, 2 H), 5.19 (d, J = 5.75 Hz, 1 H), 5.58 (s, 1 H), 5.83 (dd, J = 2.0 and 6.0 Hz, 1 H), 7.21–7.34 (m, 10 H). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.05; H, 6.21. Found: C, 74.11; H, 6.34.

Ethyl 3-hydroxy-2-vinylidene-4-tetradecynoate (3f): R_f = 0.32 on TLC (hexane/ethyl acetate = 4/1); IR (neat) 3450, 1964, 1926, 1712, 1252, 1018 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.84 (t, J = 6.5 Hz, 3 H), 1.26 (m, 17 H), 2.10 (m, 2 H), 3.60 (br s, 1 H), 4.21 (q, J = 7.2 Hz, 2 H), 5.16 (s, 1 H), 5.30 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.01, 14.07, 18.6, 22.6, 28.4, 28.5, 28.7,

(18) Commercial name of electrolytic manganese dioxide (see ref 19). We are grateful to Mitsui Mining & Smelting Co., Ltd., for the donation of p-EMD. We also thank professor Isao Tari for the fruitful discussion concerning electrolytic manganese dioxide.

(19) Tsuboi, S.; Ishii, N.; Sakai, T.; Tari, I.; Utaka, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1888.

28.9, 29.1, 29.2, 61.1, 61.6, 77.8, 81.3, 86.9, 102.1, 166.1, 212.5. Anal. Calcd for $C_{16}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.05; H, 9.81.

Ethyl 3-hydroxy-5,9-dimethyl-2-vinylidene-8-decenoate (3g): R_f = 0.43 on TLC (hexane/ethyl acetate = 2/1); IR (neat) 3450, 1965, 1940, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 6 Hz, 3 H), 1.29 (t, J = 7 Hz, 3 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 1.0–2.5 (m, 7 H), 4.18 (m, 3 H), 4.8–5.2 (m, 1 H), 5.10 (s 1 H), 5.13 (s, 1 H). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.89; H, 9.90.

Ethyl 3-Hydroxy-2-(1-propynyl)hexanoate (4h). To a solution of ethyl 2,3-pentadienoate (620 mg, 4.92 mmol) in 10 mL of dry THF at −80 °C was added butyllithium (1.63 M in hexane, 3.02 mL, 4.92 mmol). After 30 min, 1-butanal (354 mg, 4.92 mmol) was slowly added dropwise, and the mixture was stirred at −85 to −78 °C for 2 h. Wet THF (2 mL) was added, and the mixture was neutralized with 10% HCl. The organic materials were extracted with ethyl acetate, and the combined extracts were washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was chromatographed on silica gel (hexane/ethyl acetate = 20/1–2/1) to afford 509 mg (52.3%) of a mixture of two diastereomers of **4h**: R_f = 0.30 and 0.25 (hexane/ethyl acetate = 4/1). HPLC analysis (YMC-Pack (6-mm i.d. × 250 mm), hexane/ethyl acetate = 5/1, flow rate = 1.0 mL/min) showed two peaks at t_R = 18.5 and 22.5 min in a 53.4/46.6 ratio of integrated peak areas. An analytical sample was collected by preparative HPLC. The early fraction, ***anti*-4h**: IR (neat) 3450, 2950, 2855, 2230, 1730, 1460 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3 H), 1.27 (t, J = 7.04 Hz, 3 H), 1.30–1.70 (m, 4 H), 1.84 (d, J = 2.50 Hz, 3 H), 2.64 (br s, 1 H), 3.33 (dq, J = 3.80 and 2.5 Hz, 1 H), 3.92 (m, 1 H), 4.19 (q, J = 7.20 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 3.63, 13.80, 14.11, 18.57, 36.26, 44.91, 61.56, 71.98, 72.73, 80.72, 170.55. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.49; H, 9.36. The later fraction, ***syn*-4h**: IR (neat) 3450, 2950, 2855, 2230, 1730, 1460 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (t, J = 6.90 Hz, 3 H), 1.27 (t, J = 7.28 Hz, 3 H), 1.30–1.70 (m, 4 H), 1.81 (d, J = 2.50 Hz, 3 H), 2.64 (br s, 1 H), 3.30 (dq, J = 7.76 and 2.56 Hz, 1 H), 3.92 (m, 1 H), 4.20 (q, J = 7.22 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 3.63, 13.80, 14.11, 18.81, 36.76, 44.91, 61.56, 71.25, 71.61, 81.46, 170.55. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.56; H, 9.06. Found: C, 66.49; H, 9.36.

Compounds **4i** and **4j** were prepared in a manner similar to that described for the preparation of **4h**, and their physical properties and analytical data are shown below.

Ethyl 3-hydroxy-2-(1-propynyl)heptanoate (4i) was obtained in 61% yield as a mixture of two diastereomers. HPLC analysis (YMC-Pack (6-mm i.d. × 250 mm), hexane/ethyl acetate = 5/1, flow rate = 1.0 mL/min) showed two peaks at t_R = 17.2 and 21.0 min in a 53.6/46.4 ratio of integrated peak areas. Both fractions were collected by preparative HPLC. Early fraction, ***anti*-4i**: R_f = 0.30 (hexane/ethyl acetate = 4/1); IR (neat) 3450, 2950, 2850, 2225, 1730, 1460 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.00 Hz, 3 H), 1.27 (t, J = 7.00 Hz, 3 H), 1.10–1.80 (m, 6 H), 1.81 (d, J = 2.50 Hz, 3 H), 2.61 (br s, 1 H), 3.30 (dq, J = 7.50 and 2.50 Hz, 1 H), 3.92 (m, 1 H), 4.19 (br q, J = 3.59 and 7.00 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 3.58, 13.89, 14.00, 22.46, 27.45, 33.80, 45.21, 61.49, 72.19, 72.75, 80.67, 170.52. Anal. Calcd for $C_{12}H_2O_3$: C, 67.89; H, 9.50. Found: C, 67.64; H, 9.42. Later fraction, ***syn*-4i**: R_f = 0.25 (hexane/ethyl acetate = 4/1); IR (neat) 3450, 2950, 2850, 2225, 1730, 1460 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.00 Hz, 3 H), 1.27 (t, J = 7.00 Hz, 3 H), 1.10–1.80 (m, 6 H), 1.81 (d, J = 2.50 Hz, 3 H), 2.51 (d, J = 6.00 Hz, 1 H), 3.35 (dq, J = 3.30 Hz, 1 H), 3.90 (m, 1 H), 4.21 (q, J = 7.00 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 3.69, 13.93, 14.04, 22.48, 27.80, 34.40, 44.93, 61.52, 71.57, 72.22, 81.52, 170.59. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.62; H, 9.61.

Ethyl 3-hydroxy-2-(1-propynyl)nonanoate (4j) was obtained in 59% yield as a mixture of two diastereomers. HPLC analysis (YMC-Pack (6-mm i.d. × 250 mm), hexane/ethyl acetate = 4/1) showed two peaks at t_R = 15.0 and 18.5 min in a 50/50 ratio of integrated peak areas. Both fractions were collected by preparative HPLC. Early fraction, ***anti*-4j**: R_f = 0.34 (hexane/ethyl acetate = 4/1); IR (neat) 3450, 2920, 2850, 2230, 1730, 1460 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (t, J = 6.81 Hz, 3 H), 1.27 (t, J = 7.12 Hz, 3 H), 1.10–1.90 (m, 8 H), 1.80 (d, J = 2.50 Hz, 3 H), 2.61 (br s, 1 H), 3.30 (dq, J = 7.76 and 2.56 Hz, 1 H), 3.90 (m, 1 H), 4.19 (q, J = 7.12 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 3.60, 14.00 (2C), 22.53, 25.26, 29.08, 31.70, 34.13, 45.23, 61.51, 72.22, 72.78, 80.69, 170.55. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.86; H, 10.13. Later fraction, ***syn*-4j**: R_f = 0.28 (hexane/ethyl acetate = 4/1); IR (neat) 3450, 2920, 2850, 2230, 1730, 1460 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (t, J = 6.68 Hz, 3 H), 1.26 (t, J = 7.26 Hz, 3 H), 1.10–1.90 (m, 8 H), 1.83 (d, J = 2.44 Hz, 3 H), 2.60 (br s, 1 H), 3.33 (dq, J = 3.84 and 2.60 Hz, 1 H), 3.90 (m, 1 H), 4.18 (q, J = 7.16 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 3.63, 13.98 (2C), 22.47, 25.54, 29.02, 31.72, 34.65, 44.89, 61.55, 71.54, 75.72, 81.45, 170.56. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.74; H, 10.04.

Preparation of Enynes 7. A representative example is given below.

Ethyl (*E*)-2-(1-Butynyl)-2-nonenoate (7k). To a solution of ethyl 2,3-hexadienoate (1.00 g, 7.14 mmol) in 15 mL of dry THF at −85 °C was added 4.30 mL of butyllithium (1.66 M in hexane, 7.14 mmol). After 30 min, 1-heptanal (813 mg, 7.14 mmol) was slowly added. The mixture was stirred for 2 h at −85 to −70 °C. After the addition of wet THF, the mixture was allowed to come to rt, stirred for 27 h, and then neutralized with 10% HCl. The organic materials were extracted with ethyl acetate, and the combined extracts were washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel (hexane/ethyl acetate = 30/1) to give 607 mg (36%) of **7k**: R_f = 0.57 on TLC (hexane/ethyl acetate = 4/1); IR (neat) 2220, 1730, 1615 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (bt, J = 6.62 Hz, 1 H), 1.20 (t, J = 7.38 Hz, 3 H), 1.30 (t, 7.22 Hz, 3 H), 1.10–1.60 (m, 8 H), 2.40 (q, J = 7.38 Hz, 2 H), 2.41 (q, J = 7.44 Hz, 2 H), 4.21 (q, J = 7.28 Hz, 2 H), 7.11 (t, J = 7.45 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.29, 13.84, 14.00, 14.15, 22.50, 28.02, 28.95, 30.61, 61.13, 73.56, 98.45, 117.49, 152.03, 165.28. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.30. Found: C, 75.98; H, 10.50.

Other enynes **7** were prepared as described above, and their physical and analytical data are shown below.

Ethyl (*E*)-2-(1-butynyl)-2-hexenoate (7l): 36% yield; R_f = 0.56 (hexane/ethyl acetate = 4/1); IR (neat) 2960, 2860, 2200, 1720, 1610; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, J = 7.35 Hz, 3 H), 1.21 (t, J = 7.49 Hz, 3 H), 1.31 (t, J = 7.20 Hz, 3 H), 1.50 (m, 2 H), 2.38 (q, J = 7.45 Hz, 2 H), 2.42 (q, J = 7.50 Hz, 2 H), 4.23 (q, J = 7.16 Hz, 2H), 7.20 (t, J = 7.63 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.87, 13.31, 14.16, 21.47, 32.66, 61.29, 73.58, 98.49, 151.79, 117.63, 163.25. Anal. Calcd for $C_{12}H_{18}O_2$:C, 74.19; H, 9.34. Found: C, 74.17; H, 9.38.

Ethyl (*E,E*)-2-(1-butynyl)-2,4-octadienoate (7m): 20% yield; R_f = 0.67 (hexane/ethyl acetate = 4/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (t, J = 7.33 Hz, 3 H), 1.24 (t, J = 7.60 Hz, 3 H), 1.32 (t, J = 7.21 Hz, 3 H), 1.49 (m, J = 7.14 Hz, 2 H), 2.23 (dq, J = 1.17 and 7.08 Hz, 2 H), 2.47 (q, J = 7.38 Hz, 2 H), 4.24 (q, J = 7.14 Hz, 2 H), 6.24 (dt, J = 15.38 and 7.49 Hz, 1 H), 6.62 (ddt, J = 15.25, 11.15, and 1.36 Hz), 7.43 (d, J = 11.23 Hz,1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13,49, 13.72, 13.89, 14.23, 21.99, 35.41, 61.19, 74.00, 99.86, 113.51, 127.90, 146.05, 146.27, 165.86. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.05; H, 9.27.

Ethyl (*E*)-2-(butynyl)-3-phenyl-2-propenoate (7n): 12% yield; R_f = 0.55 (hexane/ethyl acetate = 4/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, J = 7.52 Hz, 3 H), 1.38 (t, J = 7.10 Hz, 3 H), 2.54 (q, J = 7.48 Hz, 2 H), 4.31 (q, J = 7.10 Hz, 2 H), 7.35–7.50 (m, 3 H), 7.83 (s, 1 H), 7.96–8.10 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.38, 13.70, 14.20, 61.59, 75.81, 101.17, 113.73, 128.30, 130.12, 130.19, 144.14, 166.04. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.07. Found: C, 79.04; H, 7.19.

Ethyl (*E*)-2-(1-butynyl)-2-tetradecen-4-ynoate (7o): 27% yield; R_f = 0.66 (hexane:ethyl acetate = 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, J = 6.59 Hz, 3 H), 1.18–1.35 (m, 20 H), 2.40–2.53 (m, 4 H), 4.24 (q, J = 7.14 Hz, 2 H), 6.87 (t, J = 2.32 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.58, 13.71, 14.08, 14.13, 20.21, 22.64, 28.41, 28.78, 29.13, 29.27, 29.45, 31.85, 61.56, 74.86, 78.55, 100.99, 106.92, 124.39, 127.19, 164.64. Anal. Calcd for $C_{20}H_{30}O_2$: C, 39.42; H, 10.00. Found: C, 79.19; H, 10.01.

Ethyl (*E*)-5-phenyl-2-(2-phenylethynyl)-2-penten-4-ynoate (7p): IR (neat) 3050, 3030, 2980, 2200, 1720; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (t, J = 7.10 Hz, 3 H), 4.33 (q, J = 7.06 Hz, 2 H),

7.20 (s, 1 H), 7.20–7.60 (m, 10 H). Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.76; H, 5.42.

Independent synthesis of 7p was carried out by the method described in the literature.[13] To a solution of ethyl (*Z*)-2,3-dibromopropenoate (8)[13] (1.00 g, 3.88 mmol), phenylacetylene (673 mg, 6.60 mmol), and diisopropylamine (851 mg, 6.60 mmol) in DMF (6 mL) at 0 °C was added in several portions a mixture of $(Ph_3P)_4Pd$ (224 mg, 0.104 mmol) and CuI (148 mg, 0.776 mmol). After the mixture was stirred for 14 h at 0 °C, saturated aqueous $NaHCO_3$ was added. After 30 min, the organic layer was extracted with hexane–ethyl acetate (1/1), washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by short column chromatography (hexane/ethyl acetate (15/1–10/1)) to give 1.04 g (96%) of ethyl (*Z*)-2-bromo-5-phenyl-2-penten-4-ynoate (11): IR (neat) 3050, 3030, 2980, 2200, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.16 Hz, 3 H), 4.32 (q, *J* = 7.22 Hz, 2 H), 7.20 (s, 1 H), 7.30–7.50 (m, 3 H), 7.50–7.65 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.13, 62.86, 86.31, 104.71, 122.05, 124.19, 126.71, 128.50, 129.70, 132.08, 162.08.

To a suspension of $(Ph_3P)_4Pd$ (137 mg, 0.119 mmol) in degassed toluene (3 mL) at rt was added 11 (800 mg, 2.87 mmol), and the mixture was stirred for 45 min. Another flask was charged with a suspension of CuI (68 mg, 0.358 mmol) in degassed toluene (2 mL), and phenylacetylene (292 mg, 2.87 mmol) and isobutylamine (261 mg, 3.57 mmol) were added in that order. Then the mixture was stirred for 15 min. The contents of the second flask were added to the Pd mixture, and then the resulting mixture was stirred for 2 h at 60 °C. After the mixture was cooled, 2 mL of saturated aqueous sodium bicarbonate and 5 mL of saturated aqueous ammonium chloride were added, and the mixture was stirred for 1 h. The organic materials were extracted with hexane–ethyl acetate (1/1). After removal of the solvent, the residue was purified by flash column chromatography (eluent: hexane/ethyl acetate (30/1–25/1) to give 835 mg (97%) of **7p**. IR and ^1H NMR data were identical with those of the sample prepared by the aldol condensation of **1p** with **2p**.

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