 Bull. Chem. Soc. Jpn., 72, 2307—2313 (1999)

A Convenient Synthesis of (*E*)-4-Alkoxy-2-amino-3-butenoic Acid Derivatives

Kazuhiro Kobayashi,* Susumu Irisawa, Hideki Akamatsu, Masaki Takahashi, Taichi Kitamura, Miyuki Tanmatsu, Osamu Morikawa, and Hisatoshi Konishi

Department of Materials Science, Faculty of Engineering, Tottori University, Koyama-minami, Tottori 680-8552

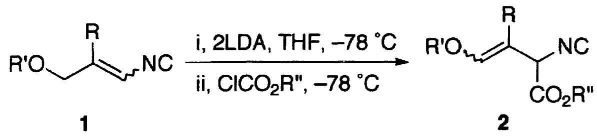
(Received March 23, 1999)

(*E*)-4-Alkoxy-2-formylamino-3-butenoic acid esters have been prepared in two steps from 3-alkoxy-1-isocyanopropenes. The method is based on the reaction of 3-alkoxy-1-isocyano-1-lithiopropenes, which can be generated by the treatment of 3-alkoxy-1-isocyanopropenes with LDA in THF at −78 °C, with alkyl chlorocarbonates, affording 4-alkoxy-2-isocyano-3-butenoates. These isocyano esters have been easily transformed into the corresponding formylamino esters by treating with concd HCl in Et_2O at −20 °C. Subsequently, the introduction of a substituent into the 2-position has been achieved by ethoxycarbonylation with ethyl chlorocarbonate, followed by alkylation with alkyl halides by using hexamethylphosphoric triamide (HMPA) as a co-solvent. The resulting alkylated isocyano 3-butenoates have been similarly hydrolyzed with concd HCl to the corresponding 2-formylamino-3-butenoates.

There has been substantial interest in (*E*)-4-alkoxy-2-amino-3-butenoic acid derivatives, because some of them are known to occur in nature,[1] and are potentially useful as inhibitors of several important enzymes.[2] One of these derivatives has been utilized as a key intermediate for the synthesis of rhizobitoxine.[3] Presently, a few methods are available for the synthesis of this class of compounds.[4] Two methods developed by Keith et al. have involved multisteps and incomplete stereoselectivity.[4a,4b] Hoppe and Schöllkopf have described the general synthesis of these derivatives based on the sodium cyanide-catalyzed addition of ethyl isocyanoacetate to methoxyacetaldehyde.[4c] However, it can not be applied to the preparation of derivatives carrying a substituent at the 3-position, which are also interesting because of their potential biological activities. Therefore, any new general route to (*E*)-4-alkoxy-2-amino-3-butenoates, including 3-substituted derivatives, is of interest and value.

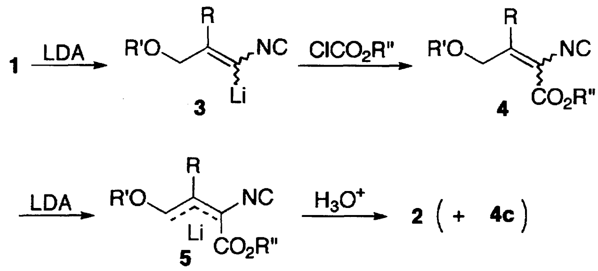
In our previous report,[5] we demonstrated that 3-benzyloxy-1-isocyano-1-lithiopropenes (**3**, R = H or Me) can serve as 3-hydroxy-1-oxopropanide anion equivalents via alkylation with alkyl halides followed by sequential hydrolysis and hydrogenolysis. As a part of our program to explore the synthetic utility and potential of these lithium products, we investigated the possibility of their use in the preparation of (*E*)-4-alkoxy-2-amino-3-butenoic acid derivatives. In this paper we wish to report in full on the results of our studies, which offer a general approach to this class of compounds, including derivatives carrying substituents at the 2- and/or 3-positions.[6]

The key reaction in our sequence is the regioselective alkoxycarbonylation reaction of 3-alkoxy-1-isocyanopropenes **1** with alkyl chlorocarbonates, affording 4-alkoxy-2-isocyano-3-butenoates **2**, as shown in Scheme 1. Thus, the treatment



Scheme 1.

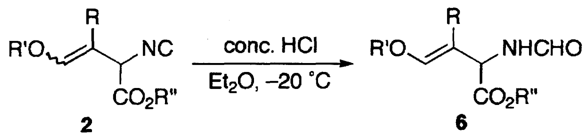
of the isocyanides **1** with 2 molar amounts of LDA in THF at −78 °C, followed by the addition of an equimolar amount of alkyl chlorocarbonates, led to the formation of the isocyano esters **2**. These products were isolated as yellow liquids after the usual work-up followed by preparative TLC on silica gel. Each of the products uniformly exhibits IR absorptions at ca. 2145 and 1755 cm^{-1}, which indicates that both of the isocyano and alkoxycarbonyl groups are not conjugated with the vinyl moiety. The production of **2** can be interpreted as illustrated in Scheme 2. Thus, the reaction of **1** with LDA generates 3-alkoxy-1-isocyano-1-lithiopropenes **3**,[7] which upon treatment with alkyl chlorocarbonates give the initial alkoxycarbonylation products, 4-alkoxy-2-isocyano-2-butenoates **4**. The migration of the double bond is thought to proceed with the help of an additional molar equivalent of LDA; deprotonation of a proton at the 4-position of the initial



Scheme 2.

products affords the allyl anions **5**, which are quenched with a proton at the 2-position to produce **2**. The results of this alkoxycarbonylation using four isocyanopropenes **1** and three chlorocarbonates are summarized in Table 1. Compounds **2a** and **2b** proved to be rather unstable under the purification conditions; although the yields based on ^{1}H NMR analyses of these crude products were both almost quantitative, separation using preparative TLC on silica gel afforded these products only in rather poor yields (24 and 12%; Entries 1 and 2, respectively). Their instability is presumed to be provided by the absence of a substituent at the 3-position. Thus, the crude products were directly used in the next step without any purification only in the cases of **2a** and **2b**. Compounds **2c**—**f** were readily isolated by preparative TLC and the yields were fair-to-good (Entries 3—6). It should be noted that the reaction of **1c** with ethyl chlorocarbonate resulted in the formation of the desired compound **2c**, together with a small quantity of the corresponding 2-butenoate **4c**; these were easy to separate from each other by preparative TLC on silica gel (Entry 3). In the other reactions, compounds **2a**, **2b**, and **2d**—**f** were obtained regioselectively without forming any detectable quantities of the corresponding 2-butenoates. It can be reasonably assumed that the *E*-isomer was exclusively (**2a**, **2b**, and **2f**) or predominantly (**2c**—**e**) formed in each case in view of the thermodynamic stability of the two stereoisomers. The stereochemistry of **2a** was unambiguously determined on the basis of a NOE experiment. Thus, irradiation of the signal at δ_H = 4.69 due to 2-H resulted in an 8.3% enhancement of the signal at δ_H = 6.76 due to 4-H. The *E*-configuration of the major isomer of **2e** was also confirmed by the observation of NOE between 2-H and 4-H protons; irradiation of the signal at δ_H = 4.57 due to 2-H resulted in an 11% enhancement of the signal at δ_H = 6.31 due to 4-H, while no NOE was observed between the signals due to 4-H and 2-H of the minor isomer.

Hydrolysis of the isocyano esters **2** was carried out with concentrated hydrochloric acid in diethyl ether at −20 °C, as shown in Scheme 3. Competition of the enol ether function with the isocyano group to be hydrolyzed could be suppressed effectively by carrying out hydrolysis at this lower temperature, and the corresponding (*E*)-4-alkoxy-2-formylamino-3-butenoic acid esters **6** were produced in satisfactory



2 6

Scheme 3.

yields without forming the corresponding stereoisomers. The results are listed in Table 2. The yields of **6a** and **6b** refer to the overall yields from the isocyanopropenes **1a** and **1b**, respectively. Stereochemical proof of these products was facilitated by ^{1}H NMR. Thus, the *E*-configurations of **6a** and **6b** were clear from analyses of the coupling constants (J_{3H-4H} = 12.3 Hz each), which were almost equal to those of the related compounds, methyl (*E*)-2-acetylamino-4-methoxy-3-butenoate, reported by Keith and co-workers (J_{3H-4H} = 13 Hz),[4a] and ethyl (*E*)-2-formylamino-4-methoxy-3-butenoate, reported by Hoppe and Schöllkopf (J_{3H-4H} = 12 Hz),[4c] and far from that of methyl (*Z*)-2-acetylamino-4-methoxy-3-butenoate (J_{3H-4H} = 7 Hz).[4a] The *E*-configuration of **6c**—**f** can be inferred from the values of the chemical shifts of the C(2) and C(4) protons (δ_{2H} = 4.98—5.04 and δ_{4H} = 6.22—6.34), when comparisons are made with those of the related methyl (*E*)- and (*Z*)-2-acetylamino-4-methoxy-3-butenoates (δ_{2H} = 4.8 and δ_{4H} = 6.64 for *E*, δ_{2H} = 4.5 and δ_{4H} = 6.10 for *Z*)[4a] while taking the effect of the 3-alkyl substituents on the chemical shift of the vinyl protons[8] into consideration. The *E*-configuration of **6c** was unambiguously confirmed on the basis of a NOE experiment. Thus, irradiation of the signal of **6c** at δ_H = 6.34 due to 4-H resulted in a 7.4% enhancement of the signal at δ_H = 4.98 due to 2-H. The stereochemistry of **6e** was also confirmed by a NOE

Table 2. Hydrolysis of Isocyano Esters **2** to Formylamino Esters **6** According to Scheme 3

Entry	**2**	**6** (Yield/%)[a)]
1	**2a**	6a (57)[b)]
2	**2b**	6b (53)[b)]
3	**2c**	6c (62)
4	**2d**	6d (69)
5	**2e**	6e (66)
6	**2f**	6f (60)

a) Isolated yields. b) Based on **1**.

Table 1. Alkoxycarbonylation of 3-Alkoxy-1-isocyanopropenes **1** According to Scheme 1

Entry	**1** (*E*/*Z*)[a)]	R″ in $ClCO_2R''$	**2** (*E*/*Z*;[a)] Yield/%)[b)]
1	**1a** [R = H, R′ = Bn] (ca. 50/50)	Et	**2a** (ca. 100/0; quant)[c)]
2	**1b** [R = H, R′ = Ph] (ca. 60/40)	Et	**2b** (ca. 100/0; quant)[c)]
3	**1c** [R = Me, R′ = Bn] (ca. 60/40)	Et	**2c** (ca. 80/20;[d)] 64)[e)]
4	**1d** [R = Et, R′ = Bn] (ca. 65/35)	Me	**2d** (ca. 80/20;[d)] 96)
5	**1d**	Et	**2e** (ca. 80/20;[d)] 84)
6	**1d**	Bn	**2f** (ca. 100/0; 62)

a) Determined by ^{1}H NMR spectrum. b) Yields refer to isolated products after preparative TLC on SiO_2 unless otherwise stated. c) Determined by ^{1}H NMR spectrum. Used without any purification in the next step. Isolated yields were 24% for **2a** and 22% for **2b**. d) Inseparable by preparative TLC on SiO_2. e) Ethyl 4-benzyloxy-2-isocyano-3-methyl-2-butenoate (**4c**) was accompanied (17%; a mixture of stereoisomers; ca. 80/20; the stereochemistry of each isomer was not determined).

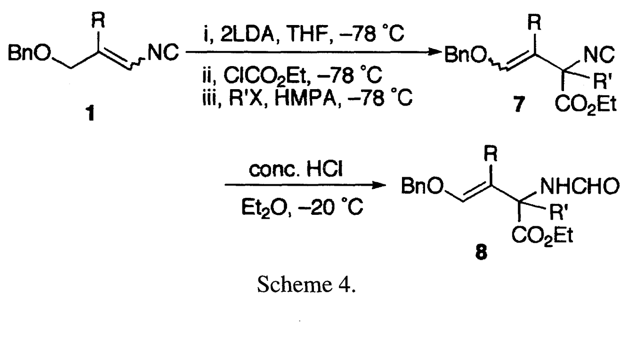
Table 3. Preparation of 2-Alkylated Isocyano Esters **7** and Their Conversion to Formylamino Esters **8** According to Scheme 4

Entry	**1**[a)]	R′X	**7** ($E:Z$;[b)] Yield/%)[c)]	**8** (Yield/%)[c)]
1	**1a** (R = H)	BnBr	**7a** (100/0; —)[d)]	**8a** (39)[e)]
2	**1d** (R = Et)	BnBr	**7b** (100/0; 74)	**8b** (71)
3	**1d**	MeI	**7c** (ca. 70/30; 73)	**8c** (61)
4	**1d**	$EtOCOCH_2Br$	**7d** (100/0; 69)	**8d** (57)

a) A mixture of stereoisomers was used in each case. See Table 1. b) Determined by ^{1}H NMR spectrum. c) Isolated yields after preparative TLC on SiO_2 unless otherwise stated. d) Used without purification in the next step. A specimen for spectral and analytical data was obtained in 15% yield by preparative TLC on SiO_2. e) Overall yield from **1a**.

experiment (2-H and 4-H, 7.8%). We assume that the acid-catalyzed isomerization of the Z-isomer to the E-isomer took place during the hydrolysis.

Subsequently, the possibility of the preparation of 4-alkoxy-2-formylamino-3-butenoates bearing an alkyl substituent at the 2-position **8** was examined. We reasoned that if an alkyl halide is added to a solution of the dienolate anion intermediate **5**, we might be able to introduce an alkyl group to the 2-position of the isocyano ester in one step. Thus, we first carried out alkylation by merely adding an alkyl halide to the reaction mixture from the reaction of the lithium product from **1a** with ethyl chlorocarbonate. The alkylation, however, did not occur even at room temperature. It was found that when hexamethylphosphoric triamide (HMPA) was added to the reaction mixture prior to treatment with an alkyl halide, the alkylation at the 2-position took place immediately to afford the desired product **7** in satisfactory yield (Scheme 4). The results are summarized in Table 3. The E-isomer was only isolated in each case with the exception of the reaction with iodomethane, in which a mixture of the corresponding E- and Z-isomeric products were formed in preference to the E-isomer (Entry 3). The formation of the Z-isomer can be rationalized on the less bulkiness of the methyl group compared to the other alkyl groups employed in these reactions. The stereochemistry of these products was determined by comparing their ^{1}H NMR data with those of compounds **2** (See Experimental section). The E-configuration of **7d** was unambiguously confirmed by an NOE between the vinyl proton and one of the 3-methylene protons (11%). Among compounds **7**, **7a** was relatively unstable under the purification conditions involving preparative TLC on silica gel, as described above for compounds **2a** and **2b**, though a pure specimen for spectral analyses was obtained. Thus, the crude product was used without purification in the hydrolysis step.



Scheme 4.

Hydrolysis of the alkylated isocyano esters **7** was also carried out under conditions similar to those described above for the preparation of **6** (Scheme 4). The reactions proceed smoothly to give the (E)-2-formylamino-3-butenoates **8** in good yields, as summarized in Table 3. As expected, the formation of each product was highly stereoselective and no trace amounts of their corresponding Z-isomer could be obtained. The stereochemistry of these products was determined on the basis of their ^{1}H NMR data, as described for that of **6** (See Experimental section). The E-configuration of **8b** was unambiguously confirmed by a NOE between one of the methylene protons of 2-benzyl group and the 4-H (13%).

In conclusion, the present study has led to the development of an efficient method for the preparation of (E)-4-alkoxy-2-formylamino-3-butenoates, including derivatives having substituents at the 2- and/or 3-positions. The present approach may find some value in organic synthesis because of the wide generality and convenience, compared to the previously reported methods.[4]

Experimental

General. All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 1600 Series FT IR spectrometer. The ^{1}H NMR spectra were determined with either a JEOL JNX-PMX 60 NMR spectrometer operating at 60 MHz or a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz. Chemical shifts were referenced relative to tetramethylsilane as an internal standard. Low-resolution MS analyses were performed on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). High-resolution MS analyses were performed a JEOL JMS-AX505 HA spectrometer (Faculty of Agriculture, this University). TLC was carried out on a Merck Kieselgel 60 PF_{254}. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use. All reactions, except for hydrolyses and hydrogenolyses, were carried out under argon.

3-Benzyloxy-2-methoxypropanenitrile: Prepared in 90% yield by the treatment of 2-benzyloxy-1,1-dimethoxyethane[9] with cyanotrimethylsilane in the presence of $OEt_2\cdot BF_3$ under the reaction conditions reported by Utimoto et al.;[10] bp 98—103 °C/80 Pa; IR (neat) 2230 and 1110 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ = 3.52 (3H, s), 3.73 (2H, d, J = 5.5 Hz), 4.23 (1H, t, J = 5.5 Hz), 4.63 (2H, s), and 7.34 (5H, s). Found: m/z 191.0947. Calcd for $C_{11}H_{13}NO_2$: M, 191.0946.

3-Benzyloxy-2-methoxy-1-propanamine. To a stirred suspension of $LiAlH_4$ (0.57 g, 15 mmol) in Et_2O (100 ml) at 0 °C was added a solution of the above-mentioned nitrile (2.5 g, 13 mmol) in Et_2O (30 ml) dropwise. The mixture was stirred at the same temperature for 2 h and at room temperature for 3 h. Excess $LiAlH_4$ was decomposed by adding several drops of aqueous saturated Na_2SO_4, and the mixture was dried over anhydrous $MgSO_4$ and evaporated. The crude product was purified by distillation to give the title amine (2.4 g, 95%); bp 94—96 °C/53 Pa; IR (neat) 3374, 3304, and 1097 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ = 2.73 (2H, br. s), 2.80 (1H, dd, J = 13.5 and 6.6 Hz), 2.90 (1H, dd, J = 13.5 and 4.3 Hz), 3.35—3.45 (4H, m including s at δ = 3.43), 3.53 (2H, d, J = 5.0 Hz), 4.53 (2H, s), and 7.32 (5H, s). Found: *m/z* 195.1248. Calcd for $C_{11}H_{17}NO_2$: M, 195.1259.

***N*-(3-Benzyloxy-2-methoxypropyl)formamide.** A solution of the above-mentioned amine (2.2 g, 11 mmol) in HCO_2Et (5 ml) was refluxed for 6 h. After evaporation of excess HCO_2Et, distillation of the residue gave the title amide (2.2 g, 90%); bp 154—156 °C/60 Pa; IR (neat) 3296, 1669, and 1095 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ = 3.25—3.65 (8H, m including s at δ = 3.40), 4.51 (1H, d, J = 12.3 Hz), 4.52 (1H, d, J = 12.3 Hz), 6.31 (1H, br. s), 7.2—7.4 (5H, m), and 8.12 (1H, s). Found: *m/z* 223.1218. Calcd for $C_{12}H_{17}NO_3$: M, 223.1208.

1-Benzyloxy-3-isocyano-2-methoxypropane. To a stirred solution of the above-mentioned amide (2.1 g, 9.4 mmol) and Et_3N (2.8 g, 28 mmol) in THF (20 ml) at 0 °C was added $POCl_3$ (1.19 g, 13 mmol) dropwise. After stirring for 3 h at the same temperature, the resulting mixture was diluted with Et_2O (50 ml), washed successively with aqueous $NaHCO_3$ and brine, and dried over anhydrous K_2CO_3. Evaporation of the solvent gave a residue, which was distilled to give the title isocyanide (1.6 g, 81%); bp 113—114 °C/53 Pa; IR (neat) 2152 and 1116 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ = 3.46 (3H, s), 3.5—3.75 (5H, m), 4.55 (2H, s), and 7.25—7.4 (5H, m). Found: *m/z* 205.1109. Calcd for $C_{12}H_{15}NO_2$: M, 205.1103.

(*E*)- and (*Z*)-3-Benzyloxy-1-isocyano-1-propene (1a).[5] A solution of the above-mentioned isocyanide (1.2 g, 5.9 mmol) in THF (10 ml) was added dropwise to a cooled (−78 °C) solution of LDA (12 mmol) in THF (40 ml), which was generated in situ by the standard method. After 30 min the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with Et_2O three times. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Kugelrohr distillation of the residue afforded **1a** (0.83 g, 81%; $E:Z$ = ca. 1:1); bp 113—115 °C (bath temp)/110 Pa.

1,1-Dimethoxy-2-phenoxyethane. To a stirred suspension of NaH (60%; 6.0 g, 0.15 mol) in DMF (100 ml) at room temperature was added PhOH (9.4 g, 0.10 mol) dropwise. After the evolution of hydrogen had subsided (ca. 15 min), a DMF (100 ml) solution of $BrCH_2CH(OMe)_2$ (17 g, 0.10 mol) was added slowly. After stirring for 1.5 h at room temperature, the resulting mixture was heated to 60 °C, and stirring was continued for 6 h. The cooled reaction mixture was then poured into saturated aqueous NH_4Cl. Organic materials were extracted with Et_2O, washed with brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by distillation to give the title compound (12.4 g, 68%); bp 116 °C/2000 Pa; IR (neat) 1600, 1497, 1247, 1136, 1082, and 755 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ = 3.33 (6H, s), 3.88 (2H, d, J = 5.2 Hz), 4.59 (1H, t, J = 5.2 Hz), and 6.65—7.3 (5H, m). Found: *m/z* 182.0929. Calcd for $C_{10}H_{14}O_3$: M, 182.0943.

2-Methoxy-3-phenoxypropanenitrile: Prepared in 96% yield by a treatment of the above-mentioned acetal with cyanotrimethylsilane in the presence of $OEt_2 \cdot BF_3$ under the reaction conditions reported by Utimoto et al.;[10] bp 125 °C/1700 Pa; IR (neat) 2248 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ = 3.55 (3H, s), 4.20 (2H, d, J = 5.4 Hz), 4.40 (1H, t, J = 5.4 Hz), 6.90 (2H, d, J = 7.6 Hz), 6.99 (1H, t, J = 7.6 Hz), and 7.28 (2H, t, J = 7.6 Hz). Found: *m/z* 177.0812. Calcd for $C_{10}H_{11}NO_2$: M, 177.0790.

2-Methoxy-3-phenoxy-1-propanamine: Prepared in 89% yield from the above-mentioned nitrile in a manner similar to that described for the preparation of 3-benzyloxy-2-methoxy-1-propanamine; bp 83 °C (bath temp)/29 Pa; IR (neat) 3369 and 3306 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ = 1.39 (2H, br. s), 2.7—2.95 (2H, m), 3.25—3.65 (4H, m including s at δ = 3.43), 3.92 (2H, d, J = 5.2 Hz), and 6.65—7.4 (5H, m). Found: *m/z* 181.1100. Calcd for $C_{10}H_{15}NO_2$: M, 181.1104.

***N*-(2-Methoxy-3-phenoxypropyl)formamide:** Prepared in 92% yield from the above-mentioned amine in a manner similar to that described for the preparation of *N*-(3-benzyloxy-2-methoxypropyl)formamide; bp 240 °C (bath temp)/19 Pa; IR (neat) 3296 and 1666 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ = 3.25—3.7 (6H, m including s at δ = 3.43), 3.92 (2H, q, J = 4.4 Hz), 6.1—6.6 (1H, br), 6.75—7.35 (5H, m), and 8.04 (1H, s). Found: *m/z* 209.1046. Calcd for $C_{11}H_{15}NO_3$: M, 209.1053.

1-Isocyano-2-methoxy-3-phenoxypropane: Prepared in 78% yield from the above-mentioned formamide in a manner similar to that described for the preparation of 1-benzyloxy-3-isocyano-2-methoxypropane; bp 230 °C (bath temp)/20 Pa; IR (neat) 2152 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ = 3.45 − 3.9 (6H, m including s at J = 3.49), 4.0—4.1 (2H, m), and 6.7—7.35 (5H, m); MS *m/z* (%) 191 (M^+; 89) and 58 (100). Found: *m/z* 191.0943. Calcd for $C_{11}H_{13}NO_2$: M, 191.0947.

(*E*)- and (*Z*)-1-Isocyano-3-phenoxypropene (1b): Prepared in 77% yield from the above-mentioned isocyanide in a manner similar to that described for the preparation of **1a**; ($E:Z$ = ca. 60:40); bp 170 °C (bath temp)/13 Pa; IR (neat) 2130 and 1649 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ = 4.48 (1.2H, d, J = 3.6 Hz), 4.75 (0.8H, d, J = 4.0 Hz), 5.7—6.3 (2H, m), and 6.65—7.35 (5H, m); MS *m/z* (%) 159 (M^+; 38), 130 (99), and 65 (100). Found: *m/z* 159.0694. Calcd for $C_{10}H_9NO$: M, 159.0685.

1-Benzyloxy-2,2-dimethoxypropane. A mixture of 1-benzyloxy-2-propanone[11] (6.4 g, 39 mmol), $CH(OMe)_3$ (5.0 g, 47 mmol), and *p*-TsOH (0.15 g, 0.78 mmol) in MeOH (20 ml) was stirred overnight at room temperature. The resulting mixture was treated with solid $NaHCO_3$ (0.10 g) and filtered in suction. The filtrate was evaporated. To the resulting residue was added hexane–Et_2O (1:1, 50 ml). The precipitates were filtered off, and the filtrate was concentrated in vacuo to give a yellow residue, which was purified by distillation to afford the title compound (7.2 g, 88%); bp 63—65 °C/40 Pa; IR (neat) 1122, 1071, and 1052 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ = 1.26 (3H, s), 3.11 (6H, s), 3.33 (2H, s), 4.51 (2H, s), and 7.26 (5H, s). Found: *m/z* 210.1260. Calcd for $C_{12}H_{18}O_3$: M, 210.1256.

3-Benzyloxy-2-methoxy-2-methylpropanenitrile: Prepared in 92% yield by a treatment of the above-mentioned acetal with cyanotrimethylsilane in the presence of $OEt_2 \cdot BF_3$ under the reaction conditions reported by Utimoto et al.;[10] bp 95 °C/100 Pa; IR (neat) 2222 and 1106 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ = 1.50 (3H, s), 3.40 (3H, s), 3.43 (1H, d, J = 10.0 Hz), 3.53 (1H, d, J = 10.0 Hz), 4.56 (2H, s), and 7.23 (5H, s). Found: *m/z* 205.1102. Calcd for $C_{12}H_{15}NO_2$: M, 205.1103.

3-Benzyloxy-2-methoxy-2-methyl-1-propanamine: Prepared in 89% yield from the above-mentioned nitrile in a manner similar to that described for the preparation of 3-benzyloxy-2-methoxy-1-propanamine; bp 230 °C (bath temp)/250 Pa; IR (neat) 3372, 3307, and 1101 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ = 1.06 (3H, s), 1.33 (2H, br. s), 2.68 (2H, s), 3.18 (3H, s), 3.27 (1H, d, J = 10.0 Hz), 3.37 (1H, d, J = 10.0 Hz),4.46 (2H, s), and 7.23 (5H, s). Found: m/z 209.1427. Calcd for $C_{12}H_{19}NO_2$: M, 209.1417.

***N*-(3-Benzyloxy-2-methoxy-2-methylpropyl)formamide:** Prepared in 86% yield from the above-mentioned amine in a manner similar to that described for the preparation of *N*-(3-benzyloxy-2-methoxypropyl)formamide; mp 70—75 °C (Et_2O–hexane); IR (KBr disk) 3305, 1672, and 1101 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ = 1.10 (3H, s), 3.16 (3H, s), 3.3—3.5 (4H, m), 4.46 (2H, s), 5.6—6.3 (1H, br), 7.20 (5H, s), and 7.86 and 8.06 (combined 1H, 2s). Found: C, 65.67; H, 8.22; N, 5.92%. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90%.

1-Benzyloxy-3-isocyano-2-methoxy-2-methylpropane: Prepared in 83% yield from the above-mentioned formamide in a manner similar to that described for the preparation of 1-benzyloxy-3-isocyano-2-methoxypropane; bp 220 °C (bath temp)/130 Pa; IR (neat) 2151 and 1103 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ = 1.20 (3H, s), 3.20 (3H, s), 3.39 (4H, br. s), 4.48 (2H, s), and 7.20 (5H, s). Found: m/z 219.1249. Calcd for $C_{13}H_{17}NO_2$: M, 219.1260.

(*E*)- and (*Z*)-3-Benzyloxy-1-isocyano-2-methyl-1-propene (1c): Prepared in 88% yield from the above-mentioned isocyanide in a manner similar to that described for the preparation of **1a**; (*E*:*Z* = ca. 1:1); bp 220 °C (bath temp)/270 Pa.[5]

3-Benzyloxy-2-ethyl-2-methoxypropanenitrile. To a stirred solution of LDA (45 mmol) in THF (100 ml) containing HMPA (8.1 g, 45 mmol) at −78 °C was added 2-methoxybutanenitrile[12] (4.5 g, 45 mmol) dropwise. After 10 min, benzyl chloromethyl ether (7.7 g, 50 mmol) was added and the mixture was allowed to stir for an additional 1 h at the same temperature. The resulting mixture was quenched by adding saturated aqueous NH_4Cl and extracted with Et_2O. The extract was washed with aqueous $NaHCO_3$ and then brine, and dried over anhydrous K_2CO_3. After evaporation of the solvent the residue was distilled to give the title compound (6.7 g, 68%); bp 105 °C/13 Pa; IR (neat) 2233 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ = 0.98 (3H, t, J = 6.8 Hz), 1.83 (2H, q, J = 6.8 Hz), 3.42 (3H, s), 3.51 (2H, s), 4.56 (2H, s), and 7.26 (5H, s); MS m/z (%) 219 (M^+; 1.6), 189 (12), and 98 (100). Found: m/z 219.1243. Calcd for $C_{13}H_{17}NO_2$: M, 219.1260.

2-Benzyloxymethyl-2-methoxy-1-butanamine: Prepared in 92% yield from the above-mentioned nitrile in a manner similar to that described for the preparation of 3-benzyloxy-2-methoxy-1-propanamine; bp 180 °C (bath temp)/21 Pa; IR (neat) 3381 and 3293 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ = 1.65—2.05 (5H, m), 1.52 (2H, q, J = 6.7 Hz), 2.61 (2H, s), 3.17 (3H, s), 3.3—3.5 (2H, m), 4.45 (2H, s), and 7.22 (5H, s). Found: m/z 223.1568. Calcd for $C_{13}H_{21}NO_2$: M, 223.1573.

***N*-(2-Benzyloxymethyl-2-methoxybutyl)formamide:** Prepared in 89% yield from the above-mentioned amine in a manner similar to that described for the preparation of *N*-(3-benzyloxy-2-methoxypropyl)formamide; bp 210 °C (bath temp)/13 Pa; IR (neat) 3303 and 1680 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ = 0.83 (3H, t, J = 6.8 Hz), 1.54 (2H, q, J = 6.8 Hz), 3.15 (3H, s), 3.25—3.4 (4H, m), 4.44 (2H, s), 7.26 (5H, s), 7.73 (1H, br. s), and 8.10 (1H, s). Found: m/z 251.1529. Calcd for $C_{14}H_{21}NO_3$: M, 251.1522.

2-Benzyloxymethyl-1-isocyano-2-methoxybutane: Prepared in 77% yield from the above-mentioned formamide in a manner similar to that described for the preparation of 1-benzyloxy-3-isocyano-2-methoxypropane; bp 200 °C (bath temp)/13 Pa; IR (neat) 2150 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ = 0.85 (3H, t, J = 7.2 Hz), 1.55 (2H, q, J = 7.2 Hz), 3.19 (3H, s), 3.40 (4H, br. s), 4.50 (2H, s), and 7.22 (5H, s); MS m/z (%) 233 (M^+; 13), 232 (67), 112 (99), and 91 (100). Found: C, 71.86; H, 8.25; N, 6.15%. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00%.

(*E*)- and (*Z*)-2-Benzyloxymethyl-1-isocyano-1-butene (1d): Prepared in 85% yield from the above-mentioned isocyanide in a manner similar to that described for the preparation of **1a**; (*E*:*Z* = ca. 65:35); bp 180 °C (bath temp)/13 Pa; IR (neat) 2124 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ = 1.06 (3H, t, J = 7.2 Hz), 2.0—2.4 (2H, m), 3.95 (0.7H, s), 4.22 (1.3H, s), 4.50 (2H, s), 5.55—5.65 (0.65H, m), 5.75—5.85 (0.35H, m), and 7.26 (5H, s); MS m/z (%) 201 (M^+; 3.2), 172 (30), 107 (69), and 91 (100). Found: m/z 201.1160. Calcd for $C_{13}H_{15}NO$: M, 201.1154.

Ethyl (*E*)-4-Benzyloxy-2-isocyano-3-butenoate (2a). Typical Procedure for the Alkoxycarbonylation of the 3-Alkoxy-1-isocyanopropenes 1 with Alkyl Chlorocarbonates. (Table 1, Entry 1): To a stirred solution of LDA (2.8 mmol) [from *n*-BuLi (1.6 M in hexane, 1 M = 1 mol dm^{-3}, 2.8 mmol) and *i*-Pr_2NH (0.28 g, 2.8 mmol)] in THF (10 ml) at −78 °C was added the isocyanide **1a** (0.24 g, 1.4 mmol) dropwise, the solution turning into orange immediately. After the mixture was stirred for 15 min at the same temperature, ethyl chlorocarbonate (0.17 g, 1.5 mmol) was added. An immediate fading of the carbanion color was noted. After stirring for an additional 15 min, the resulting mixture was quenched with saturated aqueous NH_4Cl. An organic product was extracted with Et_2O three times. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford the crude product containing **2a** as a yellow oil (0.45 g, quantitative, determined by ^{1}H NMR), which was used in the next step without purification. Purification using preparative TLC on silica gel afforded pure **2a** for spectroscopic analyses; R_f 0.48 (1:3 EtOAc–hexane); IR (neat) 2145, 1754, and 1682 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.31 (3H, t, J = 7.3 Hz), 4.26 (2H, q, J = 7.3 Hz), 4.69 (1H, d, J = 8.0 Hz), 4.84 (2H, s), 5.01 (1H, dd, J = 12.3 and 8.0 Hz), 6.76 (1H, d, J = 12.3 Hz), and 7.3—7.4 (5H, m); MS m/z (%) 245 (M^+; 4.6), 244 (20), and 91 (100). Found: m/z 245.1067. Calcd for $C_{14}H_{15}NO_3$: M, 245.1053.

The isocyano 3-butenoates **2b—f** were prepared following the above-mentioned procedure. For **2b** the crude product was also used in the next step without purification, and **2c–f** were used after purification by preparative TLC on silica gel.

Ethyl (*E*)-4-Phenoxy-2-isocyano-3-butenoate (2b): R_f 0.46 (1:3 EtOAc–hexane); IR (neat) 2143, 1759, and 1674 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.34 (3H, t, J = 7.3 Hz), 4.30 (2H, q, J = 7.3 Hz), 4.82 (1H, d, J = 7.6 Hz), 5.40 (1H, dd, J = 12.0 and 7.6 Hz), 6.93 (1H, d, J = 12.0 Hz), 7.03 (2H, t, J = 7.6 Hz), 7.23 (1H, t, J = 7.6 Hz), and 7.35 (2H, t, J = 7.6 Hz); MS m/z (%) 231 (M^+; 42) and 146 (100). Found: m/z 231.0876. Calcd for $C_{13}H_{13}NO_3$: M, 231.0896.

Ethyl (*E*)- and (*Z*)-4-Benzyloxy-2-isocyano-3-methyl-3-butenoate (2c): (*E*:*Z* = ca. 80:20); R_f 0.42 (1:3 EtOAc–hexane); IR (neat) 2144, 1752, and 1682 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.24 and 1.28 (combined 3H, 2t, J = 7.1 Hz each), 1.59 (0.6H, s), 1.72 (2.4H, s), 4.23 (2H, q, J = 7.1 Hz), 4.57 (0.8H, s), 4.84 (0.2H, s), 4.87 (2H, s), 6.33 (0.8H, s), 6.44 (0.2H, s), and 7.3—7.4 (5H, m); MS m/z (%) 259 (M^+; 21) and 91 (100). Found: m/z 259.1224. Calcd for $C_{15}H_{17}NO_3$: M, 259.1209.

Ethyl 4-Benzyloxy-2-isocyano-3-methyl-2-butenoate (4c): Obtained together with **2c**. **4c**: ca. 80:20 (stereochemistry of each product has not yet been determined); R_f 0.61 (1:3 EtOAc–hexane); IR (neat) 2116, 1727, and 1691 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.34 (3H, t, J = 7.2 Hz), 2.20 (2.4H, s), 2.29 (0.6H, s), 4.23 (2H, q, J = 7.2 Hz), 4.49 (1.6H, s), 4.59 (1.6H, s), 4.71 (0.4H, s), 4.77 (0.4H, s), and 7.24 (5H, s); MS m/z (%) 259 (M^+; 15) and 91

(100). Found: *m/z* 259.1215. Calcd for $C_{15}H_{17}NO_3$: M, 259.1209.

Methyl (*E*)- and (*Z*)-4-Benzyloxy-3-ethyl-2-isocyano-3-butenoate (2d): ($E:Z$ = ca. 80:20); R_f 0.25 (1:5 EtOAc–hexane); IR (neat) 2145, 1756, and 1675 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.00 (3H, t, J = 7.2 Hz), 2.18 (2H, q, J = 7.2 Hz), 3.73 (3H, s), 4.53 (0.8H, s), 4.83 (2H, s), 4.87 (0.2H, s), 6.27 (0.8H, s), 6.37 (0.2H, s), and 7.27 (5H, s); MS *m/z* (%) 259 (M$^+$; 19) and 91 (100). Found: *m/z* 259.1228. Calcd for $C_{15}H_{17}NO_3$: M, 259.1209.

Ethyl (*E*)- and (*Z*)-4-Benzyloxy-3-ethyl-2-isocyano-3-butenoate (2e): ($E:Z$ = ca. 80:20); R_f 0.25 (1:5 EtOAc–hexane); IR (neat) 2144, 1753, and 1675 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.03 and 1.05 (combined 3H, 2t, J = 7.6 Hz each), 1.27 and 1.29 (combined 3H, 2t, J = 7.3 Hz each), 2.1—2.3 (2H, m), 4.23 and 4.28 (combined 2H, 2q, J = 7.3 Hz each), 4.57 (0.8H, s), 4.87 (2H, s), 4.89 (0.2H, s), 6.31 (0.8H, s), 6.42 (0.2H, s), 7.25—7.4 (5H, m); MS *m/z* (%) 273 (M$^+$; 14), 107 (18), and 91 (100). Found: *m/z* 273.1362. Calcd for $C_{16}H_{19}NO_3$: M, 273.1366.

Benzyl (*E*)-4-Benzyloxy-3-ethyl-2-isocyano-3-butenoate (2f): R_f 0.26 (1:5 EtOAc–hexane); IR (neat) 2144, 1754, and 1675 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.98 (3H, t, J = 7.4 Hz), 2.1—2.25 (2H, m), 4.62 (1H, s), 4.83 (2H, s), 5.18 (1H, d, J = 12.1 Hz), 5.19 (1H, d, J = 12.1 Hz), 6.28 (1H, s), and 7.25—7.4 (10H, m); MS *m/z* (%) 335 (M$^+$; 31), 244 (54), and 91 (100). Found: *m/z* 335.1539. Calcd for $C_{21}H_{21}NO_3$: M, 335.1522.

Ethyl (*E*)-4-Benzyloxy-2-formylamino-3-butenoate (6a). Typical Procedure for the Hydrolysis of the Isocyano Esters 2. (Table 2, Entry 1): To a stirred solution of **2a** (a crude product obtained from the reaction of **1a** with ethyl chlorocarbonate) in Et_2O (8 ml) at −20 °C was added concd HCl (0.6 ml); the mixture was stirred for 10 min at the same temperature. The resulting mixture was diluted with Et_2O, followed by the addition of aqueous $NaHCO_3$. The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by preparative TLC on silica gel to give **6a** (0.15 g, 57% from **1a**); R_f 0.25 (1:3 EtOAc–hexane); IR (neat) 3302, 1740, and 1666 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.11 (3H, t, J = 6.9 Hz), 4.1—4.25 (2H, m), 4.68 (2H, s), 4.75 (1H, dd, J = 12.3 and 8.3 Hz), 4.98 (1H, dd, J = 8.3 and 7.6 Hz), 6.20 (1H, br. s), 6.63 (1H, d, J = 12.3 Hz), 7.25—7.3 (5H, m), and 8.11 (1H, s); MS *m/z* (%) 263 (M$^+$; 0.10), 190 (6.1), 172 (19), and 91 (100). Found: C, 63.66; H, 6.50; N, 5.31%. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32%.

Ethyl (*E*)-2-Formylamino-4-phenoxy-3-butenoate (6b): R_f 0.63 (3:1 EtOAc–hexane); IR (neat) 3300, 1740, and 1671 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.31 (3H, t, J = 7.3 Hz), 4.26 (2H, q, J = 7.3 Hz), 5.16 (1H, dd, J = 8.3 and 7.6 Hz), 5.29 (1H, dd, J = 12.3 and 8.3 Hz), 6.31 (1H, br. s), 6.84 (1H, d, J = 2.3 Hz), 6.99 (2H, d, J = 7.6 Hz), 7.09 (1H, t, J = 7.6 Hz), 7.33 (2H, t, J = 7.6 Hz), and 8.09 (1H, s); MS *m/z* (%) 249 (M$^+$; 8.5), 248 (51), 220 (62), and 146 (100). Found: C, 62.47; H, 5.99; N, 5.36%. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62%.

Ethyl (*E*)-4-Benzyloxy-2-formylamino-3-methyl-3-butenoate (6c): R_f 0.06 (1:3 EtOAc–hexane); IR (neat) 3294, 1738, and 1680 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.09 (3H, t, J = 7.2 Hz), 1.57 (3H, s), 4.18 (2H, q, J = 7.2 Hz), 4.85 (2H, s), 4.98 (1H, d, J = 7.6 Hz), 6.34 (1H, br. s), 6.6—6.9 (1H, br), 7.29 (5H, s), and 8.09 (1H, s); MS *m/z* (%) 277 (M$^+$; 0.06), 276 (0.39), 249 (3.5), 221 (8.7), 189 (10), and 91 (100). Found: C, 67.84; H, 6.74; N, 5.34%. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05%.

Methyl (*E*)-4-Benzyloxy-3-ethyl-2-formylamino-3-butenoate (6d): R_f 0.25 (1:1 EtOAc–hexane); IR (neat) 3304, 1744, and 1672 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.97 (3H, t, J = 7.6 Hz), 2.05—2.15 (2H, m), 3.72 (3H, s), 4.83 (2H, s), 5.00 (1H, d, J = 7.6 Hz), 6.29 (combined 2H, s and br. s), 7.3—7.35 (5H, m), and 8.18 (1H, s); MS *m/z* (%) 277 (M$^+$; 0.05), 218 (2.6), 186 (32), and 91 (100). Found: C, 64.76; H, 6.94; N, 5.12%. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05%.

Ethyl (*E*)-4-Benzyloxy-3-ethyl-2-formylamino-3-butenoate (6e): R_f 0.30 (1:1 EtOAc–hexane); IR (neat) 3312, 1738, and 1679 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.99 (3H, t, J = 7.6 Hz), 1.24 (3H, t, J = 7.3 Hz), 2.05—2.15 (2H, m), 4.18 (2H, q, J = 7.3 Hz), 4.84 (2H, s), 4.98 (1H, d, J = 7.6 Hz), 6.26 (1H, br. s), 6.29 (1H, s), 7.25—7.4 (5H, m), and 8.18 (1H, s); MS *m/z* (%) 291 (M$^+$; 0.21), 218 (12), 200 (45), and 91 (100). Found: C, 65.94; H, 7.25; N, 4.81%. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81%.

Benzyl (*E*)-4-Benzyloxy-3-ethyl-2-formylamino-3-butenoate (6f): R_f 0.14 (1:1 EtOAc–hexane); IR (neat) 3294, 1741, and 1673 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.94 (3H, t, J = 7.6 Hz), 2.05—2.15 (2H, m), 4.75 and 4.76 (combined 2H, 2d, J = 12.7 Hz each), 5.04 (1H, d, J = 7.6 Hz), 5.14 (2H, s), 6.22 (combined 2H, s and br. s), 7.25—7.35 (10H, m), and 8.17 (1H, s); MS *m/z* (%) 353 (M$^+$; 0.01), 262 (3.3), and 91 (100). Found: C, 71.23; H, 6.43; N, 4.10%. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96%.

Ethyl (*E*)-2-Benzyl-4-benzyloxy-2-isocyano-3-butenoate (7a). Typical Procedure for the Preparation of 7. (Table 3, Entry 1): To a stirred solution of LDA [from *n*-BuLi (1.6 M in hexane, 3.8 mmol) and *i*-Pr_2NH (0.38 g, 3.8 mmol)] in THF (15 ml) at −78 °C was added a solution of **1a** (0.32 g, 1.9 mmol) in THF (2 ml) dropwise. After the resulting orange yellow solution was stirred for 10 min, it was treated with ethyl chlorocarbonate (0.21 g, 1.9 mmol). After 15 min HMPA (0.68 g, 3.8 mmol) and BnBr (0.97 g, 5.7 mmol) were successively added. After stirring for an additional 40 min, the resulting reaction mixture was worked up in a similar manner as described for the preparation of **2a**. After evaporation of the solvent, the crude product was subjected to the next reaction. A specimen for spectroscopic analyses was obtained by preparative TLC on silica gel; R_f 0.53 (1:3 EtOAc–hexane); IR (neat) 2138, 1741, and 1671 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.23 (3H, t, J = 7.3 Hz), 3.06 (1H, d, J = 14.1 Hz), 3.29 (1H, d, J = 14.1 Hz), 4.19 (2H, q, J = 7.3 Hz), 4.79 (2H, s), 5.11 (1H, d, J = 2.3 Hz), 6.77 (1H, d, J = 12.3 Hz), and 7.15—7.5 (10H, m); MS *m/z* (%) 335 (M$^+$; 0.18), 308 (0.33), 280 (0.36), 244 (8.0), 218 (14), 145 (20), 127 (94), and 91 (100). Found: *m/z* 335.1522. Calcd for $C_{21}H_{21}NO_3$: M, 335.1522.

Similarly, the 2-alkylated 2-isocyano-3-butenoates **7b**—**d** were prepared and used in the next step after purification by preparative TLC on silica gel.

Ethyl (*E*)-2-Benzyl-4-benzyloxy-3-ethyl-2-isocyano-3-butenoate (7b): R_f 0.62 (1:3 EtOAc–hexane); IR (neat) 2136, 1741, and 1686 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.04 (3H, t, J = 7.3 Hz), 1.21 (3H, t, J = 7.3 Hz), 2.15—2.35 (2H, m), 3.09 (1H, d, J = 13.8 Hz), 3.39 (1H, d, J = 13.8 Hz), 4.13 (2H, q, J = 7.3 Hz), 4.85 (2H, s), 6.43 (1H, s), and 7.15—7.4 (10H, m); MS *m/z* (%) 363 (M$^+$; 0.39), 336 (0.56), 308 (0.64), 272 (31), and 91 (100). Found: *m/z* 363.1818. Calcd for $C_{23}H_{25}NO_3$: M, 363.1836.

Ethyl (*E*)- and (*Z*)-4-Benzyloxy-3-ethyl-2-isocyano-2-methyl-3-butenoate (7c): $E:Z$ = ca. 7:3; R_f 0.55 (1:3 EtOAc–hexane); IR (neat) 2135, 1749, and 1686 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.03 and 1.05 (combined 3H, 2t, J = 7.6 Hz each), 1.29 (3H, t, J = 7.3 Hz), 1.73 (3H, s), 2.17 (1.4H, q, J = 7.6 Hz), 2.23 (0.6H, J = 7.6 Hz), 4.12 (0.6H, q, J = 7.3 Hz), 4.21 (1.4H, q, J = 7.3 Hz), 4.88 and 4.89 (combined 2H, 2s), 6.42 and 6.43 (combined 1H, 2s), and 7.3—7.4 (5H, m); MS *m/z* (%) 287 (M$^+$; 0.53), 258 (1.3), 242

(3.2), 196 (42), and 91 (100). Found: m/z 287.1541. Calcd for $C_{17}H_{21}NO_3$: M, 287.1522.

Diethyl 2-[(*E*)-2-Benzyloxy-1-ethylethenyl]-2-isocyanobutanedioate (7d): R_f 0.46 (1:3 EtOAc–hexane); IR (neat) 2137, 1742, and 1666 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.02 (3H, t, J = 7.3 Hz), 1.27 and 1.29 (combined 6H, 2t, J = 7.3 Hz each), 2.20 (2H, q, J = 7.3 Hz), 2.84 (1H, d, J = 16.7 Hz), 3.27 (1H, d, J = 16.7 Hz), 4.18 and 4.26 (combined 4H, 2q, J = 7.3 Hz each), 4.88 (2H, s), 6.46 (1H, s), and 7.3—7.35 (5H, m); MS m/z (%) 359 (M$^+$; 0.02), 330 (0.03), 314 (0.14), 242 (7.0), 213 (13), 168 (15), and 91 (100). Found: m/z 359.1736. Calcd for $C_{20}H_{25}NO_5$: M, 359.1734.

Hydrolysis of the isocyano esters **7a**—**d** to the formylamino esters **8a**—**d** was carried out under conditions similar to those described for the hydrolysis of the isocyano esters **2**.

Ethyl (*E*)-2-Benzyl-4-benzyloxy-2-formylamino-3-butenoate (8a): R_f 0.54 (1:1 EtOAc–hexane); IR (neat) 3367, 1734, and 1670 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 1.26 and 1.32 (combined 3H, 2t, J = 7.3 Hz each), 3.04 and 3.33 (combined 1H, 2d, J = 13.8 Hz each), 3.42 and 3.78 (combined 1H, 2d, J = 13.8 Hz each), 4.15—4.3 (2H, m), 4.78 and 4.81 (combined 2H, 2s), 5.19 and 5.24 (combined 1H, 2d, J = 12.7 Hz each), 6.39 (1H, br. s), 6.58 and 6.60 (combined 1H, 2d, J = 12.7 Hz each), 7.05—7.15 (2H, m), 7.2—7.4 (8H, m), and 8.15—8.2 (1H, m); MS m/z (%) 353 (M$^+$; 0.60), 280 (12), and 262 (100). Found: C, 71.08; H, 6.44; N, 3.87%. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96%.

Ethyl (*E*)-2-Benzyl-4-benzyloxy-3-ethyl-2-formylamino-3-butenoate (8b): R_f 0.72 (1:1 EtOAc–hexane); mp 89—90 °C (hexane–Et_2O); IR (KBr disk) 3293, 1736, and 1667 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.98 and 1.02 (combined 3H, 2t, J = 7.4 Hz each), 1.26 and 1.31 (combined 3H, 2t, J = 6.9 Hz each), 2.09 and 2.12 (combined 2H, 2q, J = 7.4 Hz each), 2.96 and 3.35 (combined 1H, 2d, J = 13.2 Hz), 3.50 and 3.89 (combined 1H, 2d, J = 13.2 Hz), 4.1—4.25 (2H, m), 4.8—5.0 (2H, m), 6.35 (1H, br. s), 6.50 (1H, s), 7.0—7.4 (10H, m), and 8.1—8.2 (1H, m); MS m/z (%) 381 (M$^+$; 0.29), 308 (5.6), and 290 (100). Found: C, 72.14; H, 7.12; N, 3.63%. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67%.

Ethyl (*E*)-4-Benzyloxy-3-ethyl-2-formylamino-2-methyl-3-butenoate (8c): R_f 0.58 (1:1 EtOAc–hexane); IR (neat) 3344, 1732, and 1686 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.96 and 0.98 (combined 3H, 2t, J = 7.5 Hz each), 1.23 and 1.25 (combined 3H, 2t, J = 7.1 Hz each), 1.61 and 1.78 (combined 3H, 2s), 2.04 and 2.07 (combined 2H, 2q, J = 7.5 Hz each), 4.1—4.25 (2H, m), 4.8—4.95 (2H, s), 6.32 and 6.37 (combined 1H, 2s), 6.60 (1H, br. s), 7.3—7.4 (5H, m), and 8.0—8.15 (1H, m); MS m/z (%) 305 (M$^+$; 0.96), 232 (25), and 91 (100). Found: m/z 305.1646. Calcd for $C_{17}H_{23}NO_4$: M, 305.1628.

Diethyl 2-[(*E*)-(2-Benzyloxy-1-ethylethenyl]-2-(formylamino)butanedioate (8d): R_f 0.64 (1:1 EtOAc–hexane); IR (neat) 3141, 1713, and 1689 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ = 0.96 and 0.98 (combined 3H, 2t, J = 7.4 Hz each), 1.15—1.3 (6H, m), 2.05—2.15 (2H, m), 2.77 and 3.18 (combined 1H, 2d, J = 16.2 Hz each), 3.28 and 3.82 (combined 1H, 2d, J = 16.2 Hz each), 4.05—4.3 (4H, m), 4.8—4.95 (2H, m), 6.23 and 6.31 (combined 1H, 2s), 6.7—6.9 (1H, br. s), 7.3—7.4 (5H, m), and 8.0—8.15 (1H, m); MS m/z (%) 377 (M$^+$; 0.55), 304 (10), 286 (15), and 91 (100). Found: m/z 377.1859. Calcd for $C_{20}H_{27}NO_6$: M, 377.1839.

References

1 For example: L. D. Owens, J. F. Thompson, R. G. Pitcher, and T. Williams, *J. Chem. Soc., Chem. Commun.*, **1972**, 714; D. L. Pruess, J. P. Scannell, T. C. Demny, L. H. Sello, T. Williams, and A. Steempel, *J. Antibiot.*, **25**, 122 (1972); U. Sahm, G. Knoblochi, and F. Wagner, *J. Antibiot.*, **26**, 389 (1973); D. L. Pruess, J. P. Scannell, M. Kellett, H. A. Ax, J. Janecek, T. H. Williams, A. Steempel, and J. Berger, *J. Antibiot.*, **27**, 229 (1974).

2 M. J. Tisdale, *Biochem. Pharmacol.*, **29**, 501 (1980); T. Dashman, *Life Sci.*, **27**, 1415 (1980); S. B. Smith and R. A. Freedland, *Arch. Biochem. Biophys.*, **209**, 335 (1981); J. R. Sufrin, J. B. Lombardini, and D. D. Keith, *Biochem. Biophys. Res. Commun.*, **106**, 251 (1982), and the references therein.

3 D. D. Keith, S. De Bernard, and M. Weigele, *Tetrahedron*, **31**, 2629 (1975); D. D. Keith, J. A. Tortora, K. Ineichen, and W. Leimgruber, *Tetrahedron*, **31**, 2633 (1975).

4 a) D. D. Keith, J. A. Tortora, and R. Yang, *J. Org. Chem.*, **43**, 3711 (1978). b) D. D. Keith, R. Yang, J. A. Tortora, and M. Weigele, *J. Org. Chem.*, **43**, 3713 (1978). c) I. Hoppe and U. Schöllkopf, *Synthesis*, **1982**, 129. For a recent synthesis of related derivatives: D. B. Berkowitz, M. L. Pedersen, and W.-J. Jahng, *Tetrahedron Lett.*, **37**, 4309 (1996).

5 K. Kobayashi, H. Akamatsu, K. Takada, O. Morikawa, and H. Konishi, *Tetrahedron Lett.*, **37**, 2437 (1996).

6 Part of this paper has been reported as a preliminary communication: K. Kobayashi, H. Akamatsu, S. Irisawa, M. Takahashi, O. Morikawa, and H. Konishi, *Chem. Lett.*, **1997**, 503.

7 The α-lithiation of 1-isocyano-1-alkenes with butyllithium, forming 1-isocyano-1-lithio-1-alkenes, has been reported: U. Schöllkopf, D. Stafforst, and R. Jentsch, *Liebigs Ann. Chem.*, **1977**, 1167.

8 C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).

9 J. C. Sheeham, M. Goodman, and L. Richardson, *J. Am. Chem. Soc.*, **77**, 6391 (1955).

10 K. Utimoto, Y. Wakabayashi, Y. Shishiyama, M. Inoue, and H. Nozaki, *Tetrahedron Lett.*, **22**, 4279 (1981).

11 A. Manzocchi, A. Fiecchi, and E. Santaniello, *Synthesis*, **1987**, 1007.

12 H. R. Henze, G. W. Benz, and C. L. Sutherland, *J. Am. Chem. Soc.*, **71**, 2122 (1949).