Synthesis of γ,δ-Didehydrohomoglutamates by the Phosphine-Catalyzed γ-Addition Reaction to Acetylenic Esters

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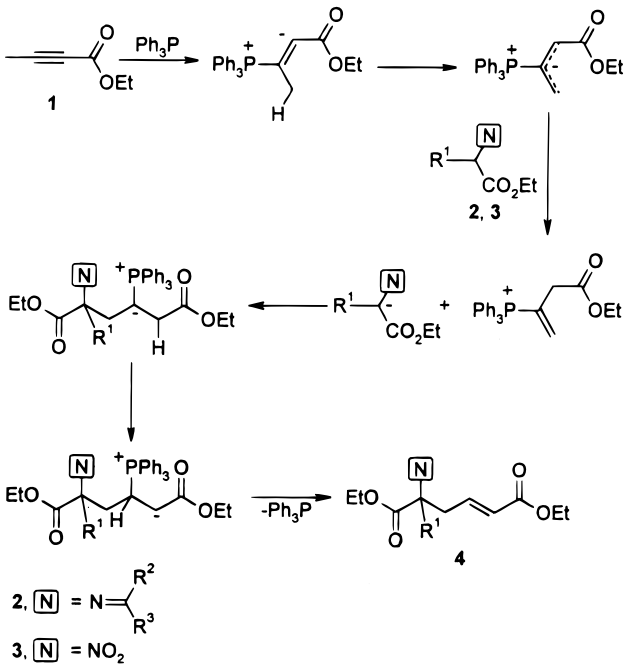
The design and synthesis of new nonproteinogenic α-amino acids is an area of current interest.[1] In particular, γ,δ-unsaturated α-amino acids have attracted attention due to their presence in natural products[2] and their usefulness as synthetic intermediates in the preparation of other α-amino acid derivatives,[3] as well as their pharmacological interest.[4]

Phosphines are known to impart electrophilic character to the γ-carbon of acetylenic esters (Trost reaction).[5] This reaction has been used for C−C bond formation at carbon C-4 of ethyl 2-butynoate (**1**) by using carbon pronucleophiles with active hydrogen atoms.[5b] Therefore, glycines that possessed an enhanced acidity of the α-CH on the basis of a suitably masked nitrogen atom (**2**, **3**) could serve satisfactorily as pronucleophiles in the Trost reaction. Their reaction with **1** should afford the N-protected γ,δ-didehydrohomoglutamates **4**, which are difficult to prepare by previously reported procedures[6] (Scheme 1).

Scheme 1



Results and Discussion

At the onset of our study, glycine imines **2** were chosen as the pronucleophilic counterpart.[7] Heating alkyne **1** with an equimolecular ammount of **2a** (R^1 = H, R^2, R^3 = Ph) with **1** in toluene solution with a catalytic ammount of triphenylphosphine (5% mol) in the presence of an acetic acid−sodium acetate buffer (50% mol)[5a] resulted in the recovery of the starting material together with (*E*)-ethyl 4-acetoxy-2-butenoate (40%).[8] The same result was obtained when the bis(methylthiomethylene)glycinate **2b** (R^1 = H, R^2, R^3 = SMe) or the aldimine[7,9] **2c** (R^1 = H, R^2 = p-Cl−C_6H_4, R^3 = H) were used as pronucleophiles.

Next, more basic reaction conditions were tested. Thus, the acetic acid−sodium acetate buffer previously used was replaced by ^{t}BuOH−KO^{t}Bu (50% mol), which should guarantee[10] the deprotonation of glycinates **2**. However, instead of the corresponding γ,δ-didehydrohomoglumates **4**, the α,β-didehydroglutamates **5** (Scheme 2) were the only products obtained. The results are given in Table 1.

It has to be pointed out that compounds **5** were not formed in the absence of Ph_3P and that the Michael addition of the potassium enolate of **2b** with **1** in THF solution did only take place in the presence of a crown ether.[11] Therefore, the formation of the α,β-didehydroglutamates **5** must be accounted for by the protonation

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(9) The α-methylene of glycine aldimines is more acidic than that of ketimines. See : López, A.; Pleixats, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1967 and references cited therein.

(10) Glycine imines and iminodithiocarbonates are deprotonated by KO^{t}Bu in THF. See, for example: (a) Stork, G.; Leong, A. Y. W.; Touzin, A. M. *J. Org. Chem.* **1976**, *41*, 3491. (b) Hoppe, D.; Beckmann, L. *Lieb. Ann. Chem.* **1979**, 2066. (c) Alvarez-Ibarra, C.; Csákÿ, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478.

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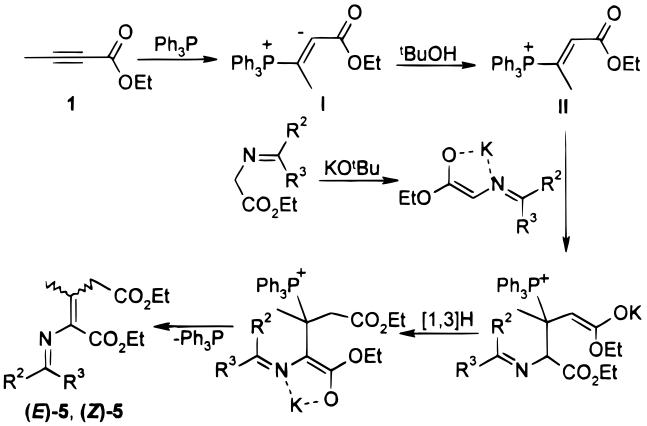
Table 1. Addition of Glycinates 2 to Alkyne 1

2	R^2	R^3	(*Z*)-**5**[a] (%)	(*E*)-**5**[a] (%)
2a	Ph	Ph	(*Z*)-**5a** (50)	(*E*)-**5a** (40)
2b	SMe	SMe	(*Z*)-**5b** (60)	(*E*)-**5b** (25)
2c	*p*-ClC_6H_4	H	(*Z*)-**5c** (55)	(*E*)-**5c** (10)

[a] Isolated yield.

Scheme 2



(^{t}BuOH) of the initially formed phosphonium enolate **I** followed by a Michael addition of the potassium enolate of **2** to the vinylphosphonium salt **II**.[12] A [1,3]H shift promoted by the acidity of the hydrogen atom α to the imine moiety, with final *β*-elimination of Ph_3P, should finally give rise to the observed products **5** (Scheme 2).

On the other hand, when a toluene solution of ethyl nitroacetate (**3a**, R^1 = H) was made to react with **1** and Ph_3P (5% mol) in the presence of the AcOH−NaOAc (50% mol) buffer, (*E*)-ethyl 4-acetoxy-2-butenoate (40%) was again isolated,[8] and none of the corresponding **4** was observed. However, when the ^{t}BuOH−KO^{t}Bu (50% mol) buffer was used, the expected *γ*-addition product **4a** was obtained, as a single (*E*)-isomer. This result was extended to the α-alkyl substituted nitroacetates **3b**−**g**, which afforded the corresponding α,α-disubstituted nitroacetates **4b**−**g**, exclusively as their (*E*)-isomers. The nitro group in compounds **4** was reduced[13] to NH_2, which finally allowed for the synthesis of the (*E*)-diethyl *γ*,*δ*-didehydrohomoglutamates **6** (Scheme 3). The results are gathered in Table 2.

Conclusion

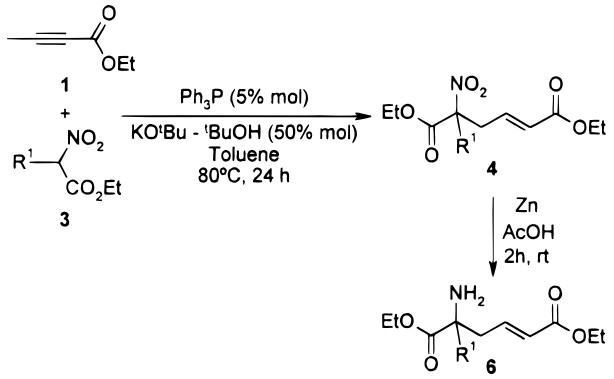
Although the Trost reaction of glycine imines **2** or nitroacetates **3** with the alkynoic ester **1** did not work under standard conditions, the enforcement of the basicity of the reaction medium by the use of a ^{t}BuOH−KO^{t}Bu buffer allowed for the *γ*-addition reaction to take place, but only in the case of compounds **3**. In this way, the Trost reaction has been extended to the synthesis of nonproteinogenic α-amino acid derivatives, by means of the addition of the nitroacetates **3** to the alkynoic ester **1** followed by reduction of the NO_2 group to NH_2.

Table 2. Addition of Nitroacetates 3 to 1[a]

no.	R^1	3	4[b] (%)	6[b] (%)
1	H	**3a**	**4a** (65)	**6a** (90)
2	Me	**3b**	**4b** (60)	**6b** (85)
3	Et	**3c**	**4c** (50)	**6c** (85)
4	$CH_2C_6H_5$	**3d**	**4d** (60)	**6d** (90)
5	CH_2-*p*-BrC_6H_5	**3e**	**4e** (55)	**6e** (85)
6	CH_2CO_2Et	**3f**	**4f** (60)	**6f** (90)
7	$CH_2CH{=}CH_2$	**3g**	**4g** (60)	**6g** (85)

[a] Synthesis of the *γ*,*δ*-didehydrohomoglutamates **6**. [b] Isolated yield.

Scheme 3



Experimental Section

All starting materials were commercially available research-grade chemicals and used without further purification. Toluene was distilled after refluxing over Na/benzophenone. Silica gel 60 F_{254} was used for TLC, and the spots were detected with UV. Flash column chromatography was carried out on silica gel 60. IR spectra have been recorded as $CHCl_3$ solutions. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.5 MHz, respectively, in $CDCl_3$ solution with TMS as internal reference. Glycine imines[10a,14] **2a**,**c**, iminodithiocarbonate[10b] **2b**, and nitroacetates[15] **3** were prepared following previously described procedures.

Addition of Compounds 2 or 3 to Ethyl 2-Butynoate (1) in the Presence of AcOH−NaOAc. General Procedure. To a solution of PPh_3 (10 mg, 37 *μ*mol) in toluene (0.75 mL) were added NaOAc (31 mg, 0.37 mmol), AcOH (25 *μ*L, 0.37 mmol), ethyl 2-butynoate (**1**) (94 *μ*L, 0.75 mmol), and a solution of the glycine imine **2** or nitroacetate **3** (0.75 mmol) in toluene (0.75 mL). The mixture was heated at 80 °C for 24 h. The solution was filtered, and the remaining solid material was washed with Et_2O (3 × 0.5 mL). Evaporation of the solvent afforded an oil that was purified by chromatography (hexane−Et_2O, 80:20).

Addition of Compounds 2 or 3 to Ethyl 2-Butynoate (1) in the Presence of ^{t}BuOH−KO^{t}Bu. General Procedure. To a solution of PPh_3 (10 mg, 37 *μ*mol) in toluene (0.75 mL) were added KO^{t}Bu (41 mg, 0.37 mmol), ^{t}BuOH (35 *μ*L, 0.37 mmol), ethyl 2-butynoate (**1**), (94 *μ*L, 0.75 mmol), and a solution of the glycine imine **2** or nitroacetate **3** (0.75 mmol) in toluene (0.75 mL). All operations were continued as above.

(*E*)-Diethyl 5-nitro-2-hexenodioate (4a): colorless oil (65%); IR ($CHCl_3$) *ν* 1751, 1718, 1662, 1566 cm^{-1}; ^{1}H NMR *δ* 6.76 (1H, dt, J = 15.5 Hz, ^3J = 7.5 Hz), 5.90 (1H, dt, J = 15.5 Hz, ^4J = 1.5 Hz), 5.16 (1H, dd, ^3J = 8.5 Hz, ^3J = 5.5 Hz), 4.24 (2H, q, ^3J = 7.0 Hz), 4.12 (2H, q, ^3J = 7.0 Hz), 3.18−2.90 (2H, m), 1.25 (3H, t, ^3J = 7.0 Hz), 1.21 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR *δ* 165.3, 163.5, 139.1, 126.2, 86.1, 63.5, 60.7, 32.5, 14.1, 13.8 ppm. Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.17; N, 5.71. Found: C, 48.91; H, 6.02; N, 5.93.

(*E*)-Diethyl 5-Methyl-5-nitro-2-hexenodioate (4b): colorless oil (60%); IR ($CHCl_3$) *ν* 1751, 1720, 1658, 1556 cm^{-1}; ^{1}H NMR *δ* 6.69 (1H, dt, J = 15.5 Hz, ^3J = 7.5 Hz), 5.88 (1H, dt, J = 15.5 Hz, ^4J = 1.5 Hz), 4.26 (2H, q, ^3J = 7.0 Hz), 4.16 (2H, q, ^3J = 7.0 Hz), 3.06 (1H, ddd, ^2J = 14.5 Hz, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 2.94

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(12) The product of the attack of the potassium enolates of **2** to the α-carbon of **1** was not observed. This reaction course has been proposed for the addition of nitrogen nucleophiles to the α-carbon of alkynoates. See: Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595.

(13) See, for example: Battersby, A. R.; Baker, M. G.; Broadbent, H. A.; Fookes, J. R.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2027.

(14) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

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(1H, ddd, ^2J = 14.5 Hz, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 1.73 (3H, s), 1.27 (3H, t, ^3J = 7.0 Hz), 1.26 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 166.5, 165.3, 138.8, 127.2, 91.4, 63.2, 60.6, 39.0, 21.3, 14.2, 13.8 ppm. Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N 5.40. Found: C, 51.23; H, 6.49; N, 5.65.

(*E*)-Diethyl 5-Ethyl-5-nitro-2-hexenodioate (4c): colorless oil (50%); IR ($CHCl_3$) ν 1751, 1720, 1658, 1556 cm^{-1}; ^{1}H NMR δ 6.64 (1H, dt, J = 15.5 Hz, ^3J = 7.5 Hz), 5.86 (1H, dt, J = 15.5 Hz, ^4J = 1.5 Hz), 4.22 (2H, q, ^3J = 7.0 Hz), 4.12 (2H, q, ^3J = 7.0 Hz), 3.01 (2H, dd, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 2.20 (1H, dq, ^2J = 13.0 Hz, ^3J = 7.5 Hz), 2.17 (1H, dq, ^2J = 13.0 Hz, ^3J = 7.5 Hz), 1.22 (3H, t, ^3J = 7.0 Hz), 1.21 (3H, t, ^3J = 7.0 Hz), 0.87 (3H, t, ^3J = 7.5 Hz) ppm; ^{13}C NMR δ 165.9, 165.3, 138.7, 126.8, 95.3, 63.0, 60.6, 36.0, 27.2, 14.0, 13.8, 7.9 ppm. Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.87; H, 7.16; N, 4.97.

(*E*)-Diethyl 5-benzyl-5-nitro-2-hexenodioate (4d): colorless oil (60%); IR ($CHCl_3$) ν 1751, 1714, 1658, 1556 cm^{-1}; ^{1}H NMR δ 7.27−7.02 (5H, m), 6.73 (1H, dt, J = 15.5 Hz, ^3J = 7.5 Hz), 5.87 (1H, dt, J = 15.5 Hz, ^4J = 1.5 Hz), 4.21 (2H, q, ^3J = 7.0 Hz), 4.13 (2H, q, ^3J = 7.0 Hz), 3.55 (1H, d, ^2J = 14.5 Hz), 3.41 (1H, d, ^2J = 14.5 Hz), 2.87 (2H, dd, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 1.24 (3H, t, ^3J = 7.0 Hz), 1.22 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 164.6, 164.3, 137.9, 131.5, 128.9, 127.9, 127.1, 126.0, 94.3, 62.2, 59.7, 38.9, 34.9, 13.2, 12.8 ppm. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.80; H, 6.43; N, 4.30.

(*E*)-Diethyl 5-(*p*-bromobenzyl)-5-nitro-2-hexenodioate (4e): colorless oil (55%); IR ($CHCl_3$) ν 1751, 1716, 1658, 1558 cm^{-1}; ^{1}H NMR δ 7.36 (2H, d, ^3J = 8.5 Hz), 6.90 (2H, d, ^3J = 8.5 Hz), 6.70 (1H, dt, J = 15.5 Hz, ^3J = 7.5 Hz), 5.87 (1H, dt, J = 15.5 Hz, ^4J = 1.0 Hz), 4.22 (2H, q, ^3J = 7.0 Hz), 4.14 (2H, q, ^3J = 7.0 Hz), 3.50 (1H, d, ^2J = 14.5 Hz), 3.37 (1H, d, ^2J = 14.5 Hz), 2.87 (2H, dd, ^3J = 7.5 Hz, ^4J = 1.0 Hz), 1.23 (3H, t, ^3J = 7.0 Hz), 1.21 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 164.4, 164.2, 137.5, 131.1, 130.5, 130.1, 126.1, 121.4, 93.9, 62.3, 59.7, 38.3, 34.9, 13.2, 12.8 ppm. Anal. Calcd for $C_{17}H_{20}BrNO_6$: C, 49.29; H, 4.87; N, 3.38. Found: C, 49.09; H, 4.95; N, 3.40.

(*E*)-Diethyl 5-ethoxycarbonyl-5-nitro-2-heptenodioate (4f): colorless oil (60%); IR ($CHCl_3$) ν 1738, 1716, 1660, 1562 cm^{-1}; ^{1}H NMR δ 6.68 (1H, dt, J = 15.5 Hz, ^3J = 7.5 Hz), 5.87 (1H, dt, J = 15.5 Hz, ^4J = 1.5 Hz), 4.25 (2H, q, ^3J = 7.0 Hz), 4.14 (2H, q, ^3J = 7.0 Hz), 4,10 (2H, q, ^3J = 7.0 Hz) 3.26 (1H, ddd, ^2J = 15.0 Hz, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 3.25 (1H, d, ^2J = 17.0 Hz) 3.16 (1H, d, ^2J = 17.0 Hz), 3.12 (1H, ddd, ^2J = 15.0 Hz, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 1.24 (3H, t, ^3J = 7.0 Hz), 1.22 (3H, t, ^3J = 7.0 Hz), 1.20 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 167.8, 165.2, 164.8, 138.4, 127.5, 91.6, 63.6, 61.6, 60.7, 38.4, 36.9, 14.2, 14.0, 13.6 ppm. Anal. Calcd for $C_{14}H_{21}NO_8$: C, 50.75; H, 6.39; N, 4.23. Found: C, 50.89; H, 6.30; N, 4.44.

(*E*)-Diethyl 5-allyl-5-nitro-2-heptenodioate (4g): colorless oil (60%); IR ($CHCl_3$) ν 1749, 1716, 1658, 1556 cm^{-1}; ^{1}H NMR δ 6.65 (1H, dt, ^3J = 15.5 Hz, ^3J = 7.5 Hz), 5.86 (1H, dt, J = 15.5 Hz, ^4J = 1.5 Hz), 5.65−5.44 (1H, m), 5.21−5.12 (2H, m) 4.22 (2H, q, ^3J = 7.0 Hz), 4.12 (2H, q, ^3J = 7.0 Hz), 2.99 (2H, ddd, ^2J = 7.5 Hz, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 2.89 (2H, dd, ^2J = 7.0 Hz,^3J = 6.5 Hz), 1.22 (3H, t, ^3J = 7.0 Hz), 1.21 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 165.5, 165.3, 138.5, 128.8, 127.0, 122.0, 94.1, 63.1, 60.7, 38.4, 36.3, 14.2, 13.8 ppm. Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.51; H, 6.36; N, 5.03.

(*Z*)-Diethyl 2-(diphenylamino)-3-methyl-2-pentenodioate ((*Z*)-5a): colorless oil (50%); IR ($CHCl_3$) ν 1724, 1654 cm^{-1}; ^{1}H NMR δ 7.68−7.08 (10H, m), 4.04 (2H, q, ^3J = 7.0 Hz), 3.78 (2H, q, ^3J = 7.0 Hz), 3.42 (2H, s), 1.82 (3H, s), 1.16 (3H, t, ^3J = 7.0 Hz), 1.01 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 169.9, 168.9, 162.9, 138.3, 136.8, 135.8, 129.7, 128.3, 127.6, 127.1, 126.9, 59.4, 59.3, 38.7, 19.8, 13.2, 13.0 ppm. Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.72; H, 6.71; N, 3.57.

(*E*)-Diethyl 2-(diphenylamino)-3-methyl-2-pentenodioate ((*E*)-5a): colorless oil (40%); IR ($CHCl_3$) ν 1718, 1600 cm^{-1}; ^{1}H NMR δ 7.68−7.12 (10H, m), 4.01 (2H, q, ^3J = 7.0 Hz), 3.60 (2H, q, ^3J = 7.0 Hz), 3.41 (2H, s), 2.01 (3H, s), 1.07 (3H, t, ^3J = 7.0 Hz), 0.96 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 171.1, 168.7, 164.5, 139.3, 137.8, 137.0, 130.4, 129.1, 128.9, 128.1, 127.7, 60.5, 59.9, 40.3, 19.1, 14.0, 13.7 ppm. Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.84; H, 6.78; N, 3.89.

(*Z*)-Diethyl 2-bis[methythiomethylene]amino-3-methyl-2-pentenodioate ((*Z*)-5b): colorless oil (60%); IR ($CHCl_3$) ν 1715 cm^{-1}; ^{1}H NMR δ 4.25 (2H, q, ^3J = 7.0 Hz), 4.15 (2H, q, ^3J = 7.0 Hz), 3.55 (2H, s), 2.47 (3H, s), 1.65 (3H, s), 1.27 (3H, s), 1.26 (3H, s) ppm; ^{13}C NMR δ 170.9 165.6, 163.5, 135.8, 128.7, 61.3, 60.7, 40.3, 19.2, 15.0, 14.2, 14.1 ppm. Anal. Calcd for $C_{13}H_{21}NO_4S_2$: C, 48.88; H, 6.63; N, 4.38. Found: C, 48.97; H, 6.81; N, 4.52.

(*E*)-Diethyl 2-bis[methythiomethylene]amino-3-methyl-2-pentenodioate ((*E*)-5b): colorless oil (25%); IR ($CHCl_3$) ν 1720 cm^{-1}; ^{1}H NMR δ 4.20 (2H, q, ^3J = 7.0 Hz), 4.03 (2H, q, ^3J = 7.0 Hz), 2.98 (2H, s), 2.43 (3H, s), 2.04 (3H, s), 1.27 (3H, s), 1.26 (3H, s) ppm; ^{13}C NMR δ 170.4 165.1, 163.9, 135.4, 128.3, 60.6, 60.5, 39.4, 20.1, 14.9, 14.1, 14.0 ppm. Anal. Calcd for $C_{13}H_{21}NO_4S_2$: C, 48.88; H, 6.63; N, 4.38. Found: C, 49.03; H, 6.85; N, 4.55.

(*Z*)-Diethyl 2-(*p*-chlorophenyl)methyleneamino-3-methyl-2-pentenodioate ((*Z*)-5c): colorless oil (55%); IR ($CHCl_3$) ν 1710, 1637 cm^{-1}; ^{1}H NMR δ 8.07 (1H, s), 7.66 (2H, d, ^3J = 8.5 Hz), 7.20 (2H, d, ^3J = 8.5 Hz), 4.20 (2H, q, ^3J = 7.0 Hz), 4.03 (2H, q, ^3J = 7.0 Hz), 3.56 (2H, s), 1.99 (3H, s), 1.25 (3H, t, ^3J = 7.0 Hz), 1.13 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 170.8, 165.5, 156.2, 139.0, 135.0, 133.5, 129.7, 128.1, 127.9, 60.9, 60.7, 38.7, 19.9, 14.3, 14.2 ppm. Anal. Calcd for $C_{17}H_{20}ClNO_4$: C, 60.45; H, 5.97; N, 4.15. Found: C, 60.34; H, 5.98; N, 4.35.

(*E*)-Diethyl 2-(*p*-chlorophenyl)methyleneamino-3-methyl-2-pentenodioate ((*E*)-5c): colorless oil (10%); IR ($CHCl_3$) ν 1700, 1620 cm^{-1}; ^{1}H NMR δ 8.14 (1H, s), 7.69 (2H, d, ^3J = 8.5 Hz), 7.24 (2H, d, ^3J = 8.5 Hz), 4.25 (2H, q, ^3J = 7.0 Hz), 4.02 (2H, q, ^3J = 7.0 Hz), 3.35 (2H, s), 2.06 (3H, s), 1.25 (3H, t, ^3J = 7.0 Hz), 1.13 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 165.4, 160.5, 156.2, 135.1, 130.5, 130.0, 129.5, 128.0, 127.5, 60.7, 60.0, 35.9, 20.5, 14.3, 14.2 ppm. Anal. Calcd for $C_{17}H_{20}ClNO_4$: C, 60.45; H, 5.97; N, 4.15. Found: C, 60.57; H, 6.12; N, 4.31

Reduction of the NO_2 Group in Compounds 4. Synthesis of the γ,δ-Didehydrohomoglutamates 6. General Procedure. To a solution of **4** (0.41 mmol) in AcOH (7 mL) at 0 °C was added Zn (685 mg, 10.5 mmol) in three portions in intervals of 5 min. The mixture was stirred for 2 h at room temperature, filtered through a pad of Celite, and washed with Et_2O (3 × 10 mL). The filtrate was diluted with water (10 mL), cooled to 0 °C, and alkalinized with 10 M NaOH to pH = 12. The mixture was extracted with Et_2O (3 × 10 mL), and the combined extracts were dried on $MgSO_4$. Evaporation of the solvent afforded an oil that was purified by chromatography (hexane−ethyl acetate 80:20).

(*E*)-Diethyl 2-amino-4-hexenedioate (6a): colorless oil (90%); IR ($CHCl_3$) ν 3394, 3327, 1716, 1656 cm^{-1}; ^{1}H NMR δ 6.84 (1H, dt, J = 15.5 Hz, ^3J = 7.5 Hz), 5.85 (1H, dt, J = 15.5 Hz, ^4J = 1.5 Hz), 4.13 (2H, q, ^3J = 7.0 Hz), 4.12 (2H, q, ^3J = 7.0 Hz), 3.53 (1H, dd, ^3J = 7.5 Hz, ^3J = 5.0 Hz), 2.66−2.35 (2H, m), 1.55 (2H, s), 1.22 (6H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 175.0, 143.5, 124.4, 61.1, 60.3, 53.5, 37.4, 14.1 ppm. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.98; H, 8.10; N, 6.42.

(*E*)-Diethyl 2-amino-2-methyl-4-hexenodioate (6b): colorless oil (85%); IR ($CHCl_3$) ν 3390, 1718, 1652 cm^{-1}; ^{1}H NMR δ 6.80 (1H, dt, J = 15.5 Hz, ^3J = 7.5 Hz), 5.83 (1H, dt, J = 15.5 Hz, ^4J = 1.5 Hz), 4.12 (2H, q, ^3J = 7.0 Hz), 4.11 (2H, q, ^3J = 7.0 Hz), 2.56 (1H, ddd, ^2J = 14.0 Hz, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 2.37 (1H, ddd, ^2J = 14.0 Hz, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 2.17 (3H, s), 1.60 (2H, s), 1.21 (3H, t, ^3J = 7.0 Hz), 1.14 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 167.9, 165.0, 142.0, 124.2, 60.3, 59.3, 56.5, 42.3, 16.1, 13.2 ppm. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.55; H, 8.47; N, 6.30.

(*E*)-Diethyl 2-amino-2-ethyl-4-hexenodioate (6c): colorless oil (85%); IR ($CHCl_3$) ν 3387, 3305, 1716, 1654 cm^{-1}; ^{1}H NMR δ 6.79 (1H, dt, J = 15.5 Hz, ^3J = 8.0 Hz), 5.83 (1H, d, J = 15.5 Hz), 4.13 (2H, q, ^3J = 7.0 Hz), 4.11 (2H, q, ^3J = 7.0 Hz), 2.60 (1H, dd, ^2J = 14.0 Hz, ^3J = 8.0 Hz), 2.38 (1H, dd, ^2J = 14.0 Hz, ^3J = 8.0 Hz), 1.95−1.45 (4H, m), 1.22 (3H, t, ^3J = 7.0 Hz), 1.21 (3H, t, ^3J = 7.0 Hz), 0.81 (3H, t, ^3J = 7.5 Hz) ppm; ^{13}C NMR δ 164.9, 142.0, 124.2, 60.3, 60.1, 59.3, 41.0, 28.7, 13.3, 13.2, 7.1 ppm. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.41; H, 8.60; N, 5.91.

(*E*)-Diethyl 2-amino-2-benzyl-4-hexenodioate (6d): colorless oil (90%); IR ($CHCl_3$) ν 3681, 3315, 1714, 1656 cm^{-1}; ^{1}H NMR

δ 7.23−7.05 (5H, m), 6.80 (1H, dt, J = 15.5 Hz, ^3J = 8.0 Hz), 5.86 (1H, d, J = 15.5 Hz), 4.11 (2H, q, ^3J = 7.0 Hz), 4.10 (2H, q, ^3J = 7.0 Hz), 3.12 (1H, d, ^2J = 13.0 Hz), 2.75 (1H, d, ^2J = 13.0 Hz), 2.72 (1H, dd, ^2J = 13.5 Hz, ^3J = 8.0 Hz), 2.41 (1H, dd, ^2J = 13.5 Hz, ^3J = 8.0 Hz), 1.73 (2H, s), 1.21 (3H, t, ^3J = 7.0 Hz), 1.19 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 174.2, 164.9, 141.6, 134.7, 129.0, 127.5, 126.2, 124.5, 60.7, 60.4, 59.4, 44.8, 41.6, 13.2 ppm. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 67.99; H, 7.50; N, 4.62.

(*E*)-Diethyl 2-amino-2-(*p*-bromo)benzyl-4-hexenodioate (6e): colorless oil (85%); IR ($CHCl_3$) ν 3683, 3381, 1716, 1656 cm^{-1}; ^{1}H NMR δ 7.36 (2H, d, ^3J = 8.5 Hz), 7.34 (2H, d, ^3J = 8.5 Hz), 6.78 (1H, dt, J = 15.5 Hz, ^3J = 8.0 Hz), 5.86 (1H, d, J = 15.5 Hz), 4.11 (2H, q, ^3J = 7.0 Hz), 4.10 (2H, q, ^3J = 7.0 Hz), 3.07 (1H, d, ^2J = 13.5 Hz), 2.70 (1H, d, ^2J = 13.5 Hz), 2.71 (1H, dd, ^2J = 14.0 Hz, ^3J = 8.0 Hz), 2.40 (1H, dd, ^2J = 14.0 Hz, ^3J = 8.0 Hz), 1.96 (2H, s), 1.21 (3H, t, ^3J = 7.0 Hz), 1.20 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 174.0, 164.8, 141.2, 133.7, 130.7, 130.5, 124.5, 120.3, 60.5, 59.4, 44.0, 41.5, 13.2 ppm. Anal. Calcd for $C_{17}H_{22}BrNO_4$: C, 53.14; H, 5.77; N, 3.65. Found: C, 53.35; H, 5.68; N, 3.81.

(*E*)-Diethyl 3-amino-2-ethoxycarbonyl-5-heptenodioate (6f): colorless oil (90%); IR ($CHCl_3$) ν 3383, 3315, 1728,1656 cm^{-1}; ^{1}H NMR δ 6.77 (1H, dt, J = 15.5 Hz, ^3J = 7.5 Hz), 5.82 (1H, d, J = 15.5 Hz), 4.13 (2H, q, ^3J = 7.0 Hz), 4.12 (2H, q, ^3J = 7.0 Hz), 4.07 (2H, q, ^3J = 7.0 Hz), 2.88 (1H, d, ^2J = 16.5 Hz), 2.48 (1H, d, ^2J = 16.5 Hz), 2.49 (1H, dd, ^2J = 14.0 Hz, ^3J = 7.5 Hz), 2.38 (1H, dd, ^2J = 14.0 Hz, ^3J = 7.5 Hz), 1.88 (2H, s), 1.22 (3H, t, ^3J = 7.0 Hz), 1.20 (3H, t, ^3J = 7.0 Hz), 1.18 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 170.3, 170.0, 164.7, 140.5, 124.7, 60.6, 59.7, 59.4, 57.8, 41.9, 41.5, 13.3 ppm. Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.97; H, 7.82; N, 4.78.

(*E*)-Diethyl 2-allyl-2-amino-4-hexenodioate (6g): colorless oil (85%); IR ($CHCl_3$) ν 3300, 1700, 1656 cm^{-1}; ^{1}H NMR δ 6.79 (1H, dt, J = 15.5 Hz, ^3J = 7.5 Hz), 5.83 (1H, d, J = 15.5 Hz), 5.73−5.53 (1H, m), 5.12−5.06 (2H, m) 4.13 (2H, q, ^3J = 7.0 Hz), 4.11 (2H, q, ^3J = 7.0 Hz), 2.66−2.10 (4H, m), 1.66 (2H, s), 1.22 (3H, t, ^3J = 7.0 Hz), 1.21 (3H, t, ^3J = 7.0 Hz) ppm; ^{13}C NMR δ 165.9, 142.6, 132.0, 225.3, 120.1, 61.4, 60.4, 43.9, 42.1, 14.2 ppm. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.31; H, 8.52; N, 5.74

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