Diastereoselective Aldol Reactions of (*Z*)-*N*-[Bis(methylthio)methylene]-α,*β*-didehydroglutamates

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In the reaction of the enolates of (*Z*)-*N*-[bis(methylthio)methylene]-α,*β*-didehydroglutamates with aldehydes, the retroaldolization process is faster than the aldol reaction, thus inhibiting the obtainment of the desired targets **6**. However, in the presence of TMS−Cl as trapping agent, the equilibrium can be deplaced and the aldols **6** are obtained in the form of their TMS-derivatives **8**. In the presence of BF_3 or TBAF, either the syn or the anti adducts can be selectively obtained with good yields and diastereoselectivities.

α,*β*-Didehydroamino acids constitute an important class of nonproteinogenic amino acids. The conformational constraints induced by these subunits in peptides can lead to conformational changes in their secondary structure, which impart an enhanced resistance to enzymatic and chemical degradation.[1] α,*β*-Didehydroamino acids are also valuable building blocks for the synthesis of other nonnatural amino acids of pharmacological interest.[2] We are particularly interested in the development of new methods of synthesis of glutamic acid derivatives, in the light of the implication of glutamate receptors in Alzheimer's disease and the therapeutic potential of substituted glutamic acid derivatives in the treatment of epilepsy and stroke.[3]

We have recently reported a new synthesis of the α,*β*-didehydroglutamic acid derivatives[4] **3** by the addition of the enolates of glycinates **1** to electron-deficient alkynes via a Michael addition/1,3-prototropic shift pathway (Scheme 1). The purpose of this work is the study of the aldol reaction of dienolates **4** with aldehydes **5**. Under suitable reaction conditions, the herein reported procedure allowed for the selective synthesis of the syn and anti isomers of the α,*β*-didehydroglutamates **6** (Scheme 1).

Results

Deprotonation of α,*β*-didehydroglutamates **3** with KO^{t}Bu or LDA (1.25 equiv, THF, −78 °C, 30 min) followed by capture with MeI allowed for the isolation of compound **7** (Scheme 1), which was exclusively obtained as the (*Z*)-isomer.

However, reaction with benzaldehyde gave the recovery of the starting materials. This was also the case in the presence of a Lewis acid ($ZnCl_2$, 1.25 equiv). We presumed that, in these systems, the retroaldol reaction could be faster than the aldol addition[5] due to the high resonance stabilization of the enolate and the high compression at the transition-state level based on the steric encumbrance.[6] Therefore, to avoid the undesired retroaldolization, a trapping agent (TMS−Cl, 1.1 equiv) was introduced, so that the reaction could be driven to the desired targets **6** in the form of their silylderivatives **8** (Scheme 2). The results are gathered in Table 1.

Whereas no reaction of the lithium enolate **4** (M = Li) with benzaldehyde was observed in the absence of TMS−Cl (entries 1 and 2), the addition of TMS−Cl (1.1 equiv) allowed us to obtain compounds **8** in good yield but with low diastereoselectivity (entry 3). A better yield was obtained in the presence of $ZnCl_2$ (1.25 equiv), although the diastereomeric excess was nil (entry 4). The same result was observed with either LDA or LiHMDS, both in THF or Et_2O (entries 4−6). No reaction took place in the case of the potassium enolate **4** (M = K, entries 7

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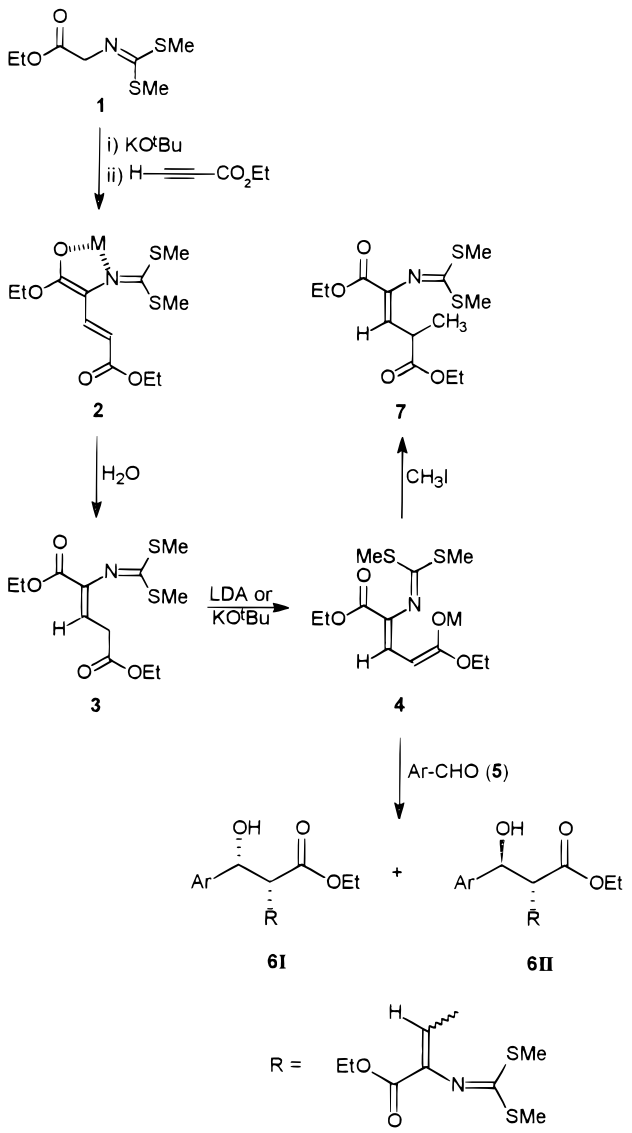
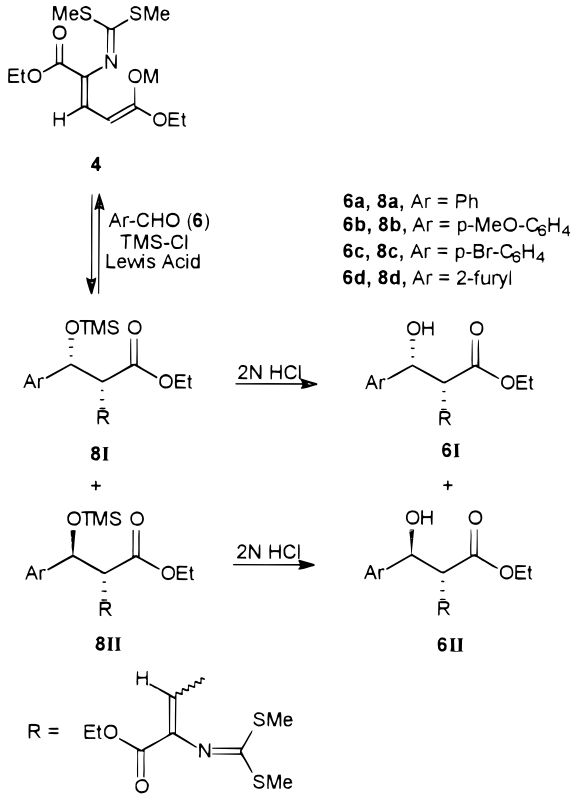
Scheme 1



and 8). To improve diastereoselectivity, different Lewis acids were tested. By using $AlMe_3$ (entry 9) or $TiCl_4$ (entry 10), the anti isomer **8aII** was obtained preferentially from the reaction of **4** (M = Li) and benzaldehyde. This was also the case when TBAF (1.25 equiv) was used as the Lewis acid (entry 11), but with lower yield as compared with the two previous cases. This was improved by making use of only catalytic amounts of TBAF (0.1 equiv) (entry 12). With BF_3, a turnover of diastereoselectivity was observed, the syn adduct **8aI** being obtained from the reaction of **4** (M = Li) and benzaldehyde with very good yield and diastereoselectivity (entry 13). It is worth mentioning that a loss of diastereoselectivity was noticed upon increasing the reaction temperature (entry 14). The best results observed for the reactions with benzaldehyde were extended to other aldehydes (entries 15−20) with production of the syn isomers **8(b−d)I** in the case of BF_3 (1.25 equiv, entries 15−17) and of the anti adducts **8(b−d)II** by making use of TBAF (0.1 equiv, entries 18−20).

We have also observed that the TMS group in compounds **8** can be easily removed in acid medium. Thus, treatment of **8a** with 2 N HCl afforded aldols **6a** with retention of configuration (Scheme 2). This explains the fact that aldols **6I** are obtained directly from the reaction

Scheme 2



medium in the BF_3-driven reactions (Table 1, entries 13−17) instead of the corresponding TMS-derivatives **8I**. The acid medium formed upon quenching the reactions in the presence of BF_3 may deprotect in situ the TMS group of compounds **8I** during workup.

Discussion

The electrophilic capture of lithium dienolates, generated by deprotonation of *Z* or *E* 3-alkenoate esters is known to be stereospecific, with retention of the position and geometry of the parent C−C double bond.[7] Therefore, for dienolates **4**, a *Z* configuration for the C2−C3 double bond can be assumed. A *Z* configuration[8] for the C4−C5 enolate double bond can be proposed on the basis of the known propensity of ester dienolates to the formation of *Z* enolates.[9] Under these circumstances, further chelation of the cation by the sp^2 nitrogen of the imine moiety is also possible, allowing for an *s-cis* conformation of the dienolate[10,11] (Scheme 3). This geometry for dienolates **4** justifies the exclusive formation of compound **(*Z*)-7** when the α,β-didehydroamino acid

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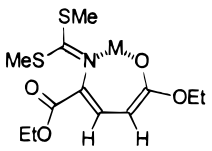
Table 1. Aldol Reaction of (*Z*)-α,*β*-Didehydroglutamate 3 with Aldehydes 5[a]

	5	base	Lewis acid (equiv)	compd (%)[b]	I:II[c]
1	Ph-CHO	LDA		*d*	
2	Ph-CHO	LDA	$ZnCl_2$ (1.25)	*d*	
3	Ph-CHO	LDA		**8a** (75)	40:60
4	Ph-CHO	LDA	$ZnCl_2$ (1.25)	**8a** (90)	50:50
5	Ph-CHO	LDA[e]	$ZnCl_2$ (1.25)	**8a** (90)	50:50
6	Ph-CHO	LiHMDS	$ZnCl_2$ (1.25)	**8a** (90)	50:50
7	Ph-CHO	KO−Bu	$ZnCl_2$ (1.25)		
8	Ph-CHO	KMHDS	$ZnCl_2$ (1.25)		
9	Ph-CHO	LDA	$AlMe_3$ (1.25)	**8a** (65)	25:75
10	Ph-CHO	LDA	$TiCl_4$ (1.25)	**8a** (55)	05:95
11	Ph-CHO	LDA	TBAF (1.25)	**8a** (30)	10:90
12	Ph-CHO	LDA	TBAF (0.1)	**8a** (85)	10:90
13	Ph-CHO	LDA	$BF_3{\cdot}OEt_2$ (1.25)	**6a** (90)[f]	95:05
14	Ph-CHO	LDA	$BF_3{\cdot}OEt_2$ (1.25)	**6a** (90)[f,g]	75:25
15	*p*-MeO-C_6H_4-CHO	LDA	$BF_3{\cdot}OEt_2$ (1.25)	**6b** (90)[f]	95:05
16	*p*-Br-C_6H_4-CHO	LDA	$BF_3{\cdot}OEt_2$ (1.25)	**6c** (90)[f]	95:05
17	(2-furyl)-CHO	LDA	$BF_3{\cdot}OEt_2$ (1.25)	**6d** (90)[f]	95:05
18	*p*-MeO-C_6H_4-CHO	LDA	TBAF (0.1)	**8b** (90)	10:90
19	*p*-Br-C_6H_4-CHO	LDA	TBAF (0.1)	**8c** (90)	10:90
20	(2-furyl)-CHO	LDA	TBAF (0.1)	**8d** (90)	10:90

[a] All reactions were carried out in THF at −78 °C and in the presence of TMS−Cl (1.1 equiv) added after enolization, unless otherwise stated. [b] Isolated yields. [c] Determined by integration of the ^{1}H NMR (300 MHz) of the crude products. [d] Carried out in the absence of TMS−Cl. [e] Et_2O was used as solvent instead of THF. [f] Aldols **6** instead of the silylderivatives **8** were directly isolated from the reaction crude products. [g] Reaction carried out at 0 °C.

Scheme 3



derivative **3** was treated with LDA or KO^{t}Bu in THF[12] and alkylated with MeI.

Compounds **6** and **8** were also obtained as *Z* isomers,[12] without the corresponding *E* isomer being observed. The relative configuration of compounds **I** as the syn isomers and **II** as the anti was based on the comparison of the magnitude of the ^3J coupling constants between H4 and H5 in the ^{1}H NMR spectra of aldols **6** (**6I**, $^3J_{H4-H5} = 6$ Hz; **6II**, $^3J_{H4-H5} = 9$ Hz) and the well-known relationship of this parameter with the geometry of aldols.[13,14]

The results obtained in the reaction of the lithium enolate **4** (M = Li) with aldehydes **5** in the presence of TMS−Cl could be interpreted on the basis of the formation of the corresponding silylenolacetals followed by a Mukaiyama reaction with the aldehydes in the presence of a Lewis acid.[15] However, this reaction pathway was ruled out on the basis of the reaction of the lithium enolate **4** (M = Li) with benzaldehyde and TMS−Cl, which also took place in the absence of a Lewis acid[16] (Table 1, entry 3). Furthermore, we did not succeed in trapping **4** neither with either TMS−Cl or TBS−Cl,[17] and no reaction was observed with potassium enolates (Table 1, entries 7, 8).

However, it is well known that the aldol reaction is an exothermic process, and the presence of a coordinating metal cation provides part of the driving force for the reaction to occur. Furthermore, steric crowding in an aldolate favors reverse aldolization, and equilibration is facilitated in less basic enolates.[6] Therefore, the results obtained with the lithium enolate **4** (M = Li) alone and in the presence of $ZnCl_2$, $AlMe_3$, and $TiCl_4$ could be better accommodated by the operation of a cyclic mechanism under thermodynamic control[14,18] (Scheme 4).

The addition of the lithium enolate **4** to the aldehydes **5** should give rise to a rapid equilibrium of the starting materials with both the syn and anti aldolates **9**. The rate of syn−anti equilibration by reverse aldolization is very sensitive to the nature of the cation associated with the aldolate[4] and should be retarded by highly coordinating cations as Zn, Al, or Ti. In this thermodynamically driven process, the formation of the most stable cyclic aldolate intermediate **9II**, with R and Ar in an equatorial disposition, should be preferred. Trapping of this equilibrium mixture with TMS−Cl affords the observed results.

It is also known that, for the alkali metal aldolates, the potassium compounds equilibrate more rapidly than the lithium ones.[18a] Complete retroaldolization may explain the failure of the addition reactions with KO^{t}Bu or KHMDS (Table 1, entries 7 and 8).

Slightly different is the case of TBAF due to the desilylation promoted by the fluoride anion[19] (Scheme 4). Here, the equilibration involves the silylated derivatives **8**, and the observed product ratios reflect their thermodynamic stability. This explains the need of keeping the amount of catalyst to a minimum (0.1 equiv), which

(12) The assignment of a *Z* geometry to **7** was carried out by comparison of the chemical shift values observed for the vinylic H3 proton in the ^{1}H NMR spectrum (300 MHz) with those previously reported for related compounds. See ref 2e and O'Donnell, M. J.; Arasappan, A.; Hornback. W.; Huffman, J. C. *Tetrahedron Lett.* **1990**, *31*, 157.

(13) Stiles, M.; Winkler, R. R.; Chang, Y.; Traynor, L. *J. Am. Chem. Soc.* **1964**, *86*, 3337.

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(16) It is well known that silicon enolates are not nucleophilic enough to undergo uncatalyzed addition to aldehydes. See: Chang, T.-H. In *Comprehensive Organic Chemistry*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, p 595.

(17) The trapping of delocalized ester enolates with silylating agents has been reported to be troublesome. See: (a) Corset, J.; Fromet, F.; Lautié, M. F.; Ratovelomana, N.; Seyden-Penne, J.; Strzalko, T.; Roux-Schmitt, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 1684. (b) Solladié-Cavallo, A.; Csákÿ, A. G. *J. Org. Chem.* **1994**, *59*, 2585 and references cited therein.

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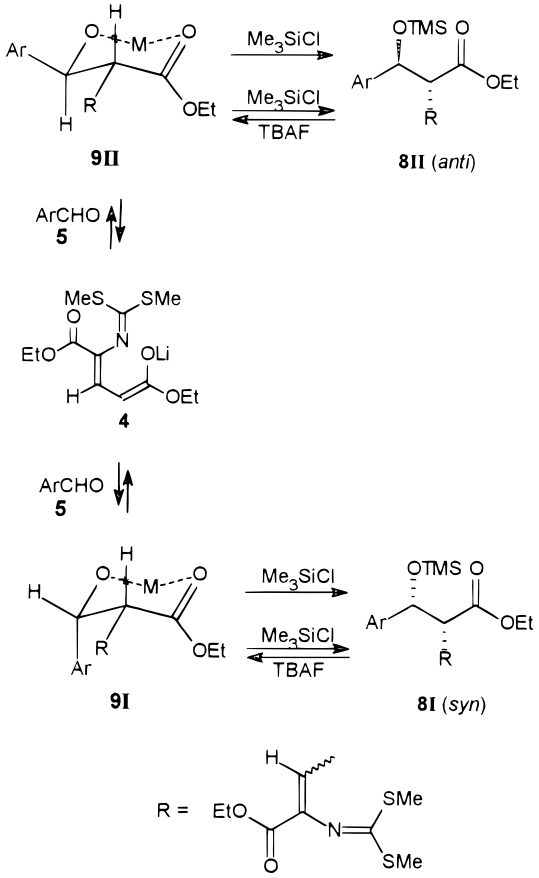
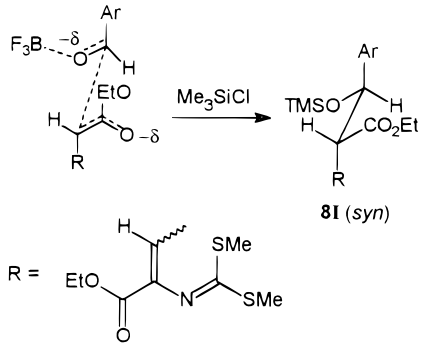
Scheme 4



Scheme 5



allows the aldol reaction to proceed and avoids the desilylation reaction that would result in full retroaldolization.[20]

The inversion of diastereoselectivity in the case of BF_3, a very strong Lewis acid, can be accounted for by an open chain mechanism, which explains the formation of the syn aldols **8I** in a kinetically controlled process (Scheme 5). As a matter of fact, a loss of diastereoselectivity was observed upon increasing the reaction temperature (Table 1, entries 13 and 14).

Conclusions

The aldol reaction of the (*Z*)-α,β-didehydroglutamate **3** is possible only in the presence of TMS−Cl as a trapping agent to avoid the retroaldolization which otherwise takes place. By using the appropriate Lewis acid, the selectivity of the process can be tuned at will, allowing for the selective production of either the *syn* (BF_3) or the anti (TBAF) aldols. New pharmacological properties for compounds **6** and their derivatives may be expected.

Experimental Section

All starting materials were commercially available research-grade chemicals and were used without further purification. THF was distilled after refluxing over Na/benzophenone. Diisopropylamine was dried over CaH_2 and freshly distilled under Ar prior to use. Silica gel 60 F_{254} was used for TLC, and the spots were detected with UV light. Flash column chromatography was carried out on silica gel 60. IR spectra have been recorded as $CHCl_3$ solutions. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, in $CDCl_3$ solution with TMS as internal reference, and full assignment of ^{13}C spectra has been carried out with the aid of the DEPT-135 pulse sequence. Compound **3** was prepared as previously described.

(*Z*)-Diethyl-4-methyl-2-[bis(methylthio)methylene]-amino-2-pentenodioate (7). To a solution of LDA or KO^{t}Bu (0.25 mmol) in THF (0.4 mL) at −78 °C was added a solution of **3** (0.2 mmol) in THF (0.3 mL), and the mixture was stirred for 30 min. MeI (1.75 mmol) was added, the temperature was raised to 25 °C over 3 h, and the mixture was stirred for 18 h. H_2O (0.5 mL) was added, and the organic layer was decanted. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were dried over $MgSO_4$. Evaporation under reduced pressure afforded an oil which was purified by column chromatography with a mixture of hexane−ethyl acetate (80:20): colorless oil (90%); IR ($CHCl_3$) 1750, 1730, 1640, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.28 (1H, d, $^3J = 9$ Hz), 4.25 (2H, q, $^3J = 7$ Hz), 4.15 (2H, q, $^3J = 7$ Hz), 3.26 (1H, dq, $^3J = 9$ Hz, $^3J = 7$ Hz), 2.51 (6H, s), 1.28 (3H, t, $^3J = 7$ Hz), 1.27 (3H, d, $^3J = 7$ Hz), 1.26 (3H, d, $^3J = 7$ Hz); ^{13}C NMR ($CDCl_3$) δ 173.9, 166.9, 163.2, 138.7, 125.5, 61.2, 60.8, 38.2, 17.4, 15.1, 14.4, 14.3. Anal. Calcd for $C_{13}H_{21}NO_4S_2$: C, 48.88; H, 6.63; N, 4.38. Found: C, 48.92; H, 6.75; N, 3.03.

Aldol Reactions of (*Z*)-α,β-Didehydroglutamate 3 with Aldehydes 5 in the Presence of $ZnCl_2$, $TiCl_4$, or BF_3OEt_2. General Procedure. To a solution of LDA, LiHMDS, KHMDS, or KO^{t}Bu (0.33 mmol) in THF (0.5 mL) at −78 °C was added a solution of (*Z*)-α,β-didehydroglutamate **3** (100 mg, 0.33 mmol) in THF (0.5 mL) with stirring. After 30 min at −78 °C, Me_3SiCl (42 μL, 0.33 mmol) was added and the mixture was stirred for 15 min. A solution of $ZnCl_2$, $TiCl_4$, or BF_3OEt_2 (0.41 mmol) and the corresponding aldehyde **5** (0.33 mmol) in THF (0.5 mL) was added, and the mixture was stirred for 4 h at −78 °C. The temperature was allowed to rise to −50 °C over 2 h, H_2O (2.5 mL) was added, and the temperature was allowed to reach rt. The organic layer was decanted, and the aqueous phase extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$. After concentration of the solution, the pale yellow oil was purified by flash chromatography (hexane−ethyl acetate, 80:20).

Aldol Reactions of (*Z*)-α,β-Didehydroglutamate 3 with Aldehydes 5 in the Presence of TBAF. General Procedure. To a solution of LDA (0.33 mmol) in THF (0.5 mL) at −78 °C was added a solution of (*Z*)-α,β-didehydroglutamate **3** (100 mg, 0.33 mmol) in THF (0.5 mL) with stirring. After 30 min at −78 °C, Me_3SiCl (42 μL, 0.33 mmol) was added and the mixture was stirred for 15 min. The corresponding aldehyde **5** (0.33 mmol) in THF (0.5 mL) was added, followed by a solution of TBAF (5 μL, 0.41 μmol) in THF (0.5 mL). The temperature was allowed to rise to rt over 3 h, and the mixture was stirred for 20 h. After addition of H_2O (2.5 mL), the organic layer was decanted and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers

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(20) Full retroaldolization was observed in an independent essay upon treatment of **8a** with 1 M TBAF solution in THF at room temperature in 1 h.

were dried over $MgSO_4$. After concentration of the solution, the pale yellow oil was purified by flash chromatography (hexane−ethyl acetate, 80:20).

Hydrolisis of the TMS Group of 8a. To a solution of **8a** (100 mg, 0.21 mmol) in THF (1.0 mL) was added 2 N HCl (1.0 mL), and the mixture was stirred for 2 h. The mixture was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried over $MgSO_4$. After concentration of the solution, the pale yellow oil was purified by flash chromatography (hexane−ethyl acetate, 80:20).

(4*R,5*S**)-(*Z*)-4-(1-Hydroxy)benzyl-*N*-[bis(methylthio)methylene]-α,β-didehydroglutamate (6aI):** colorless oil (90%); IR ($CHCl_3$) 3315, 1570, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00−7.80 (5H, m), 6.27 (1H, d, ^3J = 9.5 Hz), 4.90 (1H, d, ^3J = 6 Hz), 4.00 (2H, q, ^3J = 7 Hz), 3.85 (2H, q, ^3J = 7 Hz), 3.45 (1H, dd, ^3J = 9.5, 6 Hz), 2.30 (6H, s), 1.10 (3H, t, ^3J = 7 Hz), 0.89 (3H, t, ^3J = 7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.4, 171.0, 168.1, 141.2, 140.7, 128.2, 127.8, 126.2, 120.3, 76.6, 74.8, 61.1, 60.4, 15.8, 15.6, 14.9, 13.9. Anal. Calcd for $C_{19}H_{25}NO_5S_2$: C, 55.45; H, 6.12; N, 3.40. Found: C, 55.58; H, 6.15; N, 3.45.

(4*R,5*R**)-(*Z*)-4-(1-Hydroxy)benzyl-*N*-[bis(methylthio)methylene]-α,β-di-dehydroglutamate (6aII):** colorless oil (80%, hydrolysis of **8aII**); IR ($CHCl_3$) 3315, 1570, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00−7.80 (5H, m), 6.15 (1H, d, ^3J = 9.5 Hz), 5.10 (1H, bs), 4.05 (2H, q, ^3J = 7 Hz), 3.95 (2H, q, ^3J = 7 Hz), 3.60 (1H, dd, ^3J = 9.5, 9 Hz), 2.35 (6H, s), 1.20 (3H, t, ^3J = 7 Hz), 1.00 (3H, t, ^3J = 7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.5, 171.2, 166.3, 141.2, 139.8, 128.3, 127.5, 126.3, 121.2, 77.1, 75.0, 61.2, 60.9, 16.0, 15.8, 15.1, 14.1. Anal. Calcd for $C_{19}H_{25}NO_5S_2$: C, 55.45; H, 6.12; N, 3.40. Found: C, 55.61; H, 6.21; N, 3.35.

(4*R,5S*)-(*Z*)-4-[1-Hydroxy-1-(4′-methoxyphenyl)-methyl]-*N*-[bis(methylthio)methylene]-α,β-didehydroglutamate (6bI):** colorless oil (90%); IR ($CHCl_3$) 3315, 1570, 1720 cm^{-1};. ^1H NMR (300 MHz, $CDCl_3$) δ 7.00−7.70 (4H, m), 6.30 (1H, d, ^3J = 9.5 Hz), 4.97 (1H, d, ^3J = 5.5 Hz), 4.15 (2H, q, ^3J = 7 Hz), 3.95 (2H, q, ^3J = 7 Hz), 3.80 (3H, s), 3.50 (1H, dd, ^3J = 9.5, 5.5 Hz), 2.40 (6H, s), 1.20 (3H, t, ^3J = 7 Hz), 1.05 (3H, t, ^3J = 7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.6, 171.3, 162.7, 141.4, 139.8, 131.3, 128.0, 121.6, 119.3, 76.6, 74.0, 61.3, 60.4, 51.7, 15.5, 15.1, 14.1, 13.9. Anal. Calcd for $C_{20}H_{27}NO_6S_2$: C, 54.40; H, 6.16; N, 3.17. Found: C, 54.60; H, 6.21; N, 3.30.

(4*R,5*S**)-(*Z*)-4-[1-(4′-Bromophenyl)-1-hydroxymethyl]-*N*-[bis(methylthio)methylene]-α,β-didehydroglutamate (6cI):** colorless oil (90%); IR ($CHCl_3$) 3320, 1580, 1710 cm^{-1};. ^1H NMR (300 MHz, $CDCl_3$) δ 7.05−7.80 (4H, m), 6.25 (1H, d, ^3J = 10 Hz), 4.97 (1H, d, ^3J = 5.5 Hz), 4.07 (2H, q, ^3J = 7 Hz), 3.95 (2H, q, ^3J = 7 Hz), 3.52 (1H, dd, ^3J = 10, 5.5 Hz), 2.40 (6H, s), 1.22 (3H, t, ^3J = 7 Hz), 1.08 (3H, t, ^3J = 7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.2, 170.8, 166.1, 141.4, 136.6, 131.3, 128.1, 119.3, 110.3, 76.6, 74.1, 61.2, 60.6, 15.3, 15.1, 14.2, 13.9. Anal. Calcd for $C_{19}H_{24}BrNO_5S_2$: C, 46.53; H, 4.93; N, 2.86. Found: C, 46.66; H, 4.97; N, 2.95.

(4*R,5*S**)-(*Z*)-4-[1-(2-Furyl)-1-hydroxymethyl]-*N*-[bis(methylthio)methylene]-α,β-didehydroglutamate (6dI):** colorless oil (90%); IR ($CHCl_3$) 3310, 1590, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (1H, d, ^3J = 7.5 Hz), 6.25 (1H, t, ^3J = 7 Hz), 6.15 (1H, d, ^3J = 9.5 Hz), 6.10 (1H, d, ^3J = 9.5 Hz), 4.95 (1H, d, ^3J = 6.5 Hz), 4.15 (2H, q, ^3J = 7.2 Hz), 4.05 (2H, q, ^3J = 7 Hz), 3.75 (1H, dd, ^3J = 9.5, 6.5 Hz), 2.45 (6H, s), 1.20 (3H, t, ^3J = 7 Hz), 1.10 (3H, t, ^3J = 7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.6, 171.2, 166.6, 142.3, 139.7, 136.6, 119.8, 110.2, 107.3, 68.8, 68.6, 61.1, 60.8, 15.4, 15.0, 14.1, 14.0. Anal. Calcd for $C_{17}H_{23}NO_6S_2$: C, 50.86; H, 5.77; N, 3.49. Found: C, 51.02; H, 5.92; N, 3.60.

(4*R, 5*S**)-(*Z*)-*N*-[Bis(methylthio)methylene]-4-(1-trimethylsilyloxy)benzyl-α,β-didehydroglutamate (8aI):** colorless oil (85%); IR ($CHCl_3$) 1580, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00−7.80 (5H, m), 6.47 (1H, d, ^3J = 9 Hz), 5.18 (1H, d, ^3J = 6 Hz), 4.25 (2H, q, ^3J = 7.5 Hz), 4.08 (2H, q, ^3J = 7.5 Hz), 3.53 (1H, dd, ^3J = 9, 6 Hz), 2.45 (6H, s), 1.28 (3H, t, ^3J = 7.5 Hz), 1.20 (3H, t, ^3J = 7.5 Hz), 0.10 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.2, 170.8, 167.9, 141.5, 140.2, 136.3, 128.5, 126.2, 121.5, 76.3, 75.1, 60.9, 60.2, 15.3, 15.1, 14.5, 13.8, 0.3. Anal. Calcd for $C_{22}H_{33}NO_5S_2Si$: C, 54.63; H, 6.88; N, 2.90. Found: C, 54.78; H, 6.92; N, 2.97.

(4*R,5*R**)-(*Z*)-*N*-[Bis(methylthio)methylene]-4-(1-trimethylsilyloxy)benzyl-α,β-didehydroglutamate (8aII):** colorless oil (85%); IR ($CHCl_3$) 1580, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00−7.80 (5H, m), 6.18 (1H, d, ^3J = 10 Hz), 5.04 (1H, d, ^3J = 9 Hz), 4.30 (2H, q, ^3J = 7.5 Hz), 4.20 (2H, q, ^3J = 7.5 Hz), 3.65 (1H, dd, ^3J = 10, 9 Hz), 2.45 (6H, s), 1.30 (3H, t, ^3J = 7.5 Hz), 1.25 (3H, t, ^3J = 7.5 Hz), 0.03 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.1, 170.9, 167.7, 140.5, 139.2, 136.5, 129.3, 127.2, 121.8, 76.1, 75.6, 61.4, 60.7, 16.2, 15.0, 14.7, 13.9, 0.3. Anal. Calcd for $C_{22}H_{33}NO_5S_2Si$: C, 54.63; H, 6.88; N, 2.90. Found: C, 54.66; H, 6.95; N, 3.03.

(4*R,5*R**)-(*Z*)-*N*-[Bis(methylthio)methylene]-4-[1-(4′-methoxyphenyl)-1-trimethylsilyloxymethyl]-α,β-didehydroglutamate (8bII):** colorless oil (90%); IR ($CHCl_3$) 1590, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00−7.80 (4H, m), 6.05 (1H, d, ^3J = 10 Hz), 4.96 (1H, d, ^3J = 9 Hz), 4.18 (2H, q, ^3J = 7 Hz), 4.10 (2H, q, ^3J = 7 Hz), 3.85 (3H, s), 3.60 (1H, dd, ^3J = 10, 9 Hz), 2.45 (6H, s), 1.20 (3H, t, ^3J = 7 Hz), 1.15 (3H, t, ^3J = 7.2 Hz), 0.03 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.5, 171.2, 163.1, 139.8, 136.7, 133.9, 129.6, 128.1, 120.3, 77.4, 76.7, 61.1, 60.9, 55.3, 16.3, 15.9, 14.3, 14.2, 0.3. Anal. Calcd for $C_{23}H_{35}NO_6S_2Si$: C, 53.77; H, 6.87; N, 2.73. Found: C, 53.92; H, 6.91; N, 2.97.

(4*R,5*R**)-(*Z*)-4-[1-(4′-Bromophenyl)-1-trimethylsilyloxymethyl]-*N*-[bis(methylthio)methylene]-α,β-didehydroglutamate (8cII):** colorless oil (90%); IR ($CHCl_3$) 1570, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20−7.80 (4H, m), 6.10 (1H, d, ^3J = 10 Hz), 4.95 (1H, d, ^3J = 9 Hz), 4.12 (2H, q, ^3J = 7 Hz), 4.05 (2H, q, ^3J = 7 Hz), 3.55 (1H, dd, ^3J = 10, 9 Hz), 2.35 (6H, s), 1.25 (3H, t, ^3J = 7 Hz), 1.10 (3H, t, ^3J = 7 Hz), 0.03 (9H, s); ^{13}C NMR (75.5 MHz $CDCl_3$) δ 171.2, 171.0, 165.1, 140.5, 135.1, 131.2, 129.8, 127.6, 117.1, 76.8, 75.1, 61.2, 60.9, 15.8, 15.6, 14.2, 14.1, 0.3. Anal. Calcd for $C_{22}H_{32}BrNO_5S_2Si$: C, 46.97; H, 5.73; N, 2.49. Found: C, 47.06; H, 5.85; N, 2.61.

(4*R,5*R**)-(*Z*)-4-[1-(2-Furyl)-1-trimethylsilyloxymethyl]-*N*-[bis(methylthio)methylene]-α,β-didehydroglutamate (8dII):** colorless oil (90%); IR ($CHCl_3$) 1590, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (1H, d, ^3J = 7.5 Hz), 6.25 (1H, t, ^3J = 7 Hz), 6.15 (1H, d, ^3J = 9.5 Hz), 5.95 (1H, d, ^3J = 9.5 Hz), 4.97 (1H, d, ^3J = 9.5 Hz), 4.15 (2H, q, ^3J = 7 Hz), 4.10 (2H, q, ^3J = 7 Hz), 3.85 (1H, dd, ^3J = 9.7, 9.5 Hz), 2.45 (6H, s), 1.35 (3H, t, ^3J = 7 Hz), 1.25 (3H, t, ^3J = 7 Hz), 0.03 (9H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.9, 162.8, 142.1, 140.4, 136.7, 119.6, 110.2, 107.2, 69.5, 68.7, 61.1, 60.8, 15.3, 14.1, 13.9, 0.3. Anal. Calcd for $C_{20}H_{31}NO_6S_2Si$: C, 50.71; H, 6.60; N, 2.96. Found: C, 50.95; H, 6.85; N, 3.03.

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