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Study of the Asymmetric Synthesis of (Z)-γ-Substituted α,β-Didehydroglutamates from N-Alkylideneglycinates

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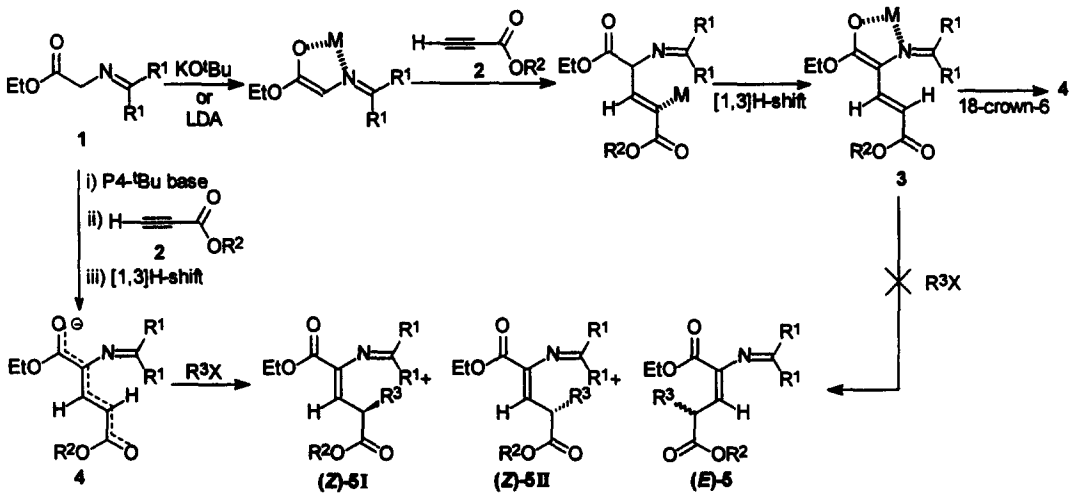
Abstract. The synthesis of (*Z*)-γ-substituted-α,β-didehydroglutamates has been accomplished either starting from the glycinates **1** or the α,β-didehydroglutamates **6**. In the first case, no reaction of the lithium enolates **3** was observed, and the use of the naked anions **4** was required; while in the second case, the lithium enolates **7** reacted successfully with alkyl halides to afford the target molecules.

Constrained glutamic acid derivatives are of interest in the light of the well known implication of glutamate receptors in neuronal diseases.[1] α,β-Didehydroamino acids can be considered as a new class of conformationally restricted non proteinogenic amino acids. Therefore, the development of new methods of syntesis of functionalized α,β-didehydroglutamates may lead to new compounds with anticipated pharmacological importance. Furthermore, α,β-didehydroglutamates can be envisioned as valuable building blocks for the synthesis of other non-natural amino acids.[2]



Scheme 1

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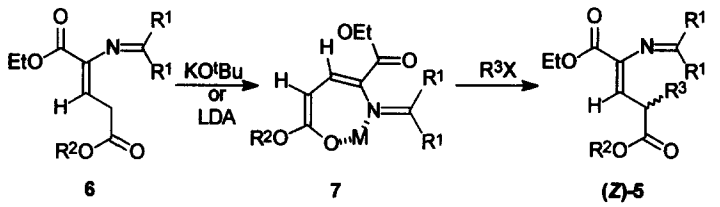
The purpose of this work is the study of the asymmetric synthesis of the (*Z*)-γ-alkyl-α,β-didehydoglutamates **5**. This has been accomplished by two different routes: (i) addition of glycinates **1** to propiolates **2** followed by electrophilic capture of the naked anions **4** (Scheme 1, Method A), and (ii) deprotonation of the (Z)-α,β-didehydroglutamates **6** followed by electrophilic capture of the alkaline enolates **7** (Scheme 2, Method B).



6 **7** **(Z)-5**

Scheme 2

Results

Treatment of glycinate **1a** with KO^{t}Bu, LDA or BuLi (1.1 equiv., THF, -78°C, 30 min) followed by reaction with ethyl propiolate (**2a**) (1.1 equiv., -78°C, 10 min) and hydrolysis (H_2O, -78°C) or protonation with AcOH (5.0 equiv., -78°C) afforded the α,β-didehydroglutamate **6a** in high yield[3] (Scheme 1). However, capture of the intermediate alkaline dienolates **3a** (M = Li, K) with an excess of MeI did not allow for the isolation of compounds **5a**, even in the presence of DMPU (30% in volume) as cosolvent. In order to enhance the nucleophilic character of the attacking species, the naked anion **4a** was prepared. This was carried out by two different procedures: (i) deprotonation of **1a** with Schwesinger's phosphazene base[4,5] P4-^{t}Bu or (ii) generation of **3a** (M = K) by deprotonation of **1a** with KO^{t}Bu followed by capture of the alkaline cation with 18-crown-6 prior to the addition of the alkyne **2a**. In either case, reaction with MeI afforded (***Z***)-**5a** together with minor ammounts of the geometrical isomer (***E***)-**5a**. This result was extended to the synthesis of the 8-phenylmenthyl derivatives (***Z***)-**5b-e**. The results are given in Table 1.

On the other hand, deprotonation of α,β-Didehydroglutamates **6** with KO^{t}Bu or LDA (THF, 1.25 equiv., -78°C, 30 min) followed by electrophilic capture allowed for the isolation of compounds (***Z***)-**5** (Scheme 2).[6] The results are gathered in Table 2.

As in the previous case, isomers **5I** largely predominated over isomers **5II**. It is worth mentioning that compounds (***Z***)-**5** were exclusively obtained in this fashion.

The assignment of an *E* or *Z* stereochemistry to compounds **5** and **6** was carried out by comparison of the chemical shift values observed for the vinylic H3 proton in their ^{1}H-NMR spectra (300 MHz) with those previously reported for related compounds.[7] For 8-phenylmenthyl esters, there is theoretical and spectroscopic evidence of a stabilising π–π interaction of the conformer which has a *cis* relative disposition between the

phenyl ring of the 8-phenylmenthyl moiety and the side chain.[8] This promotes strong shielding effects of the protons α– to the carbonyl group.[9]

Table 1. Electrophilic Capture of the Naked Enolates 4 (R^1 = SMe)

No.	Base	R^2	R^3X	R^3	5 (%)[a]	5 *Z:E ratio*[b]	(Z)-5 I:II ratio[b]
1	P4-^{t}Bu	Et	CH_3I	CH_3	**5a** (93)	94 : 06	---
2	KO^{t}Bu/18-crown-6	Et	CH_3I	CH_3	**5a** (92)	98 : 02	---
3	P4-^{t}Bu	8-phenylmenthyl	CH_3I	CH_3	**5b** (96)	82 : 18	79 : 21
4	KO^{t}Bu/18-crown-6	8-phenylmenthyl	CH_3I	CH_3	**5b** (96)	85 : 15	86 : 14
5	P4-^{t}Bu	8-phenylmenthyl	$PhCH_2Br$	$PhCH_2$	**5c** (90)	98 : 02	82 : 18
6	KO^{t}Bu/18-crown-6	8-phenylmenthyl	$PhCH_2Br$	$PhCH_2$	**5c** (82)	73 : 27	72 : 28
7	P4-^{t}Bu	8-phenylmenthyl	CH_2=CH-CH_2Br	CH_2=CH-CH_2	**5d** (82)	84 : 16	81 : 19
8	KO^{t}Bu/18-crown-6	8-phenylmenthyl	CH_2=CH-CH_2Br	CH_2=CH-CH_2	**5d** (93)	92 : 08	73 : 27
9	P4-^{t}Bu	8-phenylmenthyl	EtO_2C-CH_2Br	EtO_2C-CH_2	**5e** (94)	83 : 17	82 : 18
10	KO^{t}Bu/18-crown-6	8-phenylmenthyl	EtO_2C-CH_2Br	EtO_2C-CH_2Br	**5e** (91)	95 : 05	82 : 18

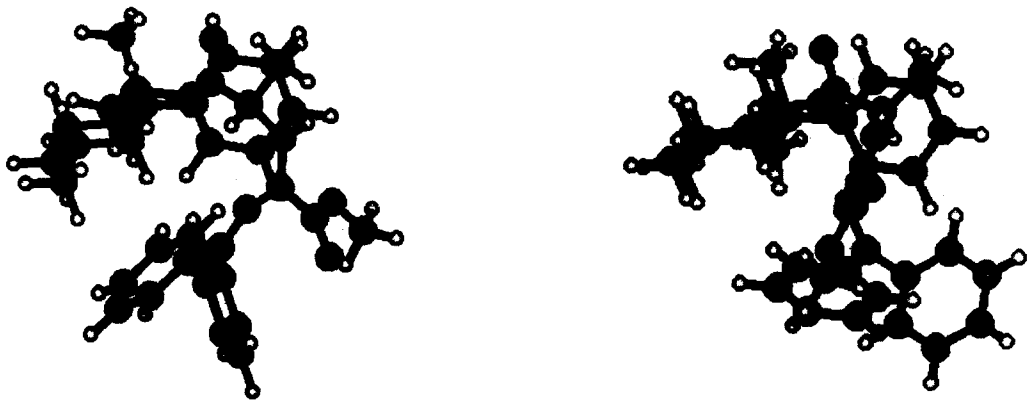
a) Pure isolated yield of the *Z/E* mixture.
b) Determined by integration of the ^{1}H-NMR spectra ($CDCl_3$, 300 MHz).

Table 2. Electrophilic Capture of the Enolates 7

No.	Base	R^1	R^2	R^3X	R^3	5 (%)[a]	(*Z*)-5 I:II ratio[b]
1	LDA	SCH_3	Et	CH_3I	CH_3	**5a** (92)	---
2	LDA	SCH_3	8-phenylmenthyl	CH_3I	CH_3	**5b** (94)	76 : 24
3	KO^{t}Bu	SCH_3	8-phenylmenthyl	CH_3I	CH_3	**5b** (94)	85 : 15
4	KO^{t}Bu	SCH_3	8-phenylmenthyl	$PhCH_2Br$	$PhCH_2$	**5c** (96)	77 : 23
5	KO^{t}Bu	SCH_3	8-phenylmenthyl	CH_2=CH-CH_2Br	CH_2=CH-CH_2	**5d** (97)	72 : 28
6	KO^{t}Bu	SCH_3	8-phenylmenthyl	EtO_2C-CH_2Br	EtO_2C-CH_2	**5e** (89)	80 : 20
7	LDA	Ph	8-phenylmenthyl	CH_3I	CH_3	**5f** (94)	79 : 21
8	KO^{t}Bu	Ph	8-phenylmenthyl	CH_3I	CH_3	**5f** (95)	82 : 18
9	LDA	Ph	8-phenylmenthyl	$PhCH_2Br$	$PhCH_2$	**5g** (93)	71 : 29
10	LDA	Ph	8-phenylmenthyl	CH_2=CH-CH_2Br	CH_2=CH-CH_2	**5h** (67)	72 : 28
11	LDA	Ph	8-phenylmenthyl	EtO_2C-CH_2Br	EtO_2C-CH_2	**5i** (77)	62 : 38

a) Pure isolated yield
b) Determined by integration of the ^{1}H-NMR spectra ($CDCl_3$, 300 MHz).

Analysis of the minimum energy conformation population[10] of epimers 4*R* and 4*S* of compounds **5f** shows that in the latter isomer, the H4 atom lies[13] inside the shielding cone of the phenyl ring of the 8-phenylmenthyl moiety (Figure 1). Therefore, the assignment of configuration *4R* to isomers **5I** and *4S* to isomers **5II** was based on the observation of a higher chemical shift value for the H4 signal of isomers **5I** in their ^{1}H-NMR spectra (300 MHz).[14]



Isomer 4R Isomer 4S

Figure 1

Discussion

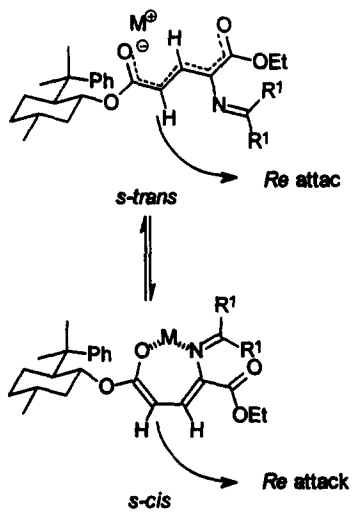
Deprotonation of glycinates **1** with alkaline bases (BuLi, LDA or KO^{t}Bu) followed by reaction with alkynes **2** gave rise to the intermediate dienolate **3** (Scheme 1, Method A). It has been previously reported[15] that lithium dienolates tend to react at the α– position (C2). However, protonation of species **3a** (M = Li, K) with H_2O or AcOH took place exclusively at the γ– position (C4) affording the most stable alkene,[16,17] and no reaction with MeI was observed. These results can be explained on the basis of an O-protonation of **3a** followed by enol tautomerization to **6a** in a thermodynamically driven process.

On the other hand, formation of the more reactive naked anions[18,19] **4** allowed for the electrophilic capture with MeI. The alkylation reaction took place exclusively at carbon C4 (Scheme 1, Method A), which could be understood on steric grounds due to hindrance of the α–position (C2). It is worth mentioning that different *Z/E* ratios as well as **I:II** ratios were observed when the naked enolates **4** were generated with the P4-^{t}Bu base or by the KO^{t}Bu-crown ether method (Table 1) and captured by the same alkylant. This may be due to the formation of differently associated ion pairs in solution,[18] which could induce conformational changes in the anion backbone.

When the α,β-didehydroamino acid derivatives **6** were treated with LDA or KO^{t}Bu in THF (Scheme 2, Method B), the alkaline dienolate **7** thus generated reacted successfully with alkyl halides allowing for the isolation of compounds (*Z*)-**5** (Table 2). Therefore, the alkaline dienolates **7**, generated by deprotonation of **6**,

show a different reactivity pattern than dienolates **3**, which were generated by deprotonation of **1** followed by reaction with alkynes **2** (Scheme 1). This difference in reactivity between these closely related anions should be the consequence of the different structure of **3** and **7**, which nonetheless, could be considered analogous species at first sight.[20]

The alkylation 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.[21] Therefore, for dienolates **7** a *Z* configuration for the C2-C3 double bond can be assumed, and a *Z* configuration for the C4-C5 enolate double bond can be proposed on the basis of the known propensity of ester dienolates for the formation of *Z* enolates.[22,23] 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[23,24] (Scheme 3). This geometry for dienolates **7** is supported because, following this reaction pathway (Table 2 and Scheme 2, Method B), compounds **(*Z*)-5** were the only isomers observed. On the other hand, the naked enolates **4** should have an enhanced ratio of *E* geometry on both the C2-C3 and C4-C5 double bonds as well as *s-trans* conformation, due to charge delocalization[25] and dipolar repulsion. This explains the observation of **(*E*)-5** under these reaction conditions (Table 1 and Scheme 1, Method A). Nevertheless, in both circumstances, and allowing for a chain-extended disposition between the phenyl ring of the chiral inducer and the enolate moiety in a chain-extended fashion,[26] steric hindrance of the *Si* face of enolates **4** and **7** is to be expected, and thus, alkylation gives rise to the predominant formation of isomers **5I** (*4R*) in both cases (Scheme 3).



Scheme 3

Conclusions

The addition of the alkaline enolates derived from glycinates **1** to propiolates **2** followed by alkylation of the intermediate enolate **3** did not allow for the obtention of the target γ-alkyl-α,β-didehydroglutamates **5**.

However, the transformation of species **3** into the naked enolates **4** (Method A) as well as the generation of the alkaline enolates **7** *via* deprotonation of the α,β-didehydroglutamates **6** (Method B) gave rise to compounds **5**, which were obtained predominantly as *Z* isomers, specially in the latter case. Therefore, enolates **3**, **4** and **7** should be considered as species with different structure and reactivity. This is reflected both in the *Z/E* ratios obtained by following either method (Method A or Method B) as well as in the **I:II** ratios observed. The best results for the obtention of γ-alkyl-α,β-didehydroglutamates (*Z*)-**5**, with *4R* configuration, were obtained by making use of the bis(methylthio)methylene moiety as N-protecting group and 8-phenylmenthol as chiral inducer.

Experimental Section

All starting materials were commercially available research-grade chemicals and used without further purification. THF was distilled after refluxing over Na/benzophenone. Diisopropylamine and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) were 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. Flash column chromatography was carried out on silica gel 60. IR spectra have been recorden as $CHCl_3$ solutions. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 MHz 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. Compounds **1a**[27] and **1b**[28] were prepared as previously described.

8-Phenylmenthylpropiolate (2b). To a solution of (-)-8-phenylmenthol (625 mg, 2.7 mmol) in toluene (20 mL) was added a 2.0 M solution of $AlMe_3$ in hexane (1.5 mL, 2.9 mmol). After 20 min, a solution of methyl propiolate (0.1 mL, 1.3 mmol) in toluene (14 mL) was added and the mixture was stirred at 60°C for 12 h. The reaction mixture was cooled to room temperature and $Na_2CO_3.10H_2O$ (1 g) was added. The mixture was stirred for 30 min, the solid was filtered and washed with Et_2O, and the solvent was evaporated under reduced pressure. The remaining oil was purified by column chromatography with a mixture of hexane - Et_2O (80:20) to give the *title compound* **2b** (295 mg, 80%) as a colourless oil. IR ($CHCl_3$), 3280, 2140, 1720 cm^{-1}; ^1H-NMR ($CDCl_3$), δ 7.36 - 7.12 (5H, m), 4.88 (1H, td, $^3J_{aa}$ = 11 Hz, $^3J_{ae}$ = 4 Hz), 2.72 (1H, s), 2.06 - 0.80 (17H, m); ^{13}C-NMR ($CDCl_3$), δ 152.1, 150.5, 128.1, 125.5, 125.4, 74.9, 74.1, 50.5, 41.3, 39.9, 34.3, 31.3, 26.9, 26.8, 22.6, 21.7. Anal. Calcd. for $C_{19}H_{24}O_2$: C 80.24; H 8.51. Found C 80.16; H 8.64.

General Procedure for the Synthesis of (*Z*)-γ-Alkyl-α,β-didehydroglutamates 5 from Glycinates 1 (Method A).

Reactions with P4-^{t}Bu base. To a solution of glycinate **1** (0.48 mmol) in THF (2.0 mL) at -78°C was added dropwise with vigorous stirring a 1.0 M solution of P4-^{t}Bu base in hexane (0.48 mL, 0.48 mmol) prediluted in THF (1.0 mL) followed by a solution of the corresponding propiolate **2** (0.48 mmol) in THF (0.5 mL). The mixture was stirred for 5 min, and the electrophile R^3X (5.0 mmol) was added. The temperature was slowly raised to 25°C and stirring was maintained for 18 h. Et_2O was added and the precipitate was filtered in vacuo and washed with Et_2O (3 x 2 mL). Evaporation of the solid afforded an oil which was purified by column

chromatography with a mixture of hexane - Et_2O (80:20). Compounds **5** (colorless oils) were obtained as a mixture of epimers **I** and **II** (Table 1).

Reactions with 18-Crown-6. To a solution of KO^tBu (0.6 mmol) in THF (1.0 mL) at -78°C was added a solution of glycinate **1** (0.48 mmol) in THF (1.0 mL), and the mixture was stirred for 30 min. A solution of propiolate **2** (0.6 mmol) in THF (0.5 mL) was added and the mixture was stirred for 10 min. A solution of 18-crown-6 (0.6 mmol) in THF (0.5 mL) was added and the mixture was stirred for 10 min. The corresponding electrophile R^3X (2.4 mmol) was added, the temperature was slowly raised to 25°C and stirring was continued for 18 h. Water (0.5 mL) was added, the organic layer was decanted, and the aqueous one extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvent afforded an oil which was purified by column chromatography with a mixture of hexane - Et_2O (80:20). Compounds **5** (colorless oils) were obtained as a mixture of epimers **I** and **II** (Table 1).

General Procedure for the Synthesis of (*Z*)-γ-Alkyl-α,β-didehydroglutamates 5 from α,β-Didehydroglutamates 6 (Method B). To a solution of LDA or KO^tBu (0.25 mmol) in THF (0.4 mL) at -78°C was added a solution of **6** (0.2 mmol) in THF (0.3 mL) and the mixture was stirred for 30 min. The corresponding electrophile R^3X was added (1.75 mmol), the temperature was slowly raised to 25°C and the mixture 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 x 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). Compounds **5** (colorless oils) were obtained as a mixture of epimers **I** and **II** (Table 2).

(*Z*)-Diethyl 4-methyl-2-[bis(methylthio)methylene]amino-2-pentenodioate (5a). IR ($CHCl_3$), 1750, 1730, 1640. 1580 cm^{-1}; ^{1}H-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, 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.

(Z)-1-Ethyl-5-(8-phenylmenthyl) 4-methyl-2-[bis(methylthio)methylene]amino-2-pentenodioate (5b). IR ($CHCl_3$) 1710, 1780, 1640, 1570 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 7.42 - 7.01 (5H, m, **I** + **II**), 6.27 (1H, d, ^3J = 9 Hz, **I**), 6.14 (1H, d, ^3J = 9 Hz, **II**), 4.72 (1H, q, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz, **I** + **II**), 4.22 (2H, q, ^3J = 7 Hz, **I** + **II**), 2.91 (1H, dq, ^3J = 9Hz, ^3J = 7 Hz, **I**), 2.83 (1H, dq, ^3J = 9 Hz, ^3J = 7 Hz, **II**), 2.50 (6H, s, **I** + **II**), 1.29 (3H, t, ^3J = 7 Hz, **I** + **II**), 1.14 (3H, d, ^3J = 7 Hz, **II**), 1.09 (3H, d, ^3J = 7 Hz, **I**), 2.10 - 0.71 (17H, m, **I** + **II**); ^{13}C-NMR ($CDCl_3$, major diastereomer) δ 173.1, 166.3, 163.1, 151.1, 138.2, 127.9, 125.9, 125.5, 125.2, 61.1, 50.4, 41.5, 39.9, 38.2, 34.5, 31.2, 27.5, 26.9, 25.9, 21.8, 17.3, 15.0, 14.2. . Anal. Calcd. for $C_{27}H_{39}NO_4S_2$: C 71.01; H 6.28; N 2.24. Found C 71.21; H 6.32; N 2.25.

(*Z*)-1-Ethyl-5-(8-phenylmenthyl) 5-benzyl-2-[bis(methylthio)methylene]amino-2-pentenodioate (5c). IR ($CHCl_3$), 1710, 1730, 1650, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 7.40 - 7.05 (10H, m, **I** + **II**), 6.37 (1H, d, ^3J = 9 Hz, **I**), 6.22 (1H, d, ^3J = 9 Hz, **II**), 4.79 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz, **I** + **II**), 4.29 (2H, q, ^3J = 7 Hz, **I** + **II**), 3.39 (1H, m, **I**), 3.26 (1H, m, **II**), 2.51 (6H, s, SMe, **I** + **II**), 2.88 (2H, m, **I** + **II**), 0.98 (3H, t, ^3J = 7 Hz, **I** + **II**), 2.10 - 0.71 (17H, m, **I** + **II**); ^{13}C-NMR ($CDCl_3$, major diastereomer) δ 172.2, 166.5, 163.1, 151.0, 139.5, 138.4,

129.1, 128.5, 127.9, 125.7, 125.4, 125.3, 123.8, 61.2, 50.4, 45.7, 41.4, 40.1, 38.4, 34.6, 31.2, 27.1, 27.0, 25.7, 21.8, 15.2, 14.3; . Anal. Calcd. for $C_{33}H_{43}NO_4S_2$: C 62.12; H 7.45; N 2.41. Found C 62.23; H 7.57; N 2.33.

(*Z*)-1-Ethyl-5-(8-phenylmenthyl) 4-allyl-2-[bis(methylthio)methylene]amino-2-pentenodioate (5d). IR ($CHCl_3$) 1750, 1730, 1660, 1650, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 7.21 - 7.08 (5H, m, I + II), 6.27 (1H, d, ^3J = 9 Hz, I), 6.11 (1H, d, ^3J = 9 Hz, II), 5.72 (1H, m, I + II), 5.02 (2H, m, I + II), 4.77 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz, I + II), 4.22 (2H, q, ^3J = 7 Hz, I + II), 2.97 (1H, m, I), 2.85 (1H, m, II), 2.52 (6H, s, SMe, I + II), 2.21 (2H, m, I + II), 1.25 (3H, t, ^3J = 7 Hz, I + II), 2.10 - 0.70 (17H, m, I + II); ^{13}C-NMR ($CDCl_3$, major diastereomer) δ 171.9, 166.4, 163.0, 151.1, 138.9, 134.5, 127.9, 125.7, 125.5, 125.2, 117.2, 61.1, 50.4, 43.9, 41.6, 39.9, 36.4, 34.5, 31.3, 27.4, 26.9, 26.0, 21.8, 15.1, 14.2. . Anal. Calcd. for $C_{29}H_{41}NO_4S_2$: C 65.50; H 7.77; N 2.63. Found C 65.62; H 7.85; N 2.55.

(*Z*)-Diethyl 4-(8-phenylmenthyl)oxycarbonyl-2-[bis(methylthio)methylene]amino-2-hexenodioate (5e). IR ($CHCl_3$) 1750, 1740, 1730,1640, 1570 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 7.20 - 7.09 (5H, m, I + II), 6.31 (1H, d, ^3J = 9 Hz, I), 6.08 (1H, d, ^3J = 9 Hz, II), 4.79 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz, I + II), 4.18 (2H, q, ^3J = 7 Hz, I + II), 4.05 (2H, q, ^3J = 7 Hz, I + II), 3.15 (1H, m, I), 3.02 (1H, m, II), 2.51 (6H, s, I + II), 1.95 (2H, m, I + II), 1.24 (3H, t, ^3J = 7 Hz, I + II), 1.23 (3H, t, ^3J = 7 Hz, I + II), 2.11 - 0.71 (17H, m, I + II); ^{13}C-NMR ($CDCl_3$, major diastereomer), δ 171.2, 171.0, 166.8, 162.8, 151.5, 139.4, 127.9, 125.5, 125.1, 122.9, 61.1, 60.6, 50.4, 41.3, 39.8, 39.5, 35.5, 34.5, 31.2, 30.3, 26.9, 26.2, 21.8, 15.1, 14.2. . Anal. Calcd. for $C_{30}H_{43}NO_4S_2$: C 62.36; H 7.50; N 2.42. Found C 62.48; H 7.66; N 2.54.

(*Z*)-1-Ethyl-5-(8-phenylmenthyl) 2-[diphenylmethylene]amino-4-methyl-2-pentenodioate (5f). IR ($CHCl_3$) 1720, 1730, 1640, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.20 - 7.0 (15H, m, I + II), 6.08 (1H, d, ^3J = 9 Hz, I), 5.90 (1H, d, ^3J = 9 Hz, II), 4.78 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz, I + II), 3.92 (2H, m, I + II), 3.29 (1H, dq, ^3J = 9 Hz, ^3J = 7 Hz, I), 2.94 (1H, dq, ^3J = 9 Hz, ^3J = 7 Hz, II), 1.31 (3H, d, ^3J = 7 Hz, I), 1.17 (3H, t, ^3J = 7 Hz, I + II), 0.93 (3H, d, ^3J = 7 Hz, II), 2.10 - 0.72 (17H, m, I + II); ^{13}C-NMR ($CDCl_3$, major diastereomer) δ 173.1, 170.4, 163.8, 151.0, 140.3, 139.1, 136.8, 130.9, 129.6, 127.9, 125.4, 125.3, 125.2, 60.7, 50.4, 41.6, 39.9, 38.3, 34.5, 31.3, 27.4, 26.9, 25.9, 21.8, 16.8, 14.0. . Anal. Calcd. for $C_{37}H_{43}NO_4$: C 78.55; H 7.66; N 2.48. Found C 78.67; H 7.77; N 2.59.

(*Z*)-1-Ethyl-5-(8-phenylmenthyl) 4-benzyl-2-(diphenylmethylene)amino-2-pentenodioate (5g). IR ($CHCl_3$) 1730, 1720, 1640, 1580; ^{1}H-NMR ($CDCl_3$), δ 7.21 - 7.01 (20H, m, I + II), 6.13 (1H, d, ^3J = 9 Hz, I), 5.97 (1H, d, ^3J = 9 Hz, II), 4.69 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz, I + II), 3.84 (2H, q, ^3J = 7 Hz, I + II), 3.81 (1H, m, I), 3.75 (1H, m, II), 2.88 (1H, B part of ABX, J_{AB} = 13 Hz, I + II), 2.71 (1H, A part of ABX, J_{AB} = 13 Hz, I + II), 1.01 (3H, t, ^3J = 7 Hz, I + II), 2.10 - 0.72 (17H, m, I + II); ^{13}C-NMR ($CDCl_3$, major diastereomer) δ 171.9, 166.8, 163.1, 151.4, 141.5, 139.0, 129.7, 128.1, 127.9, 125.4, 122.6, 61.2, 50.4, 45.8, 41.4, 40.1, 38.6, 34.6, 31.2, 27.1, 27.0, 25.7, 21.8, 14.3. . Anal. Calcd. for $C_{43}H_{47}NO_4$: C 80.97; H 6.80; N 2.20. Found C 81.10; H 6.95; N 2.34.

(Z)-1-Ethyl-5-(8-phenylmentyl) 4-allyl-2-(diphenylmethylene)amino-2-pentenodioate (5h). IR ($CHCl_3$) 1740, 1730, 1650, 1620, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 7.24 - 7.08 (15H, m, I + II), 6.09 (1H, d, ^3J =

9 Hz, I), 5.91 (1H, d, ^3J = 9 Hz, II), 5.63 (1H, m, I + II), 5.01 (2H, m, I + II), 4.80 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz, I + II), 4.01 (2H, q, ^3J = 7 Hz, I + II), 3.30 (1H, m, I), 3.20 (1H, m, II), 2.15 - 0.82 (2H, m, I + II), 1.22 - 1.01 (3H, m, I + II), 2.10 - 0.71 (17H, m, I + II); ^{13}C-RMR ($CDCl_3$, major diastereomer) δ 173.1, 170.4, 163.8, 151.1, 141.3, 139.1, 136.9, 134.5, 131.1, 129.4, 127.9, 125.7, 125.5, 125.2, 117.2, 60.8, 50.3, 44.8, 41.6, 39.5, 39.7, 34.5, 31.2, 28.5, 26.9, 26.4, 21.8, 14.1. . Anal. Calcd. for $C_{39}H_{45}NO_4$: C 79.15; H 7.66; N 2.37. Found C 79.31; H 7.85; N 2.46.

(*Z*)-Diethyl 2-(diphenylmethylene)amino-4-(8-phenylmenthyl)oxycarbonyl-2-hexenodioate (5i). IR ($CHCl_3$) 1740, 1730, 1640, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 7.45 - 7.10 (15H, m, I + II), 6.18 (1H, d, ^3J = 9 Hz, I), 5.92 (1H, d, ^3J = 9 Hz, II), 4.78 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz, I + II), 4.11 (2H, q, ^3J = 7 Hz, I + II), 3.90 (2H, q, ^3J = 7 Hz, I + II), 3.18 (1H, m, I), 3.07 (1H, m, II), 2.21 (1H, part B of ABX, J_{AB} = 15 Hz, I + II), 2.08 (1H, part A of ABX, J_{AB} = 15 Hz, I + II), 1.22 (3H, t, ^3J = 7 Hz, I + II), 1.05 (3H, t, ^3J = 7 Hz, I + II), 2.11 - 0.62 (17H, m, I + II); ^{13}C-NMR ($CDCl_3$, major diastereomer) δ 171.1, 171.0, 166.7, 162.7, 151.4, 141.5, 139.1, 139.3, 129.6, 128.0, 127.9, 125.4, 125.1, 122.6, 60.8, 60.6, 50.5, 41.3 (CH2) 40.0, 39.8, 35.1, 34.5, 31.2, 30.3, 29.7, 26.0, 21.8, 14.2, 14.0. . Anal. Calcd. for $C_{40}H_{47}NO_4$: C 75.33; H 7.43; N 2.20. Found C 75.45; H 7.51; N 2.34.

General Procedure for the Synthesis of α,β-Didehydroglutamates 6. To a solution of KO^{t}Bu (68 mg, 0.6 mmol) in THF (0.6 mL) at -78°C, a solution of the corresponding glycinate 1 (0.48 mmol) in THF (1.0 mL) was added and the mixture was stirred for 30 min. A solution of the propiolate 2 (0.6 mmol) in THF (0.6 mL) was added dropwise and the mixture was stirred for 10 min. After the addition of H_2O, the temperature was raised to 25°C. The organic layer was decanted and the aqueous extracted with Et_2O (3 x 10 mL). 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).

(*Z*)-Diethyl 2-[bis(methylthio)methylene]amino-2-pentenodioate (6a). (85%). IR ($CHCl_3$) 1750, 1730, 1640, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 6.41 (1H, t, ^3J = 9 Hz), 4.21 (2H, q, ^3J = 7 Hz), 3.08 (2H, d, ^3J = 7 Hz), 2.51 (6H, s), 1.29 (3H, t, ^3J = 7 Hz), 1.22 (3H, t, ^3J = 7 Hz); ^{13}C-NMR ($CDCl_3$), 170.7, 166.6, 162.9, 139.7, 118.5, 61.1, 60.9, 3206, 15.1, 14.3, 14.2. Anal. Calcd. for $C_{12}H_{19}NO_4S_2$: C 47.19; H 6.27; N 4.59.Found C 47.31; H 6.32; N 4.66.

(*Z*)-1-Ethyl-5-(8-phenylmenthyl) 2-[bis(methylthio)methylene]amino-2-pente-nodioate (6b) (90%). IR ($CHCl_3$) 1730, 1720, 1640, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 7.35 -7.20 (5H, m), 6.18 (2H, t, ^3J = 9 Hz), 4.81 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz), 4.20 (2H, q, ^3J = 7 Hz), 2.52 (1H, B part of ABX, J_{AB} = 19 Hz), 2.50 (6H, s), 2.37 (1H, part A of ABX, J_{AB} = 19 Hz), 2.16 - 0.61 (20H, m); ^{13}C-NMR ($CDCl_3$), δ 171.0, 166.9, 163.6, 151.5, 138.8, 127.9, 125.4, 125.3, 125.1, 61.0, 50.3, 41.7, 39.6, 34.5, 32.5, 31.2, 28.6, 26.4, 24.1, 21.8, 15.0, 14.2. Anal. Calcd. for $C_{26}H_{37}NO_4S_2$: C 63.51; H 7.58; N 2.85.Found C 63.61; H 7.63; N 2.91.

(*Z*)-1-Ethyl-5-(8-phenylmenthyl) 2-(diphenylmethylene)amino-2-penteno-dioate (6c) (90%). IR ($CHCl_3$) 1730, 1720, 1640, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ 7.40 - 6.80 (15H, m), 5.92 (1H, t, ^3J = 7 Hz), 4.73 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz), 3.93 (2H, q, ^3J = 7 Hz), 2.48 (1H, B part of ABX, J_{AB} = 19 Hz), 2.37 (1H, A

part of ABX, J_{AB} = 19 Hz), 1.06 (3H, t, ^3J = 7 Hz), 1.80 - 0.80 (17H, m); ^{13}C-NMR ($CDCl_3$), δ 171.1, 166.9, 163.4, 151.6, 141.2, 138.7, 136.8, 131.05, 129.4, 127.9, 125.4, 125.3, 125.2, 60.8, 50.3, 41.7, 39.5, 34.5, 32.9, 31.2, 28.6, 26.4, 24.1, 21.8, 14.1. Anal. Calcd. for $C_{36}H_{41}NO_4$: C 78.37; H 7.49; N 2.54.Found C 78.45; H 7.54; N 2.68.

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10. The conformational analysis of the two epimers **5f** at carbon C4 has been carried out with the conformational search module of Hyperchem 5.01 for Windows.[11a] The low energy conformations were found by varying user-specified dihedral angles. The method involves a random variation of dihedral angles to generate new structures and then energy minimization of each of these is performed. Low energy unique conformations were stored while high energy or duplicate structures were discarded. The generation of new starting conformations for the energy minimization uses random variation of all dihedral angles previously selected. Rotation is used for acyclic dihedral angles and the *torsional flexing* motion is used for dihedral angles in a ring.[11b] Initial structures of epimers 4*R* and 4*S* of compound **5f** were selected by geometry optimization with the MM+ molecular mechanic force field[11c] and the Polak-Ribiere optimizer to 0.05 kcal/mol.Å RMS gradient was used to find the local minima. All dihedral angles without rotation symmetry of epimers 4*R* and 4*S* of compound **5f** were randomly generated to explore the conformational field. Five significant conformations for isomer 4*R* and four conformers for epimer 4*S* were found.

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