Diastereoselective Synthesis of Substituted Glutamic Acid Derivatives *via* Michael Additions of *N*-[Bis(methylthio)methylene]glycinates under Solid–Liquid Phase Transfer Catalysis

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Michael additions of the enolates of ethyl and *tert*-butyl *N*-[bis(methylthio)methylene]glycinates with α,β-unsaturated esters and ketones under solid-liquid phase transfer catalysis allowed for the highly diastereoselective synthesis of substituted glutamic acid derivatives through a transition state chelation-controlled by the catalyst with a like approach of reactants. Selective removal of the iminodithiocarbonate protecting group with concomitant cyclization gave rise to 3-substituted pyroglutamates and 1,3,4-trisubstitued Δ¹-pyrrolines with retention of configuration.

The occurrence of non-proteinogenic α-amino acids in biological systems and their exceptional utility as chiral synthons underlie the importance of the development of improved preparative routes for the stereoselective synthesis of unnatural α-amino acids and their derivatives.[1,2] The conformational modifications induced by these subunits in peptides can lead to enhanced bioactivity and stability and have found application in medicinal chemistry[3] where, for example, peptide resistance to proteases has been altered. Interest has been particularly focused on the asymmetric synthesis of rare substituted glutamic acid derivatives in recent years because of their important activities on glutamic acid receptors in the CNS.[4]

Diastereoselective Michael additions constitute one of the most valuable methods for the synthesis of 1,5-dicarbonyl compounds with stereogenic centers at the 2- and 3- positions.[5] Although this approach has been made use of for the preparation of β-substituted glutamic acid derivatives,[6,7] the stereoselective conjugate addition of glycine nucleophiles[8] to α,β-unsaturated carbonyl compounds under phase transfer catalysis (PTC) has received little attention[9–11] regardless of the well known advantages offered by the PTC method from a large scale synthesis standpoint,[9] as compared with the conventional procedures, which mostly require highly anhydrous experimental set-ups as well as the use of basic organometallic reagents to ensure deprotonation.

Described herein is the development of reliable solid–liquid PTC conditions for the Michael addition of glycinates **1a** and **1b**, prepared from the corresponding *N*-unsubstituted glycine esters by treatment with CS_2 and MeI under PTC in a straightforward fashion,[12,13] to α,β-unsaturated esters **2** and ketones **3** affording glutamates **4,6** and δ-oxo-α-amino esters[14] **5,7** (Scheme 1) with good chemical yields and stereoselectivities, free

[⊗] Abstract published in *Advance ACS Abstracts*, September 15, 1995.

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(13) The iminodithiocarbonate protecting group has proven of use in the diastereoselective synthesis of glutamic acid derivatives: Alvarez-Ibarra, C.; Domínguez-Fernández, C.; Csákÿ, A. G.; Martínez-Santos, E.; Quiroga, M. L.; Gutierrez, E. *Tetrahedon Lett.* **1993**, *34*, 5463.

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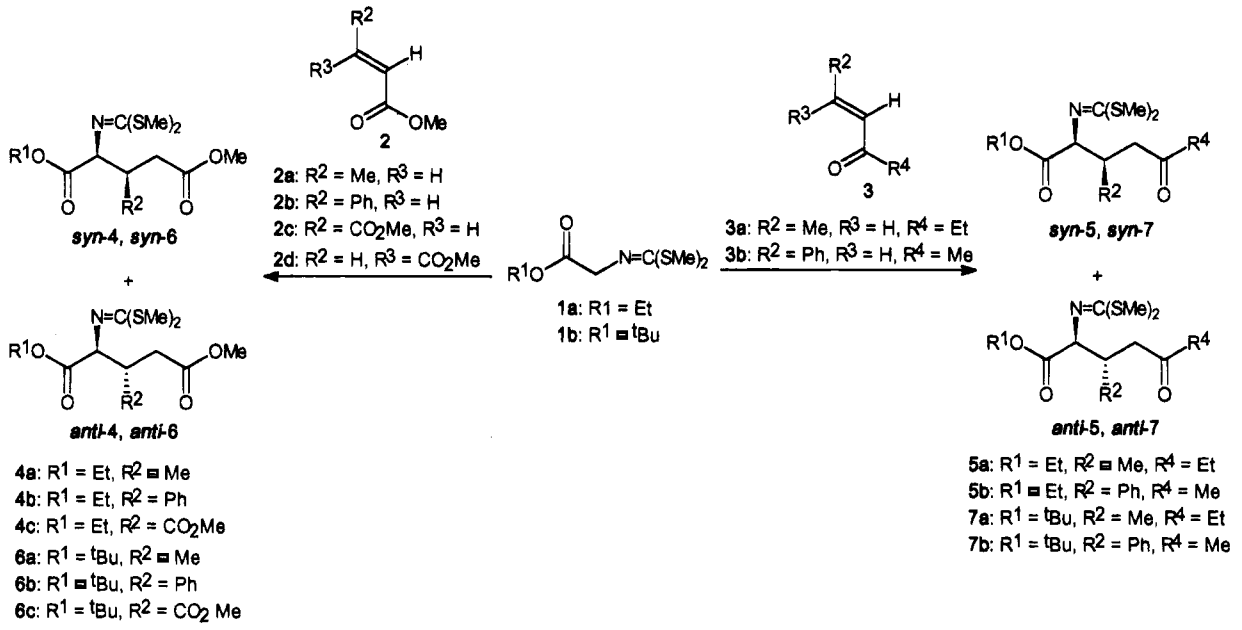
Scheme 1



from competitive 1,2-addition or cyclization pathways as well as polyadditions.

Results and Discussion

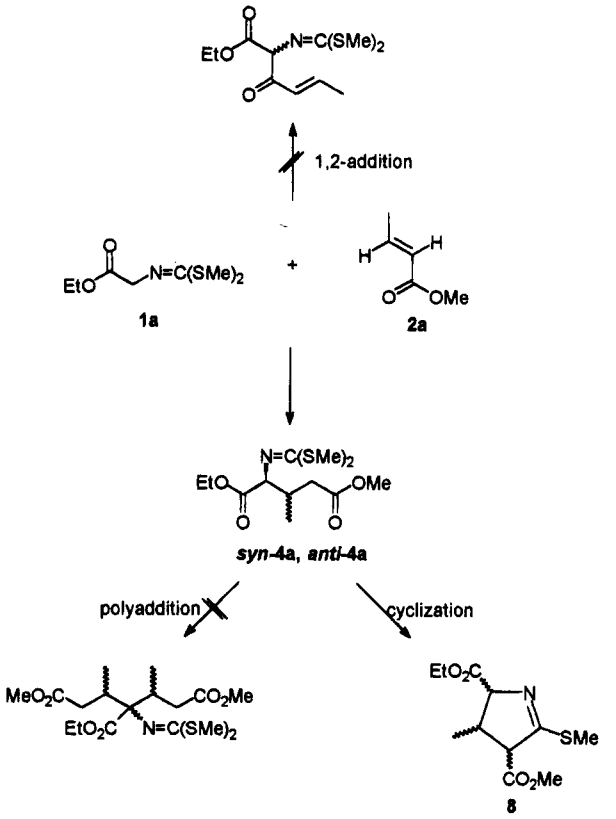
Michael additions of glycinate 1a to methyl crotonate (2a). The condensation between glycinate **1a** and methyl crotonate (**2a**) was chosen as a model reaction to establish the most suitable base and solvent combination. Benzyltriethylammonium chloride (TEBA) as catalyst gave high diastereoselectivity in the formation of the new C−C bond and avoided undesirable 1,2-addition as well as further reactions of compound **4a** with other crotonate molecules or self-condensation to form 2-methylthio-Δ^1-pyrrolines (cyclization) (Scheme 2).

The relative configuration *syn* and *anti*[15] of compounds **4a** was assigned from the NOE effects observed in the 1D NOE spectra of the *trans* cyclic derivative **9b** (*vide infra*). Thus, upon irradiation of H2 ($\delta = 4.14$, d, $^3J = 5$ Hz) a 10% enhancement was observed for aromatic signals ($\delta = 7.20-7.4$) whereas only a 2% of increase of H3 ($\delta = 3.64$, m) was noticed. By other hand, an 8% enhancement of H4a ($\delta = 2.85$) was observed by irradiation on H3 ($\delta = 3.64$) (Figure 1).

The results of the solid−liquid PTC Michael addition[16] of glycinate **1a** with methyl crotonate **2a** using NaOH as the base in different solvents are gathered in Table 1.

In THF, benzene, or CH_2Cl_2 (entries 1−3) formation of the 2-methylthio-Δ^1-pyrroline **8** was significant,[17] together with a poor level of diastereoselection in compounds **4a**. However, no cyclization and good diastereoselectivity was observed in acetonitrile (entry 4). Further

Scheme 2



improvement of the *syn*-**4a**:*anti*-**4a** ratio was observed in DMF (entry 5), although the yield was somewhat diminished due to cyclization[18] to **8**. These observations led us to keep acetonitrile as the solvent of choice.

The results of the Michael addition of glycinate **1a** to methyl crotonate (**2a**) in acetonitrile and with different bases are gathered in Table 2.

Whereas no reaction was observed with the weak base K_2CO_3 (entry 1),[19] condensation in the presence of

(14) For the synthesis of d-oxo-α-amino esters from glutamic derivatives and their transformation into prolines see: Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438.

(15) For a definition of the *syn*/*anti* convention, see: Masamune, S.; Ali Sk., A.; Snitman, D. L.; Garrey, D. S. *Angew.Chem., Int. Ed.Engl.* **1980**, *19*, 557.

(16) Classical Michael additions of **1a** to **2a** in THF using KO^{t}Bu, LiO^{t}Bu, and LDA as the bases (molar ratio **1a**:**2a** : base = 1:1.25:1.25, −78 °C, 30 min) gave low yields of adducts **4a** (<35%). However, the **4aI**:**4aII** ratio was high in the condensation with KO^{t}Bu and LiO^{t}Bu (5:95).

(17) No diastereoselectivity is observed in the cyclization step, as compound **8** was obtained as a mixture of four diastereomers.

(18) No polyaddition was observed in any case.

(19) No reaction was observed with K_2CO_3 (1.0 equiv) even after 24 h at 25 °C.

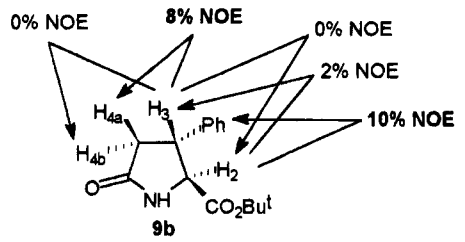


Figure 1. 1D NOE correlations on **9b**.

Table 1. PTC Michael Additions of 1a with 2a in Different Solvents[a]

entry	solvent	*syn*-**4a**:*anti*-**4a**[b]	**4a**:**8**[b]	**4a**, %[c]
1	THF	30:70	40:60	45
2	benzene	15:85	90:10	80
3	CH_2Cl_2	15:85	80:20	85
4	acetonitrile	10:90	100:–	90
5	DMF	5:95	95:5	80

[a] Molar ratio **1a:2a:**NaOH = 1.0:1.0:1.0. 0.1%. TEBA (0.1 mol%) was used as catalyst. Reaction time was 2 h. [b] *Syn*:*anti* Ratios have been determined on the crude products using ^{1}H-NMR (300 MHz) and the CH_3–C3 signal: δ (*syn*-**4a**) = 1.07 ppm, d, ^3J = 7 Hz; δ (*anti*-**4a**) = 1.00 ppm, d, ^3J = 7 Hz. [c] Determined by integration of the ^{1}H-NMR (300 MHz) of the crude products.

Table 2. PTC Michael Additions of 1a to 2a with Different Bases[a]

entry	base	*syn*-**4a**:*anti*-**4a**[b]	yield, %[c]
1	K_2CO_3	–	–
2	LiOH	–:>98	45
3	LiOH·H_2O	–:>98	50
4	NaOH	10:90	90
5	KOH	25:75	90
6	$Ba(OH)_2$	25:75	50
7	$Ba(OH)_2$·H_2O	25:75	45

[a] All reactions were carried out in acetonitrile with a molar ratio **1a:2a:**base = 1.0:1.0:1.0. TEBA (0.1 mol %) was used as PTC catalyst. Reaction time was 2 h. [b] *syn*:*anti* ratios have been determined on the crude products using ^{1}H-NMR (300 MHz) and the CH_3–C3 signal: δ (*syn*-**4a**) = 1.07 ppm, d, ^3J = 7 Hz; δ (*anti*-**4a**) = 1.00 ppm, d, ^3J = 7 Hz. [c] Determined by integration of the ^{1}H-NMR (300 MHz) of the crude products.

alkaline hydroxides (entries 2–5) was successful after 2 h. A high level of stereoselection (de > 96%) was achieved by using LiOH (entry 2) as well as LiOH·H_2O (entry 3) as the base. However yields were poor. An increase in yield was realized on passing to the more basic NaOH (entry 4) and KOH (entry 5). Poor diastereoselectivity and low yields were obtained either with $Ba(OH)_2$ or $Ba(OH)_2$·H_2O (entries 6, 7). Nevertheless, in the alkaline series (entries 2–5) a loss of diastereoselectivity was noticed upon an increase in the basicity of the hydroxide. In fact, epimerization was observed with NaOH and KOH as a function of time[20] (Table 3).

No change in diastereoselectivity was found with LiOH after 2 h (entry 1) or 24 h (entry 2), as well as with NaOH after 15 min (entry 3) or 2 h (entry 4). However, a significant decrease in the *syn*-**4a**:*anti*-**4a** ratio was observed with NaOH after 24 h (entry 5). Stronger variations were observed in the case of KOH (entries 6–9) as compared with NaOH. Thus, the Michael addition itself under solid–liquid PTC can be thought of as a kinetically controlled process producing the *anti* isomer *anti*-**4a**. Product isomerization under certain

(20) Isomerization of 1,2-addition compounds to the 1,4-adduct is known to take place under certain conditions. No 1,2-addition product was detected even after short reaction times. See: Heathcock, C. H.; Oare, D. A. *J. Org. Chem.* **1985**, *50*, 3024.

Table 3. PTC Michael Additions of 1a to 2a. Effect of the Reaction Time Together with the Base in the Diastereoselectivity[a]

entry	base	react. time (h)	*syn*-**4a**:anti-**4a**[b]	yield, %[c]
1	LiOH	2	–:>98	45
2	LiOH	24	–:>98	50
3	NaOH	0.25	10:90	90
4	NaOH	2	10:90	90
5	NaOH	24	30:70	70
6	KOH	0.08	15:85	85
7	KOH	0.25	30:70	85
8	KOH	2	25:75	90
9	KOH	24	35:65	85

[a] All reactions were carried out in acetonitrile with a molar ratio **1a:2a:**base = 1.0:1.0:1.0 and TEBA (0.1 mol %) as PTC catalyst. [b] *syn*:*anti* ratios have been determined on the crude products using ^{1}H-NMR (300 MHz) and the CH_3–C3 signal: δ (*syn*-**4a**) = 1.07 ppm, d, ^3J = 7 Hz; δ (***anti*-4a**) = 1.00 ppm, d, ^3J = 7 Hz. [c] Determined by integration of the ^{1}H-NMR (300 MHz) of the crude products.

Table 4. PTC Michael Additions of 1a with 2b–d and 3a,b[a]

entry	ester **2** or ketone **3**	*syn*:anti[b]	yield, %[c]
1	2b	*syn*-**4b**:*anti*-**4b** = 10:90	95
2	2c	*syn*-**4c**:*anti*-**4c** = 20:80	90
3	2d	*syn*-4c:*anti*-**4c** = 25:75	85
4	3a	*syn*-**5a**:*anti*-**5a** = 15:85	70
5	3b	*syn*-**5b**:*anti*-**5b** = –:>98	95

[a] All reactions were carried out in acetonitrile with a molar ratio **1a:2:**NaOH or **1a:3:**NaOH = 1.0:1.0:1.0 and TEBA (0.1 mol %) as PTC catalyst. Reaction time was 2 h [b] *Syn*:*anti* ratios have been determined on the crude products using ^{1}H-NMR (300 MHz) and the H2 signal. [c] Determined by integration of the ^{1}H-NMR (300 MHz) of the crude products.

reaction conditions gave rise to equilibrium *syn*:*anti* ratios, with increased proportions of the *syn* adduct.

Michael Additions of Glycinate 1a to Esters 2b–d and Ketones 3a,b and of Glycinate 1b to Esters 2a–d and Ketones 3a,b. In light of the observations made in the Michael addition of glycinate **1a** to methyl crotonate (**2a**), we carried out its condensations with esters **2b–d** and ketones **3a,b** using acetonitrile as the solvent, NaOH as the base, and TEBA as the PTC catalyst, restricting the reaction time to 2 h in order to ensure good yields without losing diastereoselectivity. The results are shown on Table 4.

In the additions to the (*E*)-α,β-unsaturated esters **2b,c** (entries 1, 2) and (*E*)-α,β-unsaturated ketones **3a,b** (entries 4, 5), formation of the *anti* adducts *anti*-**4** and *anti*-**5** was largely favored.[21] In the addition to methyl maleate (**2d**) ((*Z*)-α,β-unsaturated ester) (entry 3) the same stereochemical trend as in the addition to methyl fumarate (*E*) was observed (entry 2). Replacement of the ethyl glycinate **1a** by the bulkier *tert*-butyl ester **1b** gave rise to an improvement of the diastereoselectivity[7b,11,22] in the Michael addition both to esters **2a–d** and ketones **3a,b**. The results are gathered in Table 5.

(21) Assignment of the *syn* configuration to compounds *syn*-**4b-e** and *syn*-**5a,b**, and *anti* to compounds ***anti*-4b-e** and ***anti*-5a,b** was made on the basis of the comparison of the ^{1}H-NMR chemical shift and coupling constant of H2 (d) with that of the previously assigned *syn*-**4a** and *anti*-**4a**. Note that H2 for the *syn* series appears downfield with respect to H2 for the *anti* series in all compounds except *syn*-**4c** and *anti*-**4c**, where this relationship is inverted. However the coupling constant ^3J for H2 values remains constant (4 Hz for the *syn* series and 5 Hz for the *anti* series). See experimental part for δ values.

(22) Configuration assignment was made by comparison with compounds **4** and **5**. See ref 20.

Scheme 3

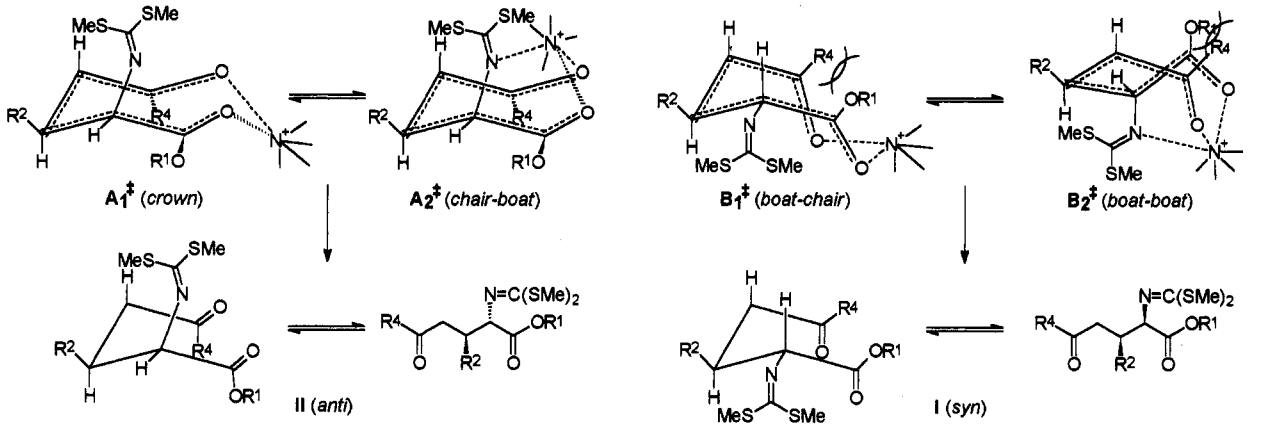


Table 5. PTC Michael Additions of 1b with 2a–d and 3a,b[a]

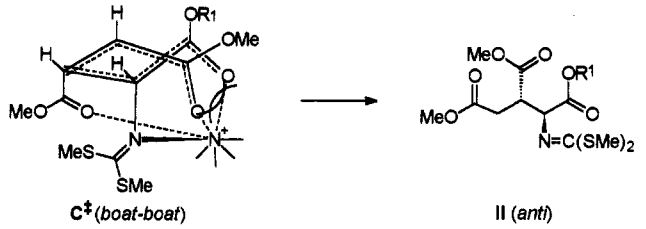
entry	ester 2 or ketone 3	*syn*:*anti*[b]	yield, %[c]
1	2a	*syn*-**6a**:*anti*-**6a** = –:>98	90
2	2b	*syn*-**6b**:*anti*-**6b** = 5:95	85
3	2c	*syn*-**6c**:*anti*-**6c** = 15:85	95
4	2d	*syn*-**6c**:*anti*-**6c** = 10:90	85
5	3a	*syn*-**7a**:*anti*-**7a** = –:>98	80
6	3b	*syn*-**7b**:*anti*-**7b** = –:>98	95

[a] All reactions were carried out in acetonitrile with a molar ratio **1b:2**:NaOH or **1b:3**:NaOH = 1.0:1.0:1.0 and TEBA (0.1 mol %) as PTC catalyst. Reaction time was 2 h. [b] *syn*:*anti* ratios have been determined on the crude products using ^{1}H-NMR (300 MHz) and the H2 signal. [c] Determined by integration of the ^{1}H-NMR (300 MHz) of the crude products.

Stereochemical Considerations. The stereochemistry of the PTC Michael additions of glycinates **1a,b** with esters **2a–c** and ketones **3a,b** can be rationalized from a kinetic point of view by considering the cyclic[23] transition states $\mathbf{A_1}^‡$, $\mathbf{A_2}^‡$ and $\mathbf{B_1}^‡$, $\mathbf{B_2}^‡$ which correspond to the two alternative topicities of the *Z*-enolate[24ab] of esters **1a** and **1b**, where chelation is exerted by the PTC countercation[24c,25] (Scheme 3).

Thus, the observed general tendency of diastereomeric excesses in favor of the *anti* adducts over the *syn* adducts could be justified on the premises of the most stable[26] crown transition state $\mathbf{A_1}^‡$, or alternatively its chair-boat conformational modification $\mathbf{A_2}^‡$, where the lone pair on the sp^2-nitrogen of the iminodithiocarbonate moiety participates in the chelation of the ammonium cation. In fact, transition state simulation with the aid of molecular models[27] puts forward that this reaction path minimizes the nonbonded interaction between OR^1 and R^4 groups as compared to that existing in transition states $\mathbf{B_1}^‡$ and $\mathbf{B_2}^‡$, which would give rise to the minoritary diastereomer *syn*. The foregoing stereoselection should then be enhanced with an increasing OR^1–R^4 interaction, as observed by replacing the Et group in **1a** by the bulkier ^{t}Bu in **1b** (Table 4 *vs* Table 5).

Scheme 4



On the other hand, it is known that an *E*/*Z*-configurational change in the acceptor reverses the stereochemical outcome of the Michael additions with a common enolate.[6b] We have noticed, however, that the same adducts *anti*-**4c** and *anti*-**6c** were predominantly formed either from the condensation with methyl fumarate (**2c**, *E*) or methyl maleate (**2d**, *Z*), although with different ***syn***:*anti* ratios (Table 4, entries 2,3 and Table 5, entries 3,4). Once either **2c** ⇌ **2d** isomerization[28] or adduct epimerization[29] is excluded, this result can be taken into account by a *unlike* approach (*si* + *re* depicted) of reactants to give the *anti* isomer *via* a boat-boat transition state $\mathbf{C}^‡$, where stabilization is attained by extra-chelation of the ammonium cation with the methoxycarbonyl group (Scheme 4).[30]

Furthermore, if the interaction between the ammonium cation and the methoxycarbonyl group in $\mathbf{C}^‡$ is a stabilizing effect, as the steric volume of R^1 increases (^{t}Bu > Et) the ring should fluctuate to prevent the unfavorable OR^1–R^4 interaction thus approaching the CO_2Me to the cationic center and hence enhacing chelation, which is in agreement with the highest stereoselection of the reaction of **1b** with methyl maleate (**2d**) (Table 5, entry 4).

(23) (a) Heathcock, C. M.; Henderson, M. A., Oare, D. A., Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019. (b) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.

(24) (a) The stereochemical descriptors *E* and *Z* are used in this context as recommended by Evans. See: Evans, D. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 11. (b) Formation of a *Z*-enolate with the benzyltriethylammonium countercation chelated by the lone pair on the sp^2-nitrogen of the iminodithiocarbonate group and not a naked species is presumed under the particular conditions used for deprotonation. See ref 9 and Mekelburger, H. B.; Wilcox, C. S. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 6. (c) No metal chelation is presumed under PTC conditions. Detailed mechanism of solid–liquid PTC can be found in refs 9 and 10a.

(25) A thermodynamical reaction pathway is discarded on the light of the results obtained in the condensation of **1a** with **2a** using NaOH and KOH (Table 3).

(26) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley: New York, 1994, pp 765–766.

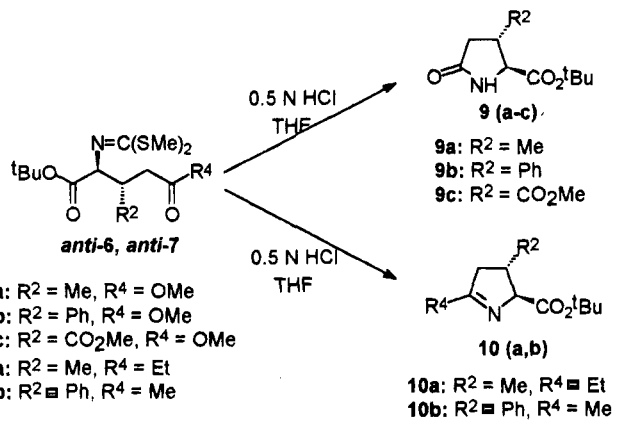
(27) *HGS-Molecular Structure Models;* Maruzen Co., Ltd.: Tokyo, Japan.

(28) No isomerization of methyl maleate **2d** to methyl fumarate **2c** was observed in a blank essay with NaOH (1 equiv) in acetonitrile in the presence of TEBA as PTC catalyst, after 2 h reaction time.

(29) Adduct epimerization favors the formation of isomers **I** (Table 3).

(30) Note that when this methoxycarbonyl group has the other configuration (**2c**), the corresponding transition state, derived in this case from a *like* (*re* + *re*) approach ($\mathbf{B_2}^‡$ *boat-boat*, Scheme 3), in the absence of interaction between the ammonium cation and R$_4$ = CO_2-Me, is not competitive against $\mathbf{A}^‡$ (*crown*/*chair-boat*).

Scheme 5



Deprotection of the Iminodithiocarbonate Group and Cyclization Reactions. *N*-[Bis(methylthio)methylene]glutamates **4a–c** and **6a–c** as well as δ-oxo-*N*-[bis(methylthio)methylene]amino esters **5a,b** and **7a,b** are stable compounds to air and moisture and can be purified by chromatography on silica gel and stored at room temperature. Treatment of the THF solutions of compounds *anti*-**6** and *anti*-**7** with 0.5 N HCl (24 h, 25 °C) promoted the hydrolysis of the iminodithiocarbonate moiety and concomitant *in situ* cyclization to pyroglutamates **9** and Δ¹-pyrrolines[31] **10** without epimerization (Scheme 5).

Conclusions

β-Substituted glutamic acid derivatives (glutamates **4** and **6**, and δ-oxo-α-amino esters **5** and **7**) are obtained from the Michael addition of ethyl glycinate **1a** and *tert*-butyl glycinate **1b** to α,β-unsaturated esters **2** and ketones **3** using solid–liquid phase transfer catalysis under kinetic conditions with very good levels of diastereoselection and without undesired 1,2-addition, polyaddition, or cyclization reactions. Smooth hydrolysis of the iminodithiocarbonate protecting group followed by *in situ* cyclization allows for the synthesis of substituted pyroglutamates and pyrrolines with high overall yields.

Experimental Section

All starting materials were commercially available research-grade chemicals and used without further purification. Ethyl *N*-[bis(methylthio)methylene]glycinate (**1a**) has been prepared according to the previously described procedure.[12] 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 CCl_4 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 assigment of ^{13}C NMR spectra has been carried out with the aid of the DEPT-135 pulse sequence.

***tert*-Butyl *N*-[bis(methylthio)methylene]glycinate (1b).** *tert*-Butyl glycinate hydrochloride (5.0 g, 29.8 mmol) was introduced in a round-bottomed flask provided with magnetic stirrer, at 0 °C. Without stirring, precooled (0 °C) solutions of NaOH (18.0 g, 450 mmol) in H_2O (20.0 mL), CS_2 (1.85 mL, 29.8 mmol) in benzene (70.0 mL), and pre-cooled (0 °C) CH_3I (6.20 mL, 100 mmol) were succesively added, followed by benzyltriethylammonium chloride (501 mg, 2.2 mmol). The mixture was then vigorously stirred at 20 °C for 20 min. The benzene phase was decanted and the water phase extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure led to a the pale yellow liquid which was purified by column chromatography (hexane:ethyl acetate, 60:40) to give a colorless oil (80%): IR (neat) ν 1750, 1580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (2H, s), 2.51 (3H, s), 2.45 (3H, s), 1.50 (9H, s). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.2, 162.5 81.0, 54.7, 28.0, 14.8, 14.5. Anal. Calcd for $C_9H_{17}NO_2S_2$: C, 45.93; H, 7.28; N, 5.95. Found: C, 45.81; H, 7.44; N, 5.69.

Michael Addition of Glycinates 1a,b with Esters 2a-d and Ketones 3a,b. General Procedure. To a solution of **1a** or **1b** (0.97 mmol) in acetonitrile (1.0 mL) at 20 °C, were succesively added NaOH (40 mg, 0.97 mmol), benzyltriethylammonium chloride (22 mg, 0.097 mmol), and the corresponding compound **2a–d** or **3a,b** (0.97 mmol). The mixture was vigorously stirred for 2 h. The mixture was filtered (fine pore filter) and the solid washed with Et_2O (3 × 5 mL). After concentration of the filtrate, the crude product was purified by column chromatography (hexane:ethyl acetate, 80:20).

α-Ethyl γ-methyl 3-methyl-*N*-[bis(methylthio)methylene]glutamate (*anti*-4a): colorless oil (50%). IR (CCl_4) ν 1740, 1580. ^1H NMR (300 MHz, $CDCl_3$) δ 4.22 (1H, d, ^3J = 5.4 Hz), 4.19 (2H, q, ^3J = 7.3 Hz), 3.67 (3H, s), 2.74–2.66 (2H, m), 2.55 (3H, s), 2.42 (3H, s), 2.27 (1H, A part of an ABX, J_{AB} = 15.7, J_{AX} = 5.7 Hz), 1.27 (3H, t, ^3J = 7.3 Hz), 1.00 (3H, d, ^3J = 6.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) (*anti*) δ 173.4, 170.6, 163.0, 68.7, 60.9, 51.5, 37.2, 34.3, 17.2, 15.0, 14.9, 14.2. Anal. Calcd for $C_{12}H_{21}NO_4S_2$: C, 46.88; H, 6.89; N, 4.56. Found: C, 46.99; H, 6.70; N, 4.51.

α-Ethyl γ-methyl *N*-[bis(methylthio)methylene]-3-phenylglutamate (4b) (*syn*/*anti* = 10:90): colorless oil (95%). IR (CCl_4) ν 1730, 1555. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.15 (5H, m, *syn* + *anti*), 4.67 (1H, d, ^3J = 4 Hz, *syn*), 4.50 (1H, d, ^3J = 5 Hz, *anti*), 4.00 (2H, q, ^3J = 7 Hz, *syn* + *anti*), 3.80 (1H, m, *syn* + *anti*), 3.53 (3H, s, *syn* + *anti*), 2.85 (1H, A part of an AB, J_{AB} = 16 Hz, *syn* + *anti*), 2.83 (1H, B part of an AB, J_{AB} = 16 Hz, *syn* + *anti*), 2.49 (3H, s, *syn* + *anti*), 2.46 (3H, s, *syn* + *anti*), 1.06 (3H, t, ^3J = 7 Hz, *syn* + *anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$) (*anti*) δ 186.6, 172.4, 164.0, 140.3, 128.2, 126.9, 69.4, 60.7, 51.4, 45.6, 36.5, 15.0, 14.9, 13.8. Anal. Calcd for $C_{17}H_{23}NO_4S_2$: C, 55.26; H, 6.27; N, 3.79. Found: C, 55.44; H, 6.06; N, 3.82.

α-Ethyl γ-methyl *N*-[bis(methylthio)methylene]-3-(methoxycarbonyl)glutamate (4c) (*syn*/*anti* = 20:80 from 2c and 25:75 from 2d): colorless oil (85%). IR (CCl_4) ν 1740, 1575. ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (1H, d, ^3J = 5 Hz, *anti*), 4.70 (1H, d, ^3J = 4 Hz, *syn*), 4.19 (2H, q, ^3J = 7 Hz, *syn* + *anti*), 3.70 (6H, s, *anti*), 3.69 (6H, s, *syn*), 3.62 (1H, m, *syn* + *anti*), 2.90 (1H, A part of an ABX, J_{AB} = 17 Hz, *syn* + *anti*), 2.56 (3H, s, *syn* + *anti*), 2.54 (1H, B part of an ABX, J_{AB} = 17 Hz, *syn* + *anti*), 2.37 (3H, s, *syn* + *anti*), 1.27 (3H, t, ^3J = 7 Hz, *anti*), 1.20 (3H, t, ^3J = 7 Hz, *syn*). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.4 (*anti*), 172.0 (*syn*), 169.4 (*anti*), 169.1 (*syn*), 165.6 (*anti*), 165.3 (*syn*), 64.7 (*anti*), 64.5 (*syn*), 61.4 (*anti*), 61.3 (*syn*), 52.2 (*anti*), 52.1 (*syn*), 51.9 (*syn*), 51.8 (*anti*), 44.8 (*syn*), 44.7 (*anti*), 32.4 (*syn*), 31.9 (*anti*), 15.2 (*syn*), 15.1 (*anti*), 15.1 (*anti*), 15.00 (*syn*), 14.1 (*anti*), 13.9 (*syn*). Anal. Calcd for $C_{13}H_{21}NO_6S_2$: C, 44.43; H, 6.02; N, 3.99. Found: C, 44.33; H, 6.26; N, 4.15.

Ethyl 3-methyl-2-[[bis(methylthio)methylene]amino]-5-oxoheptanoate (5a) (*syn*/*anti* = 15:85): colorless liquid (70%). IR (CCl_4) ν 1745, 1710, 1580. ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (1H, d, ^3J = 4 Hz, *syn*), 4.15 (1H, d, ^3J = 5 Hz, *anti*), 4.09 (2H, q, ^3J = 7 Hz, *syn* + *anti*), 2.72–2.20 (11H, m, among which: 2.50 (3H, s), 2.35 (3H, s), *syn* + *anti*), 1.20 (3H, t, ^3J = 7 Hz, *syn* + *anti*), 0.96 (3H, t, ^3J = 7 Hz, *syn* + *anti*), 0.93 (3H, d, ^3J = 7 Hz, *syn*), 0.89 (3H, d, ^3J = 7 Hz, *anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 212.5 (*syn* + *anti*), 171.0 (*anti*), 170.8 (*syn*), 162.8 (*anti*), 162.7 (*syn*), 68.9 (*anti*), 67.6 (*syn*),

(31) Δ¹-Pyrrolines can be transformed into pyrrolidine derivatives which have found use as synthetic intermediates[4a,c–f] as well as: (a) chiral auxiliaries: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (b) Chiral ligands: Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423. (c) Chiral bases: see Whitesell, J. K.; Felman. S. W. *J. Org. Chem.* **1980**, *45*, 755 and Cox., P. J.; Simpkins, N. S. *Tetrahedron Asymm.* **1991**, *2*, 1.

60.9 (*syn* + *anti*), 45.9 (*syn*), 45.3 (*anti*), 36.4 (*syn*), 36.4 (*anti*), 33.4 (*anti*), 33.1 (*syn*), 17.6 (*syn* + *anti*), 15.1 (*syn* + *anti*), 14.9 (*syn* + *anti*), 14.3 (*syn* + *anti*), 7.9 (*syn* + *anti*). Anal. Calcd for $C_{13}H_{23}NO_3S_2$: C, 51.12; H, 7.59; N, 4.59. Found: C, 51.35; H, 7.31; N, 4.73.

Ethyl 2-[[bis(methylthio)methylene]amino]-5-oxo-3-phenylhexanoate (*anti*-5b): colorless oil (95%). IR (CCl_4) ν 1745, 1715, 1575. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.19 (5H, m), 4.45 (1H, d, ^3J = 5 Hz), 4.01 (2H, q, ^3J = 7 Hz), 3.97 (1H, m), 2.97 (1H, A part of an ABX, J_{AB} = 17 Hz), 2.95 (1H, B part of an ABX, J_{AB} = 17 Hz), 2.50 (3H, s), 2.48 (3H, s), 2.03 (3H, s), 1.09 (3H, t, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 207.0, 170.1, 163.9, 140.8, 128.2, 126.9, 69.5, 60.7, 45.7, 44.7, 30.3, 15.0, 14.8, 13.8. Anal. Calcd for $C_{17}H_{23}NO_3S_2$: C, 57.76; H, 6.56; N, 3.96. Found: C, 57.55; H, 6.67; N, 4.25.

α-*tert*-Butyl γ-methyl 3-methyl-*N*-[bis(methylthio)-methylene]glutamate (*anti*-6a): colorless oil (90%). IR (CCl_4) ν 1740, 1585. ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (1H, d, ^3J = 5 Hz), 3.67 (3H, s), 2.65 (1H, m), 2.58–2.51 (4H, m, among which: 2.54 (3H, s), 2.41 (3H, s), 2.31 (1H, B part of an ABX, J_{AB} = 16Hz), 1.46 (9H, s), 1.00 (3H, d, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.7, 169.8, 162.4, 81.4, 69.4, 51.6, 37.4, 34.5, 28.1, 17.2, 15.1, 14.9. Anal. Calcd for $C_{14}H_{25}NO_4S_2$: C, 50.12; H, 7.51; N, 4.18. Found: C, 50.35; H, 7.63; N, 4.21.

α-*tert*-Butyl γ-methyl *N*-[bis(methylthio)methylene]-3-phenylglutamate (6b) (*syn*/*anti* = 5:95): colorless oil (85%). IR (CCl_4) ν 1730, 1555. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.16 (5H, m, *syn* + *anti*), 4.61 (1H, d, ^3J = 4 Hz, *syn*), 4.41 (1H, d, ^3J = 5 Hz, *anti*), 3.86 (1H, m, *syn* + *anti*), 3.52 (3H, s, *syn* + *anti*), 2.82 (1H, A part of an ABX, J_{AB} = 16 Hz, *syn* + *anti*), 2.79 (1H, B part of an ABX, J_{AB} = 16 Hz, *syn* + *anti*), 2.50 (3H, s, *syn* + *anti*), 2.46 (3H, s, *syn* + *anti*), 1.26 (9H, s, *syn* + *anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$) (*anti*) δ 172.7, 169.2, 163.5, 140.7, 128.6, 128.3, 127.0, 81.4, 70.0, 51.6, 46.0, 37.2, 27.8, 15.2, 15.1. Anal. Calcd for $C_{19}H_{27}NO_4S_2$: C, 57.40; H, 6.85; N, 3.52. Found: C, 57.51; H, 7.12; N, 3.30.

α-*tert*-Butyl γ-methyl 3-(methoxycarbonyl)-*N*-[bis-(methylthio)methylene]glutamate (6c) (*syn*/*anti* = 15:85 from 2c and 10:90 from 2d): colorless oil (85%). IR (CCl_4) ν 1740, 1580. ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (1H, d, ^3J = 5 Hz, *anti*), 4.61 (1H, d, ^3J = 4 Hz, *syn*), 3.65 (6H, s, *syn* + *anti*), 3.46 (1H, m, *syn*), 2.94 (1H, A part of an ABX, J_{AB} = 17 Hz, *syn* + *anti*), 2.56–2.49 (3H, m, among which: 2.51 (3H, s), *syn* + *anti*), 2.32 (3H, s, *syn* + *anti*), 1.40 (9H, s, *syn* + *anti*). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.6 (*anti*), 172.1 (*syn*), 169.9 (*syn*), 168.3 (*anti*), 165.1 (*anti*), 164.6 (*anti*) 82.4 (*syn* + *anti*), 65.5 (*syn* + *anti*), 52.2 (*syn* + *anti*), 51.9 (*syn* + *anti*), 45.0 (*syn* + *anti*), 32.0 (*syn* + *anti*), 28.0 (*syn* + *anti*), 15.2 (*anti*), 15.0 (*anti*), 14.3 (*syn*), 14.2 (*syn*). Anal. Calcd for $C_{15}H_{25}NO_6S_2$: C, 47.48; H, 6.64; N, 3.69. Found: C, 47.30; H, 6.49; N, 3.94.

***tert*-Butyl 3-methyl-2-[[bis(methylthio)methylene]amino]-5-oxoheptanoate (*anti*-7a):** colorless oil (80%). IR (CCl_4) ν 1740, 1720, 1580. ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (1H, d, ^3J = 5 Hz), 2.75–2.32 (11 H, m, among which: 2.53 (3H, s), 2.39 (3H, s), 1.44 (9H, s), 1.02 (3H, t, ^3J = 7 Hz), 0.93 (3H, d, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.0, 169.9, 162.1, 81.2, 69.4, 45.2, 36.4, 33.3, 28.0, 17.4, 15.0, 14.8, 7.8. Anal. Calcd for $C_{15}H_{27}NO_3S_2$: C, 54.02; H, 8.16; N, 4.20. Found: C, 53.85; H, 8.45; N, 4.46.

***tert*-Butyl 2-[[bis(methylthio)methylene]amino]-5-oxo-3-phenylhexanoate (*anti*-7b):** white solid (80%). Mp = 64–66 °C (hexane). IR (CCl_4) ν 1730, 1710, 1570. ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.10 (5H, m), 4.32 (1H, d, ^3J = 5 Hz), 3.84 (1H, m), 2.89–2.76 (2H, m), 2.42 (3H, s), 2.38 (3H, s), 1.96 (3H, s), 1.20 (9H, s). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 207.4, 169.3, 163.5, 141.1, 128.7, 128.3, 127.0, 81.4, 70.2, 46.4, 45.2, 30.6, 27.8, 15.2, 15.0. Anal. Calcd for $C_{19}H_{27}NO_3S_2$: C, 59.81; H, 7.13; N, 3.67. Found: C, 59.72; H, 7.02; N, 3.94.

Deprotection of the Iminodithiocarbonate Group of Compounds *anti*-6a-c and *anti*-7a,b. Synthesis of Pyroglutamates 9 and Δ¹-Pyrrolines 10. General Procedure. To a solution of **6a–c** or **7a,b** (100 mg) in THF (1.0 mL) was added 0.5 N HCl (1.0 mL) and the mixture stirred at room temperature for 24 h. After neutralization with 1 N NaOH, the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane:ethyl acetate, 80:20).

***trans-tert*-Butyl 4-Methylpyroglutamate (9a):** white solid (80%). Mp = 82–83 °C (hexane). IR (CCl_4) ν 3240, 1750, 1715. ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (1H, bs), 3.68 (1H, d, ^3J = 5 Hz), 2.52 (2H, m), 2.00 (1H, m), 1.46 (9H, s), 1.24 (3H, d, ^3J = 7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.1, 170.9, 82.4, 63.2, 38.3, 34.4, 28.1, 20.1. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.56; H, 8.47; N, 7.12.

***trans-tert*-Butyl 4-Phenylpyroglutamate (9b):** white solid (70%). Mp = 104–107 °C (hexane). IR (CCl_4) ν 3220, 1740, 1705. ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (5H, m), 6.10 (1H, bs), 4.14 (1H, d, ^3J = 5 Hz), 3.64 (1H, m), 2.85 (1H, A part of an ABX, J_{AB} = 16 Hz), 2.15 (1H, B part of an ABX, J_{AB} = 16 Hz), 1.40 (9H, s). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.2, 169.2, 141.3, 129.0, 127.5, 127.2, 82.8, 63.4, 44.4, 38.4, 28.0. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.73; H, 7.58; N, 5.21.

***trans-tert*-Butyl 4-(Methoxycarbonyl)pyroglutamate (9c):** white solid (90%). Mp = 115–116 °C (hexane). IR (CCl_4) ν 3230, 1750, 1720. ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (1H, bs), 4.46 (1H, d, ^3J = 5 Hz), 3.77 (3H, s), 3.37 (1H, m), 2.64–2.48 (2H, m), 1.47 (9H, s). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.5, 172.3, 169.2, 83.2, 58.2, 52.7, 42.4, 33.5, 28.1. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.58; H, 6.80; N, 5.93.

***trans*-5-(*tert*-Butoxycarbonyl)-2-ethyl-4-methyl-Δ¹-pyrroline (10a):** pale yellow oil (95%). IR (CCl_4) ν 1745. ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (1H, m), 2.79 (1H, A part of an ABX, J_{AB} = 17 Hz), 2.38 (3H, m), 2.12 (1H, B part of an ABX, J_{AB} = 17 Hz), 1.46 (9H, s), 1.18–1.12 (6H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.0, 172.3, 81.3, 80.8, 45.4, 36.5, 28.0, 27.1, 20.0, 10.6. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.11; H, 10.26; N, 6.56.

***trans*-5-(*tert*-Butoxycarbonyl)-2-methyl-4-phenyl-Δ¹-pyrroline (10b):** white solid (95%). Mp = 170–172 (hexane). IR (CCl_4) ν 1740. ^1H NMR (300 MHz, $CDCl_3$) δ 7.10–7.35 (5H, m), 4.57 (1H, m), 3.62 (1H, m), 3.14 (1H, A part of an ABX, J_{AB} = 18 Hz), 2.68 (1H, B part of an ABX, J_{AB} = 18 Hz), 2.15 (3H, s), 1.44 (9H, s). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.2, 171.7, 143.4, 128.7, 126.9, 126.7, 82.9, 81.3, 48.2, 47.2, 28.0, 19.8. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.91; H, 8.39; N, 5.52.

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