Diastereoselective Synthesis of α,α-Disubstituted γ-Carboxypyroglutamates *via* Sm(III)−Azomethine Ylide Cycloadditions

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Sm(III)−azomethine ylides **2** have been generated from ketones **1**. Cycloaddition of ylides **2** with α,β-unsaturated esters **3** through a transition state chelation-controlled by the metal allowed for the asymmetric synthesis of γ-carboxypyroglutamates having a quaternary α-carbon that are potentially useful in the synthesis of neuroprotective agents.

The implication of glutamate receptors in Alzheimer's disease[1,2] and the therapeutic potential of substituted glutamic acid derivatives in the treatment of epilepsy[3] and stroke[4] has paved the way for the asymmetric synthesis of these unnatural α-amino acids. In particular, certain derivatives of δ-carboxyglutamic acid are potent antagonists of the NMDA receptor with potential application in drug design of neuroprotective agents.[5]

Pyroglutamates (5-oxopyrrolidine-2-carboxylates) can be thought of as glutamic acid derivatives having the carboxylate γ to nitrogen internally protected (Figure 1, $R^1 = H$).[6,7] The conformational constraints induced by these subunits in peptides can lead to their enhanced bioactivity and stability, which has found pharmacological use.[8] Thus, α-alkyl α-amino acids have assumed an important role in bioorganic chemistry as subunits for the definition of the secondary structure in *de novo* design of peptides and proteins.[9] However, few efforts have been directed toward the preparation of glutamic derivatives with quaternary carbons[7,10] (Figure 1, R^1 = alkyl), despite the significant conformational modifications that this substitution could induce in peptides. For example, a total synthesis of (+)-lactacystin, a novel neurotrophic agent with an α-quaternized pyroglutamate skeleton, has been recently reported.[2]

1,3-Dipolar cycloadditions constitute one of the most useful methods for the synthesis of five-membered heterocyclic rings with good diastereoselectivity.[11] Highly substituted proline derivatives have been synthesized by using metalloazomethine ylides as the dipole.[12,13] This approach affords prolines C-substituted on C-5. In order to prepare pyroglutamate derivatives instead of prolines, we have chosen the iminodithiocarbonate[14] group as the azomethine counterpart in place of aldimines or ketimines. Sulfur-substituted azomethine ylides have been used frequently as synthetic equivalents of otherwise relatively accesible nitrile ylides by a cycloaddition and elimination sequence to give cycloaddition products one oxidation state higher than that expected from simple azomethine ylides.[15] In this work we have developed the synthetic equivalence between the iminodithiocarbonate group and the lactam moiety of the pyroglutamic derivatives.[16] High diastereoselectivities in the cycloaddition process could be expected by using Sm(III)-azomethine ylides as 1,3-dipoles due to the high coordination number of this cation,[17] which should favor tightly coordinated reaction intermediates.

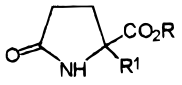

Figure 1.

We describe herein the generation of the Sm(III)−azomethine ylides **2** *via* SmI_2-induced fragmentation[18] of

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1996.

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Scheme 1

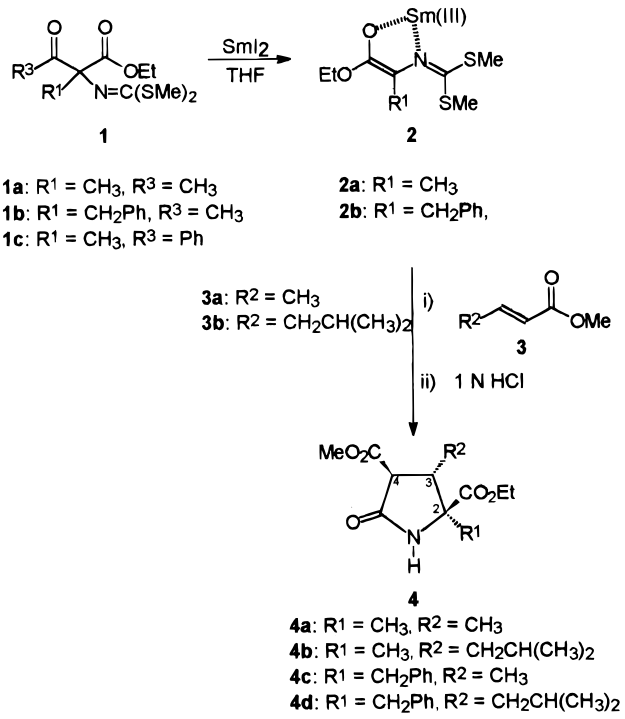


Table 1. 1,3-Dipolar Cycloaddition of Azomethine Ylides 2 with Esters 3. Synthesis of 4

no.	R^1	R^2	**4**	**4,** de[a] (%)	**4,**[b] %
1	CH_3	CH_3	**4a**	80	85
2	CH_3	^{i}Bu	**4b**	80	80
3	$PhCH_2$	CH_3	**4c**	80	75
4	$PhCH_2$	^{i}Bu	**4d**	85	75

[a] Determined by integration of the ^{1}H-NMR spectra ($CDCl_3$, 300 MHz) of the crude reaction products. [b] Pure isolated yields.

compounds **1**[14] and their 1,3-dipolar cycloaddition with the α,β-unsaturated esters **3**. This affords the pyroglutamates **4**, which are γ-carboxyglutamic derivatives in which a quaternary center has been asymmetrically introduced in the α-position of the amino acid moiety (Scheme 1).

Results

Generation of Ylides 2 and Cycloaddition to Esters 3. Compounds **1** were obtained by acylation or benzylation of *N*-[bis(methylthio)methylene]alanine ethyl ester (**5a**) or phenylalanine ethyl ester (**5b**) (KO^{t}Bu, THF) as previously described.[14] Addition of a THF solution of **1a,b** (1.0 equiv) and the corresponding ester **3** (1.5 equiv) to a freshly prepared 0.1 M solution of SmI_2 in THF (1.0 equiv) followed by *in situ* hydrolysis (1 N HCl) of the initial adducts[19] allowed for the isolation of pyroglutamates **4** in good yields (Scheme 1, Table 1).

Only two out of the four possible diastereomers were observed in the ^{1}H-NMR spectra of the crude reaction products, and one stereoisomer was always formed in large excess. Fractional crystallization of the mixture allowed for the isolation of the major one as a single diastereomer. A slight drop in yield was noticed upon increasing the steric volume of either R^1 or R^2, whereas diastereoselectivity was scarcely modified.

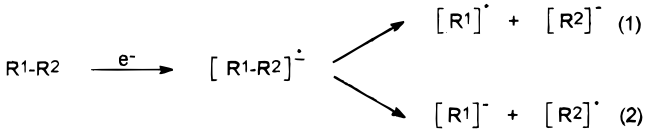
On the other hand, treatment of ketone **1c** with SmI_2 and ester **3a** under the aforementioned reaction conditions gave rise to pyroglutamate **4a** in only 45% yield. However, the same diastereoselectivity was observed as in the reaction of ketone **1a** (Table 1, entry 1). Ethyl 2-benzoylpropionate (**6**) was isolated in 50% yield.

Monitoring of the reaction of ketone **1a** with ester **3a** by TLC (hexane−ethyl acetate, 80:20) showed the formation of alaninate **5a** at the early stages of the process at the expense of the starting material.[20] In a similar fashion, formation of phenylglycinate **5b** was observed[20] in the reactions of ketone **1b**.

On the other hand, treatment of ketone **7** with SmI_2 (2.0 equiv) in THF and ester **3a** (1.5 equiv) in the presence of ^{t}BuOH (1.0 equiv) allowed for the formation of lactone **8a** (95% de). Compound **8a** isomerized on standing in $CHCl_3$ solution (72 h, 25 °C) to a 55:45 mixture of **8a** and **8b**.

Discussion

Generation of Ylides 2 and Cycloaddition with Esters 3. The generation of radical anions by a single electron transfer from SmI_2 is a well-documented process.[21] These radical anions are readily prone to unimolecular fragmentation[22] to produce a radical species plus an anion. This process is kinetically favored over dimerization or C−C bond formation. Out of the two possible reaction paths for the unimolecular fragmentation, the one that produces the most stable anionic fragment will be thermodynamically favored[23] (eqs 1 and 2).



In the presence of SmI_2, ketyl radical formation from ketones **1a,b** is to be expected.[21,24] Steric hindrance would prevent dimerization or C−C bond-forming processes at the expense of the unimolecular fragmentation to ylides **2** (Scheme 2, path A). The latter will be thermodynamically favored as a consequence of extended resonance stabilization.[25]

This reaction pathway is supported by the following facts: (1) When the reactions of ketones **1a,b** (1.0 equiv) with ester **3a** (1.5 equiv) and SmI_2 (1.0 equiv) were

(15) (a) Padwa, A.; Haffmanns, G.; Tomas, M. *Tetrahedron Lett.* **1983**, *24*, 4304. (b) Padwa, A.; Haffmanns, G.; Tomas, M. *J. Org. Chem.* **1984**, *49*, 3314. (c) Kraus, G. A.; Nagy, J. O. *Tetrahedron* **1985**, *41*, 3537. (d) Turro, N. J.; Cha, Y.; Gould, I. R.; Padwa, A.; Gasdaska, J. R.; Tomas, M. *J. Org. Chem.* **1985**, *50*, 4415. (e) Tsuge, O.; Kanemasa, S.; Matsuda, K. *J. Org. Chem.* **1986**, *51*,1997. (f) Padwa, A.; Gasdaska, J. R.; Tomas, M.; Turro, N. J.; Cha, Y.; Gould, I. R. *J. Am. Chem. Soc.* **1986**, *108*, 6739. (g) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523. (h) Padwa, A.; Gasadaska, J. R.; Haffmanns, G.; Rebello, H. *J. Org. Chem.* **1987**, *52*, 1027. (i) Pearson, W. H.; Stevens, E. P. *Tetrahedron Lett.* **1994**, *35*, 2641.

(16) (a) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1995**, *60*, 6242. (b) Bachi, M. D.; Melman, A. *Synlett* **1996**, 60.

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(18) This reaction constitutes a novel application of SmI_2 in organic synthesis. See: Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

(19) Alvarez Ibarra, C.; Csákÿ, A. G.; Martínez, M.; Quiroga, M. L. *Tetrahedron Lett.* **1996**, *37*, 6573.

(20) This observation was confirmed by aqueous quenching of the reaction followed by isolation and characterization of **5a,b**.

(21) E^o Sm(II)/Sm(III) = −1.55 V. See: Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008.

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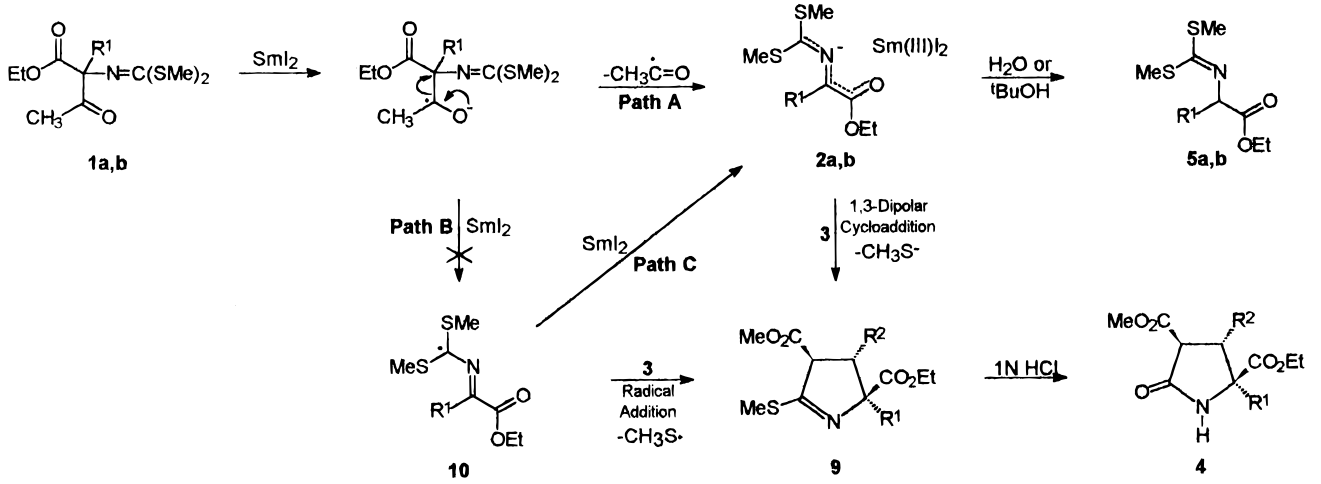
(23) Melton, C. E. In *Mass Spectrometry of Organic Ions;* McLafferty, F. W., Ed.; Academic Press: New York, 1963; p 65.

(24) Redox potential of acetone: E = −0.925 V. See: Kita, H.; Ishikura, S.; Katayama, A. *Electrochim. Acta* **1975**, *20*, 441.

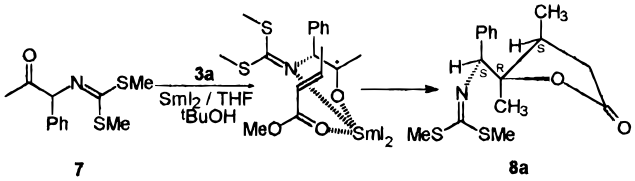
Scheme 2



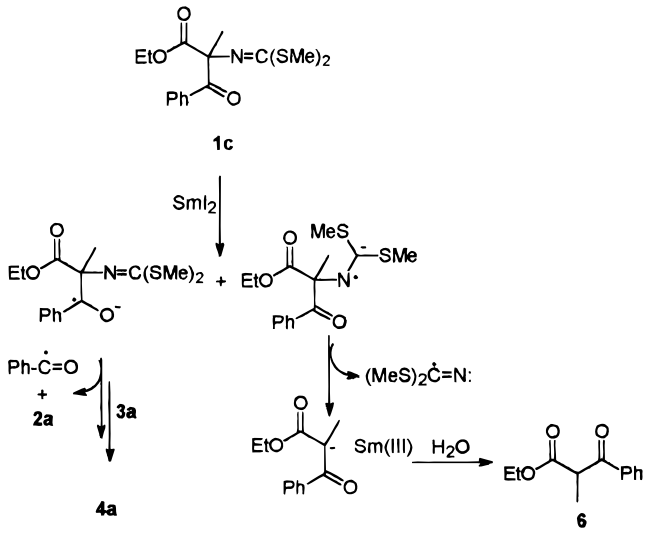
quenched (H_2O addition) prior to completion, **5a** and **5b** were isolated together with the corresponding adducts **9a,b**. Esters **5a,b** should arise from protonation of ylides **2**. This proves that ketones **1a,b** fragment prior to reaction with the dipolarophile (Scheme 2). (2) At this stage the formation of adducts **9** could be explained either by the cycloaddition of the azomethine ylides **2** (path A) or by the radical addition of species **10** (path B). It could also explain the formation of adducts **9** (Scheme 2, path B). In order to rule out the second possibility, ketones **1a,b** were treated with ester **3a** (1.0 equiv), SmI_2 (2.0 equiv), and ^{t}BuOH (1.0 equiv). Now, the presence of a second equivalent of SmI_2 should enforce the reduction of the hypothetical radical species **10** to the anions **2** (Scheme 2, path C), thus securing the cycloaddition pathway. Ester **5a,b** should stem from competition of ylides **2** between protonation by ^{t}BuOH and cycloaddition with ester **3a**. If a change in mechanism were operating, a change in diastereoselectivity should be observed. However, the reaction afforded esters **5a,b** and adducts **9a,b** after quenching with H_2O, and the latter were obtained with the same diastereoselectivity as in previous runs.[26,27] This excludes the participation of path B in the formation of **9a,b** and hence **4a,b**. (3) The presence of the ester moiety in **1** is crucial for the outcome of the process, in order to thermodynamically favor the formation of ylides **2** (Scheme 2, path A). Thus, lactone **8a** was kinetically formed in the reaction of **3a** with ketone **7**, in which the ester group had been replaced by phenyl. Lactone **8a** can be formed by reduction of the carbonyl group by a single electron transfer process followed by 1,4-addition of the resulting ketyl radical to the α,β-unsaturated ester *via* a transition state that probably involves chelation between the ester group, the oxygen atom of the ketyl radical, and the sp^2 nitrogen of the iminodithiocarbonate moiety (Scheme 3).[28]

The reduction potential of aromatic ketones[29] is more negative than that of aliphatic ones and closer to that of imines.[30] Therefore, upon treatment of ketone **1c** with SmI_2 (1.0 equiv) and ester **3a**, ketyl anion formation competes with electron transfer to the iminodithiocarbonate moiety. Fragmentation of the former gives rise to ylide **2a**, which cycloadds to ester **3a**, affording pyroglutamate **4a** after acid hydrolysis (Scheme 2). Fragmentation of the alternate radical anion gives rise to compound **6** after loss of the bis(methyltio)imine radical and protonation of the resulting anion (Scheme 4).

Scheme 3



Scheme 4



It is worth mentioning that we were not able to prepare ylide **2a** either by transmetalation[31] with $SmCl_3$ of the lithium enolates derived from **5a** or by deprotonation of **5a** with $Sm(HMDS)_3$.[32] Compound **9e** (Scheme 2, R^1 =

(25) Retroaldol condensation has been observed in the nucleophilic additions of stabilized carbanions to ketones **1a,b** in THF at −78 °C. See: Alvarez-Ibarra, C.; Domínguez, C., Csáky, A. G.; Martínez Santos, E.; Quiroga, M. L. *Tetrahedron Lett.* **1993**, *34*, 5463.

(26) 2-Methylthio-Δ^1-pyrrolines **9** were obtained as mixtures of two diastereomers in equal ratios as that observed for the corresponding pyroglutamates **4** (Table 1). See ref 18.

(27) Treatment of THF solutions of **7a,b** with 0.5 N HCl gave rise to pyroglutamates **4a** (90% yield) and **4b** (85% yield).

(28) (a) Kawatsura, M.; Matsuda, F.; Shirama, H. *J. Org. Chem.* **1994**, *59*, 6900. (b) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373.

(29) Redox potential of acetophenone: $E = -1.6$ V. See: Kryukova, E. V.; Tomilov, A. P. *Zh. Prikl. Khim.* **1972**, *45*, 861. See ref 26 for comparison with acetone.

(30) Iwasaki, T.; Harada, K. *J. Chem. Soc., Chem. Commun.* **1974**, 338.

H, $R^2 = CH_3$) had been previously obtained with low diastereoselectivity from the Michael addition of **3a** with *N*-[bis(methylthio)methylene]glycine ethyl ester (**5c**, R^1 = H) under PTC conditions and from the corresponding Li or K enolates.[33] This procedure failed for compounds **5a** ($R^1 = CH_3$) and **5b** ($R^1 = PhCH_2$).

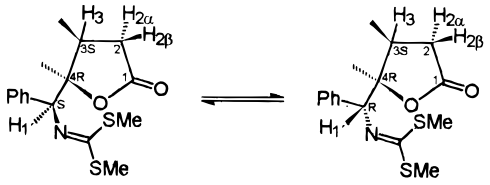
Structural Assignment of Pyroglutamates 4. Acid hydrolysis of adducts **9** afforded pyroglutamates **4**. The structural assignment of **4a** relies on the comparison of the ^{1}H-NMR spectrum of **9a** with that of **9e**[33,34] (Scheme 2, R^1 = H, $R^2 = CH_3$) and on the 1D NOE spectra. Thus, upon irradiation of the CH_3-C4 signal of **9a** (δ = 1.15, d, ^3J = 7 Hz) a 5% enhancement was observed for the H-3 signal (δ = 3.42, d, ^3J = 10 Hz), whereas no NOE effect was observed on the CH_3S signal (δ = 2.46, s). On the other hand, a 2% enhancement of the CH_3S signal was observed upon irradiation of H-3.

The relative configuration of the three contiguous asymmetric centers of compound **4a** has been determined by its 2D-NOESY spectrum. Thus, the observation of a cross peak between C-3 methyl and C-4 hydrogen is in agreement with an *anti* geometry between the C-3 methyl and the carboxylate group in C-4. A strong correlation peak between C-2 and C-3 methyl groups together with a relatively weak cross-peak between C-2 methyl and C-3 hydrogen allowed for the establishment of a *syn* geometry between C-2 and C-3 methyl groups. A weak correlation between C-2 methyl and C-4 hydrogen was also present, in agreement with previous assignments.

The examination of the NMR spectra (^{13}C and ^{1}H shifts, $^3J_{H-H}$ couplings) supported an identical structure and relative stereochemistry of the ring carbon atoms of all major isomers of **4** (see Experimental Section). Hence, in all compounds **4**, the relative orientation of the substituents at C-3/C-4 is *anti*, and the ester group on C-2 is always *anti* to the alkyl substituent on C-3 (Scheme 1).

Assignment of the Relative Configurations of Lactones 8. The relative configuration of carbons C-3 and C-4 of the lactone moiety of compounds **8a** and **8b** has been determined by their 1D-NOE spectra. Saturation of the C-3 methyl group signal of both isomers (**8a**, δ = 1.04 ppm, d; **8b**, δ = 1.04 ppm, d) allowed for an enhancement of the H-2α (**8a**, δ = 2.16 ppm, dd; **8b**, δ = 2.00 ppm, dd) and H-1′ (**8a**, δ = 4.85 ppm, s; **8b**, δ = 4.61 ppm, s) signals. NOE effects on the phenyl (**8a**, **8b**, δ = 7.32−7.20 ppm, m), H-1′ (**8a**, δ = 4.85 ppm, s; **8b**, δ = 4.61 ppm, s), H-2β (**8a**, δ = 2.83 ppm, dd; **8b**, δ = 2.81 ppm, dd), and H-3 (**8a, 8b**, 2.47−2.40, m) were noticed upon saturation of the C-4 methyl group signal of both isomers (**8a**, δ = 1.44 ppm, s; **8b**, δ = 1.50 ppm, s). This allowed for the establishment of an *anti* relative disposition between the C-3 and C-4 methyl groups. However, the relative configuration of C-1′ remained ambiguous.

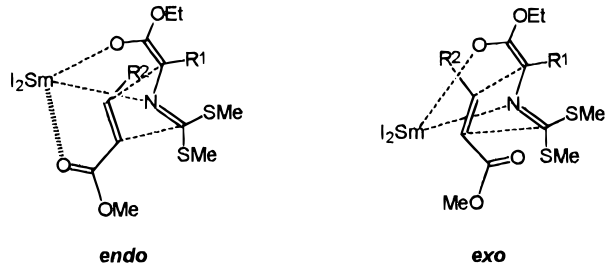
Scheme 5



8a **8b**

Semiempirical calculations (AM1) carried out for the minimum energy conformations[35] of both isomers **8** showed that **8b** was thermodynamically more stable by 3 kcal/mol (**8a**, E = −40.78 kcal/mol. **8b**, E = −43.75 kcal/mol), in agreement with the isomerization of **8a** into **8b** observed experimentally. This allowed for the proposed assignment of a (1′S^*,3S^*,4R^*) geometry for **8a** and a (1′R^*,3S^*,4R^*) geometry for **8b** (Scheme 5).

Stereochemical Considerations. Sm(III)-azomethine ylides **2** underwent highly stereoselective 1,3-dipolar cycloadditions with esters **3** (Table 1). We assume that this good diastereofacial selectivity can be accounted for by a highly ordered *endo* transition state[13] in which the Sm(III) cation is coordinated to the heteroatoms of both dipole and dipolarophile (Figure 2). This type of coordination would not be possible in an *exo* transition state.[36]



endo ***exo***

Figure 2.

The proposed model accounts for the slight drop in yield observed upon increasing the steric volume of either R^1 or R^2. Note that diastereoselectivity scarcely changed with the size of substituents, as consequence of the predominance of orbital overlap in the discussed transition states.

Conclusions

The 1,3-dipolar cycloaddition of the Sm(III)-azomethine ylides **2** with α,β-unsaturated esters **3** takes place under chelation control by the iminodithiocarbonate group and the carboxylate groups of dipole and dipolarophile. This

(31) A mixed enolate species of soft reactivity could be formed under these reaction conditions. See: van der Steen, F. H.; Boersma, J.; Spek, A.-L., van Koten, G. *Organometallics* **1991**, *10*, 2476.

(32) For the preparation of Sm(HMDS)3 from SmCl3 and NaHMDS see: Bradley, D. C.; Ghotra, J. S.; Hart, F. A. *J. Chem. Soc., Dalton Trans.* **1973**, 1021. For the generation of ketone Sm(III)-enolates with $Sm(HMDS)_3$ see: Sasai, H.; Arai, S.; Shibasaki, M. *J. Org. Chem.* **1994**, *59*, 2661. This base could be not strong enough for ester deprotonation. For a comparison of LDA and Li(HMDS) in ester deprotonation see: Williard, P. G.; Liu, Q.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 348.

(33) Alvarez-Ibarra, C.; Csáky, A. G.; Maroto, M.; Quiroga, M. L. *J. Org. Chem.* **1995**, *60*, 6700.

(34) ^{1}H-NMR (300 MHz, $CDCl_3$) of **9e**: δ (ppm) 4.24 (2H, q, ^3J = 7 Hz), 4.19 (1H, dd, ^3J = 6 Hz, ^4J = 2 Hz), 3.77 (3H, s), 3.41 (1H, dd, ^3J = 9 Hz, ^4J =2 Hz), 3.05 (1H, m), 2.49 (3H, s), 1.31 (3H, t, ^3J = 7 Hz), 1.21 (3H, d, ^3J = 7 Hz).

(35) For the AM1 Hamiltonian see: Dewar, M. S. J.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. Minimum energy conformers have been located by simulated annealing. See: (a) Kirkpatrick, S.; Gelatt, C. D.; Vecchi, M. P. *Science* **1983**, *220*, 671. (b) Wilson, S. R.; Cui, W.; Moskowitz, J. W.; Schmidt, K. W. *Tetrahedron Lett.* **1988**, *29*, 4373. The MMX force field was used in the molecular dynamics simulations: Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. In *Advances in Molecular Modeling*; JAI Press: Greenwich, 1990; Vol. 2. The conformers obtained from the simulated annealing molecular dynamics calculations were further optimized manually, searching by rotation of the CH_3−C4−C1′−H torsional angle followed by an AM1 minimization with the Polak-Ribiere conjugated gradient up to a gradient root mean square <0.1 kcal/A mol. The minimum energy conformers thus obtained for **8a** and **8b** differred by more than 2 kcal from their next minimum energy conformation.

(36) Chelation between carbonyl groups and Sm(III) has been advanced as an important elements in the stereochemical control of ketyl radical additions. See ref 28 and references cited therein.

allows for the asymmetric synthesis of γ-carboxyglutamic acid derivatives having the α-carbon quaternized, which were not accesible by previously reported procedures.[33]

Experimental Section

All starting materials were commercially available research-grade chemicals and used without further purification. Silica gel 60 F_{254} was used for TLC, and the spots were detected either with UV or with vanillin solution. Flash column chromatography was carried out on silica gel 60. IR spectra have been recorded as $CHCl_3$ solutions. Melting points are uncorrected. ^{1}H 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 NMR spectra has been carried out with the aid of the DEPT-135 pulse sequence. MS spectra were carried out by electron impact at 70 eV. SmI_2 was synthesized from Sm and 1,2-diiodoethane. Worse results were obtained with commercial solutions of SmI_2 in THF.

General Procedure for Cycloaddition of Ylides 2 with Esters 3. Step-by-Step Procedure (Method A). To a slurry of samarium metal powder (390 mg, 2.6 mmol, flamed and cooled under argon) in THF (1.3 mL) at room temperature was added a solution of 1,2-diiodoethane (560 mg, 2.0 mmol) in THF (2.5 mL). The mixture was stirred at ambient temperature for 1 h, during which time the reaction's color changed from olive-green to deep blue. The resulting solution was diluted with THF (16 mL), and a solution of **1** (1.9 mmol) and **3** (2.85 mmol) in THF (0.5 mL) under Ar was added. After the reaction mixture had been stirred for 1 h, H_2O (2.5 mL) was added, and the mixture was stirred for 15 min and was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The products were separated by flash column chromatography eluting with a mixture of hexane−ethyl acetate (80:20) and the products **9** used for the next step.

Synthesis of Pyroglutamates 4. To a solution of **9** (0.55 mmol) in THF (1.5 mL) was added 0.5 N HCl (1.5 mL) and the mixture stirred at room temperature for 24 h. The mixture was neutralized with 0.5 N NaOH and extracted with Et_2O (3 × 5 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The products were separated from the unreacted material by flash column chromatography eluting with a mixture of hexane−ethyl acetate (80:20) and finally eluted with ethyl acetate.

One-Pot Synthesis of Pyroglutamates 4 (Method B). To a slurry of samarium metal powder (190 mg, 2.6 mmol, flamed and cooled under argon) in THF (1.3 mL) at room temperature was added a solution of 1,2-diiodoethane (560 mg, 2.0 mmol) in THF (2.5 mL). The mixture was stirred at ambient temperature for 1 h during which time the reaction's color changed from olive-green to deep blue. The resulting solution was diluted with THF (16 mL), and a solution of **1** (1.9 mmol) and **3** (2.8 mmol) in THF (0.5 mL) under Ar was added. After the reaction mixture had been stirred for 1 h, 1 N HCl (25 mL) was added and the mixture stirred at rt for 24 h. The mixture was neutralized with 0.5 N NaOH and extracted with Et_2O (3 × 15 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The products were separated from the unreacted material by flash column chromatography eluting with a mixture of hexane−ethyl acetate (80:20) and finally with ethyl acetate.

(3*S,4*S**,5*S**)-5-(Ethoxycarbonyl)-3-(methoxycarbonyl)-4,5-dimethyl-2-(methylthio)-Δ^1-pyrroline (9a):** oil (90%); IR ($CHCl_3$) ν 1710, 1690 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 4.21 (2H, qd, *J* = 7, 2 Hz), 3.78 (3H, s), 3.42 (1H, d, *J* = 10 Hz), 3.11 (1H, qd, *J* = 6, 10 Hz), 2.46 (3H, s), 1.29 (3H, t, *J* = 7 Hz), 1.27 (3H, s), 1.15 (3H, d, *J* = 7 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ (ppm) 174.0, 169.9, 169.5, 78.9, 62.6, 61.4, 52.7, 44.3, 19.0, 14.2, 13.9, 13.7. Anal. Calcd for $C_{12}H_{19}NO_4S$: C, 52.73; H, 7.01; N, 5.12. Found: C, 52.89; H, 7.03; N, 5.11.

(3*S,4*S**,5*S**)-4-Isobutyl-5-(ethoxycarbonyl)-3-(methoxycarbonyl)-5-methyl-2-(methylthio)-Δ^1-pyrroline (9b):** oil (85%); IR ($CHCl_3$) ν 1710, 1680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 4.23 (2H, qd, *J* = 7, 5 Hz), 3.78 (3H, s), 3.45 (1H, d, *J* = 10 Hz), 3.18 (1H, td, *J* = 7, 10 Hz), 2.45 (3H, s), 1.49−1.32 (3H, m), 1.28 (3H, t, *J* = 7 Hz), 1.23 (3H, s), 0.89 (3H, d, *J* = 7 Hz), 0.85 (3H, d, *J* = 7 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ (ppm) 174.1, 170.5, 169.3, 79.3, 62.2, 61.4, 52.7, 47.1, 39.2, 26.6, 23.6, 21.8, 19.3, 14.2, 13.9. Anal. Calcd for $C_{15}H_{25}NO_4S$: C, 57.12; H, 7.99; N, 4.44. Found:C, 57.259; H, 8.03; N, 4.61.

(3*S,4*S**,5*S**)-5-Benzyl-5-(ethoxycarbonyl)-3-(methoxycarbonyl)-4-methyl-2-(methythio)-Δ^1-pyrroline (9c):** oil (80%); IR ($CHCl_3$) ν 1710, 1680, 1650 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.11−7.29 (5H, m), 4.15 (2H, m), 3.75 (3H, s), 3.29 (1H, d, *J* = 14 Hz), 3.21 (1H, d, *J* = 11 Hz), 2.99, 2.95 (1H, dq, *J* = 11, 4 Hz, 2.68 (1H, d, *J* = 14 Hz), 2.49 (s, 3H), 1.32 (3H, d, *J* = 7 Hz), 1.22 (3H, t, *J* = 7 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ (ppm) 173.2, 169.7, 169.6, 136.5, 130.7, 128.0, 126.7, 82.2, 62.7, 61.2, 52.7, 45.8, 39.3, 14.2, 14.0, 13.3. Anal. Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01. Found: C, 62.05; H, 6.61; N, 4.02.

(3*S,4*S**,5*S**)-5-Benzyl-4-isobutyl-5-(ethoxycarbonyl)-3-(methoxycarbonyl)-2-(methylthio)-Δ^1-pyrroline (9d):** oil (80%); IR ($CHCl_3$) ν 1710, 1690, 1660 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.28−7.18 (5H, m), 4.20 (2H, m), 3.74 (3H, s), 3.30 (1H, d, *J* = 14 Hz), 3.23 (1H, d, *J* = 10 Hz), 3.12−3.03 (1H, m), 2.66 (1H, d, *J* = 14 Hz), 2.65 (3H, s), 1.76−1.66 (2H, m), 1.62−1.53 (1H, qd, *J* = 14, 7 Hz), 1.25 (3H, t, *J* = 7 Hz), 0.93 (3H, d, *J* = 7 Hz), 0.87 (3H, d, *J* = 6 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ (ppm) 173.1, 170.3, 169.4, 136.5, 130.7, 127.8, 126.5, 82.7, 62.3, 61.1, 52.6, 48.7, 39.4, 38.6, 26.5, 23.9, 21.2, 14.1, 13.8. Anal. Calcd for $C_{21}H_{29}NO_4S$: C, 64.42; H, 7.47; N, 3.58. Found: C, 64.23; H, 7.49; N, 3.59.

(2*S,3*S**,4*S**)-Ethyl 4-(methoxycarbonyl)-2,3-dimethylpyroglutamate (4a):** mp 81−83 °C (pentane−Et_2O) (method A, 90%; method B, 85%); IR ($CHCl_3$) ν 3300, 3000, 1740, 1710 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 6.61 (1H, bs), 4.22 (2H, q, *J* = 7 Hz), 3.78 (3H, s), 3.15 (1H, d, *J* = 10 Hz), 3.07 (1H, qd, *J* = 7, 10 Hz), 1.35 (3H, s), 1.26 (3H, t, *J* = 7 Hz), 1.19 (3H, d, *J* = 7 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ (ppm) 172.9, 170.1, 169.2, 62.8, 62.0, 54.6, 52.9, 40.3, 20.9, 14.1, 14.0. MS 244 (M + 1), 212, 184, 170, 138, 110. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.25; H, 7.25; N, 5.67.

(2*S,3*S**,4*S**)-Ethyl 3-isobutyl-4-(methoxycarbonyl)-2-methylpyroglutamate (4b):** mp 98−100 (method A, 90%; method B, 80%); IR ($CHCl_3$) ν 3300, 3000, 1750, 1700 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 6.20 (1H, bs), 4.21 (2H, qd, *J* = 7, 3 Hz), 3.79 (3H, s), 3.37 (1H, d, *J* = 10 Hz), 3.15 (1H, m), 1.61−1.41 (3H, m), 1.35 (3H, s), 1.30 (3H, t, *J* = 7 Hz), 0.93 (3H, d, *J* = 6 Hz), 0.87 (3H, d, *J* = 6 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ (ppm) 172.8, 170.0, 169.7, 62.0, 54.0, 52.9, 42.8, 41.0, 39.5, 25.9, 24.2, 21.2, 21.0, 14.1; MS 286 (M + 1), 228, 212, 180, 152. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.05; H, 8.23; N, 5.03.

(2*S,3*S**,4*S**)-Ethyl 2-benzyl-4-(methoxycarbonyl)-3-methylpyroglutamate (4c):** mp 98−100 °C (pentane−Et_2O) (method A, 85%, method B, 75%); IR ($CHCl_3$) ν 3300, 3000, 1730, 1690, 1600 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.30−7.21 (3H, m), 7.07−7.04 (2H, m), 5.92 (1H, bs), 4.14 (2H, qd, *J* = 7, 2 Hz), 3.81 (3H, s), 3.30 (1H, d, *J* = 11 Hz), 3.27 (d, J =11 Hz), 3.10 (1H, qd, *J* = 7, 9 Hz), 2.66 (1H, d, *J* = 12 Hz), 1.39 (3H, d, *J* = 7 Hz), 1.20 (3H, t, *J* = 7 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ (ppm) 176.8, 169.4, 167.0, 134.3, 129.4, 128.4, 127.5, 66.5, 61.8, 54.4, 52.9, 46.0, 41.5, 39.9, 14.0, 13.5. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.11; H, 6.75; N, 4.52.

(2*S,3*S**,4*S**)-Ethyl 2-benzyl-3-isobutyl-4-(methoxycarbonyl)pyroglutamate (4d):** mp 125−127 °C (method A, 85%; method B, 75%); IR ($CHCl_3$) ν 3300, 3000, 1730, 1700, 1600 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.29−7.25 (3H, m), 7.07−7.04 (2H, m), 5.91 (1H, bs), 4.18 (2H, qd, *J* = 7, 2 Hz), 3.80 (3H, s), 3.30 (1H, d, J = 12 Hz), 3.29 (d, *J* = 11 Hz), 3.14 (1H, qd, *J* = 6, 3 Hz), 2.66 (1H, d, *J* = 12 Hz), 1.81 (1H, m), 1.62 (2H, m), 1.09 (3H, d, *J* = 7 Hz), 0.98 (3H, d, *J* = 6 Hz), 0.89 (3H, d, *J* = 6 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ (ppm) 172.1, 170.0, 169.8, 134.5, 129.8, 128.9, 127.7, 66.8, 61.9, 54.4,

53.0, 49.2, 40.4, 38.9, 25.9, 24.5, 20.9, 14.0. MS 262 (M + 1), 288, 270, 238, 210. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.60; H, 7.71; N, 3.90.

Reaction of 1a,b and 7 with 3a and SmI_2 in the Presence of ^tBuOH. To a slurry of samarium metal powder (156 mg, 1.04 mmol, flamed and cooled under argon) in THF (0.5 mL) at room temperature was added a solution of 1,2-diiodoethane (224 mg, 0.8 mmol) in THF (1.0 mL). The mixture was stirred at ambient temperature for 1 h, during which time the reaction's color changed from olive-green to deep blue. The resulting solution was diluted with THF (6.5 mL), and a solution of **1a,b** or **7** (0.4 mmol), ^{t}BuOH (31 mg, 0.4 mmol), and **3** (60 mg, 0.6 mmol) in THF (0.2 mL) under Ar was added. After the reaction mixture had been stirred for 1 h, H_2O (2.5 mL) was added, and the mixture was stirred for 15 min and was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The products were separated by flash column chromatography, eluting with a mixture of hexane−ethyl acetate (80:20).

Isomerization of 8a into 8b. A solution of **8a** (172 mg, 0.5 mmol) in $CHCl_3$ (2.0 mL) was stirred at 25°C for 72 h. The solution was evaporated to dryness under reduced pressure.

(1′*S,3*S**,4*R**)-3-Methyl-4-[1-[bis(methylthio)methyleneamino]benzyl]-4-butanolide (8a):** 85%; IR ($CHCl_3$) ν 1750, 1680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.28−7.23 (5H, m), 4.85 (1H, s), 2.83 (2H, dd, J = 10, 8 Hz), 2.48 (3H, s), 2.47−2.42 (4H, m, among which 2.45, 3H, s), 2.16 (dd, J = 4, 13 Hz), 1.44 (3H, s), 1.04 (3H, d, J = 7 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ (ppm) 176.3, 161.8, 138.4, 129.0, 127.7, 127.3, 89.4, 61.2, 39.2, 37.6, 20.9, 15.2, 14.8, 14.7. Anal. Calcd for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54; N, 4.33. Found: C, 59.65; H, 6.60; N, 4.44.

(1′*R,3*S**,4*R**)-3-Methyl-4-[1-[bis(methylthio)methyleneamino]benzyl]-4-butanolide (8b):** 45:55 mixture with **8a**; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.32−7.20 (5H, m), 4.61 (1H, s), 2.81 (2H, dd, J = 10, 8 Hz), 2.47 (3H, s), 2.45−2.40 (4H, m, among which 2.45, 3H, s), 2.00 (dd, J = 4, 13 Hz), 1.50 (3H, s), 0.89 (3H, d, J = 7 Hz); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ (ppm) 178.3, 161.8, 139.9, 129.7, 129.4, 126.9, 83.7, 68.3, 41.9, 41.8, 23.4, 15.2, 14.8, 14.6.

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