Asymmetric Oxidative Dimerization of the Enolates of *N*-[Bis(methylthio)methylene]- and *N*-(Diphenylmethylene)glycine Esters

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The oxidative dimerization of glycinates **1** with iodine takes place under kinetic control. The stereochemistry of the resulting 3-aminoaspartate **3** depends on the method used (base/solvent) to generate the corresponding enolate **2**. Under suitable conditions, high yields and diastereomeric excesses in favor of the threo derivatives **3-I**, which have C_2 symmetry, were obtained. In the presence of 8-phenylmenthol as chiral auxiliary (2*S*, 3*S*)-3-aminoaspartic acid **5-I** was synthesized.

The synthesis of unnatural α-amino acids in recent times has attracted attention due to their therapeutic potential and biological interactions. In particular, α,*β*-diamino acids, which can be considered as ethylenediamine derivatives, are components of several peptidic antibiotics and other biologically interesting targets.[1] The development of new methods of asymmetric synthesis of ethylenediamine derivatives with C_2 symmetry is of interest for the preparation of new analogs of cisplatin,[2] as well as for the synthesis of new ligands for asymmetric catalysis.[3]

3-Aminoaspartates have been obtained by the asymmetric amination of aspartic acid.[1,4] However, poor yields in the threo products (C_2 symmetry) were obtained. Oxidative coupling of enolates[5] permits, by contrast, the establishment of the relative stereochemistry of contiguous stereocenters as a function of the starting material.[6] Furthermore, high induced diasteroselectivities have been reported from the dimerization of enolates of chiral esters and amides.[7] With the aim of preparing ethylenediamine derivatives with C_2 symmetry, we describe a new method for the synthesis of threo 3-amino aspartates via asymmetric oxidative dimerization of the enolates of the *N*-[bis(methylthio)methylene]- and *N*-(diphenylmethylene) glycine esters **1**.

Results

Oxidative Dimerization of Glycinates 1a−c. The enolization of glycinates **1a,b**[8] and **1c**[9] (Scheme 1) (THF or Et_2O, −78 °C, 1 h) followed by treatment of the mixture of enolates[10] **2a−c-*E*** and **2a−c-*Z*** with iodine (0.5 equiv) allowed for the isolation of compounds **3a−c**. The results are presented in Table 1 as a function of the base and the solvent used in the deprotonation step.

Inspection of these data revealed dependence of the stereochemical outcome of the dimerization reaction on both the starting material **1a−c** and experimental deprotonation conditions. Thus, better diastereomeric excesses in favor of isomers **3-I** were obtained in the dimerization of esters **1b** and **1c** as compared with **1a**, under analogous reaction conditions. When THF was used as the solvent, isomers **3-I** predominated with ^{t}BuLi, ^{s}BuLi and LDA as bases, whereas an increase in the relative ratio of isomer **3-II** was noticed upon deprotonation with KO^{t}Bu. Dimerization of **1a** with LDA in the presence of DMPU (Table 1, entry 5) gave rise to a loss of diastereoselectivity as compared with the essay in the absence of DMPU (Table 1, entry 3). Analogous diastereoselectivities were observed for the dimerization of glycinates **1a** and **1c** either in THF or in Et_2O. On the other hand, the dimerization of **1b** in Et_2O with ^{t}BuLi, ^{s}BuLi, or LDA showed a higher relative ratio of isomer **3b-II** as compared with the same reactions in THF.

Treatment of a 98:02 mixture of **3b-I** and **3b-II** with KO^{t}Bu in *t*-BuOH (2 equiv, 25 °C, 24 h) promoted isomerization to a 45:55 mixture of **3b-I** and **3b-II**.

Furthermore, when the oxidative dimerization of glycinate **1c** under the aforementioned conditions was carried out in the presence of benzophenone (0.5 equiv) the reaction was inhibited.

The crude reaction products were purified by chromatography on silica gel. Crystallization of the resulting oils allowed for the isolation of the pure threo isomers

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(1) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017 and references cited therein.

(2) (a) Sundquist, W. I.; Lippard, S. J. *Coord. Chem. Rev.* **1990**, *100*, 293. (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed.* **1994**, *33*, 497.

(3) Gamez, P.; Dunjic, B.; Lemaire, M. *J. Org. Chem.* **1996**, *61*, 5196 and therein cited references.

(4) The relative sterochemistry of compounds **3-I** and **3-II** was assigned by comparison of the NMR data of compounds **4** with those of the known 3-aminoadipates. See: Fernández Megía, E.; Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1994**, *59*, 7643.

(5) (a) Ivanoff, D.; Spassoff, A. *Bull. Soc. Chim. Fr.* **1935**, *2*, 76. (b) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605. (c) Brocksom, T. J.; Petragnani, N.; Rodrigues, R.; Teixeira, H. l. *Synthesis* **1975**, 396. (d) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1987**, *52*, 3745. (e) Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745.

(6) Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969 and references cited therein.

(7) (a) Porter, N. A.; Su, Q.; Harp, J. J.; Rosenstein, I. J.; McPhail, A. T.*Tetrahedron Lett.* **1993**, *34*, 4457. (b) Langer, T., Illich, M., Helmchen, G. *Tetrahedron Lett.* **1995**, *36*, 4409.

(8) (a) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 424. (b) Hoppe, D.; Beckmann, L. *Liebigs Ann. Chem.* **1979**, 2066.

(9) O'Donnell, M. J.; Bennett, W. D. *Tetrahedron* **1988**, *44*, 5389 and references cited therein.

(10) The stereochemical descriptors *E* and *Z* are used in this context as recommended by Evans. See: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed., Academic Press: New York, 1984; Vol. 3, p 11.

S0022-3263(96)02116-0 CCC: $14.00

Scheme 1

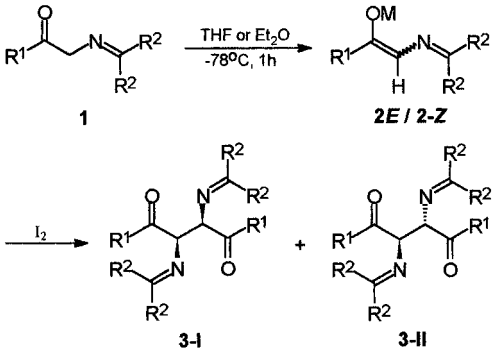


Table I. Oxidative Dimerization of Glycinates 1a−c

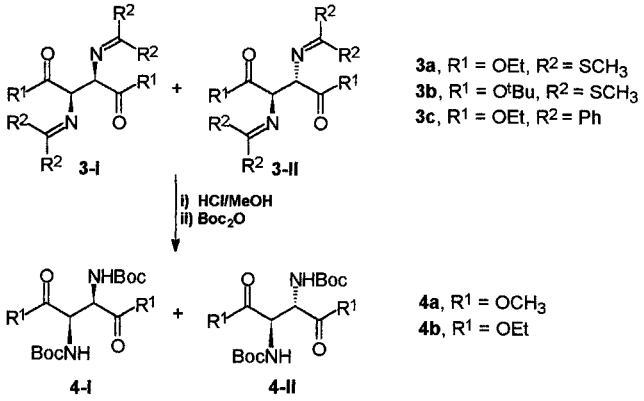
no.	1	base	solvent	3	4-I:4-II[a] (%)[b]
1	**1a**	^{t}BuLi	THF	**3a**	55:45 (80)
2	**1a**	^{s}BuLi	THF	**3a**	60:40 (80)
3	**1a**	LDA	THF	**3a**	65:35 (90)
4	**1a**	KO^{t}Bu	THF	**3a**	40:60 (85)
5	**1a**	LDA/DMPU	THF	**3a**	45:55 (85)
6	**1b**	^{t}BuLi	THF	**3b**	98:02[c] (80)
7	**1b**	^{s}BuLi	THF	**3b**	98:02[c] (80)
8	**1b**	LDA	THF	**3b**	98:02[c] (80)
9	**1b**	KO^{t}Bu	THF	**3b**	50:50 (80)
10	**1c**	^{t}BuLi	THF	**3c**	98:02[c] (80)
11	**1c**	^{s}BuLi	THF	**3c**	90:10 (90)
12	**1c**	LDA	THF	**3c**	90:10 (90)
13	**1c**	KO^{t}Bu	THF	**3c**	50:50 (75)
14	**1a**	^{t}BuLi	Et_2O	**3a**	45:55 (60)
15	**1a**	^{s}BuLi	Et_2O	**3a**	60:40 (85)
16	**1a**	LDA	Et_2O	**3a**	65:35 (80)
17	**1a**	KO^{t}Bu	Et_2O	**3a**	40:60 (85)
18	**1b**	^{t}BuLi	Et_2O	**3b**	45:55 (80)
19	**1b**	^{s}BuLi	Et_2O	**3b**	40:60 (85)
20	**1b**	LDA	Et_2O	**3b**	65:35 (90)
21	**1b**	KO^{t}Bu	Et_2O	**3b**	55:45 (60)
22	**1c**	^{t}BuLi	Et_2O	**3c**	98:02[c] (95)
23	**1c**	^{s}BuLi	Et_2O	**3c**	95:05 (95)
24	**1c**	LDA	Et_2O	**3c**	95:05 (85)
25	**1c**	KO^{t}Bu	Et_2O	**3c**	50:50 (60)

[a] Determined by integration of the crude ^{1}H-NMR ($CDCl_3$, 300 MHz) spectra. [b] Combined yield **I** + **II** in isolated product. [c] Only one diastereomer was observed in the crude ^{1}H-NMR ($CDCl_3$, 300 MHz) spectrum.

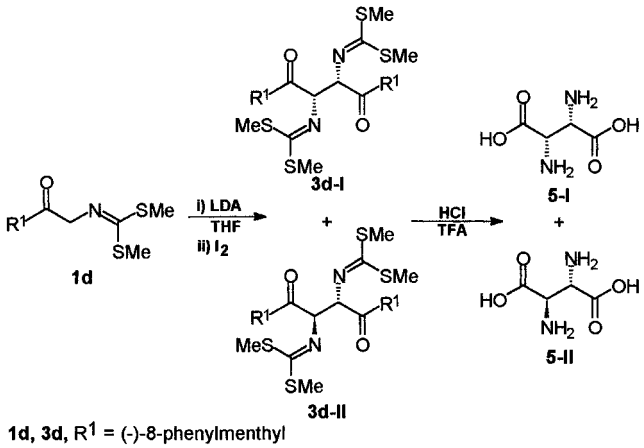
3-I. Deprotection of the iminodithiocarbonate or diphenylmethylene groups (HCl/MeOH) followed by N-Boc protection allowed for the isolation of the 3-aminoaspartates **4**[4] (Scheme 2). It is worth mentioning that the ^{t}Bu groups of ester **3b** were transformed into methyl esters in the course of the methanolysis, without racemization.[11]

Oxidative Dimerization of the Chiral Glycinates 1d. The enolization of the 8-phenylmenthyl ester **1d**[12] (Scheme 1) (LDA, THF, −78 °C, 1 h) followed by treatment with iodine (0.5 equiv) allowed for the isolation of compounds **3d** (**3d-I**:**3d-II** = 40:60, 80% yield). Silica gel chromatography of the reaction crude followed by crystallization of the resulting oil afforded the pure threo isomer **3d-I**. Nonepimerizing hydrolysis of compounds 3d-I allowed for the isolation of (2*S*,3*S*)-3-aminoaspartic

Scheme 2



Scheme 3



acid[13] **5-I**. The same treatment of isomer **3d-II** gave rise to the meso compound **5-II** (Scheme 3).

Discussion

Dimerization of Glycinates 1a-c. The inverse addition of a THF solution of an enolate to a solution of iodine in THF (1.0 equiv, −78 °C) is known to give rise to the formation of α-iodo derivatives.[14] On the other hand, the addition of a THF solution of iodine (0.5 equiv) to the enolate solution (THF, −78 °C) promotes the oxidation of the enolate.[15] The oxidation of enolate anions, species with a high energy HOMO, gives rise to electrophilic radicals (low energy SOMO). The interaction between HOMO of enolates **2** and SOMO of radicals 6 (Scheme 4) is favorable from energetic considerations. However, the reaction course of the oxidative dimerization of enolates has been the subject of some controversy.[5e,7] Our results point out that the oxidative dimerization reaction of enolates **2** takes place under kinetic control,[16] and that the stereochemical outcome of the process is a function of the *E* or *Z* geometry of

(11) A mixture 65:35 of **3b-I** and **3b-II** was transformed into a mixture 65:35 of **4a-I** and **4a-II**.

(12) Compound **1d** was prepared from (−)-8-phenylmenthol. See: Alvarez Ibarra, C.; Csákÿ, A. G.; Maroto, R.; Quiroga, M. L. *J. Org. Chem.* **1995**, *60*, 7934.

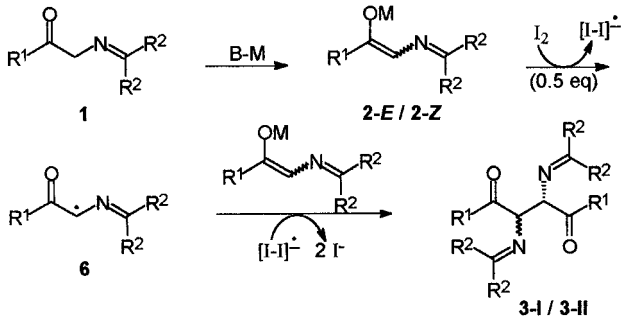
(13) The absolute stereochemistry and the optical purity of the reaction of **1d** was deduced by measuring the optical rotations of **5-I** and **5-II** and comparing the physical and spectroscopic properties with the known compounds. See: (a) McKennis H., Jr.; Yard, A. S. *J. Org. Chem.* **1958**, *23*, 980. (b) Hochstein, F. A. *J. Org. Chem.* **1959**, *24*, 679.

(14) Rathke, M. W.; Lindert, A. *Tetrahedron Lett.* **1971**, 3995. α-Halogenated esters give consecutive reactions when generated in the presence of an excess of enolate.

(15) Kochi, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed., Pergamon Press: Oxford 1991; Vol. 7, p 842.

(16) A thermodynamical reaction pathway for the oxidative dimerization of the lithium enolates in the absence of DMPU is ruled out on the basis of the isomerization of a 98:02 mixture of **3b-I** and **3b-II** to a mixture 45:55. See Results.

Scheme 4



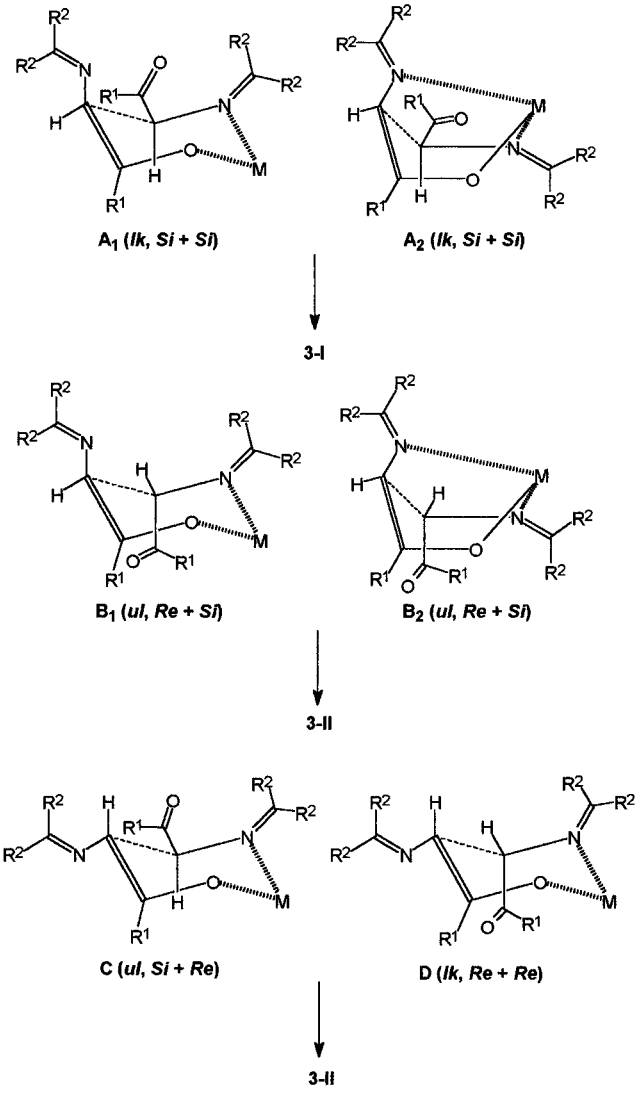
enolates **2**, which in turn depends on the method used in their generation.[17] Therefore, the reaction course of the oxidative dimerization of glycinates **1** should involve both enolates and radicals in the rate-limiting step, and it can be envisioned as an electron transfer process[18] (Scheme 4).

Maximum overlap between the HOMO of the enolate and the SOMO of the radical enforces a parallel approach of both reactants minimizing steric interactions. Thus, the stereochemistry of the reaction can be rationalized from a kinetic point of view by considering cyclic transition states (A−D) which correspond to the two alternative topicities of radicals (**6**) in their approach to enolates **2**-***Z*** and **2**-***E***. In this fashion, the metal is chelated by both counterparts in the transition state and the steric interactions between the bulky iminodithiocarbonate or diphenylmethylene groups are decreased (Scheme 5).

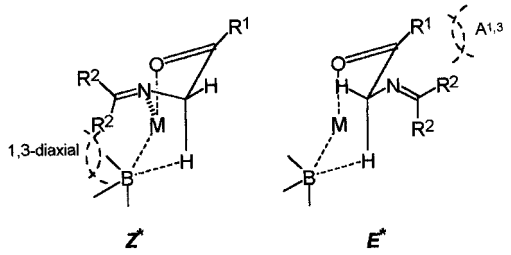
Therefore, isomers **3-I** should be favored by the generation of enolates **2**-***Z*** and their *lk* approach to the radical, on the basis of the higher stability of intermediate A_1 or alternatively its boat conformational modification A_2 where the lone pair on the sp^2-nitrogen participates in the chelation of the metal atom. This reaction path minimizes the nonbonded interaction between R^1 and CO_2R^1 groups as compared to that existing in transition states B_1 and B_2, which would give rise to diastereomer **3-II**. On the other hand, isomers **3-II** should be favored upon generation of enolates **2**-***E*** and their *ul* approach to the radical, on the basis of the higher stability of intermediate C as compared with D due to the 1,3-diaxial interaction (R^1 < > CO_2R^1) present in the latter.

In agreement with Ireland's enolization model[19] (Scheme 6), deprotonation of glycinates **1a**−**c** with hindered bases such as LDA,[20] ^{t}BuLi,[21] or ^{s}BuLi in THF should give rise to enolates **2**-***E***. However, coordination of the lithium

Scheme 5



Scheme 6



atom with the lone electron pair on the sp^2 nitrogen of the iminodithiocarbonate or diphenylmethylene groups would in part stabilize ***Z**** and thus favor enolate ***Z*** formation in comparison with simple alicyclic esters.[12] Furthermore, the enhanced steric volume of R^1 in **1b** (R^1 = ^{t}Bu) and of R^2 in **1c** (R^2 = Ph) as compared with **1a** (R^1 = Et, R^2 = SMe) should promote an increase in the ratio of enolates **2b**-***Z*** and **2c**-***Z*** due to an enhanced $A^{1,3}$-strain in ***E****.[22]

In agreement with these considerations, reactions carried out in THF resulted in **3-II** increasing in the order LDA < ^{s}BuLi < ^{t}BuLi and **1b** ≫ **1c** < **1a**, paralleling an

(17) Helmchen *et al.*[7b] obtained the same relative configuration in the dimerization of alicyclic esters independently of the *E* or *Z* geometry of the starting enolate. However DMPU was present in the reaction medium in the coupling step. DMPU is known to promote formation of *Z* enolates: (a) Helmchen, G., Selim, A.; Dorsch, D.; Taufer, I. *Tetrahedron Lett.* **1983**, *24*, 3213. (b) Helmchen, G.; Wierzchowski, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 60.

(18) An S_N2 reaction between enolates **2** and the corresponding α-iodide is ruled out on the basis of the inhibition of the oxidative dimerization in the presence of benzophenone. This results reveals the participation of radical species. See Results.

(19) (a) Ireland, R. E.; Mueller, R. H.; Williard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650.

(20) LDA is a dimer in THF. See: (a) Seebach, D.; Häsigg, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308. (b) Bauer, W.; Clark, T.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1987,** *109*, 970.

(21) ^{t}BuLi is monomeric in THF. See: Bauer, W.; Winchester, W. R.; Schleyer, P. von R. *Organometallics* **1987**, *6*, 2371. For the extension of Ireland's model to alkyllithiums see: (a) Solladié-Cavallo, A.; Csákÿ, A. G. *J. Org. Chem.* **1994**, *59*, 2585. (b) Solladié-Cavallo, A. Csákÿ, A. G.; Gantz, I.; Suffert, J. *J. Org. Chem.* **1994**, *59*, 5343.

(22) Hindered esters and amides give *Z*-enolates upon deprotonation under kinetic conditions. See for example: Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

increase in enolate **2-*E*** formation. In the presence of DMPU as cosolvent or KO^{t}Bu an open transition state should operate which rendered products **3** in expected thermodynamical ratios.[16] In Et_2O as the solvent higher aggregation of the lithium bases is expected. This increases 1,3-diaxial interactions operating in intermediate ***Z****. This interaction overwhelms the $A^{1,3}$-strain in ***E**** in the case of glycinate **1b** favoring **2b-*E*** enolate formation and **3b-II** production as compared with the assays carried out in THF.

Dimerization of the Chiral Glycinate 1d. On the basis of previous studies on alkylations of enolate **2**[12,23] steric hindrance of the *re* face of C_a of **2d-*Z*** as well as hindrance of the *si* face of C_a of **2d-*E*** is to be expected. Recent studies on radical reactions have put forward the applicability of models previously developed for ionic reactions.[24] Parallelism between enolates and carbonyl-substituted radicals has been reported.[25] Thus a *lk* approach of enolate **2d-*Z*** to radical **6d** should take place in a *si*+*si* fashion (matched pair, transition state A of Scheme 5), affording (2*S*,3*S*)-**3d-I**. The *ul* approach of enolate **2d-*E*** to radical **6d** should take place in a *si*+*re* fashion (mismatched pair, transition state C of scheme 5), giving rise to **3d-II** (meso).

Conclusions

The adequate selection of the starting material **1** and the lithium base used for its deprotonation allowed for the synthesis of the threo (C_2 symmetry) products **3** under kinetic-controlled conditions. On the other hand, the use of KO^{t}Bu as the base afforded compounds **3** in ratios corresponding to a thermodynamic control. Facial diastereoselectivity was enforced starting from a homochiral ester, albeit at the expense of simple diastereoselectivity. The extension of this methodology to other substrates could allow for the preparation of chiral ethylenediamine derivatives with anticipated utility as pharmacologically active compounds.

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(1*H*)-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 either with UV or with ninhydrin solution. Flash column chromatography was carried out on silica gel 60. Ion exchange chromatography was performed on Dowex-50(H). 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. Compounds **1a**,[26] **1b**,[27] **1c**,[28] and **1d**[12] were prepared as previously described.

General Procedure for the Oxidative Coupling of Glycinates 1. Reactions with LDA (Method A). To a solution of ^{i}Pr$_2$NH (1.06 mmol, 0.15 mL) in THF or Et_2O (1.0 mL) at −78 °C was added a 1.6 M solution of BuLi in hexane (1.1 mmol, 0.7 mL). After 30 min, a solution of **1a**−**d** (0.96 mmol) in THF or Et_2O (1.2 mL) was added, and the mixture was stirred for 1 h. A solution of I_2 (0.48 mmol, 122 mg) in THF or Et_2O (1.5 mL) was dropwise added at −78 °C with vigorous stirring. The temperature was slowly raised to 25 °C and the mixture stirred at this temperature for 20 h. The reaction mixture was hydrolyzed with brine (4 mL). The organic layer was decanted and the aqueous one extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation under reduced pressure afforded an oil which was purified by column chromatography on silica gel, eluting with a mixture of hexane−ethyl acetate 80:20.

General Procedure for the Oxidative Coupling of Glycinates 1. Reactions with ^{t}BuLi and ^{s}BuLi (Method B). To a 1.7 M solution of ^{t}BuLi in pentane or a 1.3 M solution of ^{s}BuLi in cyclohexane (1.06 mmol) in THF or Et_2O (1.0 mL) at −78 °C was added a solution of **1a**−**d** (0.96 mmol) in THF or Et_2O (1.2 mL) and all operations continued as above.

General Procedure for the Oxidative Coupling of Glycinates 1. Reactions with KO^{t}Bu (Method C). To a solution of KO^{t}Bu (1.06 mmol, 120 mg) in THF or Et_2O (1.0 mL) at −78 °C was added a solution of **1a**−**d** (0.96 mmol) in THF or Et_2O (1.2 mL) and all operations continued as above.

(2*S,3*S**)-Ethyl 3-Amino-*N*,*N*′-bis[bis(methylthio)methylene]aspartate (3a-I).** Method A (THF) (55%): IR ($CHCl_3$) 1740, 1680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.23 (6H, t, ^3J = 7 Hz), 2.36 (6H, s), 2.55 (6H, s), 4.17 (4H, q, ^3J = 7 Hz), 5.05 (2H, s); ^{13}C (75.5 MHz, $CDCl_3$) δ 14.3, 15.0, 15.4, 61.1, 68.1, 162.2, 168.9. Anal. Calcd for $C_{14}H_{24}N_2O_4S_4$: C, 40.76; H, 5.86; N, 6.79. Found: C, 40.89; H, 5.99; N, 6.90.

(2*S,3*R**)-Ethyl 3-Amino-*N*,*N*′-bis[bis(methylthio)methylene]aspartate (3a-II).** Method C (THF) (50%): mp 82−84 °C (hexane−ethyl acetate); IR ($CHCl_3$) 1740, 1680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25 (6H, t, ^3J = 7 Hz), 2.37 (6H, s), 2.56 (6H, s), 4.17 (4H, q, ^3J = 7 Hz), 5.00 (2H, s); ^{13}C (75.5 MHz, $CDCl_3$) δ 14.3, 15.1, 15.6, 61.2, 69.0, 162.4, 170.2. MS 413 (M + 1), 365, 339, 292, 206, 133. Anal. Calcd for $C_{14}H_{24}N_2O_4S_4$: C, 40.76; H, 5.86; N, 6.79. Found: C, 40.99; H, 5.99; N, 6.66.

(2*S,3*S**)-*tert*-Butyl 3-Amino-*N*,*N*′-bis[bis(methylthio)methylene]aspartate (3b-I).** Method A (THF) (80%): mp 111−112 °C (MeOH); IR ($CHCl_3$) 1740, 1690 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.50 (18H, s), 2.36 (6H, s), 2.54 (6H, s), 4.90 (2H, s); ^{13}C (75.5 MHz, $CDCl_3$) δ 14.9, 15.3, 28.1, 67.8, 81.4, 162.1, 168.8. Anal. Calcd for $C_{18}H_{32}N_2O_4S_4$: C, 46.13; H, 6.88; N, 5.98. Found: C, 46.25; H, 6.67; N, 5.79.

(2*S,3*R**)-*tert*-Butyl 3-Amino-*N*,*N*′-bis[bis(methylthio)methylene]aspartate (3b-II).** Method C (THF) (40%): mp 101−103 °C (hexane); IR ($CHCl_3$) 1740, 1690 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40 (18H, s), 2.27 (6H, s), 2.45 (6H, s), 4.84 (2H, s); ^{13}C (75.5 MHz, $CDCl_3$) δ 14.7, 15.4, 28.4, 67.5, 81.2, 161.9, 169.0; MS 469 (M+1), 421, 367, 234, 178. Anal. Calcd for $C_{18}H_{32}N_2O_4S_4$: C, 46.13; H, 6.88; N, 5.98. Found: C, 46.05; H, 6.95; N, 6.05.

(2*S,3*S**)-Ethyl 3-Amino-*N*,*N*′-bis(diphenylmethylene)-aspartate (3c-I).** Method B (^{t}BuLi, THF) (90%): mp 134−135 °C (ethyl acetate−MeOH); IR ($CHCl_3$) 1670, 1640, 1600 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20 (6H, t, ^3J = 7 Hz), 4.10 (4H, q, ^3J = 7 Hz), 4.95 (2H, s), 7.20−7.62 (20H, m); ^{13}C (75.5 MHz, $CDCl_3$) δ 14.1, 61.1, 67.9, 127.8, 127.9, 139.0, 139.4, 170.1, 171.9; MS 533 (M+1), 459, 351, 266, 193. Anal. Calcd

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for $C_{34}H_{32}N_2O_4$: C, 76.67; H, 6.06; N, 5.26. Found: C, 76.56; H, 6.15; N, 5.31.

(2*S*,3*S*)-8-Phenylmenthyl 3-Amino-*N*,*N*′-bis[bis(methylthio)methylene]aspartate (3d-I). Method A (THF) (40%) $[\alpha]_D$ +30 (*c* = 5, $CHCl_3$); IR ($CHCl_3$) 1730, 1680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.62−2.10 (34H, m), 2.28 (6H, s), 2.60 (6H, s), 4.62 (2H, s), 4.79 (2H, td, $^3J_{aa}$ = 11 Hz, $^3J_{ae}$ = 5 Hz), 7.15 - 7.32 (10H, m); ^{13}C (75.5 MHz, $CDCl_3$) δ 15.4, 16.1, 22.3, 23.4, 28.0, 31.7, 32.5, 34.9, 41.1, 41.6, 51.2, 68.0, 125.8, 126.5, 128.6, 151.0, 166.1, 169.0. Anal. Calcd for $C_{46}H_{62}N_2O_4S_4$: C, 64.08; H, 7.94; N, 3.56. Found: C, 64.25; H, 8.06; N, 3.44.

(2*S*,3*R*)-8-Phenylmenthyl 3-Amino-*N*,*N*′-bis[bis(methylthio)methylene]aspartate (3d-II). Method A (THF) (50%): $[\alpha]_D$ −16 (*c* = 5, $CHCl_3$) mp 133−135 °C (hexane); IR ($CHCl_3$) 1730, 1680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.62−2.10 (34H, m), 2.28 (6H, s), 2.51 (6H,s), 4.80 (2H, td, $^3J_{aa}$ = 11 Hz, $^3J_{ae}$ = 5 Hz), 5.12 (2H, s), 7.18−7.60 (10H, m); ^{13}C (75.5 MHz, $CDCl_3$) δ 15.4, 16.0, 22.2, 23.1, 27.8, 31.7, 32.4, 34.8, 41.1, 41.6, 51.1, 68.0, 125.7, 126.3, 128.4, 150.7, 165.3, 168.9. Anal. Calcd for $C_{46}H_{62}N_2O_4S_4$: C, 64.08; H, 7.94; N, 3.56. Found: C, 63.99; H, 7.88; N, 3.45.

General Procedure for the Deprotection of the Iminodithiocarbonate and Diphenylmethylene Groups. Synthesis of 4. HCl was bubbled for 15 min into a solution of **3a**−**c** (0.5 mmol) in anhydrous MeOH (4.0 mL). The mixture was stirred at rt for 24 h (**3a,b**) or 20 min (**3c**). The solvent was removed under reduced pressure, the remaining solid was dissolved in anhydrous CH_2Cl_2 (4.0 mL), and *N*,*N*-(dimethylamino)pyridine (DMAP, 1.0 mmol, 122 mg) and Boc_2O (1.5 mmol, 325 mg) were successively added. The reaction mixture was stirred at rt for 24 h. The solid was filtered and washed with CH_2Cl_2 (3 × 4 mL). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel eluting with a mixture of hexane−ethyl acetate 80:20.

(2*S,3*S**)-Methyl 3-amino-*N*,*N*′-bis(*tert*-butoxycarbonyl)aspartate (4a-I):** 80%; IR ($CHCl_3$) 1710, 1680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.38 (18H, s), 3.74 (6H, s), 4.77 (2H, d, ^3J = 8 Hz), 5.39 (2H, bd, *J* = 5 Hz); ^{13}C (75.5 MHz, $CDCl_3$) δ 28.1, 53.0, 55.3, 80.4, 154.8, 170.0. Anal. Calcd for $C_{16}H_{28}N_2O_8$: C, 51.06; H, 7.80; N, 7.44. Found: C, 51.35; H, 7.75; N, 7.36.

(2*S,3*R**)-Methyl 3-amino-*N*,*N*′-bis(*tert*-butoxycarbonyl)aspartate (4a-II):** 80%; IR ($CHCl_3$) 1710, 1680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.46 (18H, s), 3.77 (6H, s), 4.86 (2H, δ, ^3J = 6 Hz), 5.48 (2H, bs); ^{13}C (75.5 MHz, $CDCl_3$) δ 28.2, 52.8, 55.8, 80.5, 155.6, 169.7. Anal. Calcd for $C_{16}H_{28}N_2O_8$: C, 51.06; H, 7.80; N, 7.44. Found: C, 51.22; H, 7.99; N, 7.63.

(2*S,3*S**)-Ethyl 3-amino-*N*,*N*′-bis(*tert*-butoxycarbonyl)aspartate (4b-I):** 90%; IR ($CHCl_3$) 1720, 1680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 (6H, t, ^3J = 7 Hz), 1.45 (18H, s), 4.22 (4H, q, ^3J = 7 Hz), 4.75 (2H, bd, *J* = 8 Hz), 5.35 (2H, bd, *J* = 5Hz); ^{13}C (75.5 MHz, $CDCl_3$) δ 14.2, 28.3, 55.5, 62.4, 80.4, 154.8, 170.0. Anal. Calcd for $C_{18}H_{32}N_2O_8$: C, 53.45; H, 7.97; N, 6.93. Found: C, 53.56; H, 8.03; N, 7.11.

(2*S,3*R**)-Ethyl 3-amino-*N*,*N*′-bis(*tert*-butoxycarbonyl)aspartate (4b-II):** 80%: IR ($CHCl_3$) 1720, 1680 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.30 (6H, t, ^3J = 7 Hz), 1.45 (18H, s), 4.22 (4H, q, ^3J = 7 Hz), 4.85 (2H, δ, *J* = 6 Hz), 5.35 (2H, bs); ^{13}C (75.5 MHz, $CDCl_3$) δ 14.2, 28.3, 55.5, 62.4, 80.4, 154.8, 170.0. Anal. Calcd for $C_{18}H_{32}N_2O_8$: C, 53.45; H, 7.97; N, 6.93. Found: C, 53.34; H, 7.88; N, 7.17.

General Procedure for the Hydrolysis of Compounds 3d. Synthesis of 5. To a well-stirred solution of **3d** (0.86 mmol) in TFA (1.44 mmol) a solution of 6 M HCl (2.88 mL) was added, and the mixture was heated at reflux for 18 h. After cooling to rt, H_2O (4 mL) was added, and the mixture extracted with $CHCl_3$ (2 × 6 mL). The aqueous phase was evaporated to dryness under reduced pressure (40 °C bath), and the resulting amorphous solid was purified on an ion-exchange column (10% pyridine−water).

(2*S*,3*S*)-3-Aminoaspartic acid 5-I: 75%; $[\alpha]_D$ −57 (*c* = 1.5, 5% HCl), lit.[13] −59 (*c* = 2, 5% HCl). Anal. Calcd for $C_4H_8N_2O_4$: C, 32.44; H, 5.44; N, 18.91. Found: C, 32.61; H, 5.62; N, 19.10.

(2*S*,3*R*)-3-Aminoaspartic acid (5-II): 75%; $[\alpha]_D$ +0.1 (*c* = 1, 5% HCl). Anal. Calcd for $C_4H_8N_2O_4$: C, 32.44; H, 5.44; N, 18.91. Found: C, 32.59; H, 5.38; N, 18.88.

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