Amino Acids. 8.[1] A Novel Synthesis of γ-Carboxy-L-glutamic Acid from L-5-Oxoproline Esters

Franz Effenberger,* Wolfgang Müller,[2a] Roland Keller,[2b] Wolfgang Wild,[2c] and Thomas Ziegler

Institute for Organic Chemistry, University of Stuttgart, Pfaffenwaldring 55, D-7000 Stuttgart 80, Federal Republic of Germany

Received January 26, 1990

N-Alkyl-L-5-oxoproline esters L-**5** react with phosgene to form primarily the α-chloro enamines **6**, which then react further to give the 4-carboxylated compounds **7**. Solvolysis of the latter with an alcohol furnishes the alkyl *N*-alkyl-4-(alkoxycarbonyl)-L-5-oxoprolinates 2L,4DL-**8** in good yields. The dibenzyl *N*-benzhydryl ester 2L,4L-**8c** can be converted simply to γ-carboxyglutamic acid (L-Gla) by way of the *N*-Boc-protected dibenzyl ester 2L,4DL-**10**.

Introduction

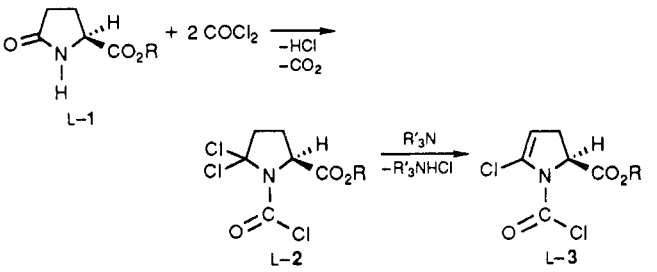
In a previous paper,[1] we have reported on a simple synthesis of L-proline starting from the L-5-oxoprolinates L-**1** (Scheme I). In this process, the first isolable compounds obtained from the reaction of the esters L-**1** with phosgene are the dichloro derivatives L-**2** from which, by cleavage of HCl with a tertiary amine, the products L-**3** are accessible.[1]

It thus seemed possible that compounds L-**3** could react with electrophiles as α-chloro enamines at the β-position with retention of chirality of the molecule. Carboxylation of L-**3** would then, for example, open up a simple access to γ-carboxy-L-glutamic acid (L-Gla), a compound that was first detected in proteins in 1974.[3]

Shortly after the discovery of L-Gla, numerous syntheses of racemic DL-Gla were published.[4] Optically pure L-Gla was obtained for the first time by Schwyzer et al.[5] through diastereomeric separation of the quinine and ephedrine salts of DL-Gla. In addition to further methods for this resolution, optically induced reactions for the preparation of L-Gla were also developed.[6] The preparation of L-Gla starting from derivatives of L-Glu was described by four groups: by Danishefsky et al.[7] from Z-protected benzyl pyroglutamate, by Zee-Cheng and Olson[8a] and Baldwin et al.[8b] by practically racemization-free carboxylation of the lithium salt of dibenzyl *N*-(triphenylmethyl)glutamate, and by Tanaka et al.[9] from an L-prolinol derivative.

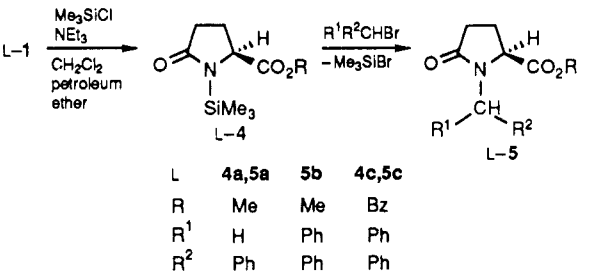
Our attempts to bring about reaction of L-**3** in the β-position by treatment with excess phosgene were unsuccessful,[1] although such a reaction was to be expected on the basis of literature data. For example, N,N-disubstituted carboxamides react with excess phosgene to furnish α-chloro-β-(chlorocarbonyl) enamines via α-chloro enamine intermediates[10] while *N*-(methoxycarbonyl)-substituted enamines can be acylated at the β-position even under mild conditions.[11] Apparently, the nucleophilicity of the β-position in compounds L-**3** is weakened by the strong chlorocarbonyl acceptor group at the nitrogen atom to such an extent that carboxylation by phosgene is no longer possible. Hence, we attempted to replace the *N*-(chlorocarbonyl) substitutent in L-**3** by donor substituents such as, for example, alkyl groups in order to increase the reactivity of the α-chloro enamines so that carboxylation at the β-position by phosgene would become possible.

Scheme I[a]



[a] R: **a** = Me; **b** = $CH_2C_6H_5$ = Bz.

Scheme II



L	4a,5a	5b	4c,5c
R	Me	Me	Bz
R^1	H	Ph	Ph
R^2	Ph	Ph	Ph

Discussion

Preparation of *N*-Alkyl-L-5-oxoproline Esters L-5. The N-substituents of the *N*-alkyl-L-5-oxoprolinates L-**5** were selected with regard to their stabilities toward acids so that, on the one hand, they would not be cleaved by the hydrogen chloride formed during the phosgenation or

(1) For part 7, see: Drauz, K.; Kleemann, A.; Martens, J.; Scherberich, P.; Effenberger, F. *J. Org. Chem.* **1986**, *51*, 3494.

(2) (a) Müller, W. Diplomarbeit, Univ. Stuttgart, 1981. (b) Keller, R. Zulassungsarbeit, Univ. Stuttgart, 1980. (c) Wild, W. Forschungspraktikum, Univ. Stuttgart, 1988.

(3) (a) Stenflo, J.; Fernlund, P. W.; Roepstorff, P. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 2730. (b) Nelsestuen, G. L.; Zytkovicz, T. H.; Howard, J. B. *J. Biol. Chem.* **1974**, *249*, 6377. (c) Magnusson, S.; Sottrup-Jensen, L.; Ellabac Petersen, T.; Morris, H. R.; Dell, A. *FEBS Lett.* **1974**, *44*, 189. (d) Gray, A. L.; Koke, R. A.; Dearfield, D. W., II; Hiskey, R. G. *J. Org. Chem.* **1985**, *50*, 2189. (e) Kasei, T.; Larsen, P. O. *Prog. Chem. Org. Prod.* **1980**, *39*, 173; *Chem. Abstr.* **1980**, *93*, 72221r.

(4) (a) Morris, H. R.; Thompson, M. R.; Dell, A. *Biochem. Biophys. Res. Commun.* **1975**, *62*, 856. (b) Boggs, N. T., III; Gawley, R. E.; Koehler, K. A.; Hiskey, R. G. *J. Org. Chem.* **1975**, *40*, 2850. (c) Bajusz, S.; Juhasz, A. *Acta Chim. Acad. Sci. Hung.* **1976**, *88*, 161. (d) Weinstein, B.; Watrin, K. G; Loie, H. J.; Marrin, J. C. *J. Org. Chem.* **1976**, *41*, 3636. (e) Juhasz, A.; Bajusz, S. *Int. J. Pap. Protein Res.* **1980**, *15*, 154.

(5) Märki, W.; Opplinger, M.; Thanei, P.; Schwyzer, R. *Helv. Chim. Acta* **1977**, *60*, 798.

(6) (a) Boggs, N. T., III; Goldsmith, B.; Gawley, R. E.; Koehler, K. A.; Hiskey, R. G. *J. Org. Chem.* **1970**, *44*, 2262. (b) Cerovsky, V.; Jost, K. *Collect. Czech. Chem. Commun.* **1984**, *49*, 2562.

(7) Danishefsky, S.; Berman, E.; Clizbe, L. A.; Hirama, M. *J. Am. Chem. Soc.* **1979**, *101*, 4385.

(8) (a) Zee-Cheng, R. K. Y.; Olson, R. E. *Biochem. Biophys. Res. Commun.* **1980**, *94*, 1128. (b) Baldwin, J. E.; North, M.; Flinn, A.; Moloney, M. G. *J. Chem. Soc., Chem. Commun.* **1988**, *12*, 828.

(9) Tanaka, K.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3879.

(10) (a) Buyle, R.; Viehe, H. G. *Tetrahedron* **1968**, *24*, 4217; **1969**, *25*, 3447. (b) Ghosez, L.; Marchand-Brynaert, J. *Adv. Org. Chem.* 9, 421, J. Wiley, N. Y., London, Sydney, Toronto 1976.

(11) Shono, R.; Matsumura, Y.; Tsubara, K.; Suginara, Y. *Tetrahedron Lett.* **1982**, 1201.

0022-3263/90/1955-3064$02.50/0

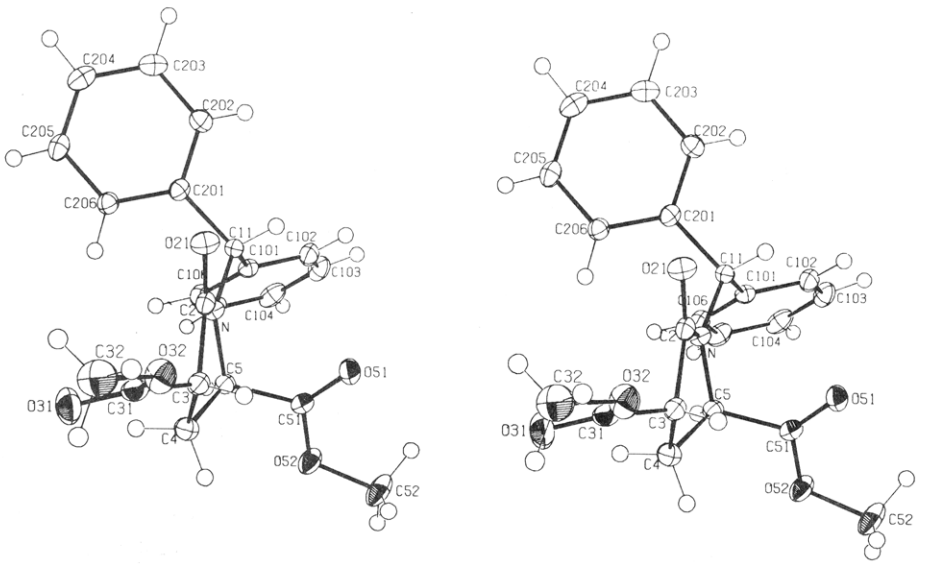


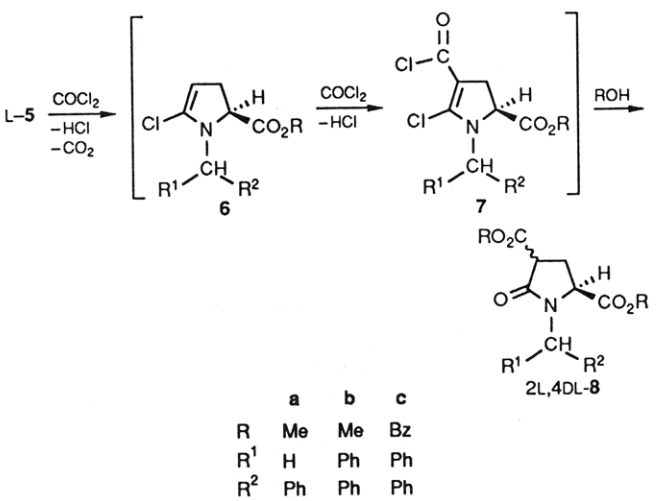
Figure 1. Stereoscopic projection of 2L,4D-**8b**.

elimination and, on the other hand, they could be removed without racemization taking place. We considered the *N*-benzyl- and *N*-benzhydryl substituents to be most suitable for this purpose on the basis of their solvolysis rates determined in trifluoroacetic acid by Weygand et al.[12] Since previously performed N-alkylations of the alkali metal salts of L-**1** were accompanied by complete racemization,[13a,b] we have prepared the *N*-benzyl- and *N*-benzhydrylprolinates **5** by way of the silyl derivatives **4**.[13c] Protodesilylation of L-**4** occurred as a side reaction, especially in reactions with benzhydryl halides, during the alkyldesilylation reaction performed with neat substance at 120–130 °C. This side reaction is apparently a result of the well-known hydrogen halide elimination on heating benzhydryl halides. By means of the rapid removal of HBr (passage of dry nitrogen over the reaction mixture or working under vacuum), we were able to suppress the protodesilylation almost completely and thus obtained the optically pure 1-benzyl- (L-**5a,b**) or 1-benzhydryl-3-oxoprolinates L-**5c**[14] in yields between 60 and 80% from L-**4** (Scheme II).

Phosgenation of *N*-Alkyl-Substituted L-5-Oxoprolinates L-5. In the course of reactions of L-**5** with phosgene under varying conditions, it was found that a reaction temperature of about 40 °C, a reaction time of <30 h, and dichloromethane, benzene, or toluene as solvent provided the best results; however, it was not possible to isolate the α-chloro enamines **6** or the acyl chlorides **7**. We therefore subjected the reaction mixtures to solvolysis with the respective alcohol and thus obtained the 1-benzyl- or 1-benzhydryl-4-(alkoxycarbonyl)-5-oxoprolinates **8** in good yields (Scheme III).

Since compounds **8** possess two asymmetric centers (at C-2 and C-4), in principle, four stereoisomers could be formed in the reactions performed. *To study the question of racemization, we carried out the* ***5c*** *→* ***8c*** *transformation using racemic starting material. Analysis of this reaction by analytical high performance liquid chromatography (HPLC) using a chiral stationary phase demonstrated that the enantiomeric products could be distinguished, that all four products are produced in the reaction of rac-****5c****, and that reaction of* L-***5c*** *gives only two diastereomers.* This result permits the assumption that the L configuration at C-2 is retained in all the steps **5** through **8** and **9c**, whereas both D and L configurations may be present at C-4.

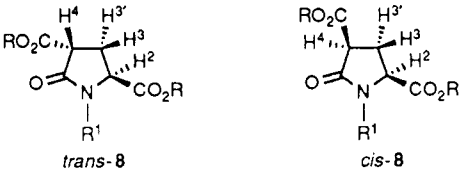
Scheme III



Determination of the Configurations of the N-Substituted 4-(Alkoxycarbonyl)-5-oxoproline Alkyl Esters 8. For the determination of the configurations of compounds **8** by X-ray crystallographic analysis, we selected **8b** that was obtained as crystals in high yield (see Experimental Section). The experimental results show that the investigated compound is unambigously the trans isomer 2L,4D-**8b** (Figure 1). A comparison of the ^{1}H NMR spectral data of this product with those of the cis/trans isomers of **8a** and **8c** (Table I) allows an unequivocal assignment of their configurations. On the basis of the characteristically differing coupling constants, it is possible by means of the *Karplus* equation to simulate the changes of the conformation with molecular models rather well. The pyrrolidinone ring in **8b**—as a consequence of the sterically demanding *N*-benzhydryl moiety—exhibits a pronounced envelope configuration, whereas in compound **8a** with the smaller *N*-benzyl substituent the ring is less markedly folded. The nature of the N-protecting group also influences the diastereomeric ratios of compounds **8**.

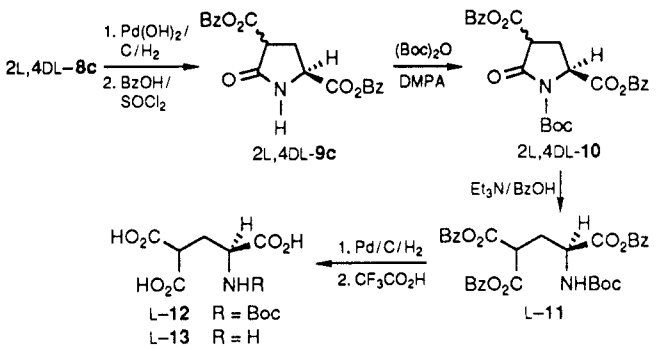
(12) Weygand, F.; Steglich, W.; Bjarnason, J.; Akhtar, R.; Chytil, N. *Chem. Ber.* **1968**, *101*, 3623.
(13) (a) Campaigne, E.; Matthews, D. P. *J. Heterocycl. Chem.* **1975**, *12*, 391. (b) Hardegger, E.; Ott, H. *Helv. Chim. Acta* **1955**, *38*, 312. (c) Burkard, U.; Walther, I.; Effenberger, F. *Liebigs Ann. Chem.* **1986**, 1030.
(14) Effenberger, F.; Müller, W.; Isak, H. *Chem. Ber.* **1987**, *120*, 45.

Table I. ^{1}H NMR Spectral Data for Isomeric *N*-Alkyl-4-(alkoxycarbonyl)-2L,4D(L)-5-oxoproline Alkyl Esters 8 [δ ppm, *J* (Hz)]



	R	R^1	2-H (dd)	3-H (ddd)	3'-H (ddd)	4-H (dd)	$J_{H,H}$ $J_{2,3}$	$J_{2,3'}$	$J_{3,4}$	$J_{3',4}$	$J_{3,3'}$
2L,4D-**8a** (trans)	Me	Bz	4.065	2.294	2.661	3.671 (ddd)	2.76	9.20	8.99	9.16	-13.29
2L,4L-**8a** (cis)			3.953	2.595	2.483	3.486	4.09	9.36	4.61	9.62	-13.59
2L,4D-**8b** (trans)	Me	$CHPh_2$	4.275	2.223	2.887	3.808	0.66	9.11	8.38	11.21	-13.33
2L,4L-**8b** (cis)			4.193	2.637	2.651	3.558	2.42	9.14	3.21	10.15	-13.67
2L,4D-**8c** (trans)	Bz	$CHPh_2$	4.284	2.205	2.873	3.822	>0.6	9.20	8.33	11.12	-13.27
2L,4L-**8c** (cis)			4.21 (m)	2.65 (m, 2 H)		3.56 (m)	not definable				

Scheme IV[a]



[a] Boc = $CO_2C(CH_3)_3$.

In the cases of **8b** and **8c**, the energy difference between the two isomers is greater as a result of the steric hindrance of the benzhydryl group than in the *N*-benzyl-protected compound **8a**. This leads to higher proportions of the more stable trans isomers of **8b** and **8c** (see Experimental Section).

Conversion of the N-Substituted 4-(Alkoxycarbonyl)-5-oxoproline Alkyl Esters 8 into L-γ-Carboxyglutamic Acid (L-Gla). For the conversion of the compounds 2L,4DL-8 into L-Gla, it is necessary to remove the N-protecting group and to cleave the lactam ring hydrolytically. Since L-Gla undergoes decarboxylation relatively easily,[3] it was expected that, under the reaction conditions required for the saponification of methyl esters, a decarboxylation of the formed L-Gla to L-Glu would take place. In contrast, the mild conditions necessary for the hydrogenolysis of benzhydryl esters would be expected to minimize the decarboxylation of the L-Gla. Hence, we have employed 2L,4DL-**8c** for the preparation of L-Gla and effected cleavage of the benzhydryl group in 2L,4DL-**8c** by means of catalytic hydrogenation with $Pd(OH)_2/C$ in acetic acid. In this case, however, simultaneous hydrogenolysis of the benzyl ester groups also occurs; subsequent treatment of the crude product with benzyl alcohol/thionyl chloride in dimethylformamide gave rise to the desired benzyl 4-(benzyloxycarbonyl)-5-oxoprolinate (2L,4DL-**9c**) in very good yield (84%, based on 2L,4DL-**8c**) (Scheme IV).

Subsequent introduction of the *tert*-butoxycarbonyl (Boc) substituent as N-protective group according to the process reported by Grehn and Ragnarsson[15] furnished benzyl 1-(*tert*-butoxycarbonyl)-4-(benzyloxycarbonyl)-L-5-oxoprolinate (2L,4DL-**10**) in 72% yield. This product had previously been obtained by Tanaka et al.[9] The title compound L-γ-carboxyglutamic acid (L-**13**) was prepared in 49% yield (based on 2L,4DL-**11**) by simple reaction of 2L,4DL-**10** with benzyl alcohol and triethylamine to effect ring opening and formation of the tribenzyl ester L-**11**; hydrogenolysis of the latter in the presence of Pd/C gave *N*-Boc-L-γ-carboxyglutamic acid (L-**12**). Finally, cleavage of the N-protective group of L-**12** with trifluoroacetic acid according to ref 9 furnished the desired product L-**13**.

The reactions described in this paper provide simple access to the important amino acid L-Gla starting from the moderately priced L-pyroglutamic acid.

Experimental Section

Preparative column chromatography was done with columns of different dimensions, packed with silica gel A 650, S 0.032–0.63 mm (Riedel-de Haen). Preparative medium performance liquid chromatography (MPLC) was performed with a Glatz system[16] by using silica gel column type C (25 × 2.4 cm) packed with silica gel 0.015–0.025 mm (E. Merck), 6300 theoretical plates. Analytical high performance liquid chromatography (HPLC) was performed with a LCD Milton Roy system with two Constametric III pumps and a UV/vis detector (Uvikon 720 LC), using a Bakerbond Chiral DNBPh column (4.6 × 250 mm, 5 μm) and *n*-hexane/2-propanol (60:40) as the mobile phase and a flow rate of 1.5 mL/min. In all cases, crude reaction products were used for HPLC, and the separation of the stereoisomers was confirmed by coinjection of the corresponding racemic compounds. ^{1}H NMR spectra were obtained at 60, 80, or 300 MHz.

Methyl 1-Benzyl-L-5-oxoprolinate (L-5a). A mixture of 19.0 g (88 mmol) of L-**4a**[1] and 15.1 g (88 mmol) of benzyl bromide was stirred and heated at 130 °C under dry nitrogen for 12 h, removing the resulting bromotrimethylsilane by distillation. The yield of L-**5a** after fractional distillation in vacuo was 16.6 g (81%): bp 125 °C (10 Torr); $[\alpha]^{20}_D = -7.3°$ (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.97–2.63 (m, 4 H, $(CH_2)_2$), 3.73 (s, 3 H, OCH_3), 2.97–4.13 (m, 1 H, 2-H), 4.04 and 5.04 (d, d, AB, J_{AB} = 15 Hz, 2 H, CH_2Ph), 7.33 (s, 5 H, Ph). Racemic **5a** was previously obtained.[13a]

Methyl 1-Benzhydryl-L-5-oxoprolinate (L-5b). As described above, 43.7 g (203 mmol) of L-**4a**[1] and 50.2 g (203 mmol) of benzhydryl bromide were stirred for 50 h at 130 °C in vacuo (12 Torr). After standing for 12 h at room temperature, the orange crystalline product was recrystallized in a 1/1 mixture of *n*-hexane/ethyl acetate, and the resulting crystalline product was washed with ice-cold *n*-hexane and dried at 0.001 Torr to yield 39.5 g. The mother liquor was evaporated and the crystalline material was recrystallized from 100 mL of *n*-hexane and 70 mL of ethyl acetate. The total yield of L-**5b** was 44.9 g (72%): mp 139 °C; $[\alpha]^{20}_D = +216.2°$ (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.80–2.83 (m, 4 H, $(CH_2)_2$), 3.18 (s, 3 H, OCH_3), 4.07–4.30 (m, 1 H, 2-H), 6.53 (s, 1 H, $CHPh_2$), 7.20 (m, 10 H, 2 Ph). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.98; H, 6.27; N, 4.38.

(15) Grehn, L.; Ragnarsson, U. *Angew. Chem.* **1984**, *96*, 291; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296.

(16) Glatz, B. Dissertation, University Stuttgart, 1976.

Alkyl 1-Benzyl- and 1-Benzhydryl-4-(alkoxycarbonyl)-5-oxoprolinates 8. General Method. An excess of phosgene was condensed into a solution of L-**5** in dichloromethane and the mixture was stirred at room temperature for 18–24 h using a reflux condenser, cooled to −30 °C to avoid the evaporation of phosgene. After removal of excess phosgene in vacuo (12 Torr), the crude product was treated with the corresponding alcohol and stirred for 12 h at 45–50 °C. The volatile components were distilled off—at last at 0.001 Torr—and the residue was treated with diethyl ether (if necessary) to cause crystallization. The crystals were filtered, dried at 0.001 Torr, and purified first over a silica gel column and then via MPLC with petroleum ether/ethyl acetate (7:3) as eluent.

Methyl 1-benzyl-4-(methoxycarbonyl)-2L,4DL-5-oxoprolinate (2L,4DL-8a) was prepared as described above from L-**5a** (1.7 g, 5 mmol) in dichloromethane (5 mL), phosgene, and absolute methanol (5 mL). After removal of the volatile components, half of the crude product was cleaned in five portions via MPLC. By this method 435 mg (60%) of 2L,4D-**8a** (*trans*-**8a**) and 193 mg (26%) of 2L,4L-**8a** (*cis*-**8a**) (yield altogether 86%) accumulated as oils; diastereomeric proportion trans/cis = 7:3 (according to ^{1}H NMR spectra): ^{1}H NMR ($CDCl_3$) for *trans*-**8a** δ 3.65 and 3.81 (each s, 3 H, OCH_3), 4.10 and 4.96 (each d, J = 14.88 Hz, 1 H, CH_2Ph), 7.18–7.36 (m, 5 H, Ph), signals for 2-, 3-, 3′-, and 4-H, see Table I; ^{1}H NMR ($CDCl_3$) for *cis*-**8a** δ 3.75 and 3.79 (each s, 3 H, OCH_3), 4.09 and 5.16 (each d, J = 14.8 Hz, 1 H, CH_2Ph), 7.18–7.36 (m, 5 H, Ph), signals for 2-, 3-, 3′-, and 4-H, see Table I. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found for *trans*-**8a**: C, 61.63; H, 5.80; N, 4.55. Found for *cis*-**8a**: C, 61.44; H, 5.72; N, 4.86.

Methyl 1-benzhydryl-4-(methoxycarbonyl)-2L,4DL-5-oxoprolinate (2L,4DL-8b) was prepared as described above for 2L,4DL-**8a** from L-**5b** (1.5 g, 5 mmol) in dichloromethane (5 mL), phosgene, and absolute methanol (5 mL); 10% of the crude product [Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.78; N, 3.81. Found: C, 68.53; H, 5.78; N, 3.81] was cleaned in four portions via MPLC to yield 146 mg (80%) of 2L,4D-**8b** (*trans*-**8b**), mp 113–115 °C, and 26 mg (14%) of 2L,4L-**8b** (*cis*-**8b**) as an oily crystalline product (overall yield 94% based on L-**5b**). Diastereomeric proportion trans/cis = 87:13 (according to ^{1}H NMR spectra): ^{1}H NMR ($CDCl_3$) for *trans*-**8b** δ 3.23 and 3.82 (each s, 3 H, OCH_3), 6.45 (s, 1 H, $CHPh_2$), 7.11–7.39 (m, 10 H, 2 Ph), signals for 2-, 3-, 3′-, and 4-H, see Table I; ^{1}H NMR ($CDCl_3$) for *cis*-**8b** δ 3.27 and 3.79 (each s, 3 H, OCH_3), 6.452 (s, 1 H, $CHPh_2$), 7.09–7.37 (m, 10 H, 2 Ph), signals for 2-, 3-, 3′-, and 4-H, see Table I.

Benzyl 1-benzhydryl-4-(benzyloxycarbonyl)-2L,4DL-5-oxoprolinate (2L,4DL-8c) was prepared as described above for 2L,4DL-**8a** from L-**5c**[14] (18.5 g, 80 mmol), dichloromethane (70 mL), phosgene, and benzyl alcohol (70 mL). The light brown colored and oily product [Anal. Calcd for $C_{33}H_{29}NO_5$: C, 76.28; H, 5.63; N, 2.70. Found: C, 76.25; H, 5.76; N, 2.63] was cleaned in four portions via MPLC and petroleum ether/ethyl acetate (8:2) as eluent. Thus 15.4 g (62%) of 2L,4D-**8c** (*trans*-**8c**) and 2.7 g (11%) of 2L,4L-**8c** (*cis*-**8c**) (total yield 73%) were collected as oils. Diastereomeric proportions trans/cis = 85:15 (according to ^{1}H NMR spectra): HPLC retention time for *trans*-**8c** 5.39 min, for *cis*-**8c** 6.46 min; ^{1}H NMR ($CDCl_3$) for *trans*-**8c** δ 4.58 and 5.23 (each s, 2 H, CH_2CO_2), 6.55 (s, 1 H, $CHPh_2$), 7.80–7.44 (m, 20 H, 4 Ph), signals for 2-, 3-, 3′-, and 4-H, see Table I; ^{1}H NMR ($CDCl_3$) for *cis*-**8c** δ 4.65 (s, 2 H, CH_2CO_2), 5.05–5.17 (m, 2 H, CH_2CO_2), 6.41 (s, 1 H, $CHPh_2$), 7.08–7.44 (m, 20 H, 4 Ph), signals for 2-, 3-, 3′-, and 4-H, see Table I.

Methyl 4-(Methoxycarbonyl)-2L,4DL-5-oxoprolinate (2L,4DL-9b). Into a heated and nitrogen-purged apparatus was added 430 mL of trifluoroacetic acid to 23.5 g (63.9 mmol) of 2L,4DL-**8b**, and the mixture was stirred for 40 h at 70 °C. The initial yellow solution quickly darkened. The superfluous trifluoroacetic acid was subsequently distilled off at 12 Torr, and the black highly viscous residue was dried for 4 h at 60 °C at 0.001 Torr, dissolved in dichloromethane, and chromatographed over a silica gel column with petroleum ether/ethyl acetate (9:1) as eluent to yield 11.6 g (90%) of 2L,4DL-**9b** as a highly viscous yellowish oil: $[\alpha]^{20}_D$ = +7.23° (c = 1, CH_2Cl_2). Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.54; H, 5.41; N, 6.74.

Benzyl 4-(Benzyloxycarbonyl)-2L,4DL-5-oxoprolinate (2L,4DL-9c). The solution of 6.3 g (12 mmol) of 2L,4DL-**8c** in 150 mL of acetic acid was hydrogenated with 0.63 g of $Pd(OH)_2$ (20% Pd) on carbon (H_2 pressure = 760 Torr) for 85 h at 40 °C. After filtration the solvent was distilled off. The resulting colorless highly viscous oil [4-(hydroxycarbonyl)-2L,4DL-5-oxoproline as crude product; ^{1}H NMR (d_6-DMSO) δ 2.07–2.83 (m, 2 H, CH_2Ph), 3.13–3.48 (m, 1 H, 4-H), 4.00–4.29 (m, 1 H, 2-H), 8.33 and 8.36 (s, 1 H, NH)] was dissolved in 31.3 g (0.29 mol) of benzyl alcohol and cooled with ice, and 0.25 mL of dimethylformamide was added. The solution was treated dropwise with 5.9 g (49 mmol) of thionyl chloride and stirred for 15 h at room temperature. The volatile components were distilled off, and the crude product was chromatographed over silica gel with petroleum ether/ethyl acetate (2:1) and then with petroleum ether/ethyl acetate (1:1). The resulting yellowish product was dried at 50 °C (0.001 Torr), yielding 3.6 g (84% based on 2L,4DL-**8c**): HPLC retention time for *trans*-**9c** 7.13 min, for *cis*-**9c** 10.01 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35–2.44, 2.64–2.70 and 2.76–2.86 (m, 2 H, CH_2), 3.42–3.53 (m, 1 H, 4-H), 4.22–4.25 and 4.32–4.37 (m, 1 H, 2-H), 5.07–5.25 (m, 4 H, 2 CH_2Ph), 6.83 and 6.9 (s, 1 H, NH), 7.25–7.40 (m, 10 H, 2 Ph). Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.89; H, 5.52; N, 3.87.

Benzyl 1-(*tert*-butoxycarbonyl)-4-(benzyloxycarbonyl)-2L,4DL-5-oxoprolinate (2L,4DL-10) was prepared by following the procedure described in ref 15 from 1.4 g (4 mmol) of 2L,4DL-**9c** in 10 mL of acetonitrile, 0.9 g (4 mmol) of di-*tert*-butyl dicarbonate [$(Boc)_2O$], and 25 mg (0.2 mmol) of (dimethylamino)pyridine (DMAP). After 1 h of stirring at room temperature, the mixture was evaporated and the yellow residue chromatographed over silica gel with petroleum ether/ethyl acetate (7:3) as eluent. The second fraction was collected to yield 1.3 g (72%) as a colorless oil: $[\alpha]^{25}_D$ = −12.2° (c = 0.3, $CHCl_3$), lit.[9] $[\alpha]^{25}_D$ = −8.7° (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) identical with values in ref 9. Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.37; H, 6.21; N, 2.92.

α,γ,γ-Tribenzyl *N*-*tert*-butoxycarbonyl-L-γ-carboxyglutamate (L-**11**) was prepared as described previously in ref 9 from 1.0 g (2 mmol) of 2L,4DL-**10** with 15 mL of benzyl alcohol and 130 μL of triethylamine. The crude product was purified by column chromatography on SiO_2 with petroleum ether/ethyl acetate (7:3), yielding 0.6 g (50%) of L-**11** as a yellowish oil, $[\alpha]^{25}_D$ = +6.3° (c = 1, $CHCl_3$), lit.[9] $[\alpha]^{25}_D$ = +7.5° (c = 1, $CHCl_3$).

L-γ-Carboxyglutamic Acid (L-13). L-**11** (0.3 g) dissolved in 20 mL of ethanol was hydrogenated over 0.2 g of Pd (10%) on carbon at room temperature as described in ref 9. The catalyst was removed by filtration, and the filtrate was evaporated, treated with 1 mL of dichloromethane and 0.5 mL of trifluoroacetic acid, stirred for 30 min at room temperature, diluted with 5 mL of benzene, and evaporated. The residue was triturated with ether, and the resulting colorless powder was collected by filtration, yielding 50 mg (49%), $[\alpha]^{20}_D$ = +32° (c = 0.5, 6 N HCl), lit.[9] $[\alpha]^{25}_D$ = +34.3° (c = 1, 6 N HCl).

Acknowledgment. We thank J. J. Stezowski and A. Maier for the performance of the X-ray crystallographic analysis. We gratefully acknowledge financial support of this research by the "Deutsche Forschungsgemeinschaft" and the "Fonds der Chemischen Industrie". W.M. is grateful to the Hermann-Schlosser-Stiftung for a postgraduate grant.

Supplementary Material Available: 2L,4DL-**8b** crystallographic data and tables of fractional coordinates and displacement parameters (anisotropic for C and O atoms, isotropic for H atoms) (3 pages). Ordering information is given on any current masthead page.