(30 mL) was heated at reflux for 24 h and then worked up as described above for **27** to give after flash chromatography (1:2 ether–petroleum ether) **42** (3.45 g, 91%) as an oil: IR (neat) 1735, 1550 cm^{-1}; ^1H NMR δ 1.92 (s, 3 H), 4.72 (dd, 1 H, J = 12, 3.8), 4.92 (dd, 1 H, J = 12, 9.8), 5.28 (m, 2 H), 5.36 (dd, 1 H, J = 9.8, 3.8), 7.4 (m, 5 H). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.25; H, 5.64; N, 6.05.

(2*S*)-1-Benzyl-2α-(hydroxymethyl)-4β-(1-methylethenyl)-4α-nitro-3β-pyrrolidineacetic Acid Ethyl Ester (43). A solution of **17** (1.25 g, 5 mmol) and **42** (1.25 g, 5 mmol) in EtOH (20 mL) was stirred at rt for 15 h and then processed as described above for **31** to give after flash chromatography (2:1 ether–petroleum ether) **43** (1.6 g, 88%) as a pale yellow oil: $[\alpha]^{20}_D$ −1.11° (*c* 2.19, $CHCl_3$); IR (neat) 3500–3300, 1735, 1530 cm^{-1}; ^1H NMR δ 1.28 (t, 3 H, J = 7), 1.64 (s, 3 H), 2.1 (dd, 1 H, J = 16.5, 9.7), 2.65 (bs, 1 H), 2.83 (dd, 1 H, J = 16.5, 2.4), 2.9 (m, 1 H), 3.2 (d, 1 H, J = 13), 3.43 (dd, 1 H, J = 9.7, 2.4), 3.59 (d, 1 H, J = 13), 3.75 (dd, 1 H, J = 12.4, 5.6), 3.8 (d, 1 H, J = 13.5), 4.05 (d, 1 H, J = 13.5), 4.2 (q, 2 H, J = 7) 5.15 (s, 1 H), 5.28 (s, 1 H), 7.3 (m, 5 H). Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.96; N, 7.23; N, 7.73. Found: C, 62.88; H, 7.31; N, 7.79.

[2*S*-(2α,3β,4β)]-1-Benzyl-2-(hydroxymethyl)-4-(1-methylethenyl)-3-pyrrolidineacetic Acid Ethyl Ester (44). A solution of **43** (1.81 mmol), ammonium formate (0.378 g, 6 mmol), Ph_3P (0.131 g), and $Pd(PPh_3)_4$ (0.29 g) in THF (30 mL) was heated at reflux for 48 h and then concentrated. The residue was flash chromatographed (2:1 ether–petroleum ether) to give quantitatively **44** as an oil: $[\alpha]^{20}_D$ −3.66° (*c* 0.75, $CHCl_3$); IR (neat) 3500–3300, 1730, 1650 cm^{-1}; ^1H NMR δ 1.26 (t, 3 H, J = 7), 1.69 (s, 3 H), 2.11 (dd, 1 H, J = 16, 9.5), 2.25 (dd, 1 H, J = 16, 6), 2.4–3.0 (m, 6 H), 3.5 (d, 1 H, J = 13.5), 3.6 (m, 1 H), 3.95 (d, 1 H, J = 13.5), 4.12 (q, 2 H, J = 7), 4.56 (s, 1 H), 4.81 (s, 1 H), 7.3 (m, 5 H). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.83; H, 8.62; N, 4.50.

[2*S*-(2α,3β,4β)]-1-Benzyl-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4-(1-methylethenyl)-3-pyrrolidineacetic Acid Ethyl Ester (45). A solution of **44** (0.8 g, 2.5 mmol), TBDMS-Cl (0.45 g, 3 mmol) and Et_3N (0.38 g, 3 mmol) in CH_2Cl_2 (10 mL) containing DMAP (61 mg) was stirred at rt for 15 h. The solvent was removed, and the residue was dissolved in ether–H_2O (25 mL each). The aqueous layer was extracted with ether, and the combined organic layers were washed with 1 M HCl and H_2O. After drying, the solvent was evaporated, and the residue was flash chromatographed (1:4 ether–petroleum ether) to afford **45** (0.9 g, 81%) as an oil: $[\alpha]^{2}10_D$ −27.2° (*c* 0.99, $CHCl_3$); IR (neat) 1735, 1650 cm^{-1}; ^1H NMR δ 0.045 (s, 6 H), 0.88 (s, 9 H), 1.25 (t, 3 H, J = 7), 1.7 (s, 3 H), 2.07 (dd, 1 H, J = 16, 9.4), 2.21 (dd, 1 H, J = 16, 6), 2.4–2.6 (m, 2 H), 2.62–2.72 (m, 1 H), 2.78–2.98 (m, 2 H), 3.54 (d, 2 H, J = 5.6), 3.58 (d, 1 H, J = 15), 4.08 (d, 1 H, J = 15), 4.12 (q, 2 H, J = 7), 4.56 (s, 1 H), 4.8 (s, 1 H), 7.3 (m, 5 H). Anal. Calcd for $C_{25}H_{41}NO_3Si$: C, 69.57; H, 9.58; N, 3.24. Found: C, 69.51; H, 9.48; N, 3.35.

[2*S*-(2α,3β,4β)]-1-[(1,1-Dimethylethoxy)carbonyl]-2-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-4-(1-methylethenyl)-3-pyrrolidineacetic Acid Ethyl Ester (46). To a cooled (0 °C) solution of **45** (1.07 g, 2.5 mmol) in dry 1,2-dichloroethane (10 mL) was added α-chloroethyl chloroformate (ACE-Cl) (0.27 mL, 2.5 mmol). After being stirred at 0 °C for 30 min and then refluxed for 2 h, the mixture was concentrated. The residue was dissolved in dioxane (10 mL) containing Et_3N (0.38 mL, 2.5 mmol) and $(Boc)_2O$ (0.545 g, 2.5 mmol), stirred at rt for 24 h, and then evaporated. Flash chromatography of the residue (1:4 ether–petroleum ether) afforded **46** (1 g, 90%) as an oil: $[\alpha]^{20}_D$ −33.07° (*c* 0.61, CH_2Cl_2) [lit.[7] $[\alpha]^{20}_D$ −31.8° (*c* 0.6, CH_2Cl_2)]; IR (neat) 1735, 1690, 1645, 1470, 1400 cm^{-1}; ^1H NMR δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.28 (t, 3 H, J = 7), 1.47 (s, 9 H), 1.72 (s, 3 H), 2.05–2.3 (m, 2 H), 2.83 (m, 1 H), 3.05–3.25 (m, 1 H), 3.3–3.5 (m, 2 H), 3.5–3.63 (m, 1 H), 3.2 (dd, 1 H, J = 5.4, 1.6), 4.15 (q, 2 H, J = 7), 4.66 (s, 1 H), 4.87 (s, 1 H). Anal. Calcd for $C_{23}H_{43}NO_5Si$: C, 62.60; H, 9.75; N, 3.17. Found: C, 62.55; H, 9.71; N, 3.25.

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Synthesis of (Optically Active) Sulfur-Containing Trifunctional Amino Acids by Radical Addition to (Optically Active) Unsaturated Amino Acids

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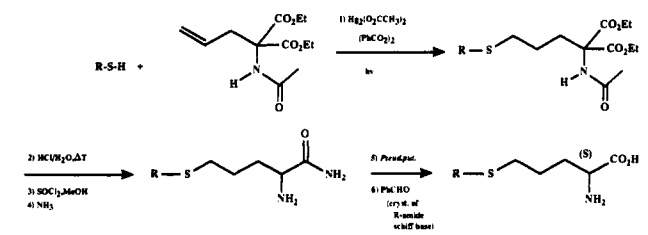
Sulfur-based radicals, generated from R–S–H-type precursors (R = alkyl, acyl) with AIBN, smoothly add to α-allylglycines protected at none, one, or both of the amino acid functions (NH_2 and/or CO_2H). Sulfur-containing trifunctional amino acids were obtained in good to excellent yields (64–100%). The solvent used for the reaction is critical. Optimal results were obtained when both the unsaturated amino acid and RSH dissolve completely in the medium (dioxane/water or methanol/water are good solvent systems). The scope of the reaction includes α-substituted α-allylglycine and derivatives as well as β-substituted β-allyl-β-amino alcohols. In the case of optically active α-allylglycine derivatives, radical addition is accompanied by a small amount of racemization, the amount depending on the type of protection and R–S–H. The products are easily optically enriched by crystallization. Addition of sulfur-based radicals to α-allylglycine is believed to be an example of a general method for synthesizing optically active trifunctional amino acids from unsaturated amino acids.

Introduction

We regard (optically active) trifunctional amino acids as versatile tools enabling medicinal chemists and agrochemists to synthesize new drugs and pesticides. The advent of rational design methods for bioactive molecules capable of a desired interaction with a selected target receptor aims at compounds acting as, e.g., a suicide inhibitor or a transition-state analog.[1] The recent revival of peptide/peptidomimetic chemistry is connected with this broad trend. Trifunctional amino acids contain not only an amino group and a carboxyl group but also a third

Scheme I



(1) See, for example: *Design of Enzyme Inhibitors as Drugs*; Sandler, M., Smith, H. J., Eds.; Oxford University Press: New York, 1989.

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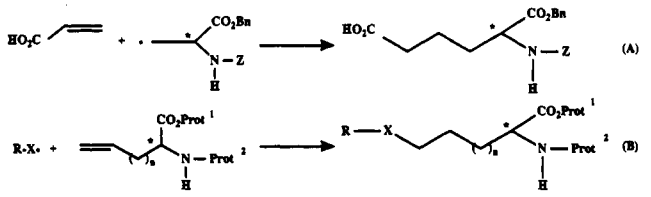
group capable of undergoing a wide variety of chemical transformations. For these reasons, simple and efficient synthetic methodology for trifunctional amino acids, including preparation in optically pure form, is believed to be of general interest.

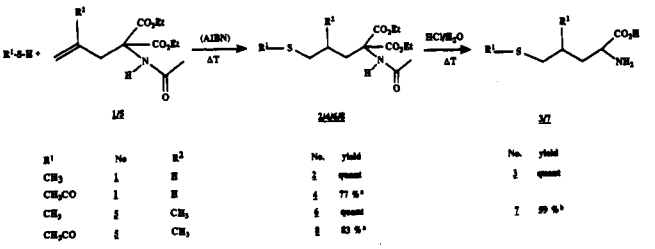
The enzymatic resolution of racemic amino acid amides with amino peptidase present in *Pseudomonas putida* has proven to be such an efficient process.[2] For example, the synthesis of L-homomethionine[3] is depicted in Scheme I (R = Me). However, each optically active amino acid requires the synthesis and resolution of a different racemic amino acid amide.

Preparation of the product with, e.g., R = Et (Scheme I), is again a six-step synthesis. Therefore, to optimize the efficiency of this methodology, development of a "common intermediate" constitutes an attractive target. This common intermediate could then be transformed into a variety of desired molecules by simple manipulations. This paper describes the use of (optically active) unsaturated amino acids as common intermediates, which can be transformed by radical addition reactions[4] of sulfur-based radicals into other trifunctional amino acids. Baldwin et al.[5] showed that addition of the radical derived from double protected 3-iodo-L-alanine to acrylic acid yields the corresponding optically pure 2-aminoadipic acid derivative (type-A addition). This result proved that this radical is configurationally stable. We reasoned that if racemization does not occur in type-A additions this might hold for type-B reactions.



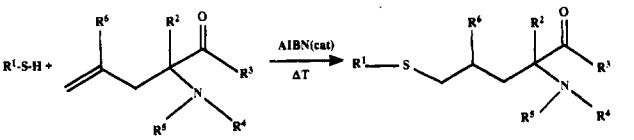
Radical-based synthesis of (un)natural amino acids is currently receiving considerable interest.[6] Some examples of recent approaches are as follows: radical addition in the side chain of acidic amino acids by decarboxylative rearrangement of *N*-hydroxy-2-thiopyridone derivatives,[6a] intermolecular[6b] or intramolecular[6c] addition reactions of

Scheme II[a]



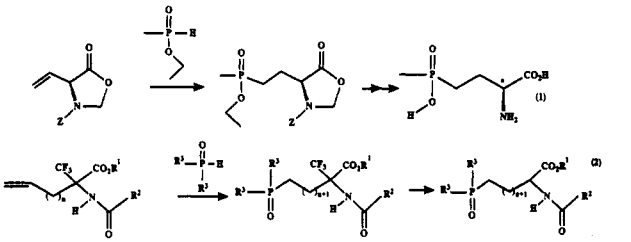
[a] Key: (a) After recrystallization. [b] After crystallization, diastereomeric ratio 79/21.

Scheme III[a]



[a] Definition of substituents in Table I.

glycidyl radicals (radical at α-position), or radical addition to suitable dehydroalanine derivatives.[6d] Most of this chemistry is very elegant, but not particularly suited for application beyond laboratory scale. One characteristic feature of all these methods is that they all use protected amino acids, requiring protection and deprotection chemistry. For instance, in two recent articles which appeared during the course of our study, phosphorus-based radicals were added to doubly protected unsaturated amino acids.[7,8] Zeiss[7] reported an elegant synthesis of enantiomerically pure phosphinothricine based on the epimerization-free radical addition of ethyl methylphosphinate to a suitable enantiomerically pure vinylglycine derivative (eq 1).



Burger et al.[8] described the radical addition of dialkylphosphine oxides to suitable racemic α-(trifluoromethyl)-α-vinylglycine (n = 0) and α-(trifluoromethyl)-α-allylglycine derivatives (n = 1, eq 2).

The aim of our study was 2-fold: to find out (a) how much protection is really essential in this type of radical chemistry and (b) to what extent radical addition is accompanied by racemization.

Results and Discussion

Earlier, we[3] used the reported conditions[9] for the addition of methyl mercaptan to 1 (Scheme II): a combination of UV-IR-irradiation benzoyl peroxide, and mercuric acetate was used to start the reaction. As these conditions were not particularly appealing, we tried to simplify them. It was found that addition of sulfur-based radicals to unsaturated malonates 1 and 5 proceeded

(2) Meijer, E. M.; Boesten, W. H. J.; Schoemaker, H. E.; van Balken, J. A. M. In *Biocatalysis in Organic Synthesis*; van der Plas, H. C., Linko, P., Eds.; Elsevier: Amsterdam, 1985; pp 135–156. Boesten, W. H. J.; Dassen, B. H. N.; Kerkhoffs, P. L.; Roberts, M. J. A.; Cals, M. J. H.; Peters, P. J. H.; van Balken, J. A. M.; Meijer, E. M.; Schoemaker, H. E. In *Enzymes as Catalysts in Organic Synthesis*; Schneider, M. P., Ed.; NATO ASI Series C; Reidel: Dordrecht, 1986; Vol. 178, pp 355–360. Boesten, W. H. J. US Pat. 3971700, 1976; British Pat. 1548032, 1976; US Pat. 4172846, 1979; US Pat. 4172846, 1979.

(3) Vriesema, B. K.; ten Hoeve, W.; Wijnberg, H.; Kellogg, R. M.; Boesten, W. H. J.; Meijer, E. M.; Schoemaker, H. E. *Tetrahedron Lett.* **1986**, *26*, 2045.

(4) A large number of methods for generating carbon-, sulfur-, phosphorus-, nitrogen-, and halogen-based radicals can be found in the literature. See, for example, the references in Chapter 1 of; *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Giese, B.; Pergamon Press: Oxford, 1986.

(5) Adlington, R. M.; Baldwin, J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 94. (Conditions: 3-iodo-L-alanine derivative, Bu_3SnH, AIBN (cat.), refluxing benzene, 30% yield.) For a recent application see: Urbach, H.; Henning, R. *Heterocycles* **1989**, *28*, 957.

(6) Some leading references are (see also references cited herein): (a) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479. (b) Baldwin, J. E.; Adlington, R. M.; Lowe, C.; O'Neil, I. A.; Sanders, G. L.; Schofield, C. J.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1031. Easton, C. J.; Hutton, C. A.; Rositano, G.; Tan, E. W. *J. Org. Chem.* **1991**, *56*, 5614. (c) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1990**, *31*, 759. (d) Beckwith, A. L. J.; Chai, C. L. L. *J. Chem. Soc., Chem. Commun.* **1990**, 1087. Crich, D.; Davies, J. W.; Negrón, G.; Quintero, L. *J. Chem. Res., Synop.* **1988**, 140. Crich, D.; Davies, J. W. *Tetrahedron* **1989**, *45*, 5641.

(7) Zeiss, H. J. *Seventh International Congress of Pesticide Chemistry*; Hamburg, Aug 5–10, 1990; Book of Abstracts, Abstract 1B-13. Zeiss, H. J. German patent application DE 3817956, Hoechst. Date of publication: December 7, 1989.

(8) Burger, K.; Goa, K.; Mütze, K. *Chem.-Ztg.* **1991**, *115*, 328.

(9) Kjaer, A.; Wagner, S. *Acta Chem. Scand.* **1955**, *9*, 721.

Table I

entry	R^1–SH R^1	unsatd allyl glycine deriv no.	R^2	R^3	R^4	R^5	R^6	ee (%) (config)	product no.	yield (%)	ee (%) (config)
1	CH_3	**9**	H	OCH_3	Z[a]	H	H	rac	**10**	88[b]	rac
2	CH_3CO	**9**	H	OCH_3	Z[a]	H	H	rac	**11**	99[c]	rac
3	CH_3CO	**12**	H	OCH_3	-Phth[d]-		H	rac	**13**	97[e]	rac
4	CH_3CO	**14**	H	OH	Z[a]	H	H	rac	**15**	87[e]	rac
5	CH_3CO	**16**	H	OH	COPh	H	H	rac	**17**	81[e]	rac
6	CH_3	**18**	H	OH	H	H	H	rac	**3**	89[e]	rac
7	CH_3CO	**18**·HCl	H	OH	H	H	H	rac	**19**·HCl	*f*	rac
8	CH_3CO	**18**	H	OH	H	H	H	rac	**20**	51[g]	rac
9	$PhCH_2$	**18**	H	OH	H	H	H	rac	**21**	69[e]	rac
10	CH_3	**22**	H	OH	H	H	CH_3	rac	**7**	64[e]	rac/2 diast
11	CH_3	(*R*)-**9**	H	OCH_3	Z[a]	H	H	>99 (*R*)	(*R*)-**10**	86[b]	98.4 (*R*)
12	CH_3	(*S*)-**18**	H	OH	H	H	H	76 (*S*)	(*S*)-**3**	quant.[c]	73 (*S*)
13	CH_3	(*S*)-**18**	H	OH	H	H	H	76 (*S*)	(*S*)-**3**	47[e]	93 (*S*)
14	$PhCH_2$	(*S*)-**18**	H	OH	H	H	H	76 (*S*)	(*S*)-**21**	45[e]	97 (*S*)
15	$PhCH_2$	(*S*)-**18**	H	OH	H	H	H	91 (*S*)	(*S*)-**21**	nd[h,i]	82 (*S*)[j]
16	$PhCH_2$	(*S*)-**18**	H	OH	H	H	H	91 (*S*)	(*S*)-**21**	nd[h,i]	>99 (*S*)
17	CH_3	(*S*)-**23**	CH_3	OH	H	H	H	78 (*S*)	(*S*)-**24**	81[e]	nd[i]
18	CH_3	(*S*)-**25**	CH_3	OCH_3	H	H	H	78 (*S*)	(*S*)-**26**	91[k]	82 (*S*)
19	$PhCH_2$	(*S*)-**25**	CH_3	OCH_3	H	H	H	78 (*S*)	(*S*)-**27**	75[l]	nd[i]
20	$HOCH_2CH_2$	(*S*)-**25**	CH_3	OCH_3	H	H	H	78 (*S*)	(*S*)-**28**	73[l]	nd[i]
21	CH_3	(*R*)-**29**	CH_3	NH_2	H	H	H	54 (*R*)	(*S*)-**30**	quant.[c]	nd[i]

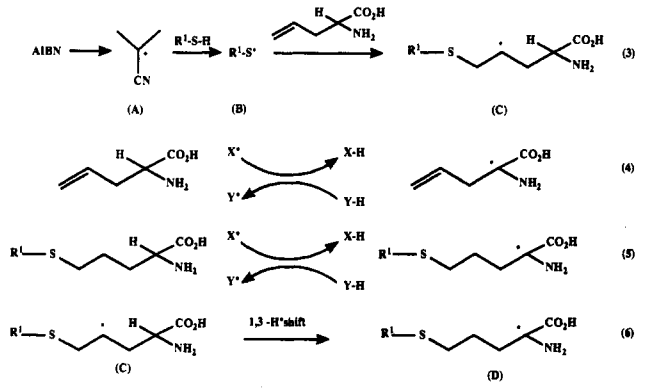
[a] Z = carbobenzoxy. [b] Isolated as oil of >90% purity (98% entry 1; 96% entry 11). [c] Isolated as NMR-pure oil. [d] Phth = phthaloyl. [e] Isolated yield after (re)crystallization. [f] Isolated as HS-product (85% pure), so R^1 = H in 19·HCl. [g] Product contained 10% N-acylated starting material. [h] Entries 15 and 16 relate to the same experiment. Entry 15: workup of part of the reaction mixture without crystallization. Entry 16: with crystallization. [i] nd = not determined. [j] The ee of unreacted (*S*)-18 present in crude reaction mixture is still 91%. [k] Isolated yield after bulb-to-bulb distillation. [l] Isolated yield after column chromatography.

smoothly with AIBN alone (1–10% of AIBN, amount not critical) or even without added radical initiator. Essentially quantitative conversion to the products **2**, **4**, **6**, and **8** was observed. In none of the radical additions described in this article was Markovnikov-orientation observed. Malonates **2** and **6** were hydrolyzed with 6 N HCl to the sulfur-containing trifunctional amino acids **3** and **7**.

Next we turned our attention to (protected) α-allylglycine and derivatives. Acidic hydrolysis of malonate **1** to α-allylglycine (**18**) is facile, but in accordance with the literature[10] acidic hydrolysis of **5** to α-methallylglycine **22** proved to be impossible. However, basic hydrolysis of **5** to the dipotassium salt of 2-(methallyl)-2-(acetamido)-malonic acid, followed by acidification, decarboxylation, and basic hydrolysis of the *N*-acetyl function, gave α-methallylglycine **22** in 75% yield.[10] Optically active α-allylglycine was prepared by the chemoenzymatic process[2] using *Pseudomonas putida* for resolving racemic α-allylglycine amide.

In all radical additions described here (Scheme III, Table I), small amounts (1–10%) of AIBN were used as radical initiator. Entries 1–3 show that addition to α-allylglycine protected both at the amino and the carboxyl group proceeds smoothly. In the case of *N*-acyl derivatives monoprotection of the amino group is sufficient. Protection of the carboxyl group was thought to be unnecessary,[11] and entries 4–5 show this to be indeed true. Entry 6 shows that

Scheme IV. Possible Mechanisms for Racemization during Radical Addition



even addition to unprotected α-allylglycine (**18**) gives the expected product **3** in high yield. In this reaction, as well as in a number of the other examples, it was found that superior results were obtained if both the thiol compound and the amino acid derivative were dissolved completely in the reaction medium. For example, use of unprotected α-allylglycine in apolar solvents like hexane afforded an inferior result. In most cases mixtures of dioxane/water or methanol/water are good solvent combinations (see Experimental Section for details). None of the reactions were optimized with respect to yield, although quantitative yields are thought possible using longer reaction times or by occasionally adding more AIBN.

The possible occurrence of racemization was investigated in entries 11–16 and 18. Protected amino acid derivative (*R*)-**9**, prepared from (*R*)-α-allylglycine ((*R*)-**18**) (ee > 99%), yielded product (*R*)-**10**. The enantiomeric excess of (*R*)-**10** was determined after hydrogenation of (*R*)-**10** to (*R*)-**31** and found to be 98.4%. Entries 12 and 15 show the results of the reaction of methyl mercaptan and benzyl mercaptan with optically enriched unprotected allylglycine ((*S*)-**18**). The ee of the product was 3% less than that of the starting material in case of methyl mercaptan and 9% less in case of benzyl mercaptan. The products of these

(10) Acidic hydrolysis of **2** gives 4,4-dimethyl-γ-butyrolactone in 96% yield. See also: Goering, H. L.; Cristol, S. J.; Dittmer, K. *J. Am. Chem. Soc.* **1948**, *70*, 3310. Albertson, N. *J. Am. Chem. Soc.* **1946**, *68*, 450.

(11) Average bond energies (March, J. *Advanced Organic Chemistry*, 2nd, ed.; McGraw-Hill Kogakusha: Tokyo, 1977; p 28) O–H 110–111 kcal/mol > C–H 96–99 kcal/mol > N–H 93 kcal/mol > S–H 82 kcal/mol. Based on these data and the assumption that the weakest bond is homolytically split by radical C in Scheme IV, normal propagation is the most likely reaction to occur with this radical. Captodative stabilization of the α-radical (D) in Scheme IV is not, however, taken into account in this assumption. When the use in this addition reaction of radicals generated from X–H compounds with X not equal to sulfur is considered, the captodative stabilization of D (Scheme IV) probably has to be minimized, e.g., by converting the NH_2 group into a less electron-donating derivative (for example, *N*-acetyl).

Scheme V

	R^1	R^2	R^3	R^4		R^5	R^6	R^7	R^8
(R)-10	CH_3	CH_3	Z	H	(R)-31	CH_3	CH_3	H	H
11	CH_3CO	CH_3	Z	H	10	CH_3	CH_3	Z	H
13	CH_3CO	CH_3	-Phth-		32	H	CH_3	-Phth-	
19·HCl	H	H	H	H	33	H	CH_3	H	H

reactions, (*S*)-**3** and (*S*)-**21**, respectively, were isolated in such a way that optical enrichment was not possible. When workup included crystallization it was found that optical enrichment by crystallization was facile (entries 13, 14, 16). Thus, enantiomerically pure products, if desired, may be obtained by (re)crystallization.

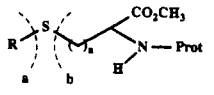
Evidently, a small amount of racemization occurs in the case of sulfur radical additions to optically active α-allylglycine derivatives. The extent of racemization seems to depend on both the thiol (entries 12, 15) and the amino acid derivative (entries 11, 12). Interestingly, unconverted (*S*)-α-allylglycine ((*S*)-**18**) was found not to be racemized under the reaction conditions with benzyl mercaptan (entry 15). This result suggests the following explanation for the racemization: the radicals A, B, and C (Scheme IV) are present during a normal radical chain reaction. Apparently, none of these radicals is capable of racemizing α-allylglycine as shown in eq 4 because it is very difficult to understand why the chemistry in eq 5 would occur while that in eq 4 would not. We propose at this point in time that eq 6 describes the racemization observed: a 1,3-H shift (radical C to D) is occurring to a small extent alongside the normal chain events. The validity of this hypothesis was not further investigated, however.

The scope of the reaction was also found to include α-alkyl-α-allylglycine derivatives (entries 17–21). As an example, three different thiols were reacted with methyl (*S*)-α-allyl-α-methylglycinate ((*S*)-**25**) (prepared from (*S*)-α-allyl-α-methylglycine ((*S*)-**22**), ee 78%).

In one instance the ee of the product was determined and found to be 82% (entry 18). Racemization was not found in this case, as expected, since racemization of α,α-disubstituted amino acids is very unlikely.

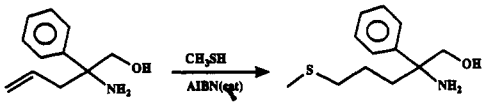
The synthesis of the amino acid with R = Et from Scheme I is now a one-step procedure provided (*S*)-α-allylglycine is present.

Scheme V shows some of the reactions which these trifunctional amino acids are able to undergo. A (slow) hydrogenation of (*R*)-**10** to (*R*)-**31** is possible and was used to determine the ee of (*R*)-**10**. It is also possible to convert the thio ester into a thio ether or free mercaptan. One-pot deacylation/alkylation of the S-atom in **11** proceeds smoothly by reaction with 1 equiv of sodium methoxide followed by 1 equiv of alkylating agent; this method is illustrated by the (quantitative) conversion of **11** to **10**. As shown in the structure below, this synthetic step forms the R–S bond in the product, indicated by line a (with $n = 3$, Prot = Z). This method is similar but complementary to



the work of Logusch[12] who synthesized trifunctional amino acids with $n = 2$ by the sodium methoxide-mediated coupling of alkyl thiolacetates with methyl *N*-phthaloyl-α-(2-bromoethyl)glycinate (according to line b). Liberation of the free –SH function from the thio acetyl group is facile via acid-catalyzed transesterification in methanol, e.g., **32** from **13** (Scheme V).

Scheme VI



34 **35**

Efficient use of protective groups is crucial in amino acid chemistry. This is even more so if broad applicability of trifunctional amino acids in synthesis is desired. Of importance too is that the three functional groups—in this paper CO_2H, NH_2, SH—can be protected in all possible combinations, as demonstrated in Table I and Scheme V.[13]

Amino alcohols derived from amino acids form an interesting class of compounds for use in asymmetric synthesis.[14] For example, homomethionine (Scheme I (R = Me)) was prepared to serve as a precursor for an optically active trifunctional ligand.[3] This ligand was used in the metal-catalyzed cross-coupling of a Grignard reagent with vinyl halide. A shorter synthesis of this type of ligand is possible provided that radical addition to unsaturated β-amino alcohols is possible.

This was found to be the case with the β,β-disubstituted β-amino alcohol **34** (prepared by reduction of the corresponding amino acid). The trifunctional compound **35** was isolated in 79% yield after reaction of **34** with methyl mercaptan under radical addition conditions. This reaction is a further illustration of the usefulness of radical addition chemistry to unsaturated α-amino acids and derivatives.

We believe that the radical addition approach to (optically active) trifunctional amino acids is a general one and that the scope of the reaction could be broadened to involve other radical additions.[4]

A useful application of this method might be the incorporation of an unsaturated amino acid in short peptide chains followed by addition on an array of thiol-based radicals.[15] This procedure would be a very efficient way

(12) Logusch, E. W. *Tetrahedron Lett.* **1988**, *29*, 6055.

(13) One of the eight possible combinations was not investigated: NH_2 protected, CO_2H and SH free. Deacetylation of the thio ester part of **20** in the presence of the acetamide part is not expected to be a problem, however.

(14) Numerous examples exist for the two following major applications: (a) incorporation of optically active amino alcohols in chiral ligands for (catalytic) asymmetric synthesis. See, for example (also references cited herein): Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442. Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095. Bolm, C. *Angew. Chem.* **1991**, *103*, 566 (review). Soai, K. *Tetrahedron Asymmetry* **1991**, *2*, 781. (b) Use of optically active amino alcohols in stoichiometric reagents for diastereoselective synthesis. See, for example (also references cited herein): Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. Evans, D. E.; Bilodecu, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750. Meyers, A. I.; Shipman, M. *J. Org. Chem.* **1991**, *56*, 7098. Snider, B. B.; Zhang, Q. *J. Org. Chem.* **1991**, *56*, 4908. Katagiri, N.; Yamamoto, M.; Iwaoka, T.; Kaneko, C. *J. Chem. Soc., Chem. Commun.* **1991**, 1429.

(15) Another interesting application is the use of "extended cysteine" residues in peptides. Williams and Im (Williams, R.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276) describe the preparation of (*S*)- and (*R*)-2-[(*t*-BOC)amino]-6-[(4-methoxybenzyl)thio]hexanoic acid (nine steps each). Footnote 14 of their paper reports that these compounds were built into small peptides; however, all attempts to cleave the 4-methoxybenzyl group to release the free –SH function failed.

(16) Nefkens, G. H. L.; Tesser, G. I.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 688.

(17) Kaptein, B.; Boesten, W. H. J.; Broxterman, Q. B.; Kamphuis, J.; Schoemaker, H. E. *Tetrahedron Lett.*, in press.

(18) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77.

to produce large numbers of functionalized peptides in a simple manner.

Experimental Section

General Remarks. Solvents of p. a. grade were purchased from Baker, Merck, and Riedel-de Haën and were used without further purification. Thiolactic acid (AcSH), benzyl mercaptan (BnSH) (Janssen Chimica), and 2-mercaptoethanol (Fluka) were used as such; methyl mercaptan (MeSH) (Aldrich Chemical Co.) was condensed from a lecture bottle at −20 °C. Silica gel 60 (230–400 mesh) from Merck was used for column chromatography.

The radical reactions performed with MeSH were first cooled to −30 °C before addition of the MeSH (condensed at −30 °C). Next, these reaction mixtures were heated at 50–60 °C in a closed pressure-resistant vessel. All radical additions should be performed in a homogeneous solution; if the amino acid derivatives were not completely dissolved poor yields resulted. Diethyl 2-allyl-2-acetamidomalonate (1),[9] diethyl 2-acetamido-2-methallylmalonate (5),[10] α-allylglycine (18),[22] α-methallylglycine (22),[10b] and α-allylglycine amide[3] were prepared according to literature methods.

Unless stated otherwise in the experimental procedures, enantiomeric excesses are determined by HPLC using a Crownpak CR(+) column, analogous to a method reported,[23] and are within 1% accuracy.

(*S*)-(−)- and (*R*)-(+)-2-amino-4-pentenoic acid (18) were prepared by enzymatic resolution with *Pseudomonas putida*.[2] Thus, 40 g (0.27 mol) of α-allylglycine amide in 360 mL of H_2O was adjusted to pH 8.2 using 1 N KOH solution. Crude cell mass of *Pseudomonas putida* (10 g) was added, and the mixture was stirred for 16 h at 37 °C. At 50% conversion the reaction was worked up. The crude enzyme was removed by centrifugation. Benzaldehyde (15.4 g, 145 mmol) was added and the mixture stirred for 3 h. The solid Schiff base of (*R*)-amide was filtered off (22 g, ±82%). The aqueous layer was evaporated until no more benzaldehyde distilled off. The resulting solution of (*S*)-18 was purified on a strong acid ion-exchange column (Dowex 50W). After being washed with H_2O the amino acid was eluted from the column with 2 N ammonia. Evaporation of the aqueous layer to dryness, and stripping with toluene, yielded the (*S*)-α-allylglycine ((*S*)-18) as a white solid. Mp: 241–243 °C dec. $[\alpha]^{20}_D$: −8.2° (*c* 2, 1 N HCl). Ee: 91.6%.

(*R*)-α-Allylglycine ((*R*)-18) was obtained after hydrolysis of the Schiff base. Thus, 18.8 g (91 mmol) of the Schiff base was dissolved in 150 mL of acetone, and 8 mL of concd HCl solution was added slowly. After being stirred for 2 h the solid was filtered off and washed with acetone yielding 14.0 g of (*R*)-α-allylglycineamide·HCl. This amide was hydrolyzed by refluxing in 225 mL of 6 N HCl solution for 8 h. Evaporation in vacuo followed by stripping with H_2O (2×) yielded (*R*)-18·HCl as a white solid. The residue was dissolved in H_2O and purified on a strongly acidic ion-exchange column (Dowex 50W). Yield: 10.5 g of (*R*)-18. Ee: 99.6%. Mp: 240–241 °C dec. ^{1}H NMR (DCl/D_2O): δ 2.57–2.83 (m, 2 H), 4.14 (dd, 1 H, *J* = 5, 6 Hz), 5.26–5.33 (m, 2 H), 5.67–5.85 (m, 1 H). ^{13}C NMR (DCl/D_2O): δ 33.7 (t), 52.0 (d), 121.5 (t), 129.9 (d), 170.8 (s).

(*R*)-*N*-(Benzyloxycarbonyl)-2-amino-4-pentenoic Acid ((*R*)-14). To a solution of 14.0 g of (*R*)-18 (117 mmol, 96% pure, ee 99.6%) in a mixture of 58 mL of 2 N NaOH solution and 70 mL of acetone at 0 °C was added 30 g of carbobenzoxy chloride in 58 mL of acetone dropwise. The pH was maintained at 9.0 by addition of 2 N NaOH solution, using an autotitrator. The solution was allowed to warm overnight. Acetone was evaporated and the remaining solution cooled to 0 °C and acidified to pH 2.5 with concd HCl solution. This solution was extracted with CH_2Cl_2 (3×) and EtOAc. The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and evaporated to yield 25 g (85%) of crude (*R*)-14 as an oil. ^{1}H NMR ($CDCl_3$): δ 2.46–2.70 (m, 2 H), 4.34 (dd) and 4.50 (dd, together 1 H, rotamers ratio 22/78), 5.14–5.20 (s + m, 4 H), 5.39 (d, 0.78 H), 5.61–5.81 (m, 1 H), 6.36 (d, 0.22 H), 7.34 (s, 5 H) (mixture of rotamers). ^{13}C NMR ($CDCl_3$): δ 36.3 (t), 53.1 (d), 66.2 (t), 119.7 (t), 128.1 (d), 128.3 (d), 128.5 (d), 131.0 (d), 136.0 (s), 156.0 and 156.7 (s, rotamers), 176.5 (s). $[\alpha]^{20}_D$: −4.8° (*c* 2, MeOH). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.06; N, 5.64. Found: C, 62.4; H, 5.9; N, 5.7.

(*RS*)-*N*-(Benzyloxycarbonyl)-2-amino-4-pentenoic Acid (14). This compound was prepared identical to (*R*)-14 from 151.5 g of (*RS*)-18·HCl (1.0 mol) to yield 231.5 g (93%) of 14 as a colorless oil which solidified on standing. Mp: 52–53 °C. For spectroscopic data see (*R*)-14.

Methyl (*R*)-*N*-(Benzyloxycarbonyl)-2-amino-4-pentenoate ((*R*)-9). Crude (*R*)-14 (25 g) was dissolved in 125 mL of MeOH, 1.25 g of TsOH added, and the mixture refluxed for 6 h. After the mixture was cooled overnight, the solvent was evaporated and the residue dissolved in Et_2O and extracted with saturated $NaHCO_3$ solution, followed by brine. The organic layer was dried (Na_2SO_4) and evaporated to yield 18.75 g (61% based on (*R*)-18) of (*R*)-9 as an oil. ^{1}H NMR ($CDCl_3$): δ 2.51 (m, 2 H), 3.62 (s, 6 H), 4.44 (br dd, 1 H), 5.05–5.15 (m, 4 H), 5.43 (br d, 1 H), 5.56–5.75 (m, 1 H), 7.28 (s, 5 H). ^{13}C NMR ($CDCl_3$): δ 36.7 (t), 52.3 (q), 53.3 (d), 67.0 (t), 119.3 (t), 128.1 (d), 128.2 (d), 128.5 (d), 132.1 (d), 136.3 (s), 155.8 (s), 172.2 (s). Exact mass ($C_{14}H_{17}NO_4$): calcd 263.1157. Found: 263.1152. $[\alpha]^{20}_D$: +5.5° (*c* 2, MeOH).

Methyl (*RS*)-*N*-(benzyloxycarbonyl)-2-amino-4-pentenoate (9) was prepared from 231 g (0.93 mol) of 14 according to the method mentioned above. Yield: 232 g (95%) of TLC pure 9 as a slightly colored oil. For spectroscopic data see (*R*)-9.

Methyl (*RS*)-*N*-Phthaloyl-2-amino-4-pentenoate (12). (*RS*)-*N*-Phthaloyl-2-amino-4-pentenoic acid was prepared analogous to a literature procedure[16] from 18 in 69% yield. Mp: 119–121 °C. ^{1}H NMR ($CDCl_3$): δ 2.90–3.14 (m, 2 H), 4.97–5.13 (m, 3 H), 5.62–5.83 (m, 1 H), 7.70–7.91 (m, 4 H), 10.56 (br, 1 H). ^{13}C NMR ($CDCl_3$): δ 34.0 (t), 52.4 (d), 120.0 (t), 124.7 (d), 132.6 (s), 133.9 (d), 135.3 (d), 168.5 (s), 175.7 (s). Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.65; H, 4.52; N, 5.73. Found: C, 63.7; H, 4.2; N, 5.8.

A solution of 23 g (94 mmol) of this acid in 120 mL of MeOH was cooled to 5 °C and 11 mL of $SOCl_2$ added dropwise over a period of 15 min. After being stirred for 0.75 h at 5 °C, the reaction mixture was allowed to warm slowly to rt and then heated to reflux for 1 h. After evaporation of the solvent an oil remained. The oil was dissolved in Et_2O, washed with 0.5 N HCl solution (3×), H_2O, saturated $NaHCO_3$ solution, saturated NaCl solution, and H_2O, and dried (Na_2SO_4). A slightly colored oil which crystallized on standing was isolated: 23 g (89 mmol, 95%) of 12. Mp: 51–54 °C. ^{1}H NMR ($CDCl_3$): δ 3.00 (t, 2 H), 3.76 (s, 3 H), 4.88–5.22 (m, 3 H), 5.62–5.83 (m, 1 H), 7.72–7.89 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 32.1 (t), 50.4 (d), 51.7 (q), 117.6 (t), 122.4 (d), 130.6 (s), 132.1 (d), 133.1 (d), 166.4 (s), 168.2 (s). Exact mass ($C_{14}H_{13}NO_3$): calcd 259.0845. Found: 259.0848.

(*RS*)-*N*-Benzoyl-2-amino-4-pentenoic Acid (16). Compound 18 (2.3 g, 20 mmol) and 9.5 g (0.11 mol) of $NaHCO_3$ were dissolved in 30 mL of H_2O. Benzoyl chloride (3.7 g, 26 mmol) was added dropwise over a period of 10 min. After being stirred for 2 h, the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The aqueous layer was acidified with 7 mL of concd HCl solution. The product which precipitated was filtered off and washed with H_2O. After drying 3.0 g (68%) of 16 was obtained. The product was recrystallized from 25 mL of toluene/heptane (70/30). Mp: 107–108 °C. ^{1}H NMR ($CDCl_3$): δ 2.59–2.84 (m, 2 H), 4.89 (dt, 1 H, *J* = 7, 7 Hz), 5.15–5.76 (m, 2 H), 5.70–5.89 (m, 1 H), 5.83 (d, 1 H, *J* = 7 Hz), 7.41–7.59 (m, 3 H), 7.79 (dd, 2 H), 10.1 (br, 1 H). ^{13}C NMR ($CDCl_3$): δ 36.1 (t), 52.1 (d), 119.8 (t), 127.2 (d), 128.7 (d), 132.0 (d), 132.1 (d), 133.4 (s), 167.9 (s), 175.3 (s). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.72; H, 5.98; N, 6.41. Found: C, 65.6; H, 5.8; N, 6.4.

(*S*)-2-Amino-2-methyl-4-pentenoic Acid (23) and (*R*)-2-Amino-2-methyl-4-pentenoic Acid Amide ((*R*)-29). (*RS*)-2-Amino-2-methyl-4-pentenoic acid amide (29) was prepared according to the literature procedure[17] by phase-transfer alkylation of *N*-benzylidenealanine amide with allyl bromide in 72% yield.

(19) Belokon, Y. N.; Chernoglazova, N. I.; Kochetkov, C. A.; Garbalinskaya, N. S.; Belikov, V. M. *J. Chem. Soc., Chem. Commun.* **1985**, 171.
(20) Kruizinga, W. H.; Bolster, J.; Kellogg, R. M.; Kamphuis, J.; Boesten, W. H. J.; Meijer, E. M.; Schoemaker, H. E. *J. Org. Chem.* **1988**, *53*, 1826.
(21) Schöllkopf, U.; Groth, U.; Westphalen, K.-O. *Synthesis* **1981**, 969.
(22) Sörensen, S. P. L. *Compt. Rend. Trav. Lab. Carlsberg* **1902–1906**, *6*, 137.
(23) Miyazawa, T.; Iwanaga, H.; Yamada, T.; Kuwata, S. *Chem. Express* **1991**, *6*, 887.

Bp: 120 °C/0.5 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 3 H), 1.43 (br, 2 H), 2.15 (dd, 1 H, J = 13, 8.5 Hz), 2.71 (ddt, 1 H, J = 13.0, 6.0, 1.0 Hz), 5.07–5.22 (m, 2 H), 5.65–5.88 (m, 1 H), 6.03 (br, 1 H), 7.39 (br, 1 H). ^{13}C NMR ($CDCl_3$): δ 27.4 (q), 45.7 (t), 57.0 (s), 119.4 (t), 133.4 (d), 180.0 (s). Exact mass (CI) ($C_6H_{12}N_2O$ + H): calcd 129.1028. Found: 129.1032.

Racemic amide **29** (20.1 g, 0.157 mol) was dissolved in 200 mL of H_2O. The pH was adjusted to 9.0 by addition of acetic acid, and 2.0 g of freeze-dried crude amino amidase from *Mycobacterium neoaurum*[20] was added. The mixture was stirred for 7 h at 37 °C until a conversion of about 50% was reached. Next, the *Mycobacterium neoaurum* residue was removed by centrifugation. (*S*)-Acid and (*R*)-amide were separated using a strongly basic ion-exchange column (Dowex 1-4) in the OH^- form. The first eluent containing free (*R*)-amide was concentrated in vacuo, yielding 10.4 g (51%) (*R*)-**29** as a colorless oil. $[\alpha]^{20}_D$: +22.4° (*c* 2, H_2O). Ee: 54% (^{1}H NMR method[20]).

(*S*)-2-Amino-2-methyl-4-pentenoic acid (**23**) was eluted from the column with 2 N AcOH solution. Evaporation of the solution followed by precipitation from 400 mL of acetone yielded 9.5 g (47%) of **23**. Mp: 300 °C dec. ^{1}H NMR (DCl/D_2O): δ 1.57 (s, 3 H), 2.56 (dd, 1 H, J = 14, 7.5 Hz), 2.74 (dd, 1 H, J = 14, 6.5 Hz), 5.24–5.36 (m, 2 H), 5.64–5.88 (m, 1 H). ^{13}C NMR (DCl/D_2O): 20.4 (q), 39.70 (t), 59.0 (s), 121.9 (t), 128.2 (d), 172.1 (s). $[\alpha]^{20}_D$: −17.6° (*c* 1.3, 1 N HCl) (lit.[19] (*S*)-(−)-isomer (HCl-salt) $[\alpha]^{25}_D$ −14.2° (*c* 1.3, D_2O)). The ee of the methyl ester (vide infra) was determined by ^{1}H NMR[20] and was 78 ± 3%.

Methyl (*S*)-2-Amino-2-methyl-4-pentenoate (25). To a suspension of 1.0 g (7.8 mmol) of **23** in 10 mL of MeOH at rt was slowly added 1.2 mL (12 mmol) of $SOCl_2$. After being stirred for 48 h the solution was concentrated in vacuo, dissolved in 0.5 N KOH solution, and extracted with CH_2Cl_2. Concentration of the organic layer and bulb to bulb distillation yielded 850 mg (77%) of **25** as a colorless oil. Bp: 100 °C/16 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 3 H), 1.65 (br, 2 H), 2.27 (ddt, 1 H, J = 13.7, 8.2, 0.8 Hz), 2.52 (ddt, 1 H, J = 13.6, 6.5, 1.2 Hz), 3.73 (s, 3 H), 5.08–5.18 (m, 2 H), 5.60–5.82 (m, 1 H). ^{13}C NMR (DCl/D_2O): δ 26.2 (q), 45.2 (t), 52.2 (q), 57.6 (s), 119.3 (t), 132.9 (d). $[\alpha]^{20}_D$: −1.5° (*c* 0.66, EtOH) (lit.[21] (*R*)-(+)-isomer $[\alpha]^{20}_D$ +2.33° (*c* 0.4, EtOH). Ee: 78% (^{1}H NMR method[20]).

Diethyl 2-Acetamido-2-[3-(methylthio)propyl]malonate (2). This compound was prepared by radical addition to 1 according to various methods. The literature method:[9] Reaction of 1 and MeSH at −20 °C in EtOH, using dibenzoyl peroxide, irradiation with a medium-pressure mercury lamp, and $Hg_2(OAc)_2$ as a photosensitizer gave a quantitative yield of **2**.

The reaction also gave a quantitative yield by heating at 50 °C in EtOH with 5 mol % of AIBN, but the reaction even proceeded without radical initiator added. Thus, stirring of a solution of 1.0 g (3.9 mmol) of 1, 1.0 mL (18 mmol) of MeSH, and 12 mL of EtOH for 66 h followed by evaporation afforded **2** as a slowly crystallizing colorless oil (100%). Mp: 51–55 °C. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 6 H, J = 7 Hz), 1.37–1.52 (m, 2 H), 2.04 (s, 3 H), 2.06 (s, 3 H), 2.37–2.51 (m, 4 H), 4.25 (q, 4 H), 6.90 (br, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.3 (q), 15.8 (q), 23.3 (t), 24.0 (q), 31.9 (t), 34.1 (t), 62.9 (t), 66.7 (s), 168.3 (s), 169.5 (s).

Diethyl 2-Acetamido-2-[3-(acetylthio)propyl]malonate (4). Compound 1 (2.0 g, 7.8 mmol) was dissolved in 30 mL of hexane by heating to 60 °C. AcSH (2.97 g, 39 mmol) (which did not completely dissolve) and 80 mg of AIBN were added. The mixture was refluxed. After 1.5 h a further 40 mg of AIBN was added, and refluxing was continued for 2 h. The solvent was evaporated yielding 3.2 g of an oil. After trituration with hexane at −20 °C overnight 2.3 g of white crystalline material was obtained. This material was recrystallized from hexane/Et_2O at −20 °C, and after filtration, washing with hexane, and drying 2.0 g (77%) of **4** was obtained as a white crystalline solid. Mp: 79.5–80.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 6 H, J = 7 Hz), 1.31–1.50 (m, 2 H), 2.04 (s, 3 H), 2.31 (s, 3 H), 2.35–2.45 (m, 2 H), 2.83 (t, 2 H, J = 7 Hz), 4.25 (q, 4 H, J = 7 Hz), 6.82 (br, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.4 (q), 23.4 (q), 24.5 (t), 29.1 (t), 31.0 (q), 31.9 (t), 63.0 (t), 66.6 (s), 168.3 (s), 169.5 (s), 195.9 (s). Anal. Calcd for $C_{14}H_{23}NO_6S$: C, 50.43; H, 6.95; N, 4.22; S, 9.62. Found: C. 50.8; H, 6.9; N, 4.2; S, 9.7.

Diethyl 2-acetamido-2-[2-methyl-3-(methylthio)propyl]malonate (6) was prepared by heating of 81.3 g (0.30 mol) of **5** and 25 mL (0.45 mol) of MeSH in 400 mL of EtOH at 50 °C. The reaction was performed for 60 h, adding 500 mg of AIBN in three portions over this period. (The reaction also proceeded without radical initiator but was much slower). Spectroscopically pure **6** was isolated as a colorless oil (97 g, 100%) after evaporation of the solvent. ^{1}H NMR ($CDCl_3$): δ 0.97 (d, 3 H, J = 6.5 Hz), 1.27 (t, 6 H, J = 7 Hz), 1.52–1.72 (m, 1 H), 2.04 (s, 6 H), 2.21–2.48 (m, 3 H), 2.60 (dd, 1 H, J = 14, 5 Hz), 4.24 (q, 4 H, J = 7 Hz), 6.94 (br, 1 H). ^{13}C NMR ($CDCl_3$): δ 12.7 (q), 14.9 (q), 18.9 (q), 21.7 (q), 27.8 (d), 36.5 (t), 41.5 (t), 61.3 (t), 64.7 (s), 167.0 and 167.2 (s, diastereotopic ester carbonyls), 167.8 (s). Exact mass ($C_{14}H_{15}NO_5S$): calcd 319.1453. Found: 319.1448.

Diethyl 2-acetamido-2-[2-methyl-3-(acetylthio)propyl]malonate (8) was prepared from 5 g (18.5 mmol) of **5** and 2.0 g (26 mmol) of AcSH in 25 mL of EtOH without addition of a radical initiator. The mixture was heated for 6 h at 75 °C. After evaporation of the solvent 6.7 g of a colorless oil remained. NMR showed quantitative conversion. The oil was crystallized from 140 mL of hexane/Et_2O (2.5:1) and yielded 4.6 g of **8**. From the mother liquid another 0.7 g of **8** was isolated after crystallization from 50 mL of hexane/Et_2O (2.5/1). Yield: 5.3 g (83%) of **8**. Mp: 59–60 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.68 (d, 3 H), 1.23 (t, 6 H, J = 7 Hz), 1.60 (m, 1 H, J = 7.9, 6.6, 6.5, 6.3, 4.1 Hz), 1.82 (s, 3 H), 2.05 (dd, 1 H, J = 14.5, 7.9 Hz), 2.54 (dd, 1 H, J = 14.6, 4.1 Hz), 2.66 (s, 1 H), 2.38 (dd, 1 H, J = 13.3, 6.5 Hz), 2.63 (dd, 1 H, J = 13.3, 6.3 Hz), 4.28 (2q, 4 H, J = 7 Hz), 8.77 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 15.6 (q), 21.8 (q), 24.6 (q), 31.3 (d), 32.2 (q), 38.1 (t), 39.3 (t), 64.2 (t), 67.5 (s), 169.8 (s) and 170.0 (s) (diastereotopic ester carbonyl), 170.8 (s), 197.2 (s). Anal. Calcd for $C_{15}H_{25}NO_6S$: C, 51.85; H, 7.25; N, 4.05; S, 9.23. Found: C, 52.2; H, 7.1; N, 4.1; S, 9.2.

Methyl (*RS*)-*N*-(benzyloxycarbonyl)-2-amino-5-(methylthio)pentanoate (10) was prepared from 20 g (76 mmol) of (*RS*)-**9**, 10 mL of MeSH, and 300 mg of AIBN in 200 mL of toluene by heating for 3 h at 65 °C. After the mixture was cooled to −20 °C additional AIBN (250 mg) was added, again followed by heating for 3 h at 65 °C and being left at rt overnight. The solvent was evaporated, and the resulting oil dissolved in EtOAc and washed with H_2O, 0.5 M citric acid, H_2O, 5% $NaHCO_3$ solution, and H_2O. After drying ($MgSO_4$), filtration, and evaporation, 23.2 g (98%) of **10** was obtained as an oil. Purity >90% according to NMR. ^{1}H NMR ($CDCl_3$): δ 1.55–2.00 (m, 4 H), 2.05 (s, 3 H), 2.49 (t, 2 H), 3.72 (s, 3 H), 4.33–4.45 (m, 1 H), 5.10 (s, 2 H), 5.46 (br d, 1 H), 7.34 (s, 5 H). ^{13}C NMR ($CDCl_3$): δ 15.4 (q), 24.7 (t), 31.6 (t), 33.5 (t), 52.4 (q), 53.5 (d), 67.0 (t), 128.1 (d), 128.2 (d), 128.5 (d), 136.9 (s), 155.9 (s), 172.8 (s). Exact mass ($C_{15}H_{21}NO_4S$): calcd 311.1198. Found: 311.1198.

This compound was also prepared from the *S*-acetyl compound **11** (vide infra). Thus, 2.0 g (5.9 mmol) of **11** was added to 30 mL of MeOH and cooled to 0 °C (heterogeneous mixture). Freshly prepared NaOMe in MeOH (0.32 g NaOMe in 6 mL of MeOH) was added dropwise. The reaction mixture was stirred for 0.5 h at 0 °C. MeI (2.0 g, 14.1 mmol) in 5 mL of MeOH was added dropwise and stirred for 10 min at 0 °C and 1 h at rt. The solvent was evaporated, and a mixture of oil and solid (NaI) resulted. This residue was slurried in CH_2Cl_2 and filtered. After evaporation 1.9 g (6.1 mmol, 103%) of **10** was obtained as a colorless oil (almost NMR pure).

Methyl (*R*)-*N*-(benzyloxycarbonyl)-2-amino-5-(methylthio)pentanoate ((*R*)-10) was prepared identically to the racemic compound in 96% yield (NMR purity >90%). The ee of this compound was determined after hydrogenation (ee 98.7%). For spectroscopic data see (*RS*)-**10**.

Methyl (*R*)-2-Amino-5-(methylthio)pentanoate ((*R*)-31). A mixture of 1.0 g of (*R*)-**10** and 5 g of Pd (10% on $BaSO_4$) was hydrogenated in 100 mL of AcOH/H_2O (9/1) for 3 h at 50–55 °C. The solvent was evaporated, and the residue was divided between H_2O at pH 2 and CH_2Cl_2. The aqueous layer was made alkaline (pH 9.5) with concd NH_3 solution and extracted with CH_2Cl_2. The product was now extracted with 1 N HCl solution, and after evaporation TLC- and NMR-pure material was obtained. Ee: 98.7%. ^{1}H NMR (D_2O): δ 1.62–1.86 (m, 2 H), 1.95–2.13 (m + s, 5 H), 2.57 (s, 3 H), 3.85 (s, 3 H), 4.17 (t, 1 H). ^{13}C NMR (D_2O): δ 14.4 (q), 24.1 (t), 29.1 (t), 32.7 (t), 53.0 (d), 54.0 (q).

Racemic **31** was prepared identically from (*RS*)-**10**.

2-Amino-4-methyl-5-(methylthio)pentanoic Acid (7) (Mixture of 2RS,4RS and 2RS,4SR Diastereomers). Method a. Compound 6 (94.0 g, 295 mmol) was heated at reflux for 18 h in 250 mL of 6 N HCl. Evolution of CO_2 was visible, and the heterogeneous reaction mixture became a clear solution after 1 h. After cooling, the reaction mixture was evaporated to dryness, dissolved in 150 mL of H_2O, and neutralized with concd NaOH solution to pH 7. After cooling, the colorless precipitate was filtered off and washed with H_2O and acetone. The yield of 7 was 31 g (59%). ^1H and ^{13}C NMR indicated that the product consisted of diastereomers in a ratio of 79/21. Mp: 258–259 °C.

Method b. A solution of 1.0 g (7.8 mmol) of **22**, 1.5 g (31 mmol) of MeSH, and 50 mg of AIBN was heated at 60 °C in a mixture of 15 mL of MeOH and 10 mL of H_2O. After 16 h an additional 50 mg of AIBN was added to the cooled solution, and heating at 60 °C was continued for a further 24 h. After cooling, 100 mL of acetone was added and the product began to crystallize. After filtration, washing with acetone, and drying 880 mg (64%) of 7 was obtained as a colorless solid, diastereomeric ratio 1/1. After one recrystallization from H_2O the diastereomeric ratio was 8/2, the major isomer being the one which was isolated predominantly with method a. After two further recrystallizations from H_2O diastereomerically pure product (99.6/0.4) was obtained. Mp: 260–262 °C dec. ^1H NMR (D_2O, 400 MHz): δ 1.30 (d, 3 H, J = 6.8 Hz), 1.88 (ddd, 1 H, J = 14.2, 8.0, 6.6 Hz), 2.16 (m, 1 H), 2.28 (ddd, 1 H, J = 14.0, 8.0, 6.6 Hz), 2.33 (s, 3 H), 2.74 (dd, 1 H, J = 12.8, 7.0 Hz), 2.80 (dd, 1 H, J = 12.8, 6.2 Hz), 4.40 (dd, 1 H, J = 8.0, 6.6 Hz). ^{13}C NMR (D_2O, 100.61 MHz): δ 15.1 and 15.2 (q), 18.1 and 18.9 (q), 29.4 (d), 37.4 (t), 40.8 and 41.1 (t), 53.4 and 53.6 (d), 175.2 and 175.3 (s) (a mixture of both diastereomers resulted in a doubling of all signals. The diastereomeric ratio could be calculated from the S-methyl signal at 2.33 and 2.34 ppm). Anal. Calcd for $C_7H_{15}NO_2S$: C, 47.41; H, 8.53; N, 7.93; S, 18.08. Found: C. 48.0; H, 8.7; N, 7.9; S, 17.1.

(RS)-2-Amino-5-(methylthio)pentanoic Acid (3). Compound 18 (1.50 g, 13.0 mmol) and 2.5 mL (38 mmol) of MeSH were heated at 60 °C in 50 mL of MeOH/H_2O (1/1) for 24 h. During the reaction the product started to crystallize. After cooling, filtration, and washing with MeOH, 1.90 g (89%) of 3 was obtained as colorless crystals. Mp: 280 °C dec. ^1H NMR (DCl/D_2O): δ 1.52–1.87 (m, 2 H), 1.94 (2t, 2 H), 2.08 (s, 3 H), 2.57 (t, 2 H), 3.74 (t, 1 H). ^{13}C NMR (DCl/D_2O): δ 14.4 (q), 24.3 (t), 29.9 (t), 33.0 (t), 54.9 (d), 175.0 (s).

This compound was also prepared by hydrolysis of 2: 77.0 g (0.25 mol) of 2 was suspended in 200 mL of 6 N HCl solution and refluxed for 6 h. Evolution of CO_2 was observed. After 1 h the solution became clear. After cooling, the reaction mixture was evaporated to dryness yielding 50 g (100%) of 3 as a colorless solid.

(S)-2-Amino-5-(methylthio)pentanoic Acid ((S)-3). From the reaction mixture of 500 mg (4.3 mmol) of (S)-18 (ee 76%) and 1.3 mL (20 mmol) of MeSH, heated for 24 h at 50 °C in 15 mL of MeOH/H_2O (1/1), 200 mg (47%) of (S)-3 crystallized as colorless crystals upon cooling. Mp: 276 °C dec. $[\alpha]^{20}_D$: +16.4° (c 1, 1 N HCl). Ee: 93%. (Under identical conditions a quantitative yield of (S)-3 was obtained in an ee of 73% after evaporation of the reaction mixture without further purification).

(S)-2-Amino-5-[(phenylmethyl)thio]pentanoic Acid ((S)-21). In the radical reaction of 320 mg (2.8 mmol) of (S)-18 (ee 76%) and 1.24 g (10 mmol) of BnSH in 20 mL of MeOH/H_2O (3/1) under reflux the product started to crystallize after 2 h. After 18 h the reaction mixture was cooled to rt, and the crystals were filtered off and washed with acetone. Yield: 300 mg (45%) of (S)-21 as colorless crystals. Mp: 244 °C dec. ^1H NMR ($CDCl_3$): δ 1.58 (m, 2 H), 1.88 (m, 2 H), 2.43 (t, 2 H), 3.68 (s, 2 H), 3.99 (t, 1 H), 7.28 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 23.9 (t), 28.5 (t), 29.8 (t), 35.0 (t), 52.4 (d), 127.1 (d), 128.7 (d), 128.8 (d), 138.4 (s), 171.3 (s). $[\alpha]^{20}_D$: +28.2° (c 1, MeOH/1 N HCl (1/1)). Ee 97.4%. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.21; H, 7.16; N, 5.88; S, 13.39. Found: C, 60.3; H, 7.1; N, 5.9; S, 13.3. Identically, starting from 500 mg (4.35 mmol) of (S)-18 (ee 91%) and 1.4 g (11.3 mmol) of BnSH in 30 mL of MeOH/H_2O (3/1) (S)-21 was formed (60 mg portions of AIBN were added at 0, 1, and 17 h). The product crystallized from the reaction mixture. A part of the reaction mixture was worked up with avoidance of enantiomeric enrichment: The heterogeneous mixture was acidified with 2 mL of 4 N HCl solution and extracted with $CHCl_3$ (3×). The clear aqueous layer was evaporated to dryness. The resulting solid ((S)-21·HCl) still contained 5% of starting material (S)-18 as determined by NMR and HPLC (ee 91%). The ee of 21 in the crude reaction product was 82.2% ≙ 0.1%. From another part of the reaction mixture the product crystallized was isolated by filtration. This material had an ee >99.5%. The racemic compound was obtained under identical conditions in 69% yield. Mp: 236 °C dec.

(S)-2-Amino-2-methyl-5-(methylthio)pentanoic Acid ((S)-24). A mixture of 500 mg (3.9 mmol) of (S)-23 (ee 78%), 1.3 mL (23 mmol) of MeSH, and 60 mg of AIBN in 10 mL of MeOH were heated for 3 h at 55 °C, followed by 18 h at rt. The solvent was evaporated, and the resulting semisolid residue was dissolved in 5 mL of hot H_2O and precipitated by addition of 100 mL of acetone. After filtration 560 mg (81%) of (S)-24 was obtained as a colorless solid. Mp: 291–293 °C dec. ^1H NMR (D_2O): δ 1.47 (s, 3 H), 1.47–1.96 (m, 4 H), 2.07 (s, 3 H), 2.53 (t, 2 H). ^{13}C NMR (D_2O): δ 14.4 (q), 22.8 (q), 23.2 (t), 33.2 (t), 36.6 (t), 61.7 (s), 177.0 (s). $[\alpha]^{20}_D$: +21.5° (c 2, 1 N HCl). Exact mass ($C_7H_{15}NO_2S$): calcd 177.0823. Found: 177.0825.

Without addition of AIBN no reaction occurred even after heating at 55 °C for 24 h.

Methyl (S)-2-Amino-2-methyl-5-(methylthio)pentanoate ((S)-26). A solution of 450 mg (3.2 mmol) of (S)-25 (ee 78%), 1.3 mL (23 mmol) of MeSH, and 60 mg of AIBN in 10 mL of MeOH was heated for 3 h at 55 °C and stirred for a further 18 h at rt. After removal of the solvent, NMR of the resulting yellow oil showed conversion to be complete. This oil was purified by bulb to bulb distillation. Yield: 550 mg (91%) of (S)-26 as a colorless oil. Bp: 120 °C/1 mmHg. ^1H NMR ($CDCl_3$): δ 1.34 (s, 3 H), 1.40–1.89 and 1.75 (m and s, 6 H), 2.08 (s, 3 H), 2.48 (t, 2 H), 3.73 (s, 3 H). ^{13}C NMR ($CDCl_3$): 15.4 (q), 23.8 (t), 26.4 (q), 34.3 (t), 40.1 (t), 52.2 (q), 57.7 (s), 177.7 (s). $[\alpha]_D$: +10.5° (c 0.42, MeOH). Ee: 82% (^1H NMR method[20]).

Methyl (S)-2-Amino-2-methyl-5-[(phenylmethyl)thio]-pentanoate ((S)-27). A mixture of 710 mg (5.0 mmol) of (S)-25, 1.24 g (10 mmol) of BnSH, and 80 mg of AIBN in 15 mL of MeOH was refluxed for 40 h. After 25 h additional AIBN (80 mg) was added. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with 1 N KOH solution. After drying (Na_2SO_4) and evaporation of the solvent 1.65 g of a yellow oil was obtained. From this oil 1.00 g (75%) of pure (S)-27 was obtained as a colorless oil after chromatography on silica gel (eluent: $CHCl_3$/5% MeOH). R_f = 0.62 ($CHCl_3$/MeOH (5/1)). ^1H NMR ($CDCl_3$): δ 1.29 (s, 3 H), 1.35–1.85 (m, 6 H), 2.38 (t, 2 H), 3.68 (s) and 3.69 (s, together 5 H), 7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 23.9 (t), 26.3 (q), 31.4 (t), 36.2 (t), 40.1 (t), 52.2 (q), 57.6 (s), 126.9 (d), 128.5 (d), 128.5 (d), 138.5 (s), 177.9 (s). Exact mass ($C_{14}H_{21}NO_2S$): calcd 267.1293. Found: 267.1294. $[\alpha]_D$: −0.4° (c 1, MeOH).

Methyl (S)-2-Amino-8-hydroxy-2-methyl-6-thiaoctanoate (28). From the radical reaction of 710 mg (5.0 mmol) of (S)-25, 780 mg (10 mmol) of 2-mercaptoethanol, and 80 mg of AIBN in 15 mL of refluxing MeOH was obtained 800 mg (73%) of 28 as a slightly yellow oil, after evaporation of the solvent and chromatography on silica gel (eluent: $CHCl_3$/5% MeOH). R_f = 0.52 ($CHCl_3$/MeOH (5/1)). ^1H NMR ($CDCl_3$): δ 1.34 (s, 3 H), 1.42–1.88 (m, 3 H), 2.03 (br, 3 H), 2.53 (t, 2 H), 2.72 (t, 2 H), 3.71 (t) and 3.73 (s, together 5 H). ^{13}C NMR ($CDCl_3$): δ 24.4 (t), 26.3 (q), 31.8 (t), 35.2 (t), 39.9 (t), 52.3 (q), 57.6 (s), 60.4 (t), 177.8 (s). This compound could not be lactonized to a 9-membered ring at 170 °C. Starting material only was recovered.

(R)-2-Amino-2-methyl-5-(methylthio)pentanoic Acid Amide ((R)-30). A solution of 500 mg (3.9 mmol) of (R)-29 (ee 54%), 1.0 mL (18 mmol) of MeSH, and 50 mg of AIBN was heated at 60 °C in MeOH for 24 h. After cooling and evaporation of the solvent 700 mg of (R)-30 was isolated as a slightly yellow oil (NMR pure, 100% yield). ^1H NMR ($CDCl_3$): δ 1.37 (s, 3 H), 1.43 (br, 2 H), 1.55–1.75 (m, 3 H), 1.91 (dd, 1 H, J = 11.0, 8.0 Hz), 2.10 (s, 3 H), 2.40–2.61 (m, 2 H), 5.82 (br, 1 H), 7.37 (br, 1 H). ^{13}C NMR ($CDCl_3$): δ 15.5 (q), 23.8 (q), 28.1 (t), 34.3 (t), 40.3 (t), 57.5 (s), 180.1 (s). $[\alpha]_D$: +2.3° (c 2, MeOH). Exact mass ($C_7H_{16}N_2OS$): calcd 176.0983. Found: 176.0979.

Methyl (RS)-N-(benzyloxycarbonyl)-2-amino-5-(acetylthio)pentanoate (11) was prepared from 35 g (133 mmol) of 9, 13.2 g (173 mmol) of AcSH, and 0.1 g of AIBN by heating at 75 °C for 4.5 h in 250 mL of toluene. After 1, 2, and 3 h additional

0.1-g portions of AIBN were added. The solvent was evaporated, and 44.8 g (99%) of 11 resulted as an oil. NMR indicated complete conversion. After standing for 2 weeks the material solidified. A portion of 19.3 g of this material was recrystallized in a wasteful crystallization from 300 mL of Et_2O/CH_2Cl_2 (9/1). After filtration, washing with hexane, and drying 12.4 g of white crystalline 11 was obtained. Mp: 79–80 °C. ^1H NMR ($CDCl_3$): δ 1.53–1.75 (m, 3 H), 1.81–1.97 (m, 1 H), 2.32 (s, 3 H), 2.87 (t, 2 H), 3.83 (s, 3 H), 4.37 (br dd, 1 H), 5.10 (s, 2 H), 5.44 (br d, 1 H), 7.33 (s, 5 H). ^{13}C NMR ($CDCl_3$): δ 23.7 (t), 26.6 (t), 28.8 (q), 29.8 (t), 50.6 (d), 51.6 (q), 65.2 (t), 126.3 (d), 126.4 (d), 126.7 (d), 134.4 (s), 154.1 (s), 170.8 (s), 193.7 (s). Anal. Calcd for $C_{16}H_{21}NO_5S$: C, 56.61; H, 6.24; N, 4.14; S, 9.55. Found: C, 57.0; H, 6.4; N, 4.2; S, 9.1.

(*RS*)-2-Amino-5-mercaptopentanoic Acid·HCl Salt (19·HCl). Compound 18 (2.0 g, 17.3 mmol) was dissolved in 5 mL of 4 N HCl solution and evaporated to dryness to obtain 18·HCl. After the compound was dissolved in 50 mL of dioxane/H_2O (15/1), 2.5 g (52 mmol) of AcSH and 60 mg of AIBN were added and the solution was heated at 80 °C for 48 h. Additional 60-mg amounts of AIBN were added after 16, 24, and 40 h. After 24 h an additional 2 g (42 mmol) of AcSH was also added. After cooling, the reaction mixture was evaporated and stripped with toluene, yielding 3.0 g (±79%) of crude 19·HCl as a yellow oil. ^1H NMR (D_2O): δ 1.64–1.80 (m, 2 H), 1.96–2.12 (m, 2 H), 2.56 (t, 2 H), 4.08 (t, 1 H). The product had a purity of about 85% and contained some *S*-acetyl-substituted product. The product was not further purified, however.

Methyl (*RS*)-2-Amino-5-mercaptopentanoate (33). The crude reaction product 19·HCl from the previous synthesis (prepared from 500 mg (4.35 mmol) of 18) was dissolved in 25 mL of MeOH containing 1.0 g of dry HCl. The clear solution was refluxed for 20 h under nitrogen. After being cooled the reaction mixture was concentrated to 1 g (yellow oil). This was dissolved in 20 mL of H_2O and extracted with $CHCl_3$ (2×). The aqueous layer was neutralized to pH 8 and extracted with $CHCl_3$ (4 × 25 mL). After drying (Na_2SO_4) and evaporation 560 mg (79%) of 33 was isolated as a yellow oil. This oil contained approximately 10% of disulfide (^1H NMR), but was not further purified. ^1H NMR ($CDCl_3$): δ 1.38 (br t, 1 H), 1.57 (br s, 2 H), 1.63–1.92 (m, 4 H), 2.56 (br q, 2 H), 3.47 (t, 1 H), 3.74 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 25.9 (t), 31.7 (t), 35.0 (t), 53.5 (q), 55.5 (d), 177.8 (s).

(*RS*)-2-Acetamido-5-(acetylthio)pentanoic Acid (20). Compound 18 (1.0 g, 8.6 mmol) was suspended in 30 mL of dioxane. To this suspension were added 50 mg of AIBN and 2.5 g (52 mmol) of AcSH, and the mixture was heated to 100 °C for 48 h. After 16 h the solution became clear. At 16, 24, and 40 h additional amounts of AIBN (50 mg) were added. After cooling the solvent was evaporated. The resulting yellow oil (2.9 g) was chromatographed on silica gel (eluent: $CHCl_3$/MeOH (4/1)). A total of 1.03 g (±51%) of 20 was isolated as a yellow oil, containing 10% of N-acetylated starting product. ^1H NMR ($CDCl_3$): δ 1.60–1.82 (m, 3 H), 1.88–2.09 and 2.04 (m and s, 4 H), 2.34 (s, 3 H), 2.88 (t, 2 H), 7.01 (br d, 1 H), 8.45 (br, 1 H). ^{13}C NMR ($CDCl_3$): δ 22.7 (q), 25.7 (t), 28.5 (t), 30.7 (q), 30.9 (t), 52.0 (d), 171.7 (s), 174.3 (s), 196.6 (s). Exact mass ($C_9H_{15}NO_4S$): calcd 233.0722. Found: 233.0716.

(*RS*)-5-(Acetylthio)-2-(benzoylamido)pentanoic Acid (17). Compound 16 (1.10 g, 5 mmol), 1.0 g (13 mmol) of AcSH, and 60 mg of AIBN were refluxed in MeOH for 20 h and afforded after workup (evaporation of the solvent and crystallization from 50 mL of $CHCl_3$/toluene (1/1)) 1.20 g (81%) of 17 as colorless crystals. Mp: 147–148.5 °C. ^1H NMR ($CDCl_3$): δ 1.80–2.20 (m, 4 H), 2.31 (s, 3 H), 2.91 (t, 2 H), 4.69 (m, 1 H), 7.37–7.55 (m, 4 H), 7.84 (dd, 2 H), ±12.0 (br). ^{13}C NMR ($CDCl_3$): δ 25.3 (t), 28.2 (t), 30.2 (q), 30.8 (t), 51.9 (d), 126.9 (d), 128.0 (d), 131.1 (d), 134.0 (s), 166.8 (s), 173.6 (s), 195.1 (s). Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.92; H, 5.80; N, 4.76; S, 10.85. Found: C, 56.9; H, 5.9; N, 4.8; S, 10.6.

(*RS*)-*N*-(Benzyloxycarbonyl)-2-amino-5-(acetylthio)pentanoic Acid (15). From the reaction of 1.25 g (5.0 mmol) of 14, 1.0 g (13 mmol) of AcSH and 60 mg of AIBN refluxed in MeOH for 18 h, and after evaporation of the reaction mixture and crystallization from 25 mL of toluene, 1.42 g (87%) of 15 was isolated as colorless crystals. Mp: 122.5–123.5 °C. ^1H NMR ($CDCl_3$): δ 1.58–2.07 (m, 4 H), 2.31 (s, 3 H), 2.87 (br t, 2 H), 4.28 and 4.40 (2br q, 1 H, 21/79 ratio of rotamers), 5.09 and 5.14 (s + shoulder, 2 H), 5.44 (d, 0.79 H) and 6.57 (d, 0.21 H), 7.33 (s, 5 H), 10.1 (br, 1 H). ^{13}C NMR ($CDCl_3$): δ 23.9 (t), 26.9 (t), 29.1 (q), 29.8 (t), 51.8 (d), 65.7 (t), 126.6 (d), 126.7 (d), 127.0 (d), 134.5 (s), 154.6 (s), 175.0 (s), 194.5 (s). Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.36; H, 5.88; N, 4.32; S, 9.85. Found: C, 55.3; H, 5.9; N, 4.3; S, 10.6.

Methyl (*RS*)-*N*-Phthaloyl-5-(acetylthio)-2-aminopentanoate (13). A solution of 19.6 g (76 mmol) of 12, 8.64 g (113.7 mmol, 1.5 equiv) of AcSH, and 20 mg of AIBN in 75 mL of toluene was heated at 92 °C for 4 h. After 1, 2, and 3 h additional 20-mg portions of AIBN were added. After evaporation 26.5 g of a yellow oil resulted which solidified on standing. This material was crystallized from 150 mL of hexane/EtOH (2/1). Yield: 23.8 g (94%) of 13 as a white crystals. From the filtrate a further 1.0 g of 13 after crystallization from 12 mL of hexane/EtOH (2/1) was obtained. Total yield: 24.8 g (97%). Mp: 71–73 °C. ^1H NMR ($CDCl_3$): δ 1.48–1.73 (m, 2 H), 2.91 (s) and 2.25–2.37 (m, together 5 H), 2.88 (t, 2 H), 3.74 (s, 3 H), 4.87 (t, 1 H, J = 8 Hz), 7.74–7.92 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 27.6 (t), 29.0 (t), 29.4 (t), 31.7 (q), 52.7 (d), 53.9 (q), 124.7 (d), 132.9 (s), 135.4 (d), 168.7 (s), 170.5 (s). Anal. Calcd for $C_{16}H_{17}NO_5S$: C, 57.29; H, 5.11; N, 4.19; S, 9.56. Found: C, 57.1; H, 5.2; N, 4.1; S, 9.7.

Methyl (*RS*)-*N*-Phthaloyl-2-amino-5-mercaptopentanoate (32). A mixture of 6.0 g (17.9 mmol) of 13 and 0.5 g of TsOH·H_2O in 100 mL of MeOH was heated to reflux. At 40 °C the solution became homogeneous. After being refluxed for 16 h, the solvent was evaporated and the residue partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with another portion of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to yield 5.35 g of 32 as a colorless oil. Purity according to NMR ±90%. The compound was not further purified. ^1H NMR ($CDCl_3$): δ 1.37 (t, 1 H, J = 8 Hz), 1.53–1.76 (m, 2 H), 2.30–2.41 (m, 2 H), 2.55 (qd, 2 H, J = 8, 2 Hz). ^{13}C NMR ($CDCl_3$): δ 22.4 (t), 26.1 (t), 29.2 (t), 50.1 (d), 51.4 (q), 122.2 (d), 130.2 (s), 132.9 (d), 166.1 (s), 168.1 (s). Exact mass ($C_{14}H_{15}NO_4S$): calcd 293.0722. Found: 293.0719.

(*RS*)-2-Amino-2-phenyl-4-pentenoic acid amide was prepared by phase-transfer allylation of 119 g (0.50 mol) of *N*-benzylidene-α-phenylglycine amide according to the literature method.[17] Yield: 58.5 g (60%) as colorless crystals. Mp: 113–114 °C. ^1H NMR ($CDCl_3$): δ 2.14 (br, 2 H), 2.59 (dd, 1 H, J = 13.5, 7.0 Hz), 2.86 (dd, 1 H, J = 13.5, 5.5 Hz), 4.95–5.08 (m, 2 H), 5.58–5.75 (m, 1 H), 7.07 (br, 1 H), 7.20–7.55 (m, 6 H). ^{13}C NMR ($CDCl_3$): δ 44.5 (t), 62.6 (s), 118.8 (t), 125.9 (d), 126.6 (d), 127.9 (d), 134.7 (d), 144.6 (s), 176.9 (s). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.40; H, 7.41; N, 14.78. Found: C, 70.2; H, 7.5; N, 14.7.

(*RS*)-2-Amino-2-phenylpent-4-en-1-ol (34). Starting with 5.0 g (26 mmol) of the amide from the previous experiment, 2-amino-2-phenyl-4-pentenoic acid was prepared by hydrolysis with 4 N HCl solution (18 h reflux). After evaporation of the solution, the residue was made alkaline with 4 N NaOH solution and was extracted with $CHCl_3$ to remove the lactonized acid (50%, diastereomeric ratio 2/1). The free acid precipitated after neutralization of the aqueous layer with 4 N HCl solution. 2-Amino-2-phenyl-4-pentenoic acid (2.1 g, 42%) was isolated as a white solid. From 2.0 g (10.5 mmol) of this acid was isolated 34 as a colorless oil by standard BH_3·SMe_2/BF_3 reduction.[18] ^1H NMR ($CDCl_3$): δ 2.44 (dd, 1 H, J = 13.5, 8.5 Hz), 2.62– (dd + long range, 1 H, J = 13.5, 6.5 Hz), 3.61 (s, 2 H), 5.02–5.13 (m, 2 H), 5.36–5.56 (m, 1 H), 7.18–7.40 (m, 5 H), the NH_2 and OH signals are visible as an elevated base line from 1.5 to 3.0 ppm. ^{13}C NMR ($CDCl_3$): δ 44.0 (t), 58.7 (s), 70.6 (t), 119.1 (t), 125.7 (d), 126.8 (d), 128.4 (d), 133.3 (d), 144.51 (s).

(*RS*)-2-Amino-5-(methylthio)-2-phenylpentan-1-ol (35). A solution of 500 mg (2.82 mmol) of 34, 1.5 mL (27 mmol) of MeSH, and 50 mg of AIBN in 10 mL of MeOH was heated for 50 h at 60 °C. After 17 h, additional AIBN (50 mg) was added after cooling the reaction mixture to −20 °C. Removal of the solvent gave 650 mg of a yellow oil which was purified by chromatography on silica gel (eluent: $CHCl_3$/MeOH (10/1), R_f = 0.23). Yield: 500 mg (79%) of 35 as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.22–1.64 (m, 2 H), 1.76 (ddd, 1 H, J = 13.5, 11.5, 5.0 Hz), 1.95 (ddd, J = 13.5, 11.5, 5.0 Hz) and 1.97 (s, together 4 H), 2.16 (br s, 3 H), 2.30–2.53 (m, 2 H), 3.62 (d, 1 H, J = 10 Hz), 3.68 (d, 1 H, J = 10 Hz), 7.20–7.44 (m, 5 H). ^{13}C NMR ($CDCl_3$): δ 16.2 (q),

23.7 (t), 30.6 (s), 35.4 (t), 39.0 (t), 72.0 (t), 126.7 (d), 127.6 (d), 129.3 (d), 145.1 (s). Exact mass (CI) ($C_{12}H_{19}NOS$ + H): calcd 226.1266. Found 226.1266.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for new compounds without elemental analyses (22 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Electron Demand in the Transition State of the Cyclopropylidene to Allene Ring Opening

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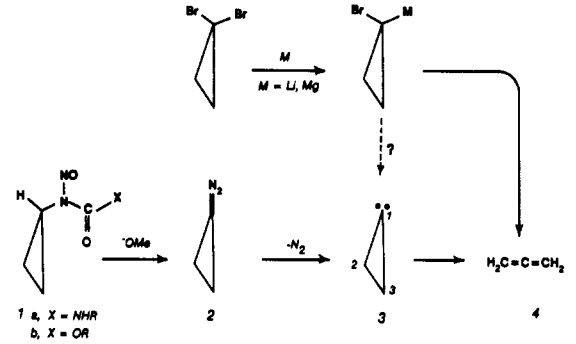
The electronic structure of the transition state for the cyclopropylidene to allene conversion has been probed. The methodology involved the relative rates of ring opening vs trapping by MeOH for a series of variously substituted 2,3-diarylcyclopropylidenes. With the assumption that the rate of trapping was unaffected by substituents, a Hammett correlation was constructed. The negative value (−0.72) for ρ indicated that the carbenic center attracts electron density in the ring-opening transition state, much like the cyclopropyl cation to allyl cation transition state. Temperature-dependent studies showed that the observed preference for ring opening was driven by entropy factors. Also, using reasonable estimates for the close to diffusion-controlled trapping activation enthalpies, the derived enthalpies for ring opening were in close agreement with the best theoretical values.

Introduction

Since the demonstration that dibromocyclopropanes could be converted to allenes over 30 years ago,[1] the possible intermediate cyclopropylidene (3) has captured the interest of experimentalists[2] and theoreticians alike.[3] While the formation of free cyclopropylidene from dibromocyclopropanes is questionable, such species may be accessed from nitrosoureas (1a, X = NHR) and nitrosocarbamates (1b, X = OR), both of which decompose to intermediate (but trappable) diazo compounds 2 under the influence of base.[4] More than 25 years ago, Jones and coworkers studied the stereochemistry of the ring opening of 3 and the effect of substituents on the stereochemistry.[5] Theoretical understanding of the observed stereochemistry has been gained recently.[3i-m]



The most recent,[3f,g,i,j,l] and even earlier,[3e] calculations indicate that the ring opening of 3 proceeds via disrotation until the C_s transition state is reached at a $C_2C_1C_3$ angle of about 84.5°;[3l] disrotation continues with maintenance of C_s symmetry until a $C_2C_1C_3$ angle of about 100° is reached, at which point the reaction surface bifurcates into enantiomers via admixture of a conrotatory component, ultimately leading to allene. The ring opening barrier was found to be about 7 kcal/mol at the MCSCF/CISD level, corrected for zero point energy effects. The finding of a disrotatory path through the transition state suggests that the process is strictly analogous to the 2e, disrotatory ring opening of a cyclopropyl cation (cf. 5 to 6).[6] This would

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(1) Doering, W.; LaFlamme, P. M. *Tetrahedron* **1958**, 75.

(2) (a) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971; pp 254, 462. (b) Jones, M., Jr. *Carbenes*; Wiley: New York, 1973. (c) Moore, W. R.; Hill, J. B. *Tetrahedron Lett.* **1970**, 4553. (d) Reinarz, R. B.; Fonken, G. J. *Ibid.* **1973**, 4591, 4595; **1974**, 441. (e) Drachenberg, K. J.; Hopf, H. *Ibid.* **1974**, 3267. (f) Paquette, L. A.; Zon, G.; Taylor, R. T. *J. Org. Chem.* **1974**, *39*, 2677. (g) Sydnes, L.; Skattebol, L. *Tetrahedron Lett.* **1975**, 4603. (h) Minter, D. E.; Fonken, G. J. *Ibid.* **1977**, 1717. (i) Seyferth, D.; Lambert, R. L., Jr. *J. Organomet. Chem.* **1975**, *91*, 31. (j) Paquette, L. A.; Taylor, R. T. *J. Am. Chem. Soc.* **1977**, 5708. (k) Shono, T.; Nishiguchi, I.; Komamura, T.; Fujita, K. *Tetrahedron Lett.* **1977**, 4327. (l) Baird, M. S. *J. Chem. Soc., Chem. Commun.* **1979**, 776. (m) Waali, E. E.; Allison, N. T. *J. Org. Chem.* **1979**, *44*, 3266. (n) Nakazaki, M.; Yamamoto, K.; Maeda, M.; Sato, O.; Tsutsui, T. *Ibid.* **1982**, *47*, 1435. (o) Taylor, K. G. *Tetrahedron* **1982**, *38*, 2751. (p) Tubul, A.; Meou, A.; Bertrand, M. *Tetrahedron Lett.* **1983**, *24*, 4199. (q) Nilsen, N. O.; Skattebol, L. *Ibid.* **1984**, *25*, 2887. (r) Warner, P.; Chu, I.-S. *J. Org. Chem.* **1984**, *49*, 3666. (s) Xu, L.; Tao, F.; Yu, T. *Tetrahedron Lett.* **1985**, *26*, 4231. (t) Holm, K. H.; Skattebol, L. *Acta Chem. Scand.* **1985**, *B 39*, 549. (u) Lisko, J. R.; Jones, W. M. *Organometallics* **1985**, *4*, 612. (v) Price, J. D.; Johnson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 2187. (w) Jorgensen, E.; Sydnes, L. K. *J. Org. Chem.* **1986**, *51*, 1926. (x) Warner, P.; Herold, R. D.; Chu, I.-S.; Lessman, J. *Ibid.* **1988**, *53*, 942. (y) Brinker, U. H. *Methoden Der Organischen Chemie*; Georg Thieme: Stuttgart, 1989; E19b, pp 391–510.

(3) (a) Borden, W. T. *Tetrahedron Lett.* **1967**, 447. (b) Dewar, M. J. S.; Haselbach, E.; Shanshal, M. *J. Am. Chem. Soc.* **1970**, *92*, 350. (c) Bodor, N.; Dewar, M. J. S.; Maksic, Z. *Ibid.* **1973**, *95*, 5245. (d) Dillon, P. W.; Underwood, G. R. *Ibid.* **1977**, *99*, 2435. (e) Pasto, D. J.; Haley, M.; Chipman, D. M. *Ibid.* **1978**, *100*, 5272. (f) Honjou, N.; Pacansky, J.; Yoshimine, M. *Ibid.* **1984**, *106*, 5361. (g) Rauk, A.; Bouma, W. J.; Radom, L. *Ibid.* **1985**, *107*, 3780. (h) Honjou, N.; Pacansky, J.; Yoshimine, M. *Ibid.* **1985**, *107*, 5332. (i) Valtazanos, P.; Elbert, S. T.; Ruedenberg, K. *Ibid.* **1986**, *108*, 3147. (j) Valtazanos, P.; Elbert, S. T.; Xantheas, S.; Ruedenberg, K. *Theor. Chim. Acta* **1991**, *78*, 287. (k) Xantheas, S.; Valtazanos, P.; Ruedenberg, K. *Ibid.* 327. (l) Xantheas, S.; Elbert, S. T.; Ruedenberg, K. *Ibid.* 365. (m) Valtazanos, P.; Ruedenberg, K. *Ibid.* 397.

(4) (a) Jones, W. M. *J. Am. Chem. Soc.* **1960**, *82*, 6200. (b) Jones, W. M.; Grasley, M. H.; Brey, W. S. *Ibid.* **1963**, *85*, 2754. (c) Jones, W. M.; Grasley, M. H.; Baarda, D. G. *Ibid.* **1964**, *86*, 912. (d) Jones, W. M.; Muck, D. L.; Tandy, J. K. *Ibid.* **1966**, *88*, 68. (e) Muck, D. L.; Jones, W. M. *Ibid.* **1966**, *88*, 74. (f) Jones, W. M.; Walbrick, J. M. *J. Org. Chem.* **1969**, *34*, 2217. (g) Kirmse, W.; Jendralla, H. *Chem. Ber.* **1978**, *111*, 1857, 1873. (h) Kirmse, W.; Hellwig, G. *Ibid.* **1982**, *115*, 2744.

(5) (a) Jones, W. M.; Wilson, J. W., Jr.; Tutwiler, F. B. *J. Am. Chem. Soc.* **1963**, *85*, 3309. (b) Jones, W. M.; Wilson, J. W., Jr. *Tetrahedron Lett.* **1965**, 1587. (c) Walbrick, J. M.; Wilson, J. W., Jr.; Jones, W. M. *J. Am. Chem. Soc.* **1968**, *90*, 2895. (d) Jones, W. M.; Krause, D. L. *Ibid.* **1971**, *93*, 551. (e) Moore, W. R.; Bach, R. D. *Ibid.* **1972**, *94*, 3148. (f) Warner, P.; Wang, C. Unpublished results.

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