(2.5), 95 (3), 93 (45), 55 (1.5), 45 (8), 43 (100).

Preparation of the Keto Acetate 40. Monoacetate **38** (233 mg) in CH_2Cl_2 (3 mL) was added dropwise to a suspension of pyridinium chlorochromate[37] (330 mg) in CH_2Cl_2 (3 mL) at room temperature. The mixture was stirred for 2 h and diluted with anhydrous ether (6 mL), the supernatant decanted, and the gummy residue extracted with ether (3 × 6 mL). After solvent evaporation, the residue (249 mg) was chromatographed through a short silica gel column ($CHCl_3$) to yield **40** (198 mg, 86%) as a colorless oil. ^1H NMR: δ 1.25 (s, 3 H), 1.29 (s, 3 H), 2.01 (s, 3 H), 3.75 and 3.97 (AB q, J = 11.5 Hz, 10-CH_2). IR (film): 1730–1750 cm^{-1} (acetate and carbonyl). MS: m/z (rel int) 153 (M – CH_2OAc; 62), 111 (153 – CH_2=C=O; 51), 109 (10), 71 (5.5), 67 (6), 57 (6), 55 (16), 43 (100).

3,6-Dimethyl-4,5-dihydrobenzofuran (42) and Menthofuran (44). The keto acetate **40** (100 mg) in benzene (3 mL) was magnetically stirred at 50 °C under an N_2 atmosphere with 2 M hydrochloric acid (10 mL) for 4 h. The benzene layer was separated, and the aqueous layer was further extracted with ether (3 × 10 mL). The organic extracts were washed with aqueous sodium hydrogen carbonate solution and brine, dried, and evaporated in vacuo, giving a residue, which was chromatographed on a Florisil column (4 g). Elution with pentane afforded **42** (13 mg, 20%) as a pale yellow oil, sensitive to air and light. ^1H NMR: δ 1.82 (br s, 3 H), 1.88 (br s, 3 H), 6.69 (m, 1 H), and 7.25 (m, 1 H). This compound, dissolved in pentane (2 mL) and cooled at 0 °C, was subjected to a microhydrogenation for 15 min using Adams' catalyst (4 mg). After solvent evaporation, the residue was analyzed by GC, showing the following composition: **44**, 82%; **45**, 12%; and minor amounts of other unidentified products. Compounds **44** and **45** were identified by comparison with authentic samples on three different GC columns. The protonic spectrum of the mixture clearly showed the signals corresponding to **44**.[43]

***exo,exo*-1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane-5,8-diol (46).** Diketone **13** (1.023 g) in methanol (25 mL) was treated with sodium borohydride (230 mg), and the mixture was stirred at room temperature for 27 h. The solution was neutralized with glacial acetic acid, then alkalized to pH 8 with sodium carbonate solution, and thoroughly extracted with ethyl acetate. After solvent evaporation, the residue was chromatographed on a silica gel column with chloroform–acetone, 7:3, to give **46** (1.003 g, 96%) as plates, mp 165–165.5 °C (ethyl acetate–heptane). IR (KBr): 3430–3180 (OH), 1370, 1355, 1250, 1220, 1115, 1030, and 970 cm^{-1}. ^1H NMR ($CDCl_3$ + Me_2SO-d_6): δ 1.08 (s, 3 H, 9-Me), 1.41 (s, 6 H, 10-Me and 11-Me), 3.80 (m, 4 H, 2 OH, C_5-H and C_8-H). MS: m/z (rel int) 171 (M – Me; 74), 142 (6), 131 (3), 127 (23), 125 (7), 109 (16), 100 (10), 93 (92), 87 (24), 85 (53), 73 (63), 43 (100).

Acknowledgment. We thank Dr. M. Gonzâlez Sierra, IQUIOS, Universidad Nacional de Rosario, for the ^{13}C NMR spectra and Prof. J. Kavka, LEA, Universidad Nacional de San Luis, for the mass spectra. We also thank the Consejo Nacional de Investigaciones Cientîficas y Tëcnicas de la Repûblica Argentina and SECYT for financial support.

(43) Zalkov, L. H.; Ellis, J. W.; Brennan, M. R. *J. Org. Chem.* **1963**, *28*, 1705.

Total Synthesis and Absolute Configuration of the Natural Dipeptide γ-Glutamylmarasmine

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The natural dipeptide γ-glutamylmarasmine (**1**) and its sulfoxide epimer **22** have been synthesized in optically active form starting from L-glutamic acid and L-cystine. In a convergent approach, the amine **14** and the anhydride **15** were synthesized and subsequently coupled by amide formation. After separation of the epimeric sulfoxides **16** and **17** and subsequent removal of the amino and carboxyl protecting groups (→ **20** and **21**), the chlorine atom was substituted by SMe by reaction with NaSMe in liquid ammonia to yield **1** and **22**, respectively. By comparison of ^3J and [α] values it was concluded that **1** is identical with γ-glutamylmarasmine. The absolute configuration of **1** was determined by CD spectroscopy; the sign of the Cotton effect was employed in the assignment of the configuration of the sulfoxide–sulfur atom. γ-Glutamylmarasmine was thus assigned the $S_cR_cS_s$ configuration.

Introduction

During the last 25 years, a large number of γ-glutamyl derivatives of amino acids and amines have been isolated from plants including mushrooms (Basidiomycetes).[1] Among these are eighteen γ-glutamyl derivatives of sulfur or selenium containing non-protein amino acids.[1] One of these is γ-glutamylmarasmine (**1**) an *N*-γ-L-glutamyl *S*-substituted L-cysteine derivative.

This dipeptide has been isolated[2] from the Basidiomyceteous mushrooms *Marasmius alliaceus*, *M. scorodonius*, and *M. prasiosmus* which are known for their garlic like odor.[3] In aqueous solution it gradually decomposes with the formation of the typical odor of the parent mushrooms.[2] This odor has been ascribed to products derived from the sulfenic acid $MeSCH_2SOH$ formed from **1** by an acid-catalyzed β-elimination[4] reaction with concomitant formation of γ-glutamyldehydroalanine. In the mushroom itself a similar degradation takes place catalyzed by the fungal C–S lyase.[2,5] However, this β-elimination reaction takes place at higher pH (8.5) and only after cleavage of the amide bond of **1** by γ-glutamyl transpeptidase.[6,7] This

(1) Kasai, T.; Larsen, P. O. In *Fortschritte der Chemie organischer Naturstoffe*; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer Verlag: New York, 1980; p 173.

(2) Gmelin, R.; Luxa, H.-H.; Roth, K.; Höfle, G., *Phytochemistry* **1976**, *15*, 1717.

(3) Michael, E.; Hennig, B.; Kreisel, H. *Handbuch für Pilzfreunde*, 6. Bd.; VEB Gustav Fischer Verlag: Jena, 1975.

(4) Ostermayer, F.; Tarbell, D. S. *J. Am. Chem. Soc.* **1960**, *82*, 3752.

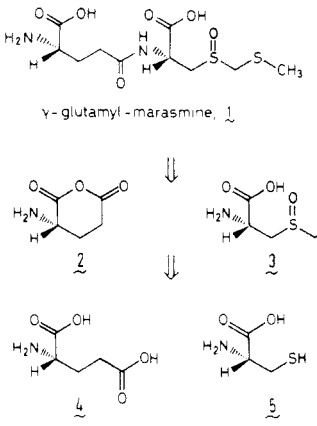
(5) A C–S lyase from the endosperm of seeds of *Albizzia lophantha* (Mimosaceae) also catalyzes the enzyme-mediated β-elimination reaction of γ-glutamylmarasmine. Both this C–S lyase and the C–S lyase (EC 4.4.1.1.*n*) extracted from the mycelium and carpophores of *M. alliaceus* and *M. scorodonius* show a broad activity spectrum against different substrates (L-cysteine, S-alkyl- or aralkyl- and aryl-L-cysteines, L-djenkolic acid, and the corresponding sulfoxides) affording H_2S, RSH, $CH_2(SH)_2$, or RSS(O)R, respectively, together with pyruvic acid and ammonia.

(6) Turner, W. B.; Aldridge, D. C. *Fungal metabolites II*; Academic: New York, 1983; pp 468, 487.

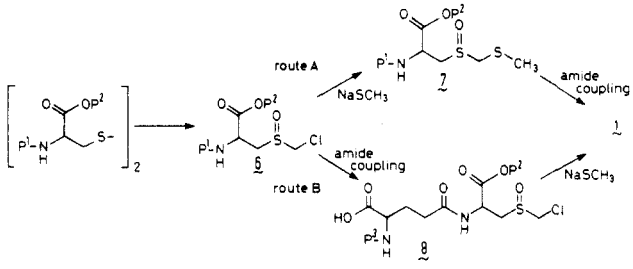
(7) Meister, A. D.; Tate, S. S.; Griffith, O. W. *Methods Enzymol.* **1981**, *77*, 237.

0022-3263/87/1952-1511$01.50/0

Scheme I



Scheme II

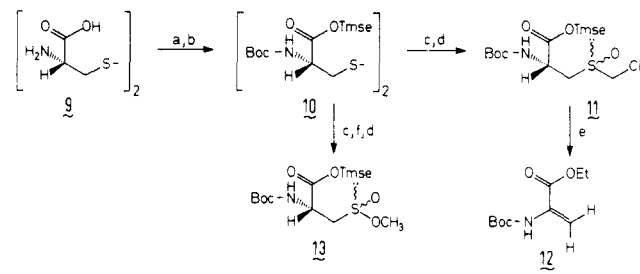


C–S lyase-induced β-elimination reaction is characteristic for many *S*-substituted γ-glutamylcysteine compounds.[8]

The presently accepted structure **1** of the title compound was proposed by R. Gmelin et al.[2] on the basis of spectroscopic methods as well as chemical and enzymatic degradation studies. The chirality of the two carbon atoms was shown to correspond to that of the L-amino acids. However, the chirality of the sulfur atom was not determined.

There is a wealth of information showing that the biological activity of naturally occurring sulfoxides is dependent upon the chirality of the sulfoxide function.[11]

Scheme III



Reagents: (a) $(Boc)_2O$, NaOH. (b) HOTmse (2-(trimethylsilyl)ethanol), DCC (c) Cl_2, Ac_2O. (d) CH_2N_2 (e) $NaSCH_3$, EtOH (f) H_2O

Therefore we decided to establish the absolute configuration of the sulfoxide sulfur atom of γ-glutamylmarasmine by total synthesis of both diastereomers.

Strategy

γ-Glutamylmarasmine (**1**) may be considered as a dipeptide derived from L-glutamic acid (**4**) and the amine **3**, i.e., marasmine (Scheme I). The latter can be viewed as a derivative of L-cysteine (**5**) having the sulfhydryl function alkylated and oxidized. The method of choice for coupling these two amino acids seems to be reaction of marasmine (**3**) with the properly *N*-protected L-glutamic anhydride **2**, which is known to react predominantly at the γ-carbonyl function.[1,14] For *N*-protection we selected the phthaloyl group which can be removed by hydrazinolysis.[15]

More challenging was the synthesis of marasmine (**3**). Its monoxodithioacetal moiety is acid labile and is also capable of undergoing thermal- or base-induced β-elimination reactions (vide supra).[16]

Recently, in the course of a total synthesis of sparsomycin we developed an approach to the monoxodithioacetal moiety employing the reaction of an α-chloro sulfoxide derivative of cysteine with sodium methyl mercaptide.[18] Here we report that this approach can also be employed for the synthesis of **1** (Scheme II). The key intermediate is the *N,O*-protected cysteine derivative **6**. Of ultimate importance is the selection of the protecting groups which had to meet the following requirements.

(8) Noteworthy examples are (epi)lentinic acid (ref 9) in *Lentinus edodes*, shiitake, the popular Japanese edible mushroom, and γ-glutamyl-*S*-(prop-1-enyl)cysteine sulfoxides in onion (*Allium cepa*) (ref 10). Via consecutive transpeptidation and C–S lyase-mediated β-elimination, these compounds give rise to the formation of pyruvic acid, ammonia, and various volatile sulfur compounds including lenthionine–the major flavoring substance obtained from *Lentinus edodes*—and thiopropanal *S*-oxide, which is the lachrymatoric substance of onions and other *Allium* species.

(9) Yasumoto, K.; Iwami, K.; Mitsuda, H. *Agric. Biol. Chem.* **1971**, *35*, 2059. Lentinic acid and epilentinic acid are supposed to be epimers that differ in chirality of one of the sulfoxide sulfur atoms: Gmelin, R.; N'Galamulume-Treves, M.; Höfle, G. *Phytochemistry* **1980**, *19*, 553.

(10) Kuttan, R.; Nair, N. G.; Radhakrishnan, A. N.; Spande, T. F., Yeh, H. J.; Witkop, B. *Biochemistry* **1974**, *13*, 4394 and references cited therein.

(11) There is a large number of naturally occurring sulfoxides for which the absolute configurations have been determined. Particularly intriguing among these are toxins obtained from poisonous mushrooms of the genus *Amanita*; whereas the compounds of one sulfoxide configuration, i.e., R_s, are very lethal, the compounds of the opposite configuration are inactive up to rather high dose levels (ref 12). Another class of naturally occurring sulfoxides, γ-glutamylcysteine sulfoxides, gives rise to a number of curious sulfur compounds that underlie the odor of garlic and the crying brought on by slicing an onion. Investigations on the chemistry of garlic and the onion revealed (ref 13) that enzymes (allinases) occurring in these plants preferentially act on (+)-*S*-(*trans*-2-propenyl)-L-cysteine sulfoxide (i.e., alliin) and (+)-*S*-(*trans*-1-propenyl)-L-cysteine sulfoxide (i.e., lacrimatory precursor of onions), leaving the isomers with opposite chirality at the sulfur atom unreacted. Another interesting occurrence of diastereomeric sulfoxides was observed in the γ-L-glutamyl-*S*-(*trans*-1-propenyl)-L-cysteine sulfoxides from both Sandal (*Santalum album L.*) and onion (*Allium cepa*) (ref 10). The sulfoxide sulfur atoms in the Sandal and onion metabolites have the *R* and *S* chirality, respectively. It is of interest that in Sandal no lacrimation was observed.

(12) Wieland, Th.; Urries, M. P. J. de; Indest, H.; Faulstich, H. *Liebigs Ann. Chem.* **1974**, 1570. Buku, A.; Altmann, R.; Wieland, Th. *Liebigs Ann. Chem.* **1974**, *1580*.

(13) SpÅre, C.-G.; Virtanen, A. I. *Acta Chem. Scand.* **1963**, *17*, 641. Virtanen, A. I. *Qual. Plant. Mater. Veg.* **1969**, *18*, 8. Block, E. *Sci. Am.* **1985**, 94.

(14) In a large-scale synthesis of N^5-(1-hydroxycyclopropyl)-L-glutamine (coprine, 250 g), however, a lesser amount of isocoprine (13 g) was isolated. See: Lindberg, P.; Bergman, R.; Wickberg, B. *J. Chem. Soc. Perkin Trans.* **1977**, 684.

(15) Houben-Weyl *Methoden der organischen Chemie*, 15/I, Georg Thieme Verlag: Stuttgart, 1974.

(16) The monoxodithioacetal moiety is rarely encountered in nature but has drawn attention recently because of its synthetic utility (ref 17). The only other natural products featuring this moiety are the antibiotics sparsomycin (ref 18–21), SE-3 (ref 6 and 22), a precursor of lenthionine, and *N*-acetyl- and djenkolic acid monosulfoxide (ref 41).

(17) The dithioacetal monoxide is a masked carbonyl compound whose carbanion can serve as an acyl anion equivalent. See: Ogura, K.; Tsuchihashi, G., *Tetrahedron Lett.* **1971**, 3151. In addition, their acidolytic cleavage can be used to prepare unsymmetric disulfides. See: Kishi, Y.; Fukuyama, T.; Nakatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490. Zwanenburg, B.; Kielbasinski, P. *Tetrahedron* **1979**, *35*, 169.

(18) Ottenheijm, H. C. J.; Liskamp, R. M. J.; van Nispen, S. P. J. M.; Boots, H. A.; Tijhuis, M. W. *J. Org. Chem.* **1981**, *46*, 3273.

(19) Liskamp, R. M. J.; Zeegers, H. J. M.; Ottenheijm, H. C. J. *J. Org. Chem.* **1981**, *46*, 5408.

(20) Ottenheijm, H. C. J.; Liskamp, R. M. J.; Helquist, P.; Lauher, J. W., Shekhani, M. S. *J. Am. Chem. Soc.* **1981**, *103*, 1720.

(21) Hwang, D.-R.; Helquist, P.; Shekhani, M. S. *J. Org. Chem.* **1985**, *50*, 1264.

(22) Morita, K.; Kobayashi, Sh. *Jpn Kokai Tokkyo Toko* **1970**, *18*, 459; *Chem. Abstr.* **1970**, *73*, 95594.

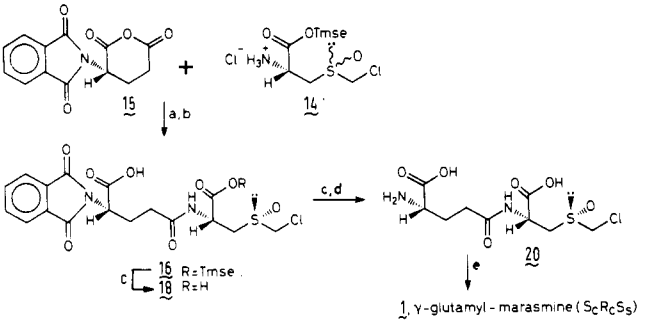
They have to be stable to the reaction conditions employed for the construction of the monoxodithioacetal function. Moreover, their removal has to avoid the use of base to prevent racemization and β-elimination. On basis of these considerations the Boc (*tert*-butyloxycarbonyl)[23] group and the Tmse (2-(trimethylsilyl)ethyl)[24,25] group were selected for protection of the amine function and the ester function, respectively. Whereas both protecting groups can be removed by treatment with trifluoroacetic acid,[23-25] they can also be removed selectively; the Boc group by treatment with hydrochloric acid in trifluoroethanol[24] and the Tmse group by treatment with fluoride ions.[24,25]

Two routes for the conversion of **6** into **1** were explored. Initially we studied coupling of the completed monoxodithioacetal **7** with **2** to yield **1** (Scheme 2, route A). As this approach failed (vide infra), the sequence of reactions was inverted; the α-chloro sulfoxide derivative **6** was coupled first with **2** to yield **8** after which the monoxodithioacetal moiety was formed to yield **1** (route B).

Route A. Cystine derivative **10** (Scheme III) was prepared in 67% overall yield from L-cystine (**9**) by subsequent introduction of the Boc group using di-*tert*-butyl pyrocarbonate[23] and the Tmse group in a DCC coupling procedure employing 2-(trimethylsilyl)ethanol.[24] Treatment of **10** with 3 equiv of chlorine in the presence of acetic anhydride, followed by reaction with dry diazomethane afforded in 59% yield the α-chlorosulfoxides **11** as a mixture of two diastereomers.[18] These could not be separated at this stage of the reaction sequence. Reaction of a mixture of the α-chlorosulfoxides **11** with sodium methyl mercaptide[26,27] in ethanol yielded the dehydroalanine derivative **12** instead of the desired compound **7**. The formation of **12** can be rationalized by a β-elimination[18] and a transesterification reaction. Reaction of **11** with sodium methyl mercaptide in DMF instead of in ethanol also led to a β-elimination product. Another attempt to synthesize **7** employed the sulfinate ester **13**. This compound was prepared in 56% yield from **10** by using wet—instead of dry—chlorine. However, reaction of **13** with methylthiomethyl lithium[19] resulted again in the formation of a β-elimination product. This apparent inclination to β-elimination, which had not played a part during the synthesis of sparsomycin[18,19] must be ascribed to the presence of the ester function; the proton at the chiral carbon atom is acidic, which—in combination with the leaving group character of the $S(O)CH_2Cl$ moiety—facilitates the observed β-elimination. To circumvent this side reaction, we decided to deprotect the acid function prior to the reaction with sodium methyl mercaptide.

By treatment of **11** or **13** with an excess of tetra-*n*-butylammonium fluoride, the Tmse group was removed; these reactions proceeded sluggishly. Unfortunately, during the workup procedure, the Boc group was largely removed. So far we have no satisfactory explanation for this observation. In view of the apparent lability of the Boc group in **11** and **13** during or after the procedure for removal of the Tmse group and the observed β-elimination caused by sodium methyl mercaptide, it seemed sensible to reconsider the sequence of reactions.

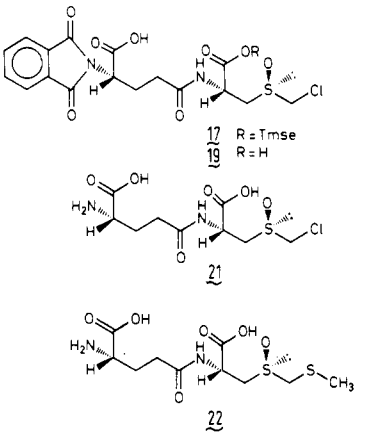
Scheme IV



Reagents: (a) Et_3N. (b) separation of diastereomers. (d) 2M N_2H_4, H_2O/HOAc in CH_3OH. (e) $NaSCH_3$, liquid NH_3. (c) TFA.

Route B. Subsequently route B was explored (Scheme II). This route allows deprotection of the cysteine-carboxylic acid function subsequent to the removal of the Boc group and prior to the displacement of the α-chloro atom by a methyl mercaptide function. The *N*-protecting group of **11**—present as a diastereomeric mixture—was removed by treatment with hydrochloric acid in trifluoroethanol[24] to give **14** (Scheme IV) in 76% yield. Coupling of the hydrochloride **14** with *N*-phthaloyl-L-glutamic anhydride **15**—prepared[28] in two steps from L-glutamic acid (**4**)—was achieved in tetrahydrofuran in the presence of triethylamine, yielding (96%) the γ-isomers **16** and **17** as a mixture of diastereomers. None of the corresponding α-isomers could be detected.[14] The diastereomeric α-chloro sulfoxides **16** and **17** were separated by careful column chromatography on silica gel, and their ratio was determined by analytical HPLC. Values for six reaction mixtures ranged between 65% and 77% de[29] in favor of **17**.

From this stage on the diastereomers were subjected separately to the following conversions. The carboxylic acid protecting group of **16** and **17** was removed by



treatment with trifluoroacetic acid at 0 °C to yield (96%) compounds **18** and **19**, respectively. We had noticed that reaction of *N*-phthaloyl-L-glutamic acid with sodium methyl mercaptide in ethanol resulted in a nucleophilic attack of the methyl mercaptide anion on the phthaloyl carbonyl group giving quantitatively a thioester. Therefore, we chose to remove the *N*-protecting group before completing the monoxodithioacetal function. Thus, the

(23) Moroder, L.; Hallett, A.; Wünsch, E.; Keller, O.; Wersin, G. *Hoppe Seyler's Z. Physiol. Chem.* **1976**, *357*, 1651.
(24) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711. Gerlach, H. *Helv. Chim. Acta* **1977**, *60*, 3039.
(25) The Tmse group has been used recently by Forsch, R. A.; Rosowsky, A., *J. Org. Chem.* **1984**, *49*, 1305 and by Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242.
(26) The quality of MeSNa was found to be crucial; see ref 18.
(27) The nucleophilic displacement of halogen by MeS^- is a known reaction for α-chloro sulfoxides. See: Ogura, K.; Tsuchihashi, G. *J. Chem. Soc., Chem. Commun.* **1970**, 1689.
(28) King, F. E.; Kidd, D. A. A. *J. Chem. Soc.* **1949**, 3315.
(29) Unfortunately, the minor isomer is the desired one. We have observed previously (ref 18) a similar induction in reactions leading to Cbo-cysteinol and Boc-cysteinol α-chloro sulfoxides; although in these examples the diastereoselectivity was less, i.e., 22 and 28%, respectively. This increase in diastereoselectivity must be attributed to the presence of the bulky 2-(trimethylsilyl)-ethyl ester in **11**.

phthaloyl group of 18 and 19 was removed by hydrazinolysis with hydrazinehydroacetate in methanol[15] at elevated temperature (35–40 °C) to give 20 and 21, respectively in yields ranging from 67 to 84%.[30] The diastereomers 20 and 21 could not be distinguished on TLC.

Finally, having accomplished the reaction sequence as depicted in Scheme IV so far, we now turned to the conversion of 20 and 21 to 1 and 22, respectively. Following the procedure we described earlier[18] for the synthesis of monoxodithioacetals we studied these conversions using sodium methyl mercaptide in ethanol. However, only starting material was isolated. We ascribe this failure to poor solubility of 20 and 21 in ethanol.[32] When the reaction was carried out at 50 °C employing ultrasonic vibration for 1 week, only 30% of the α-chloro sulfoxides were converted into the desired monoxodithioacetals 1 and 22, respectively as judged by the ^{1}H NMR spectra of the reaction products. Since the above mentioned procedure failed to give a clean conversion, we studied the use of liquid ammonia as solvent for the substitution reaction.[33] Following this procedure the α-chloro sulfoxides 20 and 21 were successfully converted into the desired monoxodithioacetals 1 and 22, respectively, in *quantitative yield*. These compounds were purified by gel filtration on Fractogel HW-40(S).

Structure Assignment. Compounds 1 and 22 could not be distinguished on TLC. Their structures were secured by ^{1}H NMR and CD spectroscopy as follows. The gross structures of 1 and 22 were deduced from proton decoupling studies.[35] The γ-linkage in both compounds was also deduced from an analysis of the respective ^{1}H NMR spectra. Both compounds show a triplet at 3.77 ppm for the α-proton of the glutamic acid moiety whereas in α-isomers of glutamic acid derivatives this proton is usually observed between 3.93 and 4.16 ppm.[1]

To establish which of the two compounds is identical with γ-glutamylmarasmine the ^3J and [α] values were compared.[36] Salient features of the ^{1}H NMR spectra of 1 and 22 are depicted in Figure 1. These data show that compound 1 and the natural product are identical.

CD Spectroscopy. As to determine the absolute configuration at the sulfoxide sulfur atom of compounds 1 and 22, circular dichroism (CD) measurements were employed.

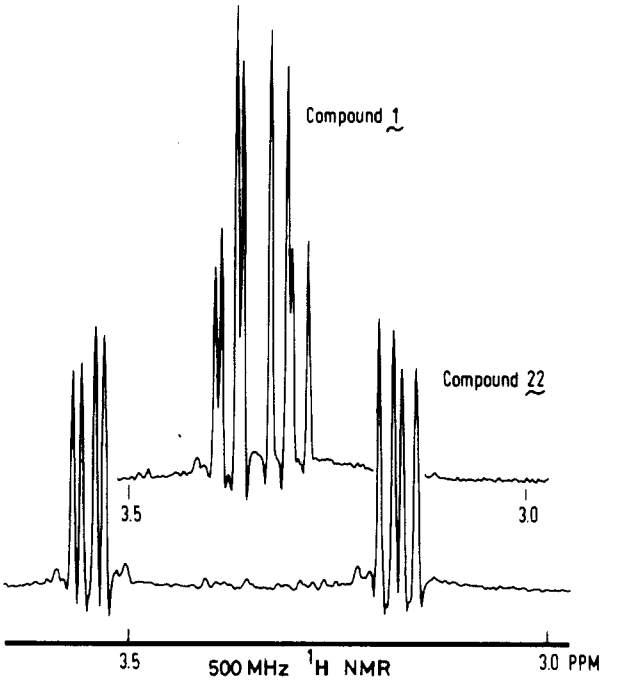


Figure 1. AB part of ABX spectrum for $CHCH_2S(O)$ of 1 and 22.

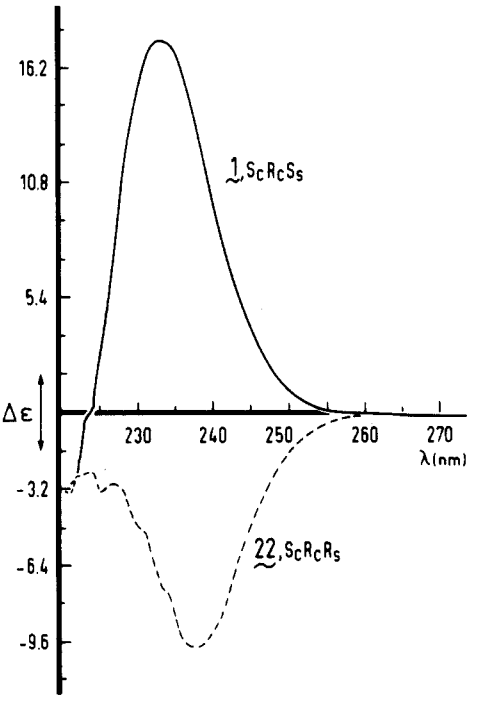


Figure 2. CD spectrum of 1 and 22.

Previously, we showed for sparsomycin[18] as well as for several other α-functionalized sulfoxides[19,20] that CD spectrscopy can be employed in the assignment of the configuration of the sulfoxide sulfur atom.[37] In the absence of strongly perturbing groups, a negative sign of the Cotton effect—centered at the S(O) absorption band in the 220–240 nm region—correlates with an *R* configuration whereas a positive sign correlates with an *S* configuration. The CD spectra of 1 and 22 as well as of their synthetic precursors 20 and 21, respectively, are shown in Figures 2 and 3.[38] Application of the above mentioned correlation

(30) This mild dephthaloylation procedure was used in order to avoid reaction of hydrazine with the α-chloro sulfoxide moiety. This side reaction had to be considered in view of the known reaction of alkylhalides with hydrazines (ref 31).

(31) Gibson, M. S.; Bradshaw, R. W. *Angew. Chem.* **1968**, *80*, 986.

(32) When the substitution reaction was carried out in water, the generation of two singlets at 5.7 and 5.9 ppm in the ^{1}H NMR spectrum of each product suggested the formation of β-elimination products.

(33) Liquid ammonia has been employed as solvent previously for the preparation of S-alkylated cysteine derivatives (ref 18 and 34).

(34) Brownlee, P. J. E.; Cox, M. E.; Handford, B. O.; Marsden, J. C.; Young, G. T. *J. Chem. Soc.* **1964**, 3822.

(35) Proton decoupling studies were carried out using a Bruker WH-90 apparatus. For both compounds irradiation at $CHCH_2S(O)$ gives a singlet for the $CHCH_2S(O)$ proton at 4.68 ppm. Irradiation at $CHCH_2CH_2$ turns the original triplet for the $CHCH_2CH_2$ proton—centered at 3.82 ppm—into a singlet. The difference in the signal pattern for the $CHCH_2S(O)$ protons of the two sulfoxide diastereomers (see Figure 1) becomes more pronounced after irradiation at $CHCH_2S(O)$. For compound 22, the eight lines pattern is transformed into an AB-quartet at 3.23 and 3.57 ppm, J_{AB} = 13.5 Hz. The five lines pattern of 1 turns into a singlet at 3.37 ppm after irradiation at $CHCH_2S(O)$. The ^{13}C NMR spectra of the diastereomers 1 and 22 are both identical with the spectrum of γ-glutamylmarasmine.

(36) 500-MHz ^{1}H NMR spectra showed the following coupling constants for the $CHCH_2S(O)$ protons (AB part of ABX spectrum) of 1 and 22. Compound 1: J_{AX} = 10.4 Hz; J_{BX} = 3.9 Hz; J_{AB} = 13.6 Hz. Compound 22: J_{AX} = 8.6 Hz, J_{BX} = 5.3 Hz; J_{AB} = 13.6 Hz. γ-Glutamylmarasmine (values from ref 2, 200-MHz spectrum): J_{AX} = 11 Hz; J_{BX} = 3.5 Hz; J_{AB} = 14 Hz. The specific rotations are: compound 1, $[\alpha]^{25}_D$ 0° (*c* 0.2, H_2O); compound 22: $[\alpha]^{25}_D$ −23° (*c* 0.2, H_2O); γ-glutamylmarasmine (ref 2), $[\alpha]^{25}_D$ −5.5° (*c* 0.1, H_2O).

(37) CD spectroscopy was also used in the determination of the configuration of the sulfoxide sulfur atom of γ-glutamylcysteine sulfoxides isolated from sandal and onion (ref 10) and of sulfoxides isolated from mushrooms of the genus *Amanita* (ref 12).

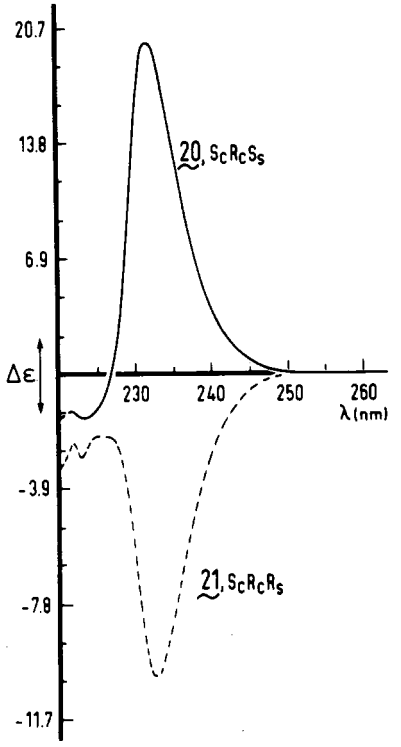


Figure 3. CD spectrum of **20** and **21**.

learns that **1** and **20**—showing a positive sign—possess the *S* configuration, while **21** and **22**—showing a negative sign—possess the *R* configuration. From this it can be concluded that *γ-glutamylmarasmine* (**1**) possesses the $S_cR_cS_s$ configuration.

Conclusion. We have developed an efficient route to the natural dipeptide γ-glutamylmarasmine (**1**) and its *S*-epimer **22**. Our approach proceeds via coupling of the L-cysteine derivative **14** with the L-glutamic acid derivative **15** and subsequent separation of the resulting epimeric sulfoxides **16** and **17** by column chromatography. Substitution of the chlorine atom in **20** and **21** by SMe was accomplished in liquid ammonia. Unlike in our studies towards the total synthesis of sparsomycin[18] β-elimination involving the cysteine α-proton was observed in some reactions. By comparison of ^3J and [α] values it was shown that **1** is identical with γ-glutamylmarasmine. The absolute configuration of γ-glutamylmarasmine was determined by CD spectroscopy.

Experimental Section

Melting points were determined on a Reichert hot stage and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WH-90 or on a Bruker WM-500 spectrometer with Me_4Si or $Me_3SiCD_2CD_2CO_2Na$ as an internal standard. ^{13}C NMR spectra were measured on a Bruker WP-60 spectrometer. IR spectra were taken on a Perkin-Elmer 257 grating spectrometer. Mass spectra were recorded on a double-focusing VG 7070E mass spectrometer. UV spectra were measured on a Perkin-Elmer Model 555 spectrophotometer. Circular dichroism spectra were recorded with a autodichrograph Mark V apparatus (Jobin Yvon). For determination of specific rotations, a Perkin-Elmer 241 polarimeter was used. Thin-layer chromatography (TLC) was carried out by using Merck precoated silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV lamp, ninhydrin, and Cl_2–TDM.[39] For column chromatography, Merck silica gel H (type 60) was used. For gel filtration Pharmacia Sephadex LH-20 and Merck Fractogel TSK HW-40 (S) were used. The HPLC analyses were performed using a "SP-8700 solvent delivery system" instrument equipped with a "SP-8400 variable wavelength" detector using a Chrompack LiChrosorb Si60-10 column (25 cm).

***N*-(*tert*-Butyloxycarbonyl)-L-cystine 2-(Trimethylsilyl)ethyl Ester (10).** *N*-(*tert*-butyloxycarbonyl)-L-cystine was prepared in 78% yield from L-cystine, **9** (9.6 g, 40 mmol), according to a procedure that has been described earlier[18] by treatment with di-*tert*-butylpyrocarbonate. The Tmse ((trimethylsilyl)ethyl) protecting group was introduced analogous to the procedure described by Sieber.[24] To a solution of *N*-Boc-cystine (8.8 g, 20 mmol) in 40 mL of acetonitrile and 15 mL of DMF was added 6.4 mL (79.1 mmol) of pyridine followed by the addition of 6.8 mL (47.5 mmol) of 2-(trimethylsilyl)ethanol. Subsequently, the reaction mixture was cooled (0 °C), and after 10 min, DCC (9.0 g, 43.6 mmol) was added. The reaction and workup procedure were carried out as described.[24] The crude product was purified by flash column chromatography on silica gel (eluent ethyl acetate/hexane, 1/8) to give **10** in 86% yield as a colorless semisolid oil: mp 45–46 °C; TLC R_f 0.55 (eluent ethyl acetate/hexane, 1/4); IR (KBr) 1720, 1680 (urethane, ester), 1510 (amide), 1250, 860, 840 cm^{-1} ($SiMe_3$); ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 9 H, $SiMe_3$), 0.78–1.35 (m, 2 H, CH_2Si), 1.42 (s, 9 H, *t*-Bu), 3.15 (d, J = 5 Hz, 2 H, CH_2S), 3.97–4.39 (m, 2 H, OCH_2), 4.39–4.72 (m, 1 H, CH), 5.17–5.52 (br d, 1 H, NH); CI MS, m/e 641.275 (M^+ + 1), calcd for $C_{26}H_{53}N_2O_8S_2Si_2$, 641.278; $[\alpha]^{25}_D$ −64° (*c* 0.22, EtOH).

(R_cS_s)/(R_cR_s)-*N*-(*tert*-Butyloxycarbonyl)-*S*-oxo-*S*-(chloromethyl)-L-cysteine 2-(Trimethylsilyl)ethyl Ester (11). These compounds were prepared from **10** (9.8 g, 15.3 mmol) following the procedure described earlier[18] for the preparation of *N*-,*O*-protected cysteine α-chloro sulfoxides. The crude reaction product was purified by flash column chromatography (silica gel 60H, eluent ethyl acetate/hexane, 1/2), yielding a mixture of diastereomers in 59% yield as a yellow oil. TLC R_f 0.46 and 0.41 (eluent ethyl acetate/hexane, 2/3); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 9 H, $SiMe_3$), 0.95–1.33 (m, 2 H, CH_2Si), 1.45 (s, 9 H, *t*-Bu), 3.30 and 3.58 (AB part of ABX spectrum, 8 lines, J_{AX} = 5.3 Hz, J_{BX} = 6.3 Hz, J_{AB} = 12.6 Hz, 2 H, $CHCH_2S(O)$), 4.00–4.79 (m, 5 H, OCH_2, $CHCH_2S(O)$, $S(O)CH_2Cl$), 4.56 (part of AB spectrum of $S(O)CH_2Cl$), 5.57 (br d, 1 H, NH); EI MS, m/e 386.121 (M^+ + 1), calcd for $C_{14}H_{29}NO_5SSiCl$, 386.122.

Ethyl *N*-(*tert*-Butyloxycarbonyl)-2-aminoacrylate (12). Treatment of compound **11** (386 mg, 1 mmol) with sodium methyl mercaptide, analogous to the procedure described earlier[18] for substitution of cysteinol α-halosulfoxides, afforded **12** in quantitative yield: TLC R_f 0.92 (eluent ethyl acetate/hexane, 1/1); ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3 H, CH_2CH_3), 1.45 (s, 9 H, *t*-Bu), 4.25 (q, 2 H, CH_2CH_3), 5.65 (s, 1 H, C=CH), 6.05 (s, 1 H, C=CH), 7.0 (br s, 1 H, NH).

(R_cS_s)/(R_cR_s)-*N*-(*tert*-Butyloxycarbonyl)-*S*-oxo-*S*-methoxy-L-cysteine 2-(Trimethylsilyl)ethyl Ester (13). The procedure used for the preparation of **11**[18] was adapted in order to prepare the sulfinate ester **13**. Wet–instead of dry–chlorine was used. The sulfinate ester–a mixture of diastereomers–was obtained after column chromatography (silica gel, eluent ethyl acetate/hexane, 1/3) in 56% yield: TLC R_f 0.77 (eluent ethyl acetate/hexane, 1/1); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 9 H, $SiMe_3$), 0.70–0.80 (m, 2 H, CH_2Si), 1.40 (s, 9 H, *t*-Bu), 2.95–3.35 (m, 2 H, $CHCH_2S(O)$), 3.75 (s, 3 H, $S(O)OCH_3$), 4.00–4.40 (m, 2 H, OCH_2), 4.40–4.85 (m, 1 H, $CHCH_2S(O)$), 5.40 (br d, 1 H, NH).

(R_cS_s)/(R_cR_s)-*S*-Oxo-*S*-(chloromethyl)-L-cysteine 2-(Trimethylsilyl)ethyl Ester Hydrochloride (14). The *N*-Boc protecting group was removed from **11** (3.4 g, 8.8 mmol) by treatment with HCl in 2,2,2-trifluoroethanol analogous to the procedure described by Sieber.[24] The crude reaction product thus obtained was purified by crystallization from methanol/hex-

(38) In the region of 220–240 nm each spectrum consists of a composite chromophore, which includes an inherently symmetric—but chirally perturbed amide band as well as an inherently chiral sulfoxide band. In studying Boc-cysteinol monoxodithioacetals (ref 18) it was shown, that the contribution due to the chiral carbon atom is small, so that the CD curves of the diastereomeric sulfoxides were nearly mirror images. In our work on sultines (ref 19), however, it was shown that the contribution of the chiral center can be significant resulting in a striking difference in the magnitude of rotational strength. Now we also found a difference in the magnitude of rotational strength for γ-glutamylmarasmine (**1**) and its precursor **20** on the one hand and their *S*-epimers **21** and **22** on the other.

(39) Arx, E. von; Faupel, M. *J. Chromatogr.* **1976**, *120*, 224.

ane/ethyl acetate to give **14** as a mixture of diastereomers in 76% yield, mp 120–123 °C. TLC Rf 0.64 (eluent acetonitrile/H_2O, 8/1); IR (KBr) 1740 (ester), 1265, 1250, 860, 840 ($SiMe_3$), 1060, 1020 (S=O), 745 cm^{-1} (Cl); ^1H NMR ($CDCl_3/CD_3OD$) δ 0.04 (s, 9 H, $SiMe_3$), 0.87–1.34 (m, 2 H, CH_2Si), 3.46–4.07 (m, 2 H, $CHCH_2S(O)$), 4.07–4.54 (m, 2 H, OCH_2), 4.54–5.17 (m, 3 H, $CHCH_2S(O)$, $S(O)CH_2Cl$); CI MS, *m/e* 286.068 (M^+ – HCl), calcd for $C_9H_{21}NO_3SSiCl$, 286.070. Anal. Calcd for $C_9H_{21}NO_3SSiCl_2$: C, 33.54; H, 6.56; N, 4.35. Found: C, 33.22; H, 6.49; N, 4.30.

***N*-Phthaloyl-L-glutamic Anhydride (15).** This compound was prepared in 51% overall yield in two steps from L-glutamic acid following procedures described in the literature.[28,40]

($S_cR_cS_s$)- and ($S_cR_cR_s$)-*N*-(*N'*-Phthaloyl-γ-L-glutamyl)-*S*-oxo-*S*-(chloromethyl)-L-cysteine 2-(Trimethylsilyl)ethyl Ester (16 and 17). To a cooled suspension (0 °C) of **14** (518 mg, 2 mmol) and **15** (644 mg, 2 mmol) in 3.5 mL of THF was slowly added triethylamine (202 mg, 2 mmol). After stirring overnight, the reaction mixture was concentrated by evaporation of the solvent. Flash column chromatography (silica gel, eluent toluene/ethyl formate/formic acid, 14/3/3) gave **16** and **17** as a mixture of diastereomers in 96% yield as a colorless oil. The diastereomers could be separated by repetition of the chromatographic procedure. Both compounds were homogeneous on TLC (**17**, R_f 0.47; **16**, R_f 0.43; toluene/ethyl formate/formic acid, 10/7/3) and were crystallized from dichloromethane/hexane.

For **16**: mp 72–75 °C; ^1H NMR (CD_3COCD_3) δ 0.04 (s, 9 H, $SiMe_3$), 0.77–1.26 (m, 2 H, CH_2Si), 2.15–2.63 (m, 4 H, CH_2CH_2), 3.23 (br d, 2 H, $CHCH_2S(O)$), 4.00–4.29 (m, 2 H, OCH_2), 4.55–5.02 (m, 2 H, $CHCH_2S(O)$, $CHCH_2CH_2$), 4.60 and 4.77 (ABq, J_{AB} = 11.3 Hz, 2 H, $S(O)CH_2Cl$), 7.70 (br d, 1 H, NH), 7.84 (s, 4 H, Ar); FAB MS, *m/e* 545 (M^+ + 1); $[\alpha]^{25}_D$ –64° (*c* 0.31, CH_3COCH_3). Anal. Calcd for $C_{22}H_{29}N_2O_8SSiCl$: C, 48.48; H, 5.36; N, 5.14. Found: C, 48.41; H, 5.47; N, 5.05. IR (KBr) 1770, 1715 (s) (ester, carboxylic acid, amide, imide), 1250, 860, 840 ($SiMe_3$), 1045 (S=O), 725 cm^{-1} (Cl).

For **17**: mp 143–145 °C; ^1H NMR (CD_3COCD_3) δ 0.05 (s, 9 H, $SiMe_3$), 0.78–1.20 (m, 2 H, CH_2Si), 2.23–2.83 (m, 4 H, CH_2CH_2), 3.45 and 3.25 (AB part of ABX spectrum, 8 lines, J_{AX} = 5.9 Hz, J_{BX} = 6.1 Hz, J_{AB} = 13.2 Hz, 2 H, $CHCH_2S(O)$), 4.05–4.36 (m, 2 H, OCH_2), 4.59–5.08 (m, 2 H, $CHCH_2S(O)$, $CHCH_2CH_2$), 4.80 (ABq, J_{AB} = 11.3 Hz, 2 H, $S(O)CH_2Cl$), 7.75 (d, 1 H, NH), 7.90 (s, 4 H, Ar); FAB MS, *m/e* 545 (M^+ + 1); $[\alpha]^{25}_D$ –23° (*c* 0.14, CH_3COCH_3); IR (KBr) 1770, 1715 (s) (ester, carboxylic acid, amide, imide), 1250, 860, 840 ($SiMe_3$), 1045 (S=O), 725 cm^{-1} (Cl). Determination of de by HPLC, Si-60, 300 nm, 1.0 mL/min; toluene/ethyl formate/formic acid (14/3/3). Anal. Calcd for $C_{22}H_{29}N_2O_8SSiCl$: C, 48.48; H, 5.36; N, 5.14. Found: C, 48.63; H, 5.33; N, 5.15.

($S_cR_cS_s$)- and ($S_cR_cR_s$)-*N*-(*N'*-Phthaloyl-γ-L-glutamyl)-*S*-oxo-*S*-(chloromethyl)-L-cysteine (18 and 19). A solution of the diastereomeric mixture of **16** and **17** (5.9 g, 10.9 mmol) in 100 mL of trifluoroacetic acid was stirred for 2 h at 0 °C. Subsequently, excess trifluoroacetic acid was removed in vacuo. Flash column chromatography (silica gel, eluent toluene/ethyl formate/formic acid, 10/7/3) of the residue gave a diastereomeric mixture of **18** and **19** in 96% yield as a colorless oil. By the same procedure, but starting now from pure **16** or **17**, the homochiral compounds **18** or **19**, respectively, were prepared. Both compounds were homogeneous on TLC (**19**, R_f 0.16; **18**, R_f 0.13; toluene/ethyl formate/formic acid, 10/7/3) and could be crystallized from methanol.

For **18**: mp 115–120 °C; ^1H NMR (CD_3OD) δ 2.41–2.94 (m, 4 H, CH_2CH_2), 3.23–3.81 (AB part of ABX spectrum, 2 H, $CHCH_2S(O)$), 4.74–5.30 (m, 4 H, $CHCH_2S(O)$, $CHCH_2CH_2$, $S(O)CH_2Cl$), 4.93 and 5.03 (part of AB spectrum of $S(O)CH_2Cl$), 8.04 (s, 4 H, Ar). FAB MS, *m/e* 445 (M^+ + 1); IR (KBr) 1770, 1710 (s) (carboxylic acid, amide, imide), 1020 (S=O), 725 cm^{-1} (Cl). Anal. Calcd for $C_{17}H_{17}N_2O_8SCl\cdot H_2O$: C, 44.11; H, 4.14; N, 6.05. Found: C, 43.95; H, 3.96; N, 5.95.

For **19**: mp 128–130 °C. ^1H NMR ($CDCl_3$, CD_3COCD_3) δ 2.28–2.75 (m, 4 H, CH_2CH_2), 3.37 and 3.58 (AB part of ABX spectrum, 8 lines, J_{AX} = 5.7 Hz, J_{BX} = 6.3 Hz, J_{AB} = 13.0 Hz, 2 H, $CHCH_2S(O)$), 4.60–5.08 (m, 4 H, $CHCH_2S(O)$, $CHCH_2CH_2$, $S(O)CH_2Cl$), 4.76 and 4.78 (part of AB spectrum of $S(O)CH_2Cl$), 7.49 (d, 1 H, NH), 7.64–7.93 (m, 4 H, Ar). FAB MS, *m/e* 445 (M^+ + 1). IR (KBr) 1770, 1710 (s), 1630 (carboxylic acid, amide, imide), 1025 (S=O), 725 cm^{-1} (Cl). Anal. Calcd for $C_{17}H_{17}N_2O_8SCl\cdot H_2O$: C, 44.11; H, 4.14; N, 6.05. Found: C, 44.41; H, 4.11; N, 5.86.

($S_cR_cS_s$)- and ($S_cR_cR_s$)-*N*-(γ-L-Glutamyl)-*S*-oxo-*S*-(chloromethyl)-L-cysteine (20 and 21). A diastereomeric mixture of **18** and **19** (2.4 g, 5.4 mmol) was treated with 21.6 mL of a 2 M solution of $N_2H_4\cdot H_2O$ and AcOH in methanol (43.2 mmol). The solution was stirred overnight at 35–40 °C. The reaction mixture, a white suspension, was concentrated to a small volume and filtered, and the filtrate was purified by gel filtration on Sephadex LH-20 (eluent water/methanol, 15/85) to give a diastereomeric mixture of **20** and **21** in 67–84% yield. By the same procedure, the homochiral compounds **20** or **21** were obtained starting from **18** or **19**, respectively. These diastereomers could not be distinguished on TLC: R_f 0.56 (eluent 2-propanol/water, 7/3), R_f 0.15 (eluent *n*-butanol/acetic acid/water/2-propanol, 8/2/5/3). Both compounds were handled and stored after freeze-drying.

For **20**: mp 187–189 °C; ^1H NMR (D_2O) δ 2.06–2.36 (m, 2 H, $CHCH_2CH_2$), 2.44–2.73 (m, 2 H, $CHCH_2CH_2$), 3.27 and 3.63 (AB part of ABX spectrum, 8 lines, J_{AX} = 5.5 Hz, J_{BX} = 3.5 Hz, J_{AB} = 13.5 Hz, 2 H, $CHCH_2S(O)$), 3.90 (t, *J* = 6.0 Hz, 1 H, $CHCH_2CH_2$), 4.61–5.01 (m, 1 H, $CHCH_2S(O)$), 4.87 and 5.15 (ABq, J_{AB} = 21.0 Hz, 2 H, $S(O)CH_2Cl$). FAB MS, *m/e* 315 (M^+ + 1). IR (KBr) 3300, 1675, 1635, 1530, 1055, 1035 cm^{-1}; $[\alpha]^{25}_D$ –51° (*c* 0.2, H_2O); CD spectrum, at 231.5 nm a single positive maximum was observed for an aqueous solution ($\Delta\epsilon$ +19.8, Figure 3). Anal. Calcd for $C_9H_{15}N_2O_6SCl$: C, 34.35; H, 4.80; N, 8.90. Found: C, 34.47; H, 4.90; N, 8.82.

For **21**: mp >200 °C; ^1H NMR (D_2O) δ 2.02–2.36 (m, 2 H, $CHCH_2CH_2$), 2.43–2.69 (m, 2 H, $CHCH_2CH_2$), 3.38 and 3.62 (AB part of ABX spectrum, 8 lines, J_{AX} = 5.3 Hz, J_{BX} = 8.5 Hz, J_{AB} = 13.6 Hz, 2 H, $CHCH_2S(O)$), 3.87 (t, *J* = 5.9 Hz, 1 H, $CHCH_2CH_3$), 4.60–4.90 (m, 1 H, $CHCH_2S(O)$), 4.80 and 4.96 (ABq, J_{AB} = 12.6 Hz, 2 H, $S(O)CH_2Cl$). FAB MS, *m/e* 315 (M^+ + 1); IR (KBr) 1630, 1530, 1030 cm^{-1}; $[\alpha]^{25}_D$ +16° (*c* 0.2, H_2O). CD spectrum: at 232.5 nm a single negative maximum was observed for an aqueous solution ($\Delta\epsilon$ –10.3, Figure 3). Anal. Calcd for $C_9H_{15}N_2O_6SCl$: C, 34.35; H, 4.80; N, 8.90. Found: C, 34.79; H, 5.04; N, 8.92.

($S_cR_cS_s$)- and ($S_cR_cR_s$)-*N*-(γ-L-Glutamyl)-*S*-oxo-*S*-((methylthio)methyl)-L-cysteine (1 and 22). In a reaction vessel containing 628 mg (2 mmol) of **20** or **21** and 420 mg (6 mmol) of sodium methyl mercaptide[26] was condensed 20 mL of liquid ammonia at –78 °C. The ammonia had been distilled from sodium in a connected vessel. Special care was taken to exclude moisture by bringing the reaction system under an argon atmosphere and by attaching tubes containing potassium hydroxide. The reaction mixture was allowed to react at –78 °C for 1 h. Subsequently, the ammonia was allowed to evaporate rapidly and completely by an argon stream. The solid remainder was dissolved in 1 mL of water after which the solution was neutralized immediately by the addition of 1 N hydrochloric acid. Nitrogen was passed through the solution to remove excess of methyl mercaptan. The reaction mixture was subjected to gel filtration on Fractogel TSK HW-40 (s) (eluent, water) to give **1** or **22** in quantitative yield. The diastereomers could not be distinguished on TLC: R_f 0.54 (eluent 2-propanol/water, 7/3), R_f 0.12 (eluent 1-butanol/acetic acid/water/2-propanol, 8/2/5/3). Both compounds were handled and stored after freeze-drying.

For **1**: mp 162–165 °C; ^1H NMR (500 MHz, D_2O, Figure 1)[35] δ 2.10–2.20 (m, 2 H, $CHCH_2CH_2$), 2.27 (s, 3 H, SCH_3), 2.50 (distorted t, *J* = 7.4 Hz, 2 H, $CHCH_2CH_2$), 3.30 and 3.37 (AB part of ABX spectrum, 8 lines, J_{AX} = 10.4 Hz, J_{BX} = 3.9 Hz, J_{AB} = 13.6 Hz, 2 H, $CHCH_2S(O)$), 3.77 (t, *J* = 6.2 Hz, 1 H, $CHCH_2CH_2$), 3.93 and 4.09 (ABq, J_{AB} = 13.9 Hz, 2 H, $S(O)CH_2S$), 4.60 (X part of ABX spectrum, 4 lines, $J_{AX} + J_{BX}$ = 14.3 Hz, 1 H, $CHCH_2S(O)$); FAB MS, *m/e* 327 (M^+ + 1); $[\alpha]^{25}_D$ ±0° (*c* 0.2, H_2O); IR (KBr) 1620, 1535, 1010 cm^{-1}; ^{13}C NMR (D_2O) δ 15.6 (SCH_3), 25.5 ($CHCH_2CH_2$), 31.0 ($CHCH_2CH_2$), 49.8 ($CHCH_2S(O)$), 52.8 (CHC-

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$H_2S(O)$), 53.6 ($CHCH_2CH_2$), 54.2 ($S(O)CH_2S$), 173.5 (Glu-COOH and Cys-COOH), 174.4 (C(O)NH); CD spectrum, at 237.5 nm a single positive maximum was observed for an aqueous solution ($\Delta\epsilon$ +17.5, Figure 2). Anal. Calcd for $C_{10}H_{18}N_2O_6S_2 \cdot H_2O$: C, 34.87; H, 5.85; N, 8.13. Found: C, 34.24; H, 6.29; N, 8.06.

For **22**: mp 169-172 °C; ^1H NMR (500 MHz, D_2O, Figure 1)[35] δ 2.07-2.20 (m, 2 H, $CHCH_2CH_2$), 2.27 (s, 3 H, SCH_3), 2.47 (distorted t, J = 7.7 Hz, 2 H, $CHCH_2CH_2$), 3.18 and 3.55 (AB part of ABX spectrum, 8 lines, J_{AX} = 8.6 Hz, J_{BX} = 5.3 Hz, J_{AB} = 13.6 Hz, 2 H, $CHCH_2S(O)$), 3.76 (t, J = 6.1 Hz, 1 H, $CHCH_2CH_2$), 3.91 and 4.11 (ABq, J_{AB} = 13.8 Hz, 2 H, $S(O)CH_2S$), 4.60 (X part of ABX spectrum, 4 lines, $J_{AX} + J_{BX}$ = 14.0 Hz, 1 H, $CHCH_2S(O)$); FAB MS, m/e 327 ($M^+ + 1$); $[\alpha]^{25}_D$ -23° (c 0.2, H_2O); IR (KBr) 1615, 1525, 1020 cm^{-1}; ^{13}C NMR (D_2O) δ 15.6 (SCH_3), 2.57 ($CHCH_2CH_2$), 31.2 ($CHCH_2CH_2$), 49.5 ($CHCH_2S(O)$), 53.0 ($CHCH_2S(O)$), 53.8 ($CHCH_2CH_2$), 54.2 ($S(O)CH_2S$), 173.5 (Glu-COOH), 173.9 (Cys-COOH), 174.9 (C(O)NH); CD spectrum: at 237.5 nm a single negative maximum was observed for an aqueous solution ($\Delta\epsilon$ -9.8, Figure 2).

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Registry No. 1, 106565-95-1; 9, 56-89-3; 10, 106501-49-9; (R_CS_S)-11, 106501-50-2; (R_CR_S)-11, 106501-56-8; 12, 96846-37-6; (R_CS_S)-13, 106501-51-3; (R_CR_S)-13, 106501-57-9; (R_CS_S)-14, 106501-52-4; (R_CR_S)-14, 106501-58-0; 15, 25830-77-7; 16, 106501-53-5; 17, 106565-96-2; 18, 106501-54-6; 19, 106565-97-3; 20, 106501-55-7; 21, 106565-98-4; 22, 106565-99-5; Boc-cystine, 10389-65-8; di-*tert*-butyl pyrocarbonate, 24424-99-5; 2-(trimethylsilyl)ethanol, 2916-68-9.

Utilization of the 1-Ferrocenyl-2-methylpropyl Substituent as a Chiral Auxiliary in the Asymmetric Syntheses of the Benzophenanthridine Alkaloids (+)- and (-)-Corynoline†

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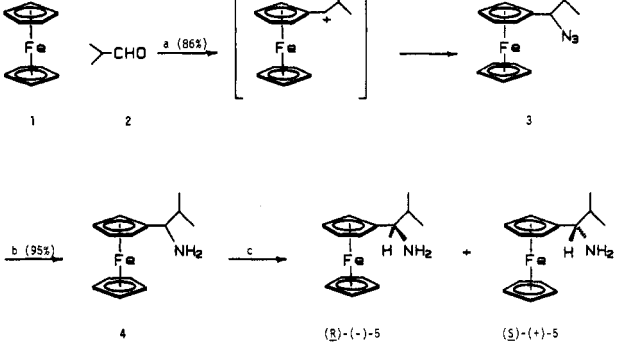
The benzophenanthridine alkaloids (+)- and (-)-corynoline have been synthesized by a route that utilizes the 1-ferrocenyl-2-methylpropyl group as a chiral auxiliary. The key step in the asymmetric synthesis of (+)-corynoline involved the condensation of the Schiff base (*R*)-(-)-**7** with the racemic homophthalic anhydride (±)-**8** to afford (-)-**9** in 81% yield and (-)-**10** in 10% yield. The chiral auxiliary thus influences both the relative and absolute configurations of two asymmetric centers. Removal of the chiral auxiliary under acidic conditions gave (-)-**11**, which was transformed into (+)-corynoline (**16**) by previously established methods. The overall yield of (+)-corynoline from piperonal was 16.5%.

Although (±)-corynoline[1] is the major alkaloid present in *Corydalis incisa*, (+)-corynoline (**16**; Scheme II) has also been detected[2] and isolated[3] from the plant. The absolute configuration of (+)-corynoline has been determined by chemical correlation with (+)-14-*epi*-corynoline,[3] whose absolute configuration has been established by X-ray analysis of the bromoacetate.[4] The CD spectra of the chiral hexahydrobenzo[*c*]phenanthridine alkaloids, including (+)-corynoline, have recently been reinterpreted in terms of revised absolute configurations.[5]

Although several syntheses of racemic hexahydrobenzo[*c*]phenanthridines have been executed,[6] no work has been reported on the asymmetric synthesis of any of the alkaloids of this class. The present report describes the utilization of the 1-ferrocenyl-2-methylpropyl substituent[7] as a chiral auxiliary modifying our previous synthesis of (±)-corynoline[8] for the asymmetric syntheses of (+)-corynoline and also (-)-corynoline.

The chiral amines (*R*)-(-)-**5** and (*S*)-(+)-**5** were prepared as depicted in Scheme I.[9,10] Thus, a mixture of ferrocene (**1**) and isobutyraldehyde (**2**) was treated with fluorosulfonic acid, resulting in the formation of an intermediate cation that was reacted with a solution of sodium azide in triethylamine. The azide **3** was then reduced with lithium aluminum hydride to afford the racemic mixture of amines

Scheme I[a]



[a] Key: (a) (1) FSO_3H, CCl_3COOH, CH_3COOH, -25 °C (50 min); (2) $CHCl_3$; (3) aqueous NaN_3, Et_3N, -25 °C to room temperature (5 h). (b) $LiAlH_4$, THF, reflux (3.5 h). (c) (+)- and (-)-tartaric acids, MeOH, Et_2O.

† This paper is dedicated to Professor George Büchi on the occasion of his 65th birthday.

(1) Isolation: Tani, C.; Takao, N. *Yakugaku Zasshi* **1962**, *82*, 594. Structure elucidation: Takao, N. *Chem. Pharm. Bull.* **1963**, *11*, 1306. Takao, N. *Chem. Pharm. Bull.* **1963**, *11*, 1312. Kamitani, T.; Honda, T.; Ihara, M.; Shimanouchi, H.; Sasada, Y. *Tetrahedron Lett.* **1972**, 3729.

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