Transworld Research Network
37/661 (2), Fort P.O., Trivandrum-695 023, Kerala, India

Recent Res. Devel. Organic Chem., 8(2004): 323-339 ISBN: 81-7895-128-2

13 Asymmetric synthesis of (*R*)- and (*S*)-α-methylcysteine

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Abstract

α-Methylcysteine is an important amino acid, which is used to confer conformational constraints, extend biological half-life, and avoid racemization. Due to the labile nature of the sulfhydryl group, asymmetric synthesis of α-methylcysteine has been rather challenging. There are mainly five strategies for synthesizing α-methylcysteine: (1) thiolation of bromomethyl bislactim ether, (2) regioselective ring opening of chiral aziridine or β-lactone with thiolate nucleophile, (3) utilization of Seebach's "self-regeneration of chirality" approach to thiomethylate oxazolidinone derived from alanine or methylate thiazolidine drivative of cysteine, (4) enzymatic resolution, and (5) use of camphorsultam chiral auxiliary to direct methylation of thiazoline. Stereochemistry of each synthesis is discussed.

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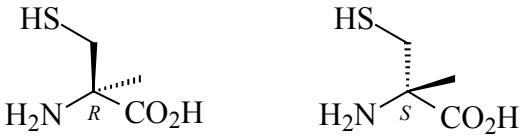
Introduction

Optically pure modified amino acids are valuable building blocks for modern drug discovery research. They have been used extensively in preparing peptidomimetics to limit conformational flexibility, enhance enzymatic stability, and improve pharmacodynamics and bioavailability.[1]



1 **2**

Figure 1. Enantiomers of α-methylcysteine.

In α-methylated amino acids, the C^{α}-H is replaced with a methyl group. C^{α}-alkylation severely restricts rotation around the N-C^{α} (ϕ) and C^{α}-C(O) (ψ) bonds of the amino acid in a peptide sequence and stabilizes preferred conformations of the peptide backbone.[2] In addition, C^{α}-methylamino acids are not prone to racemization under basic or acidic conditions because of a lack of abstractable or enolizable α-hydrogen atom. Among C^{α}-alkylated amino acids, α-methylcysteine (**1** and **2**, Figure 1) is an interesting molecule because it can impart constrained cyclic structure to a peptide via disulfide bridge formation. Furthermore, it is not susceptible to racemization unlike cysteine. Activated esters of cysteine and S-benzyl protected cysteine derivatives are known to undergo facile racemization. Two main mechanisms for racemization of cysteine have been proposed: base-catalyzed reversible β-elimination and acid-catalyzed enolization with *d*-orbitals of the sulfur atom participating in enol stabilization via intramolecular hydrogen bonding.[3,4]

α-Methylcysteine occurs naturally in both (*R*)- and (*S*)-stereochemical configurations. It is present in the thiazoline rings (**3** and **4**, Figure 2) of a number of natural products, including mirabazoles A-C,[5-8] didehydromirabazoles A,[9-11] tantazoles A, B,[12-14] thiangazole,[15-18] thiazohalostatin,[19,20] and 4-methylaeruginoic acid,[21] which exhibit antitumor and anti-HIV-1 activities. In addition, it is also present in desferrithiocin, a unique ferric ion chelator.[22]

3 **4**

Figure 2. Thiazolines of (*R*)- and (*S*)-α-methylcysteine found in natural products.

Synthesis

Asymmetric synthesis of α-methylcysteine (**1** and **2,** Figure 1) is rather challenging as a result of the labile nature of the sulfhydryl group.[23] Since **1** and **2** both contain a single stereogenic center, the key step in the synthesis is to control the stereochemistry at the α-carbon. Several strategies have been devised to synthesize **1** and **2** stereoselectively. These can be grouped into three broad categories: 1) starting from a chiral molecule, 2) starting from an achiral molecule and using a chiral reagent to deliver the required functionality at the α-carbon, and 3) enzymatic hydrolysis of racemic esters at an intermediate stage.

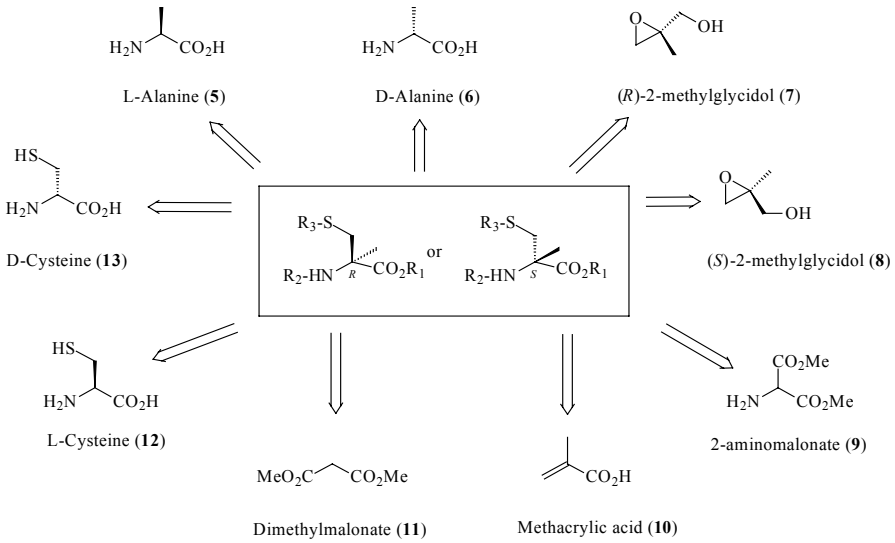


Figure 3. Starting materials for the synthesis of α-methylcysteine derivatives.

When synthesis of **1** or **2** commenced from a chiral molecule, the starting material was either converted into a diastereoisomer (with preference for a single isomer) to control the stereochemistry of the transformation at the original stereocenter, or was chosen with correct stereochemistry at the α-carbon with appropriate functional groups suitable for modifications to furnish the target molecule. The choice of configuration of the starting material or the chiral reagent depended on which stereoisomer of α-methylcysteine (**1** or **2**) was desired. In the case of enzymatic resolution, the single isomer with appropriate functional groups obtained after enantiospecific hydrolysis was selectively manipulated to obtain either **1** or **2**. As shown in Figure 3, **1** and **2** have been prepared from alanine (**5** and **6**), 2-methylglycidol (**7** and **8**), 2-amino dimethylmalonate (**9**), methacrylic acid (**10**), dimethylmalonate (**11**), and cysteine (**12** and **13**).

1. Synthesis from alanine

Alanine (**5, 6**, Figure 3) is an amino acid with a required methyl group at the α-carbon. Introduction of a methylene thiol group (-CH_2SH) at the α-carbon could

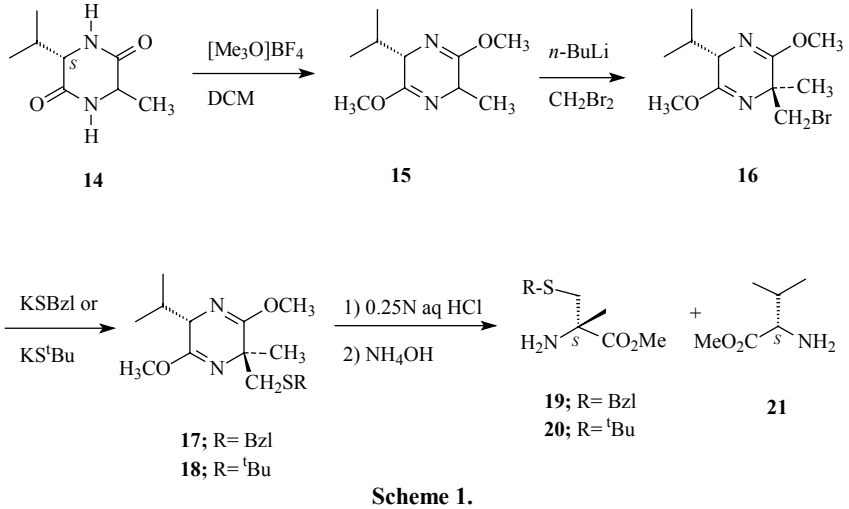
transform alanine into α-methylcysteine (**1** or **2**). Although simple, this transformation involves the abstraction of hydrogen atom from the α-carbon and thus loss of chirality. Therefore, to control the stereochemistry at the α-carbon, alanine has been converted to a single diastereoisomer. There are two strategies to convert alanine into **1** or **2**: via bis-lactim ether and via oxazolidinone.

A. Via bis-lactim ether

This is the first reported synthesis of α-methylcysteine derivatives using L-valine as a chiral auxiliary to direct alkylation of an alanine derivative at the α-carbon. Alanine was converted into cyclo(L-valine-alanine) (**14**). Such cyclic dipeptides are commonly referred as diketopiperazines or simply DKPs. Configuration of alanine did not matter because the chirality of alanine is lost during the reaction. However, configuration of valine was important in determining the stereochemical outcome of the electrophilic reaction.

Cyclic dipeptide **14** (commercially available from Bachem) was converted into bis-lactim ether **15** by treating with trimethyloxonium tetrafluoroborate in dichloromethane (DCM) at ambient temperature for 34 hours.[24] The resonance-stabilized anion derived from bis-lactim ether **15** was reacted with dibromomethane to give bromomethylated product **16** in 80% yield.[25] The diastereomeric excess (d.e.) during the alkylation step was found to be >95% (d.e. = asymmetric induction) and was determined by ^{13}C NMR, which exhibited resonances corresponding to a single isomer only. Furthermore, as shown in Scheme 1, the alkylating agent entered from the β-face, i.e. *anti* to the bulky isopropyl group.

Displacement of the bromo function with potassium α-toluenethiolate or potassium *t*-butylthiolate resulted in the S-protected thiomethylene bis-lactim ether **17** or **18** with retention of stereochemistry at C-6. Acid-mediated hydrolysis of **17** and **18** under mild conditions afforded S-protected (*S*)-α-methylcysteine methyl esters **19** and **20** in an overall yield of 36-40% as single isomers with enantiomeric excess of >95%. The chiral auxiliary L-valine methyl ester (**21**) was recovered by bulb-to-bulb distillation after neutralization of the hydrochloric acid salt with ammonium hydroxide.



14 **15** **16**

17; R= Bzl
18; R= ^{t}Bu

19; R= Bzl
20; R= ^{t}Bu

21

Scheme 1.

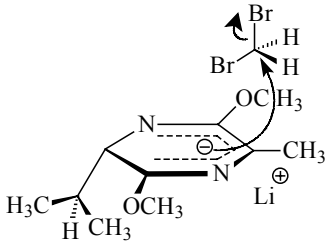


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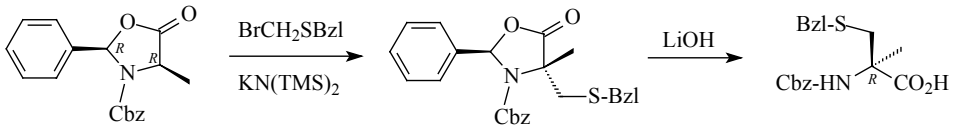
Figure 4. Structure of dihydropyrazine anion.

In order to explain the asymmetric induction, it is presumed that the lithium derivative of **15** exists as a planar dihydropyrazine anion, with one diastereotopic face strongly shielded by the comparatively large isopropyl group. Furthermore, it is proposed that the transition state assumes a 'folded' conformation and the alkylating agent (CH_2Br_2) approaches the heterocyclic anion from above the plane as shown in structure **22** (Figure 4). This conformation is presumably stabilized either by a HOMO (anion)-LUMO (CH_2Br_2) interaction or by van der Waals attraction.[26]

B. Via oxazolidinone

This strategy is based on the principle of self-regeneration of stereocenters (SRS). It allows the synthesis of α-amino acids stereoselectively with retention of configuration without the use of any external chiral auxiliary. The methodology involves four steps. (1) Creation of a new chiral center (acetalization): the chiral starting material possessing two functional groups but only one stereogenic center is allowed to react with an aldehyde to form an acetal. The configuration at the new stereocenter (acetal) depends on the configuration of the original stereocenter in the starting material. Since acetalization is a thermodynamically controlled process, *syn*-substituted product is formed. (2) Enolate generation: the original stereocenter is annihilated by abstraction of a proton with a base. The resulting trigonal center remains diastereotopic due to the adjacent stereocenter of the acetal. (3) Electrophilic substitution (alkylation): the enolate is allowed to react with an electrophile. This reaction proceeds with high diastereoselectivity at the face of the enolate double bond opposite to that shielded by the substituent on the acetal stereocenter. (4) Cleavage of acetal: finally, the acetal group is cleaved in the presence of either a base or an acid. The product contains a new substituent at the original stereogenic center.[27]

Thus, (*R*)-N-Cbz-alanine was converted into (*2R,4R*)-2-phenyl-3-benzyloxy-4-methyl oxazolidinone (**23**) by treatment with benzaldehyde diethylacetal in the presence of boron trifluoride etherate at –30 ˚C. The major isomer (*syn*) was crystallized out from ether/hexane in 53% yield.[28] The enolate was generated and quenched with bromomethyl benzylsulfide to yield (*2R,4R*)-2-phenyl-3-benzyloxycarbonyl-4-methyl-4-benzylthiomethyl-5-oxazolidinone (**24**) in 64-76% yield. It is important to note that electrophilic attack takes place from the least sterically hindered face of the enolate. After hydrolysis of oxazolidinone **24** with lithium hydroxide, (*R*)-N-Cbz-S-benzyl-α-methylcysteine (**25**) was obtained in 93% yield as shown in Scheme 2.[6] Bromomethyl



23 **24** **25**

Scheme 2.

benzyl sulfide was prepared by heating benzylmercaptan with paraformaldehyde at 0 ˚C in dichloromethane followed by passing hydrogen bromide gas.[29]

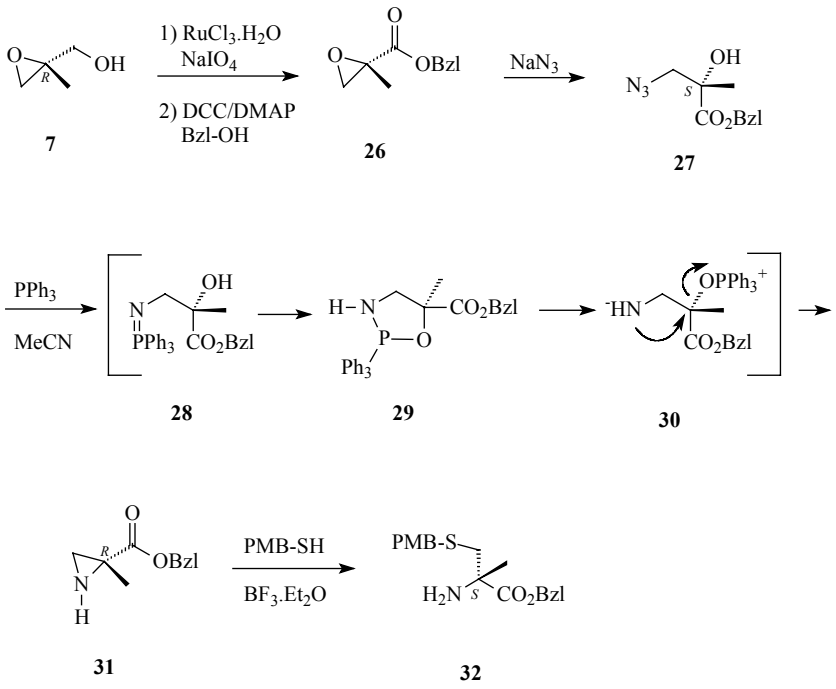
2. Synthesis from glycidol

2-Methylglycidol (**7** and **8**, Figure 3) contains all the required functional groups with correct stereochemistry at the α-carbon. There are two key steps in transforming **7** or **8** into α-methylcysteine (**1** or **2**): (1) conversion into a chiral aziridine and (2) regioselective ring opening of the aziridine with a thiolate nucleophile. Two groups have utilized this strategy.[30,31]

(*R*)-2-methylglycidol (**7**) was obtained from 2-methyl-2-propen-1-ol by Sharpless asymmetric epoxidation.[32] Both (*R*)- and (*S*)-isomers of 2-methylglycidol (**7** and **8**) are commercially available from Aldrich. Oxidation of the alcohol functionality of **7** to an acid with ruthenium (VIII) oxide,[33] followed by esterification with benzyl alcohol using standard carbodiimide chemistry afforded benzyl (*S*)-2-methylglycidate (**26**). Regioselective ring opening of the oxirane **26** with sodium azide[34] gave the azido alcohol **27**, which upon treatment with triphenylphosphine (Staudinger reaction) in acetonitrile at reflux furnished the benzyl (*R*)-2-methylaziridine carboxylate (**31**) with no loss of enantiomeric purity as determined by the Mosher ester method.[31] As shown in Scheme 3, reduction of the azido alcohol **27** with triphenylphosphine occurs via a cyclic mechanism with inversion of configuration at the α-carbon (**28-30**).

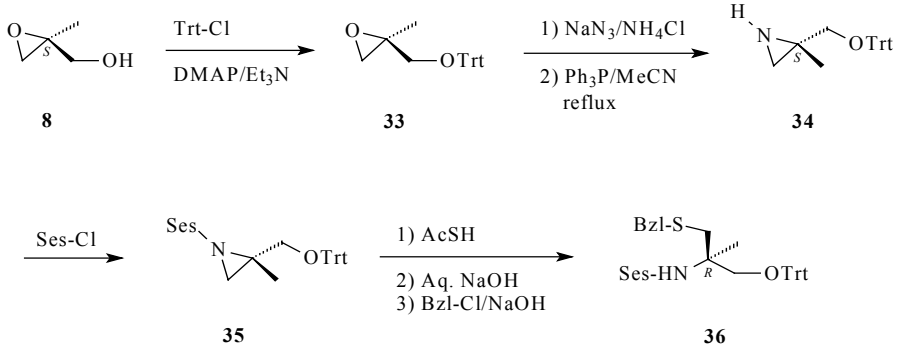
Finally, regioselective ring opening of the aziridine **31** with *p*-methoxy-α-toluenethiol (PMB-SH) in the presence of boron trifluoride etherate resulted in the formation of (*S*)-α-methylcysteine (PMB) benzyl ester (**32**) in overall good yield as shown in Scheme 3. It is important to note here that the ring opening of aziridine **31** with a thiolate nucleophile occurs predominantly at C-3.[36] The aziridine **31** is an ambident substrate and can undergo nucleophilic substitution reaction at either C-3 or C-2. Under neutral or basic conditions, **31** is expected to react at C-3 (less substituted carbon) in an SN2 fashion. However, under acidic conditions, the aziridine ring could open by SN1 or SN2 mechanism at C-2. Since boron trifluoride is a mild Lewis acid and PMB-SH is a strong nucleophile, the substitution occurs predominantly at C-3 by SN2 mechanism. Furthermore, steric hindrance caused by the presence of a methyl group at the α-carbon (C-2) favors the ring opening at C-3.

Similar to the above strategy, Wipf et al.[31] have synthesized α-methylcysteine alcohol. As shown in Scheme 4, (*S*)-2-methylglycidol (**8**) was O-tritylated with trityl chloride in the presence of triethyl amine and dimethylaminopyridine (DMAP) to give O-trityl-(*S*)-2-methylglycidol (**33**) in 72-85% yield. Ring opening of the oxirane **33** with sodium azide in methanol in the presence of ammonium chloride, followed by reduction



Scheme 3.

with triphenylphosphine (Staudinger reaction) of the intermediate azido alcohol in hot acetonitrile led to efficient formation of aziridine **34**. The enantiomeric excess of **34** was determined to be >92% by HPLC analysis of the N-benzoyl derivative on a Chiralcel OD column. N-Protection of the aziridine **34** with β-trimethylsilylethanesulfonyl chloride (Ses-Cl) led to **35**. Treatment of the N-Ses protected aziridine **35** with potassium thioacetate resulted in the formation of S-acetylcysteinol. Removal of the S-acetyl group by saponification, followed by S-benzylation gave (*R*)-N-Ses-S-benzyl-α-methylcysteinol (**36**).



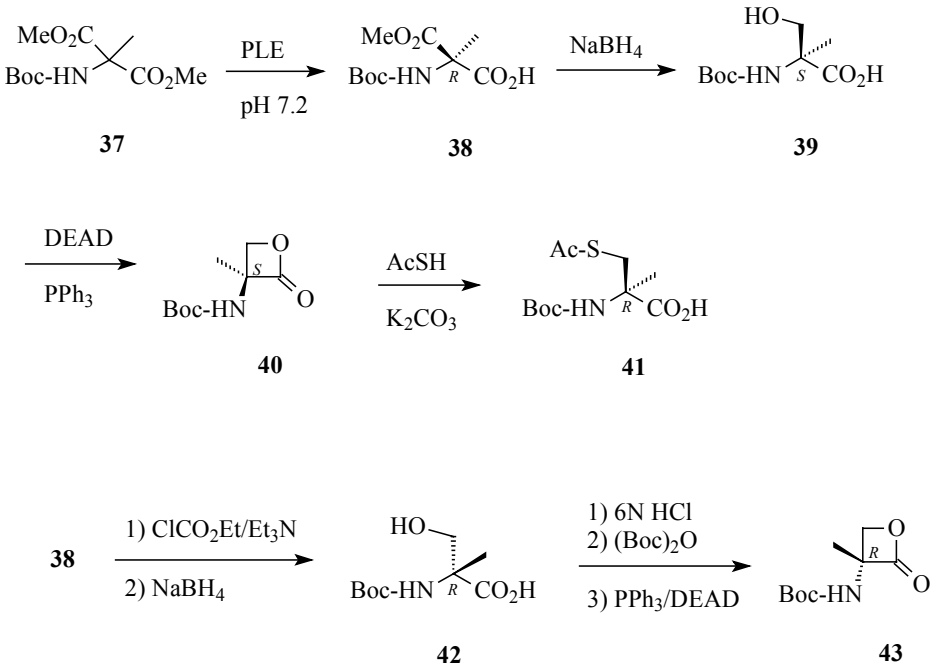
Scheme 4.

3. Synthesis from α-methylserine

This methodology utilized β-lactone to synthesize α-methylcysteine via regioselective ring opening with a thiolate nucleophile. β-Lactone has been synthesized from α-methylserine. There are several syntheses reported for the preparation of α-methylserine, but only two of them are relevant and discussed here.

Methodology of Fukuyama and Xu[14] utilized enzymatic hydrolysis to resolve the racemic mixture of 2-methyl malonate derivative **37**. Thus, methylation of a malonate derivative **9** with methyl iodide in methanol at reflux in the presence of sodium methoxide gave methylated compound **37**. The latter compound was hydrolyzed with pig liver esterase enzyme, which selectively produced (*R*)-monoester **38** in 97% yield (93% ee).[37] The ester function was selectively reduced with sodium borohydride to afford (*S*)-Boc-α-methylserine (**39**). Cyclization to (*S*)-(−)-β-lactone **40** was accomplished under Mitsunobu reaction conditions.[38] Regioselective ring opening of the β-lactone **40** with thiolacetic acid in the presence of potassium carbonate at ambient temperature afforded (*R*)-N-Boc-S-acetyl-α-methylcysteine (**41**) in 87% yield as shown in Scheme 5.

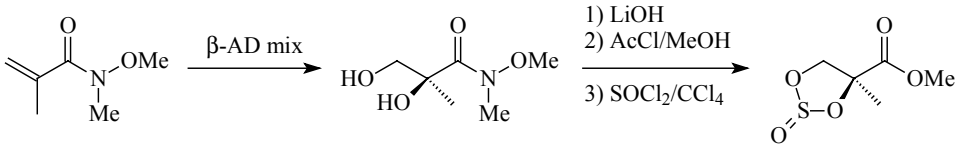
In order to obtain the other isomer, i.e. (*R*)-(+)-β-lactone (**43**), the acid function of **38** was selectively reduced via mixed anhydride method to afford (*R*)-hydroxy ester **42**.[39] The ester group was hydrolyzed to an acid using aqueous hydrochloric acid, which also cleaved the *t*-Boc group. Reintroduction of the *t*-Boc group, followed by treatment with diethylazodicarboxylate (DEAD) and triphenylphosphine afforded (*R*)-(+)-β-lactone **43** as shown in Scheme 5.[14]



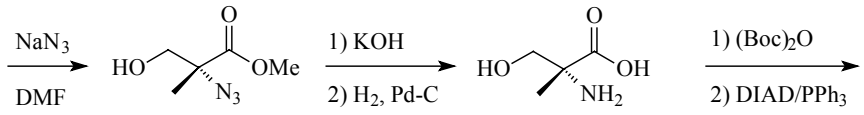
Scheme 5.

The second strategy to obtain α-methylcysteine was developed by Smith and Goodman.[40] The β-lactone was synthesized from α-methylserine, which in turn, was prepared according to the procedure reported by Avenoza et al.[41] As shown in Scheme 6, the synthesis commenced from Weinreb amide **44** of methacrylic acid (**10**), which was obtained via displacement of the acid chloride with N,O-dimethyl hydroxylamine hydrochloride. Sharpless epoxidation[42] of the amide **44** was carried out using modified β-AD mix, which contained a suspension potassium ferricyanide, potassium carbonate, $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, methanesulfonamide in *t*-butanol and water mixture as a solvent. The reaction was performed at 0 ºC for six hours and then allowed to warm to ambient temperature overnight to give diol **45**. The diol **45** was converted into methyl ester via saponification of the amide with lithium hydroxide, followed by acid-catalyzed esterification with methanol. The ester thus obtained was converted into cyclic sulfite **46** by refluxing in thionyl chloride, and subsequently into azido alcohol **47** by treatment with sodium azide.

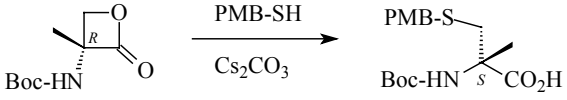
It should be noted here that the azide nucleophile preferentially attacked at the tertiary carbon in contrast to the secondary carbon (tertiary vs. secondary 80:20). The ester function was hydrolyzed to an acid in the presence of aqueous potassium hydroxide and the azide group was reduced to an amine to afford (*R*)-α-methylserine (**48**). Protection of the amino function with $(Boc)_2O$ afforded (*R*)-Boc-α-methylserine, which was subsequently converted into (*R*)-β-lactone **49** under Mitsunobu reaction conditions



44 **45** **46**



47 **48**



49 **50**

Scheme 6.

using diisopropylazodicarboxylate (DIAD) and triphenylphosphine The same compound has been prepared above by a different strategy (see Scheme 5). Regioselective ring opening of the β-lactone **49** with *p*-methoxy-α-toluenethiol (PMB-SH) in the presence of cesium carbonate resulted in the formation of α-methylcysteine derivative **50** in 91% yield. Approximately 9% thioester byproduct was also formed as a result of nucleophilic addition at the carbonyl function.

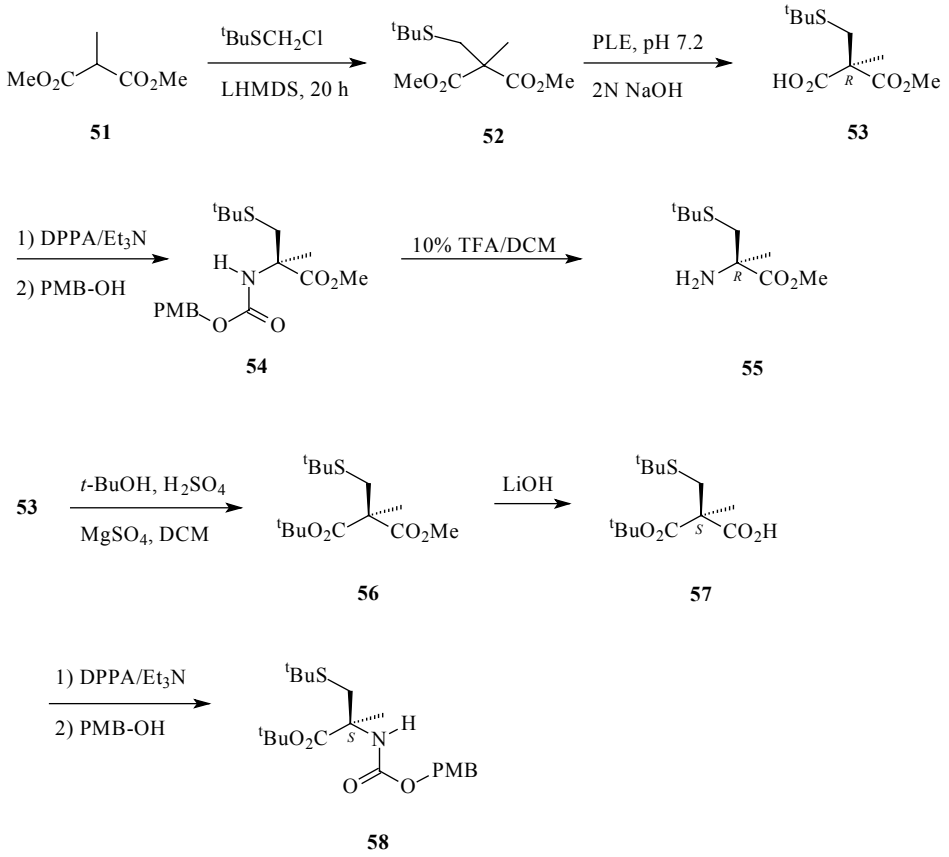
It is important to mention here that other methods of converting Boc-α-methylserine methyl ester (methyl ester of **48**) into α-methylcysteine methyl ester either did not succeed or resulted in poor yield. For example, iodination or bromination of the ester of **48** with triphenylphosphine and iodine or bromine did not result in the halogenated product. The mesylation reaction did work, however. But, the mesyl group could not be displaced with PMB-SH. The Boc-α-methylserine methyl ester could be converted into Boc-α-methylcysteine methyl ester via aziridine as described above but in low yield. The added steric hindrance from the α-methyl group in α-methylserine methyl ester prevents displacement at the methylene carbon and is the main reason for the failure of these reactions.

4. Synthesis from malonate

Dimethylmalonate (**11**) is an active methylene compound, which can be easily alkylated as well as dialkylated at the α-carbon as shown in Scheme 7.[43] Thus, monomethylation of **11** with methyl iodide gave 2-methyl dimethylmalonate (**51**).[44] Further alkylation of **51** with *t*-butyl chloromethyl sulfide[45] in the presence of lithium bis(trimethylsilyl)amide (LHMDS) in tetrahydrofuran as a solvent gave racemic diester **52**. Stereospecific hydrolysis of one ester group of **52** with pig liver esterase (PLE) in phosphate buffer (pH 7.2) yielded (*R*)-acid **53**. The pH of the reaction mixture was maintained with 2 N aqueous sodium hydroxide. The reaction was assumed to be complete after one equivalent of sodium hydroxide was consumed.

It is important to note that addition of 5% dimethylsulfoxide as a co-solvent decreased chemical as well as optical yields. The acid was treated with diphenylphosphoryl azide (DPPA) and triethylamine to form acyl azide. Refluxing this mixture in dichloromethane promoted Curtius rearrangement to the corresponding isocyanate, which upon treatment with *p*-methoxybenzyl alcohol (PMB-OH) gave the N-protected α-methylcysteine **54**. Cleavage of the N-protecting group with 10% trifluoroacetic acid in dichloromethane gave (*R*)-α-methylcysteine methyl ester **55** in 73% yield.

In order to obtain the (*S*)-isomer, the carboxylic acid function of the (*R*)-acid **53** was protected as *t*-butyl ester (compound **56**) by treating with *t*-butyl alcohol in the presence of concentrated sulfuric acid adsorbed on magnesium sulfate in dichloromethane.[46] Selective hydrolysis of the methyl ester in the presence of lithium hydroxide gave the (*S*)-acid **57**, which upon Curtius rearrangement conditions, followed by treatment with PMB-OH gave the (*S*)-N-*p*-methoxybenzyloxycarbonyl-α-methylcysteine *t*-butyl ester **58** as shown in Scheme 7.



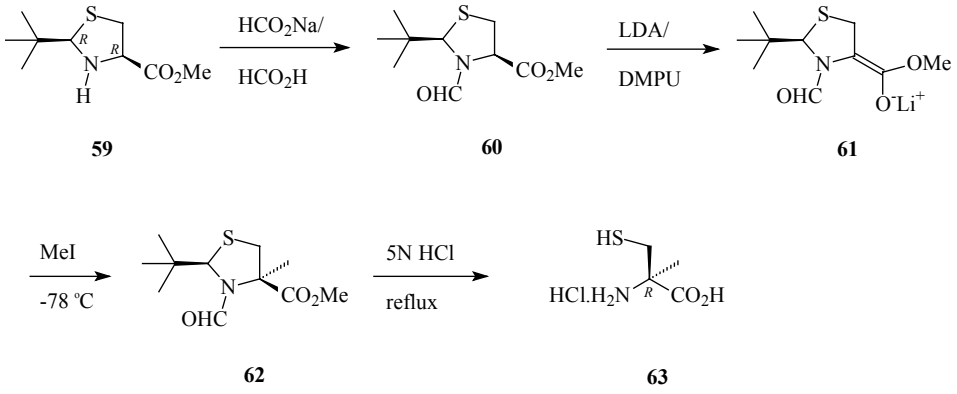
Scheme 7.

5. Synthesis from cysteine

Cysteine (**12** or **13**) is an ideal molecule for the synthesis of α-methylcysteine (**1** or **2**) by methylation at the α-carbon. As has been discussed above, abstraction of C^{α}-hydrogen from a chiral tetragonal center creates a trigonal center with loss of chirality. Therefore, to control stereochemistry at the α-carbon, methylation of cysteine molecule has been conducted only after introducing a second temporary center of chirality. There are two strategies for synthesizing **1** and **2** from cysteine derivatives: via thiazolidine and via thiazoline.

A. Via thiazolidine

In this methodology cysteine was alkylated in four steps according the principle of self-regeneration of stereocenters.[27] As shown in Scheme 8, cysteine methyl ester was reacted with pivalaldehyde to afford (*2R, 4R*)-thiazolidine **59**. Following N-formylation with sodium formate in the presence of formic acid, *syn*-diasteroisomer **60** was isolated in 82% yield. Approximately 10% *anti*-diastereoisomer was also formed during acetalization reaction.



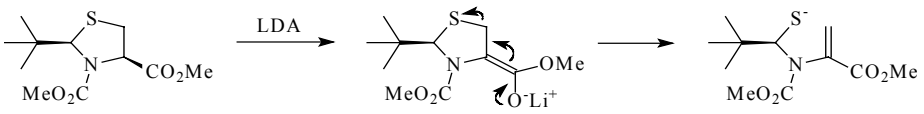
59 **60** **61**

62 **63**

Scheme 8.

Treatment of a solution of thiazolidine **60** in tetrahydrofuran at –78 ºC with lithium diisopropylamide (LDA) in the presence of dimethylpropyleneurea (DMPU), followed by quenching of the resulting enolate **61** with methyl iodide at the same temperature produced (*2R, 4R*)-4-methylthiazolidine **62** in 45% yield. In this methylation reaction, electrophilic attack occurred diastereoselectively, i.e. the methyl group was delivered predominantly *anti* to the bulky *t*-butyl group in enolate **61**. The other isomer, i.e. (*2R, 4S*)-4-methylthiazolidine was also formed in approximately 30% yield, which was removed by column chromatography. Refluxing in 5 N aqueous hydrochloric acid under an inert atmosphere for three days hydrolyzed the alkylated thiazolidine **62**. Evaporation of the volatiles afforded α-methylcysteine hydrochloride salt (**63**) in 85-90% yield. Both (*R*)- and (*S*)-isomers of α-methylcysteine have been prepared using this methodology. (*R*)-cysteine methyl ester was used to afford (*R*)-α-methylcysteine[47] and (*S*)-cysteine methyl ester was utilized to obtain (*S*)-α-methylcysteine.[22]

It is worthwhile to mention here that (*2R, 4R*)-N-ester thiozolidine **64** under the similar conditions of enolate generation and alkylation (structure **65**) underwent facile β-elimination (structure **66**) rather than alkylation as depicted in Scheme 9.[23] This implied that there are subtle differences associated with the deprotonation and alkylation of the substituted thiazolidines like **60** and **64**. Pattenden et al.[47] have proposed that increased delocalization of the nitrogen atom lone pair in the formate thaizolidine **60**, due to greater electron-withdrawing nature of the formyl group, leads to more stabilized enolate **61**. However, Seebach et al.[27] have suggested that the enolate of N-formyl thiazolidine (**61)** is more stable than the enolate of N-ester thiazolidine (**65)** because the N-formyl substituted enolate has less 1,3-allyl ($A^{1,3}$) strain than the N-ester derivative and not only because the formyl group is more electron withdrawing.

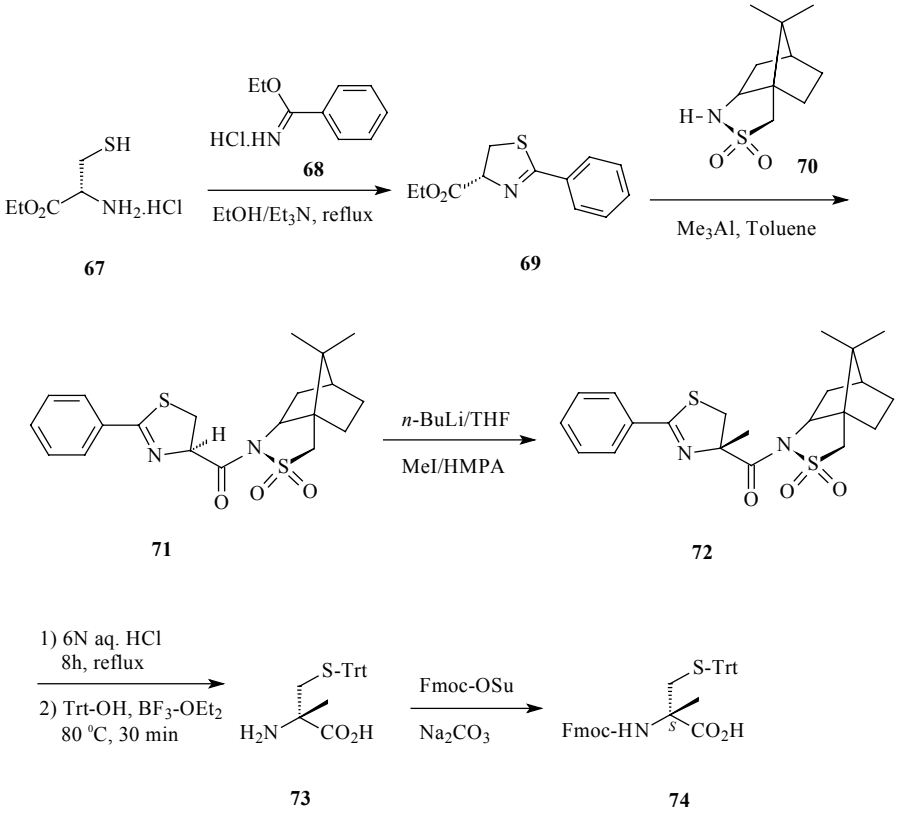


64 **65** **66**

Scheme 9.

B. Via thiazoline

This methodology has been recently developed by us.[48] As shown in Scheme 10, (*R*)-ethyl cysteine hydrochloride (**67**) was treated with ethyl benzimidate hydrochloride (**68**) in ethanol at reflux for two hours to afford 2-phenylthiazoline (**69**) in 87% yield. The thiazolines are highly reactive molecules with a labile acidic proton at C-4, and undergo facile electrophilic alkylation to yield racemic 4-methylthiazolines.[10] In order to control the stereochemistry at C-4 in thiazoline **69**, we utilized (*1R*)-(+)-2,10-camphorsultam (**70**) as a chiral auxiliary to direct alkylation stereospecifically. Thus, camphorsultam **70** was acylated with thiazoline **69** in the presence of trimethylaluminium to afford 2-phenylthiazolinylcamphorsultam **71** in 71% yield.[49] Alkylation of the enolate derived from sultam **71** with methyl iodide in the presence of *n*-butyllithium afforded alkylated sultam **72**. Enolate generation at –78 °C followed by quenching with methyl iodide at the same temperature and continuing the reaction either at –78 or –50 °C up to 24 hours resulted in poor yield. Furthermore, use of LDA or LHMDS as a base resulted in poor alkylated product. Optimum reaction conditions utilized generating the enolate at –78 °C for one hour, adding methyl iodide in hexamethylphosphoric triamide (HMPA) (both 3 molar equivalents), and allowing the



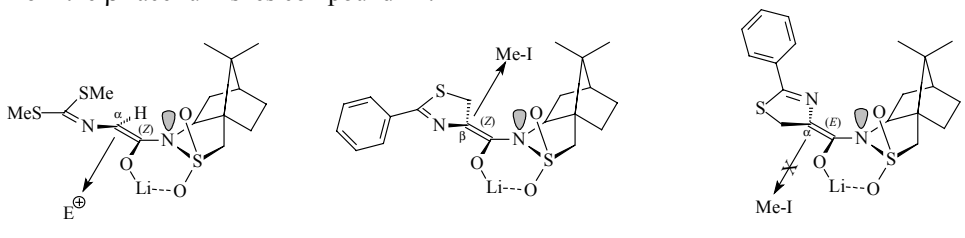
Scheme 10.

reaction to warm to ambient temperature over the period of two hours. Under these conditions, alkylated product **72** was obtained in 49% yield.

Sultam **72** was refluxed in 6 N aqueous hydrochloric acid for 8 hours to cleave the chiral auxiliary. α-Methylcysteine thus formed was not isolated but rather treated with trityl alcohol in the presence of boron trifluoride etherate to afford (*S*)-S-trityl-α-methylcysteine (**73**) in 49% yield after column chromatography over silica gel. Protection of the α-amino function of **73** with Fmoc-OSu in the presence of sodium carbonate overnight afforded (*S*)-N-Fmoc-S-trityl-α-methylcysteine (**74**) in quantitative yield.

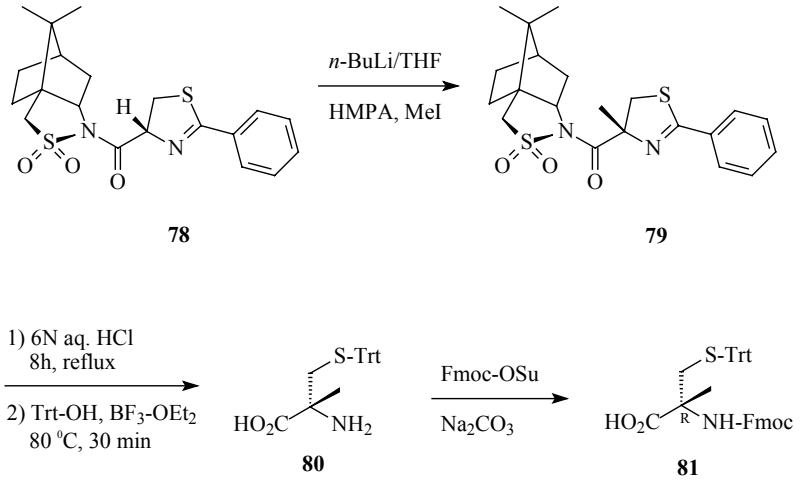
It is important to note that alkylation of glycylsultam under similar reaction conditions occurs via a kinetically controlled Li-chelated *Z*-enolate **75** (Figure 5), which is attacked by the alkylating agent from the face opposite to the lone electron pair on the nitrogen atom. The stereospecific formation of *Z*-enolate occurs as a result of the presence of the bulky camphorsultam skeleton and sterically demanding SO_2 group.[49] However, in the present case, the *Z*-enolate derived from 2-phenylthiazolinylcamphorsultam **76** (Figure 5) was attacked by the electrophile from the β-face and furnished (*S*)-α-methylcysteine as confirmed by optical rotation. High performance liquid chromatography (HPLC) and NMR spectrometry were used to determine the diastereomeric excess (asymmetric induction) during the alkylation step. The ^{1}H NMR spectrum exhibited a relatively downfield shift for the α-methyl protons (2.52 ppm) in agreement with β-alkylation product **72**. Compound **72** was the only alkylation product isolated from the reaction mixture, and there was no α-alkylated product formed as checked by HPLC. Furthermore, ^{13}C NMR spectrum exhibited resonances corresponding to a single isomer only.

To explain the unexpected stereochemical outcome on electrophilic alkylation of **71**, it can be speculated that the enolate assumes *E*-configuration (structure **77**, Figure 5), which upon alkylation from the α-face could result in the formation of product **72**. However, in the *E*-enolate transition state (**77**) increased steric interactions between the camphorsultam skeleton and the phenylthiazoline ring, as well as electronic repulsions between the lone electron pair on the nitrogen atom of thiazoline ring and the lone pair electrons on the nitrogen and SO_2 groups of the camphorsultam moiety are expected. On the contrary, the *Z*-enolate transition state (structure **76**) has minimum steric interactions. Furthermore, formation of the Li-chelated *Z*-enolate transition state under the similar reaction conditions has been demonstrated previously.[49] Therefore, deprotonation of **71** should result in the formation of *Z*-enolate transition state (**76**), which upon alkylation from the β-face furnishes compound **72**.



75 **76** **77**

Figure 5. Structures of *Z*- and *E*-enolates of camphorsultam derivatives.



Scheme 11.

Having realized the reverse stereochemical outcome from alkylation of enolate **76**, and to confirm this finding, we utilized (*1S*)-(−)-2,10-camphorsultam (enantiomer of **70**) for alkylation of thiazoline **69**. As observed above, alkylation of the enolate derived from thiazolinylsultam **78** with methyl iodide occurred from the β-face and afforded sultam **79** as shown in Scheme 11. After treatment with 6 N aqueous hydrochloric acid, protection of the side chain thiol group with trityl alcohol furnished S-trityl-α-methylcysteine (**80**), and protection of the α-amino function then afforded (*R*)-N-Fmoc-S-trityl-α-methylcysteine (**81**) in overall good yield.

Conclusion

α-Methylcysteine is a very useful amino acid because in addition to conferring conformational rigidity, it can impart constrained cyclic structure to the peptide via disulfide bridge formation. Several syntheses have been reported in literature.[50] The majority of them have commenced from a chiral molecule (**5-8, 12, 13)**. Syntheses starting from amino acids, like alanine and cysteine have utilized the principle of self-regeneration of stereocenters by converting them into diastereoisomers via acetalization.[27] The newly introduced stereocenter is cleaved after modifications at the original stereocenter. Other syntheses have started with appropriately derivatized chiral molecule to furnish a single isomer of α-methylcysteine. A few syntheses have used enzymatic resolution to separate the racemic mixtures.[14,43] After appropriate transformations, enantiomers of α-methylcysteine derivatives have been obtained in excellent optical purities.

Recently, we have utilized camphorsultam as a chiral auxiliary to direct methylation of thiazoline derived from cysteine ethyl ester. While alkylation proceeded in good yield, the stereochemistry of electrophilic attack was found to be reverse of what was expected. It was confirmed by synthesizing both the isomers of α-methylcysteine from the enantiomers of camphorsultam. Specific optical rotations are very important in determining the configuration of α-methylcysteine derivatives. Therefore, optical rotations of all the α-methylcysteine derivatives reported in literature have been summarized in Table 1.

Table 1. Specific rotations of α-methylcysteine derivatives.

Name	$[\alpha]_D$	Conc., Solvent	Reference
(*S*)-α-MeCys(Bzl)-OMe (**20**)	−32.7º	1.1, EtOH	[25]
(*S*)-α-MeCys(^{t}Bu)-OMe (**21**)	−16.3º	1.0, EtOH	[25]
(*S*)-PMZ-α-MeCys(^{t}Bu)-O^{t}Bu[a] (**58**)	−6.8º[b]	1.0, $CHCl_3$	[43]
(*S*)-DNP-α-MeCys(DNP)-OMe	−162º	0.5, $CHCl_3$	[14]
(*S*)-α-MeCys-OH.HCl	−8.07º	1.04, H_2O	[22]
(*S*)-Boc-α-MeCys(Bzl)-OH	−23.3º	1.0, MeOH	[51]
(*S*)-α-MeCys(Trt)-OH (**73**)	−32.0º	0.5, MeOH	[48]
(*S*)-Fmoc-α-MeCys(Trt)-OH (**74**)	−29.3º	0.15, MeOH	[48]
(*R*)-PMZ-α-MeCys(^{t}Bu)-OMe[l] (**55**)	+5.3º	1.0, $CHCl_3$	[43]
(*R*)-DNP-α-MeCys(DNP)-OMe	+151º	1.0, $CHCl_3$	[15]
(*R*)-Cbz-α-MeCys(Bzl)-OH (**25**)	+36.1º	1.1, EtOH	[6]
(*R*)-Boc-α-MeCys(Bzl)-OH	+26.1º	1.1, MeOH	[51]
(*R*)-α-MeCys-OH.HCl (**63**)	+8.13º	1.58, H_2O	[47]
(*R*)-α-MeCys(^{t}Bu)-OMe (**55**)	+19.6º	1.0, EtOH	[43]
(*R*)-α-MeCys(Trt)-OH (**80**)	+28.5º	0.15, MeOH	[48]
(*R*)-Fmoc-α-MeCys(Trt)-OH (**81**)	+31.9º	0.25, MeOH	[48]

[a]PM*Z*= *p*-methoxybenzyloxycarbonyl
[b]Value mistakenly quoted +6.8º

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