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Synthetic Studies Toward B-Alkylthiolanthionines

Hwa-Ok Kim
Utah State University

SYNTHETIC STUDIES TOWARD ß-ALKYLTHIOLANTHIONINES

by

Hwa-Ok Kim

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Hwa-Ok Kim

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ABBREVIATIONS

Ac	Acetyl
Bn	Benzyl
Boc	t-Butoxycarbonyl
CBz or Z	Benzyloxycarbonyl
m-CPBA	m-chloroperbenzoic acid
DCC	Dicyclohexylcarbodiimide
DHP	Dihydropyran
DIBAL-H	Diisobutyl aluminum hydride
DMAP	4-dimethylaminopyridine
DMP	2,2-dimethoxypropane
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
MPLC	Medium Pressure Liquid Chromatography
PCC	Pyridinium chlorochromate
PPTs	Pyridinium p-toluenesulfonate
p-TsOH	p-Toluenesulfonic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran

ABSTRACT

Synthetic Studies Toward

ß-Alkylthiolanthionines

by

Hwa-Ok Kim, Master of Science

Utah State University, 1987

Major Professor: Dr. Richard K. Olsen
Department: Chemistry and Biochemistry

Synthetic routes toward a ß-alkylthiolanthionine derivative, as found in the quinomycin depsipeptide antibiotics, have been studied through a sequence involving as the key intermediates and steps (a) (S)-Z-[(benzyloxycarbonyl)amino]-3,3-dimethoxy-1-propanol (2), prepared from N-benzyloxycarbonyl-L-serine in 3 or 4 steps, (b) N-benzyloxycarbonyl-O-tetrahydropyranyl-ß,ß-(ethylsulfinylethylthio)-alaninol (4a), converted from 2, and (c) attempted Lewis acid catalyzed replacement of alkylsulfinyl function by thiol moiety of cysteine, which gave undesired products. Stability of protecting groups used in this study, which are N,O-isopropylidenyl and tetrahydropyranyl functions in N-protected-L-serinol 20 or 26, under acidic conditions was found to play an important role in determining the optical purity obtained in 2. Jone's oxidation and methylation of 2 led to the formation of N-benzyloxycarbonyl-ß,ß-(dimethoxy)-alanine methyl ester (3) in low yield. Swern oxidation or Moffat oxidation of Z-L-Ser-Val-OMe dipeptide (5), which was expected to be converted to aldehyde 34, were carried out with unsuccessful results.

Swern oxidation was applied to various N-protected amino alcohols derived from α-amino acids to give the corresponding aldehydes with excellent yields and optical purities.

(68 pages)

INTRODUCTION

The quinoxaline antibiotics, which possess antibacterial[1] and cytotoxic[2] activities, consist of two families, the triostin[3] and quinomycins[1]. They are known to bind DNA by the simultaneous intercalation of both quinoxaline rings between the base pairs[4] and to thereby inhibit RNA synthesis[5].

The triostins, including its analogues which are represented by triostin A, were isolated[3a], structure-determined[3b] and synthesized[6] successfully. In contrast to the wide study for the triostins, the studies for the quinomycins, which are produced by widely distributed streptocetes, are limited except for the isolation and structure determination[7].

Echinomycin is characterized by its cyclic octapeptide structure with a novel unsymmetrical dithioacetal cross-bridge, equivalent to a ß-methylthiolanthionine unit. It also contains two sets of D-serine, L-alanine and N-methyl-L-valine residues. The 2-quinoxalinecarbonyl (Qxc) moiety is attached to the amino group of the D-serine residues (Fig. 1).

The interest in the total synthesis of the quinomycin antibiotics, as has been accomplished for the related triostins by Olsen and co-workers[6b-c] has led to a study for the preparation of echinomycin.

Two synthetic routes toward echinomycin were envisioned, which are:

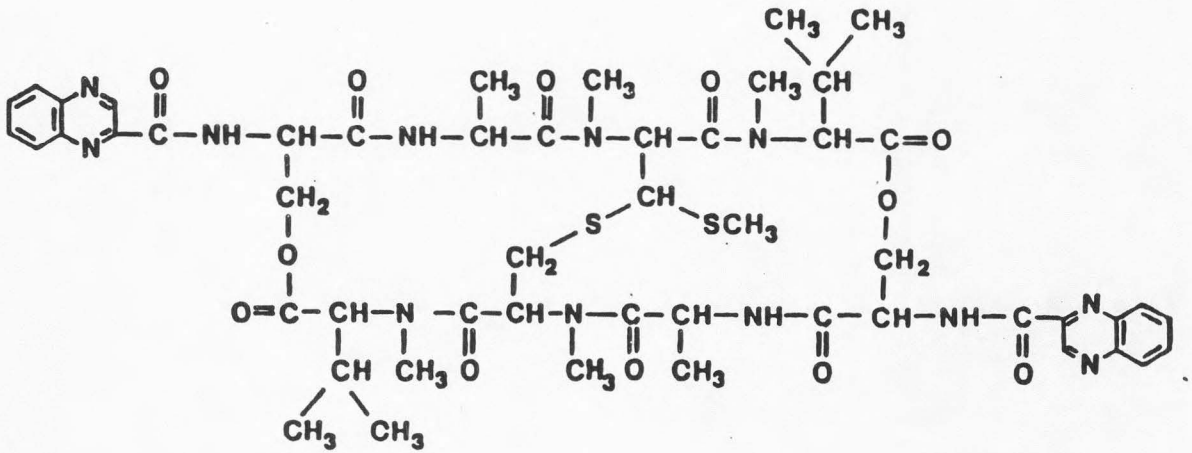
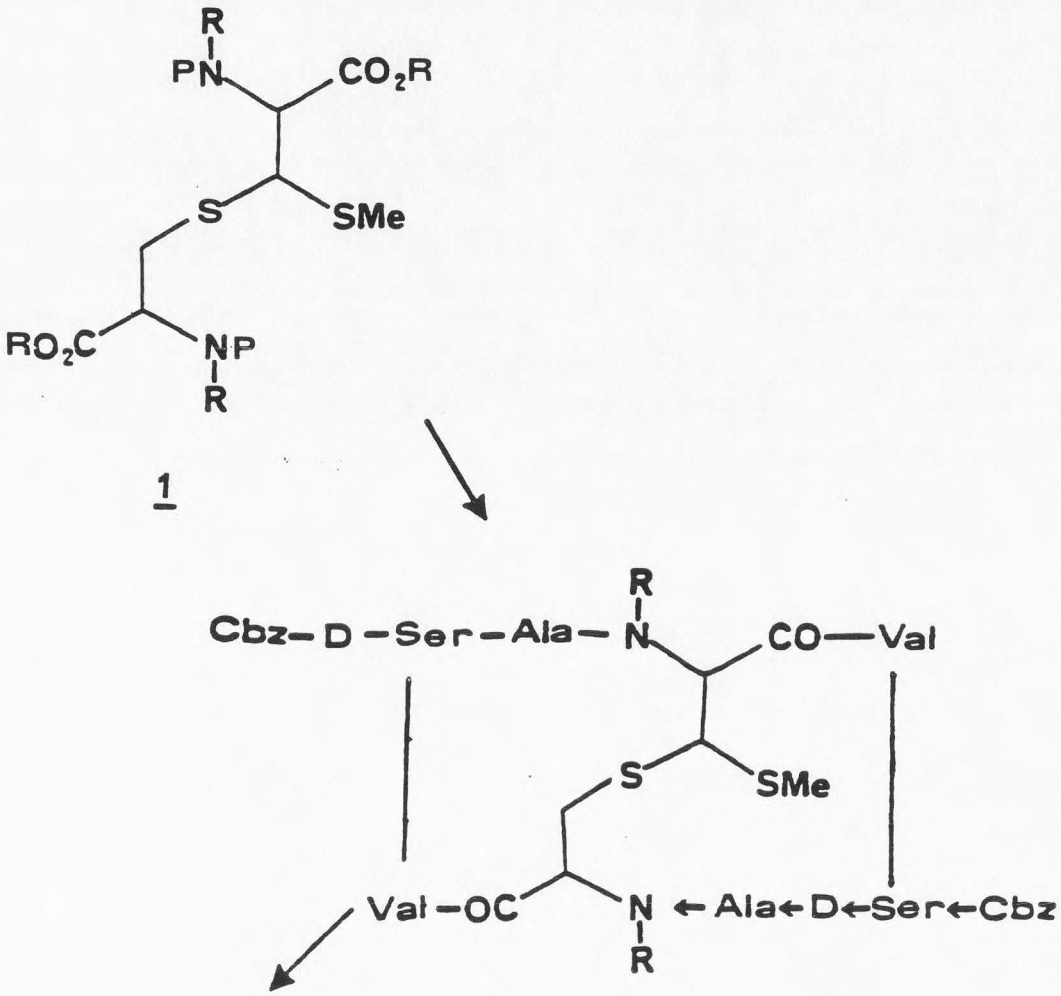


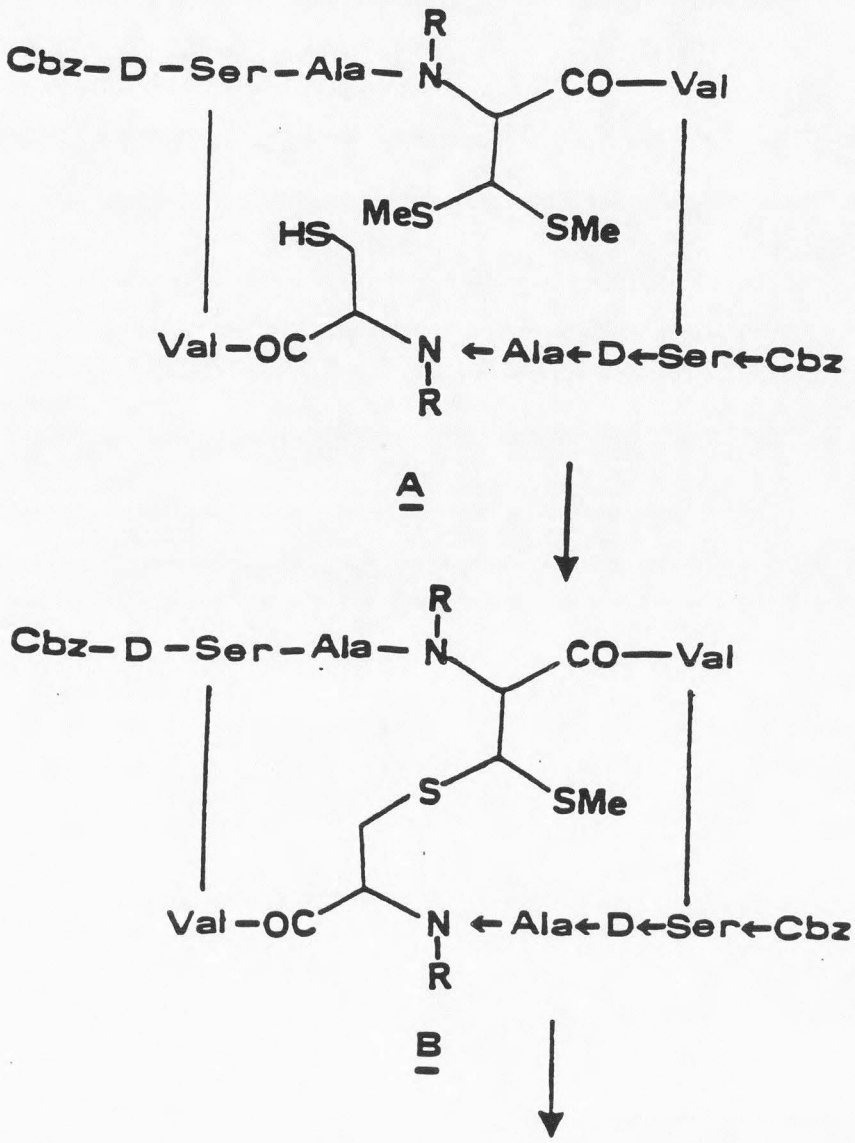
Fig. 1. Echinomycin

i) Synthesis of lanthionine derivative and attachment of other peptide fragments to this unit, followed by cyclization and quinoxalization.



Echinomycin

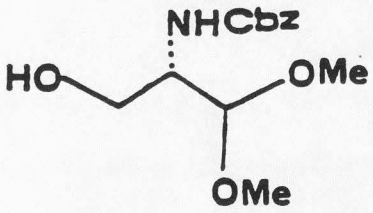
ii) As developed by Olsen and co-workers[6c], the synthesis of peptide fragments and cyclization would be accomplished first (Structure A), followed by combination of dithioacetal moiety with thiol function to give ß-methylthiolanthionine portion and quinoxalization (Structure B).



Echinomycin

Therefore, the exploration of synthetic route for the preparation of a protected ß-methylthiolanthionine, such as 1, has been a prime objective needed to synthesize echinomycin.

In this thesis, it will be discussed the successful synthesis of N-protected-2-amino-3,3-dialkoxy-1-propanol 2, which is expected to be an intermediate for the formation of ß-(dimethoxy)alanine 3,



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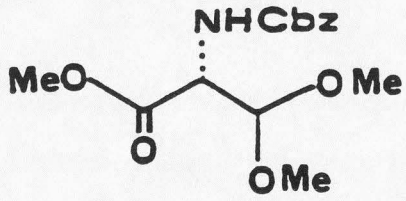
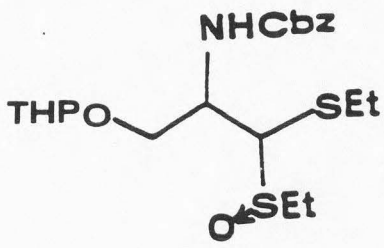


3

and attempts to prepare by the ß-alkylthiolanthionine derivative by the combination of the N-protected-O-tetrahydropyranyl-ß,ß-(alkylsulfinylalkylthio)alaninol 4a, obtained from compound 2, with suitable cysteine derivatives. Also, attempts to effect oxidation of the primary alcohol function in dipeptide 5 will be discussed.



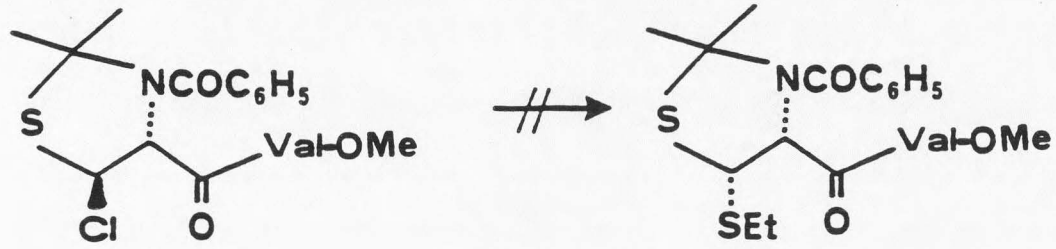
4a

Cbz-L-Ser-Val-OMe

5

BACKGROUND

Several attempts were carried out for the preparation of ß-methylthiolanthionine derivative 1 by Olsen and co-workers[8]. First, displacement study of ß-chloro group in 6 with mercaptide anions resulted in none of the desired product 7.



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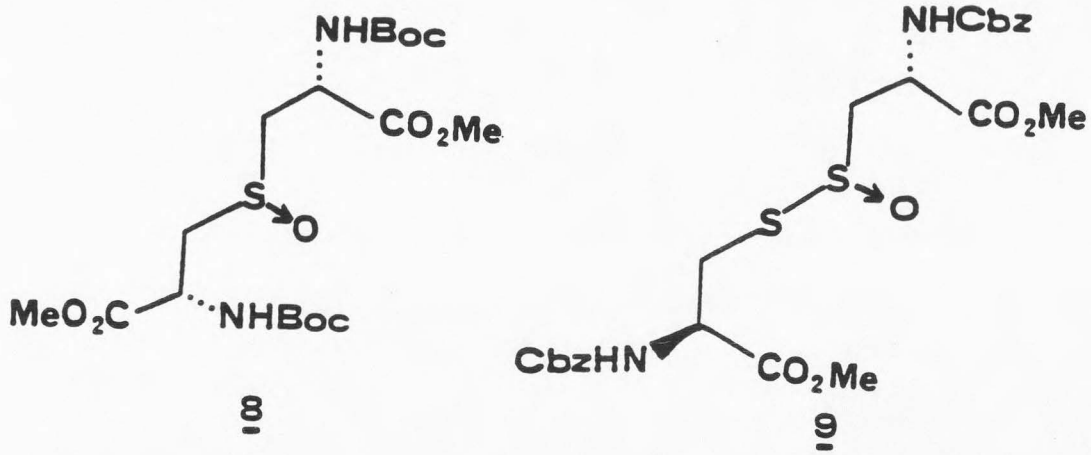
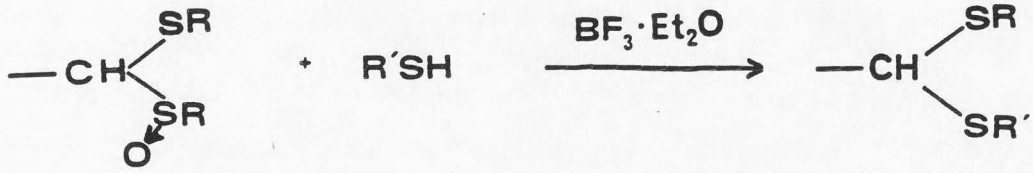
Other approaches to a derivative of 1 were investigated. Attempted Pummerer rearrangement involving the sulfoxide 8 or rearrangement of thiosulfinate 9 gave an unidentified product mixture or deoxygenated cysteine derivative, respectively.



8 9

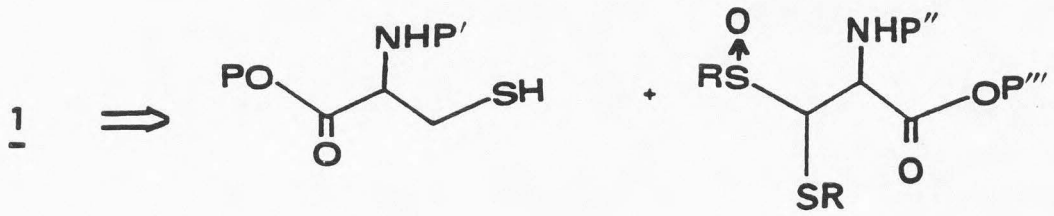
These unsuccessful results have led to the exploration of another route for the preparation of 1. Since it has been known that the exchange reaction of alkylsulfinylalkylthio compound 10 with

mercaptan and Lewis acid gave an unsymmetrical thioacetal 11 successfully[9], it could be expected for lanthionine 1 to be



10 11

prepared by the combination of thiol function of cysteine with ß,ß-(alkylsulfinylalkylthio)amino acid (12). Thus, the preparation of the compound 13 should be a prime objective.



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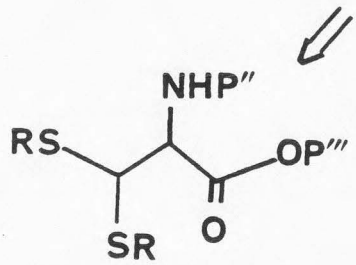
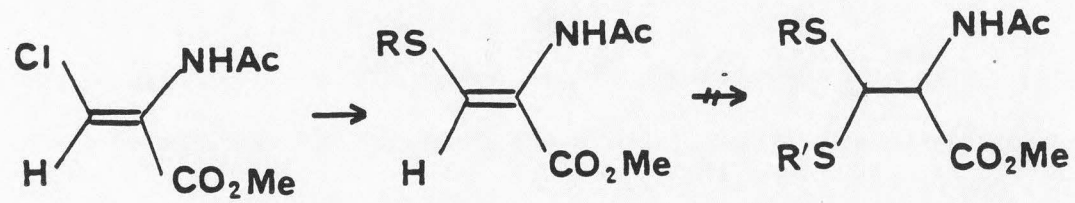


13

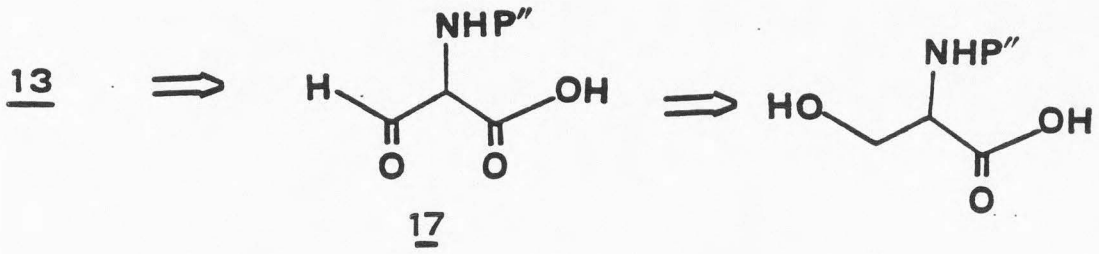
However, it has been known that this type of compound 13 is rare in nature, and the method of preparation is not known. Initially, Olsen and Kolar[10] reported efforts for the development of the methods toward ß,ß-bis(alkylthio)-α-amino acids 13 or 16.



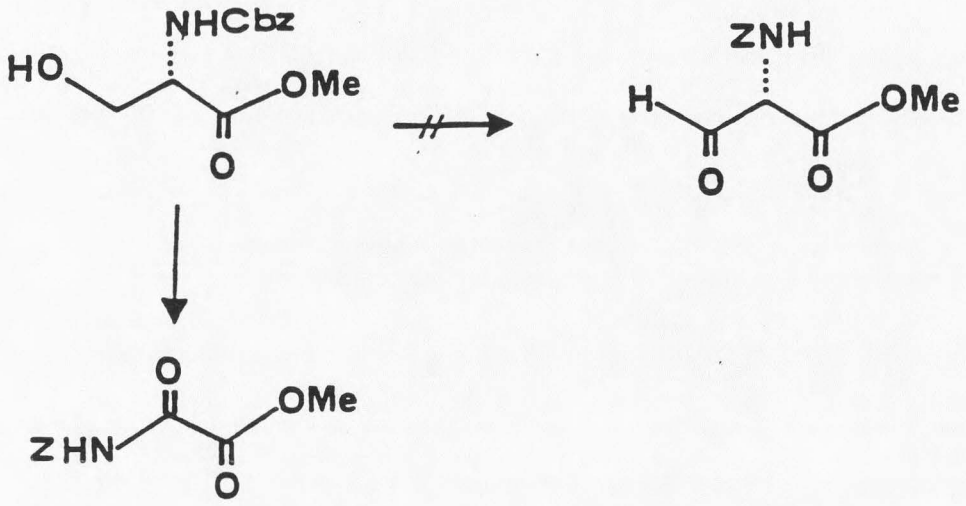
14 15 R= CH_2Ph 16

Preparation of N-acetyl- ß -(benzylthio)dehydroalanine methyl ester 15 from ß-chloro dehydroalanine 14 was accomplished. However, attempts to introduce a second molecule of mercaptan under either basic or acidic conditions failed and led only to recovered reactant.

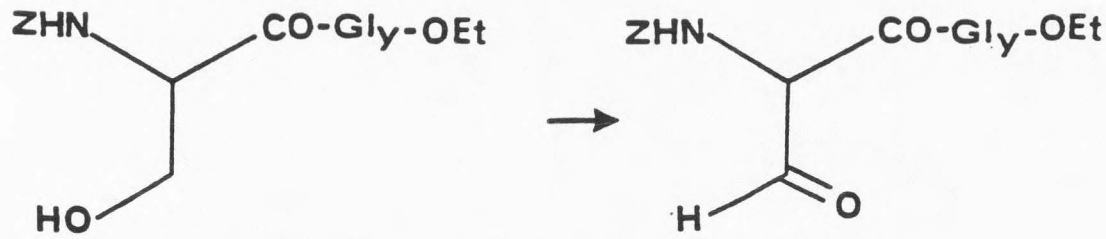
Therefore, as a new, expected route to obtain 13, it is possible to assume the following retrosynthetic scheme.



Since the aldehyde function in 17 should be equivalent to an dialkylthio methyl function, one assumption in which the primary hydroxyl function of serine might be converted to aldehyde seemed to be attractive. Unfortunately, it has been known that the oxidation of primary hydroxyl function in serine with Collin's reagent or CrO_3/AcOH gave an oxamate[11].



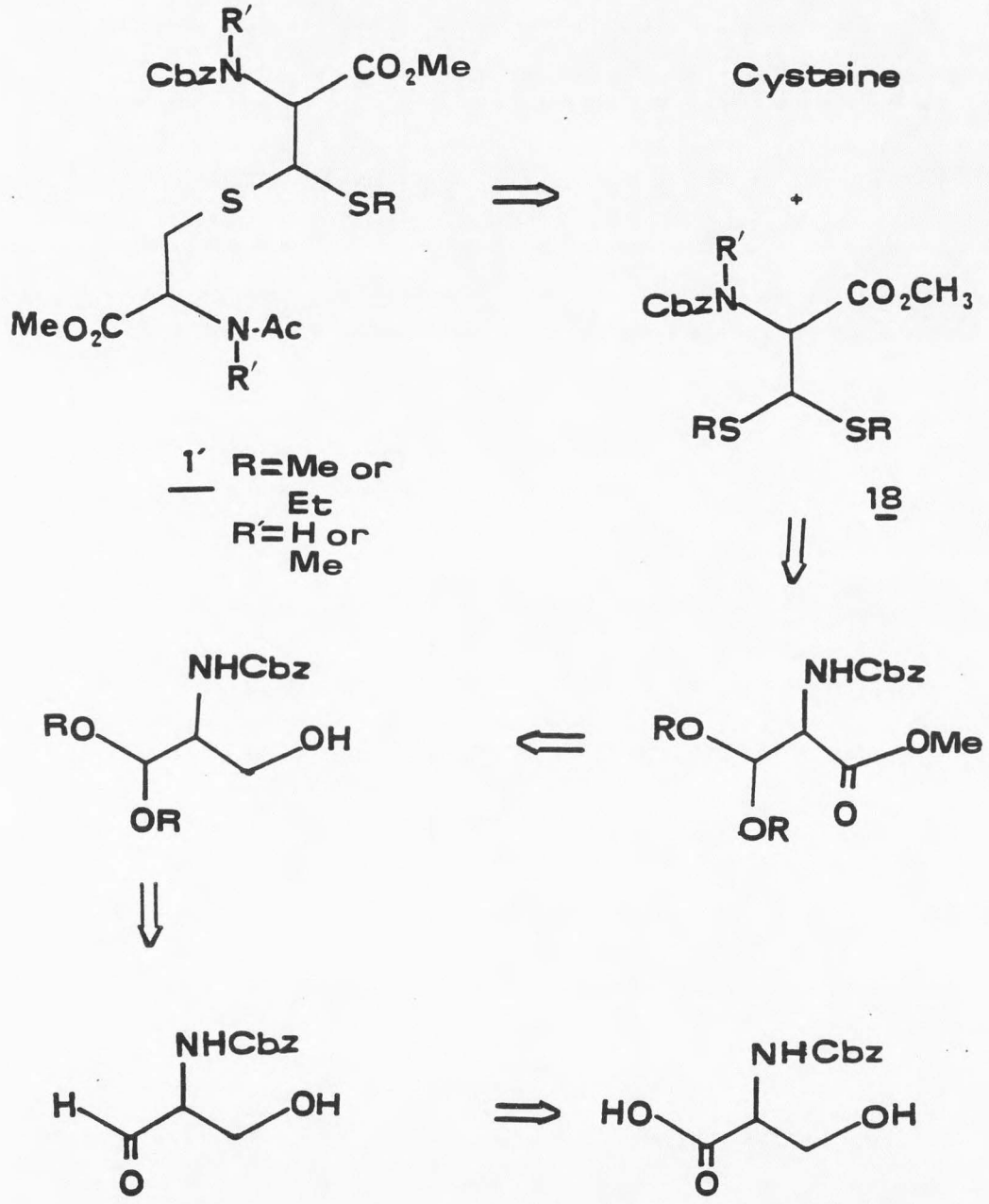
Recently, D'Angelli and co-workers[12] have reported the oxidation of primary hydroxyl function to an aldehyde in the dipeptide Z-Ser-Gly-OEt with Moffat system (dicyclohexylcarbodiimide, dimethyl sulfoxide, H_3PO_4).



This result has led to the application of the same chemistry to Z-Ser-Val-OEt (5), the oxidation product of which would be needed for incorporation into echinomycin.

STRATEGY

The basic strategy toward ß-alkylthiolanthionine 1′ is outlined in the following scheme .



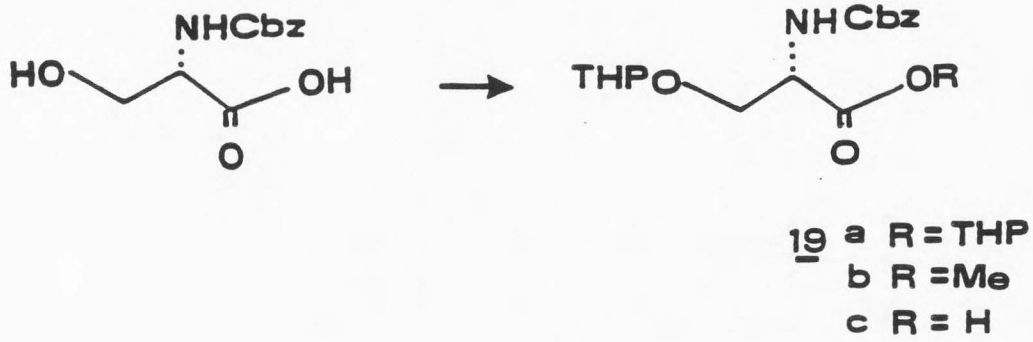
This approach was focussed on the stereospecific transformation of L-serine to the corresponding aldehyde, followed by acetalization, oxidation and transacetalization. It was expected that this strategy would allow the generalization of 18, and subsequent combination of 18 with cysteine derivative to construct the final structure 1.

RESULTS AND DISCUSSION

One approach toward methyl acetal 2 is outlined in Scheme 1.

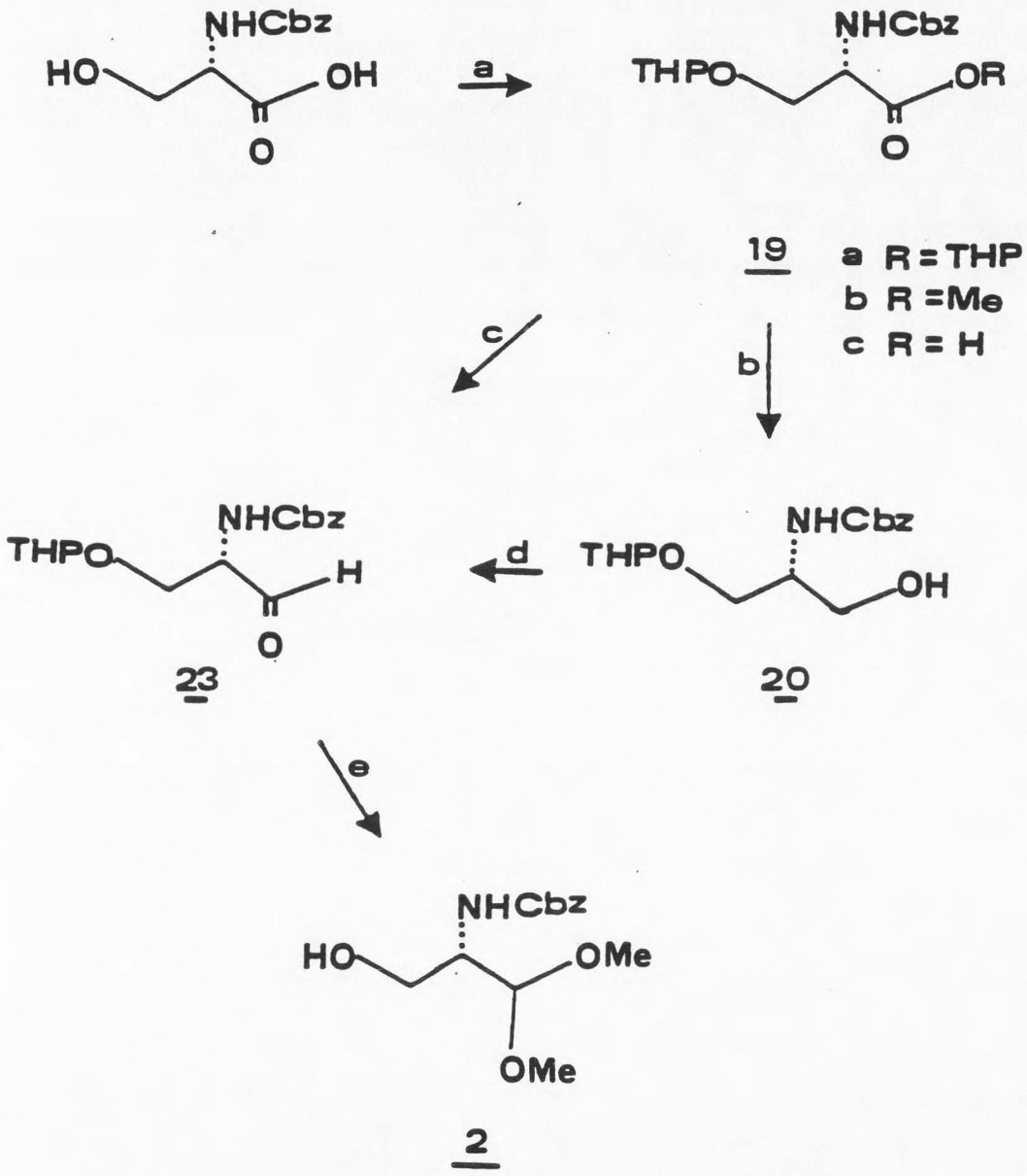
Preparation of N-(Benzyloxycarbonyl)-O-Tetrahydropyranyl-L-Serine Ester (19).

Tetrahydropyranyl ether ester 19a was readily available in quantitative yield by treatment of N-Cbz-L-serine with 4.0 eq. of dihydropyran and a catalytic amount of pyridinium p-toluenesulfonate[13]. It is noteworthy that 19a was partially deprotected to give 19c in MPLC (medium pressure liquid chromatography) purification. Also, tetrahydropyranyl ether methyl ester 19b was prepared in 80% yield by the reaction of N-Cbz-L-serine with 1.1 eq. of dihydropyran and pyridinium p-toluenesulfonate, followed by treatment with EDC (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), DMAP (4-dimethylaminopyridine) (0.1 eq.) and methanol[14].



19 a R = THP
b R = Me
c R = H

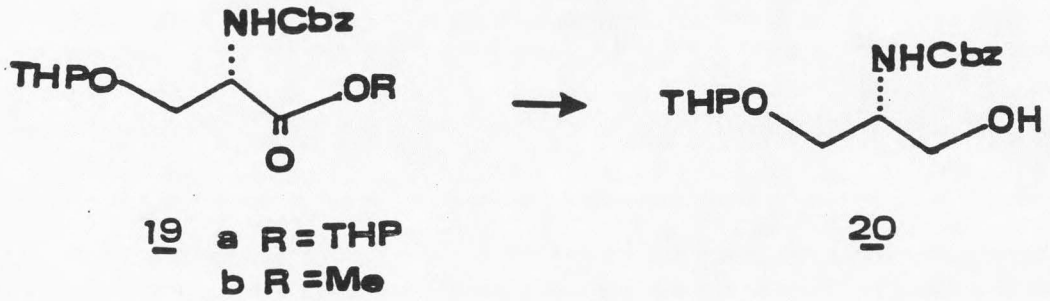
SCHEME 1*



*a) 4.0 eq. DHP, PPTs or i) 1.0 eq. DHP, PPTs ii) DMAP, MeOH, EDC b) $LiAlH_4$ or $NaBH_4/LiCl$ c) DIBAL-H or modified SMEA-H d) Swern or Pyridine.SO_3, DMSO, TEA e) MeOH, p-TsOH.

Preparation of N-(Benzyloxycarbonyl)-O-Tetrahydropyranyl-L-Serinol (20).

The N,O-protected-L-serine esters 19a and 19b were reduced to the corresponding alcohol 20 by treatment with $LiAlH_4$ or $NaBH_4/LiCl$[15] in high yield after purification.



19 a R=THP
b R=Me

20

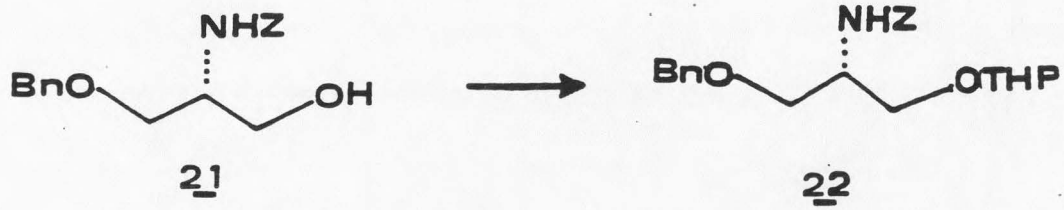
However, when the reduction of 19a or 19b was performed with various reaction conditions, the optical rotation of 20 showed variable values after silica gel chromatographic purification (Table I).

Table I. Optical Rotation of 20 with Various Reduction Conditions.*

Entry	Ester	Reducing agent	Reac. temp.	$[\alpha]_D^{23}$ **
1	19a	$LiAlH_4$	- 15 °C	+ 6.78
2	19a	$LiAlH_4$	- 15 °C	+ 13.65
3	19a	$LiAlH_4$	0 °C ----> r.t	+ 4.4
4	19b	DIBAL-H	-65 °C ---> 5 °C	+ 7.28
5	19b	$NaBH_4/LiCl$	r.t	+ 6.25
6	19b	$LiAlH_4$	15 °C	+ 4.0

* All crude materials were treated to silica gel chromatography using chloroform and acetone as an eluant.
** Solvent for optical rotation was chloroform.

In attempting to ascertain the causes of this variety of optical rotation,



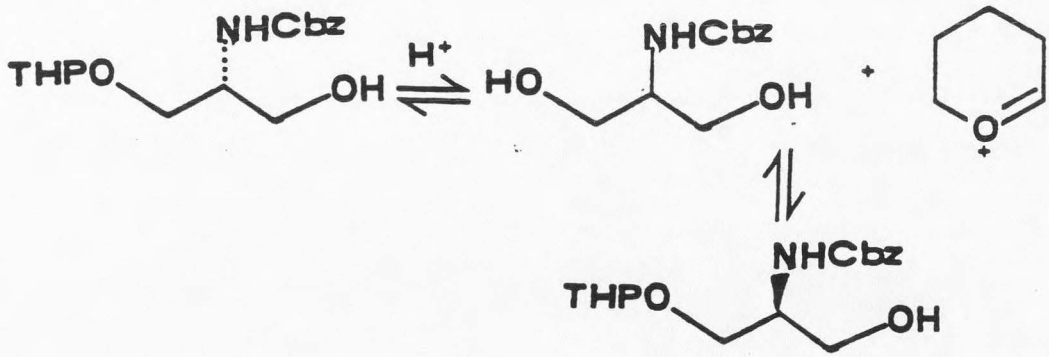
21 22

N-t-Boc-O-Bn-L-serinol (21) was chosen as a model compound and protected with dihydropyran to give 22, followed by carrying out the chromatographic elution. Two times 22 was chromatographed, and each time the sample of 22 showed complete retention of optical purity, as shown in Table II.

Table II. Optical Rotation of 22 after Chromatographic Purification.

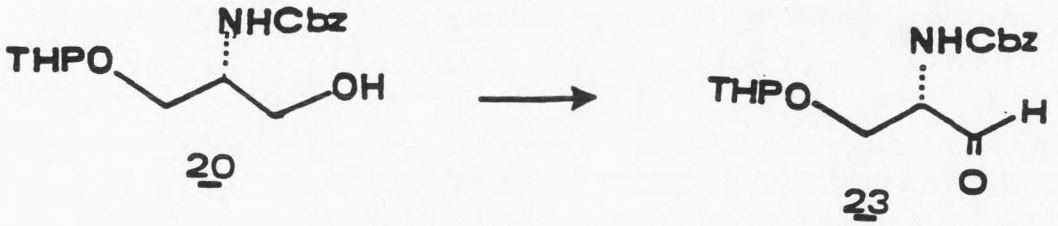
Chromatography(Hexane:EtOAc)	$[\alpha]_D^{23}$ ($CHCl_3$)
1st	+ 6.94
2nd	+ 7.37

Furthermore, since neither N,O-isopropylidenyl protected L-serinol 26a (Table VI) nor O-Bn-L-serinol (21)[16] lost optical integrity under the silica gel chromatographic condition, this loss of optical purity for 20 should have occurred by the instability of THP group in acidic condition.



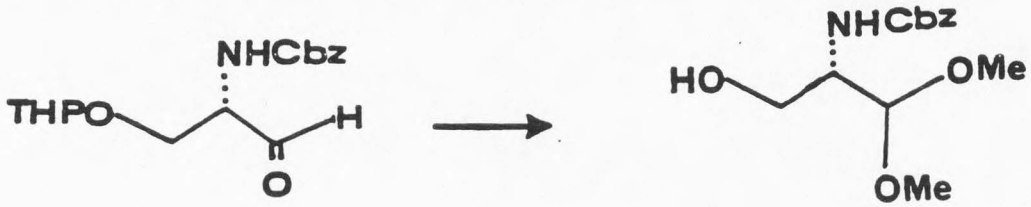
Preparation of N-(Benzyloxycarbonyl)-2-Amino-3,3-Dimethoxy-1-Propanol (2).

Alcohol 20 was subjected to Swern oxidation[17] or PCC method[18] to provide the corresponding aldehyde 23 in 80-92% or 38% yield.



Also, aldehyde 23 could be obtained from THP ester 19a by reduction with DIBAL-H[19] in 70% yield.

Without further purification of aldehyde 23, which was unstable on chromatographic purification, acetalization was carried out by treatment with methanol and a catalytic amount of p-toluenesulfonic acid to provide the acetal 2 in 55-80% yield after purification.



2

It is noteworthy that various values of the optical rotation were obtained (Table III) and that severe racemization had occurred as ascertained by conversion of 2, which was prepared from 23 via route b in Scheme 1, into the Mosher's ester[20] (entry 5 in Table III showed only 14% ee).

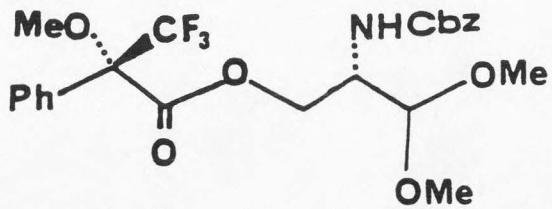
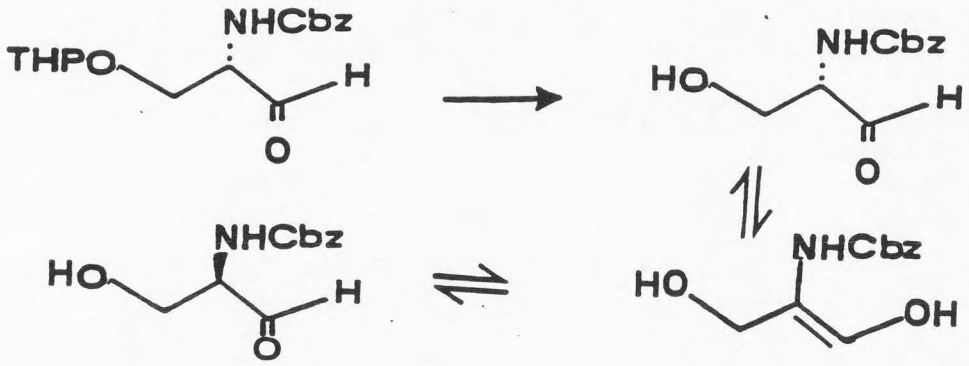


Table III. Various Reaction Conditions for Preparation of 2; Optical Rotation of 2.

Entry	Reac. Temp. (Reac. Time)	Purification	$[\alpha]_D^{23}$ *
1	r.t (30 min.)	column	+ 1.6
2	reflux (6 hrs.)	column	+ 0.2
3	reflux (4 hrs.)	column	+ 0.67
4	r.t (overnight)	column	+ 1.0
5	50 °C (12 hrs.)	MPLC	+ 0.3
6	reflux (2 hrs.)	MPLC	+ 0.63

* Solvent for optical rotation was chloroform.

Therefore, it could be concluded that the step of purification of THP ether alcohol 20 and the step of acetalization of aldehyde 23 to acetal 2 should be possible causes for racemization.



It has been reported[21] that the compound 25b can be reduced by DIBAL-H to give the corresponding aldehyde 27b, which is stable on chromatography because of the large size of t-butoxycarbonyl group and the rigid ring system (Scheme 2). Therefore, the same chemistry was applied to avoid the racemization which was shown during the preparation of 2 with THP ether serinol 20 or serinal 23.

Preparation of N-(Benzyloxycarbonyl)-N,O-Isopropylidenyl-L-Serine Methyl Ester (25a).

As a starting compound, N-Cbz-L-serine was converted to N-Cbz-N,O-isopropylidenyl-L-serine methyl ester (25a) by two different ways. First, as shown before, the methyl ester 19b was treated with methanol and a catalytic amount of p-toluenesulfonic acid to provide the hydroxyl-deprotected methyl ester 24 in 93% yield. N-Cbz-L-serine methyl ester 24 was then readily protected by reaction with 2,2-dimethoxypropane and a catalytic amount of p-toluenesulfonic acid to give compound 25a in 95% yield.

In second approach, N-Cbz-L-serine was converted to compound 25a by treatment with methanol and p-toluenesulfonic acid, followed by reaction with 2,2-dimethoxypropane and additional p-toluenesulfonic acid (90% yield).

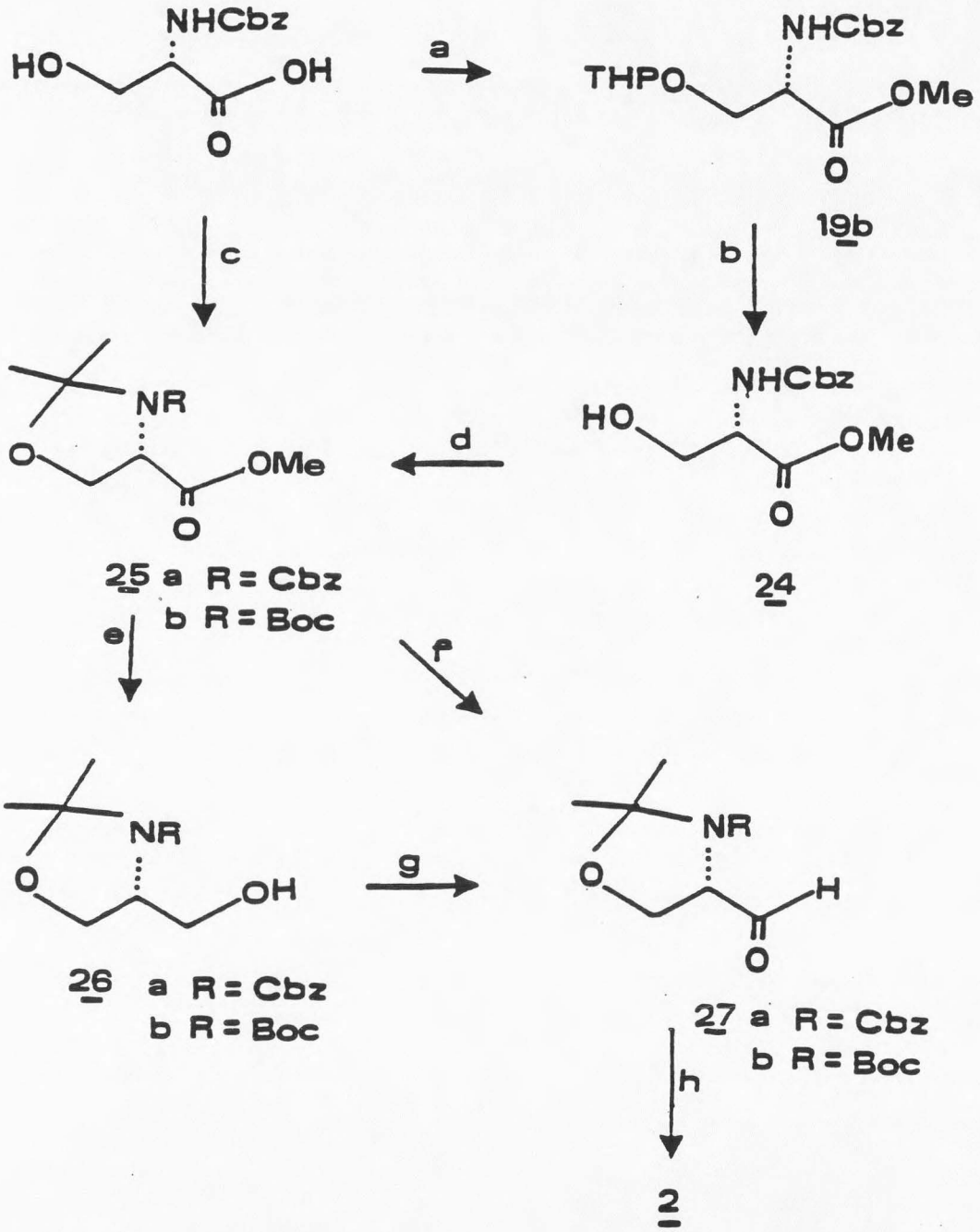
Table IV. Optical Rotation of 25a.

	Method of Preparation of 25a	$[\alpha]_D^{23}$ ($CHCl_3$)
1	1st Approach	- 51.3
2	2nd Approach	- 52.7
3	3rd Approach	- 51.5

Preparation of Acetal 2 from Methyl Ester 25a.

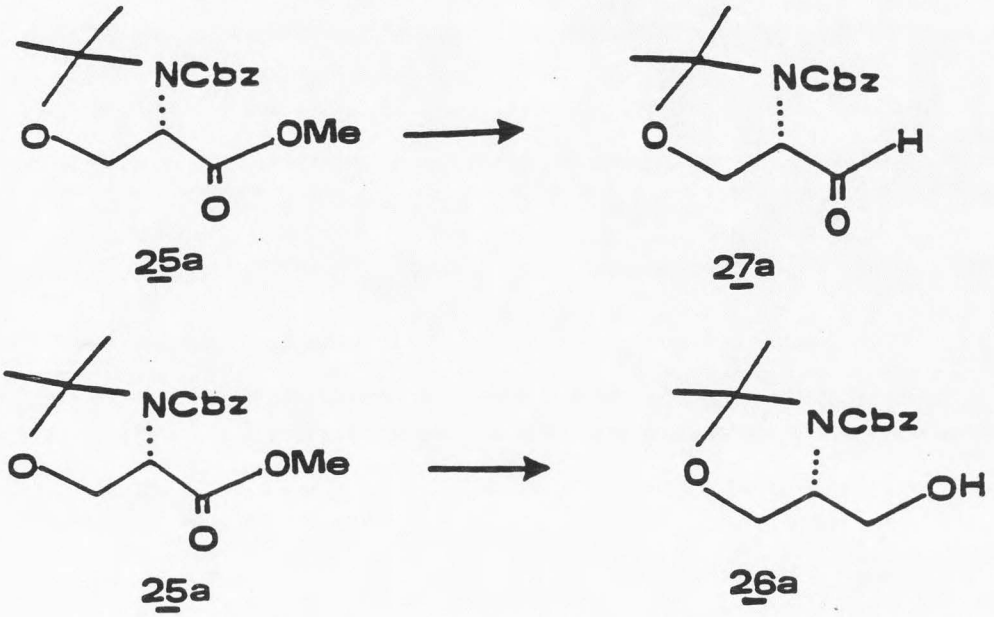
With N,O-protected-L-serine methyl ester 25a, reduction was carried out with modified sodium bis(2-methoxyethoxy)aluminum hydride (SMEA-H)[22] to the corresponding aldehyde 27a in 41% yield.

SCHEME 2*



* a) i) 1.0 eq. DHP, PPTs ii) DMAP, MeOH, EDC b) MeOH, p-TsOH c) MeOH, p-TsOH ---> DMP, p-TsOH d) DMP, p-TsOH e) $LiAlH_4$ or $NaBH_4/LiCl$ f) modified SMEA-H g) Swern oxidation h) MeOH, p-TsOH.

Another route to provide 27a was carried out. Compound 25a was treated with $LiAlH_4$ or a mixture of $NaBH_4/LiCl$[15], to give the corresponding alcohol 26a in 65-95% yield after purification.



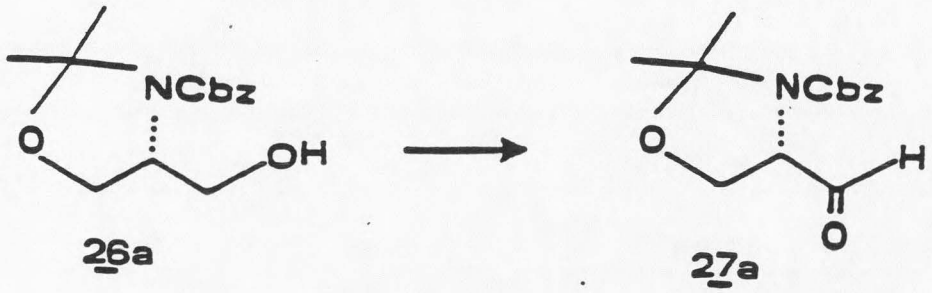
It is noteworthy to observe the difference of optical stability between 20 and 26a. Table V shows that isopropylidenyl group is more stable than THP function on silica gel purification.

The alcohol 26a was then subjected to oxidation to give aldehyde 27. Treatment of 26a with pyridine-SO_3, DMSO and triethylamine[15] gave aldehyde 27a in 84% yield.

Table V. Optical Rotation of Alcohol 26a.

Reagent	Chromatographic Method (Solvent)	$[\alpha]_D^{23}$ *
$LiAlH_4$	Flash ($CHCl_3$:acetone)	- 18.1
$LiAlH_4$	TLC (hexane:EtOAc)	- 17.5
$NaBH_4/LiCl$	MPLC ($CHCl_3$:acetone)	- 16.5

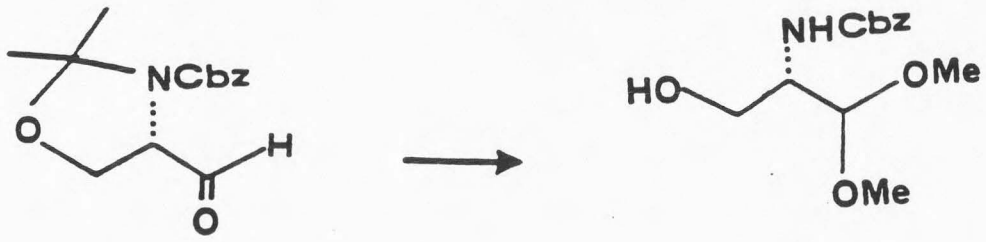
* Solvent for optical rotation was chloroform.



26a 27a

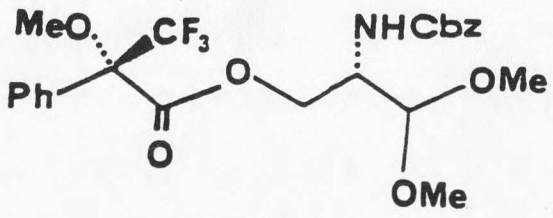
Also, alcohol 26a, could be converted to 27a with Swern oxidation in 81% yield. However, the aldehyde 27a showed much different optical rotation with various reaction conditions and chromatographic purification. This result strongly suggested that the aldehyde 27a should be unstable to silica gel chromatography.

On aldehyde 27a, which was not purified on silica gel chromatography, acetalization was carried out by reaction of methanol and a catalytic amount of p-toluenesulfonic acid to provide the desired acetal 2 in 98% yield after purification on silica.



27a 2

However, the ^{19}F NMR of Mosher's ester of 2 showed a value of 60% ee.



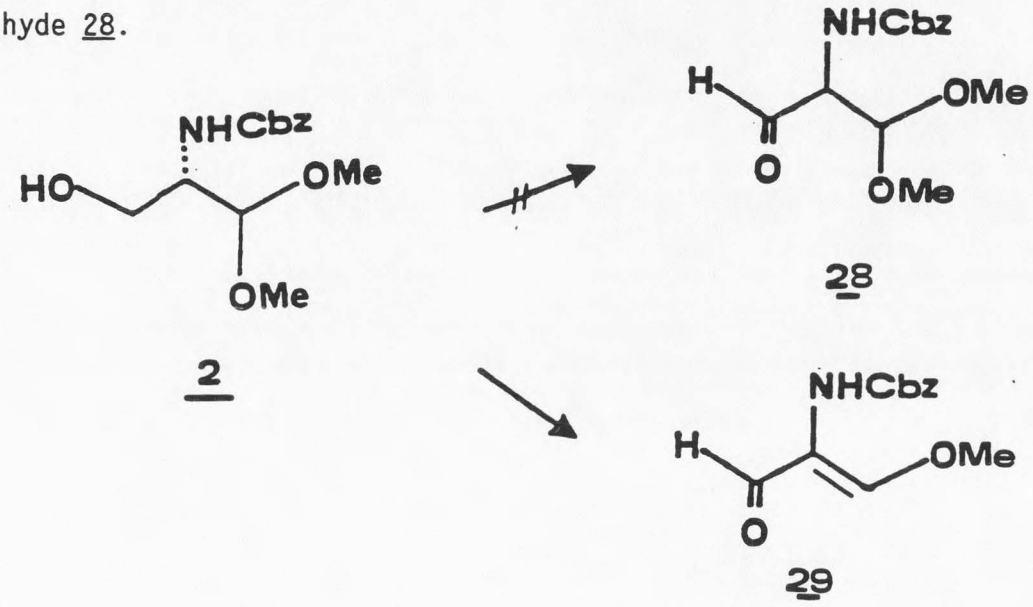
Oxidation of Acetal 2 to β,β-(Dimethoxy)alanine Methyl Ester (3).

One general approach to the preparation of carboxylic acids from alcohols is to employ an oxidizing agent such as Jone's reagent[23]. The reaction of 2 with Jone's reagent and esterification were investigated as a route to 3.

Overnight stirring of 2 with Jone's reagent at room temperature in acetone led to a complex mixture, including starting compound; subsequent methylation with known method[14] provided the target compound 3 in 9% yield after chromatographic separation.

2 3

This unsatisfactory result led to the exploration of another route for oxidation of hydroxyl function of 2. Thus, Swern oxidation was applied to 2 by usual manner to provide the undesired compound 29 as a major product from the complex mixture, instead of acetal aldehyde 28.



Other oxidation methods, such as $KMnO_4/OH^-$, O_2/PtO_2[24], $NaIO_4/RuCl_3$[25], PDC/DMF[26], gave complex mixtures of unidentified materials.

Attempts of Combination of 4a with N-Acetyl-L-Cysteine Methyl Ester.

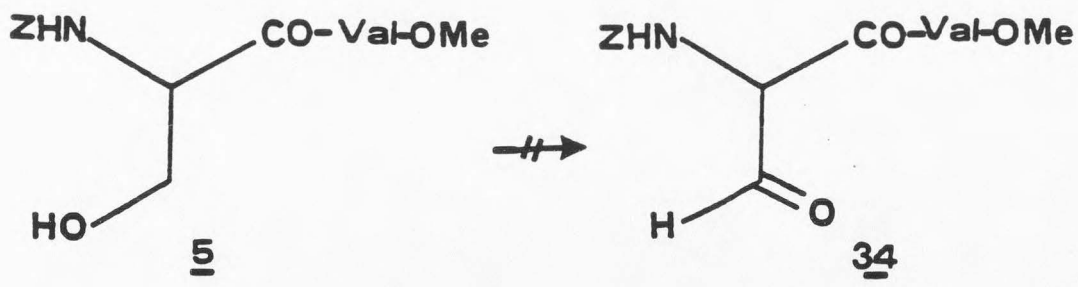
With compound 2 available, the next step toward the ß-methylthiolanthionine derivative was the conversion of acetal moiety to alkylsulfinylalkylthio group and combination with thiol function to provide the unsymmetrical thioacetal group. Accordingly, 2 was converted to thioacetal 30a by the reaction with ethanethiol and p-toluenesulfonic acid in chloroform in 75% yield. Protection of hydroxyl function, followed by oxidation with 1.0 eq. of m-chloroperbenzoic acid in ethyl acetate led to ethylsulfinylethylthio

compound 4a in 75% yield.

However, in the next step, Lewis acid (boron trifluoride) catalyzed combination of 4a with N-acetyl-L-cysteine methyl ester gave the mixture of undesired compounds, 31 and 32, which were assigned by 360 MHz NMR, as major products instead of 33. Obviously, these undesired products were made by the participation of neighboring group (e.g., benzyloxycarbonyl group). The same reaction was carried out several times using various Lewis acids ($AlCl_3$, ZnI_2, $TiCl_4$); however, the resulting products were nearly the same.

With these unsuccessful results, as a modified method, the preparation of sulfonium salt, which is expected to be an activated thio function, was investigated. First, acetal 2 was converted to methylthio acetal 30b by the reaction of methanethiol and p-toluenesulfonic acid in quantitative yield. Protection of hydroxyl function with an acetyl group, and attempt to methylate at the thio moiety with methyl iodide was carried out. However, even at reflux temperature of chloroform solvent, the reaction did not occur at all.

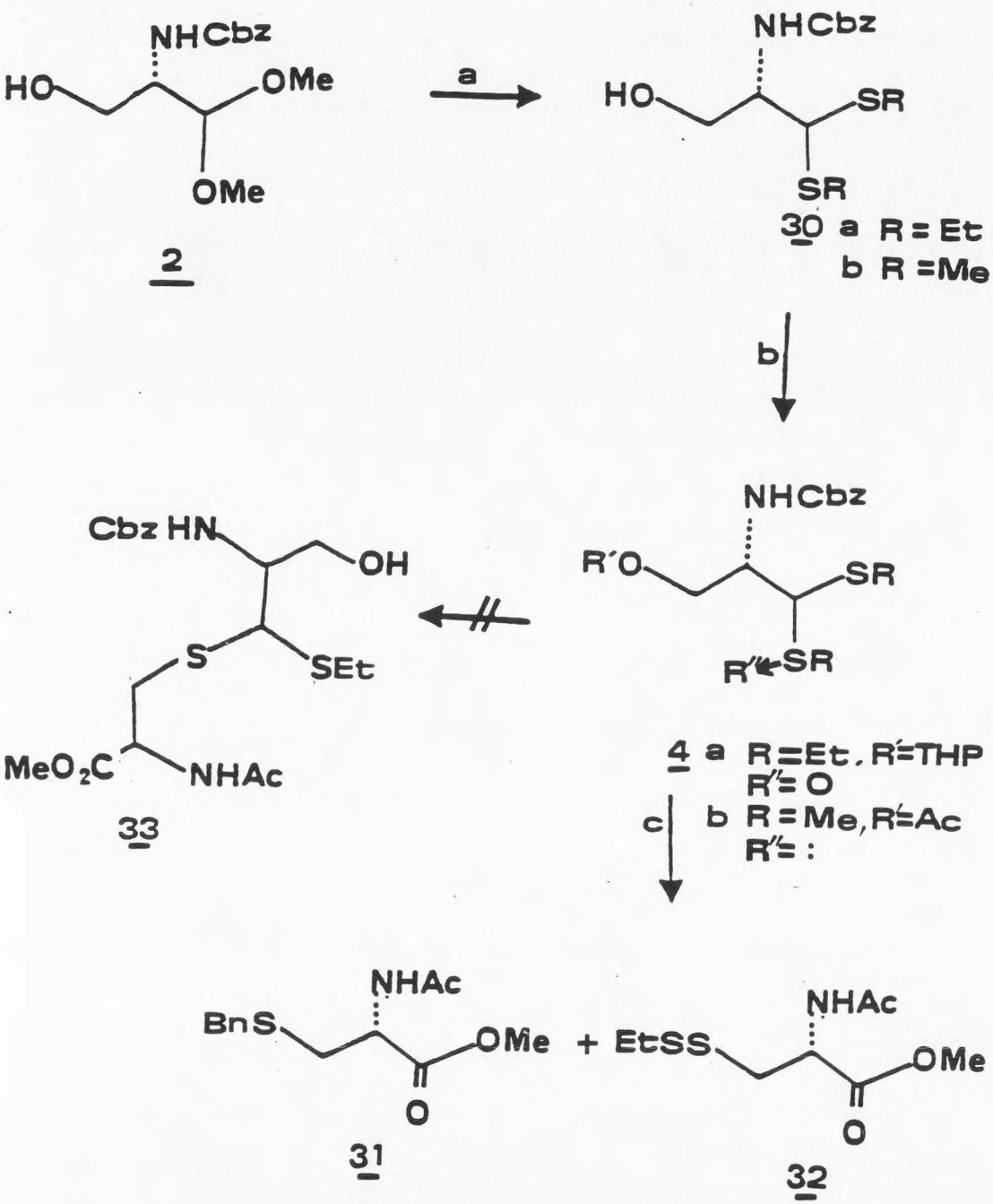
Attempted Oxidation of Cbz-L-Ser-Val-OMe.



5 34

As mentioned above, it has been reported that Cbz-L-Ser-Gly-OEt dipeptide was oxidized to the corresponding aldehyde with Moffat

SCHEME 3*



* a) EtSH, p-TsOH or MeSH, p-TsOH b) i) DHP, PPTs ii) m-CPBA or i) Ac_2O, pyridine c) Lewis acid, N-Ac-L-Cys-OMe.

system[12]. This reaction seemed to be particularly attractive, since in dipeptide (5) conversion of the hydroxyl function into aldehyde group (compound 34) would provide a potential route to an unsymmetrical thioacetal.

However, application of Moffat system to 5 by the known procedure did not provide the expected aldehyde 34 but starting material 5 was recovered. This phenomenon could be explained by the steric or conformational effect of isopropyl group in valine moiety[27]. Several different reaction conditions of Swern type reaction were applied. The results were unsatisfactory in that unreacted starting compound 5 was obtained or unseparable complex mixtures were obtained.

Preparation of Optically Active α-amino Aldehydes by Swern Oxidation.

There are many methods known for oxidation of N-protected β-amino alcohols to N-protected α-amino aldehydes[15, 19, 28]. Recently, Kanellis and co-workers reported the preparation of optically active N-protected α-amino aldehydes by the reduction of N-protected α-amino acids with borane-THF complex, followed by the oxidation of resulting alcohols with PDC[28b]. However, this method seemed to have the difficulty for preparation of the optically pure α-amino aldehydes.

Also, Hamada and co-workers[15] reported the preparation of α-amino aldehydes by the sequence of reactions which involved reduction of N-protected amino acid ethyl esters to the corresponding alcohols and subsequent oxidation to α-amino aldehydes with pyridine-SO_3 complex and DMSO in the presence of triethylamine. However, this reaction required the less milder reaction condition and an excess of

reagents.

The Swern oxidation has been applied to many systems and has shown successful results. Thus, in view of the difficulties in obtaining the optically pure α-amino aldehydes by other methods, plus the lack of application of Swern oxidation to ß-amino alcohols, we applied the Swern method to the preparation of α-amino aldehydes.

First of all, the ß-amino alcohols were prepared by various methods:

1. Reduction of mixed anhydride with $NaBH_4$[28d]; Cbz-glycine, Boc-alanine or Boc-leucine were treated with ethyl chloroformate with triethylamine at below 0 °C, followed by treatment with $NaBH_4$ in water to provide the corresponding alcohols in good yields.

2. N-t-Boc-N,O-isopropylidenyl-L-serine methyl ester (25b), which is known compound[21], was treated with mixture of $NaBH_4$/LiCl at room temperature to provide 26b in quantitative yield (Scheme 2).

3. Boc-valine was converted to methyl ester by treatment of EDC, DMAP, and methanol[14], followed by reduction with $LiAlH_4$ to yield the alcohol in 69% yield.

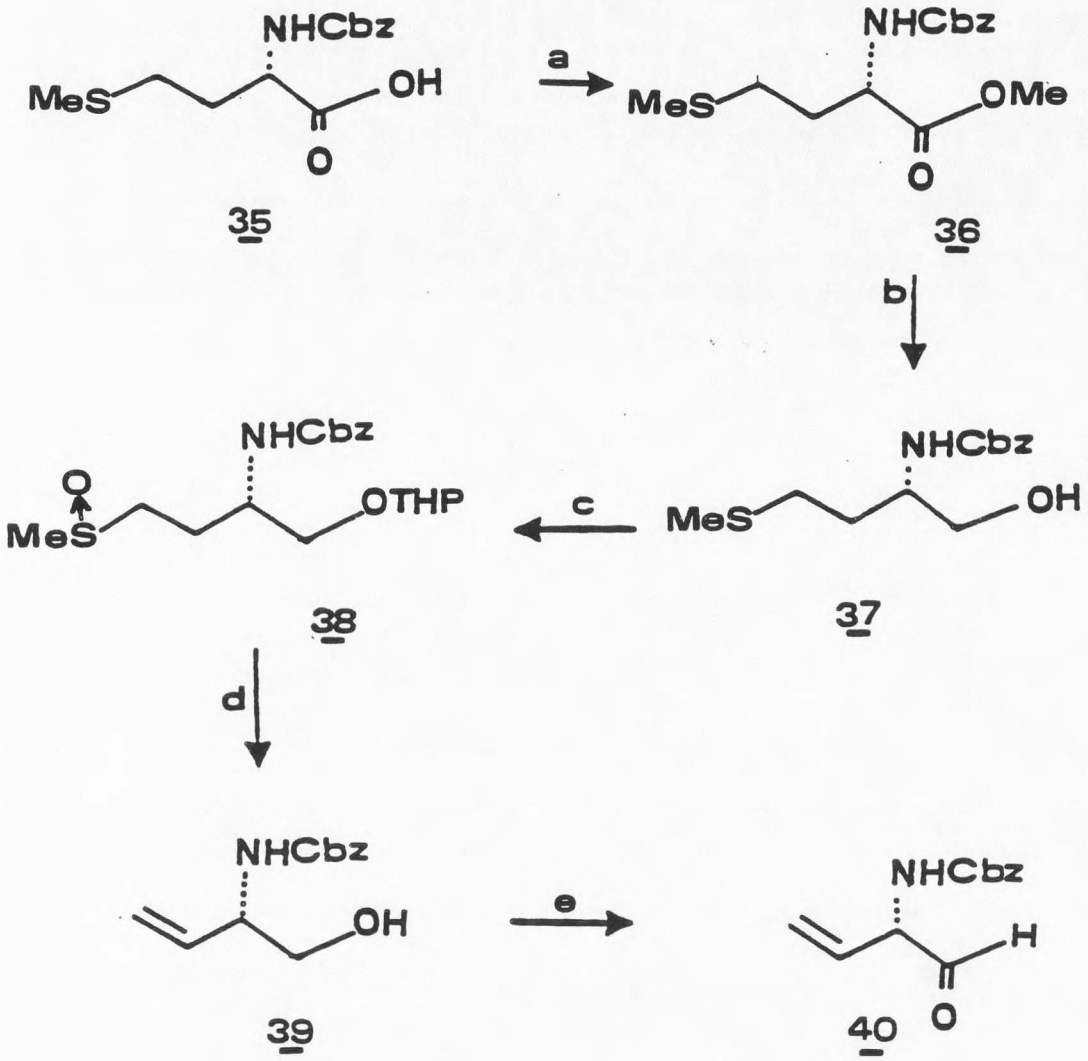
4. Compound 39 was prepared by the sequence of following reactions (Scheme 4). Commercially available N-Cbz-L-methionine (35) was converted to the corresponding alcohol 37 by the reaction with EDC, DMAP, and methanol, followed by the reduction with $LiAlH_4$ in 85% yield. Protection of hydroxyl function with dihydropyran[13] and oxidation with 1.0 eq. of m-chloroperbenzoic acid gave sulfinyl compound 38 in 91% yield. Thermal elimination reaction [29] by the heating in o-dichlorobenzene provided the target alcohol 39 in 50%

yield.

With the N-protected ß-amino alcohols in hand, Swern oxidation was carried out; N-protected ß-amino alcohols were added to the activated complex of DMSO at -65 ^{o}C. After 30-40 min. stirring, triethylamine was added to accomplish the reaction.

As shown in Table VI, the yields were very high (76-100%) and little or no racemization was detected, since the N-protected α-amino aldehydes obtained were reconverted to the starting ß-amino alcohols with $NaBH_4$ in alcoholic solvent without any loss of their optical purities.

SCHEME 4*



* a) DMAP, MeOH, EDC b) $LiAlH_4$ c) i) DHP, PPTs ii) m-CPBA d) o-dichlorobenzene, reflux e) Swern oxidation.

Table VI. Swern Oxidation of Various ß-amino Alcohols and Their Resulting Optical Rotations.

Entry	I	Yield of II (%)	$[\alpha]_D^{23}$ * Starting I	$[\alpha]_D^{23}$ * Converted From II
1	Cbz-Gly-ol	98	--	--
2	Boc-Ala-ol	100	- 10.7	- 9.2
3	Boc-Val-ol	90	- 18.1	- 18.2
4	Boc-Leu-ol	90	- 27.9	- 19.7**
5	N-Cbz-O-THP-Ser-ol (20)	80	+ 6.78	+ 1.7
6	N-Cbz-N,O-isopropyl-idenyl-Ser-ol(26a)	81	- 18.1	- 0.7
7	N-Boc-N,O-isopropyl-idenyl-Ser-ol(26b)	100	- 25.2	- 24.6
8	N-Cbz-2-amino-3-propen-1-ol(39)	76	- 31.3	- 32.0

* Solvents of optical rotation of I were $CHCl_3$ except entry 4 (methanol). All aldehydes provided not purified on silica gel except entry 5 and 6 (purified on preparative TLC).

** Reduction of Boc-Leu-al (entry 4) with $NaBH_4$ was carried after the aldehyde had been stored at room temperature for some days. This aldehyde is known to undergo partial racemization at room temperature. (Reference 28c).

SUMMARY

As shown above, the synthesis of the key compounds which were expected to be the intermediates for the preparation of ß-alkylthiolanthionine was carried out. (S)-2-[(Benzyloxycarbonyl) amino]-3,3-dimethoxy-1-propanol (2) was prepared from N-(benzyloxycarbonyl)-L-serine in 3 or 4 steps. From compound 2, N-(benzyloxycarbonyl)-ß,ß-dimethoxyalanine methyl ester (3) was provided, but in only 9% yield. The ß,ß-(ethylsulfinylethylthio)-alaninol derivative 4a, which was obtained from 2, was subjected to combine with thiol moiety of cysteine derivative; however, the desired product, ß-methylthiolanthionine derivative 33, was not obtained.

Several attempts to carry out the oxidation of the alcohol function of dipeptide 5, Cbz-Ser-Val-OMe, to an aldehyde function were not successful.

Successful preparation of α-amino aldehydes was accomplished with ß-amino alcohols by the Swern oxidation in excellent yields and optical purities.

EXPERIMENTAL SECTION

All solvents used were distilled in glass. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Methylene chloride was distilled from P_2O_5 and stored over Linde 3A molecular sieves. Methyl alcohol was distilled from sodium methoxide. Nuclear magnetic resonance (NMR) spectra were obtained for all compounds either on a Varian EM-360, JEOL FX 90Q, or Varian XL-300 spectrometer. Infra-red spectra were recorded on a Perkin-Elmer Model 297 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 automatic polarimeter. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. Preparative and analytical TLC were performed on commercially prepared silica gel on glass plates. Medium pressure liquid chromatography (MPLC) [30] was performed on column packed with silica gel 60 (0.040-0.064 mm). Flash chromatography was performed by Still's method[31].

N-(Benzyloxycarbonyl)-O-Tetrahydropyranyl-L-Serinol (20).

$LiAlH_4$ Method. To a stirred solution of Cbz-L-serine (5.5 g, 23.1 mmols) in methylene chloride (150 mL) was added dihydropyran (8.5 mL, 93 mmols) followed by pyridinium p-toluenesulfonate (500 mg) at room temperature. The reaction was allowed to stir overnight. After removal of the solvent, the oily residue was taken up in ethyl acetate (200 mLO, and the organic phase was washed with brine to remove the catalyst, dried over Na_2SO_4, and concentrated to give 19a as a yellow oil in almost quantitative yield: NMR ($CDCl_3$, 90 MHz)δ 1.59 (br s, 16H), 3.2 - 4.0 (set of m, 7H), 4.56 (br s, 2H), 5.13 (s, 2H, 5.72 (br, 1H), 7.34 (s, 5H). R_f (chloroform : acetone = 80 : 20)

0.87.

Without further purification, the above THP ether ester 19a in THF (30 mL) was added to a stirred solution of $LiAlH_4$ (1.4 g, 37 mmols) in THF (65 mL) at -15 °C. After stirring 2 hours, the reaction was quenched carefully with ethyl acetate (3 mL) and water (5 mL), and allowed to warm to room temperature. The solvent was removed in vacuo, and the resulting reside was taken up into ethyl acetate (100 mL) and filtered under suction to remove the insoluble materials.

The filtrate was separated, and the aqueous phase was extracted with ethyl acetate (50 mL). The organic phase and extract were combined, washed with brine (50 mL), dried (Na_2SO_4) and concentrated. The crude product was purified on MPLC using chloroform : acetone (90 : 10) as an eluant to give 20 as a colorless oil (5.78 g, 81% from Cbz-L-serine) : $[\alpha]_D^{23}$ +13.6 (c 0.63, $CHCl_3$); NMR ($CDCl_3$, 90 MHz)δ 1.55 (br s, 6H), 3.2 -4.0 (m, 8H), 4.51 (s, 1H), 5.08 (s, 2H), 5.61 (br, 1H), 7.32 (s, 5H). Anal. Calcd. for $C_{16}H_{23}NO_5$: C, 62.14; H, 7.44; N, 4.53. Found: C, 62.11; H, 7.68; N, 4.37. R_f (chloroform : acetone = 80 : 20) 0.58.

$NaBH_4$/LiCl Method. To a stirred solution of N-Cbz-L-serine (2.0 g, 8.4 mmomls) in methylene chloride (30 mL) was added dihydropyran (0.84 mL, 9.2 mmols), followed by pyridinium p-toluenesulfonate (200 mg). The reaction was stirred at room temperature for 4 hours. After most of the organic solvent was removed by evaporation, the residue was taken up into ethyl ether (50 mL), washed with brine (20 mL), dried (Na_2SO_4) and concentrated to give 19c as a yellow oil in quantitative yield with trace of 19a: NMR ($CDCl_3$, 90 MHz)δ 1.59 (br,

6H), 3.3 - 4.0 (set of m, 4H), 4.2 (m, 1H), 4.57 (br s, 1H), 5.13 (s, 2H), 5.87 (br m, 1H), 7.34 (s, 5H), 9.81 (br s, 1H). R_f (chloroform : acetone = 80 : 20) 0.15.

Without further purification, above oil 19c was dissolved in methylene chloride (80 mL) and methanol (5 mL) and DMAP (510 mg, 4.2 mmols) were added. After 20 min. stirring, EDC (1.91 g, 10 mmols) was added at 0 ^{o}C, and the mixture was stirred at 0 ^{o}C for 2 hours and at room temperature for overnight. Most of the solvent was removed, and the oily residue was dissolved in ethyl acetate (60 mL) and water (20 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with sat. $NaHCO_3$ (30 mL), water (30 mL), dried (Na_2SO_4), and concentrated. The product was purified on MPLC (chloroform : acetone = 80 : 20) to provide 19b as an oil (2.74 g, 97%) : $[\alpha]_D^{23}$ +21.1 (c 0.75, $CHCl_3$); NMR ($CDCl_3$) δ 1.59 (br, 6H), 3.3 - 4.1 (set of m, 5H), 3.68 (s, 3H), 4.5 (br s, 1H), 5.12 (s, 2H), 5.87 (br, 1H), 7.34 (s, 5H). Anal. Calcd. for $C_{17}H_{23}NO_6$: C, 60.53; H, 6.82; N, 4.15. Found: C, 60.65; H, 6.86; N, 4.04. R_f (chloroform : acetone = 80 : 20) 0.82.

To a stirred solution of LiCl (640 mg, 15 mmols) and $NaBH_4$ (570 mg, 15 mmols) in THF (15 mL) and ethanol (20 mL) was added dropwise 19b (2.44 g, 7.24 mmols) in THF (15 mL) and ethanol (20 mL) at room temperature under N_2 atmosphere. After 12 hours stirring, the reaction mixture was concentrated, and the residue was taken up in ethyl acetate (100 mL). The ethyl acetate solution was washed with brine (20 mL), dried (Na_2SO_4), concentrated, and the crude product was purified on column chromatography (chloroform : acetone = 80 :

20) to provide 20 as an oil (2.20 g, 98%): $[\alpha]_D^{23}$ +6.25 (c 0.8, $CHCl_3$); NMR and TLC were superimposable to authentic sample.

Reduction of 19b with DIBAL-H. To a stirred solution of 19b (6.85 g, 20.3 mmols) in THF (100 mL) was added dropwise DIBAL-H (1M in hexane, 22.3 mL) at -65 °C to stir for 5 hours at the same temperature and allowed to warm to 5 °C. The reaction was quenched with 1N HCl (70 mL) and the organic layer was separated. The aqueous phase was extracted with ethyl ether (150 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), concentrated, and purified on MPLC (chloroform : acetone = 95 : 5) to provide the alcohol 20 (2.42 g, 39%) : $[\alpha]_D^{23}$ +7.28° (c 0.98, $CHCl_3$) and the aldehyde 23 (2.22 g, 37%) : $[\alpha]_D^{23}$ +11.6° (c 1.3, $CHCl_3$).

(S)-N-(t-Butoxycarbonyl)-O-Benzyl-O-Tetrahydropyranyl-L-Serinol (22).

To a stirred solution of N-t-Boc-L-serinol (21) (480 mg, 17 mmols) in methylene chloride (30 mL) was added dihydropyran (1 mL) and pyridinium p-toluenesulfonate (50 mg) at room temperature. After overnight stirring, most of the solvent was removed in vacuo, the oily residue was taken up into ethyl ether (50 mL) and washed with brine (20 mL), dried (Na_2SO_4), concentrated to give 23 as an oil in quantitative yield. Took a small amount of sample for purification on preparative TLC (hexane : ethyl acetate = 80 : 20) two times. First value of $[\alpha]_D^{23}$ +6.94° (c 1.35, $CHCl_3$) and second value of $[\alpha]_D^{23}$ +7.37° (c 3.08, $CHCl_3$, $CHCl_3$) and second value of $[\alpha]_D^{23}$ +7.37° (c 3.08, $CHCl_3$) showed no racemization on preparative TLC.

N-(Benzyloxycarbonyl)-O-Tetrahydropyranyl-L-Serinal (23) with PCC Method from Alcohol 20.

To a stirred solution of pyridinium chlorochromate (530 mg, 2.5 mmols) and sodium acetate trihydrate (100 mg) in methylene chloride (20 mL) was added 20 (690 mg, 2.2 mmols) in methylene chloride (10 mL) at room temperature. After 20 hours stirring, the reaction mixture was diluted with ethyl ether (50 mL) and filtered. Filtrate was concentrated and residue purified on column chromatography (chloroform : acetone = 90 : 10) to give 23 as an oil (260 mg, 38%) with a recovered starting material (190 mg). NMR and TLC were superimposable to authentic sample.

N-(Benzyloxycarbonyl)-O-Tetrahydropyranyl-L-Serinal (23) with DIBAL-H from 19b.

To a stirred solution of 19b (860 mg, 2.55 mmols) in THF (20 mL) at -65 ^{o}C was added DIBAL-H (1 M in hexane, 5 mL) under N_2 atmosphere and stirred for 30 min. at -65 ^{o}C. The mixture was quenched with 1N HCl (5 mL) and extracted with ethyl ether (2 x 30 mL). Extracts were washed with brine (10 mL), dried (Na_2SO_4), concentrated, and purified on MPLC (chloroform : acetone = 95 : 5) to give 23 as an oil (550 mg, 70%) : $[\alpha]_D^{23}$ +16.2^{o} (c 0.5, $CHCl_3$).

N-(Benzyloxycarbonyl)-O-Tetrahydropyranyl-L-Serinal (23) with Swern System and Conversion to 2.

Dimethyl sulfoxide (3.5 mL, 50 mmols) in methylene chloride (5 mL) was added dropwise within a 5 min. to a cold (-63 ^{o}C) magnetically stirred solution of oxalyl chloride (1.9 mL, 21.5 mmols) in methylene chloride (15 mL) under N_2 atmosphere. The reaction mixture was stirred for 10 min. To this solution was added dropwise

the alcohol 20 (4.42 g, 14.3 mmols) in methylene chloride (30 mL) in 5 min. After reaction, mixture was stirred for 15 min., triethylamine (12 mL) was added dropwise with 5 min. with stirring at -63 °C. The cooling bath was removed, and the reaction was allowed to warm to room temperature. To this solution was added water (20 mL). The organic phase was separated, and the aqueous phase was extracted with methylene chloride (20 mL). The organic phase and extract were combined, washed with 1N HCl (20 mL), water (20 mL), 5% $NaHCO_3$ (20 mL), water (20 mL) successively and dried (Na_2SO_4), and concentrated to give 23 as an oil (4.03 g, 92%) : NMR ($CDCl_3$) δ 9.72 (d, 1H).

Without further purification, above aldehyde 23 with p-toluenesulfonic acid (400 mg) in methanol (50 mL) was stirred at 50 °C for 12 hours. After concentration of the reaction mixture, the residue was dissolved in ethyl acetate (50 mL), washed with brine (20 mL), dried (Na_2SO_4), concentrated, and purified on MPLC (chloroform : acetone = 90 : 10) to give 2 as an oil (2.03 g, 53% yield 20) : $[\alpha]_D^{23}$ +0.31° (c 0.66, $CHCl_3$, 90 MHz) δ 2.63 (s, 1H), 3.44 (s, 6H), 3.6-3.9 (m, 3H), 4.43 (d, 1H), 5.11 (s, 2H), 5.42 (br s, 1H), 7.34 (s, 5H). Anal. Calcd. for $C_{13}H_{19}NO_5$: C, 57.99; H, 7.06; N, 5.20. Found: C, 58.00; H, 6.94; N, 5.45. R_f (chloroform : acetone = 80 : 20) 0.44.

Mosher's Ester of 2. To a stirred solution of 2 (110 mg, 0.4 mmols) in methylene chloride (15 mL) was added (+)-α-methoxy-α-trifluoromethylphenylacetic acid (105 mg, 0.45 mmols) and DMAP (6 mg, 0.05 mmols). The reaction was cooled to 0 °C, EDC (114 mg, 0.6 mmols) was added and stirred at 0 °C for 4 hours and at room

temperature for overnight. Most of the solvent was removed and the residue was dissolved in ethyl acetate (20 mL) and 1N HCl (5 mL). The organic layer was separated, washed with sat. $NaHCO_3$ (10 mL), water (10 mL), dried (Na_2SO_4) and concentrated to give colorless oil in quantitative yield. Since the product was pure enough to run ^{19}F NMR, the oil was dissolved in $CDCl_3$ and trifluoroacetic acid (80 : 20 v/v) and the ^{19}F NMR spectrum taken to show -71.526 ppm, -71.642 ppm with ratio of 4:3 (14% ee).

N-(Benzyloxycarbonyl)-N,O-Isopropylidenyl-L-Serine Methyl Ester (25a).

Method A. N-Cbz-O-THP-L-serine methyl ester (19b) (5.0 g, 14.8 mmols) in methanol (80 mL) with p-toluenesulfonic acid (300 mg, 1.7 mmols) was heated at reflux for 3.5 hours. Most of the solvent was removed in vacuo, the oily residue eluated on flash chromatography (chloroform : acetone = 80 : 20) to give 24 as an oil (3.5 g, 94%) : NMR ($CDCl_3$) δ 3.47 (s, 1H), 3.68 (s, 3H), 3.86 (t, 2H), 4.39 (m, 1H), 5.07 (s, 2H), 6.11 (d, 1H), 7.29 (s, 5H). R_f (chloroform : acetone = 80 : 20) 0.53.

To a stirred solution of above compound 24 (3.5 g, 13.9 mmols) in acetone (80 mL) and 2,2-dimethoxypropane (20 mL) was added p-toluenesulfonic acid (250 mg, 1.45 mmols) at room temperature. The reaction was stirred at room temperature for 24 hours. Most of the solvent was removed in vacuo and the oily residue was eluated on flash chromatography (chloroform : acetone = 80 : 20) to provide 25a as an oil (3.9 g, 96%) : $[\alpha]_D^{23}$ - 51.3° (c 0.75, $CHCl_3$); NMR ($CDCl_3$, 90 MHz) δ 1.4 -1.7 (set of d, 6H), 3.6 - 3.76 (d, 3H), 4.16 (m, 2H), 4.47 (m, 1H), 5.12 (m, 2H), 7.31 (d, 5H) shown as 2:1 ratio of

rotamers or geometric isomers at the urethan function. Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 61.43; H, 6.48; N, 4.78. Found: C, 61.17; H, 6.58; N, 4.72. R_f (hexane : ethyl acetate = 50 : 50) 0.71.

Method B. The reaction mixture of N-Cbz-L-serine (3.0 g, 12.6 mmols) with p-toluenesulfonic acid (434 mg, 2.52 mmols) in methanol (80 mL) was heated at reflux for 2.5 hours. Most of the solvent was removed in vacuo and the oily residue was dissolved in 2,2-dimethoxypropane (16 mL) and acetone (100 mL) with additional p-toluenesulfonic acid (210 mg). The reaction was stirred at room temperature for 9 hours. Most of the solvent was removed in vacuo and the red-black oily residue was dissolved in ethyl acetate (100 mL), washed with sat. $NaHCO_3$ (20 mL), brine (30 mL), dried (Na_2SO_4) and concentrated to provide the oil. Purification of product on MPLC (hexane : ethyl acetate = 80 : 20) gave 25a as an oil (3.31 g, 90%) : $[\alpha]_D^{23}$ -52.7° (c 1.83, $CHCl_3$); NMR and TLC were superimposable to the product of Method A.

N-(Benzyloxycarbonyl)-N,O-Isopropylidenyl-L-Serinal (27a) with Modified SMEA-H.

To a stirred solution of 25a (450 mg, 1.54 mmols) in toluene (15 mL) was added DIBAL-H (1M in hexane, 3.9 mL) under N_2 atmosphere at -65 °C. After 30 min. stirring, modified SMEA-H (1M solution, mixture of N-methyl morpholine and Red-Al in toluene, 3.85 mL) was added and reaction was stirred at -65 °C for 1 hour. The reaction mixture was poured into the cooled 1N HCl (20 mL) and extracted with ethyl ether (70 mL) and ethyl acetate (60 mL). The extracts were combined, washed with brine (30 mL), dried (Na_2SO_4) and concentrated to give the oil. Purification on preparative TLC (hexane : ethyl acetate =

60 : 40) gave 27a as an oil (170 mg, 42%) : $[\alpha]_D^{23}$ -28.1° (c 0.27, $CHCl_3$); NMR ($CDCl_3$) δ 1.56 (d, 6H), 4.0 - 5.0 (set of m, 3H), 5.23 (s, 2H), 7.46 (s, 5H), 9.73 (s, 1H); IR ($CHCl_3$, NaCl) 1730, 1700 cm^{-1}. Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.88; H, 6.46; N, 5.32. Found: C, 63.94; H, 6.52; N, 5.20. R_f (chloroform : acetone = 90 : 10) 0.52.

N-(Benzyloxycarbonyl)-N,O-Isopropylidenyl-L-Serinol (26a).

$LiAlH_4$ Method. To a stirred solution of lithium aluminum hydride (200 mg, 5.3 mmols) in THF (25 mL) was added dropwise 25a (720 mg, 2.5 mmols) in THF (25 mL) at -15 °C. The reaction was stirred at -15 °C for 2 hours. Water (5 mL) was added and the reaction was allowed to warm to room temperature. Most of the solvent was removed in vacuo, the residue was taken up into ethyl acetate (50 mL) and filtered under suction to remove the insoluble materials. The filtrate was separated and the organic layer was dried (Na_2SO_4) and concentrated to give an oil. Purification of the crude product on flash chromatography (chloroform : acetone = 90 : 10) gave 26a as an oil (420 mg, 65%) : $[\alpha]_D^{23}$ -18.1° (c 1.8, $CHCl_3$); NMR ($CDCl_3$, 90 MHz) δ 1.55 (m, 6H), 3.49 (s, 1H), 3.5 - 4.2 (set of m, 5H), 5.20 (d, 2H), 7.40 (d, 5H); showed 2:1 ratio of rotamer. Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.40; H, 7.17; N, 5.28. Found: C, 63.17; H, 7.28; N, 5.21. R_f (chloroform : acetone = 80 : 20) 0.53.

$NaBH_4$/LiCl Method. To a stirred solution of sodium borohydride (740 mg, 20 mmols) and lithium chloride (850 mg, 20 mmols) in THF (20 mL) and ethanol (30 mL) was added dropwise solution of 25a (3.0 g, 10 mmols) in THF (20 mL) and ethanol (30 mL) at room temperature. The

reaction was stirred for 4 hours. The solvents were removed in vacuo, the residue was taken up into ethyl acetate (150 mL), washed with brine (2 x 30 mL), dried (Na_2SO_4), concentrated and purified on MPLC (chloroform : acetone = 95 : 5) to provide 26a as an oil (2.52 g, 95%) : $[\alpha]_D^{23}$ -16.5° (c 0.87, $CHCl_3$); NMR ($CDCl_3$) is superimposable to the product of above method; IR (neat,NaCl)3600-3100, 1690 CM^{-1}.

N-(Benzyloxycarbonyl)-N,O-Isopropylidenyl-L-Serinal (27) by Oxidation of 26a.

Method A. To a stirred solution of oxalyl chloride (0.35 mL, 4.0 mmols) in methylene chloride (2 mL) was added dropwise dimethyl sulfoxide (1 mL, 14.1 mmols) in methylene chloride (2 mL) at -65 °C, followed by alcohol 26a (360 mg, 1.36 mmols) in methylene chloride (20 mL). After 40 min. stirring at -65 °C, triethylamine (3 mL) was added dropwise and the cooling bath was removed. The reaction was allowed to warm to room temperature. Water (10 mL) was added and organic phase was separated. The aqueous layer was extracted with methylene chloride (15 mL). The organic phase and extract were combined, washed with 1N HCl (10 mL), water (10 mL), 5% $NaHCO_3$ (10 mL), water (10 mL) successively, dried (Na_2SO_4), concentrated and purified on preparative TLC (chloroform : acetone = 95 : 5) to provide 27a as an oil (290 mg, 81%) : $[\alpha]_D^{23}$ -2.0 (c 0.85, $CHCl_3$); NMR was superimposable to the product of modified SMEA-H reduction of 25a. R_f (chloroform : acetone = 80 : 20) 0.68.

Method B. To a stirred solution of alcohol 26a (2.3 g, 8.7 mmols) in methylene chloride (20 mL) with triethylamine (4.34 mL, 31.2 mmols) was added dropwise sulfur trioxide-pyridine complex (5.0

g, 31.2 mmols) in methylene chloride (20 mL) at room temperature. The reaction was stirred at room temperature for 5.5 hours, was poured into the ice-cold water (30 mL) and extracted with ethyl ether (3 x 50 mL) and ethyl acetate (50 mL). The combined extracts were washed with 1N HCl (30 mL), water (30 mL), sat. Na_HCO_3 (30 mL) and water (30 mL), dried (Na_2SO_4), and concentrated to give the aldehyde 27a as an oil (1.92 g, 84%) : $[\alpha]_D^{23}$ -10.08 (c 2.28, $CHCl_3$); IR was superimposable to the product of modified SMEA-H reduction of 25a.

Conversion of 27a to Alcohol 26a with $NaBH_4$. The reaction mixture of above pure aldehyde 27a (250 mg, 0.95 mmols) with $NaBH_4$ in ethanol (15 mL) was stirred at 0 °C for 2 hours. Most of the solvent was removed in vacuo, the residue was taken up into ethyl acetate (40 mL), washed with brine (10 mL), dried (Na_2SO_4), and concentrated to provide an oil. Purification on preparative TLC (hexane : ethyl acetate = 80 : 20) provided the alcohol 26a in quantitative yield : $[\alpha]_D^{23}$ -0.71° (c 3.25, $CHCl_3$).

N-(Benzyloxycarbonyl)-2-Amino-3,3-Dimethoxy-1-Propanol (2) from 27a.

The mixture of aldehyde 27a (250 mg, 0.95 mmols) with p-toluenesulfonic acid (20 mg) in methanol (20 mL) was stirred at room temperature for 20 hours. The solvent was removed in vacuo, the residue was dissolved in ethyl acetate (40 mL), washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give an oil. Purification of this crude product on flash chromatography (hexane : ethyl acetate = 60 : 40 and chloroform : acetone = 80 : 20) provided the acetal 2 as an oil (250 mg, 98%) : $[\alpha]_D^{23}$ - 5.05° (c 4.93, $CHCl_3$); NMR was superimposable to the product from acetalization of 23; IR (neat,

NaCl) 3600 - 3100, 1700 cm $^{-1}$. Conversion to Mosher's ester and ^{19}F NMR analysis showed 4:1 ratio of enantiomers (60% ee).

N-(Benzyloxycarbonyl)-β,β-Dimethoxyalanine Methyl Ester (3).

To a stirred solution of 2 (220 mg, 0.82 mmols) in acetone (20 mL) was added 1 mL of Jone's reagent (6.68 g of CrO_3, 5.58 mL of H_2SO_4 in 25 mL of water) at room temperature. The reaction was stirred at room temperature for 15 hours and filtered on Celite pad. Filtrate was evaporated to give oily residue, which was dissolved in 1N HCl (2 mL) and acidified with 3 N HCl (pH 2). The aqueous solution was extracted with ethyl acetate (2 x 30 mL), and the extracts were dried (Na_2SO_4) and concentrated to give a yellow oil (220 mg). By NMR and TLC analysis, the product was obtained in a complex mixture: NMR ($CDCl_3$) δ 10.8.

Without further purification, the above oil was dissolved in methylene chloride (30 mL) with DMAP (10 mg) and methanol (2 mL). The solution was cooled to 2 ^{o}C and EDC (153 mg, 0.8 mmols) was added. The reaction was stirred at 2 ^{o}C for 2 hours and at room temperature for overnight. Most of the solvent was removed in vacuo, the residue was taken up in ethyl acetate (30 mL) and 1N HCl (10 mL). The organic phase was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic phase and the extracts were washed with sat. $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated to give an oil. Purification of the crude product on flash chromatography (hexane : ethyl acetate = 80 : 20) provided the compound 3 as an oil (20 mg, 9%) : NMR ($CDCl_3$, 300 MHz) δ3.40 (d, 3H or 6H), 3.77 (s, 3H), 4.60 (m, 2H), 5.11 (m, 2H), 5.5

(br d, 1H), 7.34 (m, 5H). R_f (chloroform : acetone = 80 : 20) 0.78.

Attempt of Swern Oxidation of 2. To a stirred solution of oxalyl chloride (0.4 mL) in methylene chloride (2 mL) was added dropwise dimethyl sulfoxide (1 mL) in methylene chloride (2 mL) at-65 °C, followed by acetal 2 (90 mg, 3.3 mmols) in methylene chloride (10 mL). The reaction was stirred at -65 °C for 30 min. Triethylamine (3 mL) was added dropwise at -65 °C and the reaction was allowed to warm to room temperature. Water (5 mL) was added and stirred for 20 min. The organic phase was separated and the aqueous layer was extracted with methylene chloride (20 mL). The combined organic phases were washed with 1N HCl (10 mL), water (10 mL), sat. $NaHCO_3$ (10 mL), water (10 mL), successively. Dried (Na_2SO_4), concentration and purification of the crude product on preparative TLC (hexane : ethyl acetate = 80 : 20) provided 29 as a white solid (45 mg) : NMR ($CDCl_3$, 300 MHz) δ 4.07 (s, 3H), 5.15 (s, 2H), 6.0 (br s, 1H), 6.81 (s, 1H), 7.37 (m, 5H), 9.11 (s, 1H). R_f (hexane : ethyl acetate = 50 : 50) 0.62.

N-(Benzyloxycarbonyl)-2-Amino-3,3-Diethylthio-1-Propanol (30a).

To a stirred solution of 2 (790 mg, 2.93 mmols) in chloroform (30 mL) was added ethanethiol (1.5 mL), followed by p-toluenesulfonic acid (80 mg) at 0 °C. After 6 hours stirring at 0 °C, the reaction was stirred at room temperature for overnight. Water (5 mL) was added to separate the organic phase. The organic phase was dried (Na_2SO_4), concentrated, and the crude product was purified on MPLC (chloroform : acetone = 95 : 5 and 80 : 20) to provide 30 as an oil (720 mg, 75%) : NMR (CDCl3, 90 MHz) δ 1.24 (t, 6H), 2.33 (br, 1H),

2.63 (q, 4H), 3.85 - 4.07 (set of m, 4H), 5.12 (s, 2H), 5.44 (br, 1H), 7.34 (s, 5H). Anal. Calcd. for $C_{15}H_{23}NO_3S_2$: C, 54.71; H, 6.99; N, 4.26; S, 19.45. Found: C, 54.70; H, 7.11; N,4.22; S, 19.23. R_f (chloroform : acetone = 80 : 20) 0.76.

N-(Benzyloxycarbonyl)-O-Tetrahydropyranyl-2-Amino-3,3-Ethylsulfinylethylthio-1-Propanol (4a).

To a stirred solution of 30a (630 mg, 1.9 mmols) in methylene chloride was added dihydropyran (2 mL), followed by pyridinium p-toluenesulfonate (50 mg) at room temperature. After 5 hours stirring methylene chloride was removed in vacuo, the residue was taken up in ethyl ether (20 m), washed with brine (10 mL), dried (Na_2SO_4) and concentrated to give a brown oil.

Without further purification, above oil was dissolved in ethyl acetate (15 mL) and to this solution was added dropwise the solution of m-chloroperbenzoic acid (85%, 350 mg, 1.9 mmols) in ethyl acetate (10 mL) at -40 ^oC within 10 min. After 1 hour stirring at -40 to -20 ^oC, the reaction was washed with sat. $NaHCO_3$ (3 x 10 mL), dried (Na_2SO_4), concentrated and purified on MPLC (chloroform : acetone = 95 : 5) to provide 4a as an oil (610 mg, 75%) : NMR ($CDCl_3$, 90 MHz) δ1.24 (set of m, 6H), 1.4 - 1.9 (br s, 6H), 2.74 (set of m, 4H), 3.0 - 4.0 (set of m, 5H), 4.59 (br s, 1H), 5.09 (s, 2H), 5.4 (br s, 1H), 7.34 (s, 5H). Anal. Calcd. for $C_{20}H_{31}NO_5S_2$: C, 55.94; H, 7.23; N, 3.26; S, 14.92. Found: C, 56.14; H, 7.23; N, 3.36; S, 15.09. R_f (chloroform : acetone = 95 : 5) 0.36.

O-Acetyl-N-(Benzyloxycarbonyl)-2-Amino-3,3-Dimethylthio-1-Propanol (4b).

The mixture of compound 2 (1.8 g, 6.7 mmols) with p-

toluenesulfonic acid (115 mg) in chloroform (30 mL) was stirred at 0 ^{o}C for 6 hours and at room temperature for overnight. After evaporation of most of the solvent, the brown residue was eluated on short column chromatography (ethyl acetate) to give the brown oil.

To a stirred solution of above oil in pyridine (50 mL) was added acetic anhydride (30 mL) and mixture stirred at room temperature for 48 hours. Most of pyridine was removed in vacuo, the brown oily residue was dissolved in ethyl acetate (100 mL), washed with 1N HCl (20 mL), 5% $NaHCO_3$ (20 mL), brine (20 mL), dried ($NaSO_4$), and concentrated to give an oil. Purification on MPLC (hexane : ethyl acetate = 80 : 20) provided 4b as a white solid. Recrystallization from ethyl acetate and hexane gave white needles (1.84 g, 80%) : m.p 66 - 88 ^{o}C; NMR ($CDCl_3$) δ 2.0 (s, 3H), 2.1 (s, 6H), 3.6 - 4.6 (set of m, 4H), 5.2 (s, 2H), 5.4 (br s, 1H), 7.4 (s, 5H). Anal. Calcd. for $C_{15}H_{21}NO_4S_2$: C, 52,48; H, 6.12; N, 4.08. Found: C, 52,62; H, 6.24; N, 4.14. R_f (hexane : ethyl acetate = 80 : 20) 0.27.

Attempts of Combination of 4a with N-Acetyl-L-Cysteine Methyl Ester. To a stirred solution of compound 4a (210 mg, 0.49 mmols) in chloroform (5 mL) was added BF_3 etherate (1 mL), followed by N-acetyl-L-cysteine methyl ester (170 mg, 0.9 mmols) in chloroform (10 mL) at room temperature. After 24 hours stirring, the reaction was concentrated and the residue was taken up in ethyl acetate (10 mL) and water (5 mL). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (2 x 10 mL). The organic phase and extracts were combined, washed with sat. $NaHCO_3$ (15 mL), brine (15 mL), dried (Na_2SO_4), and concentrated to give brown oil. Separation on column chromatography (hexane : ethyl acetate : acetone

= 60 : 30 : 10) provided a colorless oil (65 mg) as a major product: NMR ($CDCl_3$, 360 MHz) 32: δ 1.32 (t, 3H, $CH_2\underline{CH_3}$), 2.06 (s, 3H, CH_3CO), 2.72 (q, 2H, $\underline{CH_2}CH_3$), 3.18 (t, 2H, $S\underline{CH_2}CH$), 3.78 (s, 3H, OCH_3), 4.9 (m, 1H, $NH\underline{CH}$), 6.5 (br, 1H, NH). 31: 2.00 (s, 3H, CH_3CO), 2.9 (m, 2H, $S\underline{CH_2}CH$), 3.70 (s, 2H, $PH\underline{CH_2}S$), 3.75 (s, 3H, OCH_3), 4.80 (m, 1H), 7.3 (m, 5H). ^{13}C; 14.34, 23.15, 23.19, 32.80, 33.64, 36.83, 40.66, 51.70, 51.93, 52.62, 52.66, 127.19, 128.51, 128.77, 137.57, 169.65, 170.81, 171.12. Based on NMR analysis, the product was assigned as the mixture of compound 31 and 32.

Attempted Oxidation of Z-L-Ser-Val-OMe (5). To a stirred solution of DCC (Dicyclohexylcarbodiimide) (820 mg, 4.0 mmols) in dimethyl sulfoxide (4 mL) was added the solution of dipeptide Z-L-Ser-Val-OMe[27] (1.0 g., 2.74 mmols) in dimethyl sulfoxide (3.5 mL) and methylene chloride (10 mL), followed by the solution of H_3PO_4 (85%, 0.2 mL) in dimethyl sulfoxide (3 mL) and methylene chloride (30 mL) at room temperature. After 2 hours stirring, acetic acid (1 mL) in methylene chloride (5 mL) was added dropwise within 30 min. The reaction was stored in the freezer for overnight. The white ppt. was removed by filtration. The filtrate was concentrated in vacuo and the residue was dissolved in ethyl acetate (80 mL), washed with water (3 x 20 mL), dried (Na_2SO_4), concentrated to provide an oil (1.2 g). By TLC analysis, the reaction did not occur at all and the product was the recovered starting material.

Preparation of N-(t-Butoxycarbonyl)-L-Alaninal and Conversion to the Corresponding Alcohol.

To a stirred solution of oxalyl chloride (0.4 mL) in methylene chloride (2 mL), was added dropwise dimethyl sulfoxide (2 mL) at -60

^{o}C, followed by Boc-alaninol[16] ($[\alpha]_D^{23}$ -10.67^{o} (c 0.75, $CHCl_3$), 190 mg, 1.09 mmols) in methylene chloride (15 mL). After the reaction was stirred at -60 ^{o}C for 40 min., triethylamine (2 mL) was added dropwise at -60 ^{o}C and the reaction was allowed to warm to room temperature. Water (5 mL) was added and the organic phase was separated and the aqueous phase was extracted with methylene chloride (10 mL). The organic phase and extract were combined, washed with 1N HCl (10 mL), water (10 mL), 5% $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated to give a yellow oil in quantitative yield (190 mg). By TLC analysis, the product was contaminated by little impurities: NMR ($CDCl_3$) δ 1.36 (d, 3H), 1.45 (s, 9H), 4.4 (m, 1H), 5.3 (m, 1H), 9.66 (s, 1H). R_f (hexane : ethyl acetate = 50 : 50) 0.55.

To a stirred solution of above aldehyde in methanol (5 mL) was added $NaBH_4$ (76 mg, 2 mmols) in one portion at 0 ^{o}C. After 2 hours stirring at 0 ^{o}C, the methanol was removed in vacuo, and the resulting solid was taken up in ethyl acetate (15 mL), washed with brine (5 mL), dried (Na_2SO_4) and concentrated to provide a yellow oil. Purification of the product on preparative TLC (hexane : acetone = 90 : 10) to gave the pale yellow oil (120 mg, 63%) : $[\alpha]_D^{23}$ -9.2^{o} (c 1, $CHCl_3$); TLC was coincident to the starting alcohol. These results showed the alcohol to be 86% optical purity.

Preparation of N-(t-Butoxycarbonyl)-L-Leucinal and Conversion to the Corresponding Alcohol.

To a stirred solution of oxalyl chloride (0.15 mL, 1.0 mmols) in methylene chloride (2 mL) was added dropwise dimethyl sulfoxide (0.3 mL, 2 mmols) in methylene chloride (2 mL) at -60 ^{o}C, followed by Boc-

leucinol[16] (116 mg, 0.53 mmols) ($[\alpha]_D^{23}$ -27.9° (c 1.7, MeOH)) in methylene chloride (15 mL). After 35 min. stirring at -60 °C, triethylamine (2 mL) was added dropwise and the reaction was warmed to room temperature. Water (3 mL) was added, the organic layer was separated and the aqueous layer was extracted with methylene chloride (10 mL). The organic phase and extract were combined, washed with 1N HCl (3 x 10 mL), water (2 x 10 mL), 5% $NaHCO_3$ (3 x 10 mL), brine (2 x 10 mL), dried (Na_2SO_4), and concentrated to give a yellow oil (110 mg, 90%) : NMR ($CDCl_3$) δ 0.96 (d, 6H), 1.45 - 1.0 (s and m, 12H), 4.2 (m, 1H), 5.1 (m, 1H), 9.6 (s, 1H). R_f (hexane : ethyl acetate = 50 : 50) 0.72.

The above aldehyde (95 mg, 0.44 mmols), which was stored at room temperature for several days, was dissolved in methanol (5 mL) at 0 °C and $NaBH_4$ (20 mg, 0.48 mmols) was added in one portion. After the reaction was stirred at 0 °C for 2 hours, most of solvent was removed in vacuo and the solid residue was taken up in ethyl ether (3 x 10 mL). The etheral solution was washed with brine (2 x 10 mL), dried (Na_2SO_4), and concentrated to give a yellow oil. Purification of the crude product on preparative TLC (hexane : ethyl acetate = 80 : 20) provided the colorless oil (75 mg, 79%) : $[\alpha]_D^{23}$ -19.7 (c 1, MeOH); NMR was superimposable to starting compound. R_f (hexane : ethyl acetate = 50 : 50) 0.58.

Preparation of N-(t-Butoxycarbonyl)-L-Valinal and Conversion to the Corresponding Alcohol.

To a stirred solution of $LiAlH_4$ (161 mg, 4.6 mmols) in THF (20 mL) was added dropwise Boc-valine methyl ester[14] (540 mg, 2.3 mmmols) in THF (20 mL) at 0 °C. The reaction was stirred at 0 °C for 1.5

hours. Water (5 mL) was added carefully and the reaction was allowed to warm to room temperature. Most of the organic solvent was removed in vacuo, the aqueous residue taken up into ethyl acetate (30 mL) and the insoluble material was removed by filtration. The filtrate was separated and the organic layer was washed with brine (20 mL), dried (Na_2SO_4), concentrated, and purified on flash chromatography (chloroform : acetone = 98 : 2) to provide the alcohol as a colorless oil (321 mg, 69% from Boc-valine) : $[\alpha]_D^{23}$ -18.08° (c 1.2, $CHCl_3$). R_f (chloroform : acetone = 95 : 5) 0.32.

To a stirred solution of oxalyl chloride (0.6 mL) in methylene chloride (2 mL) was added dropwise dimethyl sulfoxide (1.4 mL) in methylene chloride (2 mL) at -60 °C, followed by the above alcohol (290 mg, 1.43 mmols) in methylene chloride (15 mL). The reaction was stirred for 40 min. Triethylamine (2 mL) was added and the reaction was warmed to room temperature. Water (10 mL) was added, the organic layer was separated, and the aqueous layer was extracted with methylene chloride (15 mL). The organic phase and the extract were combined, washed with 1N HCl (10 mL), water (10 mL), 5% $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4), and concentrated to provide the corresponding aldehyde as an oil in quantitative yield: NMR ($CDCl_3$) δ1.0 (d of d, 6H), 1.45 (s, 9H), 2.3 (m, 1H), 4.3 (m, 1H), 5.4 (br, 1H), 9.7 (s, 1H). R_f (chloroform : acetone = 95 : 5) 0.44.

The above crude aldehyde was dissolved in ethanol (15 mL) and $NaBH_4$ (114 mg, 3.0 mmols) was added at 0 °C. The reaction was stirred at 0 °C for 2 hours and at room temperature for overnight. The solvent was removed and the residue was taken up into ethyl acetate (20 mL), washed with brine (10 mL), dried (Na_2SO_4),

concentrated, and purified on preparative TLC (chloroform : acetone = 95 : 5) to give an oil (220 mg, 76% from alcohol) : $[\alpha]_D^{23}$ -18.03 (c 4, $CHCl_3$), 99% ee; NMR was superimposable and R_f value of TLC was same to the starting alcohol.

N-(Benzyloxycarbonyl)glycinal.

To a stirred solution of Cbz-glycine (500 mg, 2.4 mmols) in THF (10 mL) at -20 °C was added dropwise triethylamine (0.42 mL, 3.0 mmols) followed by ethylchloroformate (0.29 mL, 3.0 mmols) in THF (3 mL) over 10 min. The reaction was stirred at -20 to -25 °C for 30 min. The white precipitate was removed by filtration and filtrate was added to a solution of $NaBH_4$ (228 mg, 6.0 mmols) in water (10 mL) at 5 °C. The reaction was allowed to stir at 5 °C for 20 min. and at room temperature for 4 hours. The reaction was acidified with 1N HCl solution (pH 3). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (30 mL). The organic layer and extract were combined, washed with 10% NaOH (20 mL), water (20 mL), dried (Na_2SO_4) and concentrated to give white solid. Purification on flash chromatography (chloroform : acetone = 80 : 20) gave the white solid (440 mg, 95%) : NMR ($CDCl_3$) δ 3.3 (t, 2H), 3.7 (m, 2H), 4.1 (s, 1H), 5.1 (s, 2H), 6.0 (br, 1H), 7.4 (s, 5H). R_f (chloroform : acetone = 80 : 20).

To a stirred solution of oxalyl chloride (0.54 mL) in methylene chloride (5 mL) was added dropwise dimethyl sulfoxide (1.0 mL) in methylene chloride (2 mL) at -60 °C followed by above alcohol (400 mg, 2.05 mmols) in methylene chloride (20 mL). The reaction was stirred at -60 °C for 30 min., and triethylamine (3 mL) was added dropwise. The reaction was allowed to warm to room temperature, and

water (5 mL) was added. The organic phase was separated and the aqueous layer was extracted with methylene chloride (10 mL). The organic phase and extract were combined, washed with 1N HCl (10 mL), water (10 mL), 5% $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated to give the Cbz-glycinal as an oil (390 mg, 98%) : NMR ($CDCl_3$) δ 9.6. R_f (chloroform : acetone = 80 : 20) 0.57.

N-(t-Butoxycarbonyl)-N,O-Isopropylidenyl-L-Serinol (26b).

The mixture of Boc-L-serine (3.0 g, 14.6 mmols) with p-toluenesulfonic acid (530 mg, 3.0 mmols) in methanol (100 mL) was heated at reflux for 2 hours. Most of solvent was removed in vacuo, and the residue was dissolved in the mixture of acetone (50 mL), 2,2-dimethoxypropane (20 mL), methanol (50 mL) and additional p-toluenesulfonic acid (500 mg). The reaction was heated at reflux for 6 hours. Most of solvent was removed in vacuo, the oily residue was dissolved in ethyl acetate (100 mL), washed with brine (20 mL), dried (Na_2SO_4) and concentrated to give 26b as an oil (3.5 g, 95%) : $[\alpha]_D^{23}$ -60.2° (c 4.2, $CHCl_3$) (lit[21]. + 65.4° for D-isomer); NMR ($CDCl_3$)δ 1.3 -1.9 (3 x s, 15H), 3.85 (s, 3H), 4.0 - 4.7 (m, 3H). R_f (hexane : ethyl acetate = 50 : 50) 0.83.

The above oxazolidine methyl ester (1.4 g, 5.4 mmols) in THF (20 mL) and ethanol (40 mL) was added dropwise to the mixture of $NaBH_4$ (400 mg, 10.8 mmols) and LiCl (460 mg, 10.8 mmols) in THF and ethanol (20 + 40 mL) at room temperature. The reaction was stirred for 2 hours, most of solvent was removed and the white residue was taken up into ethyl acetate (150 mL) and water (30 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated to give an oil.

Purification on flash chromatography (hexane : ethyl acetate = 90 : 10) provided 26a as an oil (1.3 g, 100%) : $[\alpha]_D^{23}$ -25.2° (c 1, $CHCl_3$); NMR ($CDCl_3$) δ 1.55 (s, 15H), 2.0 (t, 1H), 3.5 - 4.5 (m, 5H); IR (neat, NaCl) 3700 - 3100, 1670 cm^{-1}. R_f (hexane : ethyl acetate = 50 : 50) 0.45.

N-(t-Butoxycarbonyl)-N,O-Isopropylidenyl-L-Serinal (27b) and Conversion to (26b).

To a stirred solution of oxalyl chloride (1.2 mL, 13.6 mmols) in methylene chloride (5 mL) was added dimethyl sulfoxide (3 mL) in methylene chloride (10 mL) at -60 °C, followed by alcohol 26b (1.2 g, 5.2 mmols) in methylene chloride (20 mL). The reaction was stirred for 30 min., triethylamine (5 mL) was added, and the reaction was warmed to room temperature. Water (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with methylene chloride (50 mL). The organic phase and extract were combined, washed with 1N HCl (20 mL), water (20 mL), 5% $NaHCO_3$ (20 mL), water (20 mL), dried (Na_2SO_4) and concentrated to provide an oil in quantitative yield. Small amounts of crude product was taken and purified on preparative TLC (hexane : ethyl acetate = 80 : 20) for analysis : $[\alpha]_D^{23}$ -76.8° (c 0.29, $CHCl_3$); NMR ($CDCl_3$) δ 9.7. R_f (hexane : ethyl acetate = 50 : 50) 0.59.

To a stirred solution of above crude aldehyde (130 mg, 0.56 mmols) in methanol (20 mL) was added $NaBH_4$ (50 mg) at room temperature. The reaction was stirred for 4 hours and most of the organic solvent was removed. The residue was taken up in ethyl acetate (20 mL) and brine (10 mL). The organic layer was separated, dried (Na_2SO_4), concentrated and purified on preparative TLC (hexane

: ethyl acetate = 90 : 10) to provide a colorless oil (85 mg, 65%) : $[\alpha]_D^{23}$ -24.64 (c 1.1, $CHCl_3$), 98% ee; NMR was superimposable to the starting alcohol.

N-(Benzyloxycarbonyl)-L-Methionol (37).

To a stirred solution of N-Cbz-L-methionine (2.0 g, 7.07 mmoml) in methylene chloride (30 mL) was added methanol (4 mL) and DMAP (86 mg, 0.7 mmols). The reaction was cooled to 0 ^oC, EDC (1.62 g, 8.5 mmols) was added and the reaction was stirred at 0 ^oC for 2 hours and at room temperature for overnight. The organic solvent was removed by evaporation and the resulting oily residue was taken up in ethyl acetate (20 mL) and water (20 mL). The organic layer was separated and aqueous phase was extracted with ethyl acetate (20 mL). The organic phase and extract were combined, washed with sat. $NaHCO_3$ (30 mL), brine (30 mL), dried (Na_2SO_4), and concentrated to provide the colorless oil (2.12 g, quantitative). R_f (chloroform : acetone = 80 : 20) 0.69.

Without further purification, above oil was dissolved in THF (35 nmL) and was added dropwise to $LiAlH_4$ (500 mg, 14.1 mmols) in THF (35 mL) at 5 ^oC. The reaction was stirred at 5 ^oC for 1.5 hours. After the reaction was quenched with water (20 mL), most of organic solvent was removed by evaporation and the resulting gray residue was taken up in ethyl acetate(100 mL). The insoluble materials were filtered off and from the filtrate was separated the organic phase. The aqueous layer was extracted with ethyl acetate (20 mL). The organic phase and extract were combined, washed with brine (30 mL), dried (Na_2SO_4) and concentrated. Purification on MPLC (chloroform : acetone = 90 : 10) provided 37 as an oil (1.61 g, 85% from Cbz-L-

methionine) : $[\alpha]_D^{23}$ -16.8° (c 0.5, $CHCl_3$); NMR ($CDCl_3$) δ 1.84 (m, 2H), 2.09 (s, 3H), 2.51 (m, 3H), 3.48 - 4.09 (m, 3H), 5.12 (s, 2H), 5.33 (m, 1H), 7.36 (s, 5H). Anal. Calcd. for $C_{13}H_{19}NO_3S$: C, 58.00; H, 7.06; N, 5.20. Found: C, 57.84; H, 6.91; N, 5.31. R_f (chloroform : acetone = 80 : 20) 0.35.

(S)-2-(Benzyloxycarbonylamino)-4-Methylsulfinyl-O-(Tetrahydropyranyl)-Butan-1-ol (38).

The mixture of 37 (1.2 g, 4.5 mmols), dihydropyran (2 mL), and pyridinium p-toluenesulfonate (120 mg) in methylene chloride (50 mL) was stirred at room temperature for 12 hours. Most of organic solvent was removed in vacuo and the resulting oil was dissolved in ethyl acetate (80 mL), washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give an oil. R_f (chloroform : acetone = 80 : 20) 0.69.

To a stirred solution of above compound in ethyl acetate (30 mL) was added dropwise m-chloroperbenzoic acid (85%, 1.0 g, 5 mmols) in ethyl acetate (20 mL) at -40 °C. The reaction was stirred at -35 to -40 °C for 1 hour and the reaction was warmed to room temperature. The ethyl acetate solution was washed with sat. $NaHCO_3$ (20 mL), water (20 mL), dried (Na_2SO_4) and concentrated to provide the brown oil. Purification on MPLC (chloroform : acetone = 80 : 20) gave the compound 38 as a colorless oil (1.50 g, 90%) : $[\alpha]_D^{23}$ -12.63° (c 4.3, $CHCl_3$); NMR ($CDCl_3$) δ 1.54 (br s, 6H), 2.15 (m, 2H), 2.48 (s, 3H), 2.69 (q, 2H), 3.4 - 4.3 (m, 5H), 4.54 (br s, 1H), 5.15 (s, 2H), 7.39 (s, 5H). Anal. Calcd. for: $C_{18}H_{27}NO_5S$; C, 58.54; H, 7.32; N, 3.79. Found: C, 58.36; H, 7.22; N, 3.67. R_f (chloroform : acetone = 80 : 20) 0.15.

(S)-2-(Benzyloxycarbonylamino)-3-Buten-1-ol (39).

The solution of 38 (1.3 g, 3.54 mmols) in o-dichlorobenzene (50 mL) was heated at reflux for 24 hours. Most of the organic solvent was removed in vacuo, the resulting black residue was eluated on flash chromatography (chloroform : acetone = 95 : 5) to provide the compound 38 as an oil (390 mg, 50%) : $[\alpha]_D^{23}$ -31.3° (c 0.6, $CHCl_3$) [lit[30]. -32.1°]; NMR ($CDCl_3$) 3.69 (br d, 3H), 4.34 (m, 1H), 5.15 (s, 2H), 5.24 - 5.48 (m, 2H), 5.78 (ddd, 1H), 7 (m, 1H), 7.42 (s, 5H). R_f (chloroform : acetone = 80 : 20) 0.66.

(S)-2-(Benzyloxycarbonylamino)-3-Buten-1-al (40) and Conversion to 39.

To a stirred solution of oxalyl chloride (0.36 mL, 4.0 mmols) in methylene chloride (5 mL) was added dropwise dimethyl sulfoxide (1 mL) at -65 °C under N_2 atmosphere, followed by 39 (330 mg, 1.5 mmols) in methylene chloride (25 mL). The reaction was stirred for 30 min., triethylamine (3 mL) was added and the reaction was allowed to warm to room temperature. Water (10 mL) was added and the organic phase was separated. The aqueous layer was extracted with methylene chloride (20 mL). The organic phase and extract were combined, washed with 1N HCl (10 mL), water (10 mL), sat. $NaHCO_3$ (10 mL), water (10 mL), dried (Na_2SO_4) and concentrated to give a brown oil (250 mg, 76%). By TLC analysis showed the product was contaminated by small amount of impurities. R_f (chloroform : acetone = 80 : 20) 0.77.

To the above aldehyde (31 mg, 0.14 mmols) in methanol (5 mL) was added $NaBH_4$ (20 mg) in one portion at room temperature. After 12 hours stirring, most of solvent was removed by evaporation, and the residue was eluated on short column chromatography (ethyl acetate) to

provide an oil. Purification on preparative TLC (hexane : ethyl acetate = 80 : 20) gave a colorless oil (30 mg, 96%) : $[\alpha]_D^{23}$ -32.0^o (c 0.05, $CHCl_3$) showed >98% optical retention.

REFERENCES

1) Yoshida, T; Katagiri, K. J. Antibiot. 1961, A14, 330.

2) Matusuura, S. J. Antibiot. 1965, A18, 43.

3) a) Isolation: Shoji, J.; Katagiri, K. J. Antibiot. 1961, A14, 335.

b) Structure: Otsuka, H.; Shoji, J. ibid. 1963, A16, 52; Shoji, J.; Tori, K.; Otsuka, H. J. Org. Chem. 1965, 30, 2772; Otsuka, H.; Shoji, J. J. Antibiot. 1965, A18, 134; Otsuka, H.; Shoji, J. Tetrahedron. 1965, 21, 2931; 1967, 23, 1535.

4) a) Wiring, M. J.; Walkelin, L. P. G. Nature. 1974, 252, 653.

b) Walkelin, L. P. G.; Waring, M. J. Biochem. J. 1976, 157, 721.

5) a) Waring, M. J.; Markoff, A. Mol. Pharmacol. 1974, 10, 214.

b) Gauge, G. G. Jr.; Loshkareva, N. P.; Zbarsky, I. B. Biochim. Biophys. Acta. 1968, 166, 752.

6) a) Shin, M.; Inouye, K.; Otsuka, H. Bull. Chem. Soc. Jpn. 1984, 37, 2203.

b) Chakravarty, P. K.; Olsen, R. K. Tetrahedron Lett. 1978, 1618.

c) Ciardelli, T. L.; Chakravarty, P. K.; Olsen, R. K. J. Am. Chem. Soc. 1978, 100, 7684.

d) Ciardelli, T. L.; Olsen, R. K. ibid. 1977, 99, 2806.

e) Dhaon, M. K.; Olsen, R. K. J. Org. Chem. 1981, 46, 3436.

f) Dhaon, M. K.; Olsen, R. K. Tetrahedron. 1982, 38, 57.

7) a) Martin, D. G.; Mizsak, S. A.; Biles, C.; Stewart, J. C.; Baczynsky, J. L.; Mewlman, P. A. J. Antibiot. 1975, 28, 332.

b) Dell, A.; Williams, D. H.; Morris, H. R.; Smith, G. A.; Feeny, J.; Roberts, G. C. K. J. Am. Chem. Soc. 1975, 97, 2497.

c) Cheung, H. T.; Feeney, J.; Roberts, G. C. K.; Williams, D. H.; Ughetto, G.; Waring, M. J. J. Am. Chem. Soc. 1978, 100, 46.

8) Olsen, R. K. Unpublished results.

9) Tatsuka, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. Tetrahedron Lett. 1981, 22, 3997.

10) Kolar, A. J.; Olsen, R. K. J. Org. Chem. 1980, 45, 3246.

11) Stachulski, A. V. Tetrahedron Lett. 1982, 3789.

12) Giormani, V.; Filira, F.; D'Angeli, F. J. Chem. Soc. Perkin Trans I. 1984, 2721.

13) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. J. Org. Chem. 1977, 42, 3772.

14) Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. J. Org. Chem. 1982, 47, 1962.

15) Hamada, Y.; Shioiri, T. Chem. Pharm. Bull. 1982, 30, 1921.

16) Olsen, R. K.; Krishina, B. Unpublished results.

17) Omura, K.; Swern, D. Tetrahedron. 1978, 34, 1651.

18) Corey, E. J.; Suggs, J. W. Tetrahedron Lett. 1975, 2647.

19) Itoh, A.; Takahashi, R.; Baba, Y. Chem. Pharm. Bull. 1977, 23, 3081.

20) Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem. 1969, 34, 2543.

21) Garner, P. Tetrahedron Lett. 1984, 5855.

22) Kanazawa, R.; Tokoroyama, T. Synthesis. 1976, 526.

23) Olsen, R. K.; Hennen, W. J.; Wardle, R. B. J. Org. Chem. 1982, 47, 4605.

24) Maurer, P. J.; Takahata, H.; Rapoport, H. J. Am. Chem. Soc. 1984, 106, 1095.

25) Carson, P. J.; Katsuki, T.; Martin, V. S.; Sharpless, B. J. Org. Chem. 1981, 46, 3936.

26) Corey, E. J.; Schmit, G. Tetrahedron Lett. 1979, 399.

27) Olsen, R. K.; Kini, G. D.; Hennen, W. J. J. Org. Chem. 1985, 50, 4332.

28) a) Castro, B.; Fehrentz, J. A. Synthesis. 1983, 676.

b) Stanfield, C. F.; Parker, J. E.; Kanellis, P. J. Org. Chem. 1981, 46, 4797.

c) Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. J. Org. Chem. 1982, 47, 3016.

d) Ramasamy, K.; Olsen, R. K.; Emery, T. Synthesis. 1982, 42.

29) Ohfune, Y.; Kurokawa, N. Tetrahedron Lett. 1984, 1071.

30) Meyer, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D. J. Org. Chem. 1979, 44, 2247.

31) Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2933.