SYNTHESIS OF β-OXYGENATED γ-AMINO ACIDS AND γ-OXYGENATED δ-AMINO ACIDS FROM α-AMINO ACIDS

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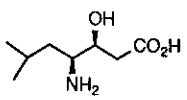
Abstract— A diastereoselective synthesis of 2-amino alcohols toward a synthesis of β-oxygenated γ-amino acids, γ-oxygenated δ-amino acids, and related compounds was summarized.

Contents

1. Introduction

The 2-amino alcohol moiety is an important structural unit in a number of biologically active amino sugar antibiotics[1] and unusual amino acids.[2] (3*S*,4*S*)-Statine (**1**), 4-amino-3-hydroxy-6-methylheptanoic acid is an essential component of pepstatin (**2**)[2] that is the microbially produced asparatic proteinase inhibitor for proteolytic enzyme such as renin. The hypothesis that the inhibitory effect of **2** rises from the similarity between 2-amino alcohol moiety of **1** and hydrolysis transition state (**3**) of peptide

bond led to development of an introduction of a transition state analogues in small peptide molecule aimed at a synthesis of peptidic enzyme inhibitors. Thus, stereoselective synthesis of 2-amino alcohols has been greatly stimulated in peptidomimetic chemistry,[3] and recent research has been directed toward a synthesis of peptides containing **1** or side-chain modified analogues[3] in the hope that they function as potent, selective inhibitors among the group of enzymes, pepsin, cathepsin D, and renin. A number of potent and promising renin inhibitors which would be beneficial in the treatment of human hypertention have been prepared.[4] Based on this concept, homostatine derivatives (**4**)[4] containing hydroxyethylene dipeptide isostere have also been synthesized and incorporated into peptides to get effective drugs as renin inhibitors. (3*S*,4*R*,5*S*)-Isostatine (**5**)[5] also occurs naturally as an esterified component of the cyclic depsipeptides, didemunins A and B, which were isolated from a *Trididemnum* species of Caribbean tunicate.[5] Recently, (3*R*,4*S*,5*S*)-*N*,*O*-dimethylisostatine called dolaisoleuine (**6**) was also found as a key unusual amino acid in dolastatin 10.[6] These peptides containing **5** and **6** are very significant from their promising antitumor and antiviral activities.[5,6]



1

Iva-Val-Val-Sta-Ala-Sta
(Iva = isovaleric)

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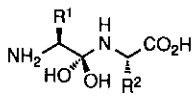

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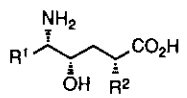

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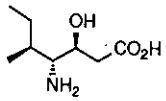

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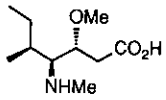


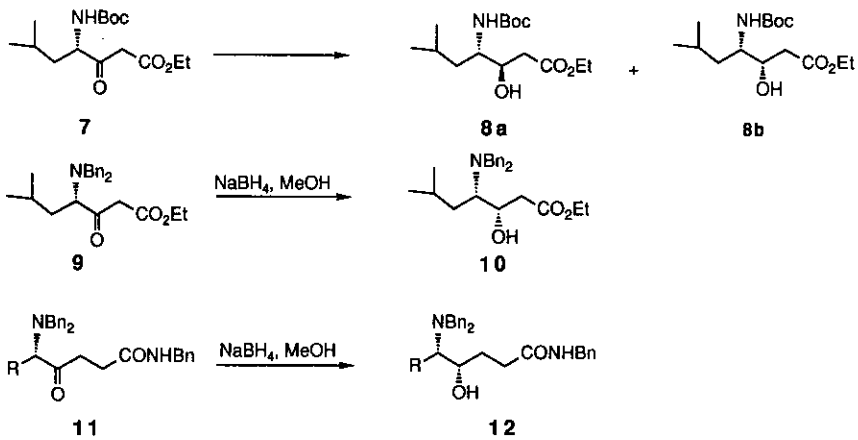
6

In the present paper, among synthetic procedures for an effective chiral synthesis of **1** and its *N*-protected esters and their related analogues, we wish to focus on a highly diastereoselective synthesis of 2-amino alcohols toward a diastereoselective synthesis of β-hydroxy-γ-amino acids and γ-hydroxy-δ-amino acid derivatives, mainly reported from our laboratory.

2. Asymmetric Reduction of Amino Keto Esters

Reduction of the γ-amino β-keto ester (**7**), derived from *N*-Boc-(*S*)-leucine, would be one of the most significant method from the point of view of commercial production of

1 and related compounds, since it would be suitable for scaling up to large quantities. However, stereochemical control of the reduction has been known to be difficult.[7,8] Reduction of **7** with usual reducing reagents such as $NaBH_4$, $LiBH_4$, $Zn(BH_4)_2$ afforded a mixture of **8a** and **8b** with only moderate *erythro* selectivity.[8] Chirally modified $LiBH_4$[8] and K-selectride[9] were found to be effective for increasing the degree of diastereoselectivity. The diastereoselectivity was reversed when *N*-dibenzyl was used as the protected group for nitrogen instead of *N*-Boc. Reetz[10] reported that reduction of **9** with $NaBH_4$ resulted in a formation of *threo* isomers (**10**) with high diastereoselectivity. We also observed high *threo* selectivity in reduction of **11** with $NaBH_4$ to give **12** predominantly.[11] In a diastereoselective reduction of **7**, Raddatz[12] employed pure cultures of particular yeast strains as a reducing enzyme and Noyori[13] used (*R*)-BINAP-Ru(II) complex as a catalyst for the diastereoselective hydrogenation. These two methods would be the most useful for preparation of large quantities of **1**



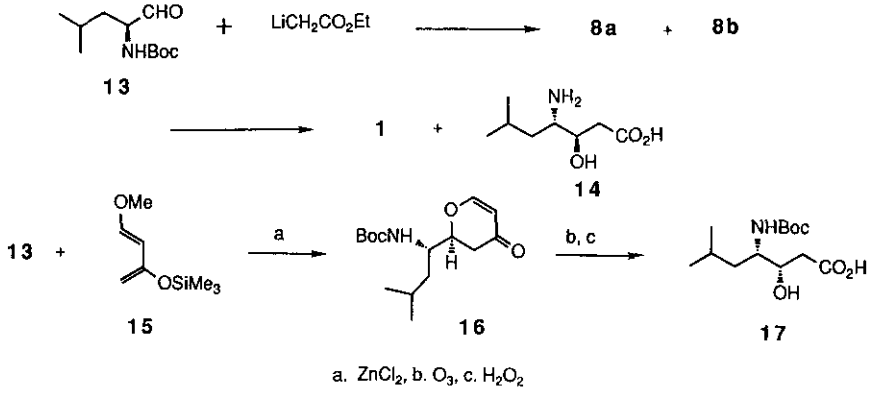
3. Diastereoselective Synthesis of 2-Amino Alcohols by Alkylation of Chiral α-Amino Aldehyde

In this chapter, we disclose a synthetic strategy for a highly diastereoselective synthesis of 2-amino alcohols from α-amino aldehydes.

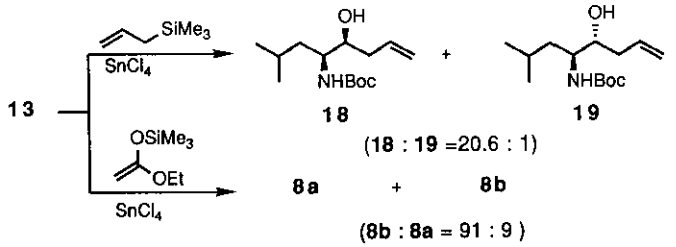
3.1 Alkylation with Enolate, Grignard Reagent, and Allylmetal

Although alkylations of *N*-protected chiral α-amino aldehyde would be apparently most facile method to yield 2-amino alcohols, high diastereoselectivity has not been observed in most of reactions with alkylating reagent[14] such as Grignard, organozinc

bromide, and organolithium reagents. The early attempts to synthesis of **1** also involved a laborious separation by fractional crystallization of a mixture of **1** and (3*R*,4*S*)-isomer (**14**), obtained through aldol condensation of *N*-Boc-(*S*)-leucinal (**13**) with acetate anion and subsequent deprotection of a mixture of **8a** and **8b** with trifluoroacetic acid.[15] Furthermore, usually, separation of the *threo* and *erythro* isomers is considerably difficult.[14] In the meantime, highly *threo* selective synthesis of *N*-Boc-(3*S*,4*S*)-statine (**17**), syntheticaly equivalent of **1**, was achieved by Danishefsky[16] *via* the cycloadduct (**16**) obtained by Lewis acid catalyzed hetero Diels-Alder reaction of **13** with Danishefsky's diene (**15**).

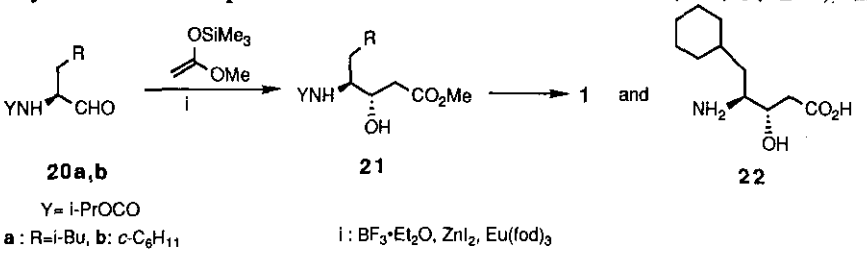


Recently, synthetic strategies for the stereocontrolled synthesis of 2-amino alcohols by alkylation of *N*-protected α-amino aldehyde have been devised based on chelation controlled addition and Felkin-Anh addition. Rich[17] reported allylation of **13** with allyltrimethylsilane in the presence of stannic chloride to yield *threo* 2-amino alcohol (**18**) and the *erythro* isomer (**19**)(**18**/**19**=20.6). Mikami[18] reported the reaction of **13** with enol silyl ether resulted in a predominat formation of **8b** by chelation control.



In a similar asymmetric aldol reaction in terms of chelation control, Terashima[19] prepared **1** and (3*S*,4*S*)-cyclohexylstatine (**22**) *via* *threo* 2-amino alcohols (**21a,b**)

obtained with high diastereoselectivity by the reaction of α-amino aldehydes (**20a,b**) with enol silyl ether in the presence of Lewis acid such as $BF_3{\cdot}Et_2O$, ZnI_2 and $Eu(fod)_3$.



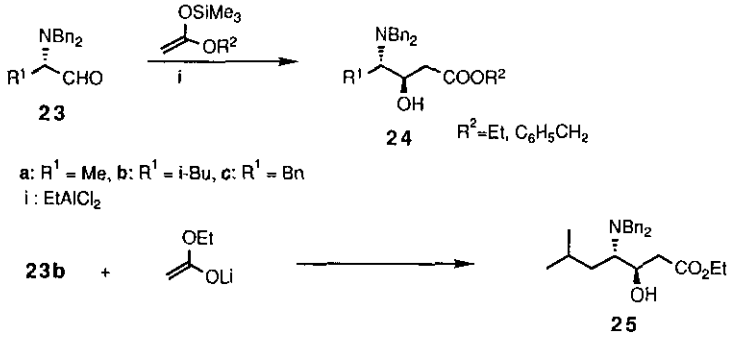
20a,b **21** **22**

Y= i-PrOCO

a : R=i-Bu, **b**: c-C_6H_{11}

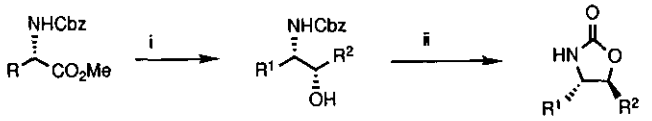
i : $BF_3{\cdot}Et_2O$, ZnI_2, $Eu(fod)_3$

In these alkylations, when *N*-dibenzyl-α-amino aldehydes (**23**) were used, high *erythro* selectivity was observed owing to the addition to the Felkin-Anh model. Mikami[18] obtained **24** by the reaction of **23** with enol silyl ether in the presence of ethylaluminum dichloride. Reetz[20] obtained **25** with *erythro* selectivity (*threo/erythro*=7:93) by the aldol condensation reaction of **23** with lithium enolate.



In the alkylation of *N*-Cbz α-amino aldehyde with Grignard reagents, we realized that the degree of the diastereoselectivity of 2-amino alcohols could be improved by employing one-pot manner for the two step-sequence; preparation of α-amino aldehyde by reduction of *N*-Cbz-α-amino ester with DIBAL-H and subsequent alkylation with Grignard reagent.[21] Thus, 2-amino alcohols (**27a-i**) were obtained with considerably high dia-stereoselectivity from *N*-Cbz-α-amino esters (**26a-c**). The ratio for *threo/erythro* of **27a-i** was determined after conversion to the corresponding 4,5-disubstituted oxa-zolidin-2-ones (**28a-i**) by treatment with base (7.5 N KOH-MeOH-THF; 1:2:4). The ratio for 4,5-*trans/cis* isomer of **28a-h** could be easily determined based on the signals due to 4-*H* and 5-*H* in their ^{1}H-nmr spectra. The ratio for *threo/erythro* of **27a,g,h** was also determined by conversion to the corresponding

acetates and the results were consistent with those obtained by conversion to **28g,h**. The remarkably high dia-stereoselectivity in the formation of 2-amino alcohols can be accounted for by the aluminum-mediated chelation control in the alkylation of the α-amino aldehyde intermediates.



26 Cbz=$CO_2CH_2C_6H_5$ **27** **28**

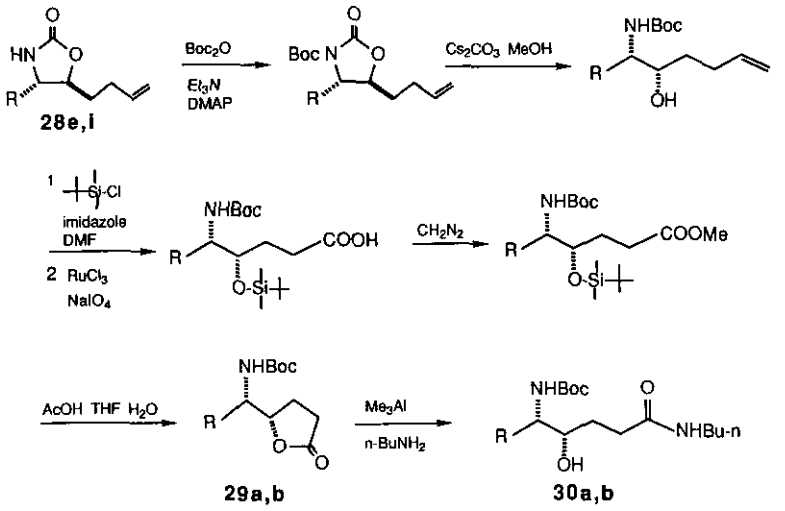
28	Yield (%)	*trans/cis*
a	57	9:1
b	62	3.5:1
c	60	7:1
d	58	10:1
e	58	13:1
f	60	11:1
g	60	10:1
h	62	12:1
I	57	13:1

a: R=Me
b: R=i-Bu
c: R=$C_6H_5CH_2$

For **27** and **28**
a: R^1=Me, R^2=Et
b: R^1=Me, R^2=CH_2CH=CH_2
c: R^1=Me, R^2=C_6H_5
d: R^1=i-Bu, R^2=Et
e: R^1=i-Bu, R^2=CH_2CH_2CH=CH_2
f: R^1=i-Bu, R^2=$C_6H_5CH_2$
g: R^1=$C_6H_5CH_2$, R^2=Me
h: R^1=$C_6H_5CH_2$, R^2=Et
I: R^1=$C_6H_5CH_2$, R^2=CH_2CH_2CH=CH_2

i : DIBAL-H, –78 °C, then R^2MgBr, room temperature.
ii : 7.5 M KOH-MeOH-*THF* (1: 2 : 4), room temperature.

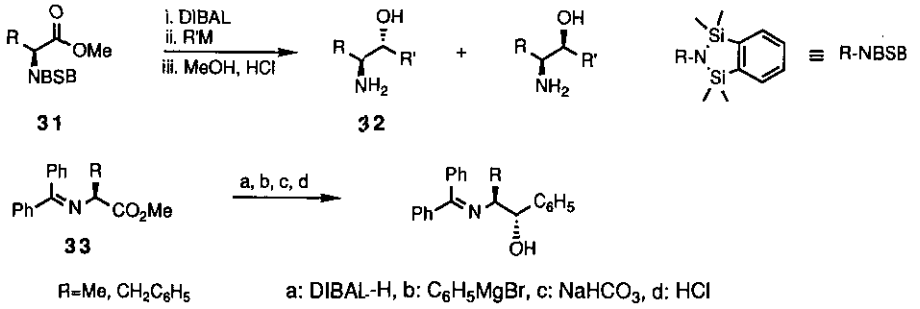
Conversion of **27e,i** to the amides (**30a,b**) was easily achieved via lactones (**29a,b**) obtained through oxidation of double bond as shown in the following scheme.[22]



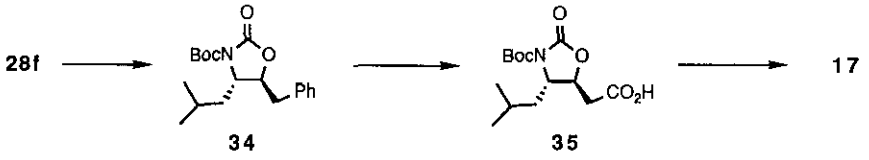
a: R=$PhCH_2$, **b**: R=i-Bu

Recently, Davis[23] reported a predominant formation of the *erythro* 2-amino alcohols (**32**) with high diastereoselectivity when *N*-protected α-amino esters (**31**) was reduced with DIBAL-H, followed by treatment with the Grignard reagent in an one-pot manner. In this reaction, Felkin-Anh model was proposed to account for the high *erythro* selectivity as the reaction mechanism. In a similar way, conversion of α-

amino ester to *threo* 2-amino alcohols was also reported by Polt[24] who used the Shiff base (**33**) as the protected form of α-amino esters.

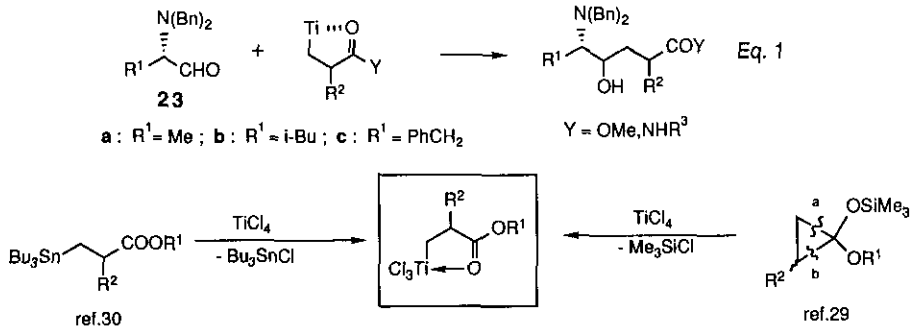


Phenyl group has been often treated as effective synthon for carboxyl group[25,26] since it is easily oxidized by $RuCl_3$-$NaIO_4$ under Sharpless conditions.[27] Our synthetic protocol for (3S,4S)-statine is the use of **28f**, the phenyl group of which was used as the masked form of carboxyl group. *N-tert*-Butoxycarbonylation of **28f** with Boc_2O in the presence of 4-dimethylaminopyridine, followed by oxidation of **34** with $RuCl_3$-$NaIO_4$ afforded the carboxylic acid (**35**) in 71% yield. Oxazolidin-2-one ring was easily cleaved by treatment with lithium hydroxide in methanol to give **17**.[28]

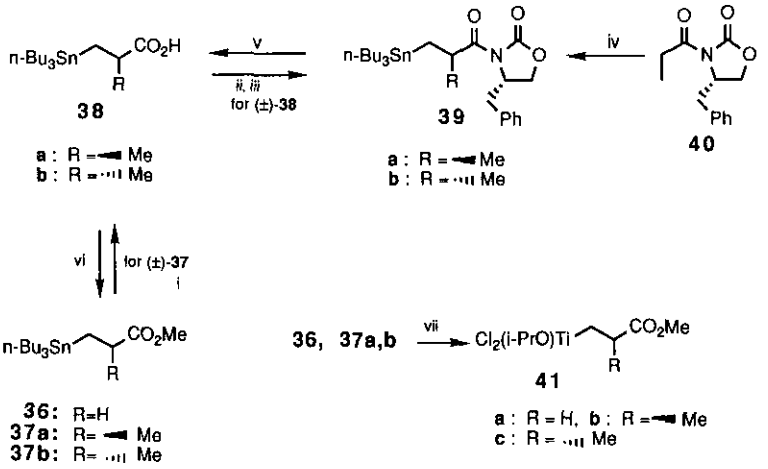


3.2. Alkylation with Titanium Homoenolate[11]

In this chapter, we wish to explore the stereocontrolled convergent sequence[11] of peptidomimic as a hydroxyethylene dipeptide isostere by condensation of α-amino aldehydes (**23a-c**) with titanium homoenolates as shown in the Eq. 1. Although there have been reported a number of work on a synthesis of hydroxyethylene dipeptide isosteres,[4] construction of α-alkyl-γ-hydroxy acid moiety has been achieved through multi-step sequence. Titanium homoenolates can be obtained by the following routes. One is cleavage of cyclopropane ring reported by Nakamura.[29] Another is by direct tin-titanium exchange method reported by Goswami.[30] Decamp[31] also reported a preparation of titanium homoenolate by transmetallation of the iodozinc homoenolate



with *chlorotitanium isopropoxides*. We prepared titanium homoenolates *in situ* according to Goswami's method. The 3-(tri-*n*-butylstannyl)propionic acids were obtained by treatment of methyl acrylate and methyl methacrylate with tri-*n*-butyltin hydride to give **36** and **37**. Optically active **37a,b** were also obtained by esterification of **38a,b**, derived from **37** through condensation with (*S*)-4-benzyloxazolidin-2-one, separation of diastereomer, and subsequent hydrolysis of **39** as outlined in the following scheme.



Reagents and Conditions: i. NaOH/EtOH; ii. $(COCl)_2$/hexane; iii. lithium amide of (*S*)-4-benzyloxazolidin-2-one, iv. $NaN(TMS)_2$, n-Bu_3SnCH_2I, –50 °C; v. LiOH/THF/H_2O; vi. CH_2N_2, vii. $TiCl_4$, –20 °C,CH_2Cl_2, 0.5h then 0.5 equiv. $Ti(i\text{-}PrO)_4$

Alternative procedure for a synthesis of **37** was also achieved by tri-*n*-butylstannylmethylation of **40** by an application of Evans' *method*[32] to result in a predominant formation of **39a**. The reaction of **36, 37a,b** with titanium tetrachloride and further addition of titanium tetraisopropoxide (0.5 eq.) gives rise to a formation of the corresponding dichloro-*i*-propoxytitanium homoenolates (**41a-c**); these, generated *in situ*,

were used for the reaction with α-amino aldehyde. The reaction of *N*-Cbz amino aldehyde with **41a** yielded the corresponding 2-amino alcohols in high yield, but resulted in low diastereoselectivity (*erythro/threo* =1-3). However, the reaction of **23a,b** with **41a-c** gave the lactones (**42a,b**) with high *erythro* selectivity. The lactones were converted to the amides (**43a,b**) by treatment with benzylamine in the presence of trimethylaluminum. The reaction of *N*-Boc-phenylalaninal with titanium homoenolate prepared by Decamp's method[31] afforded a *threo* form of **42c** by chelation control owing to a formation of zinc halide which acted as chelate agent. They reported that the *threo* selectivity increased as the number of chlorides on the titanium homoenolate in the reaction with *N*-Boc-phenylalaninal.

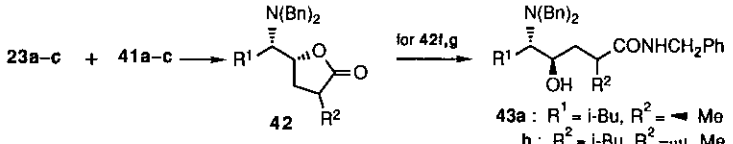
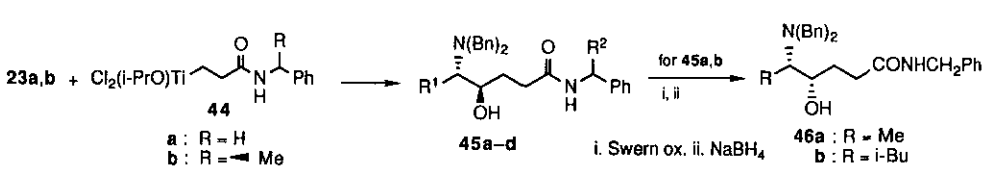


Table 1 Yield and Ratio for erythro/ threo of **42a-g**

42	R^1	R^2	Yield(%)	erythro/threo	$[\alpha]_D$ ($CHCl_3$)
a	Me	H	45	13 : 1	+24.0° (c 0.5)
b	i-Bu	H	65	10 : 1	–43.9° (c 0.5)
c	$PhCH_2$	H	60	12 : 1	+0.2° (c 1.0)
d	Me	Me	42	10 : 1	+19.8° (c 0.6)
e	Me	Me	39	10 : 1	+22.7° (c 0.6)
f	i-Bu	Me	53	10 : 1	–38.5° (c 0.6)
g	i-Bu	Me	54	10 : 1	–43.2° (c 0.6)

It is of interest to examine the direct synthesis of this type of amides, which would be considered as tripeptide isosteres. The reaction of **23a,b** with amides (**44a-c**), derived from **36** and **37a,b**, afforded the corresponding amino alchols (**45a-d**) with



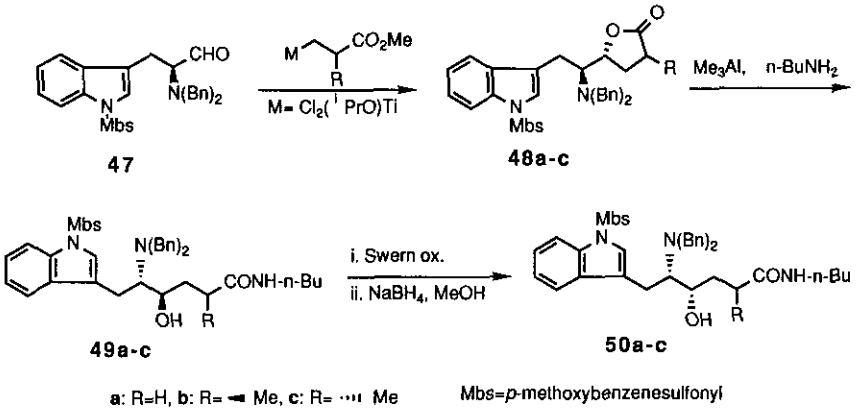
For **45a-d**

a: R^1=Me, R^2=H
b: R^1=i-Bu, R^2=H
c: R^1=i-Bu, R^2= Me
d: R^1=i-Bu, R^2= Me

Table 2. Yield and ratio for erythro / threo of **45a-d**

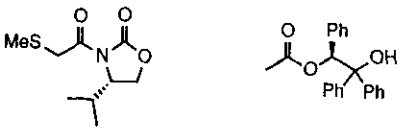
45	Yield(%)	erythro/threo
a	60	>10 : 1
b	55	10 : 1
c	58	10 : 1
d	63	11 : 1

high *erythro* selectivity (see Table 2). The formation of lactones and 2-amino alcohols was found to proceed with retention of >95% ee. Conversion of the *erythro* isomers (**45a,b**) to the *threo* isomers (**46a,b**) was easily performed by Swern oxidation and subsequent reduction with $NaBH_4$. Our final example of the use of titanium homoenolate is focused on a synthesis of 2-amino alcohols (**50a-c**) according to the same conditions as above by starting with L-tryptophane.[11] Condensation of **47** with **41a-c**, followed by ring-opening of the resulting lactones (**48a-c**) with *n*-butylamine afforded **49a-c**, which might be useful as intermediates for a synthesis of potentially inhibitory active compounds to the endothelin converting enzyme. Swern oxidation of **49a-c**, followed by reduction with $NaBH_4$ afforded **50a-c**.



4. Double Diastereodifferentiation Strategies in an Alkylation of Chiral α-Amino Aldehydes

In the asymmetric aldol reaction of α-amino aldehyde, double diastereodifferentiation strategies have been examined to get **1** and related compounds with high diastereoselectivity. The following are some examples.[33,34] Woo[33] used **51**, in which SMe



51 **52**

was easily removed after addition to **13**. Devant[34] used **52** in a synthesis of statine analogue. In these reactions, alkylation proceeded with high diastereoselectivity.

Although allylation of *N*-Cbz-(*S*)-leucinal with allyltrimethylsilane in the presence of titanium tetrachloride gave 2:3 mixture of **53** and **54** in a slight favor of *threo* isomer (**54**). In contrast to this result, the ratio of *threo/erythro* isomer reversed in a favor of *erythro* isomers (**56**) than **57** upon using **55a-c** as shown in the Table 3.[35] Yields depend critically on the size of alkyl substituent at the α-position. The results indicated that the reaction proceeds predominantly *via* the S_N2 type transition states (**58**) over the transition state (**59**) giving *threo* isomers.

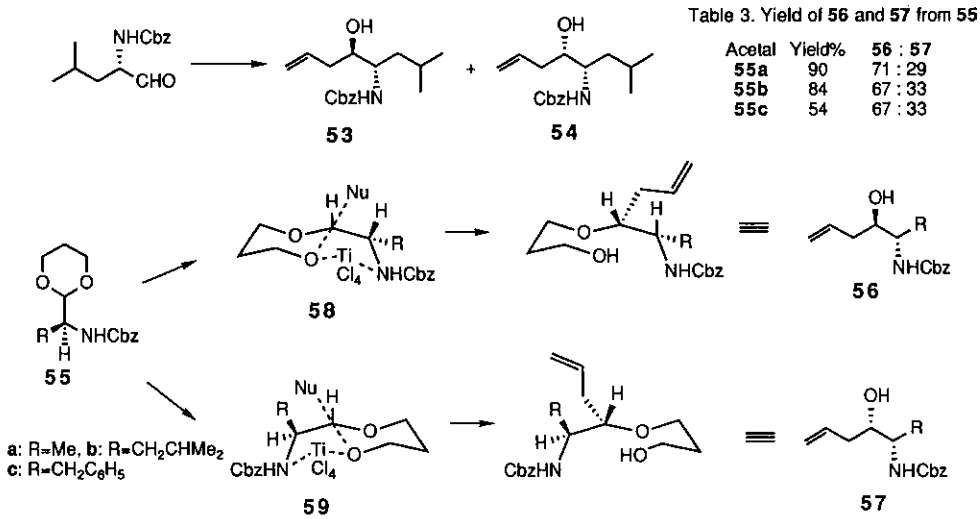
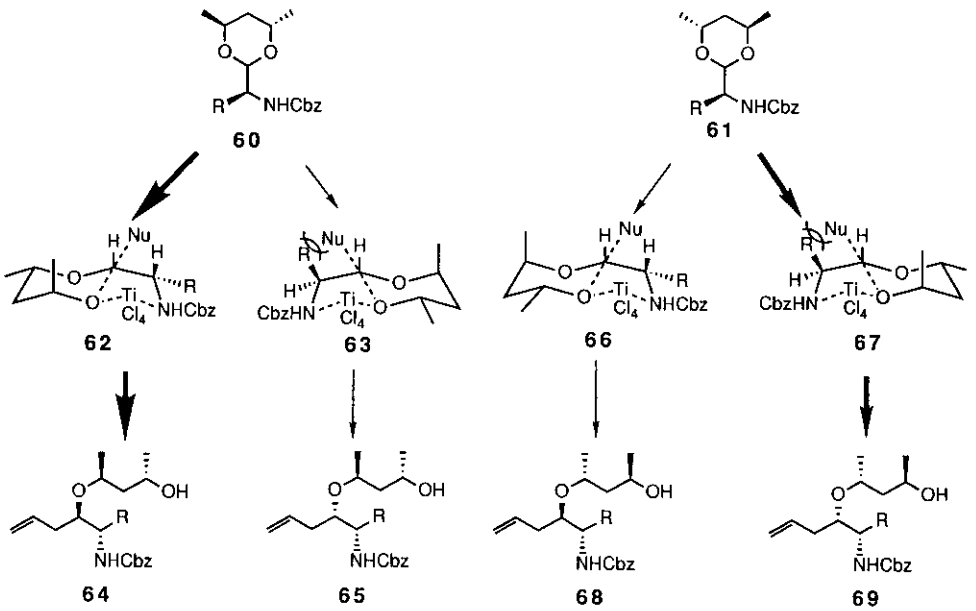


Table 3. Yield of **56** and **57** from **55**

Acetal	Yield%	56 : 57
55a	90	71 : 29
55b	84	67 : 33
55c	54	67 : 33

It can be expected that increase of diastereoselectivity would be effected by introduction of chiral auxiliary at the α-position of acetal oxygen likewise the chiral template effect works. The theory of this chiral template effect has been used in a side chain modification at 17-position of steroidal system.[36,37] We expected the regioselective cleavage of C-O bond to produce either *threo* or *erythro* 2-amino alcohols depend on the chirality on the acetals. Thus, we[35] examined this allylation by using two acetals (**60,61**). In the case of **60a-c**, of the two transition states (**62,63**), **62** leading to *erythro* isomers (**64**) should be sterically more favorable than **63** giving *threo* isomers (**65**). In addition, the template effect would work more effectively in **62** better than in **63**. In fact, allylation of **60a-c** resulted in a predominat formation of *threo* isomers (**64a-c**) over **65a-c** as shown in the Table 4. Both isomers were easily separated by column chromatography. Allylation of **61a-c** yielded *threo* isomers

(**69a-c**) as major products. Of the two transition states (**66,67**), although **66** seems to be sterically more favorable than **67**, chiral template can be anticipated to work more effectively in **67** than in **66**. Formation of **69a-c** as major products can be accounted for mainly by this reason. The diastereoselectivity decreased in order of **69a**, **69b**, **69c**, which was consistent with the size of alkyl substituent at the α-position. The chemical behavior seems in such addition reaction correlates with the chiral template effect as well as steric effect. Conversion of **64a-c** and **69a-c** to the corresponding oxazolidin-2-ones (**70a-c**) and (**71a-c**) was easily achieved by Jones oxidation, followed by treatment with base (7.5 N KOH-methanol-THF, 1:2:4), respectively, through the retro Michael elimination of the chiral auxiliary.[35]



a: R=Me, **b**: R=CH_2CHMe_2, **c**: R=CH_2Ph, **d**: R=H

Jones oxidation of **64b**, followed by treatment with *p*-toluenesulfonic acid afforded **53**. Protection of 3-nitrogen of **70b** with Boc, followed by oxidation with $RuCl_3$-$NaIO_4$, subsequent ring cleavage of the resulting acid (**72**) with lithium hydroxide in aqueous methanol afforded **73**. Thus, enantioselective synthesis of both *threo* and *erythro* 2-amino alcohols could be effected by an application of chiral template effect.

We should add two other papers by Johnson[38] and Herranz[39] related to our work.[35]

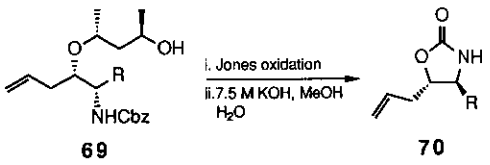
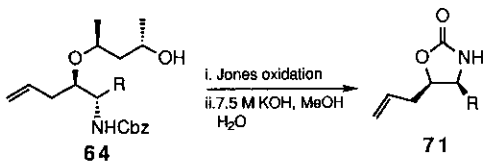
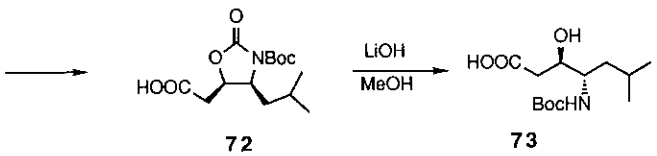


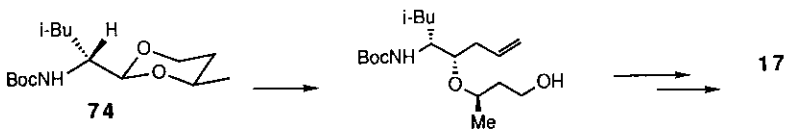
Table 4. Yield and ratio of **64** / **65**, **68** /**69**

Acetal	Yield %	**64** : **65**	Acetal	Yield %	**68** : **69**
60a	92	85 : 15	**61a**	70	20 : 80
60b	97	86 : 14	**61b**	75	28 : 72
60c	72	84 : 16	**61c**	62	33 : 67

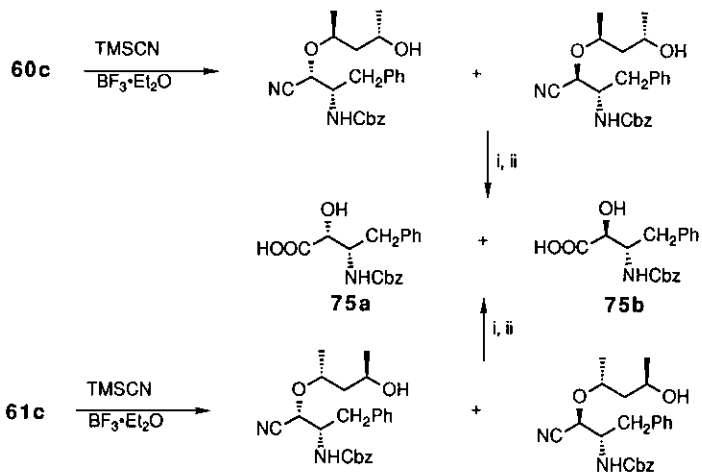




Johnson[38] also reported a synthesis of **17** through allylation of **74**.

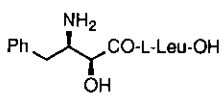


We examined the cyanation of **60c** and **61c** with trimethylsilyl cyanide under the same conditions using titanium tetrachloride as Lewis acid. Although we could not



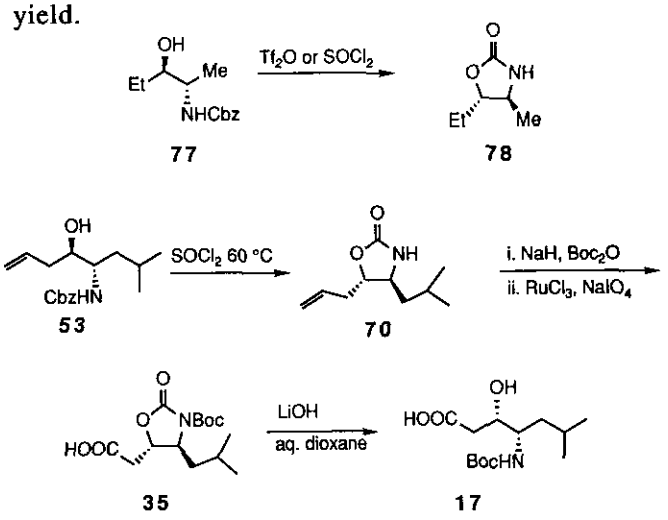
Acetal	**75a** : **75b**
60c	30 : 70
61c	70 : 30

i. pyridinium chlorochromate: ii. HCl (MeOH/Et_2O), H_2O



obtain the desired cyanation products, Herranz[39] obtained the cyanation products by using $BF_3 \cdot Et_2O$ but in low degree of diastereoselectivity. The cyanation products were led to α-hydroxy-β-amino acids (**75a,b**), key intermediates for a synthesis of bestatine (**76**) and related compounds.

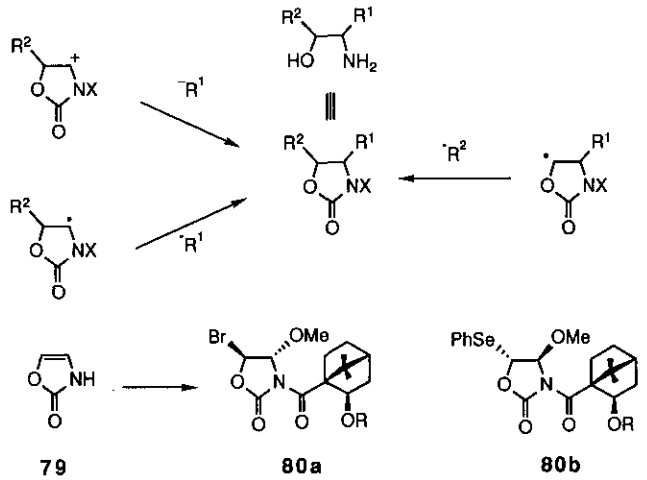
Although a variety of stereocontrolled synthesis of 2-amino alcohols have been reported, little attention has been paid to a conversion of one isomer to the another. Investigation on a practical method for diastereoconversion of chiral 2-amino alcohols in a stereospecific manner without racemization would be important from both synthetic and pharmacological points of view. Thus, two reagents, trifluoromethanesulfonic anhydride and thionyl chloride, were used for diastereoconversion of 2-amino alcohols (**53**) based on cyclocarbamation through S_N2 type C-O bond formation.[40,41] Both of them acted effectively in a diastereoconversion of **77** to **78** in 48% yield by the use of trifluoromethanesulfonic anhydride and 65% yield by the use of thionyl chloride. By an application of this diastereoconversion, **53** was led to **70b** in 67% yield by treatment with thionyl chloride. Protection of nitrogen with Boc, followed by oxidation with $RuCl_3$-$NaIO_4$[27] and subsequent ring cleavage of the resulting acid (**35**) afforded **17** in 76.5% yield.



5. Application of Oxazolidin-2-one as a Synthon for 2-Amino Alcohol

Chiral heterocycles such as *N*-substituted pyrrolidin-2-one[42] and oxazolidin-2-ones have been used for a synthesis of statine and related compounds. The methodology

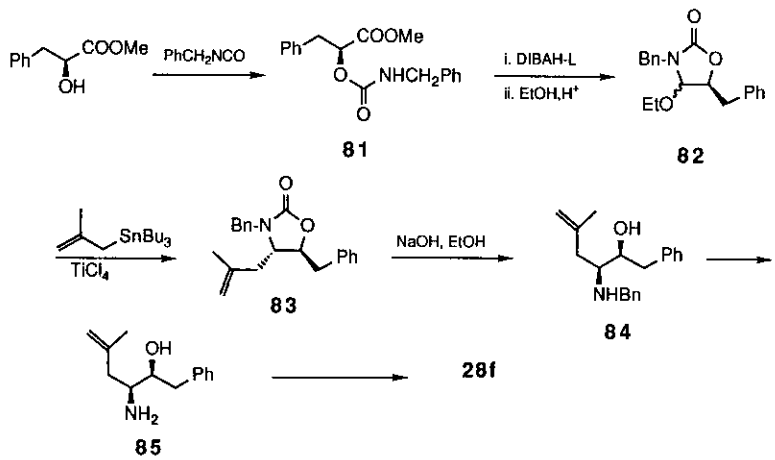
for the introduction of alkyl substituent at the 4- and 5-position of oxazolidin-2-ones with diastereoselective manner received attention as an effective synthetic route to 2-amino alcohols, since oxazolidin-2-ones can be easily cleaved under mild conditions. Indeed, chiral oxazolidin-2-ones have been used as a chiral synthon for 2-amino alcohols or as protective form of 2-amino alcohols. Kunieda[43] led oxazolin-2-one (**79**), after addition of the correspodning chiral auxiliary, to **80a,b** by methoxyselenylation and methoxybromination, respectively, which were used as the excellent tool for a chiral synthesis of 2-amino alcohol moiety after removal of the chiral auxiliary. By an application of this synthetic tool, they prepared **1** and **22** from **80a**.



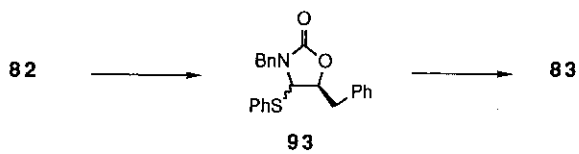
79 **80a** **80b**

We also used chiral oxazolidin-2-ones as a synthon for 2-amino alcohols.[28, 43] First, we examined a method for introduction of alkyl substituent at the 4-position.[28] The chiral oxazolidin-2-ones were synthesized from chiral α-hydroxy esters. Our synthetic strategy is a conversion of ester moiety to an amino alkyl group with diastereoselective manner. Another point is an use of phenyl group as a synthon for a carboxyl group. Condensation of methyl (*S*)-2-hydroxyphenypropionate with benzylisocyanate in benzene under reflux or in the presence of $BF_3 \cdot Et_2O$ afforded the carbamate (**81**). Reduction of **81** with DIBAL-H, followed by treatment with ethanol under acidic conditions (pH 1-2) for 4 h yielded the 4-ethoxy derivatives (**82**) as a 1:1 mixture of

4,5-*cis* and 4,5-*trans* isomers in 95% yield from **81**. Isobutenylation at the 4-position was achieved by treatment of **82** with β-methallyltriphenylstannane or β-methallyltri-*n*-butylstannane in the presence of titanium tetrachloride in CH_2Cl_2 in 84 % yield as a single product. Ring cleavage of **83** with 10% NaOH-EtOH under reflux gave the corresponding *threo* (4*S*,5*S*)-4-benzylamino-5-hydroxy-2-methyl-6-phenylhex-1-ene (**84**) in 88% yield. The optical purity of **84** was determined as >98% ee by analysis of the Mosher esters prepared by esterification of the carbamate (**86**) with both (+)- and (-)-α-trifluoromethyl-α-methoxyphenylacetic acid.[44] Catalytic hydrogenation of **84** on 10% Pd-C in ethanol gave 83% yield of 2-amino alcohol (**85**). Benzyloxycarbonylation of **85** with benzyl chloroformate in the presence of triethylamine afforded the oxazolidin-2-one (**28f**), which was converted to **17** as mentioned above. These results establish a diastereoselective synthesis of (3*R*,4*R*)-statine by begining with methyl (*R*)-α–hydroxyphenylpropionate by repetition of the synthetic steps described above.

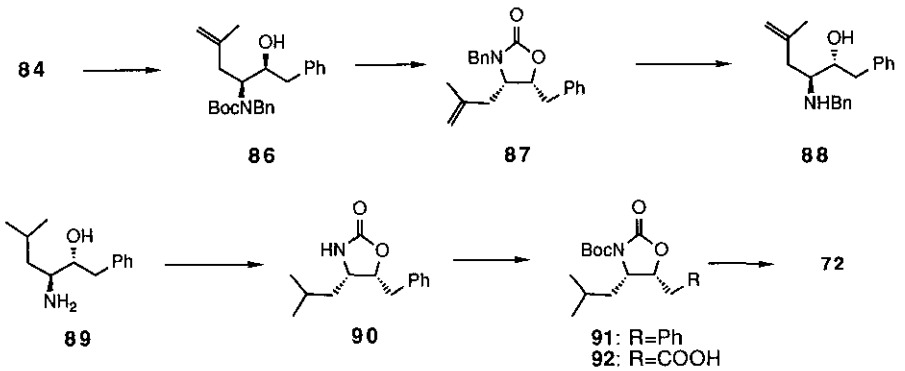


Alternatively, **83** was prepared in 82% yield by the photo reaction of **93**, derived from **82**, in the presence of β-methallytri-*n*-butylstannane and tri-*n*-butylbisstannane under irradiation with 500 W Hg lamp.[22]



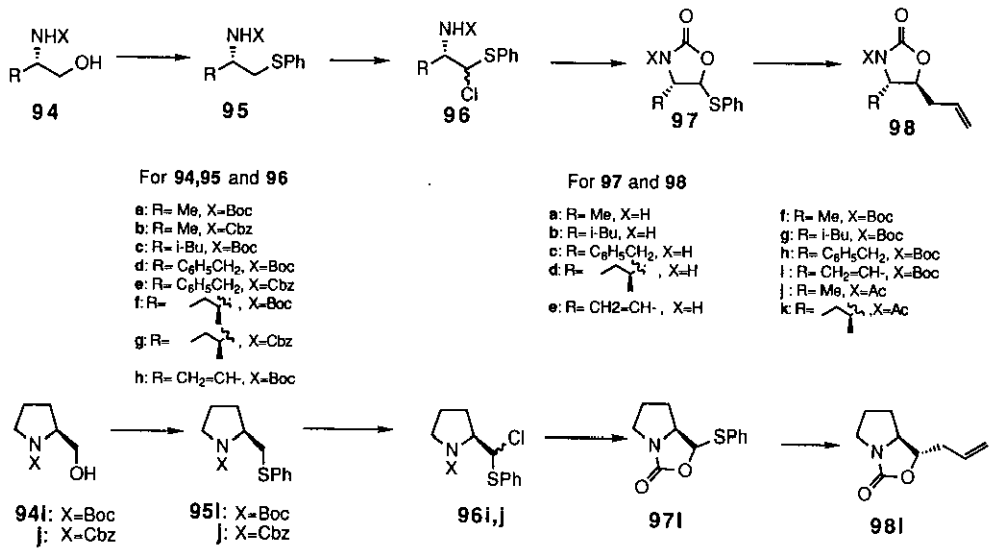
Next, our attention was turned to a synthesis of oxazolidin-2-ones (**87**), which would be convertible to *erythro* isomers (**88**), by an application of diastereoconversion via

S_N2 type cyclocarbamation.[28,40,41] Treatment of **86** with thionyl chloride at room temperature or with methanesulfonyl chloride in the presence of triethylamine resulted in configurational inversion at the carbinol carbon to give (4*S*,5*R*)-3,5-dibenzyl-4-isobutenyloxazolidin-2-one (**87**) in 88 % yield. Ring cleavage of **87** as in **83** gave the amino alcohol (**88**), which was converted to **91** through **89** and **90** according to the same conditions as in **85**. Oxidation of **91** with $RuCl_3$-$NaIO_4$ gave **92**, which was converted to (3*R*,4*S*)-statine *via* *N*-Boc-(3*R*,4*S*)-statine. In a similar way, (3*S*,4*R*)-statine was also prepared from methyl (*R*)-α-hydroxyphenylpropionate by repetition of the same reaction described above. Thus diastereoselective synthesis of four of all enatiomers of statine was established.

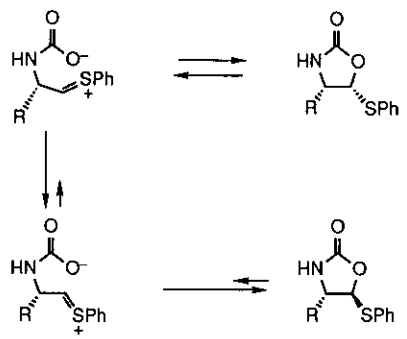


Our another synthetic strategy is an introduction of an alkyl substituent at the 5-position of oxazolidin-2-ones with high diastereoselectivity. α-Heteroatom-substituted sulfides have been used for the generation of radical carbon by homolytic cleavage of C-S bond.[44,45] We expected a generation of radical carbon at the 5-position upon treatment of 5-phenylthiooxazolidin-2-ones with appropriate radical initiator. Our synthetic strategy[46] involves a synthesis of 5-phenylthiooxazolidin-2-ones by an acid catalyzed cyclocarbamation of sulfonium ion. (*S*)-*N*-Cbz- or (*S*)-*N*-Boc amino alcohols (**94a-j**) were easily converted to the corresponding sulfides (**95a-j**) in 80-95% yield by conventional method (diphenyl disulfide, tri-*n*-butylphoshine, THF or DMF). Chlorination of **95a-j** was easily achieved by treatment with *N*-chlorosuccinimide in carbon tetrachloride to yield **96a-j**. Cyclocarbamation of these was carried out by treatment with stannic chloride. In the cases of *N*-Boc sulfides, cyclization proceeded

smoothly even at -78 °C but in the cases of *N*-Cbz sulfides, rather higher temperature required for cyclization, actually at -30 °C. Upon quenching the reaction mixtures at low temperature applied, a mixture of 4,5-*trans*- and 4,5-*cis*-5-phenylthiooxazolidin-2-ones (**97a-j**) were obtained. However, *trans* isomers were obtained with high diastereoselectivity upon warming the reaction mixture at room temperatue (20 min) before quenching. These results were summarized in the Table 5. *N*-Boc sulfides are superior to *N*-Cbz derivatives in yields for **96**. Formation of cyclization products was observed at the chlorination step in *N*-Boc sulfides by partial cyclocarbamation. In the case of **96j**, the *N*-Cbz prolinal was obtained without formation of the desired cyclization product.



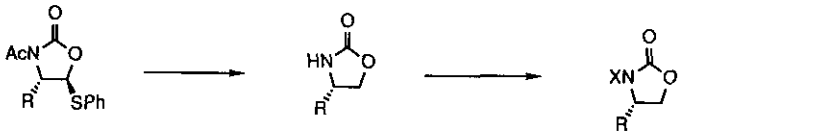
An interesting feature of this cyclocarbamation is that it involves equilibrium between *cis* and *trans* isomers and results in a predominant formation of the thermo-



Eq. 2

dynamically more stable *trans* isomers by elevating the reaction temperature. The *cis* isomers were isomerized to the *trans* isomers without racemization by treatment with stannic chloride (Eq. 2)

The optical purity of the 5-phenylthiooxazolidin-2-ones, thus obtained, was determined as >99% ee by ^{1}H-nmr analysis of (+)- and (-)-α-methoxy-α-trifluoromethylphenylacetylimide (**101a-d**) derived from **99a,c**, through desulfurization, respectively, as depicted in the following scheme.



99 **100**

101a: R=Me, X=(+)-MTPA
b: R=Me, X=(–)-MTPA
c: R=$C_6H_5CH_2$, X=(+)-MTPA
d: R=$C_6H_5CH_2$, X=(–)-MTPA

N-Boc and *N*-acetyl derivatives were subjected to the following allylation reaction. Photo-initiated radical allylation of **97a,c** was carried out by modification of Keck's condition[45] by using allyltri-*n*-butylstannane in toluene-acetonitrile (7:3) in the presence of tri-*n*-butylbisstannane with 300 W or 500 W Hg lamp to afford the corresponding 5-allyloxazolidin-2-ones (**99a,b**) in 45 and 55% yield, respectively, as a single diastereomer without racemization. Yields for allylation products were considerably improved by protection of nitrogen with Boc or acetyl group as shown in the Table 6.

Table 5. Yield and trans / cis ratio of 5-(phenylthio)oxazolidin-2-ones

sulfide	product	yield, %	trans:cis
95a	**97a**	79	10:1 (3:1)[a]
95b	**97a**	72	10:1
95c	**97b**	80	20:1 (3:1)[a]
95d	**97c**	85	20:1 (4:1)[a]
95e	**97c**	72	20:1
95f	**97d**	82	30:1 (3:1)[a]
95g	**97d**	70	30:1
95h	**97e**	67	1.2:1[a]
95i	**97l**	50	2.4:1[a]
95j	**97l**	0	

[a]The reaction was quenched at -78 °C rather than -20 °C

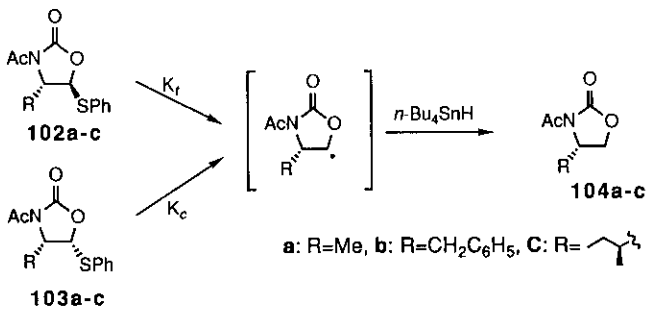
Table 6. Allylation of **97**

substrate	product	yield, %
97a	**98a**	45
97b	**98b**	71
97c	**98c**	55
97f	**98f**	72
97g	**98g**	76
97h	**98h**	81
97i	**98i**	60
cis-**97i**	**98i**	20
97j	**98j**	62
97k	**98k**	81
cis-**97k**	**98k**	30
97l[a,b]	**98l**	57

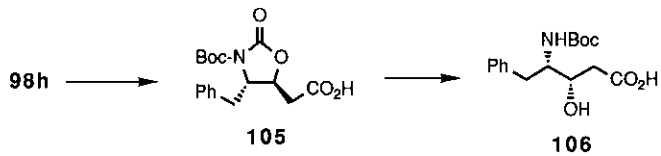
[a] 2.4:1 trans / cis mixture was used.
[b] The reaction was continued for 40h

In this photo-initiated radical allylation reaction, it is noteworthy that the reactivity of 4,5-*cis* isomers toward generation of radical species is remarkable low compared

with that of *trans* isomers.[47] This was clearly demonstrated by using **97i** and **97k**, which were isolated as a pure state (see Table 6).[46] We interested in a examination of the relative rate for generation of cyclic carbamoyloxy radical from 4,5-*trans* (**102a-c**) and 4,5-*cis* isomers (**103a-c**). Each of these (0.5 M solution in C_6D_6) was subjected to desulfurization reaction by monitoring by ^{1}H-nmr spectra to give the corresponding desulfurization products (**104a-c**). The *trans* isomers were found to be about six times as reactive as the corresponding *cis* isomers by comparison with their half life.[50] These results indicate that the reaction is strongly affected by the stereochemistry and the *trans*-oriented phenythio group is more reactive than the *cis*-oriented one. The low reactivity of the *cis* isomers could be, most possibly, due to the steric congestion.

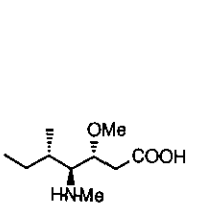


Oxidation of **98h** with $RuCl_3$-$NaIO_4$, followed by ring cleavage of the resulting acid (**105**) afforded the corresponding β-oxygenated γ-amino acid (**106**) as in a formation of **26** from *N*-Boc **70**.

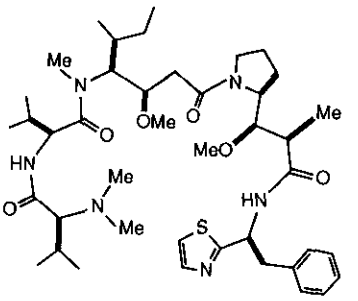


This radical allylation reaction at the 5-position of oxazolidin-2-ones was extensively applied to a synthesis of dolaisoleuine (**6**),[48] a key component of dolastatin 10 (**107**)[6,49] and its stereoisomers.

Ring cleavage of **108**, obtained from **97d** through *tert*-butoxycarbonylation and subsequent allylation, with cesium carbonate in methanol afforded the *threo* 2-amino alcohol (**109**) in 78% yield. For the approach to **6**, epimerization at 3-OH is essential

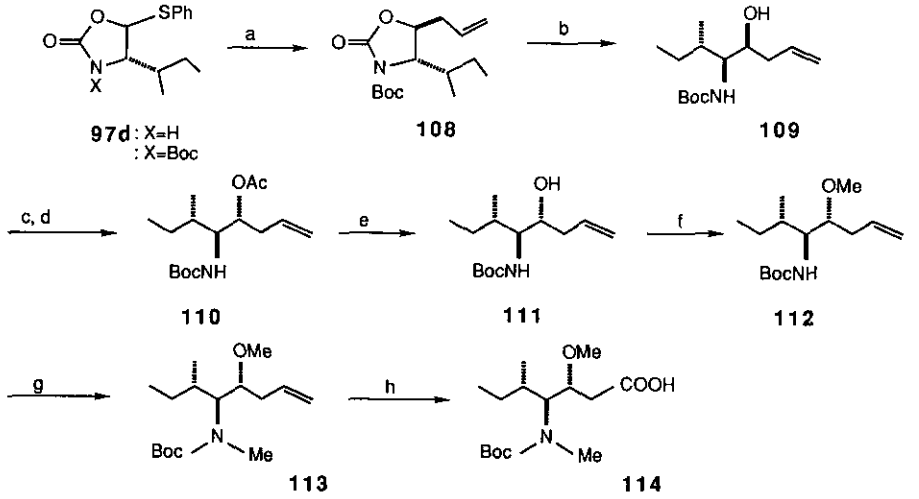


6



107

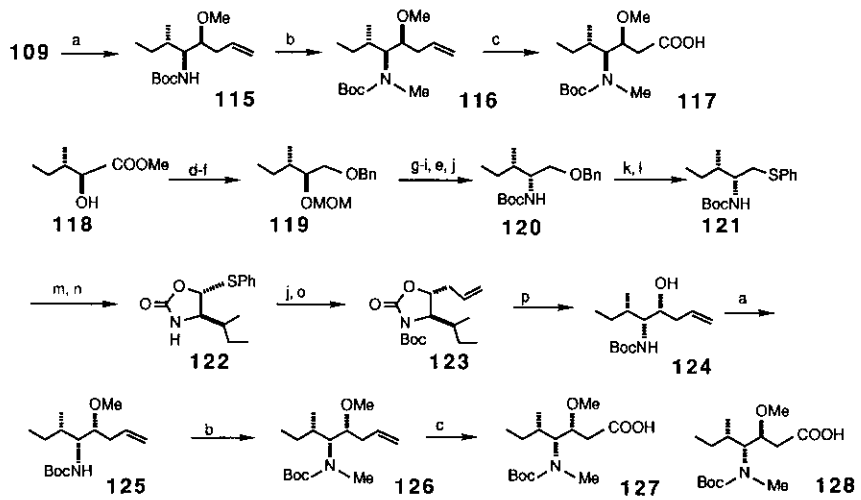
problem solved. Methanesulfonylation of **109**, followed by treatment with cesium acetate in benzene in the presence of 18-crown-6 under reflux and subsequent hydrolysis with K_2CO_3 in methanol of the resulting acetate yielded the *erythro* 2-amino alcohol (**111**) in 68% yield. Selective *O*-methylation was achieved by treatment with methyl iodide in the presence of thallium ethoxide in DMF gave **112**, which was successively subjected to *N*-methylation (NaH, MeI, THF) to give rise to a formation of *N*,*O*-dimethyl derivative (**113**). Oxidation of **113** with $RuCl_3$-$NaIO_4$ yielded *N*-Boc dolaisoleuine (**114**). In a similar way, the *N*-Boc-(3*S*,4*S*,5*S*)-isomer (**117**) was prepared from **106** *via* **115** and **116** as depicted in the following scheme.



Reagents and conditions: a. n-$Bu_3SnCH_2CH{=}CH_2$ / (n-$Bu_3Sn)_2$ /*hv*.; b. Cs_2CO_3 /MeOH.
c. $MeSO_2Cl$ /Et_3N; d. CsOAc /18-crown-6 / benzene / reflux; e. K_2CO_3 /MeOH;
f. TlOEt /MeI /DMF; g. NaH /MeI /THF; h. $RuCl_3$ /$NaIO_4$ /CCl_4-MeCN-H_2O

Preparation of stereoisomers of dolaisoleuine should be significantly important from

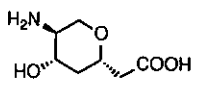
the point of view of the effect of chirality in the evaluation of biological activity of dolastatin 10 possessing stereoisomer of dolaisoleuine. Then, the other two isomers were synthesized by starting with compounds readily available. The sulfur containing *N*-Boc amine (**120**) was synthesized from (*S*)-α-hydroxy ester (**118**) *via* **119** and **120** by the usual way. Conversion of **120** to 5-allyloxazolidin-2-one (**123**) was achieved according to the same manner as in a synthesis of **108** . Ring cleavage of **123**, followed by *O*-methylation of the resulting *N*-Boc amino alcohol (**124**), and subsequent *N*-methylation of **125** gave **126**, which was oxidized to (3R,4R,5S)-*N*-Boc-dolaisoleuine (**127**).[51] Furthermore, (3S,4S,5S)-isomer (**128**) was also obtained from the *erythro* 2-amino alcohols (**124**), prepared from **123** by repetition of the same procedure as in a preparation of **116** from **109**.



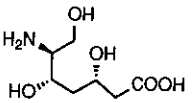
Reagents and conditions: a. TlOEt / MeI / DMF; b. NaH /MeI /DMF; c. $RuCl_3$ / $NaIO_4$ / CCl_4-MeCN-H_2O; d. $MeOCH_2Cl$ / i-$PrNEt_2$; e. $LiAlH_4$, f. NaH / $C_6H_5CH_2Br$; g. conc. HCl;h. $MeSO_2Cl$ / Et_3N / CH_2Cl_2; i. NaN_3 /DMF; j. Boc_2O / Et_3N; k.H_2 /Pd-C; l. $(PhS)_2$ / n-Bu_3P /THF; m. NCS /CCl_4; n. $SnCl_4$ /CH_2Cl_2; o. n-Bu_3CH_2CH =CH_2 / *hv*; p. Cs_2CO_3 / MeOH

Our own contribution to the chemistry of radical allylation involving sulfonium ion-induced cyclocarbamation procedure was further applied to a synthesis of the degradation product of peptide antibiotic galantin 1.[51] Previously, the compounds (**129**) was treated as a key component of galantin 1 and was called galantinic acid, later it was found to be degradation product and the structure of galatinic acid was revised to **130**.[52,53] During the preparation of **129**, we received this information from Dr.

Ohfune.[54] Photo-initiated radical allylation of 5-phenylthiooxazolidin-2-ones was applied to a synthesis of **129**.[55,56]



129



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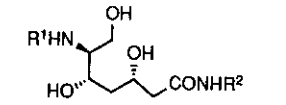
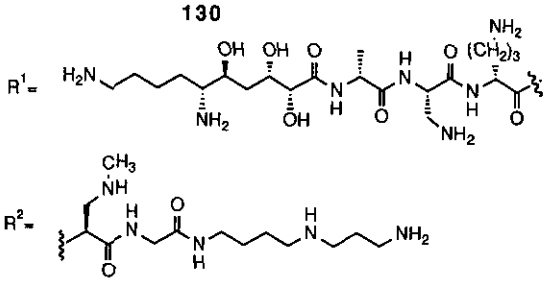
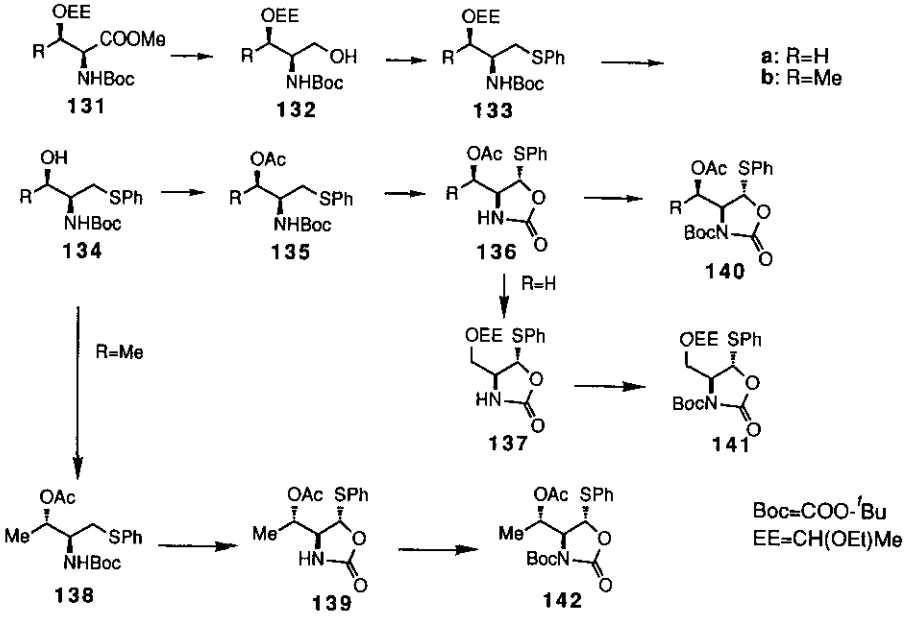


revised structure for galantin I

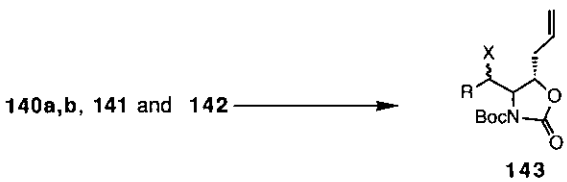


Sulfur containing *N*-Boc-amino alcohols (**134**) were easily prepared from (*S*)-serine and (*S*)-threonine *via* **132** and**133**. For the step of sulfonium ion induced cyclocarbamation reaction, ethoxyethyl group was replaced with acetyl group, since it is too unstable under acidic conditions. Chlorination of **135** with *N*-chlorosuccinimide and subsequent cyclization with stannic chloride yielded the corresponding 4-substituted 5-phenylthiooxazolidin-2-ones (**136**) in 84-86% yield. Hydrolysis of **136** with cesium carbonate in methanol, followed by ethoxyethylation with ethyl vinyl ether in the



presence of PPTS yielded **137.** Inversion of the chiral center at the hydroxy group of **134b** according to the method as **109** afforded the *erythro* isomer (**138**), which was led to **139**.

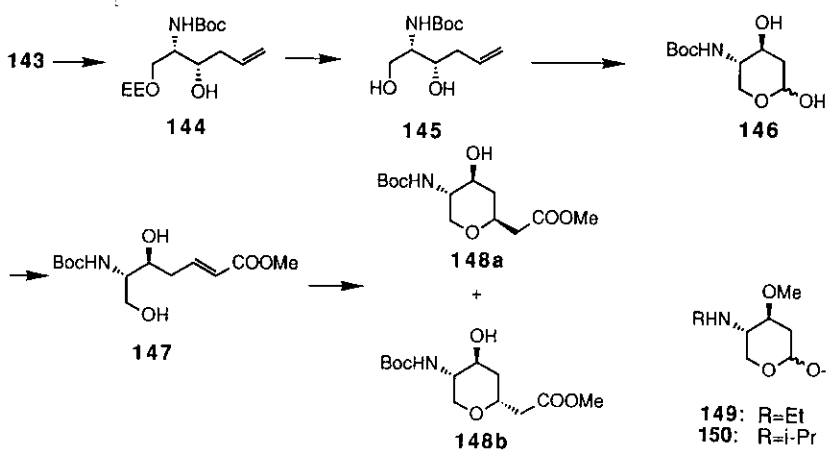
Photo-induced radical allylation of **140a,b, 141, 142**, obtained by *tert*-butoxycarbonylation of **136a,b, 137** and **138**, afforded the corresponding allylation products (**143a-d**), respectively, in 75-81% yield.



143

143	R	X	Yield(%)
a	H	—OAc	80.5
b	Me	—OAc	75.0
c	H	—OEE	75.8
d	Me	···OAc	81.0

Ring cleavage of **143a** with cesium carbonate yielded the expected **145** but in quite low yield. However, ring cleavage of **143c** gave **144** in 84 % yield. Subsequent *O*-deprotection of **144** afforded **145**. The desired 4-amino-3-hydroxypyranose (**146**) was successfully prepared from **145** in 76% yield by ozonolysis as an 1:4 anomeric mixture. Wittig reaction of **146** with methyl triphenylphospholideneacetate afforded **147** cyclization of which with potassium carbonate in methanol afforded **148a** in 43.4% yield and its C_3-epimer (**148b**) in 34.2% yield. This method should be potentially useful for a synthesis of this type of amino sugars such as **149** in calichemicin[57] and **150** in esperamicin.[58]



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