

# Stereoselective Routes toward the Synthesis of Unusual Amino Acids

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More than 700 amino acids that are the so-called unusual, unnatural, or nonproteinous amino acids have been found in nature in the free zwitterionic form or as constituents of peptides. These amino acids have attracted much attention from scientists due to their important biological activities as antibiotics, metal chelators, neurotoxins, enzyme inhibitors, etc.<sup>1</sup> Because in many cases only minute quantities have been isolated and because their structures are unique, they are interesting synthetic targets.<sup>2-4</sup>

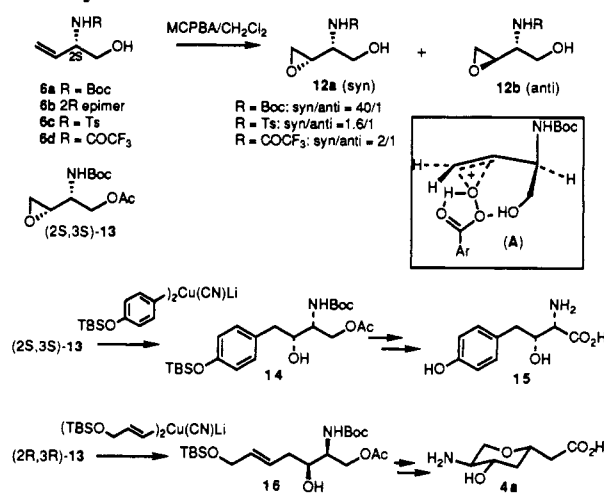
A feature common to many of these unusual amino acids is the 1,2- or 1,3-amino hydroxyl system. In particular, such amino acids are often found as constituents of peptides. Our research group has been involved in the development of new methods for the elaboration of such 1,2- and 1,3-amino hydroxyl systems. Our chief focus has been on the total synthesis of the peptide antibiotics echinocandins (1)<sup>5,6</sup> and galantin I (2: the structure has been revised to 5 as a result of our synthesis),<sup>7-11</sup> which have a variety of new amino acids. Echinocandins, isolated from *Aspergillus rugulosus* or *nidulans*, exhibit potent antifungal and anti-yeast activities.<sup>5</sup> The structures of 1a-c are composed of a highly hydrophilic cyclic peptide and a hydrophobic linoleyl moiety. Galantin I is a metabolite of *Bacillus pulvifaciens* with antibacterial activity.<sup>7</sup> Galantin I has two new amino acids, named galantinamic acid (Glm, 3a assigned as its primary structure) and galantinic acid (Gla, 4b: isolated as an anhydro form 4a) (Figure 1).<sup>11</sup>

In recent years, great progress in the asymmetric synthesis of both the 1,2- and 1,3-amino hydroxyl systems has been reported. The available methods for the synthesis of the 1,2-amino hydroxyl system are the following: (i) nucleophilic opening of an epoxide with amines, isonitriles, and azides; (ii) reduction of amino ketones or hydroxyl imines; (iii) nucleophilic addition of organometallic reagents to amino ketones; and (iv) coupling of an achiral or a chiral glycine equivalent with aldehydes.<sup>3,12</sup> However, several basic problems regarding stereocontrol, racemization, protecting groups, etc. still remain.

Our approach to the 1,2- and 1,3-amino hydroxyl systems is the diastereoselective introduction of a hydroxyl group into the allyl or homoallyl amines 6-11, which are readily available from commercial  $\alpha$ -amino acids. These unsaturated amines can be viewed as

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## Scheme I Epoxidation of 2-Amino-3-butenol Derivatives



useful synthetic building blocks because of the presence of chirality and appropriate functionalities accessible to a variety of chemical transformations. Using the above synthons, their diastereoselective conversions to syn and anti 1,2- and 1,3-amino hydroxyl systems (methods a-f) were examined as summarized in Figure 2. The total synthesis of 1c and the right-half equiv-

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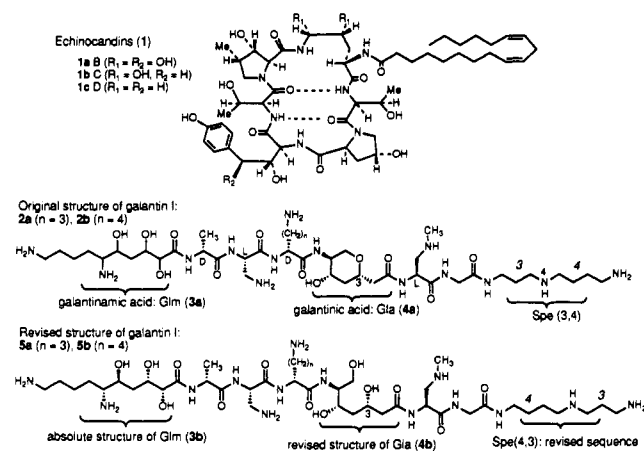


Figure 1.

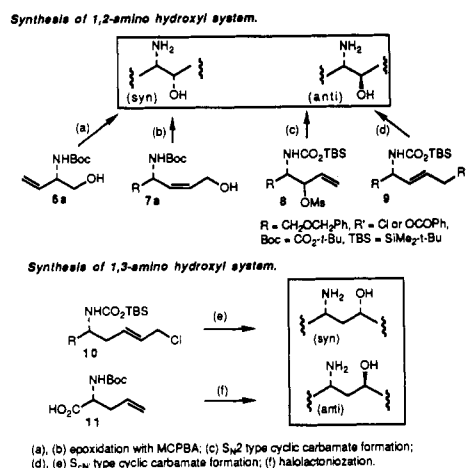


Figure 2.

alent of 1a,b and 5 has been accomplished on the basis of these methods.

### Epoxidation of 2-Amino-3-butenol Derivatives

Both enantiomers of *N*-(*tert*-butoxycarbonyl)-2-amino-3-butenol (6), a masked form of chiral serine, have been synthesized from L- or D-methionine.<sup>13</sup> Compound 6a, upon treatment with 3-chloroperoxybenzoic acid (MCPBA), underwent stereoselective epoxidation to give *syn*-epoxide 12a (*syn/anti* = 40/1). The reaction likely proceeds through an internal chelation of MCPBA with the primary hydroxyl group, since epoxidation after protection of the hydroxyl group of 6a with the *tert*-butyldimethylsilyl (TBS) group required a prolonged reaction time (~1 week) and resulted in reduced *syn* selectivity (*syn/anti* = 3/1).<sup>14,15</sup> The bulky *tert*-butoxycarbonyl (Boc) group may hinder the undesired chelation with the amino group (A).

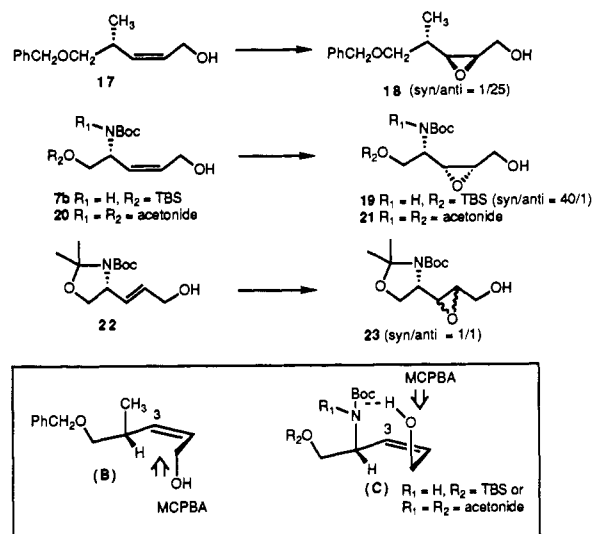
The *syn*-epoxide 12a proved to be useful as a precursor for the synthesis of various  $\beta$ -hydroxy  $\alpha$ -amino acids. For example, the reaction of the acetate 13 with the appropriate cuprate resulted in regioselective nucleophilic opening of the epoxide to give *syn*-1,2-amino alcohols 14 and 16, respectively, which were converted to  $\beta$ -hydroxyhomotyrosine 15<sup>6a</sup> and anhydro Gla 4a,<sup>9,16</sup>

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### Scheme II Epoxidation of Hydroxymethyl Allylamines



which are constituents of 1 and 2, respectively (Scheme I).

### Epoxidation of Hydroxymethyl (*Z*)-Allylamines

Epoxidation of the allyl alcohol 17, which has a methyl group at C4, has been shown to give *anti*-epoxide 18 with high stereoselectivity (*syn/anti* = 1/25).<sup>17</sup> The mechanism involves less hindered side attack (*re* face on C3) of an internal chelate complex of MCPBA on the C-C double bond (Scheme II, B). Contrary to this, epoxidation of the hydroxymethyl (*Z*)-allylamine 7b yielded *syn*-epoxide 19a (*syn/anti* = 40/1), stereoselectively.<sup>10,18</sup> This example indicated that MCPBA attacked from the more hindered *si* face on C3. The epoxidation of 20, in spite of the lack of an amide hydrogen, was also *syn* selective to afford *syn*-epoxide 21 exclusively. The protection of the hydroxyl group of 20 with the TBS group resulted in a decrease in both yield (>20%, 3 days) and product ratio (~3/1). Therefore, the high *syn* selectivity in the epoxidation of hydroxymethyl (*Z*)-allylamine was attributed to the fact that the epoxidation proceeded through a chelation complex C. The (*E*)-allyl alcohol 22 provided a 1/1 mixture of *syn*- and *anti*-epoxides 23.<sup>11c</sup> Thus, epoxidation of hydroxymethyl (*Z*)-allylamine proved to be a potential method for the preparation of *syn*-1,2-amino alcohols.

### *S<sub>N</sub>2* Type Cyclic Carbamate Formation from *tert*-Butyldimethylsilyl Carbamate

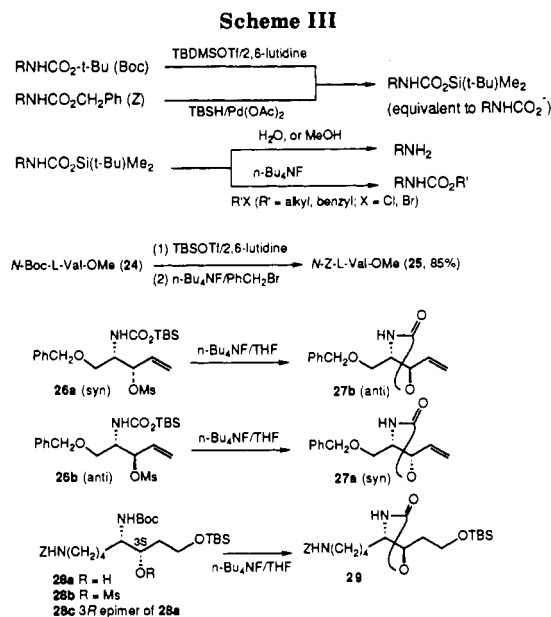
*N*-*tert*-Butoxycarbonyl (Boc) and *N*-benzyloxy-carbonyl (*Z*) groups are the most common amino protecting groups used for the synthesis of amino acids, amino sugars, and peptides.<sup>19</sup> These groups can be transformed into the *N*-(*tert*-butyldimethylsilyl)oxy-

(16) (a) Golebiowski, A.; Kozak, J.; Jurczak, J. *J. Org. Chem.* 1991, 56, 7344. (b) Ikota, N. *Heterocycles* 1991, 32, 521. (c) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* 1991, 56, 240. (d) Kano, S.; Yokomatsu, T.; Shibuya, S. *Heterocycles* 1990, 31, 13. (e) Golebiowski, A.; Kozak, J.; Jurczak, J. *Tetrahedron Lett.* 1989, 30, 7103.

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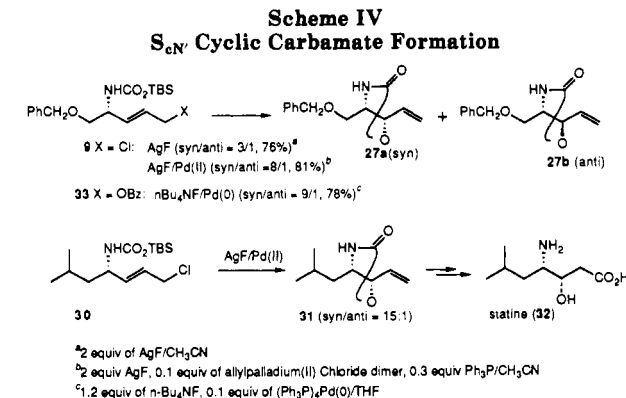


carbonyl group<sup>20</sup> by treatment of the *N*-Boc derivative with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine and the *N*-Z compound with *tert*-butyldimethylsilane (TBSH) in the presence of a catalytic amount of Pd(OAc)<sub>2</sub>, respectively.<sup>21</sup> The silyl carbamate is stable under ambient conditions and can be activated by fluoride ion to undergo various electrophilic substitution reactions. In the presence of an alkyl halide, the silyl carbamate yielded the corresponding alkyl carbamate. For example, the *N*-Boc amino ester 24 was converted, efficiently, to the corresponding *N*-Z amino ester 25 via the silyl carbamate. Thus, the silyl carbamate prepared from an *N*-Boc or *N*-Z compound is a useful intermediate which can be converted to a variety of urethane-type compounds.<sup>21</sup>

Furthermore, the silyl carbamate can be trapped by an internal electrophile with complete inversion of configuration. Treatment of the *syn*-mesylate 26a with *n*-Bu<sub>4</sub>NF gave the cyclic carbamate 27b having an *anti*-amino hydroxyl system. The *anti*-mesylate 26b gave the *syn*-carbamate 27a. This method proves to be useful when the Mitsunobu reaction is not effective.<sup>22</sup> For example, under Mitsunobu conditions the conversion of the *syn*-amino alcohol 28a to the corresponding anti isomer 28c was not effective due to the bulky nature of the neighboring *N*-Boc group. However, the silyl carbamate method was successfully applied to this conversion to give the desired anti cyclic carbamate 29 (Scheme III).<sup>10,23</sup>

### S<sub>C<sub>N</sub></sub> Cyclic Carbamate Formation via Silyl Carbamate

Because of its high reactivity, a silyl carbamate can be viewed as an *N*-carboxylate ion equivalent. Thus, intramolecular trapping of this reactive species in an S<sub>C<sub>N</sub></sub> manner<sup>24</sup> provides a stereoselective method for the



synthesis of the 1,2- and 1,3-amino hydroxyl systems as a cyclic carbamate. AgF was chosen in order to activate both the silyloxycarbonyl and the allyl chloride groups. Compound 9 with AgF underwent cyclic carbamate formation in an S<sub>C<sub>N</sub></sub> manner to give a mixture of *syn*-27a and *anti*-27b (AgF, *syn*/*anti* = 3/1). The use of AgF in the presence of a Pd(II) catalyst (0.1 equiv of allylpalladium(II) chloride dimer and 0.3 equiv of triphenylphosphine) was superior to AgF in view of its *syn* selectivity (*syn*/*anti* = 8/1). As an additional example, treatment of the allyl chloride 30 with AgF or AgF/Pd(II) gave cyclic carbamate 31 (AgF, *syn*/*anti* = 5/1; AgF/Pd(II), *syn*/*anti* = 15/1). The carbamate 31 was readily converted into statine (32), a constituent of pepstatin, which is a well-known potent renin inhibitor.<sup>23,25</sup>

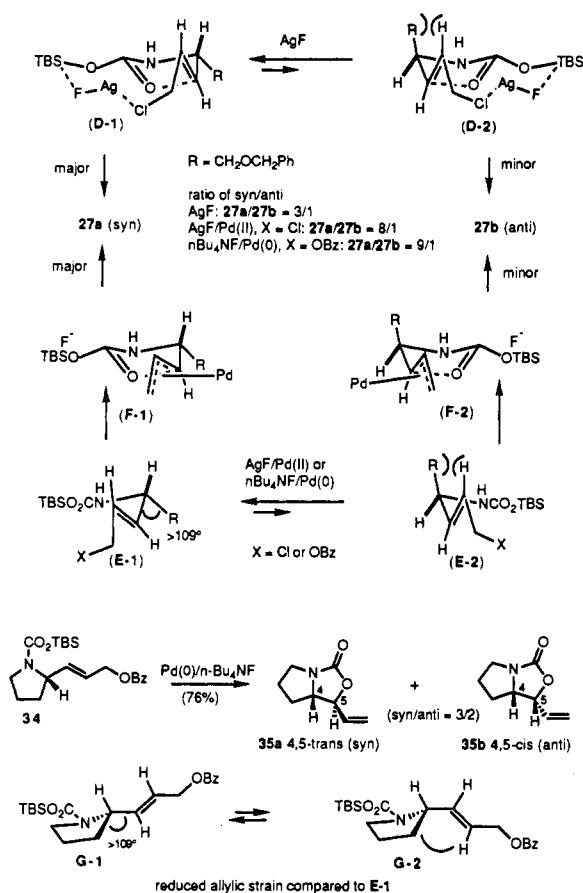
Allyl esters are more attractive than allylic chlorides as internal electrophiles in view of their ease of preparation and stability.<sup>26</sup> Also, the use of stoichiometric amounts of AgF can be avoided. Thus, treatment of the benzoate (Bz) 33 with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and 1 equiv of *n*-Bu<sub>4</sub>NF gave *syn*-27a as the major product (*syn*/*anti* = 9/1) (Scheme IV).

The *syn* selectivity using AgF can be understood from the examination of the hypothetical cyclic intermediates D-1 and D-2. Due to the presence of severe allylic strain<sup>27</sup> in the transition-state conformer D-2, the reaction proceeds via the thermodynamically more favored transition-state D-1 to give *syn*-27a. Using AgF/Pd(II) or *n*-Bu<sub>4</sub>NF/Pd(0), the major isomer 27a could be derived via ( $\pi$ -allyl)palladium complex F-1 from the thermodynamically more favored conformer E-1, which has less allylic strain than E-2 (rate-determining step) (Scheme V).<sup>28</sup> It is noted that the proline derivative 34 gives a mixture of cyclic carbamates 35a,b [4,5-*trans* (*syn*)/4,5-*cis* (*anti*) = 3/2] in good yield. The decreased *syn* selectivity can be attributed to the reduced steric bulkiness of the conformationally constrained CH<sub>2</sub> group in a five-membered ring (G-1 and G-2) when compared to the freely rotating CH<sub>2</sub>R of 33

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 (21) (a) Sakaitani, M.; Ohfuné, Y. *Tetrahedron Lett.* 1985, 26, 5543.  
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 (27) (a) Johnson, F. *Chem. Rev.* 1968, 68, 375. (b) Hoffmann, R. W. *Chem. Rev.* 1989, 89, 1841.  
 (28) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* 1977, 1, 61.

**Scheme V**  
Proposed Mechanism of  $S_N2$  Cyclic Carbamate Formation

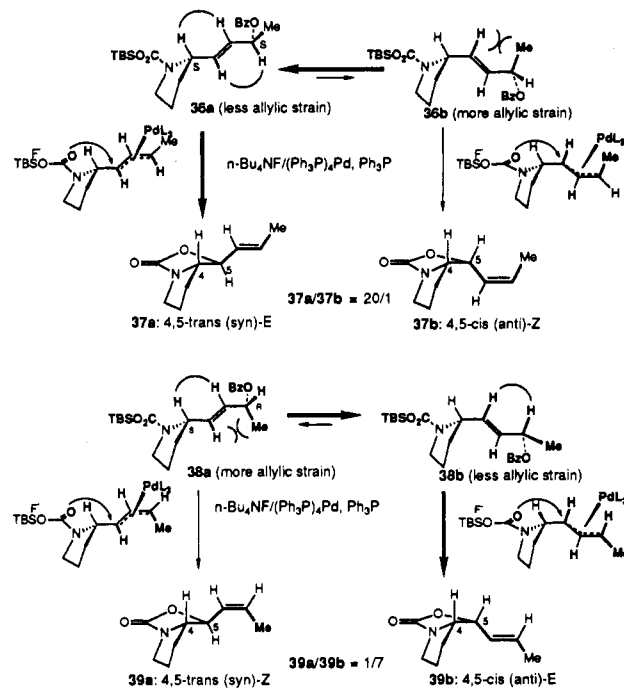


(the structure is shown in Scheme IV).<sup>29</sup>

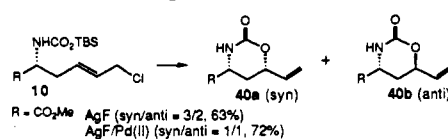
The use of secondary allylic esters is of interest since there are four possible products considering both the ring stereochemistry and double-bond geometry. From the (*S,S*) isomer **36**, the 4,5-*trans* (*E*) product (*syn*) **37a** was produced with high stereoselectivity ( $37\mathbf{a}/37\mathbf{b} = 20/1$ ), while (*S,R*)-**38** gave the 4,5-*cis* (*E*) adduct (*anti*) **39b** as the major product ( $39\mathbf{b}/39\mathbf{a} = 7/1$ ). In each case, the other stereoisomers were not detected. Formation of the *syn* adduct **37a** from the (*S,S*) isomer **36** and primarily the *anti* adduct **39b** from the (*S,R*) isomer **38** suggests that these transformations proceed via double inversion (net retention): (1) the leaving group and silyloxycarbonyl group are placed on the same face in the ground-state conformers (**36a** and **36b**, **38a** and **38b**) (the major or exclusive isomer is produced from the conformers, **36a** and **38b**, having the least  $A^{1,3}$  strain); (2) palladium(0) attacks from the back side of the leaving group; and (3) attack of the *N*-carboxylate ion species on the ( $\pi$ -allyl)palladium complex gives the cyclic carbamates **37a** and **39b**, respectively. These transformations provide stereoselective access to the *syn*- or *anti*-1,2-amino hydroxyl systems (Scheme VI).<sup>29</sup>

The present method was also employed for the synthesis of a 1,3-amino hydroxyl system (method e, Figure 2). The chloromethyl homoallylamine **10** produced a mixture of six-membered cyclic carbamates **40a,b**. The *syn/anti* ratio was  $\sim 1/1$ . However, greater *syn* selectivity was observed when the reaction was applied to the peptide system (vide infra) (Scheme VII).<sup>23</sup>

**Scheme VI**  
Cyclic Carbamate Formation from Secondary Allyl Esters



**Scheme VII**  
Six-Membered-Ring Cyclic Carbamate Formation



**Syntheses of Gln (3b) and Glu (4b)**

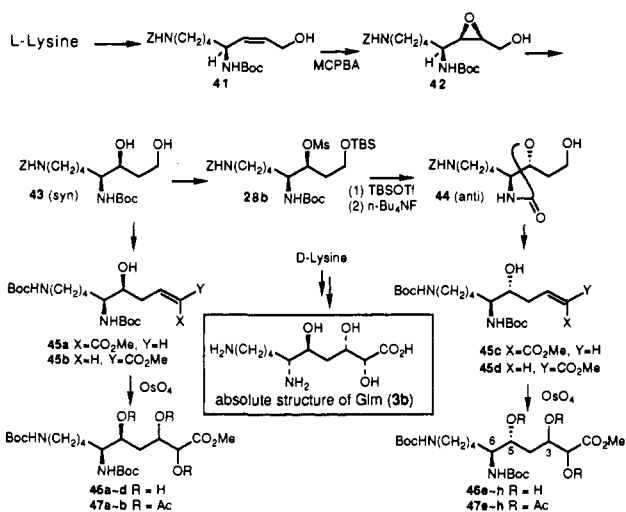
Before this work, only the primary structure of Gln (**3a**) was reported.<sup>8</sup> The structure determination of **3a** required the synthesis of eight diastereomers from L- or D-lysine. The methods elaborated in our laboratory (Figure 2a-d) were used for the synthesis of the key intermediates **43** and **44**. The hydroxymethyl (*Z*)-allylamine **41** on epoxidation (method b, Figure 2) gave the *syn*-epoxide **42**, which upon subsequent reduction with  $\text{LiAlH}_4$  afforded, regioselectively, the desired *syn* amino diol **43**. Upon  $S_N2$  type cyclic carbamate formation using method c (Figure 2), the mesylate **28b** provided the *anti* cyclic carbamate **44**, exclusively.

Each isomer was then converted to the corresponding *Z* and *E* unsaturated esters **45a-d** using a Wittig or Horner-Emmons type olefination.<sup>30</sup> Upon osmium tetroxide oxidation of **45a-d**, each gave a 1/1 mixture of diols **46a-h**, a total of eight diastereomers. Thus, eight diastereomers with unambiguous stereochemistry were prepared. Spectroscopic comparisons of the triacetates **47a-h** prepared from **46** with the natural product **3b** indicated that (*2S,3R,5R,6S*)-**47** derived from **45d** was identical with the natural triacetate in all respects except the sign of its optical rotation. Thus, the absolute structure of Gln was confirmed to be (*2R,3S,5S,6R*)-**3b**. Finally, the synthesis of the natural form **3b** was accomplished in a straightforward manner starting from D-lysine ( $43 \rightarrow 44 \rightarrow 45d \rightarrow 3b$ ) (Scheme VIII).<sup>10</sup>

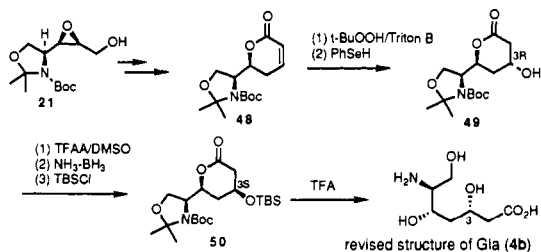
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### Scheme VIII Synthetic Structure Determination of Glm (3b)



### Scheme IX Synthesis of Revised Structure of Gla (4b)



Synthesis of the reported structure of galantin I (2) and comparison with the natural product showed that the two components were not identical. The structure of galantin I was then revised to 5 with the change of the structure of Gla to 4b from 4a.<sup>11a,c</sup>

The revised structure of Gla (4b) and its C3 epimer was synthesized, stereoselectively, starting from epoxide 21. The epoxide was converted to the unsaturated  $\delta$ -lactone 48, which upon epoxidation followed by reductive cleavage of the resulting epoxide<sup>31</sup> regio- and stereoselectively gave the alcohol 49. The desired 3*S* isomer 50 was obtained from 49 by an oxidation/reduction sequence.<sup>32,33</sup> Removal of the protecting groups with trifluoroacetic acid (TFA) afforded Gla (4b) (Scheme IX).

### Electrophilic Lactonization of 2-Amino-4-pentenoic Acid Derivatives

Halolactonization of 3-substituted 4-pentenoic acid derivatives has been shown to be an efficient entry for the stereoselective construction of either 3,4-syn or -anti stereochemistry.<sup>34</sup> However, 2-substituted 4-pentenoic acid derivative 51a produced a mixture of 2,4-disubstituted  $\gamma$ -butyrolactones 52 with poor stereoselectivity (cis/trans =  $\sim$ 3/2).<sup>35,36</sup> On the other hand, Witkop

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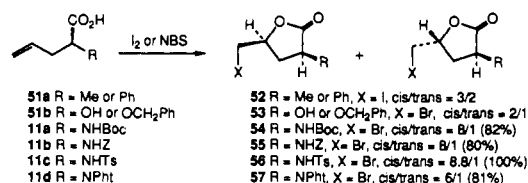
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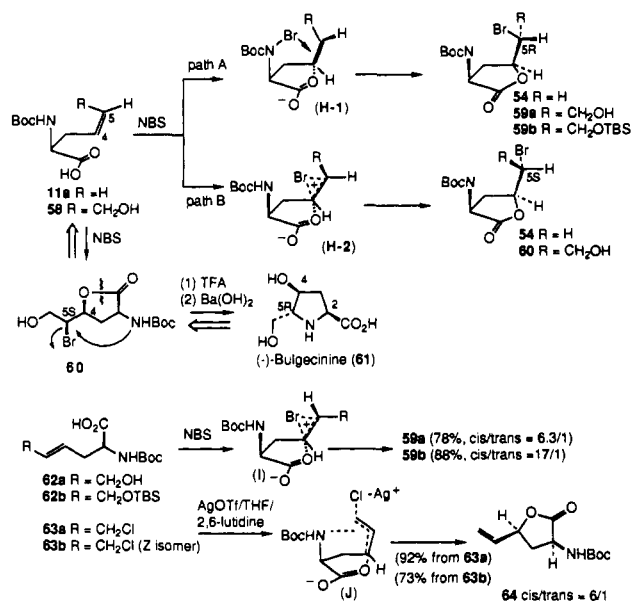
(35) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* 1978, 100, 3950.

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### Scheme X Halolactonization of 2-Substituted 4-Pentenoic Acids



### Scheme XI



et al. reported that 2-amino derivative 11b gives *cis*- $\gamma$ -butyrolactone 55 as the major isomer (cis/trans = 4.6/1).<sup>37</sup> Since this method appeared to be potentially useful for the synthesis of the *anti*-1,3-amino hydroxyl systems (method f, Figure 2), we reexamined the bromolactonization of 2-amino-4-pentenoic acids with *N*-bromosuccinimide (NBS) in order to optimize the reaction conditions with respect to improving both the yield and stereoselectivity. The use of anhydrous tetrahydrofuran (THF) as the solvent afforded satisfactory results (cis/trans =  $>$ 8/1,  $>$ 80%). The product ratio was independent of the nature of the *N* protecting group (Scheme X).<sup>6a,38,39</sup>

It has been proposed that the reaction proceeds through an initial bromination of the amino group and a subsequent internal bromonium ion transfer to the C-C double bond (Scheme XI, H-1 via path A) to give *cis*- $\gamma$ -butyrolactone as the major product.<sup>37</sup> However, despite the fact that the *N*-phthaloyl group of 11d cannot be brominated, the *cis* selectivity remains unchanged (cis/trans = 6/1). This fact led to an alternative mechanism (path B) in which the C2 amino group would stabilize, stereoelectronically, the putative halonium species of the *cis* transition state (H-2).

In order to determine the favored pathway, the halolactonization of 5-substituted (*Z*)-allylglycine 58 was examined: the reaction of 58 would produce the  $\gamma$ -butyrolactone (5*R*)-59a via H-1 (path A) or (5*S*)-60 via H-2 (path B). Determination of the stereochemistry of the resulting lactone should give an answer.

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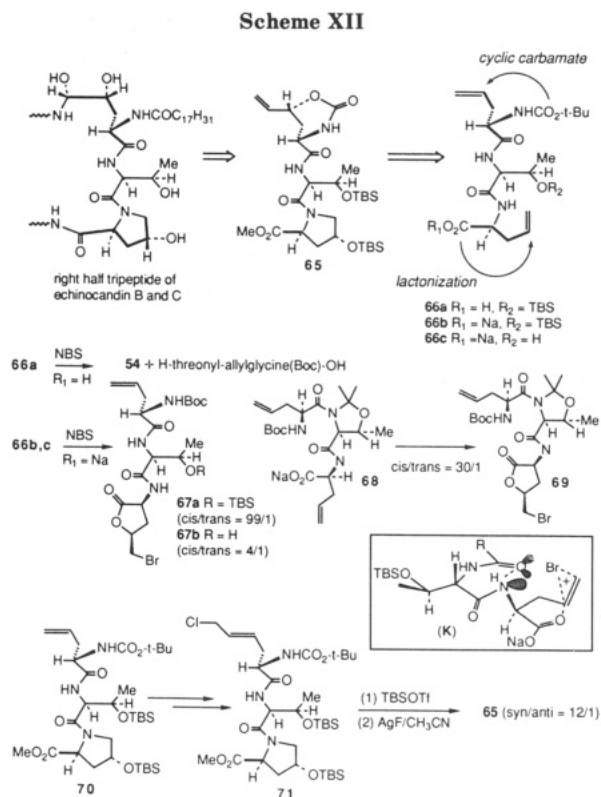
Treatment of the (*Z*)-allyl alcohol **58** with NBS in THF gave a mixture of *cis*-2,4-disubstituted  $\gamma$ -butyrolactone (either **59a** or **60**) and its *trans* isomer (*cis/trans* = 8.8/1, 95%). The structure of the major isomer was determined by its conversion to the amino acid bulgecinine (**61**), a constituent amino acid of the glycopeptide bulgecin. Thus, the structure of the lactone obtained from **58** was shown to be **60**. It was concluded that the bromolactonization of 2-amino-4-pentenoic acid derivatives proceeded via **H-2** (path B). This mechanism was further supported by the halolactonization of **62a** having a 5(*E*)-substituent. This yielded *cis*- $\gamma$ -lactone **59a** as the major product (*cis/trans* = 6.3/1), which indicated that the reaction proceeded through intermediate **I**. Protected alcohol **62b** showed greater *cis* selectivity to afford **59b** (*cis/trans* = 17/1).<sup>39</sup>

In addition to a bromonium cation, an allyl cation could also be stabilized by the C2 amino group. Treatment of either the (*E*)- or (*Z*)-allyl chlorides **63a,b** with silver trifluoromethanesulfonate (AgOTf) gave the same *cis*-4-vinyl  $\gamma$ -butyrolactone **64** as the major product (*cis/trans* = 6/1). The mechanism of this transformation appears to involve intermediate **J**.<sup>39</sup> Thus, halolactonization of 2-amino-4-pentenoic acid derivatives proved to be useful for the synthesis of the chiral lactones which are equivalent to the *anti*-1,3-amino hydroxyl systems.

### Stereoselective Conversion of a Simple Tripeptide to the Echinocandin Right Half Equivalent

Diastereoselective synthesis of the constituent amino acids of echinocandins (**1**) followed by the coupling of these constituents has led to the successful total synthesis of echinocandin D (**1c**).<sup>6</sup> In conjunction with this study, we also examined the synthesis of the right half equivalent (tripeptide **65**) from a simplified tripeptide **66**. Our idea was to examine the applicability of methods e and f (Figure 2) in the peptide system. Moreover, it was expected that this novel strategy might provide information concerning chemo- and stereoselectivity induced by the peptide functionality and/or peptide conformation.<sup>42</sup> The key transformation was a stereoselective introduction of the requisite  $\gamma$ -hydroxyl group into both the N- and the C-termini of allylglycyl moieties.

Halolactonization of **66** was highly dependent on the reactivity of the COOH vs CONH group. Using the free carboxyl compound **66a**, peptide bond cleavage occurred at the N-terminal of threonine to give *cis*- $\gamma$ -butyrolactone **54** and H-threonyl-*N*-Boc-allylglycine-OH. On the other hand, the sodium salt **66b**, which is more nucleophilic than the free carboxyl, provided the desired *cis*- $\gamma$ -butyrolactone **67a**, exclusively. The *cis* selectivity (>99/1) was much greater than that of *N*-Boc-allylglycine **11** (*cis/trans* = 8/1). On the other hand, unprotected **66c** showed a decrease in *cis* selectivity (*cis/trans* = 4/1). In order to examine the stereochemical outcome of this transformation, we exam-



ined halolactonization of the structurally rigid analogue **68** in which the *N,O*-acetonide constrained the structure to be U-shaped ( $\gamma$ -turn conformation).<sup>43</sup> The reaction provided *cis*-lactone **69** as the major product (*cis/trans* = 30/1). These results suggested that the bulky silyloxy group of **66b** constrained the conformation to be U-shaped (Scheme XII, **K**), where the bromonium cation was stabilized by a cooperative stereoelectronic effect of the neighboring amide and carbonyl groups. Unprotected **66c** might have a linear conformation which results in a decrease of *cis* selectivity. The desired **67a** was then converted to the protected tripeptide **70**.

Although the silyl carbamate method e (Figure 2) was shown to give poor 1,3-*syn* selectivity (**10**, *syn/anti* = ~1/1, Scheme VII), this method (e) was applied to introduce a hydroxyl group into the allyl chloride **71** prepared from **70**. Surprisingly, successive treatment of **71** with TBSOTf and AgF gave the desired *syn* cyclic carbamate **65** as the major product (*cis/trans* = 12/1). The AgF/Pd(II) system was not effective in this case. Both participation from the proximal functional groups and steric effects derived from the peptide conformation at the reaction site may have contributed to the high stereoselectivity observed. Thus, the conversion of a simple tripeptide **66** into the right half equivalent of echinocandins **65** was accomplished.<sup>44</sup>

### Conclusions

The basic stereochemical consequences of hydroxylation of allyl- or homoallylamines which lead to the *syn* and/or *anti* 1,2- and 1,3-amino hydroxyl systems have been described. The synthetic methods developed in our group have also been used for the structure determination and synthesis of several unusual amino acids. In spite of these advances, more efficient methods are

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still required for the synthesis of such amino acids due to their important biological activities and medicinal interests.<sup>45</sup> Furthermore, it is suggested that a hydroxyl group placed on the backbone of an amino acid is an active site when bound to a receptor protein or a biomembrane. When such amino acids are incorporated into peptides, the hydroxyl group plays an essential role in constraining the peptide structure into a specific conformation through intramolecular or external hydrogen bonding.<sup>1a,b,25</sup> Recent interest in the family of

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unusual amino acids is focused not only on chemistry but also on the impacts on interdisciplinary scientific fields. These amino acids are expected to function as useful probes to investigate molecular mechanisms of a variety of biological functions.<sup>1,46</sup>

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## Prediction of High Concentration Band Profiles in Liquid Chromatography

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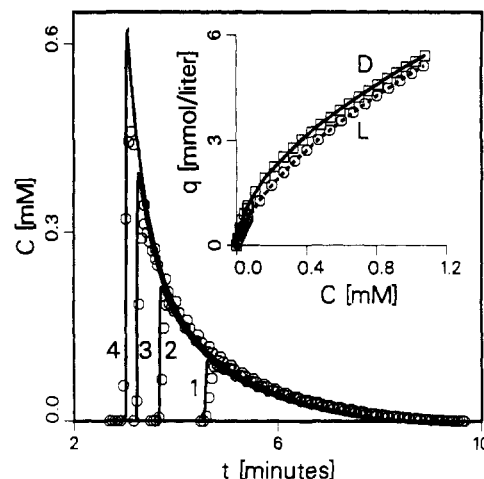
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### Introduction

When samples of increasingly large sizes of a pure component are injected in a chromatographic column, the elution profiles change progressively from a nearly Gaussian shape at very low sizes to an increasingly wide, highly unsymmetrical outline, usually characterized by an extremely steep front and a continuous rear boundary (Figure 1). More complicated profiles are also possible (Figure 2a). For mixtures, increasing the sample size leads to higher degrees of interference between the component bands. The decrease in band resolution is accompanied by increasing band interactions, and the profile of a band is modified by the presence of other components. Thus, the elution profile of a component in a mixture becomes different from the profile obtained for the same amount of the same compound injected alone (Figure 3). It is the essential purpose of this Account to show how these phenomena can be accounted for, both qualitatively and quantitatively.

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**Figure 1.** Comparison of experimental and calculated single-component overloaded elution profiles of *N*-benzoyl-L-alanine, using a bilangmuir isotherm model. Effect of sample size:<sup>11</sup> (1) 0.145, (2) 0.290, (3) 0.434, and (4) 0.580  $\mu\text{mol}$ . Experimental conditions:  $L = 15$  cm, i.d. = 0.4 cm; immobilized BSA on silica; mobile phase, 10 mM phosphate buffer at pH 6.8 with 3% 1-propanol, 1 mL/min. Insert: Experimental adsorption isotherm data (symbols) and best fit with the bilangmuir model (lines) for the D isomer ( $\square$ , —) and the L isomer ( $\circ$ , ---).

Their most common interpretation is that, because the band width increases, the column loses its efficiency when the sample size is increased. Under various forms,

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