Stereoselective Routes toward the Synthesis of Unusual Amino Acids

YASUFUMI OHFUNE

Suntory Institute for Bioorganic Research, Shimamoto-cho, Osaka 618, Japan

Received January 22, 1992

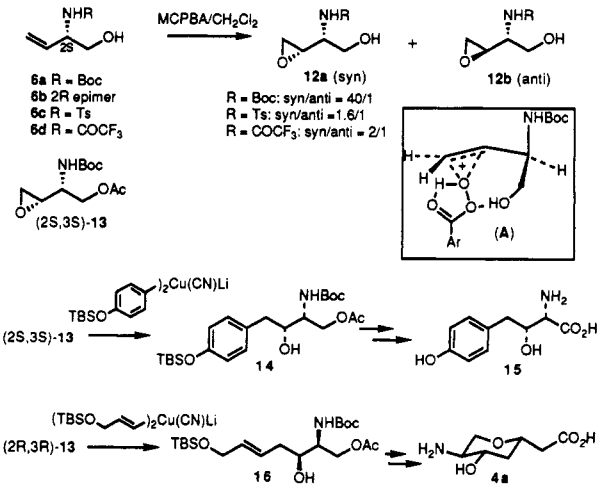
More than 700 amino acids that are the so-called unusual, unnatural, or nonproteinous amino acids have been found in nature in the free zwitterionic form or as constituents of peptides. These amino acids have attracted much attention from scientists due to their important biological activities as antibiotics,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

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**)[5,6] and galantin I (**2**: the structure has been revised to **5** as a result of our synthesis),[7-11] which have a variety of new amino acids. Echinocandins, isolated from *Aspergillus ruglosus* or *nidulans*, exhibit potent antifungal and anti-yeast activities.[5] 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.[7] 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).[11]

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.[3,12] 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 α-amino acids. These unsaturated amines can be viewed as

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-

Yasufumi Ohfune was born in Asahikawa, Japan, in 1948. He received his B.Sc. Degree from Hokkaido University in 1971 and his Dr.Sc. degree from the same university in 1976, where he worked with Professor Takeshi Matsumoto. After a postdoctoral position with Professor Paul A. Grieco at the University of Pittsburgh, he was appointed to the position of Researcher at the Suntory Institute for Bioorganic Research in 1979 and is currently Chief Researcher. His research interests include the development of new synthetic methods for bioactive amino acids and peptides, biomimetic reactions, and studies on excitatory amino acid receptors in mammalian CNS.

(1) (a) *Amino acids, Peptides and Proteins*; The Chemical Society: Cambridge, 1968-1991; Vols. 1-22. (b) Hunt, S. *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p 55. (c) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.

(2) Coppola, G. M.; Shuster, H. F. *Asymmetric Synthesis, Construction of Chiral Molecules Using Amino Acids*; John Wiley & Sons: New York, 1987; pp 127, 204, and 267.

(3) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: London, 1989; pp 1, 167, 186, 208, and 304.

(4) *α-Amino Acid Synthesis*; Tetrahedron Symposium-in-Print; O'Donnell, M. J., Ed. *Tetrahedron* **1988**, *44*, 5253.

(5) (a) Benz, F.; Knüsel, F.; Nuesch, J.; Treichler, H.; Voser, W.; Nyfeler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 2459. (b) Keller-Juslen, C.; Kuhn, M.; Loosli, H.-R.; Petcher, T. J.; Weber, H. P.; von Wartburg, A. *Tetrahedron Lett.* **1976**, 4147.

(6) (a) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6041. (b) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6043. (b) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151.

(7) Shoji, J.; Sakazaki, R.; Wakisaka, Y.; Koizumi, K.; Mayama, M.; Matsuura, S. *J. Antibiot.* **1975**, *28*, 122.

(8) (a) Ando, T.; Terashima, S.,; Kawata, M.; Teshima, T.; Wakamiya, T.; Shiba, T. *Peptide Chemistry 1980*; Okawa, K., Ed.; Protein Research Foundation: Osaka, Japan, 1981; p 113. (b) Wakamiya, T.; Ando, T.; Teshima, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 142. (c) Wakamiya, T.; Terashima, S.; Kawata, M.; Teshima, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1422.

(9) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587.

(10) Hori, K.; Ohfune, Y. *J. Org. Chem.* **1988**, *53*, 3886.

(11) (a) Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 3183. (b) Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1991**, *32*, 4151. (c) Sakai, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1992**, *114*, 998.

(12) Zurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. Other references are cited therein.

0001-4842/92/0125-0360$03.00/0

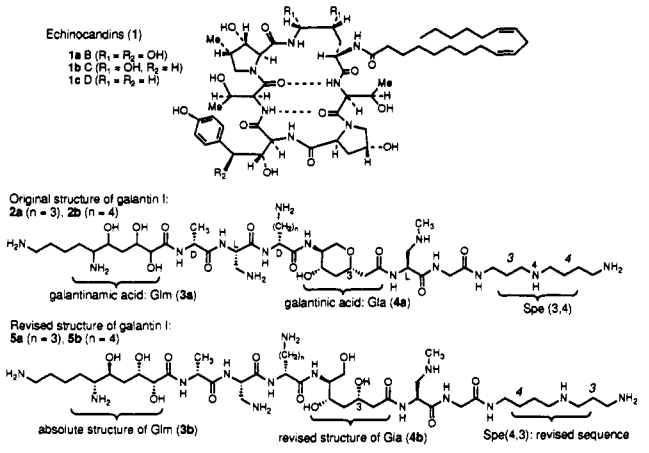


Figure 1.

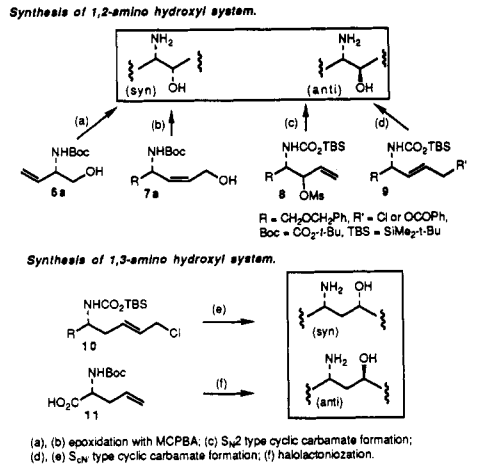


Figure 2.

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

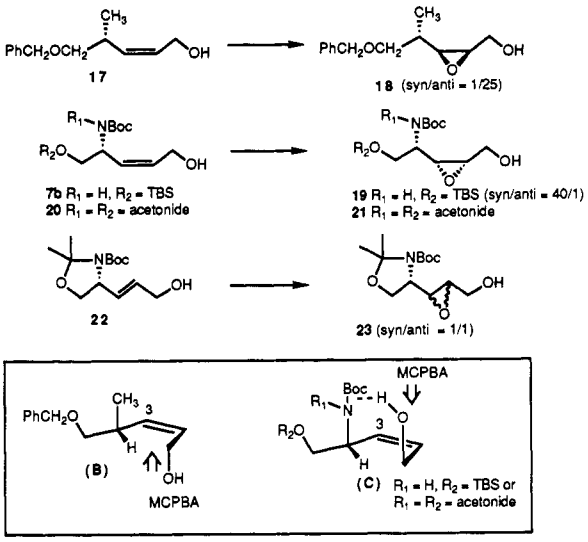
Epoxidation of 2-Amino-3-butenol Derivatives

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.[13] 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).[14,15] 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 β-hydroxy α-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 β-hydroxyhomotyrosine **15**[6a] and anhydro Gla **4a**,[9,16]

(13) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1071.
(14) (a) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2333. (b) Narula, A. S. *Tetrahedron Lett.* **1981**, *22*, 2017.
(15) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

Scheme II
Epoxidation of Hydroxymethyl Allylamines



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

Epoxidation of Hydroxymethyl (*Z*)-Allylamines

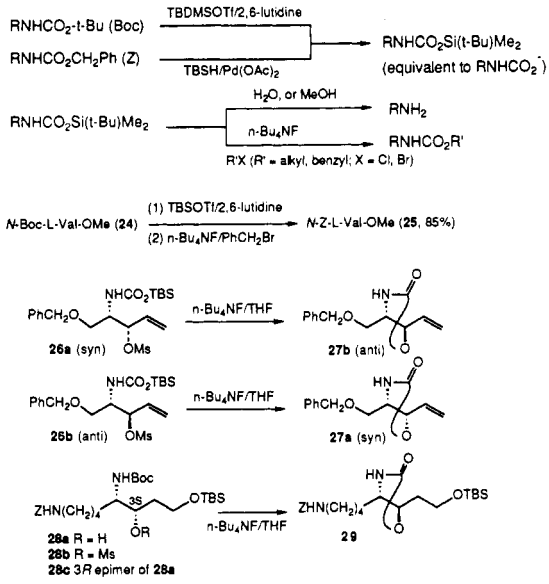
Epoxidation of the allyl alcohol **17**, which has a methyl group at C4, has been shown to give *anti*-epoxide **18** with high stereoselectivity (syn/anti = 1/25).[17] The mechanism involves less hindered side attack (*re* face on C3) of an internal chelate complex of MCPBA on the C–C double bond (Scheme II, **B**). Contrary to this, epoxidation of the hydroxymethyl (*Z*)-allylamine **7b** yielded *syn*-epoxide **19a** (syn/anti = 40/1), stereoselectively.[10,18] 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**.[11c] Thus, epoxidation of hydroxymethyl (*Z*)-allylamine proved to be a potential method for the preparation of *syn*-1,2-amino alcohols.

S_N2 Type Cyclic Carbamate Formation from *tert*-Butyldimethylsilyl Carbamate

N-*tert*-Butoxycarbonyl (Boc) and *N*-benzyloxycarbonyl (Z) groups are the most common amino protecting groups used for the synthesis of amino acids, amino sugars, and peptides.[19] 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.
(17) Nagaoka, N.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
(18) Kogen, H.; Nishi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 311.
(19) (a) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: Berlin, 1984; pp 7 and 151. (b) Greene, Y. W. *Protective Group in Organic Synthesis*; Wiley: New York, 1982; pp 232 and 239.

Scheme III



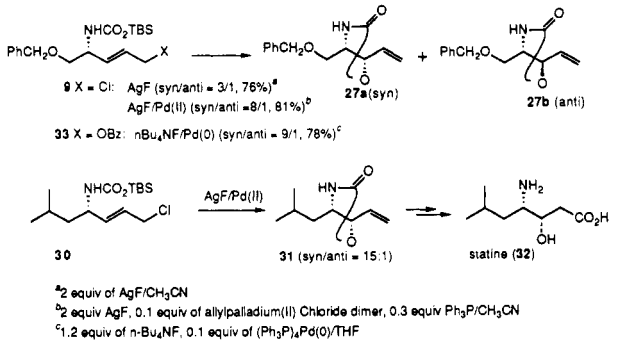
carbonyl group[20] by treatment of the *N*-Boc derivative with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine and the *N*-Z compound with *tert*-butyldimethylsilane (TBSH) in the presence of a catalytic amount of $Pd(OAc)_2$, respectively.[21] The silyl carbamate 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.[21]

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_4NF gave the cyclic carbamate **27b** having an *anti*-amino hydroxyl system. The *anti*-mesylate **26b** gave the *syn*-carbamte **27a**. This method proves to be useful when the Mitsunobu reaction is not effective.[22] 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).[10,23]

$S_{cN'}$ 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 $S_{cN'}$ manner[24] 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 $S_{cN'}$ 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 pepstatine, which is a well-known potent renin inhibitor.[23,25]

Scheme IV
$S_{cN'}$ Cyclic Carbamate Formation



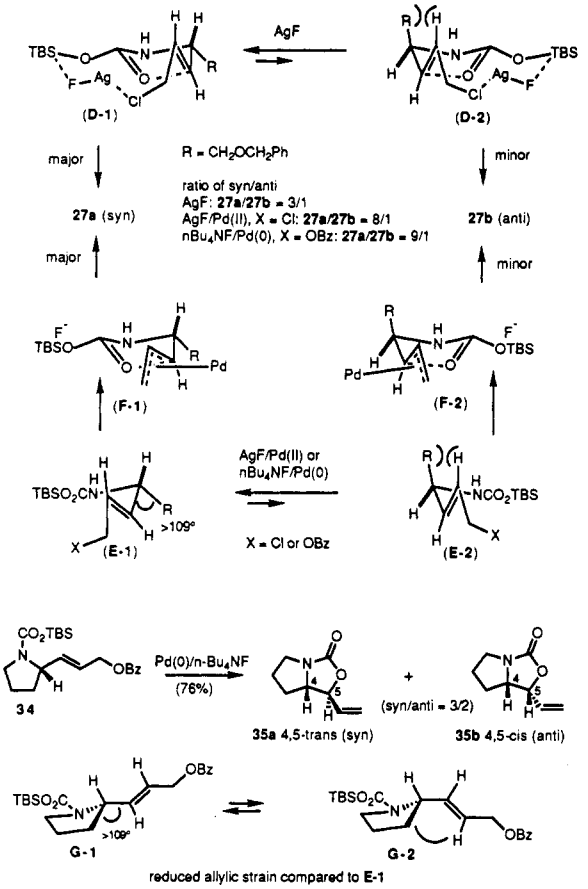
[a] 2 equiv of AgF/CH_3CN
[b] 2 equiv AgF, 0.1 equiv of allylpalladium(II) Chloride dimer, 0.3 equiv Ph_3P/CH_3CN
[c] 1.2 equiv of n-Bu_4NF, 0.1 equiv of $(Ph_3P)_4Pd(0)$/THF

Allyl esters are more attractive than allylic clorides as internal electrophiles in view of their ease of preparation and stability.[26] 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_4NF 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[27] 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_4NF/Pd(0), the major isomer **27a** could be derived via (π-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).[28] 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_2 group in a five-membered ring (**G-1** and **G-2**) when compared to the freely rotating CH_2R of **33**

(20) Breederveld, H. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 276.
(21) (a) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543. (b) Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 2983. (c) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.
(22) Mitsunobu, O. *Synthesis* **1981**, 1.
(23) (a) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150. (b) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1987**, *28*, 3987.
(24) Stork, G.; Schoofs, A. R. *J. Am. Chem. Soc.* **1979**, *101*, 5081.
(25) (a) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, H.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 2569. (b) Rich, D. H. *Proteinase Inhibitors*; Barrett, A. J.; Salvensen, G., Eds.; Elsevier: New York, 1986; p 179. (c) Omura, S.; Inamura, N.; Kawakita, K.; Mori, Y.; Yamazaki, Y.; Masuma, R.; Takahashi, Y.; Tanaka, H.; Huang, L.-Y.; Woodruff, H. B. *J. Antibiot.* **1986**, *39*, 1079.
(26) (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (b) Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Sir, Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; p 799.
(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 $S_{cN'}$ Cyclic Carbamate Formation



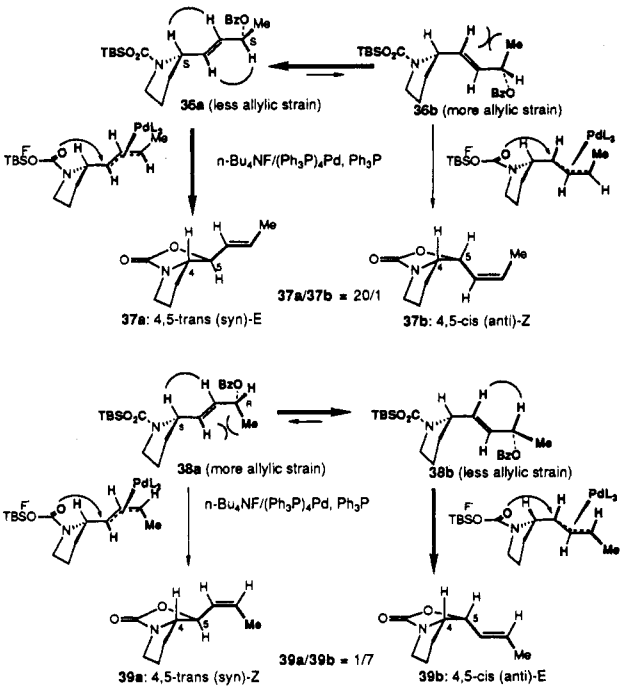
(the structure is shown in Scheme IV).[29]

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 stereoselectivty (**37a/37b** = 20/1), while (*S,R*)-**38** gave the 4,5-cis (*E*) adduct (anti) **39b** as the major product (**39b/39b** = 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 (π-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).[29]

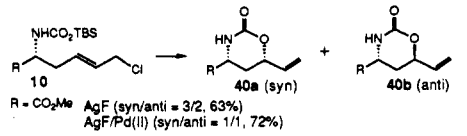
The present method was also employed for the synthesis of a 1,3-amino hydroxyl system (method e, Figure 2). The chloromethyl homoallylamine **10** produced a mixture of six-membered cyclic carbamates **40a,b**. The syn/anti ratio was ~1/1. However, greater syn selectivity was observed when the reaction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

(29) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 5339.

Scheme VI
Cyclic Carbamate Formation from Secondary Allyl Esters



Scheme VII
Six-Membered-Ring Cyclic Carbamate Formation



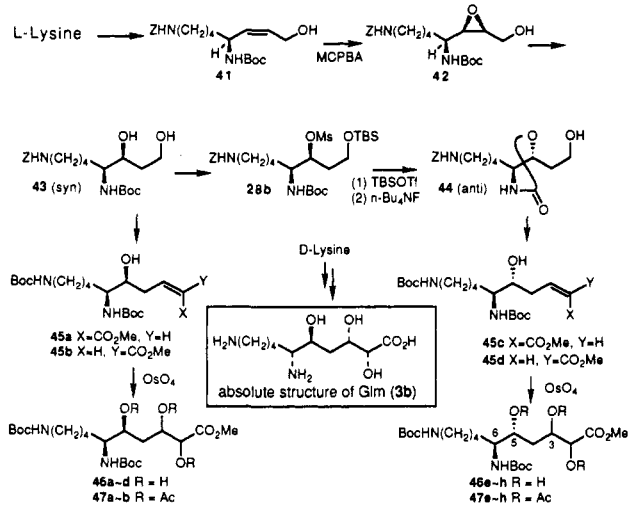
Syntheses of Glm (3b) and Gla (4b)

Before this work, only the primary structure of Glm (**3a**) was reported.[8] 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 $LiAlH_4$ 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.

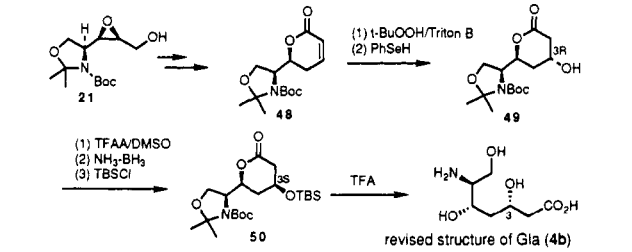
Each isomer was then converted to the corresponding *Z* and *E* unsaturated esters **45a–d** using a Wittig or Horner–Emmons type olefination.[30] Upon osmium tetraoxide oxidation of **45a–d**, each gave a 1/1 mixture of diols **46a–h**, a total of eight diastereomers. Thus, eight diastereomers with unambiguous stereochemistry were prepared. Spectroscopic comparisons of the triacetates **47a–h** prepared from **46** with the natural product **3b** indicated that (2*S*,3*R*,5*R*,6*S*)-**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 Glm was confirmed to be (2*R*,3*S*,5*S*,6*R*)-**3b**. Finally, the synthesis of the natural form **3b** was accomplished in a straightforward manner starting from D-lysine (**43** → **44** → **45d** → **3b**) (Scheme VIII).[10]

(30) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

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**.[11a,c]

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

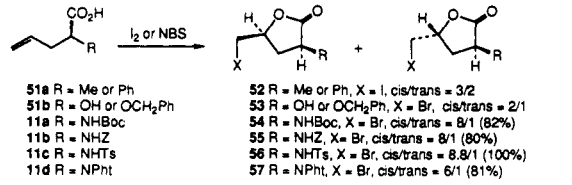
Electrophilic Lactonization of 2-Amino-4-pentenoic Acid Derivatives

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.[34] However, 2-substituted 4-pentenoic acid derivative **51a** produced a mixture of 2,4-disubstituted γ-butyrolactones **52** with poor stereoselectivity (cis/trans = ~3/2).[35,36] On the other hand, Witkop et al. reported that 2-amino derivative **11b** gives *cis*-γ-butyrolactone **55** as the major isomer (cis/trans = 4.6/1).[37] 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).[6a,38,39]

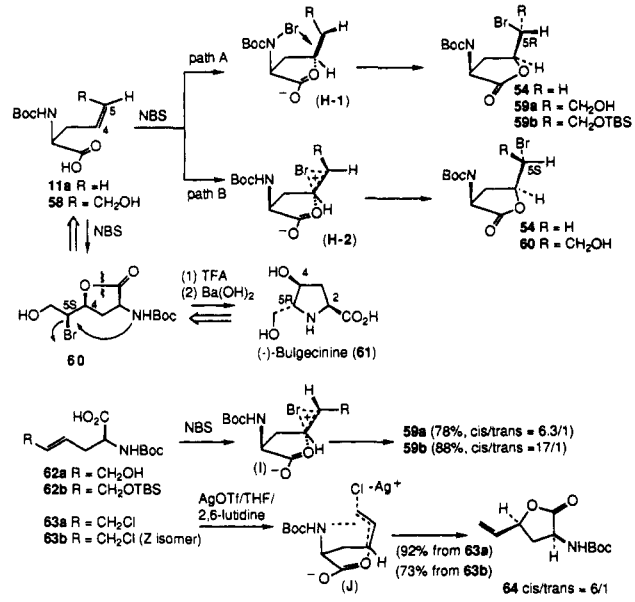
It has been proposed that the reaction proceeds through an initial bromination of the amino group and a subsequent internal bromonium ion transfer to the C–C double bond (Scheme XI, **H-1** via path A) to give *cis*-γ-butyrolactone as the major product.[37] However, despite the fact that the *N*-phthaloyl 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 γ-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.

Scheme X
Halolactonization of 2-Substituted 4-Pentenoic Acids



Scheme XI



(31) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1987**, *28*, 4293.
(32) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Smith, A. B., III; Levenberg, P. A. *Synthesis* **1981**, 567.
(33) Hausler, J. *Liebigs. Ann. Chem.* **1983**, 982.
(34) (a) Dowle, M. D.; Davis, D. I. *Chem. Soc. Rev.* **1979**, 171. (b) Bartlett, P. A.; Richardson, D. R.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317. (c) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819.
(35) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950.
(36) Ohfune, Y.; Kurokawa, N. Unpublished results.
(37) Izumiya, N.; Witkop, B. *J. Am. Chem. Soc.* **1963**, *85*, 1835.
(38) Ohfune, Y.; Kurokawa, N. *J. Synth. Org. Chem., Jpn.* **1986**, *44*, 647.
(39) Ohfune, Y.; Hori, K.; Sakaitani, M. *Tetrahedron Lett.* **1986**, *27*, 6079.

Treatment of the (*Z*)-allyl alcohol **58** with NBS in THF gave a mixture of cis 2,4-disubstituted γ-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 bulgecine.[39-41] 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*-γ-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).[39]

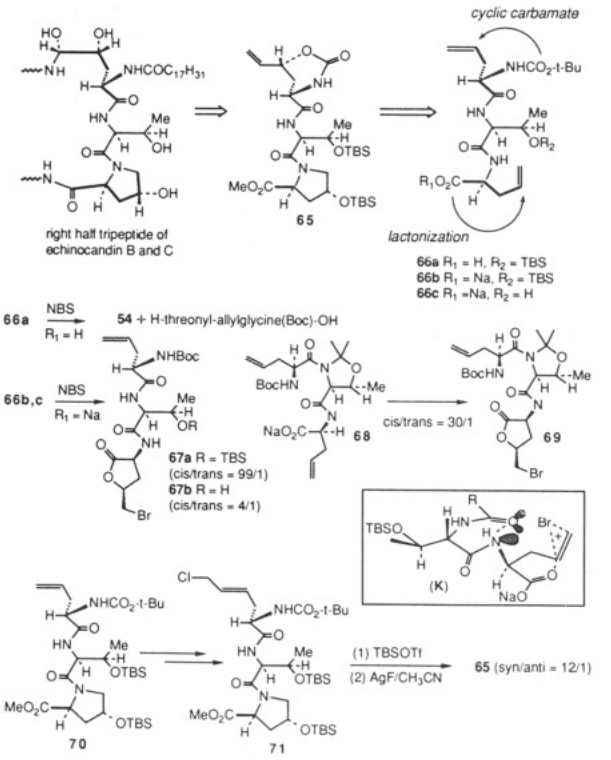
In addition to a bromonium cation, an allyl cation could also be stabilized by the C2 amino group. Treatment of either the (*E*)- or (*Z*)-allyl chlorides **63a,b** with silver trifluoromethanesulfonate (AgOTf) gave the same *cis*-4-vinyl γ-butyrolactone **64** as the major product (cis/trans = 6/1). The mechanism of this transformation appears to involve intermediate **J**.[39] 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**).[6] 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.[42] The key transformation was a stereoselective introduction of the requisite γ-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*-γ-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*-γ-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 examined halolactonization of the structurally rigid analogue **68** in which the *N,O*-acetonide constrained the structure to be U-shaped (γ-turn conformation).[43] 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**.

Scheme XII



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.[44]

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

(40) Imada, A.; Kintaka, K.; Nakao, M.; Shinagawa, S. *J. Antibiot.* **1982**, *35*, 1400.
(41) (a) Wakamiya, T.; Yamanoi, K.; Nishikawa, M.; Shiba, T. *Tetrahedron Lett.* **1985**, *26*, 4759. (b) Bashyal, B. P.; Cho, H.-F.; Fleet, G. W. J. *Tetrahedron Lett.* **1986**, *27*, 3205.
(42) (a) Izumiya, N.; Francis, J. E.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.* **1962**, *84*, 1702. (b) Wilchek, M.; Patchornik, A. *J. Am. Chem. Soc.* **1962**, *84*, 6079.
(43) Chon, P. Y.; Fasman, G. D. *J. Mol. Biol.* **1977**, *115*, 135.
(44) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1989**, *30*, 2251.

still required for the synthesis of such amino acids due to their important biological activities and medicinal interests.[45] 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.[1a,b,25] Recent interest in the family of 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.[1,46]

It is a pleasure to acknowledge the contribution of my colleagues: their names are recorded in the references. I am grateful to Professor Koji Nakanishi for his continuous encouragement. The financial support of a grant-in-aid from the Ministry of Education, Sciences, and Culture, Japan, is appreciated.

(45) (a) Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 5177. (b) Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 2983. (c) Spears, G. W.; Nakanishi, K.; Ohfune, Y. *Synlett* **1991**, 91.

(46) (a) Axelrod, J. *Science* **1971**, *173*, 598. (b) Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364. (c) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167.

Prediction of High Concentration Band Profiles in Liquid Chromatography

ANITA M. KATTI,† MOUSTAPHA DIACK, M. ZOUBAIR EL FALLAH,‡ SADRODDIN GOLSHAN-SHIRAZI, STEPHEN C. JACOBSON, ANDREAS SEIDEL-MORGENSTERN,§ and GEORGES GUIOCHON*

Department of Chemistry, The University of Tennessee, Knoxville, Tennessee 37996-1501, and Division of Analytical Chemistry, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37831-6120

Received January 21, 1992

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.

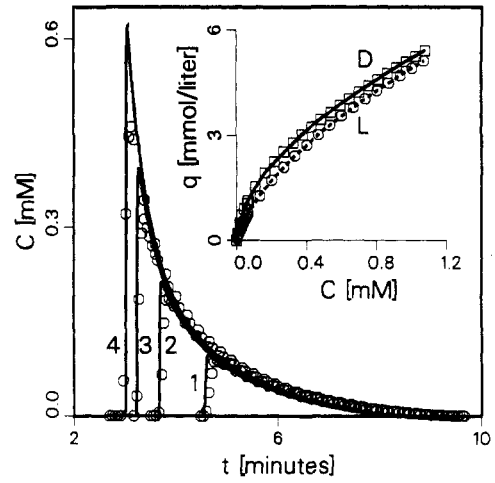


Figure 1. Comparison of experimental and calculated single-component overloaded elution profiles of *N*-benzoyl-L-alanine, using a bilangmuir isotherm model. Effect of sample size:[11] (1) 0.145, (2) 0.290, (3) 0.434, and (4) 0.580 μmol. Experimental conditions: L = 15 cm, i.d. = 0.4 cm; immobilized 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 (□, —) and the L isomer (○, - - -).

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,

Dr. A. M. Katti received a Ph.D. in chemical engineering from the University of Tennessee in 1990; she is a Senior Development Engineer with Mallinckrodt Specialty Chemicals (St. Louis, MO). Dr. Moustapha Diack received a Ph.D. in chemistry from the University of Metz (France) in 1990; he is a postdoctoral research associate at the University of Tennessee. Dr. M. Zoubair El Fallah received a Ph.D. in chemistry from the University of Paris (France) in 1989; after working as a postdoctoral research associate at the University of Tennessee, he is now with Millipore Waters Chromatography, Milford, MA. Dr. Sadroddin Golshan-Shirazi received a Ph.D. in chemistry from Georgetown University in 1988; he is a postdoctoral associate at the University of Tennessee. In May 1992, Mr. Stephen C. Jacobson defended for his Ph.D. in chemistry at the University of Tennessee. Dr. Andreas Seidel-Morgenstern, who received a Ph.D. in chemical engineering in 1990 from the University of Berlin (Germany), is on leave from the Technical University of Berlin (Germany). Dr. Georges Guiochon is a Distinguished Scientist at the University of Tennessee and Oak Ridge National Laboratory.

† Present address: Mallinckrodt Specialty Chemicals, St. Louis, MO.
‡ Present address: Millipore Waters Chromatography, Milford, MA.
§ On leave from the Institute of Technical Chemistry, Technical University of Berlin, Berlin, Germany.

0001-4842/92/0125-0366$03.00/0