Pergamon

Tetrahedron Vol. 51, No. 14, pp. 3939-3958, 1995

0040-4020/95 $29.00+0.00

0040-4020(94)01096-X

TETRAHEDRON REPORT NUMBER 369

Total Synthesis of Phytosiderophores

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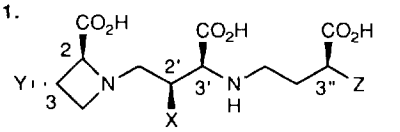
1. Introduction

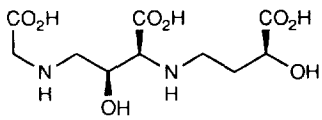
Iron is one of the essential elements for plant growth and maintenance. It is especially required in the chlorophyll biosynthesis, and the deficiency of iron causes iron chlorosis which turns young leaves to yellow or white. As a result, plants cease to grow and wither.

Uptake of iron from soil and its transport in plants are carried out by use of iron-chelators of amino acid types which are called "phytosiderophores." When higher plants are kept under iron-deficient conditions, they excrete phytosiderophores from their roots to solubilize and absorb iron(III) from soil.[1] The phytosiderophores so far known have been mainly isolated from higher plants such as barley, oats, and wheat. They are amino acid chelators containing α-hydroxy and α-amino carboxylate ligands, as shown in Fig. 1, and different from the siderophores of bacterial origin which have hydroxamate or phenolate ligands.

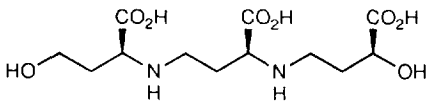
Fig. 1.



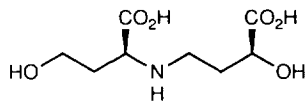
mugineic acid (**1**) : X = Z = OH, Y = H
3-epi-hydroxymugineic acid (**2**) : X = Y = Z = OH
2'-deoxymugineic acid (**3**) : X = Y = H, Z = OH
nicotianamine (**4**) : X = Y = H, Z = NH_2



distichonic acid A (**5**)

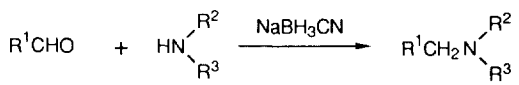


avenic acid A (**6**)



avenic acid B (**7**)

The importance of the phytosiderophores in plant physiology as well as their unique amino acid structures have led several groups to synthesize them.[2] In general, these phytosiderophores are composed of three parts, each of which is connected through the nitrogen atom. Thus, first of all, the three fragments should be synthesized and then the coupling of each fragment will follow to construct the whole molecule. The connection has been usually done by the reductive alkylation at the nitrogen atom using sodium cyanoborohydride,[3] shown in Scheme 1, after the pioneering works by Nozoe[4] and Ohfune.[5] Using this methodology, all of the phytosiderophores in Fig. 1 have been already synthesized and they are reviewed here.



Scheme 1

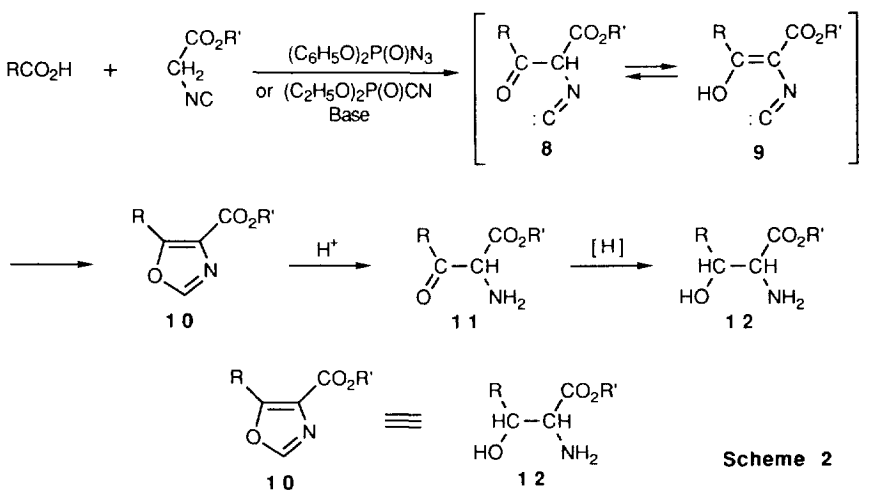
2. Mugineic Acid

Mugineic acid (**1**) is a typical phytosiderophore isolated from barley (*Hordeum vulgare* L. var. Minorimugi) by Takagi and co-workers.[2c,6] Its structure was unambiguously determined by an X-ray analysis.[6] Interestingly, it has been reported that mugineic acid exerts an inhibitory effect against angiotensin-converting enzyme.[7] We have achieved the synthesis of mugineic acid in several ways.[8-11]

2.1. The Oxazole Route

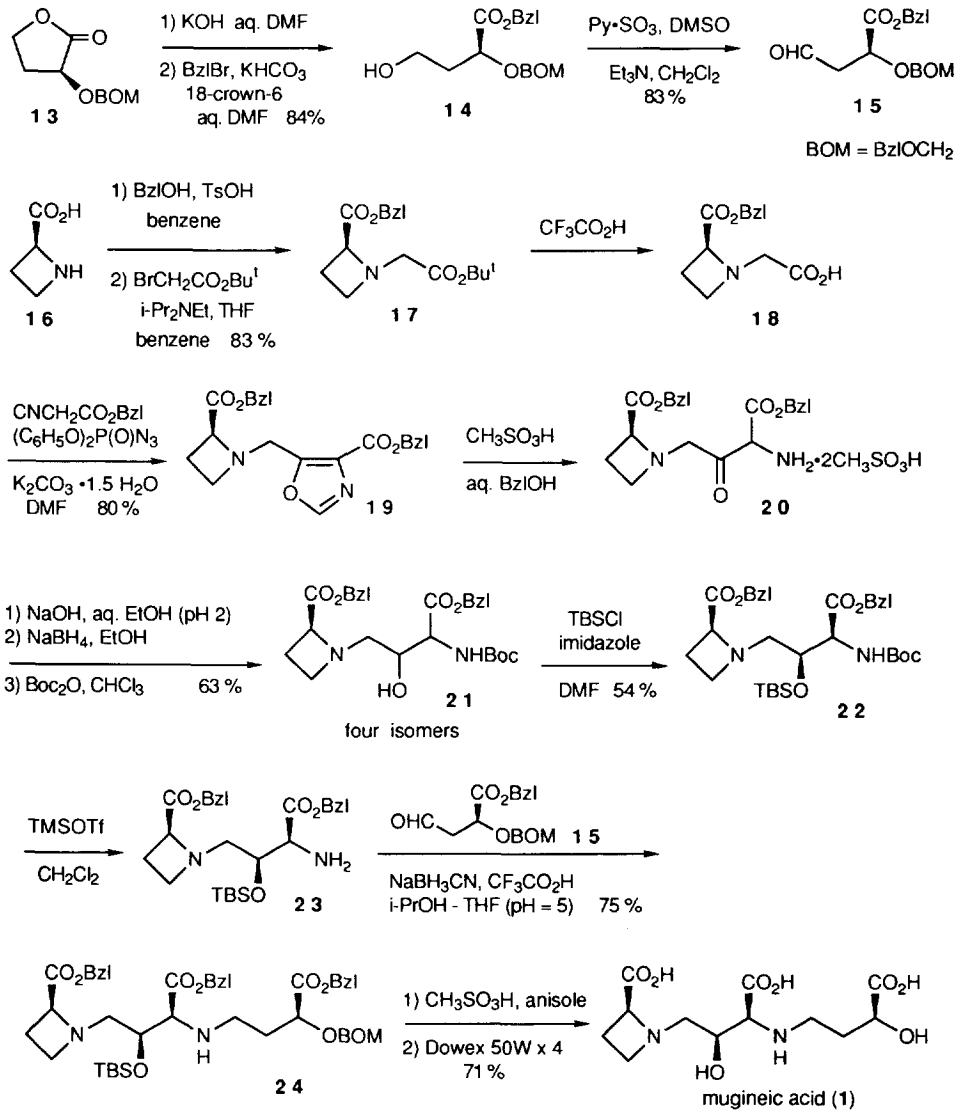
We have already developed the synthetic strategy to some of natural products utilizing 4-alkoxycarbonyl-5-substituted oxazoles as β-hydroxy-α-amino acid synthons.[12] As shown in Scheme 2, diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$)[13,14] and diethyl phosphorocyanidate (DEPC,

$(C_2H_5O)_2P(O)CN$),[14-16] in combination with base, can be used for the direct C-acylation[17] of isocyanoacetates with carboxylic acids, giving the oxazole derivatives **10** via the C-acylated products **8** then their enols **9**. When optically active carboxylic acids having the stereogenic center at the α-position are used, DPPA causes no or little, if any, racemization at the stereogenic center[18] while DEPC causes racemization to some extent.[19] Acidic treatment of the oxazoles **10** easily affords β-keto-α-amino acid derivatives **11**, which are readily reduced to give β-hydroxy-α-amino acid derivatives **12**. Thus, 4-alkoxycarbonyl-5-substituted oxazoles **10** are regarded as β-hydroxy-α-amino acid **12** synthons. Utilizing this methodology as a key step, we have succeeded in the synthesis of some natural products such as prumycin,[20] L-daunosamine,[21,22] L-vancosamine,[22,23] D-ristosamine,[22,24] the side chain part of AI-77-B,[22,25] and so on.[26] We applied this method to the synthesis of mugineic acid (**1**).[8]



The known [27] γ-lactone **13** obtained from L-malic acid in 4 steps was converted to the right-hand fragment **15** of **1** via **14** in 3 steps, as shown in Scheme 3. The synthetic route is essentially the same as the one employed for the synthesis of 2'-deoxymugineic acid (**3**).[5]

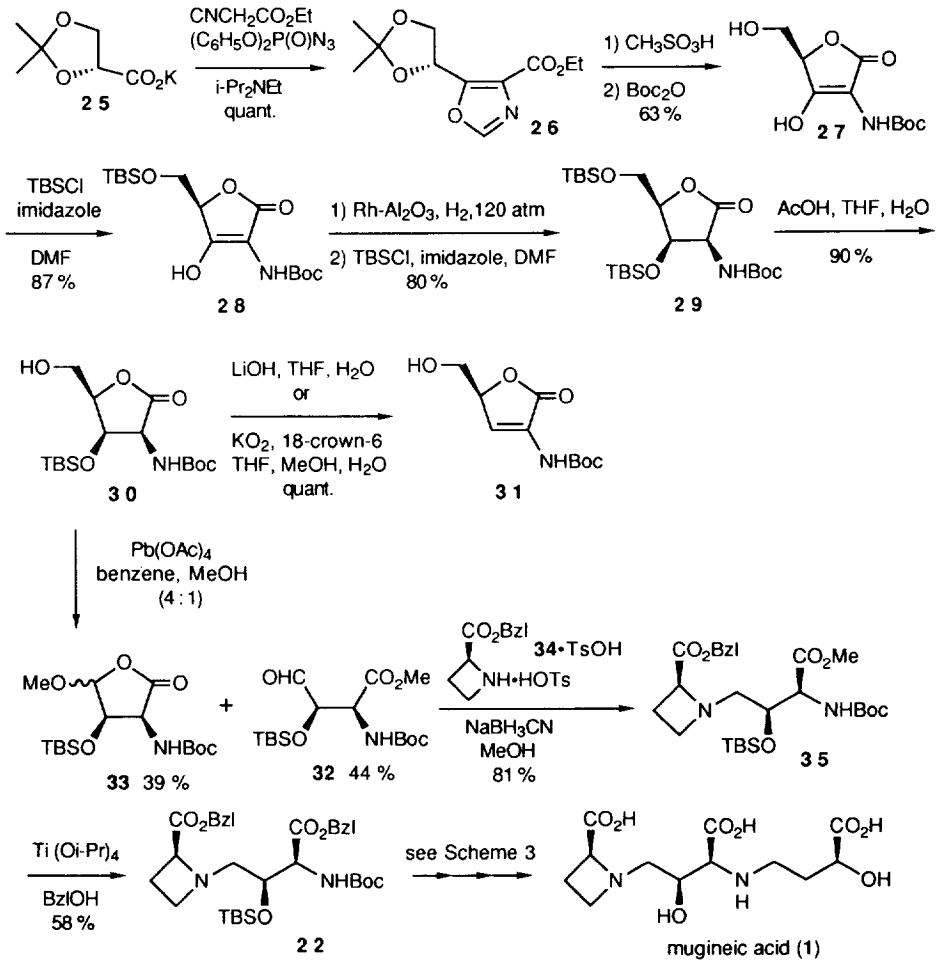
The synthesis of the left-hand fragment **23** started from (S)-azetidine-2-carboxylic acid (**16**), outlined in Scheme 3. The amino acid **18** obtained from **16** via **17** reacted with benzyl isocyanoacetate by use of DPPA in the presence of potassium carbonate sesquihydrate to give the oxazole **19**. Treatment of the oxazole **19** with methanesulfonic acid afforded the β-keto ester **20**, which was reduced with sodium borohydride. The products were separated as their tert-butoxycarbonyl (Boc) derivatives **21** to the pairs of erythro and threo isomers. The erythro isomers were further separated as their tert-butyldimethylsilyl (TBS) derivatives. Selective deprotection of the Boc group from the major isomer **22** with trimethylsilyl triflate (TMSOTf) afforded the left-hand fragment **23** of mugineic acid (**1**). Reductive alkylation of **23** with the right-hand fragment **15** by use of sodium cyanoborohydride afforded the fully protected mugineic acid **24**. Final deprotection was achieved with methanesulfonic acid to give mugineic acid (**1**). This synthesis of **1** requires 11 steps from **16** in an overall yield of 8.4%.[8] The efficiency in this synthesis is not necessarily unsatisfactory, but the separation of the four isomers is rather troublesome, and not suitable for large scale production. Thus, we explored another route to **1**.



Scheme 3

To construct the most complicated central part of **1**, we employed another oxazole route,[9] as shown in Scheme 4. The oxazole **26**, obtained by C-acylation of ethyl isocyanoacetate with the glyceric acid derivative **25** by use of DPPA, underwent acidic cleavage followed by Boc protection to give the aminotetronic acid derivative **27**.[22] After protection of its primary alcohol function with TBSCl, high pressure catalytic hydrogenation over rhodium-alumina, followed by treatment with TBSCl stereoselectively afforded the γ-lactone **29**. After removal of the TBS group at the primary alcoholic function, opening of the lactone ring of the alcohol **30** was attempted under alkaline conditions, resulting in the formation of the elimination product **31**. However, glycol cleavage with lead tetraacetate in the presence of methanol afforded a mixture of the

desired aldehyde **32** and the methyl ether **33**. The major product **32** was coupled with the azetidine ester **34** by use of sodium cyanoborohydride to give the methyl ester **35**, which underwent ester exchange by use of titanium tetraisopropoxide as catalyst[28] to give the desired left-half fragment **22**, which had already been converted to mugineic acid (**1**), as described above.[8]



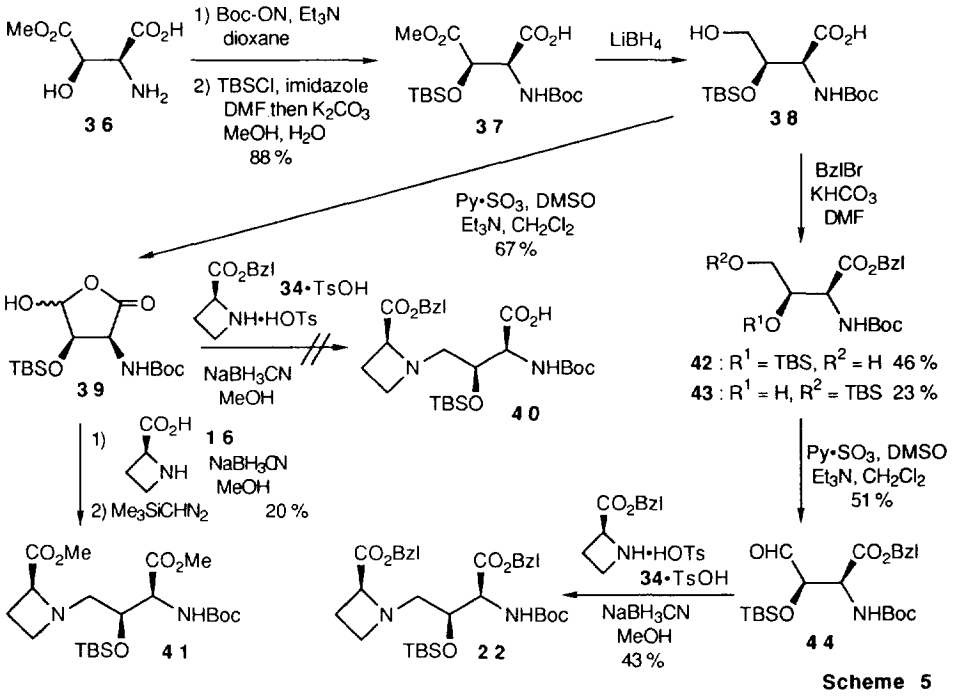
Scheme 4

Another synthesis[10] of the central part in mugineic acid (**1**) started from the known β-hydroxy aspartic acid derivative **36**,[29] as shown in Scheme 5. After protection of the amino and hydroxyl functions, the resultant half ester **37** was reduced with lithium borohydride to give the alcohol **38**. Parikh-Doering oxidation of the alcohol **38** afforded the 4-hydroxy-γ-butyrolactone **39**. Although reductive amination of **39** with the azetidine ester **34** failed to give **40**, use of (S)-azetidine-2-carboxylic acid (**16**) gave the left-hand fragment **41** after methyl esterification, though in poor yield.

Alternatively, benzyl esterification of **38** afforded the desired alcohol **42** together with the silyl-migrated

product **43**. Oxidation of **42** furnished the aldehyde **44**, which underwent reductive amination with the benzyl ester **34** to give the left-hand fragment **22**.

The latter two routes will be comparatively useful for large-scale production of mugineic acid (**1**) because of the ease of handling each synthetic reaction, though the overall yield should be improved.



Scheme 5

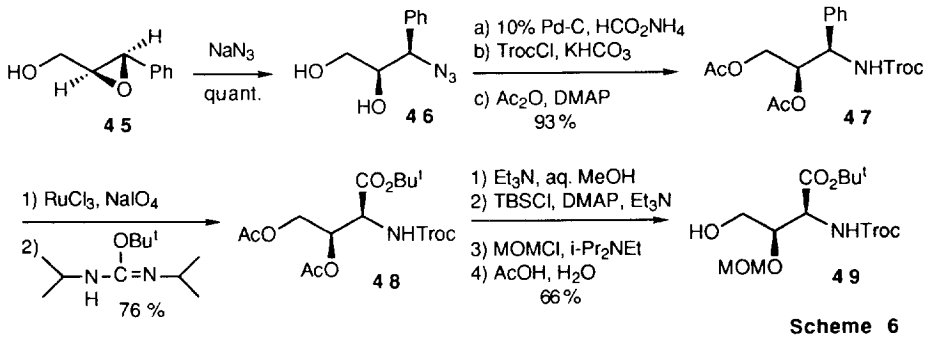
2.2. Use of the Phenyl Group as the Carboxyl Synthon

Reactivity and water solubility of carboxyl groups sometimes preclude the efficient and convenient synthesis of some natural products having carboxyl functions. Sharpless and co-workers[30] reported in 1981 that aromatic rings were smoothly degraded to carboxylic acids by a greatly improved procedure for ruthenium tetroxide (ruthenium trichloride-sodium metaperiodate) catalyzed oxidations. Since then, several synthetic studies[31] have adopted this procedure and employed aryl groups as a substitute for the carboxylic acid during the synthesis. We have also encountered some trouble using the carboxylates, as described above (e.g., formation of **31** from **30**). Thus, we decided to use aryl groups as the carboxyl synthon for the synthesis of mugineic acid.[11]

$$Ar \equiv CO_2H \qquad \left(Ar \xrightarrow{RuO_4} CO_2H \right)$$

Our synthesis of the central fragment **49** of mugineic acid started from (2S,3S)-2,3-epoxycinnamyl alcohol (**45**),[32] which was efficiently converted to the O,O'-diacetyl benzylamine derivative **47** via the azide **46**,[33] outlined in Scheme 6. Oxidation of the phenyl group with ruthenium trichloride-sodium metaperiodate followed by tert-butyl esterification afforded the amino acid derivative **48** in good yield. We have found that the protective groups of the hydroxyl functions in ruthenium tetroxide oxidation should be electron-

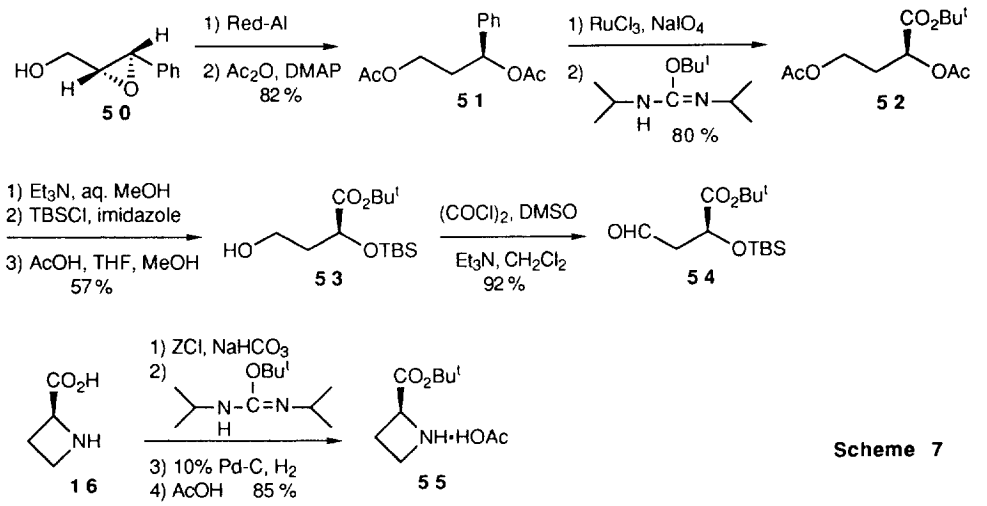
withdrawing, (e.g., acetyl) while use of an electron-donating protective group (e.g., tert-butyldimethylsilyl (TBS) or methoxymethyl (MOM)) resulted in low efficiency. Sequential deprotection and protection of the hydroxyl function in **48** produced the required central fragment **49** in 66% yield in 4 steps.



45 **46** **47** **48** **49**

Scheme 6

Preparation of the right and left fragments, **54** and **55**, is summarized in Scheme 7. Reductive ring opening[34] of (2R,3R)-2,3-epoxycinnamyl alcohol (**50**) followed by acetylation gave the diacetyl compound **51**. Transformation of the phenyl function to the carboxyl one was performed with ruthenium trichloride-sodium metaperiodate, and the resulting carboxylic acid was converted to the tert-butyl ester **52**. Hydrolysis and silylation followed by selective desilylation afforded the alcohol **53**, which underwent oxidation to give the required right fragment **54**. The remaining left fragment **55** was prepared from (S)-azetidinecarboxylic acid by the known procedure,[35] as shown in Scheme 7.

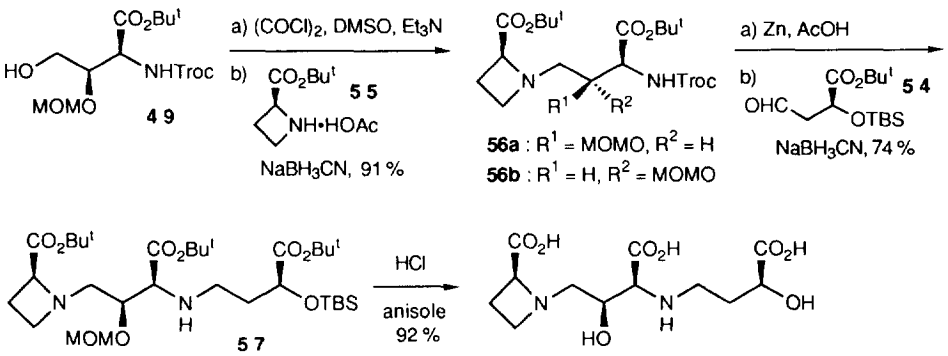


50 **51** **52** **53** **54** **16** **55**

Scheme 7

Assembling each fragment was accomplished through reductive alkylation by use of sodium cyanoborohydride, as outlined in Scheme 8. Conversion of the alcohol **49** to the aldehyde followed by reductive alkylation with **55** afforded a mixture of the key intermediate **56a** and its C-2' epimer **56b** in a ratio of 8:1. Epimerization has occurred during aldehyde formation as well as reductive alkylation. Deprotection of

the trichloroethoxycarbonyl (Troc) group from the epimeric mixture **56** and then reductive coupling with the aldehyde **54** produced the fully protected mugineic acid **57** after chromatographic separation. Removal of all of the protecting groups from **57** under acidic conditions yielded mugineic acid (**1**). This synthesis of **1** consists of 15 steps from readily available (2S,3S)-2,3-epoxycinnamyl alcohol (**45**) in an overall yield of 29%, which will be suitable for large scale production of **1**. In fact, we could prepare 10 grams of mugineic acid (**1**) according to this method, while less than 1 gram of **1** could be isolated from natural sources during a year.



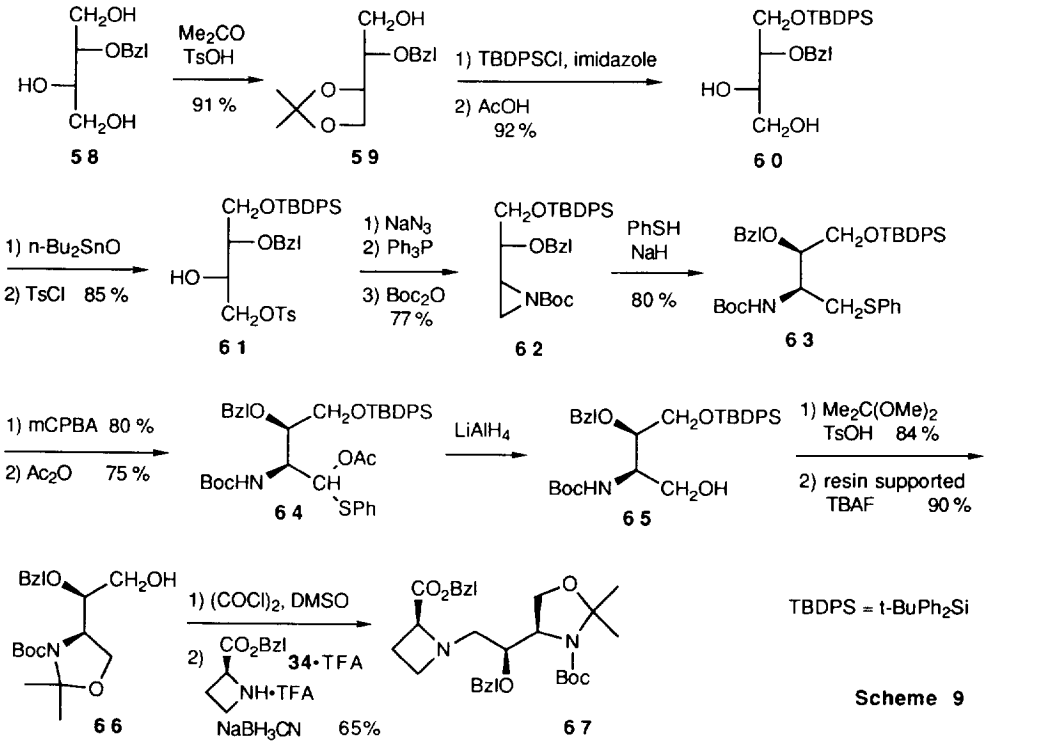
Scheme 8

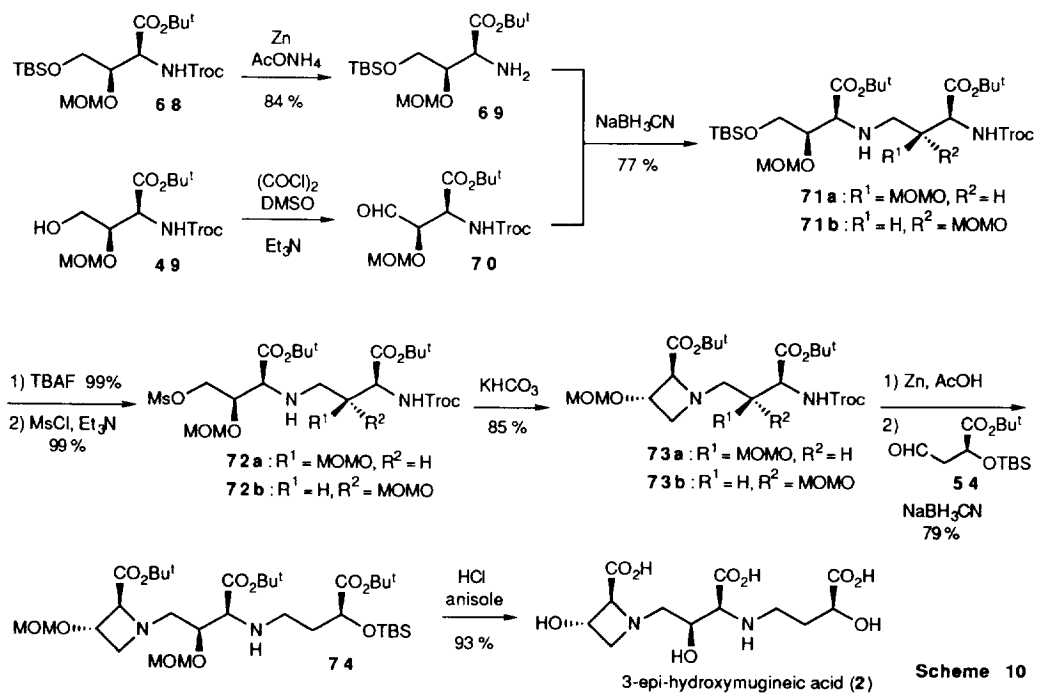
2.3. The Other Approach

The other approach to mugineic acid[36] involves nucleophilic phenylthiolate opening of a sugar derived chiral aziridine followed by Pummerer rearrangement, as outlined in Scheme 9. Although this approach has not been completed yet, it will be interesting since it has some generality for the synthesis of amino compounds. The starting 2-O-benzyl-L-threitol (**58**) was first converted to the acetonide **59**, which underwent silylation and then hydrolysis to give the diol **60**. Regioselective tosylation was achieved through stannylidene activation to give the tosylate **61**. Successive treatment of **61** with sodium azide, triphenylphosphine, and Boc_2O afforded the aziridine **62** in good yield. Phenylthiolate opening of the aziridine ring of **62** afforded the β-amino thioether **63**, which was converted to the acetoxy sulfide **64** through oxidation followed by Pummerer rearrangement. Mild reduction of **64** afforded the alcohol **65**, which underwent acetalization and then desilylation to give the α-amino alcohol **66**. Swern oxidation followed by reductive coupling with the TFA salt of benzyl (S)-2-azetidinecarboxylate (**34**) afforded the γ-azetidinyl-β-hydroxy-α-amino alcohol moiety **67** of mugineic acid.

3. 3-Epi-hydroxymugineic Acid

3-Epi-hydroxymugineic acid (**2**) has been isolated from beer barley (*Hordeum vulgare* L. var. distichum).[2,37] Since 3-epi-hydroxymugineic acid (**2**) has the same carbon skeleton as that of mugineic acid (**1**) except the azetidine moiety, the same starting materials can be used,[38] as shown in Scheme 10. Our synthesis of **2** started from the β-hydroxy homoserine derivative **49** and its TBS derivative **68**, the important intermediates for the synthesis of **1**. Removal of the Troc group from **68**, followed by reductive coupling of the resulting amine **69** with the aldehyde **70** derived from **49** afforded a diastereoisomeric mixture of **71a** and


Me2CO
TsOH
91 %
1) TBDPSCl, imidazole
2) AcOH
92 %
58
59
60
1) n-Bu2SnO
2) TsCl 85 %
1) NaN3
2) Ph3P
3) Boc2O
77 %
PhSH
NaH
80 %
61
62
63
1) mCPBA 80 %
2) Ac2O 75 %
LiAlH4
1) Me2C(OMe)2
TsOH 84 %
2) resin supported
TBAF 90 %
64
65
66
1) (COCl)2, DMSO
2) 34•TFA
NaBH3CN 65%
67
TBDPS = t-BuPh2Si
Scheme 9


Zn
AcONH4
84 %
68
69
NaBH3CN
77 %
71a : R1 = MOMO, R2 = H
71b : R1 = H, R2 = MOMO
(COCl)2
DMSO
Et3N
49
70
1) TBAF 99%
2) MsCl, Et3N
99 %
72a : R1 = MOMO, R2 = H
72b : R1 = H, R2 = MOMO
KHCO3
85 %
73a : R1 = MOMO, R2 = H
73b : R1 = H, R2 = MOMO
1) Zn, AcOH
2)
54
NaBH3CN
79%
74
HCl
anisole
93 %
3-epi-hydroxymugineic acid (2)
Scheme 10

71b in a ratio of 10 : 1. Transformation of the TBS group to the methanesulfonyl (Ms) one was smoothly performed in 2 steps to give the mesylate **72**, which underwent intramolecular cyclization under basic conditions[38,39] to give the azetidine carboxylic acid derivatives **73a** and **73b** (10:1). Deprotection of the Troc group, separation of the C-2' epimer, and then reductive N-alkylation with the aldehyde **54** afforded the protected 3-epi-hydroxymugineic acid **74**. Acidic removal of all of the protecting groups of **74** produced 3-epi-hydroxymugineic acid (**2**) in 47% overall yield in 8 steps from **49**.

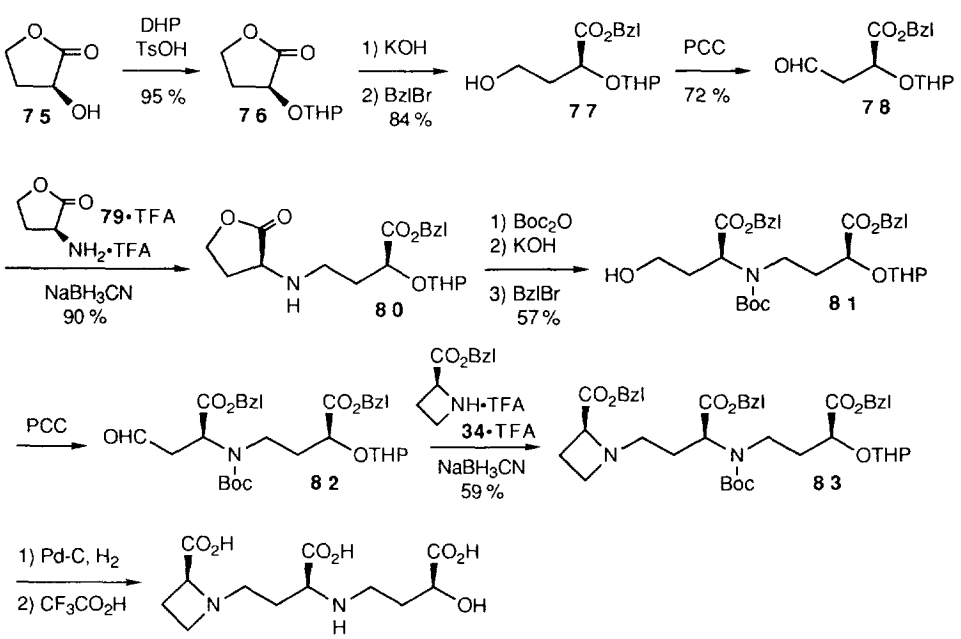
4. 2'-Deoxymugineic Acid

2'-Deoxymugineic acid (**3**) has been isolated from the root washing of wheat (*Triticum aestivum* L.) under iron deficient conditions.[40] It was demonstrated that the addition of **3** to the medium of water-cultured rice at pH 7 increases the chlorophyll content just like mugineic acid (**1**). 2'-Deoxymugineic acid (**3**) has been synthesized three times,[5,41,42] which has unambiguously established its absolute configuration.

4.1. From the Right Part to the Left One

The synthesis of **3** by Ohfune and co-workers[5] proceeded from the right part to the left one by stepwise attachment through reductive alkylation, as outlined in Scheme 11.

L-α-Hydroxy-γ-butyrolactone (**75**), readily available from L-malic acid according to a known method,[27] was converted to a diastereoisomeric mixture of the tetrahydropyranyl (THP) derivatives **76**, which were separated by column chromatography. The synthesis was carried out using each diastereoisomer independently. Hydrolysis of **76** followed by benzylation afforded the alcohol **77**, which was oxidized with pyridinium chlorochromate (PCC) to give the aldehyde **78** (cf. Scheme 3). Reductive amination of **78** with the TFA salt of the homoserine derivative **79**[43] produced the lactone **80**. Protection of the amino group, and lactone ring opening followed by benzylation furnished the alcohol **81**, which was again oxidized with



Scheme 11

PCC. The resulting aldehyde **82** was reductively coupled with benzyl (S)-azetidinecarboxylate **34** to give the fully protected 2'-deoxymugineic acid **83**, which underwent deprotection by catalytic hydrogenolysis, and then acid treatment, giving 2'-deoxymugineic acid (**3**). The overall yield of **3** from **75** was 12%.

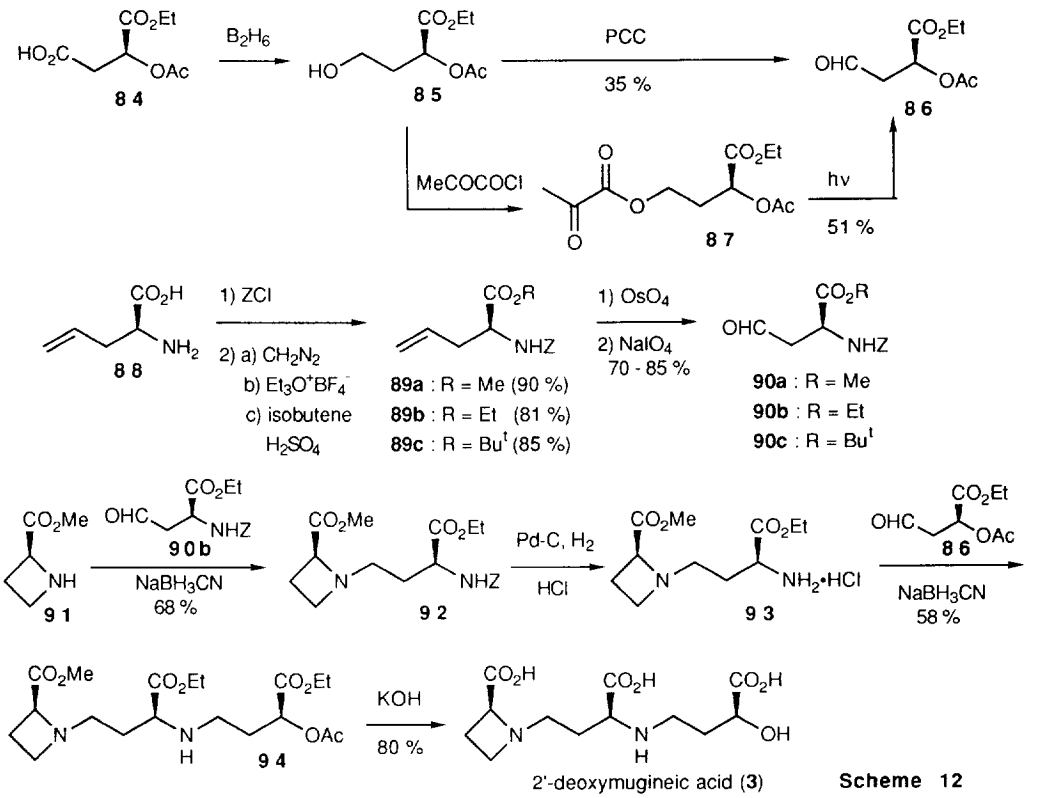
4.2. From the Left Part to the Right One

A little bit later than the above synthesis, Nozoe and co-workers reported[41] the synthesis of 2'-deoxymugineic acid (**3**), which proceeded from the left part to the right one.

The right fragment **86** was prepared from the L-malic acid half ester **84** through diborane reduction followed by PCC oxidation.[4] Alternatively, the aldehyde **86** was obtained by photoreaction of the pyruvyl ester **87** derived from the alcohol **85**.[41]

The aldehydes **90a-c** (R=Me, Et, and Bu^t), the central part of **3**, were prepared[44] from L-allylglycine (**88**) by treatment with benzyloxycarbonyl chloride (ZCl), esterification, osmium tetroxide oxidation, followed by glycol cleavage of **89**,[45] as shown in Scheme 12.

The aldehyde **90b** was reductively coupled with methyl (S)-azetidinecarboxylate (**91**) to give the diester **92**. Catalytic debenzyloxycarbonylation, followed by reductive coupling of the hydrochloride of the amine **93** with the aldehyde **86** afforded the triester **94**, which on alkaline treatment gave 2'-deoxymugineic acid (**3**).

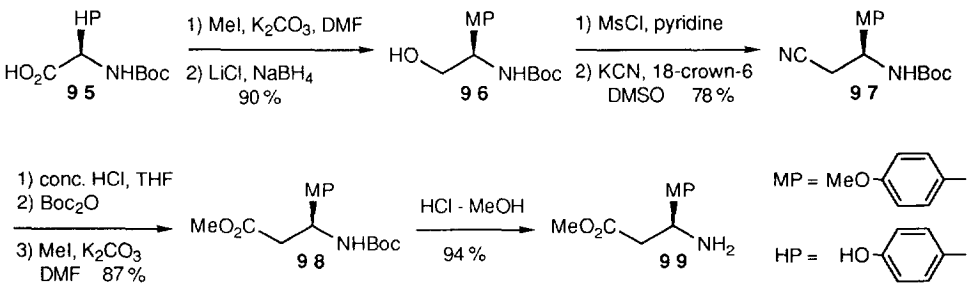


Scheme 12

4.3. Use of the p-Methoxyphenyl Group as the Carboxyl Synthon

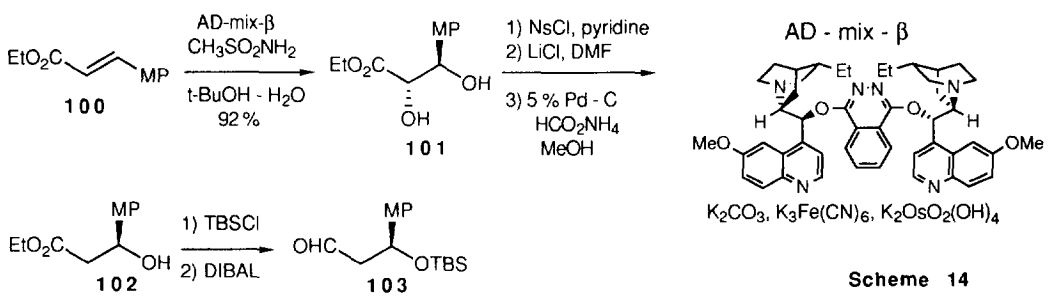
We also recently succeeded in the efficient synthesis of 2'-deoxymugineic acid (**3**),[42] in which the p-methoxyphenyl group was utilized as the carboxyl synthon. The strategy was quite similar to our efficient synthesis of mugineic acid (**1**),[11] described in 2.2.

The central fragment **99** of **3** was first synthesized, as outlined in Scheme 13. N-Boc-(R)-p-hydroxyphenylglycine (**95**) was dimethylated and reduced to give the alcohol **96**. Treatment of **96** with mesyl chloride and then potassium cyanide afforded the cyanide **97**, which was converted to the β-tyrosine derivative **98** by acidic hydrolysis followed by protection of both amino and carboxyl functions. Removal of the Boc group afforded the required central fragment **99** in 57% overall yield.



Scheme 13

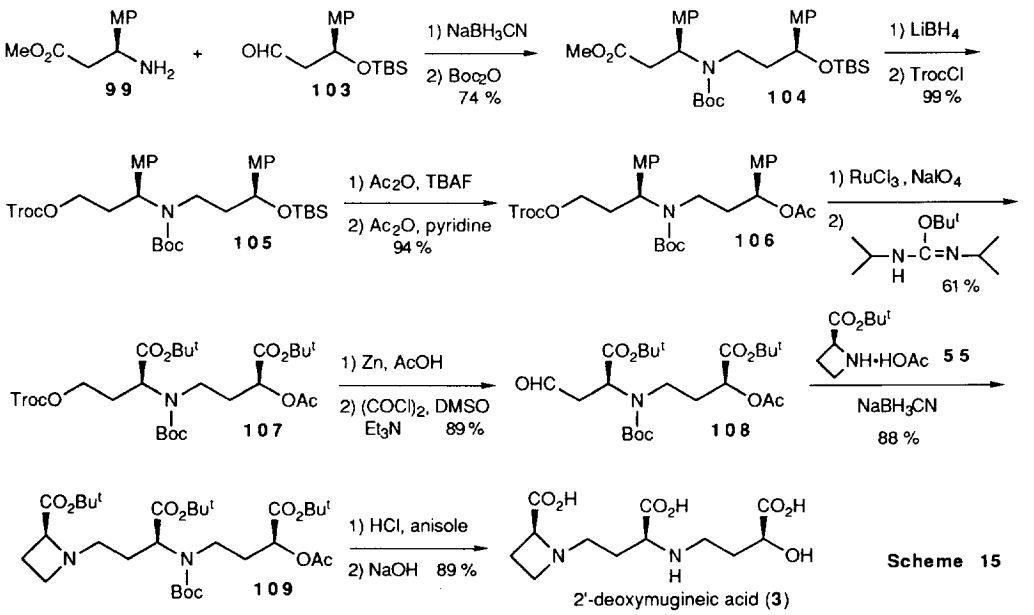
Synthesis of the right fragment **103** of **3** started by asymmetric dihydroxylation of ethyl p-methoxycinnamate (**100**) using AD-mix-β as a catalyst,[46] as shown in Scheme 14. Removal of the C-2 hydroxyl group from the resulting diol **101** with more than 99% e.e. was accomplished in 3 steps, i.e., (1) selective transformation of the C-2 hydroxyl group to the p-nitrobenzenesulfonyl (Ns) one, (2) chlorination, and (3) transfer hydrogenation, giving the alcohol **102**. Protection of the C-3 hydroxyl group by the TBS group followed by reduction afforded the right fragment **103** in an overall yield of 50.5% from **100**.



Scheme 14

Coupling of the amine **99** with the aldehyde **103** by use of sodium cyanoborohydride afforded the di-p-methoxyphenyl derivative, whose amino group was protected by the Boc function. Treatment of the resulting Boc derivative **104** with lithium borohydride then TrocCl afforded the TBS derivative **105**, whose TBS group was transformed to the acetyl one, as shown in Scheme 15. This transformation was necessary since the electron-withdrawing acetyl group facilitates oxidation of the aryl groups, as described in 2.2. The acetyl

derivative **106** underwent ruthenium catalyzed oxidation to give the ester **107** after tert-butyl esterification. Removal of the Troc group followed by Swern oxidation produced the aldehyde **108**, which was coupled with tert-butyl (S)-azetidinecarboxylate (**55**) to give the fully protected 2'-deoxymugineic acid **109**. Stepwise removal of all of the protective groups under acidic and then alkaline conditions afforded 2'-deoxymugineic acid (**3**). The overall yield of **3** from Boc-(R)-p-hydroxyphenylglycine (**95**) was 17%.



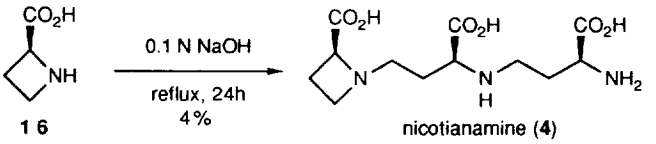
Scheme 15

5. Nicotianamine

Nicotianamine (**4**) was first isolated from the leaves of *Nicotiana tabacum* L.,[47] and has been found in many species of *Solanacea* and some other plants.[2b,48] It has been identified as the normalizing factor which restores chlorophyll biosynthesis and growth of the auxotroph tomato mutant *chloronerva*, and is regarded as an essential constituent of higher plants as a phytosiderophore.

5.1. Trimerization of Azetidine-2-carboxylic Acid

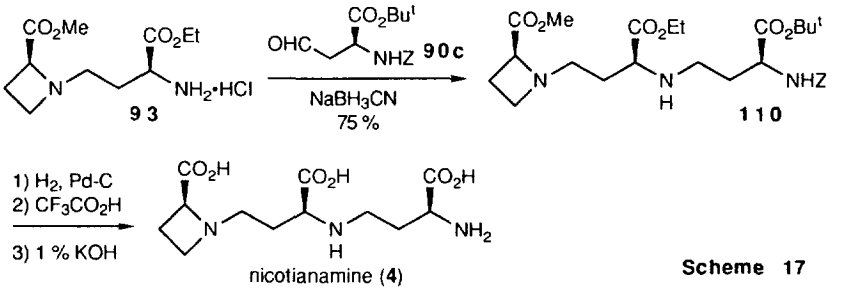
The structure of nicotianamine has been elucidated to be **4**, in which the 3"-hydroxyl function of 2'-deoxymugineic acid (**3**) is replaced with the primary amino function, by spectral studies and synthesis through the trimerization of (S)-azetidine-2-carboxylic acid (**16**) under alkaline conditions,[49] shown in Scheme 16. Use of (R)-isomer of **16** afforded (+)-nicotianamine.[50] Interestingly, both natural (-)-nicotianamine and the unnatural (+)-isomer have been reported to exhibit the same biological activity with regard to chlorophyll formation of chlorotic leaflets of the mutant *chloronerva*.[50]



Scheme 16

5.2. From the Left Part to the Right One

A more efficient synthesis was accomplished[44] through the reductive coupling of the amine **93** with the aldehyde **90c** with sodium cyanoborohydride,[51] as shown in Scheme 17. The fully protected nicotianamine **110** thus obtained was converted to nicotianamine (**4**) in 3 steps.

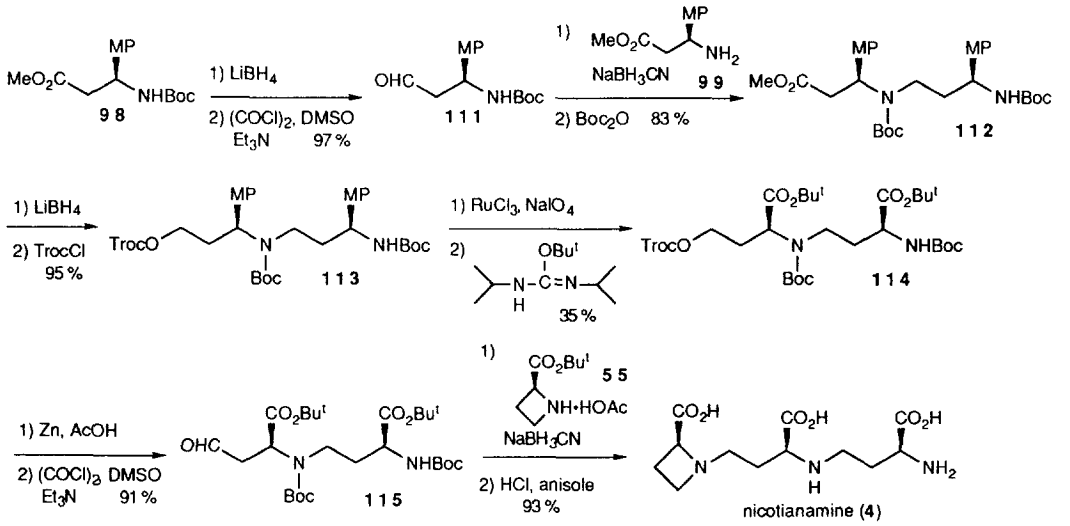


Scheme 17

5.3. From the Right Part to the Left One. Use of the p-Methoxyphenyl Group as the Carboxyl Synthon

Our synthesis of nicotianamine (**4**) was based on use of the p-methoxyphenyl group as a carboxyl synthon,[42] which was analogous to our synthesis of 2'-deoxymugineic acid (**3**), described in 4.3.

The β-tyrosine ester **98** was first converted to the aldehyde **111** by reduction and then Swern oxidation, as shown in Scheme 18. Coupling of **111** with the amine **99**, followed by Boc protection of the imino group afforded the di-Boc derivative **112**. Successive treatment with lithium borohydride and TrocCl produced the Troc derivative **113**, which underwent ruthenium catalyzed oxidation and then esterification to give the tert-butyl ester **114**. Reductive removal of the Troc group with zinc followed by Swern oxidation gave the aldehyde **115**, which was subsequently transformed to nicotianamine (**4**) by reductive coupling with **55** and

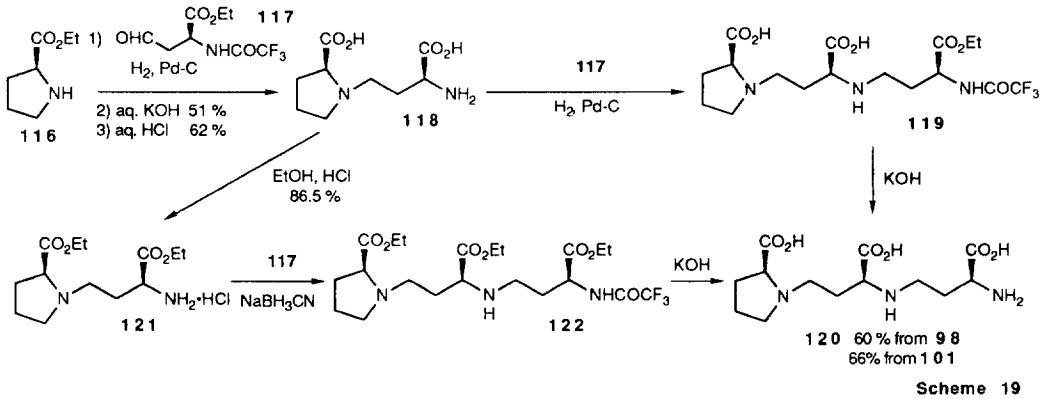


Scheme 18

then final acidic deprotection.

5.4. The Proline Analogue of Nicotianamine

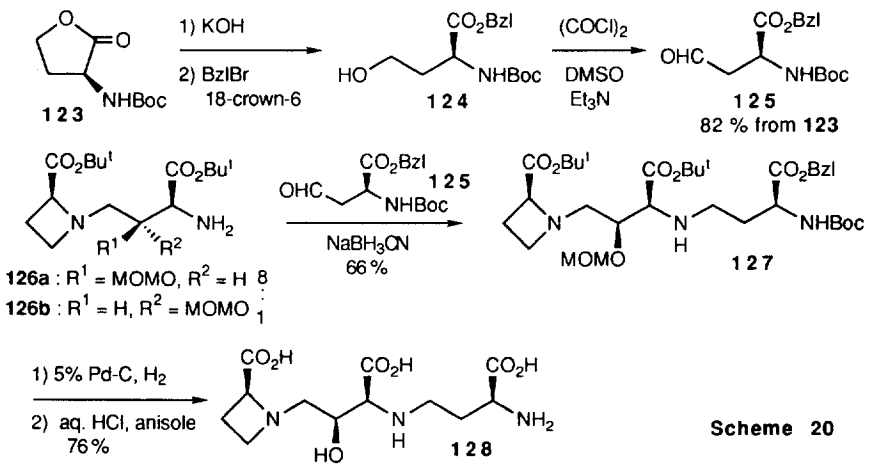
To investigate the role of the azetidine ring of nicotianamine (**4**) in terms of its biological activity, the proline analogue **120** of **4** was synthesized.[52] The route is quite analogous to the one adopted for the synthesis of **4**, as shown in Scheme 19. The main difference is the use of the trifluoroacetyl group for amino protection and catalytic hydrogenation for reductive coupling. The efficiency of the catalytic hydrogenation over palladium-carbon was similar to that of the sodium cyanoborohydride reduction. Interestingly, the proline analogue **120** exhibits biological activity with respect to chlorophyll formation of chlorotic leaflets and root development of the tomato mutant *chloronerva*, but to a lesser extent compared to nicotianamine. Obviously the azetidine ring of nicotianamine is not essential for the biological activity. The compound **118** lacking the right part is biologically inactive.



Scheme 19

5.5. 2'-Hydroxynicotianamine

2'-Hydroxynicotianamine (**128**), 3''-amino-3''-deoxymugineic acid, was also synthesized[38b] as an analogue of nicotianamine (**4**) by use of the same intermediate, a diastereoisomeric mixture of **126a** and **126b** (8:1), for the mugineic acid synthesis (see Scheme 8),[11] as shown in Scheme 20. After the right



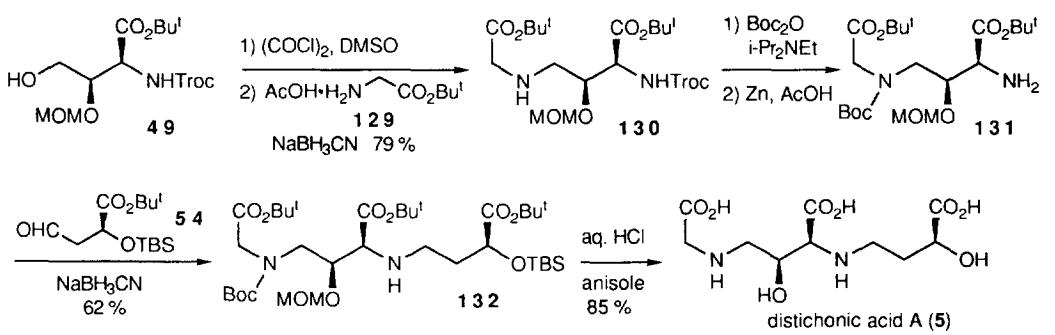
Scheme 20

fragment **125** was prepared from the known[5] γ-lactone **123** in 3 steps, reductive coupling of **125** with **126** followed by chromatographic purification afforded the fully protected 2'-hydroxynicotianamine **127**, which was converted to 2'-hydroxynicotianamine (**128**) by catalytic hydrogenation and then acidic treatment in 41% overall yield in 6 steps from **123**.

6. Distichonic Acid A

6.1. Distichonic Acid A

Distichonic acid A was isolated from beer barley (*Hordeum vulgare* L. var. distichum).[2a,2c] As shown in the structure **5**, the left part of distichonic acid A is composed of glycine instead of azetidine-2-carboxylic acid in mugineic acid (**1**). The synthesis of distichonic acid A (**5**) was quite analogous to that of mugineic acid (**1**),[11] as outlined in Scheme 21.[38] Swern oxidation of **49**,[11] followed by reductive coupling of the resulting aldehyde, a 15:1 diastereoisomeric mixture, with tert-butyl glycinate acetic acid salt (**129**) afforded the diester **130**, which was converted to the amine **131**. Reductive alkylation of the amine **131** with the aldehyde **54**[11] afforded the precursor **132** of **5**, which underwent acidic deprotection to give distichonic acid A (**5**) in 42% yield in 6 steps from **49**.

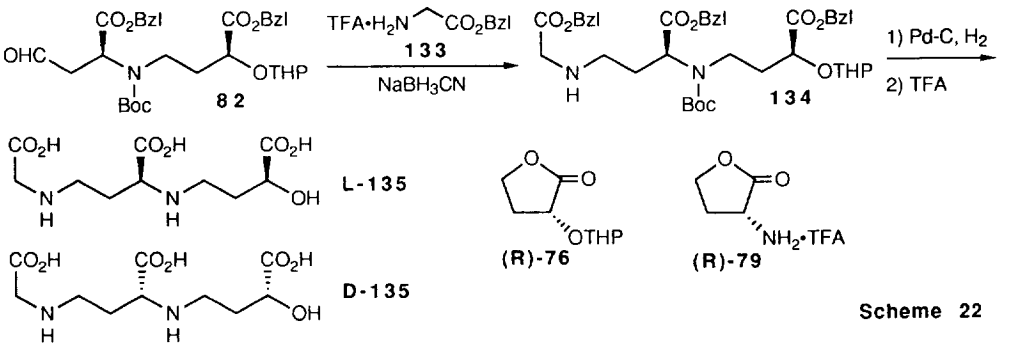


Scheme 21

6.2. 2'-Deoxydistichonic Acid A and Its Enantiomer

2'-Deoxydistichonic acid A (**L-135**) and its enantiomer **D-135**, neither of which has been isolated yet from plants, were prepared to investigate the iron-transport mechanism of the phytosiderophores in the membrane of the plant's root.[53] 2'-Deoxydistichonic acid A (**L-135**) was synthesized by reductive coupling of the aldehyde **82** (see Scheme 11 for its preparation)[5] with benzyl glycinate trifluoroacetate, followed by deprotection of **134**, as shown in Scheme 22. Its enantiomer **D-135** was prepared in the same manner from the enantiomer of **82** which was obtained using (R)-α-hydroxy-γ-butyrolactone ((**R**)-**76**) and (R)-homoserine γ-lactone trifluoroacetate ((**R**)-**79**) as starting materials.

Investigation on the iron-uptake activity for rice plant (*Oriza sativa* L. var. Koshihikari)[53] has revealed that 2'-deoxydistichonic acid (**L-135**) of natural type demonstrates high activity while the activity of antipodal **D-135** dramatically decreases, though their metal coordination properties are very similar. This result suggests that there will be a strict stereospecific recognition system (function) for the Fe(III) complex molecule on the membrane.

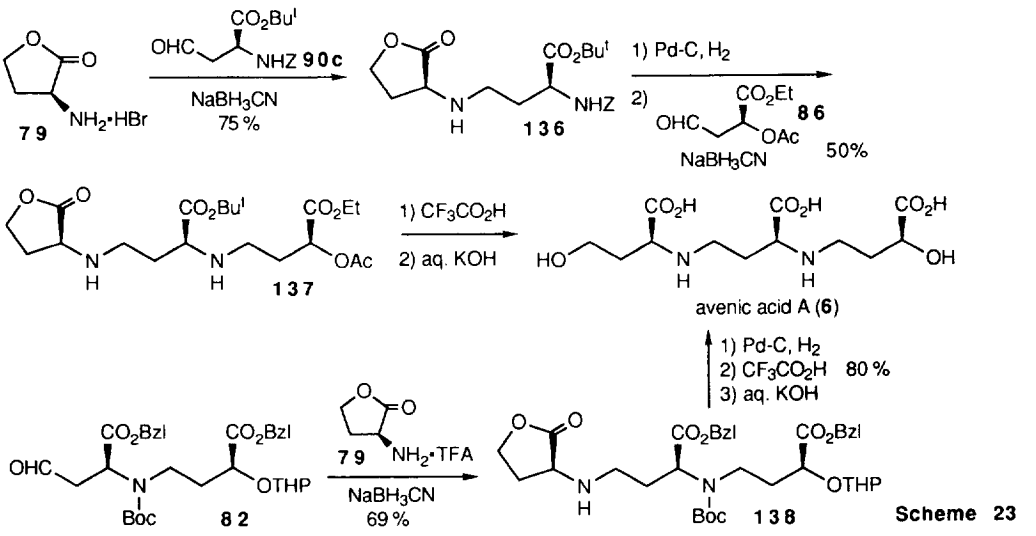


Scheme 22

7. Avenic Acid A

Avenic acid A (**6**) has been isolated[54] from oats (*Avena sativa* L.) cultured under iron deficient conditions together with 2'-deoxymugineic acid (**3**) and avenic acid B (**7**). Two syntheses of avenic acid A (**6**) have been reported. One synthesis[41] proceeded from the left part to the right one via **136** and **137** while another[55] proceeded in the opposite way via **138**, as shown in Scheme 23.

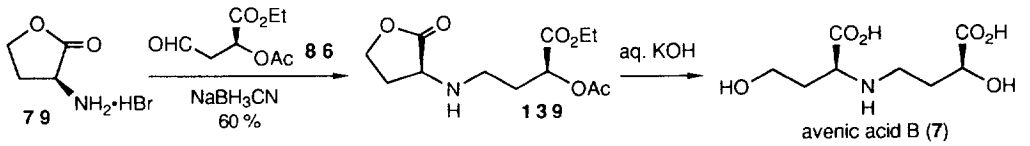
The enantiomer **D-6** of avenic acid A was also prepared for comparison of their phytosiderophoric activity.[53] Analogously to the case of 2'-deoxyditichonic acid A (**135**), the stimulation effect of **D-6** on the iron uptake in the leaves of the water-cultured rice plant was less than 30% of that of natural avenic acid A (**6**).



Scheme 23

8. Avenic Acid B

Avenic acid B (**7**), isolated from oats (*Avena sativa* L.), was synthesized[4] by reductive coupling of (S)-homoserine γ-lactone (**79**) with the aldehyde **86** via **139**, shown in Scheme 24.



Scheme 24

9. Conclusions

As shown by this review, the synthetic methods for the phytosiderophores have been almost established. This will help to supply the phytosiderophores in large amounts and to prepare analogues for the investigation of chemical structure-biological activity relationships. Furthermore, the methodologies adopted here will have generality and can be applied to the synthesis of other functionalized carboxylic acids.[56]

The remaining problem which should be solved is how to prepare and supply radioactive phytosiderophores to investigate biosynthesis and biological roles of the phytosiderophores in detail. Further development along this line will be a matter of importance.

Acknowledgments Our work has been financially supported in part by the Japan Research Foundation for Optically Active Compounds, Foundation for the Promotion of Research on Medicinal Resources, the Sasagawa Foundation, and Ministry of Education, Science and Culture, Japan, to which our thanks are due. We thank Dr. K. Nomoto of Suntory Institute for Bioorganic Research for helpful discussions. F.M. gratefully acknowledges a postgraduate fellowship from the Japan Society for the Promotion of Science.

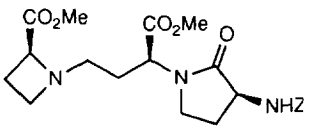
References and Notes

1. Takagi, S. *Soil. Sci. Plant Nutr.* **1976**, *22*, 423.
2. For reviews, see (a) Nomoto, K.; Ohfune, Y. *J. Synth. Org. Chem. Japan* **1982**, *40*, 401. (b) Ripperger, H.; Schreiber, K. *Heterocycles* **1982**, *17*, 447. (c) Sugiura, Y.; Nomoto, K. *Structure and Bonding* **1984**, *58*, 107.
3. Borch, R.F.; Bernstein, M.D.; Durst, H.D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
4. Fushiya, S.; Sato, Y.; Nozoe, S. *Chem. Lett.* **1980**, 1215.
5. Ohfune, Y.; Tomita, M.; Nomoto, K. *J. Am. Chem. Soc.* **1981**, *103*, 2409.
6. (a) Takemoto, T.; Nomoto, K.; Fushiya, S.; Ouchi, R.; Kusano, G.; Hikino, H.; Takagi, S.; Matsuura, Y.; Kakudo, M. *Proc. Japan. Acad.* **1978**, *54B*, 469. (b) Metal chelation of mugineic acid was confirmed by X-ray crystallographic analysis using its Cu(II) complex: Nomoto, K.; Mino, Y.; Ishida, T.; Yoshida, H.; Ota, N.; Inoue, M.; Takagi, S.; Takemoto, T. *J. Chem. Soc., Chem. Commun.* **1981**, 338.
7. Funahashi, K.; Tanaka, H.; Muramatsu, M.; Sato, F.; Nomoto, K.; Abstract of papers, 104th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, March 1984, p. 426.
8. Hamada, Y.; Shioiri,T. *J. Org. Chem.* **1986**, *51*, 5489.
9. Hamada, Y.; Iwai, K.; Shioiri, T. *Tetrahedron Lett.* **1990**, *31*, 5041.
10. Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron : Asymmetry* **1992**, *3*, 1069.
11. (a) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1992**, *33*, 7917, and **1993**, *34*, 2394. (b) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1993**, *49*, 8211. See also (c) Shioiri, T; Hamada,

Y.; Matsuura, F. *Pure Applied Chem.* **1994**, *66*, 2151.
12. For a review, see Shioiri, T.; Hamada, Y. *Heterocycles* **1988**, *27*, 1035.
13. (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Shioiri, T.; Yamada, S. *Org. Synth., Coll. Vol. 7* **1990**, 206.
14. For a review, see Shioiri, T. *Ann. Rept. Pharm. Nagoya City Univ.* **1977**, *25*, 1.
15. (a) Yamada, S.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, 1595. (b) Takuma, S.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 3147.
16. Shioiri, T. *J. Synth. Org. Chem. Japan* **1979**, *37*, 856.
17. Shioiri, T.; Hamada, Y. *J. Org. Chem.* **1978**, *43*, 3631.
18. Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1982**, *23*, 235.
19. Hamada, Y.; Morita, S.; Shioiri, T. *Heterocycles* **1982**, *17*, 321.
20. Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1982**, *23*, 1193.
21. Hamada, Y.; Kawai, A.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 5409.
22. Hamada, Y.; Kawai, A.; Matsui, T.; Hara, O.; Shioiri, T. *Tetrahedron* **1990**, *46*, 4823.
23. Hamada, Y.; Kawai, A.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 5413.
24. Hamada, Y.; Kawai, A.; Shioiri, T. *Chem. Pharm. Bull.* **1985**, *33*, 5601.
25. Kawai, A.; Hara, O.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 6331.
26. cf. (a) Hara, O.; Hamada, Y.; Shioiri, T. *Synlett* **1991**, 283 and 285. (b) Matsubara, J.; Nakao, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1992**, *33*, 4187.
27. Collum, D.B.; McDonald, J.H.III; Still, W.C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.
28. Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, Weidmann, B.; Züger, M. *Synthesis* **1982**, 138; Rehwinkel, H.; Steglich, W. *Synthesis* **1982**, 826.
29. Sendai, M.; Hashiguchi, S.; Tomimoto, M.; Kishimoto, S.; Matsuo, T.; Ochiai, T. *Chem. Pharm. Bull.* **1985**, *33*, 3798.
30. Carlsen, P.H.J.; Katsuki, T.; Martín, V.S.; Sharpless, K.B. *J. Org. Chem.* **1981**, *46*, 3936.
31. (a) Weller, H.N.; Gordon, E.M. *J. Org. Chem.* **1982**, *47*, 4160. (b) Kasai, M.; Ziffer, H. *J. Org. Chem.* **1983**, *48*, 712. (c) Kasai, M.; Ziffer, H. *J. Org. Chem.* **1983**, *48*, 2346. (d) Kalvin, D.M.; Woodard, R.W. *J. Org. Chem.* **1985**, *50*, 2259. (e) Takano, S.; Yanase, M.; Sekiguchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1987**, *28*, 1783. (f) Kobayashi, Y.; Kusakabe, M.; Kitano, Y.; Sato, F. *J. Org. Chem.* **1988**, *53*, 1586. (g) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* **1988**, *53*, 3865. (h) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Chem. Pharm. Bull.* **1988**, *36*, 3341. (i) Nuñez, M.T.; Martín, V.S. *J. Org. Chem.* **1990**, *55*, 1928.
32. Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
33. Caron, M.; Carlier, P.R.; Sharpless, K.B. *J. Org. Chem.* **1988**, *53*, 5185.
34. Gao, Y.; Sharpless, K.B. *J. Org. Chem.* **1988**, *53*, 4081.
35. Fushiya, S.; Tamura, T.; Tashiro, T.; Nozoe, S. *Heterocycles* **1984**, *22*, 1039.
36. Carreaux, F.; Duréault, A.; Depezay, J.C. *Synlett* **1992**, 527.
37. The absolute configurations at the C-3 position of 3-hydroxymugineic acid and its C-3 epimer are rather confusing. We adopt here Dr. K. Nomoto's view that 3-epi-hydroxymugineic acid has (3S)-configuration (private communication from Dr. K. Nomoto).
38. (a) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1992**, *33*, 7921 and **1993**, *34* , 2394. (b)

Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 265

39. (a) Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M.A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6935. (b) Duréault, A.; Portal, M.; Carreaux, F.; Depezay, J.C. *Tetrahedron* **1993**, *49*, 4201.
40. Nomoto, K.; Yoshioka, H.; Arima, M.; Fushiya, S.; Takagi, S.; Takemoto, T. *Chimia* **1981**, 249.
41. Fushiya, S.; Sato, Y.; Nakatsuyama, S.; Kanuma, N.; Nozoe, S. *Chem. Lett.* **1981**, 909.
42. Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 9457.
43. Obtained by treatment of Boc-homoserine lactone with trifluoroacetic acid (TFA) or L-homoserine with TFA.
44. Fushiya, S.; Nakatsuyama, S.; Sato, Y.; Nozoe, S. *Heterocycles* **1981**, *15*, 819.
45. cf. Neuberger, A.; Tait, G.H. *J. Chem. Soc.* **1962**, 3963.
46. Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
47. Noma, M.; Noguchi, M.; Tamaki, E. *Tetrahedron Lett.* **1971**, 2017.
48. For reviews on nicotianamine (**4**), see reference 2b and Procházka, Z.; Sholz, G. *Experientia* **1984**, *40*, 794.
49. Kristensen, I.; Larsen, P.O. *Phytochemistry* **1974**, *13*, 2791.
50. Ripperger, H.; Faust, J.; Scholz, G.; *Phytochemistry* **1982**, *21*, 1785.
51. When the methyl ester **90a** was used instead of the tert-butyl ester **90c**, the coupling with **16a** afforded the lactam as shown below.[44]



52. Faust, J.; Preiss, A.; Schreiber, K.; Ripperger, H. *Tetrahedron* **1983**, *39*, 1593.
53. Oida, F.; Ota, N.; Mino, Y.; Nomoto, K.; Sugiura, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3436.
54. Fushiya, S.; Sato, Y.; Nozoe, S. *Tetrahedron Lett.* **1980**, *21*, 3071.
55. Ohfune, Y.; Nomoto, K. *Chem. Lett.* **1981**, 827.
56. For example, the methodology utilizing the aryl groups as the carboxyl synthon was successfully applied to an efficient synthesis of polyoxamic acid, the side chain moiety of the antifungal antibiotics polyoxins, see Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 733.

(*Received* 8 *December* 1994)