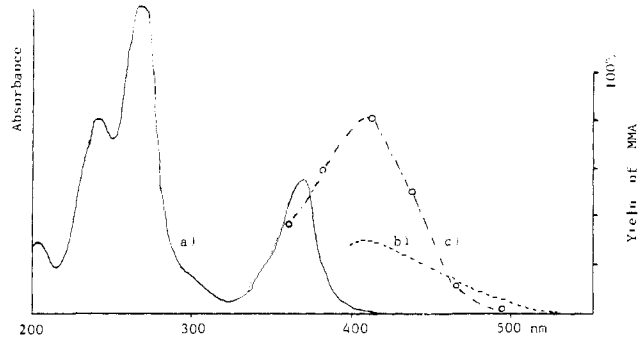

Figure 1. (a) UV-visible absorption spectrum of pyrimido[5,4-*g*]pteridine *N*-oxide **1** (5×10^{-5} M) in MeCN. (b) Difference spectrum of the mixture of **1** (5 mM) and DMA (250 mM) vs. **1** (5 mM) in MeCN. (c) Wavelength dependence (presented by the yield of MMA) in the photochemical demethylation of DMA by **1**. A solution of **1** (5 mM) and DMA (50 mM) in MeCN was irradiated by using a grating monochromator (JASCO Model CRM-FA) with 2-kW Xe lamp and 4-nm band width under argon atmosphere for 2 h.

CT complex formation of the *N*-oxides **5** and **6** with DMA[7] into consideration, a plausible mechanism for the present demethylation of DMA by the *N*-oxides **1**–**6** is depicted in Scheme I by using for an example the case of **3**.

The reaction could be initiated by the formation of the *N*-oxide/DMA charge-transfer complex in a ground state followed by a single-electron transfer from DMA to the *N*-oxides in the excited complex to give the *N*-oxide radical anion A and anilinium radical cation B. Subsequent steps of proton transfer from B to A generating *N*-methyl radical C and nitroxyl radical D, coupling of the resulting radical C with D leading to a transient adduct E, and heterocyclic fragmentation of N–O bond in E give the deoxygenated heterocycles and carbinolamine F.[8] Elimination of formaldehyde from F would produce the final demethylated product (MMA). In agreement with the proposed electron-transfer mechanism, the addition of *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (TMPD)[9] or tetracyanoethylene into the reaction media of **1** with DMA inhibited the formation of MMA even at very low concentration (0.1 equiv to **1**). The present result formally parallels the mechanism proposed for the cytochrome P-450 catalyzed N-dealkylation which involves an initial single-electron-transfer process.[10]

Acknowledgment. We express our grateful acknowledgment to Dr. M. Kuzuya of our university for invaluable discussions.

Registry No. **1**, 33070-58-5; **1** (deoxygenated), 103620-51-5; **2**, 103620-50-4; **3**, 694-59-7; **3** (deoxygenated), 110-86-1; **4**, 1613-37-2; **5**, 1124-33-0; **5** (deoxygenated), 1122-61-8; **6**, 56-57-5; **6** (deoxygenated), 3741-15-9; DMA, 121-69-7; MMA, 100-61-8; CH_2O, 50-00-0.

(7) Okano, T.; Uekama, K.; Isawa, Y.; Tsukuda, K. *Yakugaku Zasshi* **1967**, *87*, 1309. Okano, T.; Miura, T.; Yoshida, M.; Uekama, K. *Ibid.* **1969**, *89*, 1379. Kubota, T.; Akazawa, H.; Yamakawa, M. *Chem. Lett.* **1972**, 1147.

(8) Another possible mechanism for the formation of F can be considered, involving the addition of water arising from D to the iminium ion species generating from C after further redox reaction between C and D. This stepwise mechanism, however, is less favorable because the photoreaction of **1** with DMA in acetonitrile containing methanol in various concentrations did not afford *N*-(methoxymethyl)-*N*-methylaniline which could be formed as a result of capture of the generated iminium ion species by methanol. Cf.: Miyata, N.; Kiuchi, H.; Hirobe, M. *Chem. Pharm. Bull.* **1981**, *29*, 1489.

(9) When a solution of **1** and TMPD in dry acetonitrile was irradiated, the absorption (568 and 612 nm) of the well-known TMPD radical cation was observed. The present result suggests that **1** possesses a one-electron-accepting ability in the photoreaction conditions. Cf.: Michaelis, L.; Schubert, M. P.; Granick, S. *J. Am. Chem. Soc.* **1939**, *61*, 1981. Franzen, V. *Chem. Ber.* **1955**, *88*, 1697.

(10) Hanzlik, R. P.; Tullman, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 2048. Macdonald, T. L.; Zirvi, K.; Burka, L. T.; Peyman, P.; Guengerich, F. P. *Ibid.* **1982**, *104*, 2050. Guengerich, F. P.; Macdonald, T. L. *Acc. Chem. Res.* **1984**, *17*, 9. Miwa, G. T.; Walsh, J. S.; Kedderis, G. L.; Hollenberg, P. F. *J. Biol. Chem.* **1983**, *258*, 14445. Lindsay Smith, J. R.; Mortimer, D. N. *J. Chem. Soc., Chem. Commun.* **1985**, 64. Burka, L. T.; Guengerich, F. P.; Willard, R. J. Macdonald, T. L. *J. Am. Chem. Soc.* **1985**, *107*, 2549.

Total Synthesis of Echinocandins. 1. Stereocontrolled Syntheses of the Constituent Amino Acids

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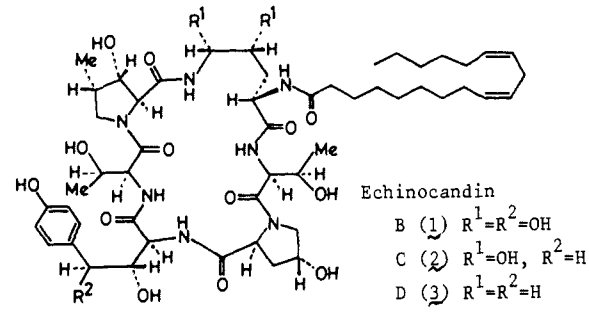
Echinocandins isolated from a strain of *Aspergillus ruglosus* and *Aspergillus nidulans* are novel oligopeptide antibiotics characterized by their high antifungal and antiyeast activities.[1-3] Recently, their potent effectiveness against candidosis has been examined.[4] The structure of echinocandin B determined by chemical degradation studies in combination with the X-ray crystallographic analysis of its derivative was found to be an unique 21-membered cyclic lipopeptide as shown in **1**.[2,5] The structures of echinocandin C (**2**) and D (**3**) were elucidated by converting them into a common intermediate derived from **1**.[6]



On the basis of our previous results related to the stereoselective syntheses of biologically active amino acids starting from vinylglycine equivalent **5a** and allylglycine derivative **6a** as the chiral building blocks,[7] we focused our attention on the synthesis of peptides constructed from unusual amino acids, where synthetic methods are extremely limited. Since **1** is chemically unstable in the presence of a benzylic hydroxyl group,[8] echinocandin C and D were chosen for the present study. Described, herein, are the stereocontrolled syntheses of the constituent amino acids. The following paper will describe the total synthesis of echinocandin D (**3**).[9] All constituent amino acids in **2** and **3** are composed of β- and/or γ-substituted α-amino acids. Initially, the strategies to synthesize the amino acids were from the acyclic precursors **4a**, **5b**, and **6a**.

Synthesis of (2*S*,3*S*,4*S*)-3-Hydroxy-4-methylproline (4). Disconnection of the pyrrolidine ring at the C5–N bond provides the acyclic intermediate **4c**, in which the consecutive 3*S*,4*S* chiral centers corresponded to those of a known epoxy alcohol **4a**.[10]

(1) Benz, F.; Knüsel, F.; Nüesch, J.; Treichler, H.; Voser, W.; Nyfeler, R.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 2459.

(2) Keller-Juslén, C.; Kuhn, M.; Loosli, H.-R.; Petcher, T. J.; Weber, H. P.; von Wartburg, A. *Tetrahedron Lett.* **1976**, 4147.

(3) Related compounds have been isolated: (a) Mizuno, K.; Yagi, A., Satoi, S.; Takada, M.; Hayashi, M.; Asano, K.; Matsuda, T. *J. Antibiot.* **1977**, *30*, 297. (b) Satoi, S.; Yagi, A.; Asano, K.; Mizuno, K.; Watanabe, T. *J. Antibiot.* **1977**, *30*, 303. (c) Abbott, B. J.; Fukuda, D. S. US Patent **1981**, 4 293 482 and 4 293 490. (d) Kotani, M.; Satoi, S.; Takada, M. Japanese Patent **1979**, 54-160301.

(4) (a) Mizoguchi, J.; Saito, T.; Mizuno, K.; Hayano, K. *J. Antibiot.* **1977**, *30*, 308. (b) Bagnley, B. C.; Rommele, G.; Gruner, J.; Wehrli, W. *Eur. J. Biochem.* **1979**, *97*, 345.

(5) Koyama, G. *Helv. Chim. Acta* **1974**, *57*, 2477.

(6) Traber, R.; Keller-Juslén, C.; Loosli, H.-R.; Kuhn, M.; von Wartburg, A. *Helv. Chim. Acta* **1979**, *62*, 1252.

(7) (a) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, 1071. (b) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, 1587. (c) Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, 4133. (d) Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1985**, 83. (e) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1985**, 5307.

(8) Keller-Schierlein, W.; Joos, B. *Helv. Chim. Acta* **1980**, *63*, 250.

(9) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, following paper.

(10) Nagaoka, N.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

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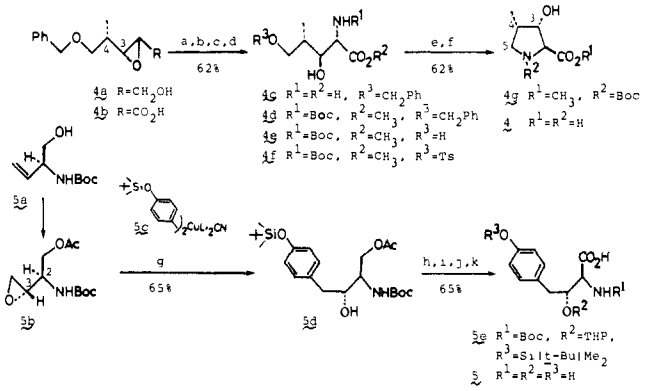
Scheme I[a]

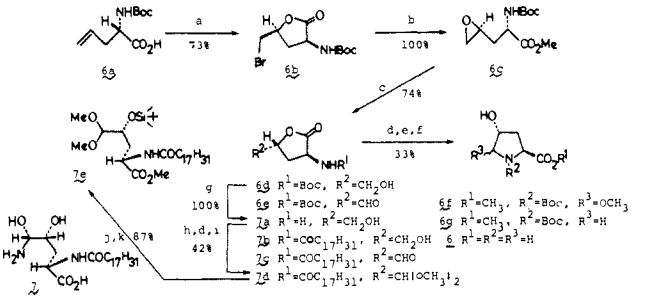


[a] (a) 28% aqueous NH_3, room temperature, 5 days; (b) (1) Boc-ON, Et_3N, dioxane/H_2O, room temperature, 4 h; (2) CH_2N_2; (c) H_2/5% Pd–C, MeOH; (d) TsCl, pyridine, room temperature, 8 h; (e) 1.0 equiv of NaH, THF, 0 °C, 3 h; (f) (1) 1 N NaOH, 0 °C, 14 h; (2) CF_3CO_2H, CH_2Cl_2, 0 °C, 30 min; (g) **5c**, THF, −78 °C, 2 h, 0 °C, 3 h; (h) dihydropyran, CSA, CH_2Cl_2, 0 °C, 20 min; (i) 0.1 equiv of K_2CO_3, MeOH, 0 °C, 3 h; (j) PDC, DMF, 40 °C, 16 h; (k) CF_3CO_2H, CH_2Cl_2, 0 °C, 30 min.

Since high regioselectivity at the α-position is obtained from the nucleophilic epoxide opening of an α,β-epoxy carboxylic acid,[11] the conversion of the alcohol **4a** (100% ee) to **4b**[12] was accomplished with a pyridinium dichromate (PDC) oxidation in 80% yield. As expected, treatment of **4b** with 28% aqueous ammonia yielded the desired (2*S*,3*S*,4*S*)-**4c**, exclusively, in 70% yield: mp 188 °C dec; $[\alpha]^{25}_D$ +17.7° (*c* 1.0, 1 N HCl). At this stage, α-amino acid functionalities were protected with (i) 2-[(*tert*-butoxycarbonyloxy)imino]-2-phenylacetonitrile (Boc-ON) and (ii) CH_2N_2, to give the methyl ester **4d**. Removal of the benzyl group (H_2/Pd–C, MeOH) gave the diol **4e**,[13] which upon treatment with *p*-toluenesulfonyl chloride/pyridine gave the monotosylate **4f** as the sole product, 98% from **4d**. **4f** was successfully transformed to the desired pyrrolidine **4g** with 1.0 equiv of NaH/tetrahydrofuran in 62% yield. The protecting groups were removed, quantitatively, in two steps: (i) 1 N NaOH and (ii) trifluoroacetic acid (TFA). The resultant trifluoroacetate was treated with Dowex 50W × 4 (H^+ form; elution with 1 N NH_3) to give **4** (100% ee) as white crystals: mp 260 °C dec; $[\alpha]^{25}_D$ −27.0° (*c* 0.8, H_2O).[14]

Synthesis of (2*S*,3*R*)-3-Hydroxyhomotyrosine (5). The use of the epoxide **5b**, prepared stereoselectively from the chiral 2-amino-3-butenol derivative **5a**,[7b] has the requisite 2*R*,3*R* chiral centers corresponding to those of **5**. Coupling of the epoxy acetate **5b** with the diaryl cuprate **5c**[15] gave the desired acetate **5d** (65%) and the secondary acetate (15%). **5d** was converted to the protected homotyrosine **5e** in the following sequence of reactions: (i) dihydropyran/*dl*-10-camphorsulfonic acid (CSA), (ii) 0.1 equiv of K_2CO_3/CH_3OH, and (iii) PDC/DMF, 65%. Finally, the protecting groups were removed with TFA and the resultant trifluoroacetate was treated in the same manner as **4** to give **5** (78%, 100% ee) as white crystals: mp 200–203 °C dec; $[\alpha]^{25}_D$ +54.1° (*c* 1.22, 1 N HCl) (Scheme I)[16]

Scheme II[a]



[a] (a) NBS, THF, 0 °C, 30 min; (b) K_2CO_3, MeOH, 0 °C, 30 min; (c) (1) 1 N NaOH, 0 °C, 14 h; (2) CSA, CH_2Cl_2, room temperature, 20 h; (d) $(COCl)_2$, CH_2Cl_2/Me_2SO, −78 °C, 15 min, −45 °C, 1 h, Et_3N, 0 °C, 15 min; (e) CSA, MeOH, room temperature, 14 h; (f) (1) 60% AcOH, room temperature, 48 h; (2) $NaBH_3CN$, EtOH/60% AcOH, room temperature, 45 min; (3) 1 N NaOH, 0 °C, 14 h; (4) TFA, CH_2Cl_2, 0 °C, 30 min; (g) TFA, CH_2Cl_2, 0 °C, 1 h; (h) $C_{17}H_{31}COSPy$, K_2CO_3, DMF, room temperature, 45 min; (i) 2,2-dimethoxypropane, CSA; CH_2Cl_2, room temperature, 14 h; (j) (1) 1 N NaOH, 0 °C, 14 h; (2) CH_2N_2; (k) $Me_2(t\text{-Bu})SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, room temperature, 10 min.

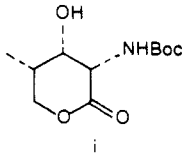
Syntheses of γ-Hydroxy α-Amino Acids in the Right Half of Echinocandins. The 1-amino-3-hydroxyl system[17] in the right half of echinocandins has attracted interest due to its presence in a variety of natural products. We have examined the syntheses of **6** and **7** via a 1,3-asymmetric induction of a hydroxyl group at the C4 of chiral allylglycine derivative **6a** using halolactonization.[18] The bromolactonization of **6a** with *N*-bromosuccinimide/THF provided a mixture (cis/trans = 8) of γ-butyrolactones: *cis*-**6b**, 73%, mp 119.5–120.0 °C, $[\alpha]^{23}_D$ +24.5° (*c* 1.0, $CHCl_3$); trans isomer, 9%.[19] The major isomer **6b** possessed the undesired *S* configuration at C4; therefore, its inversion to the 4*R* which will lead to the desired **6d** was thus examined.[20] Sequential treatment of **6b** with (i) K_2CO_3/MeOH, (ii) 1 N NaOH, and (iii) CSA/CH_2Cl_2 provided **6d** (75%): mp 208–209 °C; $[\alpha]^{25}_D$ −34.0° (*c* 0.3, MeOH). Swern oxidation[21] of the alcohol **6d** followed by a methanolysis (CSA/MeOH) provided the pyrrolidine **6f** (58%). This was subjected to an acid hydrolysis (60% acetic acid) followed by reduction with sodium cycanoborohydride to give **6g** (41%). Deprotection and purification were carried out in the same manner as above to give **6** as white crystals: mp 260–265 °C dec; $[\alpha]^{25}_D$ −46.4° (*c* 1.0, 1 N HCl) (Scheme II).[14,22]

On the other hand, γ,δ-dihydroxyornithine **7** must be synthesized as its equivalent **7e**, where γ- and δ-functionalities are

(11) (a) Liwschitz, Y.; Rabinsohn, Y.; Perera, D. *J. Chem. Soc.* **1962**, 1116. (b) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (c) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1561.

(12) All new compounds exhibited satisfactory ^1H NMR, IR, MS, and elementary analytical or high-resolution mass spectral data.

(13) The δ-lactione (i) was a by-product (20–30%). This was converted



i

to the diol **4e**, quantitatively, by alkaline hydrolysis (1 N NaOH) followed by esterification with CH_2N_2.

(14) The synthetic material showed identical ^1H NMR, IR, mp, and $[\alpha]_D$ with those reported. Synthetic **4**: ^1H NMR (360 MHz, D_2O) δ 1.04 (d, 3 H, *J* = 6.5 Hz), 2.24 (m, 1 H), 3.03 (t, 1 H, *J* = 11.5 Hz), 3.58 (dd, 1 H, *J* = 8, 11.5 Hz), 4.06 (br s, 1 H), 4.41 (d, 1 H, *J* = 4 Hz). Synthetic **6**: ^1H NMR (360 MHz, D_2O) δ 2.15 (dddd, 1 H, *J* = 0.5, 4, 10, 14 Hz), 2.43 (dddd, 1 H, *J* = 2, 2, 8, 14 Hz), 3.34 (ddd, 1 H, *J* = 1.5, 2, 12.5 Hz), 3.48 (dd, 1 H, J = 4, 12.5 Hz), 4.33 (dd, 1 H, *J* = 8, 10.5 Hz), 4.66 (m, 1 H).

(15) Prepared from *p*-bromophenol in two steps: (i) *tert*-butyldimethylsilyl chloride/imidazole/DMF, 3 h; bp 137 °C (25 mmHg) and (ii) *n*-BuLi/CuCN/THF, −78 °C, 1 h.

(16) Since **5** was not obtained in the chemical degradation studies of the natural products, this is its first description: ^1H NMR (360 MHz, 1 N DCl) of **5** δ 2.28 (dd, 1 H, *J* = 10, 14 Hz), 2.41 (dd, 1 H, *J* = 5, 14 Hz), 3.58 (d, 1 H, *J* = 4 Hz), 3.91 (ddd, 1 H, *J* = 4, 5, 10 Hz), 6.33 (d, 2 H, *J* = 8.5 Hz), 6.67 (d, 2 H, *J* = 8.5 Hz).

(17) For recent examples, see: (a) Jäger, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199. (b) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 814. (c) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797.

(18) For reviews, see: (a) Dowle, M. D.; Davis, D. I. *Chem. Soc. Rev.* **1979**, 171. (b) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317.

(19) Halolactonization of *N*-benzyloxycarbonylallylglycine has been reported by Witkop et al. to give the cis γ-butyrolactone as the major product: Izumiya, N.; Witkop, B. *J. Am. Chem. Soc.* **1963**, *85*, 1835.

(20) Configuration of the major isomer **6c** to be cis was unambiguously determined by converting this to *trans*-4-hydroxyproline **6**.

(21) Mancuso, A.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(22) Ramaswamy, S. G.; Adams, E. *J. Org. Chem.* **1977**, *42*, 3440.

appropriately protected to avoid the γ-butyrolactonization as well as pyrrolidine formation. Introduction of the linoleyl moiety onto the amino group (**6d** → **7b**) followed by the oxidation of the alcohol gave the aldehyde **7c**, which upon protection with the dimethyl acetal moiety gave the acetal **7d** (42% from **6d**). This was converted to **7e** by the following sequence of reactions: (i) 1 N NaOH, (ii) CH_2N_2, and (iii) *tert*-butyldimethylsilyl trifluoromethanesulfonate/2,6-lutidine;[23] **7e**, 87% from **7d**; $[\alpha]^{25}_D$ −8.3° (*c* 0.7, $CHCl_3$). Thus we have efficiently completed the syntheses of the constituent amino acids of echinocandins. A total synthesis of echinocandin D (**3**) will be described in the following paper.

Acknowledgment. We are grateful to Professor Koji Nakanishi, Director, for continuous encouragement.

Supplementary Material Available: Spectroscopic (^{1}H NMR, IR, MS, $[\alpha]_D$) and analytical data (elementary analysis or high-resolution mass spectral analysis) for key compounds (21 pages). Ordering information is given on any current masthead page.

(23) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, 3455.

Total Synthesis of Echinocandins. 2. Total Synthesis of Echinocandin D via Efficient Peptide Coupling Reactions

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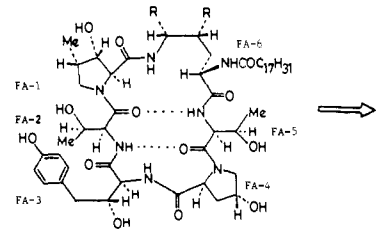
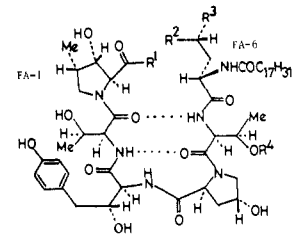
In the preceding paper,[1] we described the syntheses of the constituent amino acids of echinocandins. Now, we turned our attention to the total synthesis of these cyclic hexapeptides using a new peptide coupling reaction. According to the structural studies of echinocandins, their relatively rigid conformation has been suggested due to the internal hydrogen bondings between the two threonine moieties as well as the β-turn conformation of the two proline analogues.[2,3] The existence of a stable hemiaminal bond[4] connecting the fragment amino acid 1 (FA-1) and FA-6 was considered as the reason. Therefore, FA-1 and FA-6 of the acyclic hexapeptide **3** were expected to be spatially proximal as shown in Scheme I. In the present study, the syntheses of both echinocandin C (**1**) and D (**2**) were designed by using **3b** and **3d**, respectively, which are constructed from the same intermediate **12a** (vide infra).

An efficient method for the coupling of the highly functionalized amino acids was examined first. Mild reaction conditions were required to avoid side reactions such as racemization and β-elimination. Therefore, to carry out the entire process under neutral conditions, thiopyridyl esters were chosen as the acid component.[5] On the other hand, unprotected amino acids were chosen as the amine component[6] which would provide the following

Scheme I

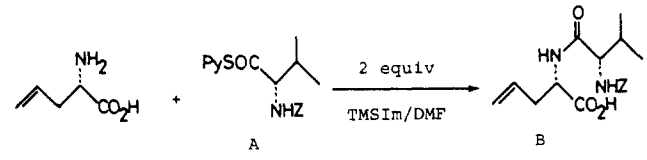


echinocandin C (**1**), R = OH
echinocandin D (**2**), R = H



3a, $R^1 = NH_2$, $R^2 = CH(OMe)_2$, $R^3 = OSi(t\text{-Bu})Me_2$, $R^4 = Si(t\text{-Bu})Me_2$
b, $R^1 = NH_2$, $R^2 = CHO$, $R^3 = OH$, $R^4 = H$
c, $R^1 = OMe$, $R^2 = CH_2NHBoc$, $R^3 = H$, $R^4 = Si(t\text{-Bu})Me_2$
d, $R^1 = OH$, $R^2 = CH_2NH_2$, $R^3 = R^4 = H$

Scheme II



advantages: (i) protection from racemization by zwitterion formation, (ii) shortening of sequence, and (iii) synthesis of carboxylic acid free peptide. As a model study, unprotected L-allylglycine was treated with 2 equiv of 1-(trimethylsilyl)imidazole (TMSIm)/dimethylformamide (DMF)/room temperature, 2 h. To the resulting solution was added the thiopyridyl ester A in DMF (room temperature, 14 h) to give, after acidic work up, a dipeptide B (87%) in one pot.[7] This reaction suggests the preliminary formation of the (trimethylsilyl)amino trimethylsilyl ester[8] which then reacts with A (Scheme II).

Coupling of the thiopyridyl ester **4b**, prepared from the synthetic intermediate **4a** of homotyrosine,[1] with the partially protected threonine **5**[9] was effected by means of TMSIm method (2 equiv of TMSIm/DMF) to give the dipeptide **6** in 88% yield. In order to carry out the coupling of **6** with **7**,[10] diethyl phosphorocyanidate (DEPC)[11] was examined as the condensing agent, since thiopyridyl ester of **6** had not been obtained in satisfactory yield. This reaction

(1) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) Keller-Juslén, C.; Kuhn, M.; Loosli, H.-R.; Petcher, T. J.; Weber, H. P.; von Wartburg, A. *Tetrahedron Lett.* **1976**, 4147.
(3) Traber, R.; Keller-Juslén, C.; Loosli, H.-R.; Kuhn, M.; von Wartburg, A. *Helv. Chim. Acta* **1979**, *62*, 1252.
(4) The same system has been appeared in maytansine, see: Kupchan, S. M.; Komada, Y.; Court, W. A.; Thomas, G. T.; Smith, R. M.; Karim, A.; Gilmor, C. J.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 1354.
(5) Although examples using thiopyridyl esters for peptide synthesis[a] were quite rare,[b,c] the neutral nature of the entire process (preparation and coupling)[7,16] prompted us to employ it in this study. (a) Matsueda, R.; Maruyama, H.; Ueki, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1373. (b) Klausner, Y. S.; Bodanszky, M. *Synthesis* **1972**, 543. (c) Bodanszky, M.; Bodanszky, A.; *The Practice of Peptide Synthesis*; Springer-Verlag: New York, 1984; p 227.
(6) In the peptide synthesis, the use of unprotected amino acids as the amine component in aqueous solution is known as Schotten-Baumann method, see: Bodanszky, M.; Klausner, Y. S.; Ondetti, M. A. *Peptide Synthesis*, 2nd ed.; Wiley: New York, 1976; p 85.
(7) In order to examine the extent of racemization, the peptide B was converted to the methyl ester [CH_2N_2; mp 116.5–117.0 °C; $[\alpha]^{25}_D$ +12.9° (*c* 1.01, $CHCl_3$)] and compared with the mixture of Z-L-valyl-DL-allylglycine methyl ester by ^{1}H NMR (360 MHz) and HPLC (Develosil ODS-5) (see supplementary material). Less than 1% (if any) of racemization was found. Details are currently investigated.
(8) The use of 1.0 equiv of TMSIm resulted in decrease of yield (22%). In the case of 3.0 equiv of TMSIm, only trace amount of dipeptide was obtained. The synthesis of (trimethylsilyl)amino trimethylsilyl ester using 1,1,1,3,3,3-hexamethyldisilazane and reaction with an activated ester were reported, see: Birkofer, L.; Konkol, W.; Ritter, A. *Chem. Ber.* **1961**, *94*, 1263.
(9) Prepared from *N*-benzyloxycarbonyl-L-threonine in two steps: (i) 2 equiv of *tert*-butyldimethylsilyl chloride/DMF/imidazole, acidic workup (pH 3), **10a**; mp 150.5–152.5 °C; $[\alpha]^{23}_D$ +13.2° (*c* 1.0, $CHCl_3$); (ii) H_2/Pd–C/AcOEt, **5**; mp 152–169 °C dec; $[\alpha]^{23}_D$ −28.7° (*c* 1.0, MeOH); 89% in two steps.
(10) Prepared from (2*S*,3*S*,4*S*)-*N*-*tert*-butoxycarbonyl-3-hydroxy-4-methylproline[1] (TFA/CH_2Cl_2, room temperature, 1 h).
(11) Yamada, S.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, 1595.

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