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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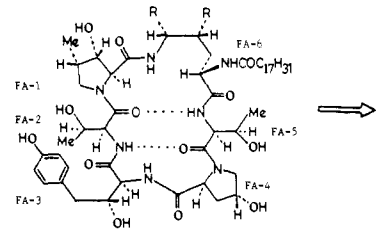
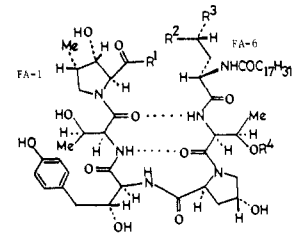
In the preceding paper,[1] we described the syntheses of the constituent amino acids of echinocandins. Now, we turned our attention to the total synthesis of these cyclic hexapeptides using a new peptide coupling reaction. According to the structural studies of echinocandins, their relatively rigid conformation 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

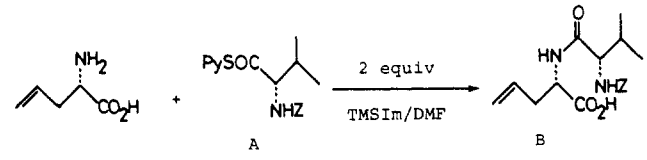


echinocandin C (**1**), R = OH
echinocandin D (**2**), R = H



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

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(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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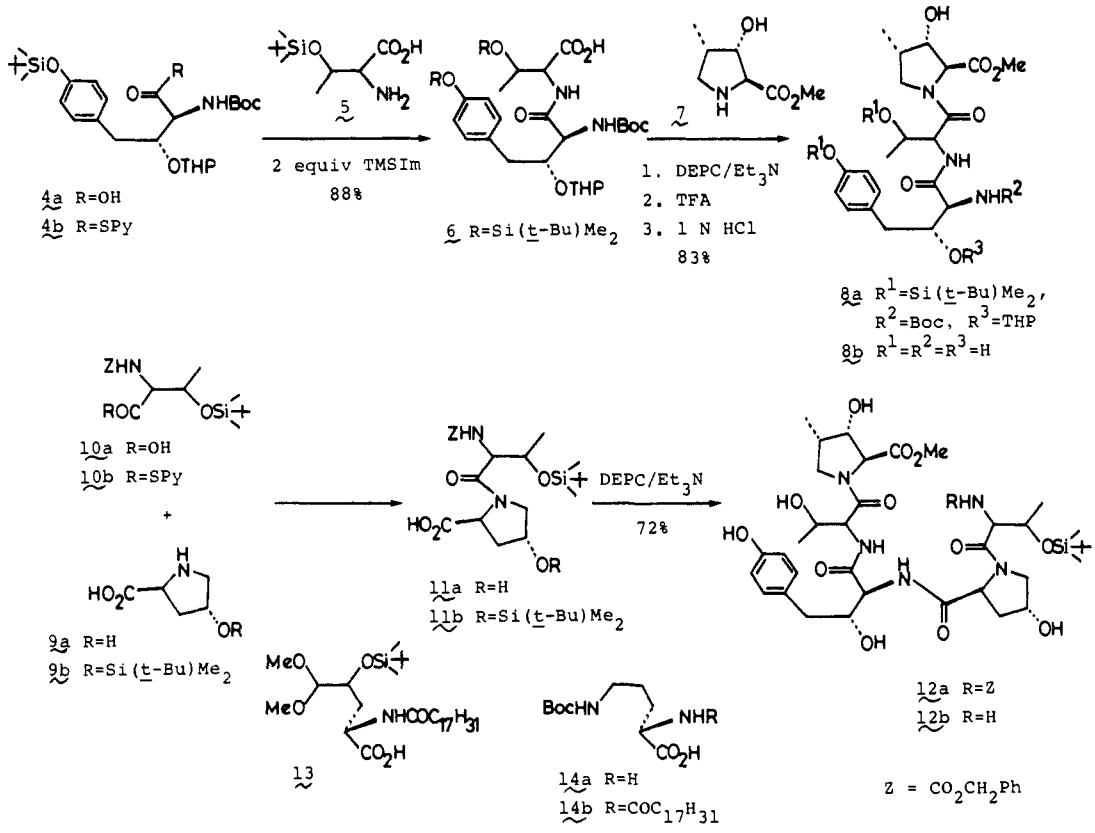
Scheme III



proceeded smoothly yielding the tripeptide **8a** (83%), which upon acidic treatments, (i) trifluoroacetic acid (TFA) and (ii) 1 N HCl, afforded the tripeptide **8b**,[12] quantitatively: amorphous solid; $[\alpha]^{28}_D$ −11.8° (*c* 1.7, MeOH).

In spite of our numerous efforts, coupling of **9a** with the thio ester **10b**[13] using TMSIm was not successful probably due to its poor solubility in the solvent.[14] However, addition of triethylamine (0.9 equiv) in combination with TMSIm (2.0 equiv) gave the dipeptide **11a** in 67% yield.[15] It is noteworthy that *the condensation of imino acid with thiopyridyl ester can be carried out in the presence of catalytic amounts of tertiary amines.* For example, reaction of the 4-O-protected **9b** with **10b** using diisopropylethylamine (0.1 equiv) provided **11b** in 87% yield.[16] Thus obtained **11a** was submitted to the coupling with **8b** (DEPC/Et_3N/DMF) to give the pentapeptide **12a** [72%; amorphous solid; $[\alpha]^{26}_D$ −83.9° (*c* 1.27, MeOH)],[12] which may be used as the common synthetic intermediate for both **1** and **2** (Scheme III). Approaches to **1** and the synthesis of **2** are described in the following.

According to our initial synthetic plan for **1**, **12a** was converted to the hexapeptide **3a** in three steps: (i) NH_3/MeOH, (ii) H_2/Pd–C/MeOH, and (iii) **13**[1]/DEPC/DMF, 33% from **12a**; amorphous solid; $[\alpha]^{26}_D$ −51.6° (*c* 1.11, MeOH). Upon treatment with acidic conditions (0.1 N HCl, 60% acetic acid, etc.), all protecting groups of **3a** were removed. Although the formation of cyclized **1** was expected under the present conditions, no such product was obtained.[17] We then turned our attention to the synthesis of **2**. The N^{α}-linoleylornithine **14b** was prepared from **14a** in one step using 2.0 equiv of TMSIm ($C_{17}H_{31}COSPy$/DMF, 89%) and was condensed with **12b**, prepared from **12a** by H_2/Pd–C, using DEPC to give the hexapeptide **3c** in 68% yield: amorphous solid; $[\alpha]^{24}_D$ −25.0° (*c* 1.07, MeOH).[12] Removal of the protecting groups was carried out in two steps, (i) 1 N NaOH and (ii) TFA, to give **3d** (78%). The cyclization was accomplished by using diphenylphosphoryl azide (DPPA)[18] to give **2** in 50% yield as a glassy solid: mp 172–174 °C dec; $[\alpha]^{22}_D$ −46.1° (*c* 0.9, MeOH).[3] Synthetic **2** was identical in all respects with those reported.[3,19,20] Further studies dealing with the hemiaminal bond

(12) Homogeneity of this compound was examined by its ^{1}H NMR (360 MHz) as well as HPLC (Develosil ODS-5; elution with MeOH/H_2O).

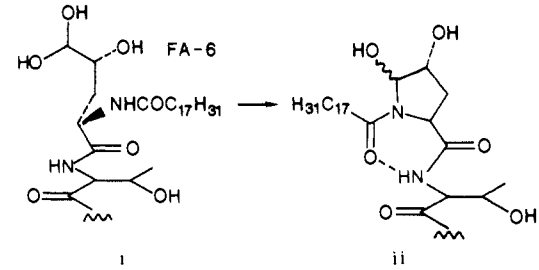
(13) Prepared from **10a** (Py_2S_2/Ph_3P/CH_2Cl_2, 92%).

(14) Limitation of the TMSIm method is its inapplicability to imino acid systems with a stronger zwitterion than amino acids which probably prevent the trimethylsilyl ester formation.

(15) The present reaction was assumed to proceed via preliminary silylation of 4-hydroxyl group followed by esterification with trimethylsilyl group to give the basic amino character, which reacted with activated ester.

(16) The neutral thiopyridyl leaving group may play a key role for the present reaction. Exchange of the tertiary amine salt between the product (dipeptide) and substrate (unprotected amino acid) might occur. However, in the case of amino acids, the reaction proceeded very slowly to give the dipeptide in poor yield, probably because of the poor nucleophilicity of the primary amine. Details are currently investigated.

(17) Deprotection of **3a** proceeded cleanly to give 3b as its hydrate (i) at FA-6; MS (SIMS, *m/z*) 1044 (M + H)$^+$. Many attempts to cyclize by dehydration from (i) were not successful probably because of the pyrrolidine (ii) formation.



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(18) Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 855. Examples in the cyclization of peptide using DPPA, see: (a) Brady, S. F.; Varga, S. L.; Freidinger, R. M.; Schwenk, D. A.; Mendlowski, M.; Holly, F. W.; Veber, D. F. *J. Org. Chem.* **1979**, *44*, 3101. (b) Hamada, Y.; Shibata, M.; Shioiri, T. *Tetrahedron Lett.* **1985**, 5155.

(19) Further proof has been obtained by converting synthetic **2** into its tetrahydro derivative (tetrahydroechinocandin D) (H_2/Pd–C/EtOH, 100%, linoleyl side chain was reduced to the stearyl group), which was identical in all respects with a sample provided by Dr. von Wartburg: mp 180–185 °C dec; $[\alpha]^{22}_D$ −38.5° (*c* 0.61, MeOH).[3]

(20) Analytical data (^{1}H NMR, IR, MS, etc. for all new compounds) and combustion analysis or high-resolution mass spectral data (for key intermediates) were obtained.

formation for the synthesis of **1** are still under investigation.

Acknowledgment. We thank Professor Koji Nakanishi, Director, for continuous encouragement. We are indepted to Dr. Albert von Wartburg, Sandoz AG, for generous gifts of authentic samples of tetrahydroechinocandin C and D as well as spectroscopic data of **1** and **2**.

Supplementary Material Available: ^{1}H NMR, IR, $[\alpha]_D$, mp, and elemental analytical or high-resolution mass spectral data for key intermediates and synthetic **2**, ^{1}H NMR (360 MHz) and HPLC analysis data of dipeptide B, and ^{1}H NMR (360 MHz) data of synthetic tetrahydroechinocandin D and natural tetrahydroechinocandin D (18 pages). Ordering information is given on any current masthead page.

Dramatic Differences in Intramolecular Reactivities of Singlet Arylcarbenes and Benzyl Cations

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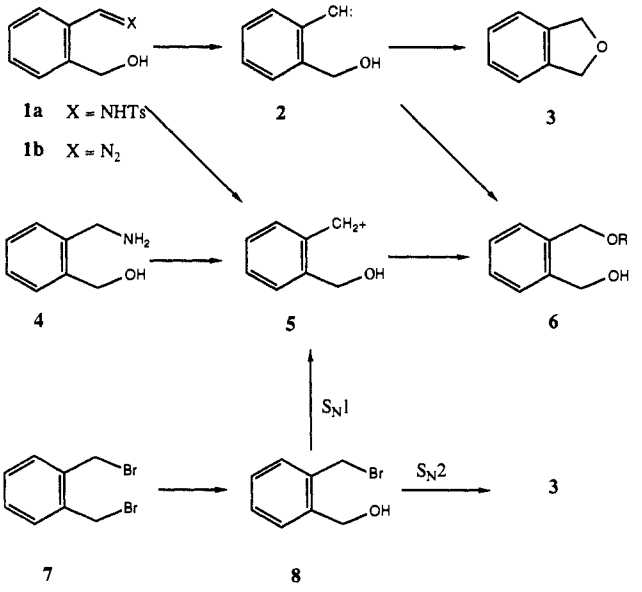
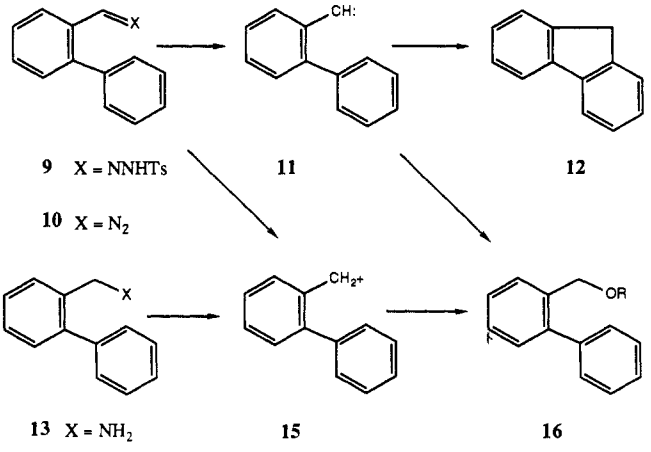
Many reactions of singlet carbenes are closely analogous to those of carbocations,[1,2] since the reactivities of both species are dictated by an electrophilic vacant 2p orbital. Nevertheless, we report here experimental evidence that arylcarbenes react readily with nucleophilic groups on ortho substituents, whereas simple benzyl cations do not, in spite of similar intermolecular reactivities of carbenes and cations. This difference can be rationalized in terms of the rotational barriers of the two systems, which we have determined by ab initio molecular orbital calculations.

Photolysis of the sodium salt of tosylhydrazone **1a** proceeds via diazo compound **1b**[3] and gives a strongly solvent-dependent ratio of intramolecular and intermolecular O–H insertion products. The ratio of **3**/**6** is 71:29, 51:49, 38:62, 10:90, and 2:98 in *tert*-butyl alcohol, ethanol, methanol, water, and trifluoroethanol, respectively, using 0.2 M sodium alkoxide in alcohol as the base. Although it might be expected that increasing solvent nucleophilicity should lead to more of the intermolecular trapping product **6**, the opposite is found experimentally. As solvent nucleophilicity decreases, the amount of **6** increases. This parallels the increase in solvent acidity, which should increase the rate of formation of the cation, **5**, from carbene **2**.[4] This trend indicates that the benzyl cation **5** does not undergo intramolecular nucleophilic substitution whereas the carbene **2** gives rise to both **3** and **6**. In fact, nitrous acid deamination of 2-(aminomethyl)benzyl alcohol (**4**) affords **6**-OH exclusively. The hydrolysis of α,α'-dibromo-*o*-xylene (**7**), which proceeds via bromo alcohol **8**, yields large quantities of **3** under S_N2 conditions. For example, **3** and **6** are formed in 74:26 ratio in 9:1 NaOH/dioxane. Essentially only **6** is formed when polar solvents (e.g., 7:93 **3**/**6** in 1:1 H_2O/dioxane) and electrophilic catalysis are employed (e.g., 3:97 **3**/**6** in 1:1 H_2O/dioxane with 1 equiv of $AgBF_4$).

Carbene **11** gives fluorene (**12**) by intramolecular insertion.[5] In the presence of alcohols, intermolecular O–H insertion competes



with the formation of **12**. Thus, **12** and **16** are formed in ratios of 67:33, 57:43, 54:46, and 14:86 in *tert*-butyl alchol, ethanol, methanol, and trifluoroethanol, respectively. Nitrous acid



deamination of **13** and deacylation of **14** did not produce fluorene; the benzyl cation **15** does react intermolecularly with arenes, for example, in benzene–methanol mixtures.

The rate constants for the reaction of aromatic carbenes with alcohols are known to be on the order of 10^9–10^{10} M^{-1} s^{-1}.[6] The rate constant for the reaction of *p*-methylphenethyl cation in water is also estimated to be 10^{10} M^{-1} s^{-1}, while stabilized cations react more slowly.[7] Reaction rates in ethanol are known to be of the same order of magnitude.[8] These data suggest that the difference in selectivity observed in our systems does not arise from a higher reactivity of the cation than the carbene with alcoholic solvents. Instead, the difference in reactivity must arise from the difference in ability of carbenes and cations to achieve a reactive conformation.

Rotation about the bond connecting the sp^2 carbon of the carbene or cation to the ring must occur in order for intramolecular insertions to take place. We postulate that arylcarbenes have considerably lower barriers to rotation about this bond than do

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(3) Dauben, W. G.; Willey, F. G. *J. Am. Chem. Soc.* **1962**, *84*, 1497.
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