Tetrahedron Letters,Vol.30,No.17,pp 2251-2254 ,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

STEREOSELECTIVE HYDROXYLATION OF A PEPTIDE SIDE CHAIN. THE SYNTHESIS OF THE ECHINOCANDIN RIGHT-HALF EQUIVALENT

Masahiro Sakaitani and Yasufumi Ohfune*

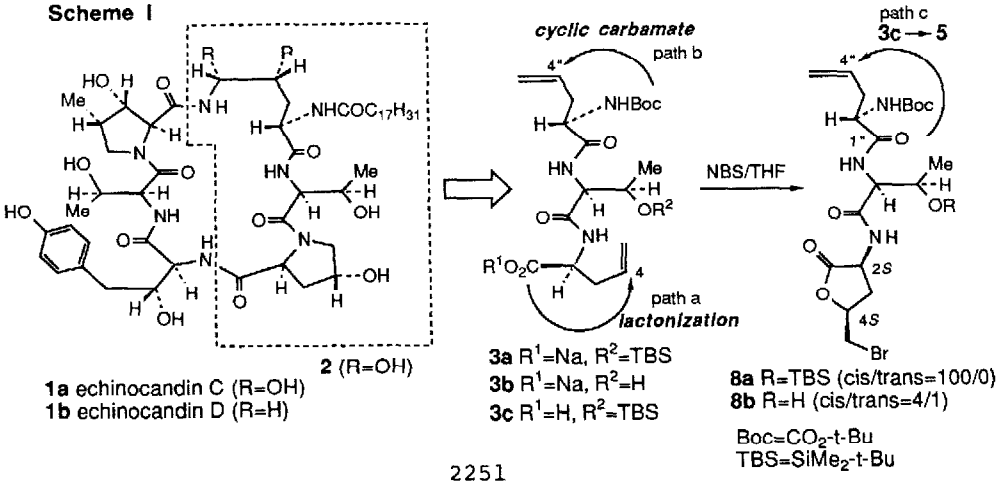
Suntory Institute for Bioorganic Research, Shimamoto-cho, Mishima-gun, Osaka 618, Japan

Summary: Highly stereoselective synthesis of the functionalized tripeptide **15a**, equivalent to the echinocandin right-half **2**, from the simple and rather symmetrical tripeptide **3** has been accomplished based on the halolactonization from the C-terminal of **3** and the cyclic carbamate formation from the N-terminal of **3**.

Methods for nonenzymatic cleavage of peptide bonds as well as modification of peptide side chains are important tools for structure determination or structure transformation of a variety of peptides.[1] From a synthetic point of view, it is of great interest to examine chemo- and stereoselective introduction of new functional groups onto peptides using a variety of synthetic reagents since the dynamic role of peptide functionality and/or peptide conformation has not yet been fully rationalized during these transformations. In conjunction with the studies of the total synthesis of echinocandins **1**,[2] isolated from strains of *Aspergillus ruglosus* and *Aspergillus nidulans*,[3] we designed a new strategy focusing on a novel transformation of the simple tripeptide **3** into the echinocandin right-half **2**: both N- and C-terminals of threonine in **2** are composed of C5 amino acids possessing a γ-hydroxy-α-amino group which can be replaced by L-allylglycine as shown in Scheme I. Described herein is the highly stereoselective synthesis of the echinocandin right-half equivalent **15a** from **3a**.

Since introduction of a hydroxyl group into the γ-position of each allylglycine fragment plays a key role in the above strategy, we examined a halolactonization from the C-terminal of **3** (path a) and cyclic carbamate formation from the N-terminal of **3** (path b) to control the hydroxyl group stereochemistry (Scheme I). These methods are summarized in eq 1 (halolactonization)[4,5] and 2 (S_N2' cyclic carbamate

Scheme I



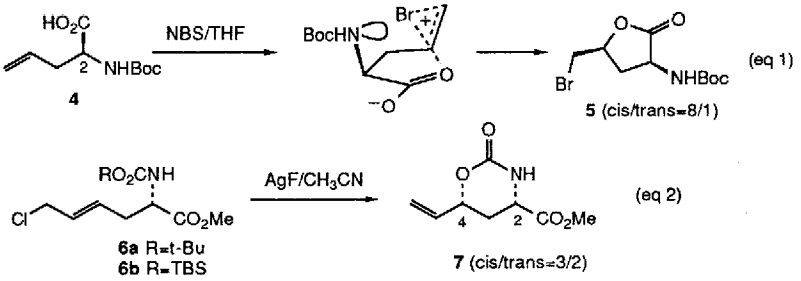
2 (R=OH)

1a echinocandin C (R=OH)
1b echinocandin D (R=H)

3a R^1=Na, R^2=TBS
3b R^1=Na, R^2=H
3c R^1=H, R^2=TBS

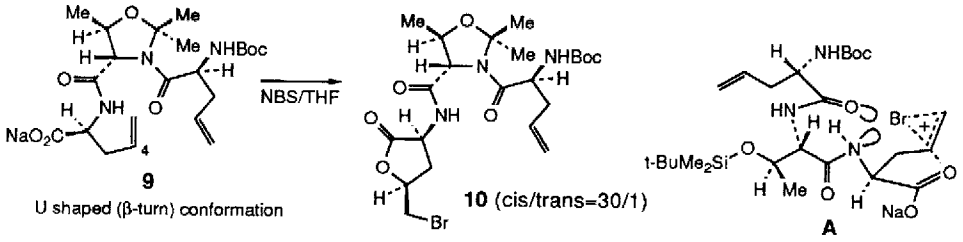
8a R=TBS (cis/trans=100/0)
8b R=H (cis/trans=4/1)

Boc=CO_2-t-Bu
TBS=$SiMe_2$-t-Bu



formation via a silylcarbamate **6b** prepared from **6a**[6] (*vide infra*). The tripeptide **3a-3c** was prepared efficiently from N-*tert*-butoxycarbonyl (*t*-Boc)-allylglycine **4** using the 1-(trimethylsilyl)-imidazole (TMSIm) method[2b] in 4 steps (70% overall yield).[7] We have demonstrated that electrophile mediated lactonization of 2-amino-4-pentenoic acid derivatives shows significant cis selectivity in the γ-butyrolactonization (cis/trans=6~8/1) due to a stereoelectronic stabilization of halonium ion intermediate from the C2 amino group (eq 1).[5] Initial attempts using this method on **3c** with N-bromosuccinimide (NBS), THF, 0 °C were not successful due to participation by the amide group rather than the carboxyl group and resulted in the regioselective cleavage of the peptide bond at C1"-N eliminating the γ-butyrolactone **5** (path c). However, treatment of the sodium salt **3a** under the same conditions gave the desired γ-butyrolactone **8a** (76%), exclusively, without any elimination of **5**. The increased nucleophilicity of the carboxyl group by forming a sodium salt may be the major reason for this regioselectivity.

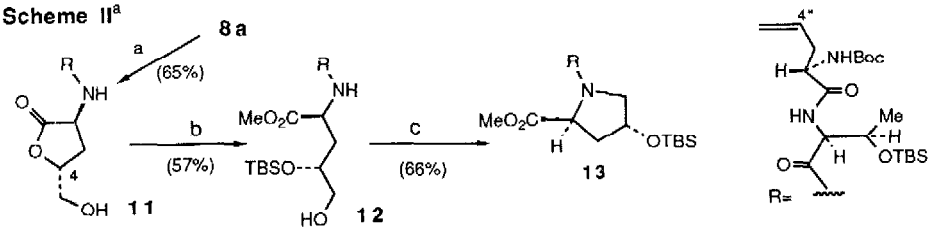
It is interesting to note that this lactonization product is composed of a single isomer, cis-**8a**[8] with 2*S*,4*S* stereochemistry. In order to explain this dramatic increase of cis selectivity in comparison with that of amino acid **4** (cis/trans=8/1), we examined the same reaction using structurally rigid analogue **9**[9] in which the N,O-acetonide constrains the tripeptide structure to be U shaped (β-turn conformation).[10] The reaction of **9** with NBS provided the cis-γ-butyrolactone **10** (79%) as the major product (cis/trans=30/1). However, reaction of unprotected **3b** which might have a linear conformation resulted in a decrease in selectivity (cis/trans= 4/1).[10] From these results, it is suggested that the bulky silyl group of **3a** plays a role in fixing its conformation to be U shaped **A** where the bromonium cation is stabilized by a cooperative



stereoelectronic effect of the neighboring amide and carbonyl groups.[5] Thus, cis-γ-butyrolactone **8a** was converted into the tripeptide **13** as illustrated in Scheme II.

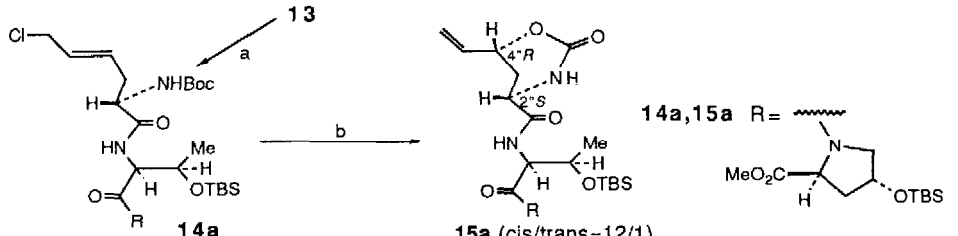
In order to carry out the introduction of C4" hydroxyl group into **13**, it is necessary to modify its vinyl group into an allyl chloride (**13→14a**). Cleavage of the double bond of **13** (O_3/MeOH) and subsequent introduction of a C2 moiety ($Ph_3PCHCHO$/benzene) gave an aldehyde (94%) which upon reduction (LiAlH(O-*t*-Bu)$_3$/THF) followed by chlorination (NCS/Ph_3P) yielded the allylchloride **14a**. In our previous

Scheme II[a]



[a](a) (1) K_2CO_3, MeOH, 0 °C, 3 h; (2) 0.5 N NaOH, THF, 0 °C, 3h; (3) *dl*-10-camphorsulfonic acid (CSA), THF, room temperature, 15 h; (b) (1) 3,4-dihydro-2*H*-pyran, CSA, CH_2Cl_2, 0 °C, 5 h; (2) 0.5 N NaOH, 0 °C, 3 h; (3) CH_2N_2. (4) *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), 2,6-lutidine, 0 °C, 15 min; (5) CSA, MeOH, 0 °C, 3 h; (c) (1) TsCl, pyridine, room temperature, 15 h; (2) NaH, THF, 0 °C, 2 h.

Scheme III[a]



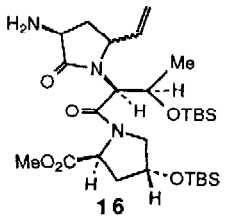
[a](a) (1) O_3, MeOH, -78 °C, Me_2S, room temperature, 15 h; (2) $Ph_3PCHCHO$, benzene, 2 h; (3) $LiAlH(O\text{-}t\text{-}Bu)_3$, THF, -78 °C, 1 h, -30 °C, 2 h; (4) N-chlorosuccinimide (NCS), Ph_3P, CH_2Cl_2, 0 °C, 2 h (50% from **13**); (b) (1) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 15 min; (2) AgF, CH_3CN, room temperature, 20 h.

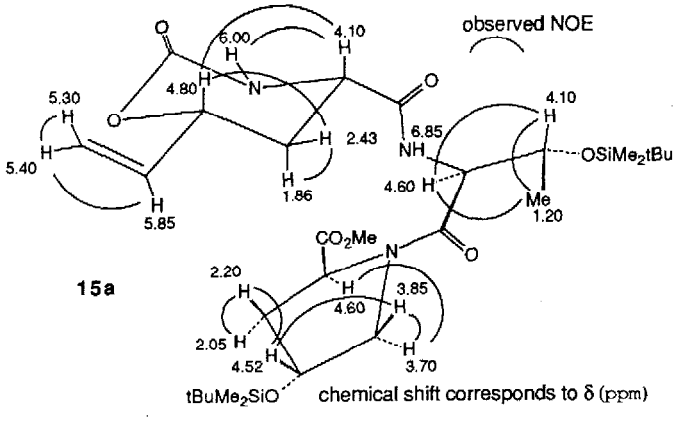
studies on S_N2' cyclic carbamate formation, poor stereoselectivity was observed in producing a new stereogenic center at C4 (cis/trans=3/2, eq 2).[6] We expected greater selectivity by the use of peptide systems and, first, examined cyclic carbamate formation of the dipeptide **14b**. However, treatment of **14b** with TBSOTf/2,6-lutidine followed by AgF gave diastereomeric **15b** in a poor ratio (cis/trans=1.5/1, 50%). In contrast to these results, treatment of the tripeptide **14a** by the same conditions yielded, stereoselectively, the 2"*S*,4"*R* isomer **15a**, as the major product (cis/trans=12/1, 21%), of which the stereochemistry was ascertained by its H,H-COSY and NOESY data.[12,13] Although the increased stereoselectivity in this case can not be well explained, it is suggested that both participation from the proximal functional groups and steric effects derived from peptide conformation at the reaction site might contribute to the product stereoselectivity. The cyclic carbamate **15a** possessing appropriate functional groups with a masked hemiaminal at C5" can be viewed as an equivalent to the target structure **2**. Further studies related to nonenzymatic reactions on peptides are under investigation.

Acknowledgement: We thank Professor Koji Nakanishi, Director of the Suntory Institute for Bioorganic Research, for continuous encouragement. This work was supported in part by a grant-in-aid from the Ministry of Education, Science and Culture, Japan.

References

1. (a) Kasper, C. B. Protein Sequence Determination, *Molecular Biology, Biochemistry and Biophisics;* vol 8.; Needleman, S. B. Ed.; Springer-Verlag: New York, 1970; p 137. (b) *Amino Acids, Peptides and Proteins*; Royal Society of Chemistry; London, Vol **1-19**, 1968-1986.
2. (a) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**,*108*, 6041. (b) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**,*108*, 6043. (c) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**,*109*, 7151.
3. v. Traber, R.; Keller-Juslén, C.; Loosli, H.-R.; Kuhn, M.; v. Wartburg, A. *Helv. Chim. Acta* **1979**, *62*, 1252.
4. (1) For a review of halolactonization, see: Bartlett, P. A.; Richardson, D. R.; Myerson, J. *Tetrahedron*, **1984**, *40*, 2317. (2) Nonenzymatic peptide cleavage using halolactonization, see: (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*, 4613.
5. Ohfune, Y.; Hori, K.; Sakaitani, M. *Tetrahedron Lett.* **1986**, *27*, 6079.
6. Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1987**, *28*, 3987.
7. Synthetic procedure for **3a**: (1) 2,2'-dipyridyl disulfide, Ph_3P, CH_2Cl_2, room temperature; (2) 2 equiv TMSIm, O-*tert*-butyldimethylsilyl-L-threonine, DMF, room temperature, 15 h; (3) (1); (4) 2 equiv TMSIm, L-allylglycine, DMF, room temperature,15 h.
8. Comparison of the reaction mixture with an authentic trans (2*S*,4*R*)-**8a**, prepared form **11** by the treatment with NBS/Ph_3P, indicated that (2*S*,4*R*)-**8a** could not be detected by ^1H NMR or HPLC analysis (99>1).
9. Prepared from N-*t*-Boc-L-allylglycyl-L-threonine N,O-acetonide; (i) Py_2S_2,Ph_3P and (ii) allylglycine, TMSIm.[2b,7]
10. Chon, P. Y.; Fasman, G. D. *J. Mol. Biol.* **1977**, *115*, 135.
11. Employment of D-allylglycine instead of the L-isomer at the C-terminal of **3a** resulted in a decrease in the products stereoselectivity (cis/trans=4/1) probably due to a conformational change of the peptide. Further studies related to this work are in progress.
12. Low yield in this reaction was due to a formation of unidentifiable amines. It should be noted that treatment of **14a** with AgF in the presence of catalytic Pd (AgF, allylpalladium chloride dimer, Ph_3P, room temperature, 3h)[6] gave pyrrolidone **16** as a mixture of diastereomers in 51% yield.
13. Spectroscopic data and physical constants of the selected compounds. Methyl ester of **3**, mp135-136 °C, $[\alpha]_D$ -3.1° (*c* 0.89, MeOH); **8a**, amorphous solid, $[\alpha]_D$ +4.2° (*c* 0.46, MeOH); **10**, oil, $[\alpha]_D$ -22.4° (*c* 1.0, MeOH); **13**, mp 141-142 °C, $[\alpha]_D$ -36.6° (c 1.0, MeOH); **14a**, oil, $[\alpha]_D$ -30.6° (*c* 1.0, MeOH); **15a**, oil, ^1H NMR ($CDCl_3$) δ 6.85 (d, 1 H, *J* = 7 Hz), 6.00 (d, 1 H, *J* = 4 Hz), 5.85 (ddd, 1 H, *J* = 17, 10, 5 Hz), 5.40 (brd, 1 H, *J* = 17 Hz), 5.30 (brd, 1 H, *J* = 10 Hz), 4.80 (m, 1 H), 4.60 (m, 2 H), 4.52 (m, 1 H), 4.10 (m, 2 H), 3.85 (dd, 1 H, *J* = 10, 5 Hz), 3.70 (s, 3 H), 3.70 (dd, 1 H, *J* = 10, 3 Hz), 2.43 (brd, 1 H, *J* = 12 Hz), 2.20 (m, 1 H), 2.05 (m, 1 H),1.86 (ddd, 1 H, *J* = 12, 11, 11 Hz), 1.20 (d, 3 H,*J* = 7 Hz), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.10 (s, 6 H), 0.07 (s, 6 H); MS (SIMS), m/z 628 $(M)^+$, 612, 570; Anal. Calcd. for $C_{29}H_{53}O_8N_3Si_2$: C, 55.47; H, 8.51; N, 6.69. Found: C, 55.33; H, 8.52; N, 6.63. The structure of **15a** was confirmed by its H,H-COSY and NOESY studies as shown below.





(Received in Japan 2 February 1989)