Communications to the Editor

[Chem. Pharm. Bull. 30(9)3457—3460(1982)]

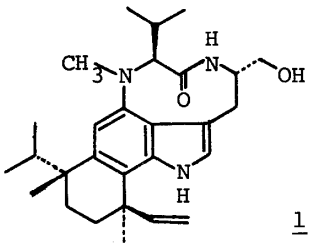
MOLECULAR REQUIREMENTS FOR EPIGENETIC MODULATORS. SYNTHESIS OF ACTIVE FRAGMENTS OF TELEOCIDINS AND LYNGBYATOXIN

Yasuyuki Endo, Koichi Shudo and Toshihiko Okamoto*
Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Tokyo, 113, Japan

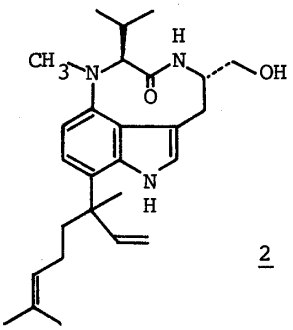
A synthesis of 3,4,5,6,7,8-hexahydro-6-oxo[1,4]diazonino[7,6,5-cd]indoles (3 and 18) which have active fragments of teleocidins (1) and lyngbyatoxin (2) is described.

KEYWORDS——3,4,5,6,7,8-hexahydro-6-oxo[1,4]diazonino[7,6,5-cd]-indole; nine-membered lactam; tryptophan; teleocidin B; carcinogenesis promotors

Epigenetic modulators which control cell differentiation, cell prolification, and some hormonal phenomena are attracting great interest. One of the most interesting epigenetic modulators is a carcinogenesis promotor which enhances chemically-induced malignant cell transformation and promotes tumor developement.[1] In particular, 12-O-tetradecenoylphorbol-13-acetate[2] and dihydroteleocidin B[3] (a catalytically hydrogenated compound of teleocidin B (1))[4] have strong activities. We have been interested in the chemical structure of teleocidins and lyngbyatoxin (2)[5] and the minimum structure required for appearance of their activities.



1



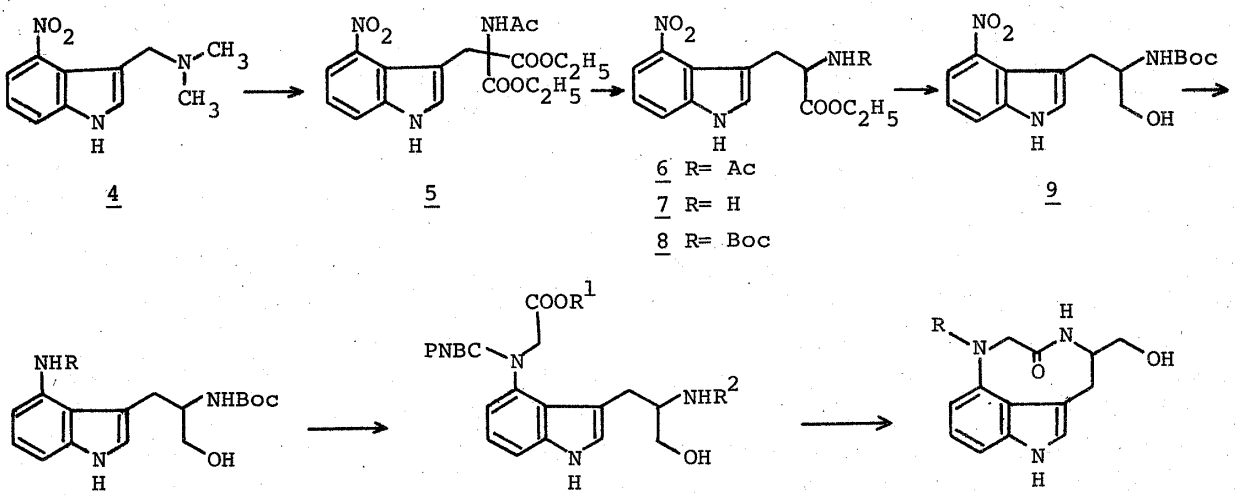
2

The common structural fragment includes an indole and a nine-membered lactam, which seems to be indispensable to the biological activities. Thus, we started the synthesis of 3,4,5,6,7,8-hexahydro-4-hydroxymethyl-8-methyl-6-oxo[1,4]diazonino[7,6,5-cd]indole (3). The only synthetic problem is how to constitute the nine-membered ring: successful synthetic methods of nine-membered rings are limited.[6] The first attempt to cyclize by intramolecular reductive condensation of 4-amino-N-acetoacetyl-tryptophan ethyl ester was unsuccessful. Pathways through the formation of a bicyclic ring as an intermediate and the following ring cleavage are under study. After these efforts, the desired compounds could be prepared by cyclization of succinimide esters. This method can be applied to the synthesis of related compounds and to the total

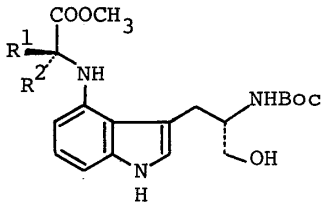
synthesis of the natural products.

The starting material, 4-nitrogramine (4)[7], was converted to DL-4-nitrotryptophan ethyl ester (7). Alkylation of 4 with ethyl iodide in the presence of diethyl acetoamidomalonate and sodium ethoxide (EtOH, reflux, 7 h) afforded diester 5 in a 51% yield. The diester was hydrolyzed (2.5N NaOH, H_2O, reflux, 1.5 h), decarboxylated (H_2O, reflux, 1 h) and esterified ($SOCl_2$, EtOH, 0°C, 1 h, 60°C, 3 h) to give N-acetyl-4-nitrotryptophan ethyl ester (6) (61%). The N-acetyl group was removed by EtOH-HCl (reflux, 48 h) to give 7, whose amino group was reprotected by t-butoxycarbonyl ($BocN_3$, $NaHCO_3$, dioxane-H_2O, 45°C, 40 h) to 8 (80%). Reduction of 8 with lithium borohydride (THF, r.t., 2 h) gave N-Boc-4-nitrotryptophanol (9) in a quantitave yield. The nitro group was catalytically reduced by Pd-charcoal in EtOH to N-Boc-4-amino-tryptophanol (10) in 87% yield.

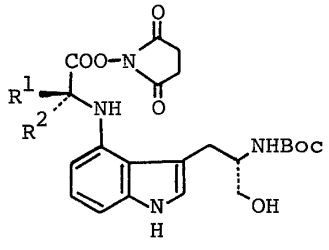
N-Alkylation of 10 with ethyl bromoacetate ($NaHCO_3$, EtOH, reflux, 1 h) gave 11 in 72% yield. The amino group was protected by 4-nitrocarbobenzoxy (PNBC)[8] group (4-NO_2-$PhCH_2OCOCl$, $NaHCO_3$, ether-H_2O, r.t., 3 h, 95% yield), which could be removed catalytically and probably resulted in the favorable comformation for the cyclization. The ester group of 12 was hydrolyzed by 2N KOH-MeOH to the acid 13 (98% yield). Treatment of 13 with N-hydroxysuccinimide-DCC (CH_3CN, r.t., 2 h) gave the activated ester 14 in 74% yield, which was stable enough to be purified by silica gel column chromatography. Deprotection of the Boc group of 14 by the use of CF_3COOH (CH_2Cl_2, 0°C, 30 min) gave an amino ester 15, which almost spontaneously cyclized to the lactam 16, though the completion of the cyclization seemed to require treatment with weak alkali ($NaHCO_3$, H_2O, 80°C, 15 min). The cyclization did not require highly diluted conditions. Removal of the PNBC group of 16 (10% Pd-charcoal, H_2, 1 atm, EtOH, r.t., 30 min) afforded 17 in 81% yield. N-Methylation of 17 proceeded smoothly (CH_3I, $NaHCO_3$, EtOH, reflux, 4 h, 85% yield) to the objective 3, mp 231-232°C, IR (KBr); C=O 1638 cm^{-1}, MS (M^+) 259, Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C: 64.85, H: 6.57, N: 16.20, Found: C: 64.84, H: 6.63, N: 16.01. The ^1H-NMR spectral data is summarized in Table I. The structure was finally determined by X-ray crystallography.[9]



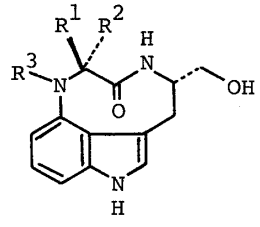
3,4,5,6,7,8-Hexahydro-4-hydroxymethyl-8-methyl-7-methylethyl-6-oxo[1,4]diazonino[7,6,5-cd]indole (18) is provided with the functions of teleocidin B exept for the terpenoid hydrocarbon chain. N-Alkylation of 10 with methyl 2-bromoisovalerate did not proceed, probably because of steric hindrance by the isopropyl group. 10 was treated with methyl 2-oxoisovalerate ($CHCl_3$, reflux, 4 h), and, following reduction with sodium cyanoborohydride (THF, r.t., 18 h), gave 19 in 51% yield. Two diastereomeric isomers (19A, 19B; 1:1) were separated by column chromatography on silica gel. The reaction of activated ester to the aromatic amino group seemed to be suppressed because of steric hindrance by the isopropyl group, so the activation of carboxyl group and the cyclization were carried out without protection by PNBC group. 19 was hydrolyzed by 2N KOH ($MeOH-H_2O$, r.t., 24 h), treated with N-hydroxysuccinimide-DCC (CH_3CN, r.t., 1 h) to give activated ester 20 (57% for 20A, 69% for 20B). Deprotection of the Boc group of 20 employing CF_3COOH (CH_2Cl_2, 0°C, 1 h) gave an amino ester, which was more stable than 15 in neutral solution. Consequently, the amino ester was treated with weak alkali ($NaHCO_3$, H_2O, 80°C, 1 h) to give lactam 21 (64% for 21A, 75% for 21B). N-Methylation of 21 required more severe conditions than N-methylation of 17 (CH_3I, $NaHCO_3$, EtOH, reflux 60 h for 21A, 40 h for 21B) to give 18 (57% for 18A, 79% for 18B). 18A, mp 256-257°C, IR(KBr) C=O 1638 cm^{-1}, MS (M^+) 301, Anal. Calcd. for $C_{17}H_{23}N_3O_2$: C: 67.75, H: 7.69, N: 13.94. Found: C: 67.48, H: 7.71, N: 13.66. 18B, mp 214-216°C, IR(KBr) C=O 1630 cm^{-1}, MS (M^+) 301, Anal. Found: C: 67.56, H: 7.77, N: 13.71. The ^{1}H-NMR spectral data of the lactams are summarized in Table I. All the absorptions of the spectrum of 18B were easily assigned. However, several signals in the NMR spectrum of 18A were split in ca. 2:1 ratio: two singlets for N-CH_3 and two doublets for each methyl of the isopropyl group in CD_3OD. A temperature study in CD_3OD at 23-95°C suggested that the splitting of signals could be due to two comformational isomers of 18A. The NMR is also dependent on the solvent. In CF_3COOD, one comformer predominates, but in deuteropyridine two comformers are present.[10] It is reported that several signals of the NMR spectrum of lyngbyatoxin A were also split in a 5:1 ratio.[5] The existence of two comformers for 18A and 2 suggests that the stereochemistry of 18A corresponds to the natural products: The stereochemistry of 18A and 18B were assigned to 18a and 18b, respectively.



19a R^1=$CH(CH_3)_2$, R^2=H
19b R^1=H, R^2=$CH(CH_3)_2$



20a R^1=$CH(CH_3)_2$, R^2=H
20b R^1=H, R^2=$CH(CH_3)_2$



21a R^1=$CH(CH_3)_2$, R^2=H, R^3=H
21b R^1=H, R^2=$CH(CH_3)_2$, R^3=H
18a R^1=$CH(CH_3)_2$, R^2=H, R^3=CH_3
18b R^1=H, R^2=$CH(CH_3)_2$, R^3=CH_3

Biological activities and structure-activity relationships of the compounds will be published in the near future.

Table I. ^{1}H-NMR spectral Data of Lactams 3, 18a and 18b

	3	18a		18b
		Major comformer	Minor comformer	
$CH(CH_3)_2$	———	0.63(d)	0.92(d)	0.72(d)
		0.92(d)	1.25(d)	0.77(d)
$CH(CH_3)_2$	———	2.5(m)		2.5(m)
N-CH_3	2.90(s)	2.90(s)	2.73(s)	3.08(s)
3-CH_2	3.0-3.2(m)	3.0-3.25(m)		2.9-3.1(m)
CH_2OH	3.5-3.8(m)	3.50(dd) 3.64(dd)		3.6-3.9(m)
4-CH	3.5-3.8(m)	4.20(m)		3.6-3.9(m)
7-CH_2	3.96(dd)	———		———
7-CH	———	4.48(d)		4.05(d)
9-H	6.83(dd)	6.43(dd)		6.70(dd)
2,10,11-H	6.9-7.2(m)	6.8-7.3(m)		6.8-7.0(m)

The spectra were determined in CD_3OD at 23°C at 100 MHz (JEOL FX-100).

REFERENCES AND NOTES

1) Carcinogenesis -- A Comprehensive Survey. Vol.7. Cocarcinogenesis and biological effects of tumor promotors. Eds.E.Hecker et al. Raven Press, New York (1982).
2) E.Hecker, Pure Appl. Chem., 49, 1423 (1977).
3) H.Fujiki, M.Mori, M.Nakayasu, M.Terada, and T.Sugimura, Biochem. and Biophys. Res. Comm., 90, 976 (1976). T.Hirakawa, T.Kakunaga, H.Fujiki, and T.Sugimura, Science, 216, 527 (1982).
4) M.Takashima and H.Sakaki, Bull. Agr. Chem. Soc. Japan, 24, 647 (1960). H.Harada, H.Nakata, and Y.Hirata, Nippon Kagaku Zasshi, 87, 86 (1966). N.Sakabe, H.Harada, Y.Hirata, Y.Tomii, and I,Nitta, Tetrahedron Lett., 1966, 2523.
5) J.H.Cardellina II, F_J. Marner, and R.E.Moore, Science, 204, 193 (1979).
6) G.Illuminati and L.Mandolini, Accounts. Chem. Res., 14, 96 (1981).
7) J.B.Hester, J.Org. Chem., 29, 1158 (1964).
8) J.E.Shields and F.H.Carpenter, J.Am.Chem.Soc., 83, 3066 (1961).
9) Y.Hashimoto, K.Yamaguchi, and Y.Iitaka, unpublished results.
10) Stereochemistry and comformational studies are in progress.

(Received August 9, 1982)