SYNTHETIC STUDIES ON TELEOCIDIN III.[1] REGIOSELECTIVE INTRODUCTION OF NITRO GROUP AT 4-POSITION OF SUBSTITUTED INDOLE DERIVATIVES

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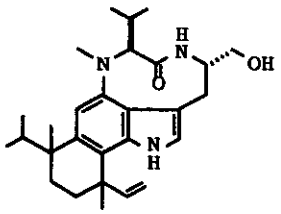
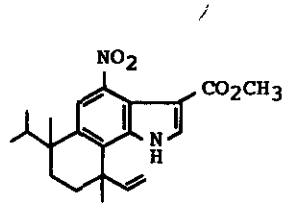
Abstract ——Regioselectivities of nitration of substituted indole derivatives were studied and compound 2 containing three substituents similar to teleocidin B (1) was selectively synthesized.

Potent tumor promoter teleocidin B (1)[2] and related indole alkaloids[3] are one of the most interesting group of natural products for the synthetic chemists because of their challengable highly substituted indole skeletons. Recently, we found novel synthetic methods for direct introduction of substituents at benzene part of indole derivatives.[4] In our synthetic studies on teleocidin, nitrogen function was efficiently introduced[5] at 4-position of stabilized indole derivative 3 and that method was applied to the synthesis[6] of (-)-indolactam V from L-tryptophan. Furthermore, we succeeded in the syntheses[7] of 6,7-disubstituted indole derivative 14 and 16 having similar structure to teleocidin B by regiospecific intramolecular cyclization of 1-geranylindole derivative. In this paper, we report the selecti-



Teleocidin B (1)



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vities of nitration of substituted indoles and synthesis of 2 containing the same substituents with teleocidins at the 4, 6, and 7-positions.

In the previous paper,[5] we reported that stabilized indole derivative such as compound 3 afforded corresponding 4- and 6-nitro derivatives in about 1:1 ratio. Although we supposed that nitration of 6-substituted compound in the same reaction condition would afford only the corresponding 4-nitro derivative, methyl 6-ethyl-1-methyl-indole-3-carboxylate 6[8] in HNO_3(d=1.38)/AcOH at 25°C for 20 min gave no 4-substituted product 7 but 5-nitro derivative 8[9] in 58% yield. we assumed that the ethyl substituent increases the electron density at 5-position.

Teleocidin B (1) contains an alkyl substituent at 6-position of indole nucleus but it is a very bulky quaternal carbon substituent. To examine the influence of such bulky substituent on the selectivity of nitration, we chose compound 9,[8] which contains similar substituent at 7-position to teleocidin A[2d,3] (lyngbyatoxin A), and compound 12,[8] which contains similar substituent at 6 and 7-position to teleocidin B. Nitration of 9 occurred mainly at 4-position[10] rather than 6-position[11] in 44% yield (4:1 ratio) as shown in Table I. In the case of compound 12,[8] 4-nitro derivative 13[12] was obtained in 40% yield and the corresponding 5-nitro derivative was not detected. These results indicated the high possibility of our synthetic route toward teleocidin B (1) and A (lyngbyatoxin A).

Compound 14 (3:1 mixture of stereoisomers) and 16 (pure trans isomer), which were prepared as shown in the previous paper,[7] were also nitrated with conc. HNO_3 (d=1.38) in AcOH at 25°C for 5 min. After usual work up, preparative TLC of each reaction mixture gave desired 4-nitro derivative 15[13] and 2[14] in 50% and 43% yields respectively.[15] The substituted positions of 15 and 2 were determined by comparison of chemical shifts of aromatic protons in ^{1}H-nmr spectra of 15, 2, and corresponding amino derivatives prepared by reduction with Zn in acetic acid.

Thus, obtained compounds 15 and 2 contain three substituents similar to teleocidin B (1) at the 4, 6, and 7-positions of indole nucleus. These selective nitration of 6- and 7-substituted indole derivatives must be very useful for the syntheses of teleocidin B and also related natural products. Further synthetic studies toward them are now in progress.

ACKNOWLEDGEMENT

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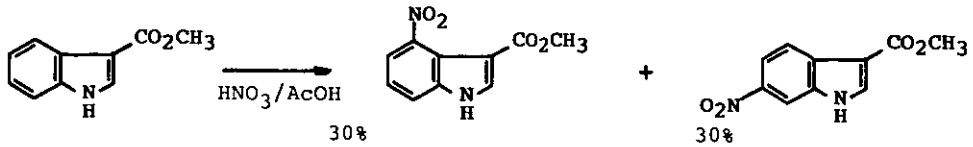

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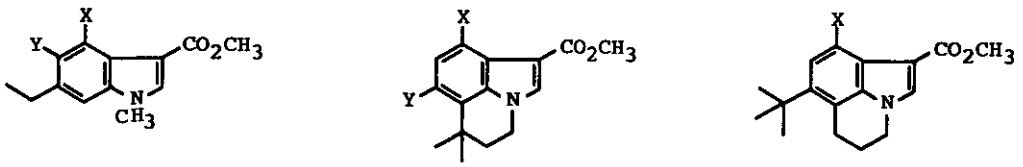
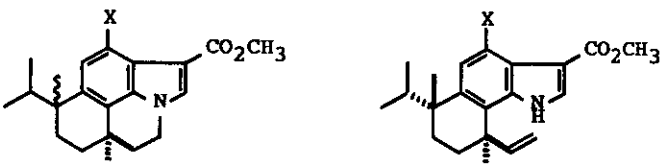


6 : X=Y=H
7 : X=NO_2, Y=H
8 : X=H, Y=NO_2

9 : X=Y=H
10 : X=NO_2, Y=H
11 : X=H, Y=NO_2

12 : X=H
13 : X=NO_2



14 : X=H
15 : X=NO_2

16 : X=H
2 : X=NO_2

Table I. Regioselectivities of nitration of substituted indoles with HNO_3 (d=1.38) in AcOH.

Starting material	Products		
	4-nitro deriv.	5-nitro deriv.	6-nitro deriv.
3	4 (30%)	-	5 (30%)
6	7 (0%)	8[9] (58%)	-
9	10[10] (35%)	-	11[11] (9%)
12	13[12] (40%)	-	-
14	15[13] (50%)	-	-
16	2[14] (43%)	-	-

REFERENCES AND FOOTNOTES

1. Synthetic studies on teleocidin I, II, and IV were cited in ref. 5-7.
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4. S. Nakatsuka et al., Tetrahedron Lett., 1980, 21, 2817 and 1986, 27, 4757; Chemistry Lett., 1981, 407; Heterocycles, 1986, 24, 2109 and 1987, 26, 65.
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6. S. Nakatsuka, T. Masuda, K. Sakai, and T. Goto, Tetrahedron Lett., 1986, 27, 5735.
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8. Unpublished results. Those compounds were prepared from indole.
9. 8: ^{1}H-NMR ($CDCl_3$) δ 1.30 (3H,t,J=8Hz), 2.81 (2H,q,J=8Hz), 3.81 (3H,s), 3.84 (3H,s), 7.20 (1H,br.s), 7.40 (1H,br.s), 7.68 (1H,s).
10. 10: ^{1}H-NMR ($CDCl_3$) δ 1.43 (6H,s), 2.07 (2H,m), 3.84 (3H,s), 4.24 (2H,m), 7.15 (1H,d,J=8Hz), 7.63 (1H,d,J=8Hz), 7.83 (1H,s).
11. 11: ^{1}H-NMR ($CDCl_3$) δ 1.54 (6H,s), 2.05 (2H,m), 3.90 (3H,s), 4.25 (2H,m), 7.37 (1H,d,J=8Hz), 7.88 (1H,s), 7.94 (1H,d,J=8Hz).
12. 13: ^{1}H-NMR ($CDCl_3$) δ 1.46 (9H,s), 2.26 (2H,m), 3.28 (2H,m), 3.83 (3H,s), 4.20 (2H,m), 7.71 (1H,s), 7.80 (1H,s).
13. 15: *a 3:1 mixture of trans and cis isomers,* ^{1}H-NMR ($CDCl_3$) of trans isomer δ 0.74 (3H,d,J=8Hz), 1.06 (3H,d,J=8Hz), 1.20 (3H,s), 1.24 (3H,s), 1.20-2.20 (7H,m), 3.84 (3H,s), 4.28 (2H,m), 7.60 (1H,s), 7.79 (1H,s).
14. 2: ^{1}H-NMR ($CDCl_3$) δ 0.60 (3H,d,J=8Hz), 1.02 (3H,d,J=8Hz), 1.33 (3H,s), 1.50 (3H,s), 1.20-2.00 (4H,m), 2.30 (1H,m), 3.80 (3H,s), 5.38 (1H,d,J=10Hz), 5.58 (1H,d,J=16Hz), 6.19(1H,dd,J=16 and 10Hz), 7.66 (1H,s), 7.81 (1H,d,J=2Hz), 9.26 (1H,br.s).
15. The other major by-products were the corresponding 2-nitro derivatives (15% and 23% yields respectively).

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