Tetrahedron Letters,Vol.27,No.36,pp 4327-4330,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

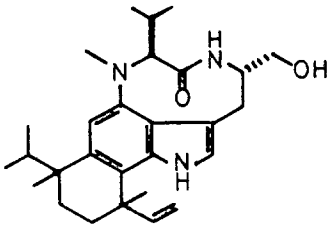
SYNTHETIC STUDIES ON TELEOCIDIN I.
REGIOSELECTIVE INTRODUCTION OF 4-AMINO AND 7-ACYL GROUPS ON INDOLE DERIVATIVE

Shin-ichi Nakatsuka,* Toshiya Masuda, Osamu Asano, Tomohiro Teramae, and Toshio Goto
Laboratory of Organic Chemistry, Faculty of Agriculture, Nagoya University,
Chikusa, Nagoya 464, Japan

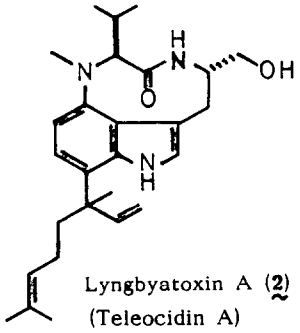
Summary: Nitration of indole-3-carboxylic esters, **3** and **9**, afforded 4-nitro derivatives, **4** and **10**. **10** was regioselectively derived to **15**, which contains substituents at 4- and 7-positions of indole nucleus similarly to teleocidins.

Teleocidin B,[1] lyngbyatoxin A[2] (teleocidin A[1a,d]), and olivoletins[3] are potent tumor promoters. Dihydroteleocidin B, which was obtained by hydrogenation of teleocidins, has been found to be comparable[4] in its tumor promoting activity to 12-O-tetradecanoylphorbol 13-acetate (TPA). They are novel indole alkaloids containing many substituents at the benzene part of indole nucleus. Although many synthetic studies[5-9] toward them have been appeared recently, no successful total synthesis was reported.

We have reported unique methods[10-13] for direct introduction of substituent(s) at benzene part (4-7 positions) of simple indoles, whose pyrrole part was stabilized by conjugation with carbonyl group etc. at 3-position. We report herein the results of introductions of amino and acyl groups at the appropriate positions of indole nucleus for teleocidins.



Teleocidin B (**1**)



Lyngbyatoxin A (**2**)
(Teleocidin A)

Many studies for the direct introduction of nitro group onto the indole derivatives have been studied[14]. But 4-nitro compounds were obtained only in a few cases[15] as a minor component. We started our synthetic studies on teleocidins from the direct nitration of indole derivatives because it would be most useful method for those synthesis.

Majima and Kotake[16] reported the nitration of ethyl indole-3-carboxylate to give its 6-nitro derivative, but 4-nitro derivative was not mentioned in their report. We reexamined the same nitration of its methyl ester **3** instead of ethyl ester. Very interestingly, we observed two major spots (1:1) on a silica gel TLC plate after development of the reaction mixture which was obtained

by nitration of **3** with nitric acid (d=1.38) in acetic acid at 60°C for 1 hr. After addition of ice-water, the reaction mixture was extracted with dichloromethane and dried over Na_2SO_4. Pure 4- and 6-nitro derivatives, **4** and **5**, were obtained in each 30% yield by silica gel column chromatography [**4**, mp 183-184.5°C; MS m/z 220(M^+); ^{1}H-NMR δ(CD_3OD-$CDCl_3$ 1:2) ppm 3.85(3H, s), 7.33(1H, t, J=8 Hz), 7.65(1H, dd, J=8, 1 Hz), 7.73(1H, dd, J=8, 1 Hz), 8.01(1H, s); **5**: MS m/z 220(M^+); ^{1}H-NMR δ (CD_3OD-$CDCl_3$ 1:2) ppm 3.95(3H, s), 8.12(1H, dd, J=9, 2 Hz), 8.19(1H, s), 8.23(1H, d, J=9 Hz), 8.42 (1H, d, J=2 Hz)]. The position of nitro group of **4** was determined by following derivation of **4** to 4-nitrogramine **7** by 1) decarboxylation with conc. HCl at 100°C, 2) HCHO/$NH(CH_3)_2$, which was previously synthesized[15] from gramine **6** in 7% yield together with 6-nitro derivative **8** (42%).

Methyl 1-methylindole-3-carboxylate **9** was also nitrated in the same reaction condition to afford 4- and 6-nitro derivatives, **10** and **11**, in each 30% yield [**10**: MS m/z 234(M^+); ^{1}H-NMR δ(DMSO-d_6) ppm 3.71(3H, s), 3.93(3H, s), 7.42(1H, t, J=8 Hz), 7.68(1H, d, J=8 Hz), 7.91(1H, d, J=8 Hz), 8.31(1H, s); **11**: MS m/z 234(M^+); ^{1}H-NMR δ(DMSO-d_6) ppm 3.83(3H, s), 3.88(3H, s), 8.06-8.17(2H, m), 8.49(1H, s), 8.96(1H, m)]. Hydrogenation of **10** with H_2/Pd-C in methanol gave 4-amino derivative **12** [MS m/z 206(M^+); ^{1}H-NMR δ($CDCl_3$) ppm 3.70(3H, s), 3.82(3H, s), 5.30(2H, br.s), 6.40(1H, d, J=7.5 Hz), 6.61(1H, d, J=7.5 Hz), 7.04(1H, t, J=7.5 Hz), 7.61(1H, s)]. 4-Acetamido derivative **13** was obtained by acetylation of **12** with acetic anhydride in 95% yield [IR ν_{max} (KBr) 1687, 1670, 1632 cm^{-1}; MS m/z 246(M^+); ^{1}H-NMR δ ($CDCl_3$) ppm 2.27(3H, s), 3.79(3H, s), 3.89(3H, s), 7.01(1H, dd, J=8, 1 Hz), 7.27(1H, t, J=8 Hz), 7.85(1H, s), 8.41(1H, dd, J=8, 1 Hz)]. Thus, nitration of **3** and **9** gave not only 6-nitro derivatives but also 4-nitro derivatives in 1:1 ratio. We assume that less solubility of 6-nitro derivative may be one of the reasons[17] why only 6-nitro derivative was obtained in the previous studies.[16]

Acylation of **13** was achieved by treatment with acid anhydride or acid chloride in trifluoroacetic acid and the results were shown in Table 1. For instance, **13** was acylated with propionic anhydride in trifluoroacetic acid at 20°C for 2 hr to afford 5-propionyl derivative **14b** and 7-propionyl derivative **15b** in 77% and 15% yield respectively [**14b**: mp 176-178°C; MS m/z 302(M^+); ^{1}H-NMR δ($CDCl_3$) ppm 1.23(3H, t, J=8 Hz), 2.20(3H, s), 2.86(2H, q, J=8 Hz), 3.80(3H, s), 3.88(3H, s), 7.08(1H, d, J=8 Hz), 7.44(1H, d, J=8 Hz), 7.79(1H, s); **15b**: MS m/z 302(M^+); ^{1}H-NMR δ($CDCl_3$), ppm 1.26(3H, t, J=8 Hz), 2.30(3H, s), 3.05(2H, q, J=8 Hz), 3.71(3H, s), 3.91(3H, s), 7.58(1H, d, J=8.5 Hz), 7.77(1H, s), 8.43(1H, d, J=8.5 Hz)]. The acylated positions were determined on the bases of chemical derivation of **14a**[18] to the correponding 5-ethyl derivative[19] and comparison of their ^{1}H-NMR spectral data. The regioselectivity for 7-position was higher in the case of bulky acylating reagents than small case. Acylation of **13** with 3-methylbutenoyl chloride afforded only 7-substituted product **15d** in 40% yield [**15d**: mp 178-180°C; MS m/z 328(M^+); ^{1}H-NMR δ($CDCl_3$) ppm 2.03(3H, br.s), 2.18(3H, br.s), 2.30(3H, s), 3.76(3H, s), 3.91(3H, s), 6.58(1H, m), 7.50(1H, d, J=8.5 Hz), 7.77(1H, s), 8.41(1H, d, J=8.5 Hz)].

Thus we could introduce an amino group onto 4-position of indole nucleus and subsequent acylation occurred onto the 7-position. Our synthetic method of **15b-d**, which contain similar substituents to teleocidins and related natural products on 4- and 7-position of indole nucleus, seems to be useful for those synthesis. Further synthetic studies on teleocidins are now in progress.

ACKNOWLEDGEMENT This work was supported by the Grants-in-Aid for Cancer Research No. 60010095 from the Ministry of Education, Science and Culture.

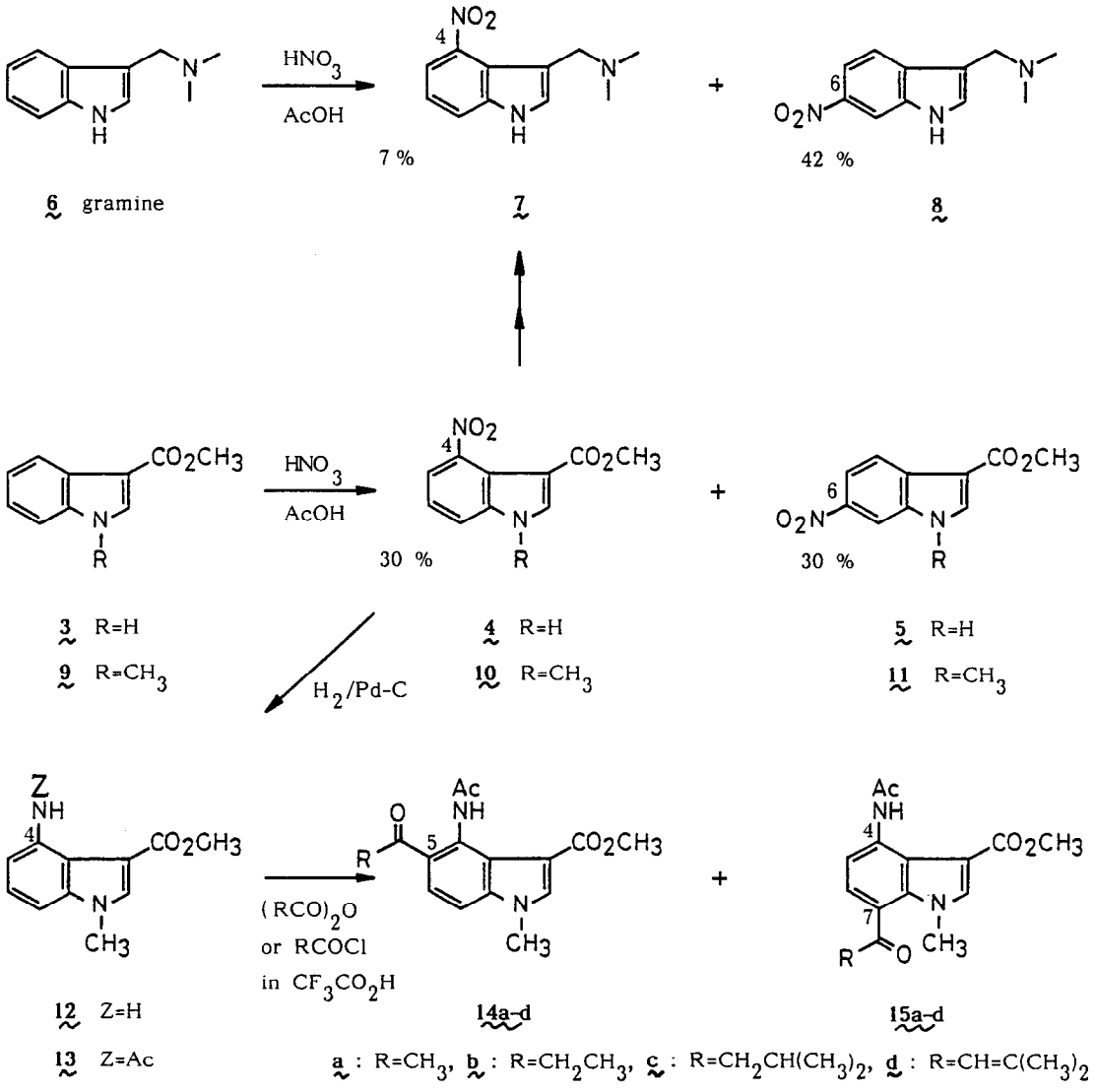


Table 1. Reaction conditions and regioselectivities of acylating reactions of **13**

Reagent	Temp.	Time	Products (Yield)	
$(CH_3CO)_2O$	60°C	45 min	**14a** (64%)	-
$(CH_3CH_2CO)_2O$	20°C	2 hr	**14b** (77%)	**15b** (15%)
$(CH_3)_2CHCH_2COCl$	40°C	4 hr	**14c** (35%)	**15c** (21%)
$(CH_3)_2C=CHCOCl$	40°C	50 min	-	**15d** (40%)

REFERENCES AND FOOTNOTES

1. a) M. Takashima and H. Sakai, Agric. Biol. Chem., **24**, 647 (1960). b) H. Nakata, H. Harada, and Y. Hirata, Tetrahedron Lett., 2515 (1966). c) H. Harada, N. Sakabe, Y. Hirata, Y. Tomiie, and I. Nitta, Bull. Chem. Soc. Japan, **39**, 1773 (1966). d) Y. Hitotsuyanagi, H. Fujiki, M. Suganuma, N. Aimi, S. Sakai, Y. Endo, K. Shudo, and T. Sugimura, Chem. Pharm. Bull., (Japan), **32**, 4233 (1984).
2. J. H. Cardellina II, F. -J. Marner, and R. E. Moore, Science, **204**, 193 (1979).
3. a) S. Sakai, N. Aimi, K. Yamaguchi, Y. Hitotsuyanagi, C. Watanabe, K. Yokose, Y. Koyama, K. Shudo, and A. Itai, Chem. Pharm. Bull. (Japan), **32**, 354 (1984). b) Y. Hitotsuyanagi, K. Yamagochi, K. Ogata, N. Aimi, S. Sakai, Y. Koyama, Y. Endo, K. Shudo, A. Itai, and Y. Iitaka, ibid, **32**, 3774 (1984).
4. H. Fujiki, M. Suganuma, N. Matsukura, T. Sugimura, and S. Takayama, Carcinogenesis, **3**, 895 (1983).
5. a) Y. Endo, K. Shudo, and T. Okamoto, Chem. Pharm. Bull. (Japan), **30**, 3457 (1982). b) Y. Endo, K. Shudo, K. Furuhata, H. Ogura, S. Sakai, N. Aimi, Y. Hitotsuyanagi, and Y. Koyama, Chem. Pharm. Bull. (Japan), **32**, 358 (1984).
6. a) C. J. Moody, J.C.S. Chem. Commun., 1129 (1983). b) idem, J.C.S. Perkin I, 1333 (1984).
7. a) S. V. Ley and R. A. Porter, J.C.S. Chem. Commun., 1356 (1982). b) S. E. Laszlo, S. V. Ley, and R. A. Porter, J. C. S. Chem. Commun., 344 (1986).
8. A. P. Kozikowski and X.-M. Cheng, Tetrahedron Lett., **26**, 4047 (1985).
9. H. Muratake and M. Natsume, Heterocycles, **24**, 261 (1986).
10. S. Nakatsuka, H. Miyazaki, and T. Goto, Tetrahedron Lett., **21**, 2817 (1980).
11. S. Nakatsuka, H. Miyazaki, and T. Goto, Chemistry Lett., 407 (1981).
12. S. Nakatsuka, O. Asano, K. Ueda, Y. Yamamoto, and T. Goto, Tetrahedron Lett., submitted.
13. S. Nakatsuka, O. Asano, and T. Goto, Heterocycles, in press.
14. R. J. Sundburg, "The Chemistry of Indole", Academic Press, Yew York and London, 1970, p14.
15. a) G. Berti and A. D. Settimo, Gazz. Chim. Ital., **90**, 524 (1960). b) W. E. Noland, L. R. Smith and K. R. Rush, J. Org. Chem., **30**, 3457 (1965). c) W. E. Noland and K. R. Rush, **ibid**, **31**, 70 (1966). d) M. Colonna, L. Greci, and M. Poloni, J. C. S. Perkin II, 628 (1981).

16 R. Majima and M. Kotake, Ber., **63**, 2237 (1930).

17. In fact, 6-nitro derivatives, **5** and **11**, were easily obtained as pure crystals from the reaction mixture by crystallization.
18. **14a**: mp 199-201°C; MS m/z 288(M^+); ^{1}H-NMR δ($CDCl_3$) ppm 2.22(3H, s), 2.58(3H, s), 3.81(3H, s), 3.89(3H, s), 7.09(1H, d, J=8 Hz), 7.48(1H, d, J=8 Hz), 7.79(1H, s).
19. ^{1}H-NMR δ($CDCl_3$) ppm 1.24(3H, t, J=7 Hz), 2.23(3H, s), 2.78(2H, q, J=7 Hz), 3.77(3H, s), 3.85 (3H, s), 7.12(1H, d, J=8.5 Hz), 7.26(1H, d, J=8.5 Hz), 7.70(1H, s).

(Received in Japan 17 May 1986)