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SYNTHETIC STUDIES ON TELEOCIDIN II.[1)]
SYNTHESIS OF INDOLE DERIVATIVES CONTAINING THE SAME SUBSTITUENT TO TELEOCIDIN B AT 6- AND 7-POSITIONS OF INDOLE NUCLEUS.

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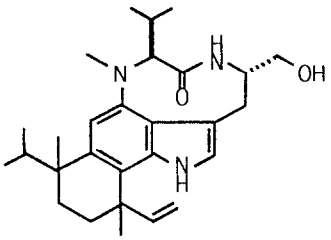
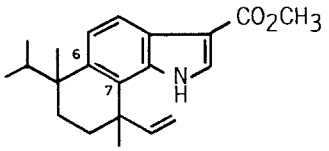
Abstract: The same substituent to teleocidin B at 6- and 7-positions of indole nucleus was introduced *via* intramolecular cyclization and oxidative cleavage of C-N bond at 1-position starting from simple indole.

Teleocidin B (1)[2)] is one of the most interesting natural products because of its potent biological activity as tumor promoter and unique structures possessing highly substituted indole nucleus. Recently, many synthetic studies[2)] toward it have been reported but no total synthesis is reported.

In the previous report,[1)] we succeeded in regioselective introduction of an amino group onto 4-position and an acyl group onto 7-position of indole nucleus. Teleocidin B contains two quarternal carbon atoms on 6- and 7-positions of indole nucleus. Introduction of such substituent(s) at appropriate position(s) of indole derivative is one of the most difficult problems[3)] in the field of indole chemistry. We have reported unique methods[4-6)] for direct introduction of substituent at benzene part of simple indole derivatives. Now we report a synthetic method for indole derivatives 2a and 2b from methyl indole-3-carboxylate 3.



Teleocidin B (1)



2a,b

Methyl 1-geranylindole-3-carboxylate 4 was synthesized by alkylation of 3 with NaH and geranyl bromide in 88% yield. Unfortunately, treatment of 4 with Lewis acid in several different reaction conditions afforded no desired double cyclization product onto 6, 7-positions. Cyclization onto 7-position was achieved after derivation of 4 to terminal benzoate 5 [oil; MS

m/z 391(M^+)] by 1) m-CPBA, 2) HIO_4, 3) $NaBH_4$, 4) BzCl/Py in 76% overall yield.

Compound 5 was treated with BF_3OEt_2 in trifluoroacetic acid (TFA) at 25° C. After evaporation of TFA, the residue was treated with diazomethane (partialy produced carboxylic acid were methylated) and separated by silica gel TLC to afford a desired cyclization product 6 [oil; MS m/z 391(M^+); ^{1}H-NMR δ($CDCl_3$) ppm 7.09(1H, dd, J=7.5 and 1 Hz), 7.22(1H, t, J=7.5 Hz), 7.78(1H, s), 7.93(1H, dd, J=7.5 and 1 Hz)] in 50% yield. These spectroscopic data clearly indicated the structure to be pyrrolo[3,2,1-ij]-indole derivative 6. Cyclization product onto 2-position of indole nucleus was not detected in the reaction mixture. The reason of no reactivity of the 2-position as a nucleophilic center seems to be stabilization of pyrrole ring by conjugation with ester carbonyl group connected at 3-position.

Hydrolysis of benzoyl group of 6 with NaOMe and oxidation with PCC in dichloromethane afforded an aldehyde 7 in 71% overall yield [oil; ^{1}H-NMR ($CDCl_3$) ppm 9.72(1H, br.s)].

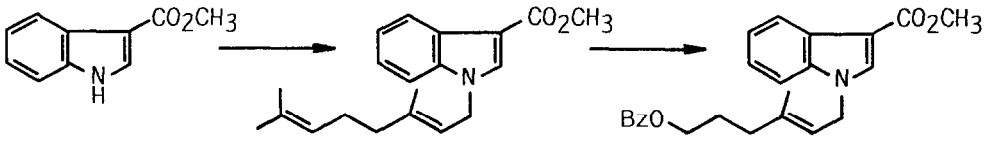
An isopropyl group was introduced to 7 by treatment of 7 with isopropyl magnesium bromide in THF to afforded a secondary alcohol 8 in 73% yield. Oxidation of a hydroxy group of 8 with PCC followed by methyl addition with methyl lithium gave tertialy alcohol 9 [oil; 2:1 mixture of stereoisomers; MS m/z 343(M^+); ^{1}H-NMR δ($CDCl_3$) ppm(major isomer) 1.07(3H, s), 1.38(3H, s)].

Intramolecular cyclization of 9 was achieved by treatment with BF_3OEt_2 in acetic acid at 25°C for 2 min to give 10 [7)][oil; 3:1 mixture of stereo-isomers[8)]; MS m/z 325 (M^+)] in98% yield. Compound 10 contains similar substituents to teleocidin B at 6- and 7-positions of indole nucleus.

Terminal olefin found in teleocidin B (1) was prepared from 10 by oxidative cleavage of C-N bond as follows. Compound 10 was treated with benzoyl peroxide in dichloroethane at 80°C for 2 h as reported.[9)] But many products were ditected on silica gel TLC. After further investigation, oxidation of 10 with benzoyl peroxide in the presence of K_2CO_3 and radical initiator (AIBN) afforded desired benzoate 11. 11 was a mixture of four stereoisomers and could not be separated on silica gel TLC each other. Interestingly, hydrolysis of 11(four isomers) with NaOMe in methanol at 25°C afforded only two stereoisomers 12[10)][3:1 mixture of stereoisomers[8)]; MS m/z 341(M^+)] in 30% yield from 10. In this reaction, a ring opened product was not detected. Reductive ring opening also failed.

Ring opening reaction was achieved by aminolysis of lactam, which was prepared by oxidation of 12 with PCC in 82% yield, with dimethylamine in DMF afforded 3:1 mixture of amides 13a and 13b. These were easily separated on silica gel TLC [13a: 63%; mp 171-172°C; 13b: 23%; mp 176-177°C].

An amide group of 13a and 13b was selectively reduced with $LiAlH_4$ in THF at 25°C and followed by oxidation with H_2O_2 in methanol at 25°C and heated in DMF at 120°C for 30 min to give 2a and 2b respectively in 14% and 11%



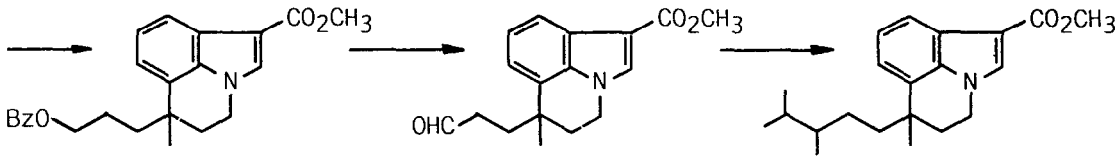
3

1) NaH
2) geranyl bromide

4

1) m-CPBA
2) HIO_4
3) $NaBH_4$
4) BzCl/Py

5



1) BF_3OEt_2
2) CH_2N_2

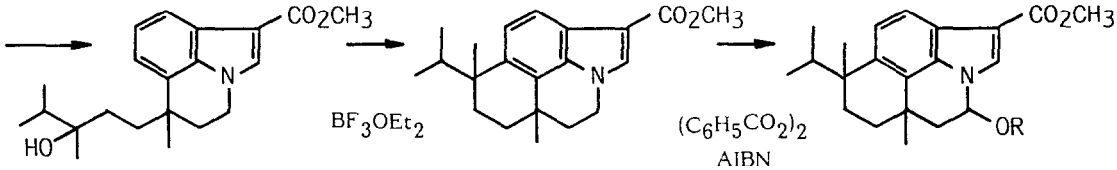
6

1) NaOMe
2) PCC

7

$(CH_3)_2CHMgBr$

8



1) PCC
2) MeLi

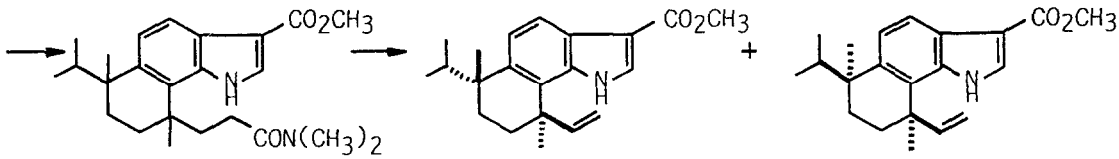
9

BF_3OEt_2

10

$(C_6H_5CO_2)_2$
AIBN

11 : R=COC_6H_5
12 : R=H



1) PCC
2) $HN(CH_3)_2$

13a,b

1) $LiAlH_4$
2) H_2O_2
3) 120°C

2a + 2b

overall yield {2a: mp 164.5°C; IRν_{max}(KBr) 3385, 1690 cm^{-1}; MS m/z 325(M^+); ^{1}H-NMR δ($CDCl_3$) ppm 0.56(3H, d, J=7.5 Hz), 1.01(3H, d, J=7.5 Hz), 1.33(3H, s), 1.48(3H, s), 1.26-1.60(2H, m), 1.84-2.05(2H, m), 2.31(1H, m), 3.86(3H, s), 5.25(1H, dd, J=10 and 1 Hz), 5.44(1H, dd, J=17 and 1 Hz), 6.20(1H, dd, J=17 and 10 Hz), 7.22(1H, d, J=8 Hz), 7.74(1H, d, J=3 Hz), 7.97(1H, d, J=8 Hz), 9.01(1H, br.s); 2b: solid, MS m/z 325(M^+); ^{1}H-NMR δ($CDCl_3$) ppm 0.59(3H, d, J=7.5 Hz), 0.96(3H, d, J=7.5 Hz), 1.33(3H, s), 1.49(3H, s), 1.20-2.00(4H, m), 2.13(1H, m), 3.88(3H, s), 5.00(1H, dd, J=17 and 1 Hz), 5.20(1H, dd, J=10 and 1 Hz), 6.10(1H, dd, J=17 and 10 Hz), 7.26(1H, d, J=8 Hz), 7.78(1H, d, J=3 Hz), 7.98(1H, d, J=8 Hz), 8.65(1H, br.s)}. The stereochemistry of 2a and 2b were determined to be trans and cis isomer respectively by the comparison of their ^{1}H-NMR spectra with those of olivoretin A[11a] and B[11b]. Thus obtained 2a and 2b contain the same terpenyl unit at 6- and 7-positions of indole nucleus with teleocidin B, olivoletin A, and B. Further synthetic studies on teleocidin are now in progress.

ACKNOWLEDGEMENT This work was supported by the Grants-in-Aid for Cancer Research No.61010093 from the Ministry of Education, Science and Culture.

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5. S. Nakatsuka, H. Miyazaki, and T. Goto, Chemistry Lett., 407 (1981).
6. S. Nakatsuka, O. Asano, and T. Goto, Heterocycles, 24, 2109 (1986).
7. 10: ^{1}H-NMR δ($CDCl_3$) ppm(major isomer) 0.74(3H, m), 1.05(3H, m), 1.25(3H, s), 1.38-2.42(7H, m), 3.88(3H, s), 4.14-4.42(2H, m), 7.14(1H, d, J=8 Hz), 7.74(1H, s), 7.83(1H, d, J=8 Hz).
8. These stereoisomers were could not be separated on silica gel TLC.
9. S. Nakatsuka, O. Asano, and T. Goto, Heterocycles, 24, in press.
10. 12: ^{1}H-NMR δ($CDCl_3$) ppm(major isomer) 0.70(3H, d, J=7.5 Hz), 1.04(3H, d, J=7.5 Hz), 1.19(3H, s), 1.25(3H, s), 1.38-1.80(4H, m), 2.09(1H, m), 2.34(2H, m), 3.40(1H, br.s), 3.86(3H, s), 5.87(1H, m), 7.10(1H, d, J=8 Hz), 7.78(1H, d, J=8 Hz), 8.06(1H, s).
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