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TOTAL SYNTHESES OF (±)-TELEOCIDIN B-3 AND B-4[1)]

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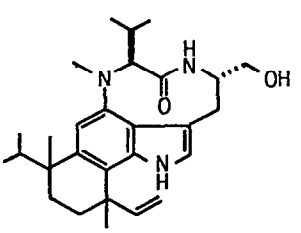
Abstract; First total syntheses of (±)-Teleocidin B-3(1c) and B-4(1d) were achieved by several functionalizing reactions starting from indole.

Teleocidin B was first isolated as a strong skin-irritant compound from the mycelium of Streptomyces mecliocidicus by Takashima and Sakai.[2)] Recently, Fujiki et al.[4)] reported that teleocidin B is one of the most potent tumor promoters known. The chemical structure was determined by Hirata's group[3)] by chemical methods and X-ray analysis of the monobromoacetate of its dihydro derivative in 1966. Fujiki and Sakai's group[5)] found that the compound was a mixture of four stereoisomers [B-1(1a), B-2(1b), B-3(1c), and B-4(1d)] and that Hirata's teleocidin B derivative used for X-ray analysis was derived from teleocidin B-4. Teleocidin B is a unique natural product having an amino group at the 4-position and a modified mono terpenyl moiety at the 6,7-positions of the indole nucleus.

We have developed new functionalizing methods[6,7)] for the benzene part of indole derivatives and applied them to the efficient syntheses of indolactam V[8)] (the minimum structure for biological activity of teleocidin) and an indole derivative[9)] containing the same substituents at the 6,7-positions of teleocidin B. Now we report the first total syntheses[10)] of teleocidin B-3 (1c) and B-4(1d).

We prepared benzoate 3[9)] by radical oxidation of 2 with benzoyl peroxide in 30% yield. Selective nitration[11)] of 3 was achieved by treatment with $AcONO_2$ in acetic anhydride. Other nitration conditions (for instance, conc. HNO_3 in acetic acid) could not be used because of instability of the product in such



Teleocidin B (1)
[mixture of B-1(1a), B-2(1b), B-3(1c), and B-4(1d)]

acidic conditions. The position of the nitro group was established by comparison of the chemical shift of the 5-proton with those of the other 4-nitro derivatives.[11] The benzoyl group of the nitro compound was selectively hydrolyzed with 1 N NaOH to give 4[12] in 60% overall yield from 3. Oxidation of 4 with MnO_2 in CH_2Cl_2 at 25°C for 1.5 hr afforded a lactam 5[12] in 74% yield. Although the lactam 5 was a mixture of trans- and cis-isomers (5a:5b = 5:1), the former (5a), mp 178.5-180 °C, was obtained in pure form by crystallization.

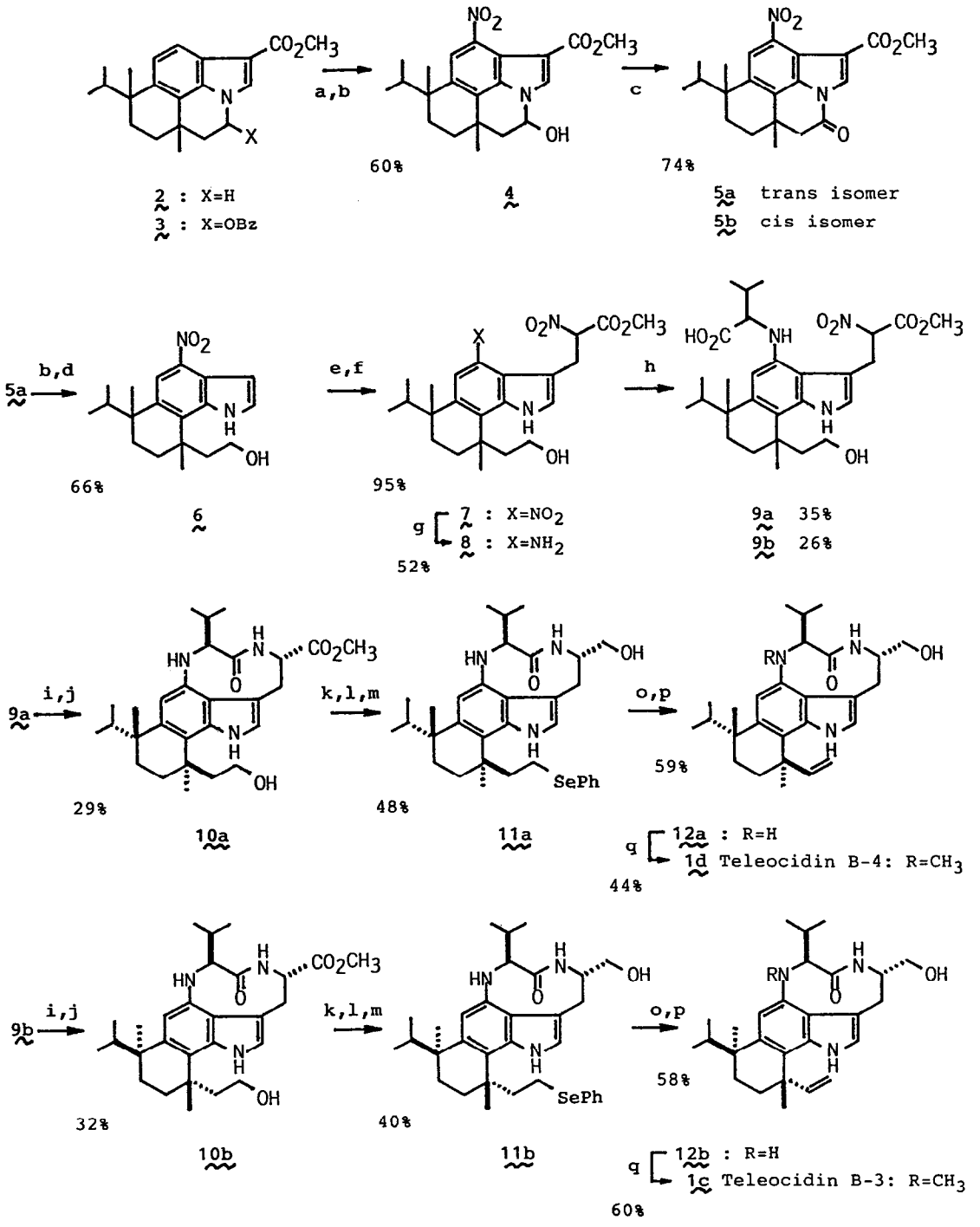
Interestingly, hydrolysis of 5a with 6 N NaOH at 60°C was accompanied by decarboxylation and subsequent reduction of the product with BH_3 in THF at 25 °C for 20 min afforded an alcohol 6[12] in 66% yield. Compound 6 was treated with formalin and dimethylamine in acetic acid at 60°C for 15 min and followed by treatment with methyl nitroacetate in the presence of Et_3N in chlorobenzene at 100°C for 10 min to give 7 (95%, 1:1 mixture of stereoisomers).

Selective reduction of the 4-nitro group of 7 by catalytic hydrogenation was unsuccessful, unlike our indolactam V synthesis,[8] but reduction with sodium dithionite in the presence of Et_3N in MeOH-H_2O gave the corresponding 4-amino compound 8 in 52% yield. Introduction of a C_5 unit to 8 was achieved with 2-oxoisovaleric acid in DMF and subsequent reduction with $NaBH_3CN$ to give 9. Compound 9 was a mixture of four stereoisomers and could be easily separated on a silica gel TLC plate into two mixtures containing two stereoisomers, 9a[12] (35%, 1:1 mixture) and 9b[12] (26%, 1:1 mixture). Presumably these isomers are epimers related to the stereochemistry between the valinyl moiety and the terpenyl substituent at the 6,7-position because of the interaction of those substituents on the very flat tetrahydrobenzindole system. These stereochemistries were confirmed by the subsequent derivations to teleocidin B-3 and B-4.

Compound 9a gave a lactam 10a[12] in 29% yield by the treatment with N-hydroxysuccinimide (HOSU) and dicyclohexylcarbodiimide (DCC) in CH_3CN at 25°C for 30 min followed by H_2/PtO_2 in methanol for 15 min. The epimer of 10a was not isolated.

Transformation of the hydroxyethyl group of 10a to the terminal olefin found in teleocidin B was a very difficult process because this alcohol cyclized[13] easily at the 1-position of the indole nucleus. We chose the cis-elimination method of selenoxide derivative. Treatment of 10a with MsCl in pyridine followed by NaSePh in ethanol to give a selenide. Reduction of the ester group of the selenide with $NaBH_4$/LiCl in THF-EtOH gave 11a which was isolated on silica gel TLC in 48% yield. Oxidation of the phenylselenenyl group of 11a with KIO_4 in THF-MeOH followed by heating at 60°C gave terminal olefin 12a[12] in 59% yield.

Methylation[3g] of 12a was achieved with CH_3I/ $NaHCO_3$-$Na_2S_2O_3$ in EtOH at 70 °C in a sealed tube for 4.5 hr to give teleocidin B-4 (1d) in 44% yield (54% of 12a was recovered). In the same manner, we also prepared teleocidin B-3



a) $AcONO_2$ b) NaOH c) MnO_2 d) BH_3-THF e) $CH_2=N^+(CH_3)_2(OAc)^-$ f) $O_2NCH_2CO_2CH_3$ / Et_3N g) $Na_2S_2O_4$ h) $(CH_3)_2CHCOCO_2H/NaBH_3CN$ i) HOSu / DCC j) H_2 / PtO_2 k) MsCl/Py l) NaSePh m) $NaBH_4$-LiCl o) KIO_4 p) 60 °C q) CH_3I

(1c) from 9b in 4.5% overall yield. ^{1}H-NMR, MS, and UV spectra and retention times on HPLC of the synthetic (±)-teleocidin B-3 (1c) and B-4 (1d) were completely identical with those of natural teleocidin B-3 and B-4, respectively.

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12. Typical proton signals of ^{1}H-NMR spectra in $CDCl_3$ δ(ppm). 4(major isomer): 5.92(1H,br.m),7.59(1H,s),8.05(1H,s). 5a:0.73(3H,d,J=8),1.08(3H,d,J=8),1.28 (3H,s),1.32(3H,s),2.77(1H,d,J=16),2.90(1H,d,J=16). 5b:0.80(3H,d,J=8),0.98 (3H,d,J=8),1.28(3H,s),1.52(3H,s),2.85(2H,s). 6:2.20(2H,t,J=8),3.36(1H,m), 3.68(1H,m),7.22(1H,dd,J=3 and 2),7.38(1H,t,J=3),8.13(1H,s). 9a:3.79 and 3.83(3H,s),3.93 & 3.94(1H,d,J=7). 9b:3.80 and 3.82(3H,s),3.98 and 4.00(1H, d,J=6). 10a:3.73(3H,s),5.12(1H,br.d,J=10),5.40(1H,br.d,J=10). 12a:5.24 (1H,d,J=10),5.38(1H,d,J=18),6.14(1H,dd,J=18 and 10).
13. For instance, treatment of 7 with formic acid at 25°C afforded a cyclized product similar to 2.

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