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SYNTHETIC STUDIES ON TELEOCIDIN IV.[1] AN EFFICIENT SYNTHESIS OF (-)-INDOLACTAM V

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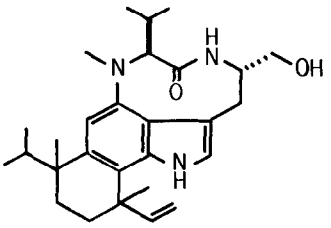
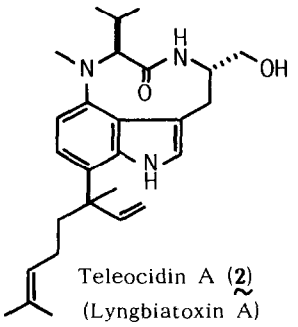
Abstract: An efficient synthesis of (-)-indolactam V (3) was achieved in 12 steps starting from L-tryptophan.

Irie et al. obtained (-)-indolactam V (3),[2] which contains a common structure of strong tumor promoters teleocidin B[3] (1) and A[3] (2), from a culture filtrate of Actinomycetes NA34-17. Two syntheses of indolactam V (3) have been reported recently.[4] But more efficient synthetic method for (3) was needed for the total synthesis teleocidins and related compounds.

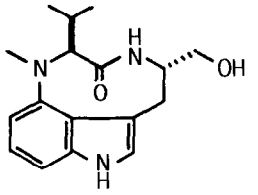
We planed new synthetic rout to 3 starting from L-tryptophan.[5] The most difficult problem in its synthesis is the introduction of an amino function to the 4-position of indole nucleus of L-tryptophan. In the previous paper,[6] we reported that the nitration of methyl indole-3-carboxylate gave 4- and 6-nitro derivatives in each 30% yields. The reason of this selectivity was not clear but if a carbonyl group at 3-position of indole nucleus is essencial for the selectivity, 4-nitrotryptophan derivative can be synthesized from L-tryptophan derivative containing the carbonyl group at the appropriate position.



Teleocidin B (1)



Teleocidin A (2)
(Lyngbiatoxin A)



Indolactam V (3)

We started the nitration of 3-acyl indole derivative 5, which was obtained by DDQ oxidation[7] of 4 and subsequent methylation in 73% overall yield. 5 was treated with conc HNO_3 (d=1.38) at 25°C for 1 h to give desired 4-nitro derivative 6 combined with 6-nitro derivative 7 in each 35% yields [6: ^{1}H-NMR ($CDCl_3$) ppm 3.94(3H, s), 4.53(2H, d, J=6 Hz), 5.14(2H, s), 5.87(1H, m), 7.30-7.43(5H, m), 7.47(1H, t, J=8 Hz), 7.61(1H, d, J=8 Hz), 7.69(1H, d, J=8 Hz),

7.91(1H, s); 7: ^{1}H-NMR $\delta(CDCl_3)$ ppm 3.99(3H, s), 4.59(2H, d, J=6 Hz), 5.17(2H, s), 5.84(1H, m), 7.30-7.43(5H, m), 8.05(1H, s), 8.22(1H, dd, J=8, 1 Hz), 8.35(1H, d, J=1 Hz), 8.46(1H, d, J=8 Hz)].

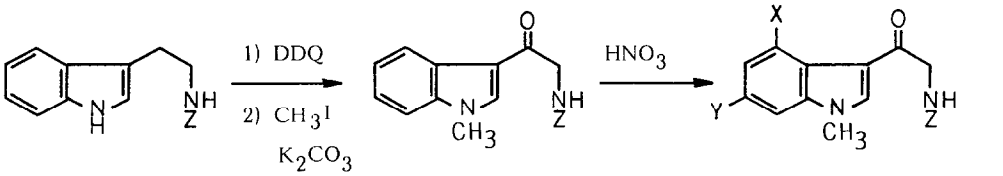
L-tryptophan derivative 8 was treated with $LiBH_4$ at 25°C for 4.5 hr and following acetylation (Ac_2O/Py) to give 9 in 97% yield. DDQ oxidation of 9 (2 eq. DDQ in THF-H_2O (9:1) at 25°C for 1 hr) afforded 10 in 74% yield [^{1}H-NMR($CDCl_3$) ppm 2.02(3H, s), 4.10(1H, dd, J=13 and 8 Hz), 4.61(1H, dd, J=13 and 3 Hz), 5.16(2H, s), 5.44(1H, m), 6.10(1H, d, J=8 Hz), 7.24-7.50(8H, m), 8.20(1H, d, J=2 Hz), 8.32(1H, m), 9.46(1H, br.s)].

Nitration of 10 with conc. HNO_3 also gave 4- and 6-nitroderivative, 11 and 12. These were easily separated with silica gel column chromatography to give pure 11 and 12 in 40% and 35% yields respectively [11: ^{1}H-NMR($CDCl_3$) ppm 2.07(3H, s), 4.32(1H, dd, J=12 and 7 Hz), 4.61(1H, dd, J=12 and 3 Hz), 5.17(2H, s), 5.33(1H, m), 6.15(1H, d, J=8 Hz), 7.25(1H, d, J=7.5 Hz),7.30-7.40 (5H, m), 7.47(1H, d, J=7.5 Hz), 7.55(1H, d, J=7.5 Hz), 8.13(1H, d, J=2 Hz); 12: ^{1}H-NMR($CDCl_3$) ppm 2.06(3H, s), 4.13(1H, dd, J=11 and 8 Hz), 4.67(1H, dd, J=11 and 4 Hz), 5.20(2H, s), 5.46(1H, m), 6.02(1H, d, J=8 Hz), 7.30-7.48(5H, m), 8.14(1H, dd, J=8 and 1.5 Hz), 8.32(1H, d, J=1.5 Hz), 8.38(1H, d, J=8Hz), 8.49(1H, d, J=3 Hz)].

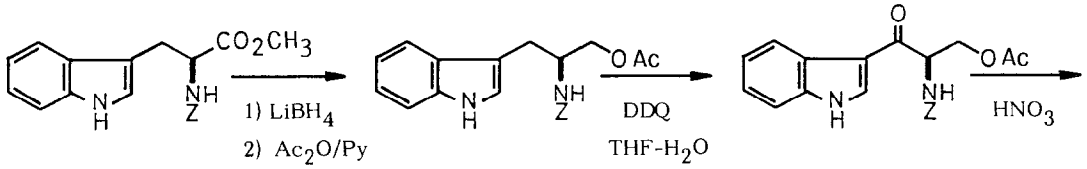
Catalytic hydrogenation of 11 was achieved with H_2/PtO_2 in MeOH for 1 hr to give 13 in 60% yield[13: ^{1}H-NMR($CDCl_3$) ppm 2.03(3H, s), 4.04(1H, dd, J=12 and 7.5 Hz), 4.62(1H, dd, J=12 and 5 Hz), 5.10(1H, d, J=14 Hz), 5.18(1H, d, J=14 Hz), 5.38(1H, m), 5.93(1H, d, J=9 Hz), 6.44(1H, d, J=8 Hz), 6.70(1H, d, J=8 Hz), 7.08(1H, d, J=8 Hz), 7.30-7.48(5H, m), 8.20(1H, d, J=3 Hz), 8.90(1H, br.s)]. Reduction of carbonyl group of 13 with $NaBH_3CN$ in AcOH was failed. But 13 was reduced with $NaBH_4$ in DMF-H_2O(4:1) at 25°C for 2.5 Hr to give 14 in 96% yield [14: ^{1}H-NMR($CDCl_3$) ppm 3.02(1H, dd, J=15 and 8 Hz),3.26(1H, dd, J=15 and 6 Hz), 3.40-3.68(2H, m), 3.80(1H, m), 5.12(2H, s), 5.66(1H, br.d, J= 7.5 Hz), 6.43(1H, d, J=7.5 Hz), 6.92(1H, d, J=7.5 Hz), 6.07(1H, br.s), 7.00 (1H, t, J=7.5 Hz), 7.30-7.40(5H, m), 8.00(1H, br.s)]. The optical purity of 14 was more than 90% by comparison of its NMR spectrum in the presence of chiral shift reagent [Eu(TFC)$_3$] with that of DL-derivative 14, which was synthesized from DL-tryptophan by the same method.

Compound 14 was treated with 2-oxoisovaleric acid in DMF at 25°C for 10 min and then reduced with $NaBH_3CN$ at 25°C for 15 min in the same flask. The crude product was derived to the activated ester 15 with HOSu and DCC in acetonitrile at 25°C for 20 min to give 15 (5:6 mixture of stereoisomers) in 76% overall yield. Interestingly, hydrogenolysis of carbobenzoxy group of 15 with H_2/Pd-C in MeOH gave desired cyclized product 16 [5:6 mixture of stereoisomers; MS m/z 287(M^+)] in 73% yield.

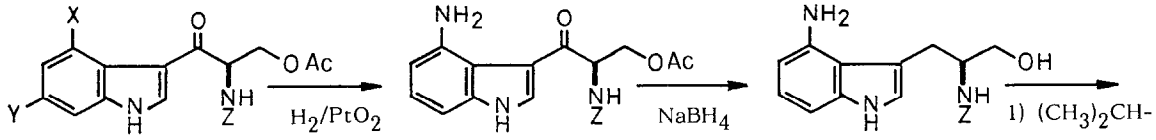
Methylation of 16 was achieved by the modified method reported by Endo et al.[4a] [methyliodide in the presence of $NaHCO_3$ in MeOH in sealed tube at 70 °C for 4.5 hr] to give a mixture of(-)-indolactam V (3) and its stereoisomer 17.



4 → 73% → 5 → 6 : X=NO_2, Y=H 35%; 7 : X=H, Y=NO_2 35%

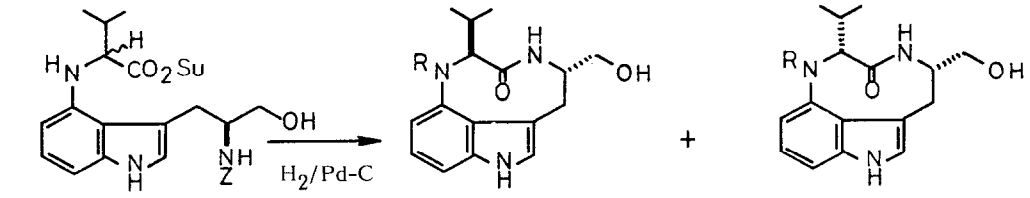


8 → 97% → 9 → 74% → 10



11 : X=NO_2, Y=H 40%; 12 : X=H, Y=NO_2 35%

66% → 13 → 96% → 14



76% → 15 → 73% → 16 : R=H, 5:6 mixture of stereoisomers; 3 : R=CH_3, Indolactam V; 17: R=CH_3

These were easily separated on silica gel TLC to give pure 3[8] and 17[9] in 32% and 53% yields respectively. The spectrometric data of thus obtained (-)-indolactam V (3) and that[4a] of natural product were completely identical each other. Further synthetic studies on teleocidins are now in progress.

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8. 3: MS m/z 301(M^+); UV(EtOH) λ_{max} 299, 285, 229 nm; CD_{MeOH} $[\theta]_{308}$;+7700, $[\theta]_{294}$ ±0, $[\theta]_{256}$ -21800, $[\theta]_{245}$ -18900, $[\theta]_{225}$ -48400, $[\theta]_{211}$ ±0; ^{1}H-NMR δ ($CDCl_3$) ppm(major) 0.62(3H, d, J=6.8 Hz), 0.93(3H, d, J=6.3 Hz), 2.60(1H, m), 2.92(3H, s), 3.00(1H, dd, J=18 and 3.5 Hz), 3.20(1H, br.d, J= 18 Hz), 3.52(1H, m), 3.76(1H, dd, J=11 and 4 Hz), 4.32(1H, m), 4.40(1H, d, J=10 Hz), 6.51(1H, d, J=7.5 Hz), 6.71(1H, br.s), 6.89(1H, s), 6.90(1H, d, J=7.5 Hz), 7.05(1H, t, J=7.5 Hz), 7.99(1H, br.s)].
9. 17: MS m/z 301(M^+); UV(EtOH) λ_{max} 301, 291, 230 nm; CD_{MeOH} $[\theta]_{308}$ -5400, $[\theta]_{292}$ ±0, $[\theta]_{285}$ +2200, $[\theta]_{276}$ ±0, $[\theta]_{257}$ -7600, $[\theta]_{248}$ ±0; ^{1}H-NMR($CDCl_3$) ppm 0.69(3H, d, J=6.8 Hz), 0.76(3H, d, J=6.8 Hz), 2.64(1H, m), 2.94(1H, br.d, 15.5 Hz), 3.12(3H, s), 3.27(1H, br.d, J=15.5 Hz), 3.78-4.00(3H, m), 3.96(1H, d, J=10.5 Hz), 6.77(1H, dd, J=7.2 and 1 Hz), 6.89(1H, d, J=2.5 Hz), 6.98(1H, dd, J=7.2 and 1 Hz), 7.05(1H, t, J=7.2 Hz), 7.96(1H, br.s).

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