Communications to the Editor

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SYNTHESIS OF OPTICALLY ACTIVE TELEOCIDIN DERIVATIVES. ABSOLUTE CONFIGURATION OF TELEOCIDIN B AND OLIVORETIN A

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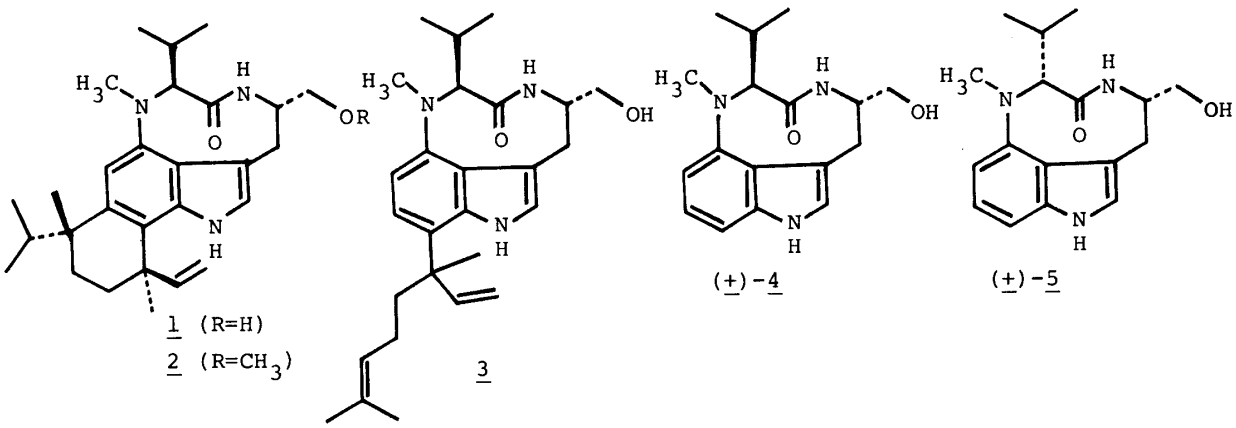
Optically active 3,4,5,6,7,8-hexahydro-4(S)-hydroxymethyl-7(S)-isopropyl-8-methyl-6-oxo[1,4]diazonino[7,6,5-cd]indole was synthesized from N-Boc-4-nitro-L-tryptophanol and a circular dichroism study of the compound shows that the nine-membered ring of teleocidin B and olivoretin A is S,S configuration.

KEYWORDS ——— 3,4,5,6,7,8-hexahydro-6-oxo[1,4]diazonino[7,6,5-cd]indole; nine-membered lactam; tryptophan; teleocidin B; circular dichroism; absolute configuration; tumor promoter

Tumor promoters are attracting great interest.[1] Phorbol esters including 12-O-tetradecanoylphorbol-13-acetate (TPA) have been extensively examined as tumor promoters.[2] The high activity of teleocidin B and lyngbyatoxin A as tumor promoters was found recently.[3] The biological activities *in vitro* and *in vivo* of dihydroteleocidin B[4] (catalytically hydrogenated compound of teleocidin B) were equivalent to or stronger than those of TPA.[5] The structures of teleocidin B (1)[6] and olivoretin A (2)[7] were determined by X-ray crystallography, and the structure of lyngbyatoxin A (3) was determined by ^{1}H- and ^{13}C-NMR spectroscopy and by comparing its circular dichroism (CD) with that of dihydroteleocidin B.[8] However, their absolute configuration was not determined. We have been interested in the structure of teleocidin B and lyngbyatoxin A and the minimum structure required for their activities. In the previous paper,[9] we described a synthesis of (±)-3,4,5,6,7,8-hexahydro-4(R^*)-hydroxymethyl-7(R^*)-isopropyl-8-methyl-6-oxo[1,4]diazonino-[7,6,5-cd]indole ((±)-4) which has the same relative configuration of the nine-membered ring structure as teleocidin B and lyngbyatoxin A. We also described the synthesis of its diastereomeric isomer ((±)-5). In this paper, we report a synthesis of optically active 4 and 5, and the establishment of the absolute configuration

of the lactam ring by chemical transformation.



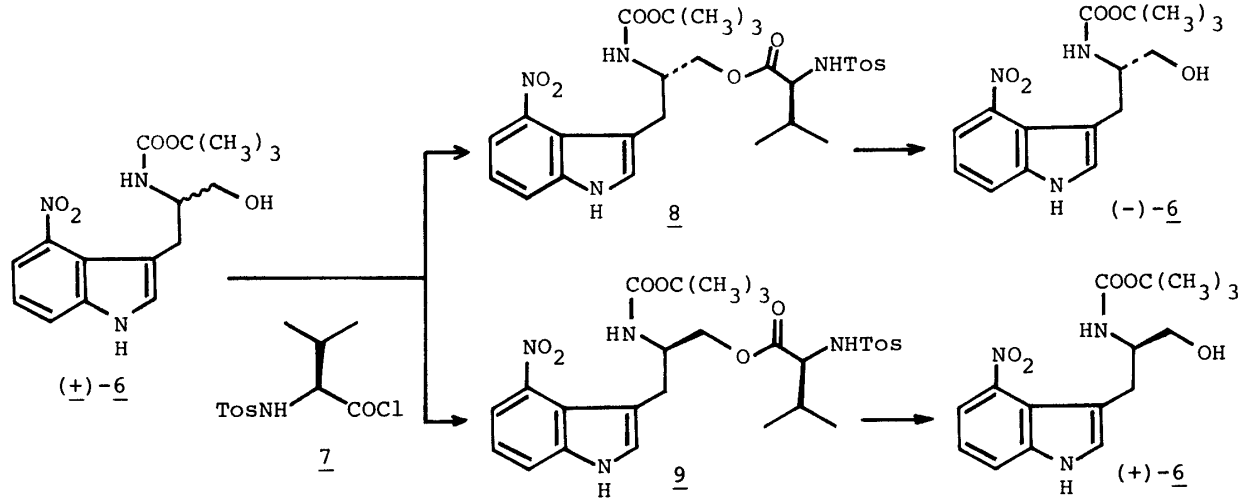
1 (R=H)
2 (R=CH_3)

3

(±)-4

(±)-5

The synthesis of the desired compounds was carried out as in the previous paper.[9] Optical resolution was carried out on N-Boc-4-nitrotryptophanol ((±)-6) which was prepared from 4-nitrogramine for 8 steps. The compound ((±)-6) was treated by (+)-N-tosylvaline chloride (7: mp 64-65°C, $[\alpha]_D^{20}$ +53.5° (c=4.5,$CHCl_3$) prepared from L-valine to give a mixture of diastereomeric esters (8 and 9), which were separated by column chromatography on silica gel using methylene chloride/acetone (10:1,v/v) as an eluent. Compounds (8) and (9) were hydrolyzed by 2N-KOH (CH_3OH, r.t. 96 h) to give (-)-6 and (+)-6, respectively; (-)-6; mp 240-242°C(dec.), $[\alpha]_D^{20}$ -246.0° (c=1.0,$CHCl_3$), (+)-6; mp 234-235°C(dec.), $[\alpha]_D^{20}$ +248.2° (c=1.0,$CHCl_3$). The recovery of each asmmetric isomer was about 85% in each case.



(±)-6

7

8

(-)-6

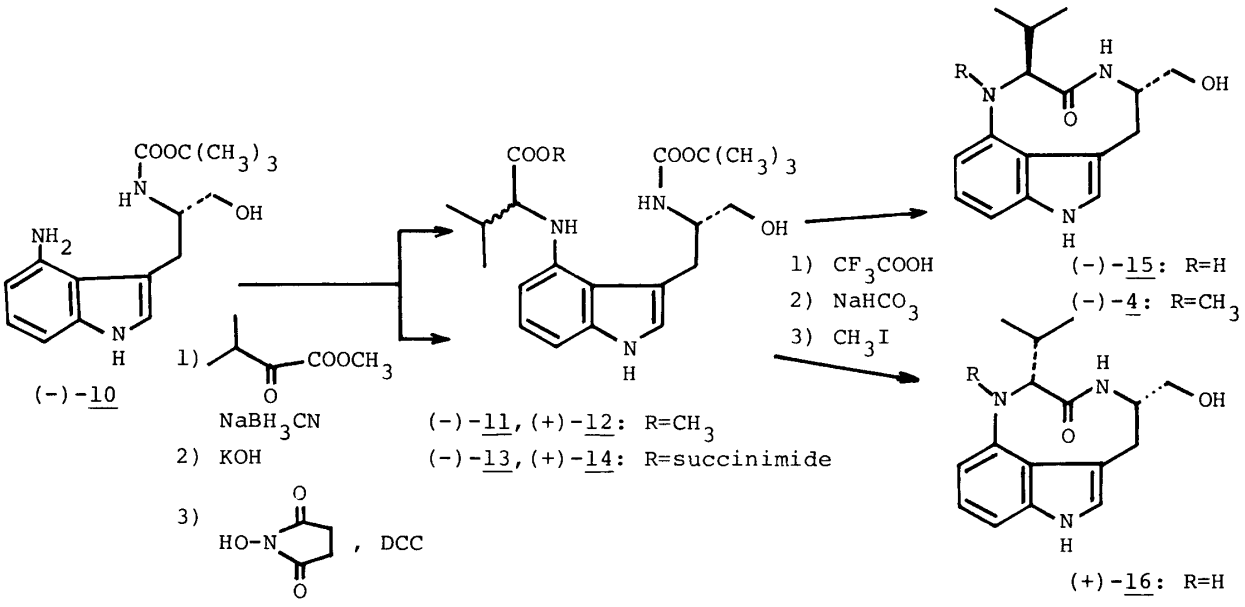
9

(+)-6

Catalytic reduction of (-)-6 by Pd-charcoal in C_2H_5OH gave (-)-N-Boc-4-amino-tryptophanol ((-)-10) a viscous liquid, in 88% yield; $[\alpha]_D^{20}$ -12.6° (c=1.0,$CHCl_3$). The compound ((-)-10) was treated with methyl 2-oxoisovalerate ($CHCl_3$,reflux, 5 h) then reduced with sodium cyanoborohydride (THF, r.t. 18 h) to give a mixture of two N-isovaleric esters; diastereomeric isomers with the isopropyl group ((-)-11 and (+)-12), (-)-11; 32%, mp 187-189°C, $[\alpha]_D^{20}$ -69.8° (c=0.96,$CHCl_3$), (+)-12; 28%, amorphous powder, $[\alpha]_D^{20}$ +16.3° (c=1.02,$CHCl_3$). The compound ((-)-11) was hydrolyzed by 2N-KOH (CH_3OH, r.t. 24 h), treated with N-hydroxysuccinimide-DCC (CH_3CN, r.t. 1 h) to give the activated ester ((-)-13) in 53% yield. Compound ((+)-12) was converted

to activated ester ((+)-14) by the same procedure in 74% yield. Deprotection of the Boc group of (-)-13 employing CF_3COOH (CH_2Cl_2, 0°C, 1 h), followed by cyclization ($NaHCO_3$, H_2O, 80°C, 1 h) gave lactam ((-)-15) in 55% yield. The compound ((+)-14) was converted to lactam ((+)-16) in 68% yield in the same manner. N-Methylation of (-)-15 (CH_3I, $NaHCO_3$, CH_3OH, reflux, 40 h) gave (-)-4 in 52% yield; amorphous powder, $[\alpha]_D^{20}$ -134.8° (c=0.7,CH_3OH). N-Methylation of (+)-16 gave (+)-5 in 73% yield; mp 138-139°C, $[\alpha]_D^{20}$ +86.5° (c=0.83,CH_3OH).

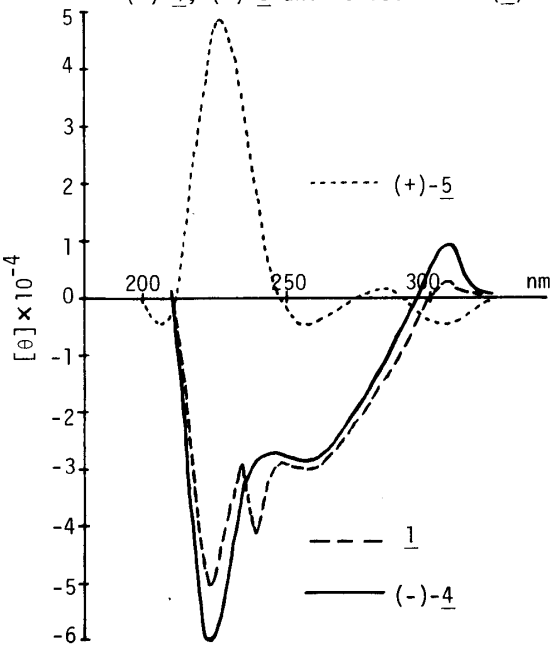
The compound ((+)-6) was converted to (+)-4 and (-)-5 by a procedure similar to that described above. (+)-4; amorphous powder, $[\alpha]_D^{20}$ +135.6° (c=0.56,CH_3OH), (-)-5; mp 134-136°C, $[\alpha]_D^{20}$ -84.9° (c=0.77,CH_3OH).



Since all the stereoisomers were obtained,[10] a CD study has been carried out. Chart 1 shows the CD curves in methanol of teleocidin B[7] and of (-)-4 and (+)-5 which were prepared from (-)-6. The CD curves of (+)-4 and (-)-5 are strictly antipodal to (-)-4 and (+)-5,respectively. The CD curves of (-)-4 and teleocidin B indicate that (-)-4 and teleocidin B have the same stereochemistry in the nine-membered ring, particularly regarding the CD originating from the lactam carbonyl chromophore. The CD peaks at 220nm can be assigned to the lactam carbonyl chromophore and the terpenoid moiety may significantly affect the CD based on the aromatic chromophore.[11]

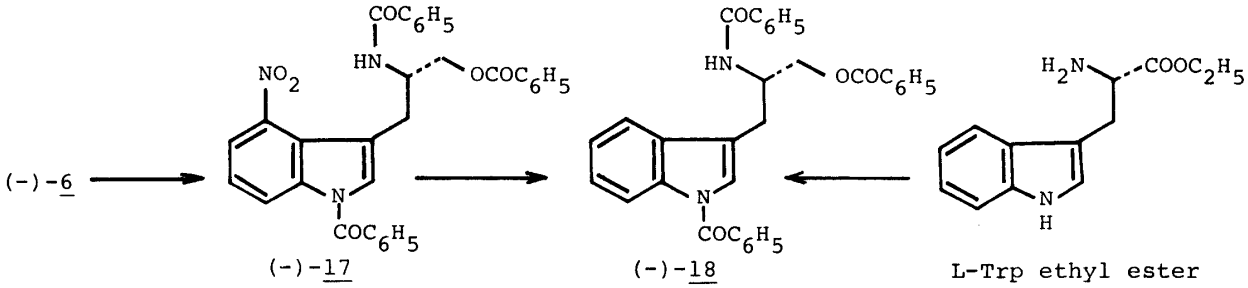
Chart 1.

Circular Dichroism Curves of (-)-4, (+)-5 and Teleocidin B (1)



The absolute configuration of (-)-6 was determined as follows. The compound ((-)-6) was benzoylated (PhCOCl,pyridine,

0°C, 3 h), deprotected (CF_3COOH, CH_2Cl_2, 0°C, 1 h), benzoylated (PhCOCl, pyridine, 0°C, 3 h), and further benzoylated ((1) NaH, THF, 0°C, 30 min, (2) PhCOCl, r.t. 3 h) to give 4-nitro-N,N,O-tribenzoyltryptophanol ((-)-17) in 62% yield. The compound ((-)-17) was catalytically reduced (10% Pd-charcoal, H_2, 1 atm, C_2H_5OH, r.t. 1 h), diazoniated ($NaNO_2$, conc.HCl, 0°C, 1 h) and then reductively dediazoniated (H_3PO_2, r.t. 1 h) to give (-)-N,N,O-tribenzoyltryptophanol ((-)-18) in 54% yield; mp 229-231°C, $[\alpha]_D^{20}$ -6.9° (c=0.51,$CHCl_3$). The compound ((-)-18) was identified as S-18 by comparing its optical rotation with authentic S-18 prepared from L-tryptophan ethyl ester.



Thus, the stereochemistry of the chiral centers on the nine-membered ring of (-)-4, teleocidin B, olivoretin A and lyngbyatoxin A must be the S,S configuration, suggesting that the nine-membered rings originate from L-tryptophan and L-valine. The present result makes it possible to discuss the stereochemical aspects of the tumor promoters.

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10) We termed (-)-4 and its isomers indolactam-V; (-)-4: (-)-indolactam-V, (+)-4: (+)-indolactam-V, (+)-5: (+)-epi-indolactam-V, (-)-5: (-)-epi-indolactam-V. The results of testing for biological activities will be published elsewhere.
11) The temperature and solvent effects will be discussed later.

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