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TOTAL SYNTHESIS OF DIHYDROTELEOCIDIN B-4 (DIHYDROTELEOCIDIN B)

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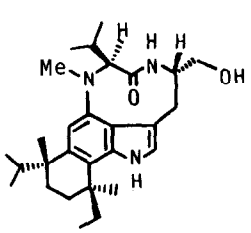
Abstract: A potent tumor promoter, dihydroteleocidin B-4 (=dihydroteleocidin B) (1) was synthesized from L-valine derivative 8 using an acid-catalyzed cyclization of 15 to 16a to construct the teleocidin B structure unit.

Dihydroteleocidin B was first described in the literature as the sole crystalline derivative of "teleocidin B," a highly toxic and skin-irritating substance obtained from the mycelia of *Streptomyces mediocidicus*.[1] The structure was studied extensively by chemical means,[1,2,3] and finally the X-ray crystallographic analysis of its monobromoacetate revealed it to be 1.[4] Later, dihydroteleocidin B was found to have a potent tumor promoting activity,[5] and so-called "teleocidin" from the above species was reinvestigated thoroughly. As a result, it was concluded that "teleocidin B" is actually composed of four stereoisomers, teleocidins B-1 (2), B-2 (3), B-3 (4), and B-4 (5),[6] whose structures are now unambiguously established, including the absolute configuration.[7,8] Thus dihydroteleocidin B-4 (dihydro-5) is the above dihydroteleocidin B (1), which was obtained by chance from the catalytic hydrogenation mixture of "teleocidin B" due to its nice crystalline nature. Here we report a total synthesis of 1 in the optically active form utilizing our efficient synthetic pathway for teleocidins A-1 (6) and A-2 (7).[9] Total synthesis of (±)-teleocidin B-3 and B-4 has already been reported.[10]

Our synthetic plan relied upon the Friedel-Crafts type of cyclization reaction (15 → 16a) to construct the desired carbon framework, the 6,7,8,9-tetrahydrobenzo[*g*]indole ring system, carrying the requisite alkyl substituents, the methyl, ethyl, and isopropyl groups at the proper locations. For this purpose,



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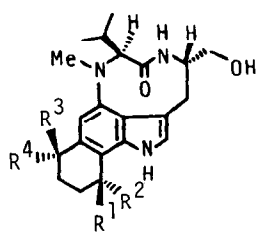
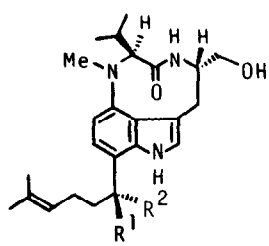


2 R^1=vinyl, R^2=Me, R^3=*i*-Pr, R^4=Me
3 R^1=Me, R^2=vinyl, R^3=Me, R^4=*i*-Pr
4 R^1=Me, R^2=vinyl, R^3=*i*-Pr, R^4=Me
5 R^1=vinyl, R^2=Me, R^3=Me, R^4=*i*-Pr

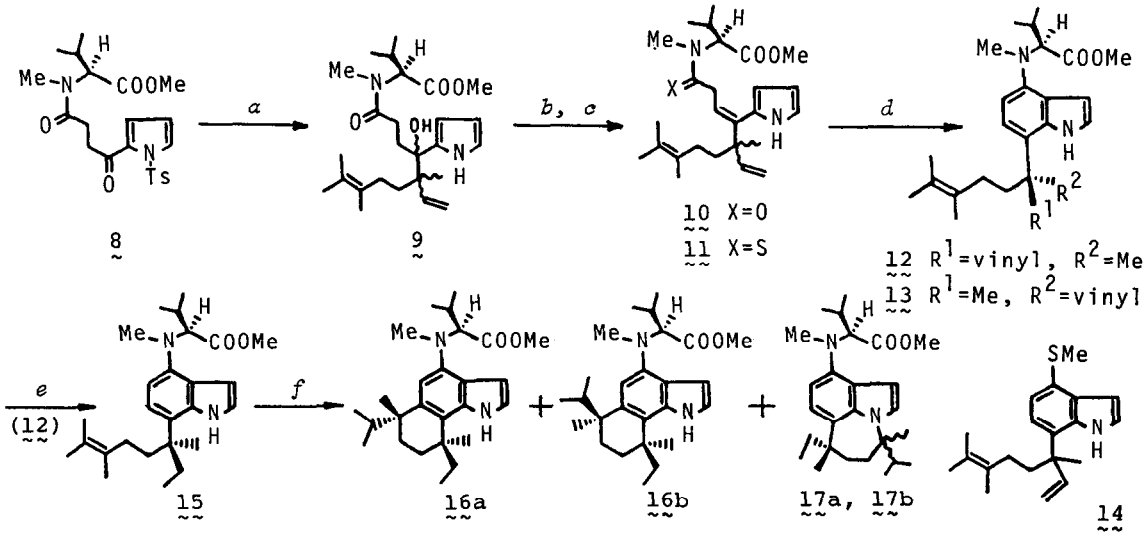


6 R^1=vinyl, R^2=Me
7 R^1=Me, R^2=vinyl

preparation of the 4-aminoindole derivative 15 with a 1,4,5-trimethyl-1-ethyl-4-hexenyl side chain was necessary and this was achieved in the following way.

L-Valine derivative 8[9] was treated with 3,6,7-trimethylocta-2,6-dienyl bromide[11] and Mg in THF to afford 9[12] in 70% yield, which was successively dehydrated with a catalytic amount of *p*-TsOH in boiling benzene to give 10[12] in 90% yield. 10 was converted to 11[12] with Lawesson's reagent[13] in refluxing THF in 74% yield, and the subsequent indole formation from 11 was readily attained with MeI in DMF at room temperature to provide 4-amino-7-alkylindole derivatives 12[12] and 13,[12] mp 68-70°C, in 38% and 25% yields, respectively, accompanied by the formation of a by-product 14 in 30% yield. Stereochemistry of the side chain at the C-7 position of 12 and 13 was tentatively assigned by analogy with the corresponding intermediates for teleocidins A synthesis. Catalytic hydrogenation of the major isomer 12 on PtO_2 proceeded without difficulty in MeOH at room temperature to furnish 15[12] in 92% yield.

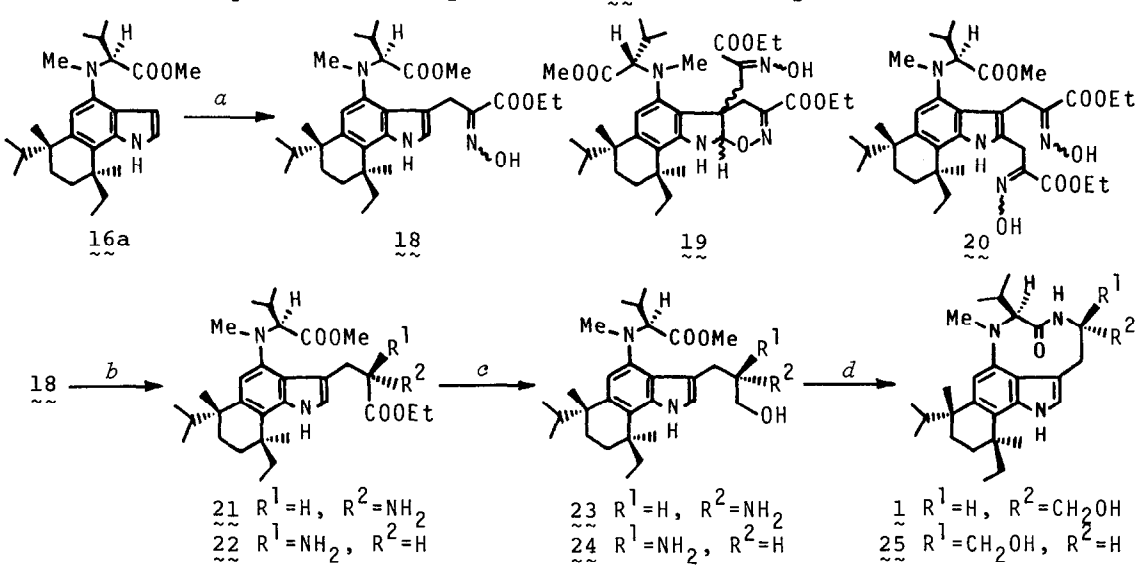
The acid-mediated cyclization reaction of 15 was examined by using a variety of Lewis and protonic acids to find a reaction condition to afford the highest yield of the isomer 16a, which has the correct stereochemical arrangement of the alkyl groups for the synthesis of 1. Treatment of 15 in CH_2Cl_2 with *ca.* 30 equiv. of 95% H_2SO_4 at 0°C for 4 h was found to be the best reaction condition, and 16a,[12] mp 134-136°C, $[\alpha]_D^{24}$ -102° (c=0.495, CH_2Cl_2) was obtained in 40% yield along with 16b,[12] mp 195-196°C, $[\alpha]_D^{24}$ -179° (c=0.500, CH_2Cl_2) in 10% yield. Formation of undesired by-products, 17a,[12] mp 100-101°C, and 17b[12] was inevitable and these were produced in 15% and 8% yields, respectively. $BF_3.OEt_2$ (*ca.* 40 equiv., 0°C → r.t., 7 h) and $SnCl_4$ (*ca.* 50 equiv., -20 → -10°C, 1.3 h) in CH_2Cl_2 were less satisfactory in terms of the ratio of 16a and 16b.



a: 3,6,7-trimethylocta-2,6-dienyl bromide, Mg, THF, Ar, 0°C, 3 h.
b: *p*-TsOH·H_2O, PhH, Ar, reflux, 2 min.
c: Lawesson's reagent, THF, Ar, reflux, 1 h.
d: MeI, DMF, r.t., 4 h.
e: H_2 (1 atm.), PtO_2, MeOH, r.t., 3 h.
f: 95% H_2SO_4, CH_2Cl_2, 0°C, 4 h.

Other acids such as $EtAlCl_2$, CF_3SO_3H and *p*-TsOH gave only disappointing results.

With the important intermediate 16a in hand, the indolactam V part of 1 was constructed according to our standard procedure developed in the synthesis of teleocidins A.[9] The functionalized three-carbon unit was introduced into the C-3 position of 16a using one equiv. of ethyl 3-bromo-2-hydroxyiminopropanoate[14] in the presence of Na_2CO_3 (2 equiv.) with the recovery of 16a in 11% yield. The desired compound 18 was obtained in 57% yield together with two 1:2 adducts 19 and 20 in 9% and 2.5% yields, respectively. With the increased ratio of the reagent to the substrate, the by-products were formed in much higher yields. Al amalgam reduction[15] of the hydroxyimino function of 18 readily afforded a mixture of amino ester compounds. Fortunately these were separated by applying preparative silica gel TLC [hexane-EtOAc (1:4)] to give 21 (40% yield) and 22 (39.5% yield). This made it easy to purify the final compound from a supposed by-product originating from the partial racemization of the valinate residue. The ethyl ester group of 21 was selectively reduced with $NaBH_4$ in the presence of LiCl[16] to yield 23, which was submitted to the next step without further purification, since the attempted purification by silica gel or alumina chromatography caused a great loss of the material. The crude 23 was hydrolyzed with 10% KOH in MeOH-H_2O (4:1) under reflux and the nine-membered lactam ring was constructed with diphenylphosphoryl azide (DPPA),[17] bearing in mind the series of pre-treatments described in the previous report,[9] to afford dihydroteleocidin B-4 (1),[12] mp 154-156°C and 232-235°C (decomp.),[18] in 18% yield from 21 after recrystallization from



a: Ethyl 3-bromo-2-hydroxyiminopropanoate, Na_2CO_3, CH_2Cl_2, r.t., 16 h.
b: Al-Hg, THF-H_2O (9:1), r.t., 4.5 h.
c: $NaBH_4$, LiCl, EtOH-THF (4:3), r.t., 23 h.
d: i) 10% KOH in MeOH-H_2O (4:1), Ar, reflux, 48 h; ii) Et_3N·HCl, 0°C, 2 min and r.t., 10 min; iii) evaporation *in vacuo* and dryness over P_2O_5; iv) DPPA, Et_3N, DMF, r.t., 62 h.

acetone-H_2O. In the same manner, 9-epidihydroteleocidin B-4 (25),[12] mp 259-261°C (decomp.) was obtained from 22 by way of 24 in 13% yield. The synthetic 1 was completely identified with the authentic specimen derived from natural teleocidin B-4 (5) in all respect (mixed mp determination, MS, IR, ^{1}H NMR, CD spectra, mobility of HPLC, and biological assay[19]).

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18) Solidified once at *ca.* 170°C. See reference 1) above.

19) Irritation on mouse ear and inhibition of specific ^{3}H-TPA binding.

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