SYNTHESIS OF OPTICALLY ACTIVE TELEOCIDINS B-3 AND B-4

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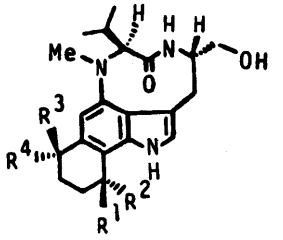
The potent tumor promoters, optically active teleocidins B-3 (3) and B-4 (4), were totally synthesized mostly using our synthetic pathway for the teleocidin A series. The key reaction, the BF_3·Et_2O-catalyzed intramolecular Friedel-Crafts cyclization, was applied at the final stage of the synthesis to the acetates (18a and 18b) to form the teleocidin B framework.

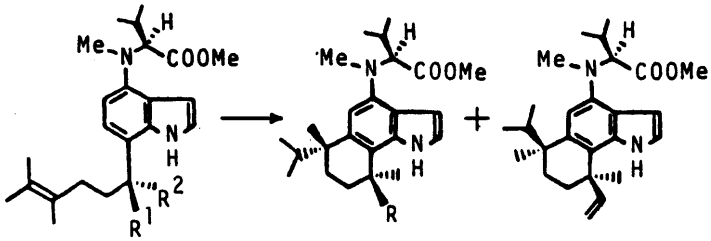
KEYWORDS teleocidin B-3; teleocidin B-4; tumor promoter; total synthesis; BF_3·Et_2O-catalyzed reaction; intramolecular Friedel-Crafts reaction

Teleocidins B-1 (1), B-2 (2), B-3 (3), and B-4 (4) are metabolites of *Streptomyces mediocidicus*[1] and are strong tumor promoters comparable to the TPA (12-*O*-tetradecanoylphorbol 13-*O*-acetate) in croton oil.[2] Continuing our synthsis studies on teleocidins A[3] and B,[4] we report here a total synthesis of teleocidins B-3 and B-4 in the optically active form. Racemic 3 and 4 were synthesized before.[5]

In the previous synthesis of dihydroteleocidin B-4 (5),[4] an acid-catalyzed intramolecular Friedel-Crafts reaction (6→7) using 95% H_2SO_4 was a key step to construct the 6,7,8,9-tetrahydrobenz[*g*]indole system. However, with the vinyl group required to synthesize teleocidin B, this reaction turned out to be very difficult. Treatment of 8 with acids such as 95% H_2SO_4, CF_3COOH, CF_3SO_3H, HBF_4·Et_2O, BCl_3, $MgBr_2$·Et_2O, $AlCl_3$, $SnCl_4$, $TiCl_4$, and $SbCl_3$ gave intractable mixtures or the recovery of 8. BF_3·Et_2O was the only reagent which afforded a positive result (Chart 1), but the yield was rather low in CH_2Cl_2 [8a→9+10 (10:1), 17%] or in $ClCH_2CH_2Cl$ (8a→9 only, 20%). It was helpful to find that the latter solvent favored the complete trans selectivity with respect to the arrangement of the vinyl and isopropyl groups. The rest of products were an inseparable complex mixture of compounds originating from the acid-catalyzed cyclization reaction of the terpenic side chain. Therefore, we decided to postpone the desired cyclization until the final stage of the synthesis in the light of Koshimizu and collaborators' success in conversion from blastmycetin D to olivoretin A.[6]



	R^1	R^2	R^3	R^4
1	vinyl	Me	i-Pr	Me
2	Me	vinyl	Me	i-Pr
3	Me	vinyl	i-Pr	Me
4	vinyl	Me	Me	i-Pr
5	Et	Me	Me	i-Pr



6 R^1=Et R^2=Me
8a R^1=vinyl R^2=Me
8b R^1=Me R^2=vinyl

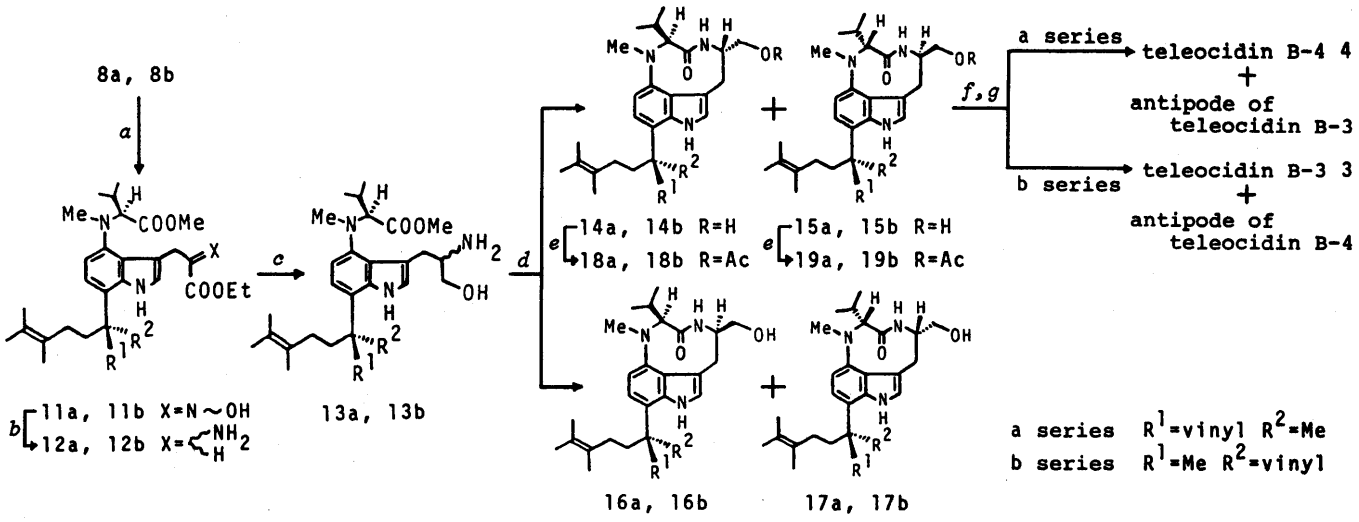
7 R=Et
9 R=vinyl

10

Chart 1

Previously reported compounds 8a and 8b[4] (a and b represent the B-4 and B-3 series respectively) were transformed into (*R*)- and (*S*)-7-(3,6,7-trimethyl-1,6-octadien-3-yl)indolactam V (14a and 14b) using the standardized four-step operation established in the teleocidin A synthesis[3] shown in Chart 2. A minor modification was adopted concerning the reagent for the formation of nine-membered lactam, because diethylphosphoryl cyanide (DEPC)[7] afforded much better results than diphenylphosphoryl azide (DPPA).[8] The indolactam V derivative 14a containing an inseparable by-product 15a, originating from the inevitable partial racemization at the alkalline hydrolysis of the methyl ester 13a, was acetylated to a mixture of

18a and 19a, followed by treatment with $BF_3 \cdot Et_2O$ in $ClCH_2CH_2Cl$ applying a knowledge of the preliminary experiment described above. The resulting mixture of products was hydrolyzed for the acetate cleavage and purified by preparative TLC, followed by HPLC,[9] to give teleocidin B-4 (4) and antipode of teleocidin B-3 in 18% and 2% yields, respectively. The same treatment of 14b containing 15b afforded teleocidin B-3 (3) and antipode of teleocidin B-4 in 17% and 2% yields. The synthetic 3 and 4 were identical with the authentic specimens in all respects (mp, ^1H NMR, IR, CD, mass spectra, and bioassay).



a: Ethyl 3-bromo-2-hydroxyiminopropanoate, Na_2CO_3, CH_2Cl_2, 20°C, 14-16.5 h. 11a,* 57%; 11b,* 61%.
b: Al-Hg, THF-H_2O (9:1), 40°C, 1 h for 12a, 87%; 20°C, 4 h for 12b, 90%.
c: $NaBH_4$, LiCl, EtOH-THF (4:3), 20°C, 12-22 h. 13a, 78%; 13b, 84%.
d: i) 10% KOH in MeOH-H_2O (4:1), Ar, reflux, 21-22 h; ii) $Et_3N \cdot HCl$, 0°C, 1 min and 20°C, 10 min; iii) evaporation *in vacuo* and dryness over P_2O_5; iv) DEPC, Et_3N, DMF, 20°C, 25-28 h. 14a+15a, 33%, 16a+17a, 28%; 14b+15b, 32%, 16b+17b, 28%.
e: Ac_2O, Py, CH_2Cl_2, 0°C, 1-1.3 h. 18a+19a, 100%; 18b+19b, 97%.
f: $BF_3 \cdot Et_2O$ (*ca.* 40 equiv.), $ClCH_2CH_2Cl$, 0°C, 1-1.3 h.
g: K_2CO_3 (5 equiv.), MeOH, 0°C, 40 min.

* By-products having 5-mono- (22%, 16%), 3,3-di- (7%, 5%), and 3,5-di- (7%, 5%) substituents were produced.

Chart 2

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