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TOTAL SYNTHESIS OF LYNGBYATOXIN A (TELEOCIDIN A-1) AND TELEOCIDIN A-2

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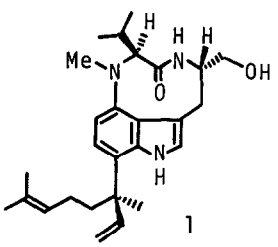
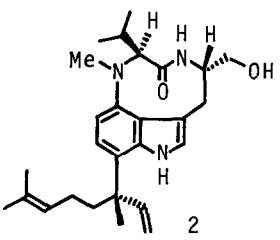
Summary: An eleven-step synthesis of tumor promoters, lyngbyatoxin A (=teleocidin A-1) (1) and teleocidin A-2 (2) was achieved from 1-tosylpyrrole (4) using a novel reaction forming 7-alkyl-4-aminoindoles (11).

Teleocidins A-1 (1) and A-2 (2) are metabolites of *Streptomyces mediocidicus*.[1,2,3] They are produced together with teleocidins B-1, B-2, B-3 and B-4.[4] One of these substances, teleocidin A-1 was shown to be identical with lyngbyatoxin A, isolated as a highly inflammatory and vesicatory compound from the blue-green alga *Lyngbya majuscula* in Hawaii.[5] Furthermore, teleocidin B-4 had the same structure as teleocidin B[6] obtained in the earlier investigation of a teleocidin B mixture.[7] All of these six teleocidins are proved to be potent tumor promoters.[8] A biogenetically related alkaloid, (-)-indolactam V[9] (3) has been synthesized in both optically active and racemic forms.[10,11] Here we describe the first total synthesis of lyngbyatoxin A (teleocidin A-1) (1) and teleocidin A-2 (2) in a short step.



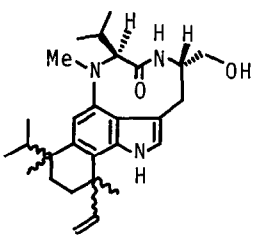
1

lyngbyatoxin A
=teleocidin A-1

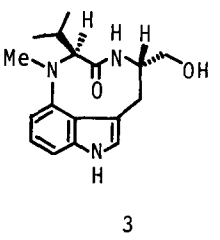


2

teleocidin A-2



teleocidin B-1, B-2
B-3, B-4



3

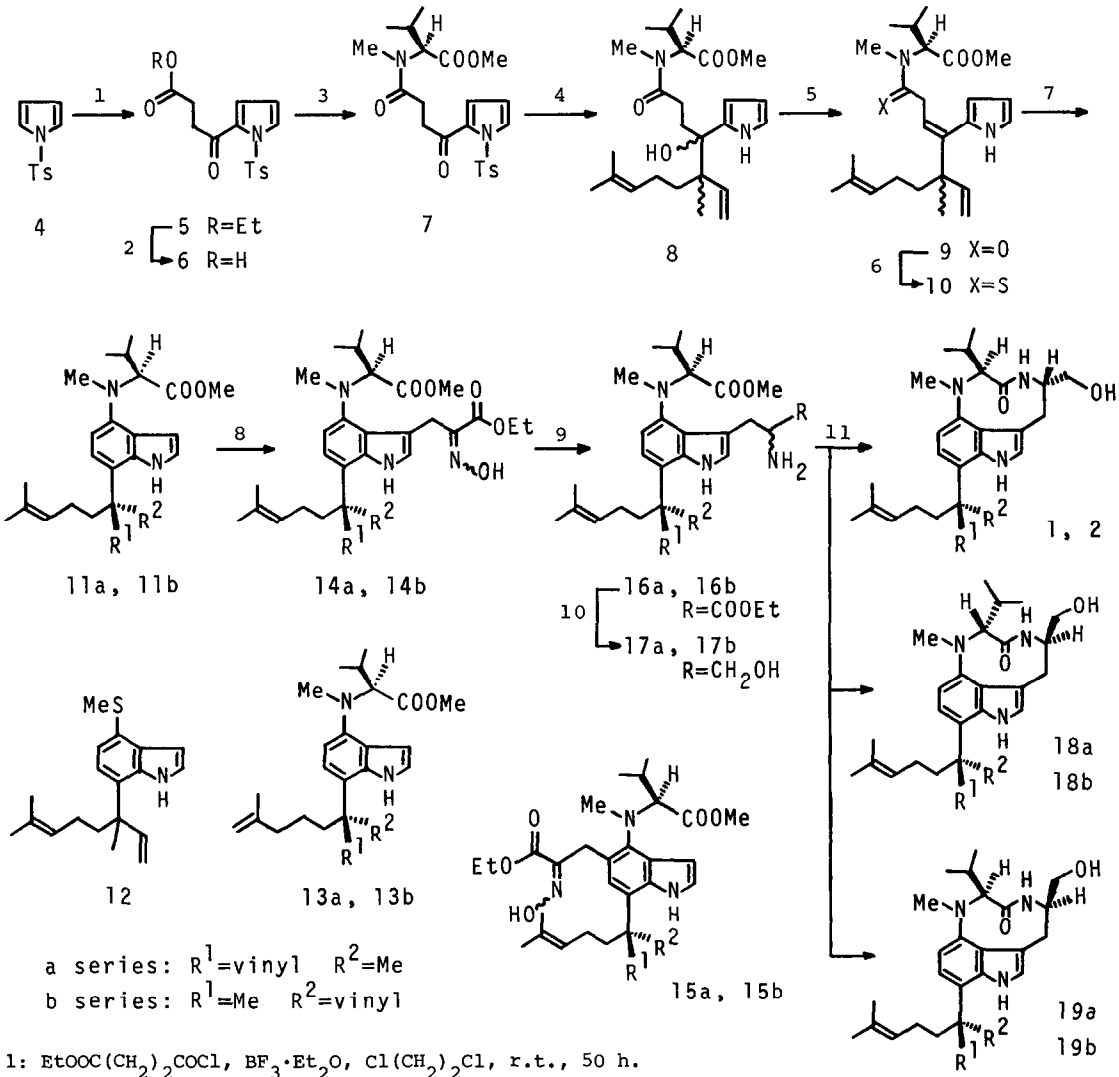
(-)-indolactam V

Our synthesis is based on the discovery of a new method leading to the formation of an optically active pair of isomers, 11a and 11b, having a 1,5-dimethyl-1-vinyl-4-hexenyl (linalyl) side chain. Their chiral centers correspond to *R* and *S* configuration of 1 and 2. The ketoamide 7 is a suitable intermediate, since the Grignard reaction on 7 using *E*-3,7-dimethyl-2,6-octadienyl (geranyl) bromide afforded only 8 with a linalyl side chain.[12] The amide group in 8 is the reaction center for constructing the indole ring to produce 7-alkyl-4-aminoindole derivatives 11.

The ester 5, mp 90.5-91.5°C, was prepared from 4[13] according to the literature[14] in 80% yield. Alkaline hydrolysis of 5 afforded the acid 6, mp 177-178 °C, in 95% yield. It was condensed with methyl *N*-methyl-L-valinate[15] to give the above-mentioned compound 7,[16] mp 132-133°C, $[\alpha]_D^{22}$ -69.4° (c=1.010, CH_2Cl_2),

in 87% yield. The Grignard reaction was performed by stirring a THF solution of 7 and geranyl bromide with Mg at 0°C. Both the amide and the ester groups remained intact and a mixture of tertiary alcohols 8,[16] lacking the *N*-tosyl group, was obtained in 80% yield. Brief treatment of 8 with *p*-TsOH in boiling benzene afforded readily an inseparable mixture 9[16] in 88% yield.

The Bischler-Napieralski type of cyclization to the indole nucleus was found to be the most crucial step because of the presence of the unstable pyrrole ring. After spending much effort with disappointing results,[17] 9 was



1: $EtOOC(CH_2)_2COCl$, $BF_3 \cdot Et_2O$, $Cl(CH_2)_2Cl$, r.t., 50 h.
2: 2.5% KOH in $THF-H_2O$ (3:1), r.t., 3 h.
3: ClCOOEt, Et_3N, THF, -20°C, 10 min; and methyl N-methyl-L-valinate hydrobromide, -20°C, 10 min, and then r.t., 45 min.
4: Geranyl bromide, Mg, THF, Ar, 0°C, 3.5 h. 5: p-TsOH·H_2O, PhH, Ar, reflux, 2 min.
6: Lawesson's reagent, THF, Ar, reflux, 50 min. 7: MeI, DMF, r.t., 3 h.
8: Ethyl 3-bromo-2-hydroxyiminopropanoate, Na_2CO_3, CH_2Cl_2, r.t., 14-15 h.
9: Al-Hg, $THF-H_2O$ (9:1), r.t., 4 h. 10: $NaBH_4$, abs. EtOH, Ar, reflux, 20 h.
11: i) 10% KOH in MeOH-H_2O (4:1), Ar, reflux, 22-26 h; ii) Et_3N·HCl, 0°C-r.t., 10 min; iii) DPPA, Et_3N, DMF, 0°C, 1 h, and then r.t., 17-24 h.

converted to a thioamide 10[16] in 65% yield using Lawesson's reagent[18] in refluxing THF, and 10 was treated with alkyl halides in a variety of solvents. Stirring a DMF solution of 10 and MeI at room temperature for 3 h gave the best result[19] and separation of the reaction mixture by silica gel chromatography produced the crystalline substances 11a and 11b in 37% and 24% yields, respectively, accompanied by an undesired product 12[16] in 30% yield. About 4-6% of the crude 11a and 11b was double bond isomers 13a and 13b, which were formed during the TsOH dehydration of 8. Repeated recrystallization of both crystals from MeOH-H_2O afforded pure 11a,[16] mp 58-59.5°C, $[\alpha]_D^{22}$ -157.7° (c=0.995, CH_2Cl_2) and pure 11b,[16] mp 75-77°C, $[\alpha]_D^{22}$ -191.1° (c=1.005, CH_2Cl_2), in 27% and 19% yields, respectively, calculated from 10. The configuration of the linalyl side chain was uncertain at this stage, and completion of the synthesis established the chirality of 11a and 11b as shown.

The next step was the introduction of an appropriate functional group into the C-3 position of 11a and 11b. For further derivatization, common reactions such as catalytic hydrogenation, $LiAlH_4$ reduction, and treatment with acids and strong bases should be avoided because of the chemical behavior of 11a and 11b. For this requirement ethyl 3-bromo-2-hydroxyiminopropanoate[20] was chosen as the most pertinent reagent. The reaction with 11a and 11b was effected in the presence of Na_2CO_3, and the anticipated products 14a[16] and 14b[16] were isolated respectively in 59% and 65% yields as single compounds having an unknown stereochemistry of the oxime group. This was accompanied by the formation of 15a[16] (20%) and 15b[16] (15%), and the recovery of 11a (8%) and 11b (9%). The oxime group was reduced to the primary amine by treatment of 14a and 14b with Al amalgam in aqueous THF[21] to give 16a[16] and 16b[16] in the respective yields of 92% and 89%. Each was an inseparable 1:1 mixture of diastereoisomers with respect to the chiral center in the newly formed amino ester part. This ester group was sterically less crowded than the valinate, so the reduction of 16a and 16b with $NaBH_4$ in refluxing EtOH[22] afforded 17a[16] and 17b[16] in 51% and 53% yields, respectively.

The final step, formation of a nine-membered lactam ring, was performed according to Ley and co-workers' procedure for indolactam V synthesis.[11] The ester group of 17a was hydrolyzed with caustic alkali and the excess alkali was neutralized with $Et_3N.HCl$. The solvent was evaporated *in vacuo*. The remaining solid was dried over P_2O_5 and treated with diphenylphosphoryl azide[23] (DPPA) and Et_3N in DMF. Separation of the reaction mixture over silica gel, followed by preparative HPLC[24] gave 1 in 23% yield, accompanied by the formation of 18a (*ca.* 4% yield) and crude 19a[16] (27% yield). The same treatment starting from 17b gave 2 (21% yield), 18b (*ca.* 4% yield) and crude 19b[16] (25% yield). Identification[24] of synthetic 1 and 2 with lyngbyatoxin A (=teleocidin A-1) and teleocidin A-2 was verified by comparison of MS, ^1H NMR (270 MHz, $CDCl_3$), and CD spectra as well as the mobility of HPLC. 18a and 18b are enantiomers of 2 and 1, formed by partial racemization during the treatment with caustic alkali. Their structures were determined by the HPLC, MS, and CD spectra. Thus, the

first total synthesis of 1 and 2 from 4 was completed in eleven steps.[25]

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