Communications to the Editor

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THE STRUCTURES OF ADDITIONAL TELEOCIDIN CLASS TUMOR PROMOTERS

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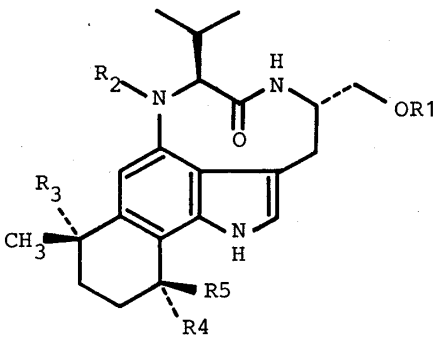
The known tumor promoter des-O-methylolivoretin C, and a new possible tumor promoter, des-N-methylteleocidin B-4, were isolated from Streptomyces mediocidicus and the structure of the latter metabolite was elucidated by chemical correlation with the known teleocidin B-4. The structures of teleocidin B-2 and a new metabolite, olivoretin E, obtained from Streptomyces mediocidicus and Streptoverticillium olivoreticuli respectively, were determined by means of single-crystal X-ray diffraction analysis.

KEYWORDS—— Streptomyces mediocidicus; Streptoverticillium olivoreticuli; des-O-methylolivoretin C; des-N-methylteleocidin B-4; teleocidin B-2; olivoretin E; spectral analysis; X-ray analysis; tumor promoter

In previous papers, we reported on the isolation and structure elucidation of teleocidins B-1, B-2, B-3 and B-4,[1] and on the absolute configuration of teleocidins A-1 (lyngbyatoxin A) and A-2[2]. Here, we describe the isolation from Streptomyces mediocidicus of a known tumor promoter, des-O-methylolivoretin C[1] (**1**) and a new possible tumor promoter, des-N-methylteleocidin B-4 (**2**). We also isolated a new metabolite, olivoretin E (**3**) from Streptoverticillium olivoreticuli. All of these metabolites are more polar than the compounds of the teleocidin A and B groups, and they are only minor components.

Des-N-methylteleocidin B-4 is a gummy solid and shows the same type of UV absorption[3] as other teleocidin B group compounds. Its molecular ion peak appeared at m/z 437.3038 (base peak) and the molecular formula was thus established as $C_{27}H_{39}N_3O_2$ (Calcd. 437.3039). The mass spectrum [m/z 437 (100), 394 (81), 351 (30), 307 (74)] showed a pattern parallel to, but separated by 14 mass units from,



des-O-methylolivoletin C (**1**)
R_1=H, R_2=R_4=CH_3, R_3=vinyl, R_5=iso-propyl

des-N-methylteleocidin B-4 (**2**)
R_1=R_2=H, R_3=iso-propyl, R_4=CH_3, R_5=vinyl

olivoretin E (**3**)
R_1=R_2=CH_3, R_3=vinyl, R_4=H, R_5=tert-butyl

teleocidin B-2 (**4**)
R_1=H, R_2=R_5=CH_3, R_3=iso-propyl, R_4=vinyl

that of teleocidin B-4 [m/z 451 (100), 408 (36), 365 (42), 321 (44)]. Its ^{1}H-NMR spectrum (CD_3OD, 270 MHz) was similar to that of teleocidin B-4, except that it lacked the signal of the N-methyl group. From the above observations, we assumed the structure to be des-N-methylteleocidin B-4 or a stereoisomer involving the substituted cyclohexane ring. On methylation by the use of $CH_3I/NaHCO_3$ in EtOH, this compound gave teleocidin B-4, which was confirmed to be identical with an authentic sample by comparison of the ^{1}H-NMR and CD spectra and the retention time in HPLC.[1] It is interesting to note that a similar des-N-methyl analogue has been found, des-N-methylindolactam V,[4] corresponding the parent N-methyl derivative, indolactam V. These metabolites have the same teleocidin B type structures but lack the substituted cyclohexane ring. Total synthesis of des-N-methylindolactam V has been achieved by two groups.[5,6]

Olivoretin E (**3**) obtained as colorless prisms with a mp of 266-269° C (dec.; hot plate). Its UV spectrum was typical of a 4-aminoindole chromophore.[7] The ^{1}H-NMR spectrum of **3** ($CDCl_3$) indicated the presence of an N-CH_3, an isopropyl, a methyl on the ethereal oxygen atom, a vinyl, and three methyl groups on a tert-butyl group.[7] The mass fragmentation pattern indicated the presence of a tert-butyl group (M^+- tert-butyl, m/z 408, 100%) and showed a molecular ion peak (m/z 465, 6%). On the basis of these spectral data, we assumed the structure of olivoretin E to be **3**, except for the stereochemistry. Finally, the structure of **3** was determined by X-ray analysis.[8] An ORTEP diagram of the X-ray-determined structure of **3** is shown in Figure 1. In the solid state, the nine-membered lactam takes the trans conformation and the biggest substituent, the tert-butyl group, has a quasi-axial conformation due to repulsion by the NH group in the indole moiety. The CD spectrum of **3** showed the same type of curve as those of olivoretins B and C. Therefore all three compounds should have the same absolute configuration.[7]

We previously assigned the structure (**4**) to teleocidin B-2 based on the ^{13}C-NMR and other spectral data. Now the X-ray crystallographic structure of **4** was also determined.[9] An ORTEP drawing of the X-ray-determined structure of teleocidin B-2 was in agreement with the previously presented structure.

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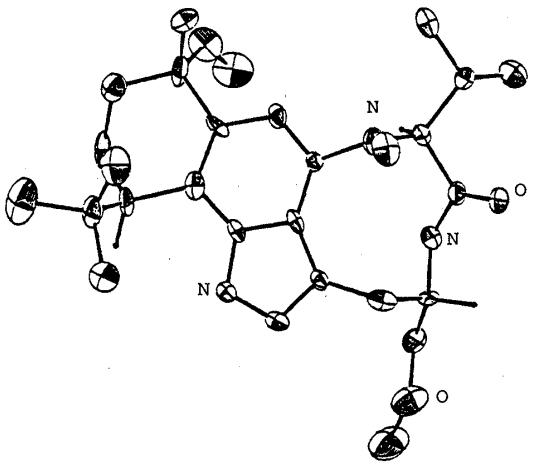

Fig. 1. ORTEP Drawing of Olivoretin E (**3**)

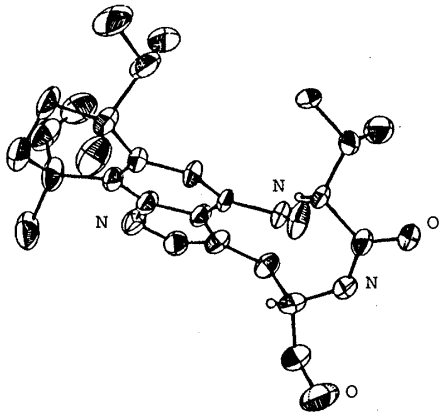

Fig. 2. ORTEP Drawing of Teleocidin B-2 (**4**)

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3) Spectra of **2**, UV: λ_{max}^{MeOH} nm (log ε); 230 (4.55), 281 (3.92), CD (c, 2.7×10^{-2}, MeOH, 18 °C): $/\theta/_{337}$ 0, $/\theta/_{305}$ -4,400, $/\theta/_{291}$ -4,200, $/\theta/_{274}$ -6,200, $/\theta/_{271}$ - 6,100, $/\theta/_{253}$ -12,500, $/\theta/_{243}$ 0, $/\theta/_{235}$ +20,100, $/\theta/_{230}$ 0, $/\theta/_{220}$ -36,300, $/\theta/_{209}$ -28,200, $/\theta/_{205}$ -29,900.

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7) Spectra of **3**, UV: λ_{max}^{MeOH} nm(log ε): 234 (4.51), 291 (3.93), 300sh (3.91), ^{1}H-NMR ($CDCl_3$) signals of the major conformer [ratio of major to minor conformer was 1.7 : 1 (cis : trans of nine-membered lactam) a few hours after dissolution of **3** in $CDCl_3$, 0.019 M, 27 °C]. 2.90 (3H, s), 0.92, 0.63 (each 3H; d, J=6.3 Hz, d, J=6.9 Hz, respectively), 2.59 (1H, m), 1.51(3H, s), 4.76 (1H, dd, J=10.6, 1.3 Hz) 4.37 (1H, dd, J=17.1, 1.3 Hz), 5.83 (1H, dd, J=17.1, 10.6 Hz) and 1.03 (9H, s), CD (c, 5.4×10^{-3}, MeOH, 17°C): $/\theta/_{331}$ 0, $/\theta/_{312}$ +2,600, $/\theta/_{301.5}$ 0, $/\theta/_{267}$ -51,900, $/\theta/_{244.5}$ 0, $/\theta/_{237}$ +3,960, $/\theta/_{226}$ +4,000, $/\theta/_{210}$ +72,300.

8) X-ray analysis of **3**: Crystals of **3** belong to orthorhombic space group $P2_12_12_1$ with cell constants of a=17.448(3) Å, b=22.686(3) Å, c=7.018(1) Å. A total of 3411 unique independent intensities were measured within the range of $3° < 2\theta < 155°$ on a 4-circle diffractometer (Rigaku AFC-5) using Cu Kα radiation (λ = 1.54 Å). The structure was solved by the direct method using MULTAN 80 (UNICS III system[10]) and refined anisotropically (isotropically for H) by the least-squares method, using the 1322 reflections for which $/Fo/ > 3\sigma /Fo/$. The final R-factor was 8.5%.

9) X-ray analysis of **4**: Crystals of **4** belong to monoclinic space group P2 with unit cell dimensions of a=19.014(2) Å, b=7.521(1) Å, c=10.692(2) Å, β (deg)= 101.48(1)° and Z=2. A total of 3559 unique and significant reflections $/Fo/ > 3\sigma/Fo/$ within the range of $3° < 2\theta < 155°$ were measured on a 4-circle diffractometer (Rigaku AFC-5) using Cu Kα radiation (λ =1.54 Å). The final R-factor was 10.00%.

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