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ABSOLUTE CONFIGURATION OF LYNGBYATOXIN A (TELEOCIDIN A-1) AND TELEOCIDIN A-2

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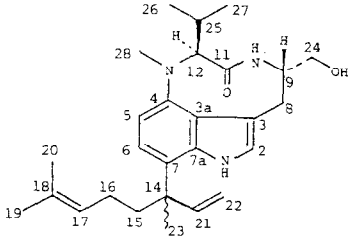
Summary: The absolute configuration of lyngbyatoxin A (teleocidin A-1) and teleocidin A-2, potent tumor promoters on mouse skin, has been determined by chemical degradation including ozonolysis.

One (Fujiki's group)[1] of the present authors has published the tumor-promoting activity of lngbyatoxin A isolated from the blue-green alga Lyngbya majuscula in Hawaii.[2] The same group reported that lyngbyatoxin A is identical with one isomer of teleocidin A group.[3)4)] Chemical structure study group (Sakai's group) presented already studies for the structure elucidation of teleocidin B-1, B-2, B-3 and B-4, metabolites of Streptomyces mediocidicus,[5] and olivoretin A, B, C, des-O-methylolivoretin C, olivoretin D (=teleocidin B-4 = teleocidin B by Hirata), metabolites of Streptoverticillium olivoreticuli, by use of X-ray and spectral analysis.[6)7)] Teleocidin A-1 and A-2 were obtained together with teleocidin B group from S. mediocidicus. The pure metabolites were obtained by use of flash column chromatography (SiO_2), Lober column chromatography, MPLC (ODS) and finally HPLC[8)9)] from methanol extract of the mycelia. Teleocidin A-1 (1): gummy solid. $/\alpha/_D^{18}$ -108.4° (c=0.14, MeOH). It was shown to be identical with the authentic sample of lyngbyatoxin A.[2] Teleocidin A-2 (2): gummy solid. $/\alpha/_D^{18}$ -185.1° (c=0.18, MeOH), $C_{27}H_{39}N_3O_2$ (M^+, Found. m/z 437.3008).

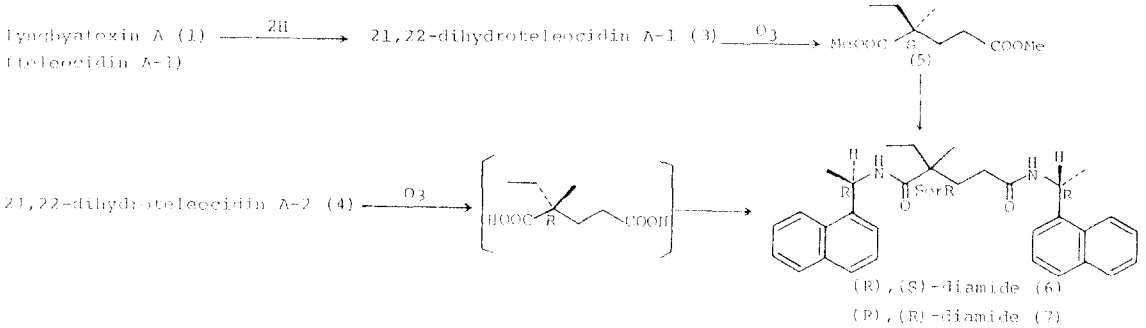


lyngbyatoxin A (1): 14R
(teleocidin A-1)

teleocidin A-2 (2): 14S

Respective hydrogenation of 1 and 2 using Wilkinson catalyst gave rise to an amorphous 21,22-dihydroteleocidin A-1 (3) ($C_{27}H_{41}N_3O_2$, M^+, Found. m/z 439.3168, δ 0.66 (3H, t, J=7.3Hz, C_{22}-H_3)) and an amorphous 21,22-dihydroteleocidin A-2 (4) ($C_{27}H_{41}N_3O_2$, M^+, Found. m/z 439.3177, δ 0.67 (3H, t, J=7.4Hz, C_{22}-H_3)). Compound 3 (91mg) was ozonolyzed in aq-HOAc for 17 hr at rt and the ozonide was decomposed by 10% H_2O_2 solution for 60 hr at rt. Acidic part was methylated with CH_2N_2. The methyl ester was obtained in the crude state (22mg) which was shown to have the same retention time with dimethyl S(-)-α-methyl-α-ethylglutarate (5)[10] by G.C.[11] and indistinguishable ^{1}H-NMR spectra (60MHz) with the synthetic sample.[10] The ester obtained from the above ozonolysis was hydrolysed in 0.7 N alcoholic KOH sol. with a refluxing 7 hr under Ar. After treatment with oxalyl chloride, acidic part gave rise to the dichloride which reacted with R(+)-1-(1-naphthyl)ethylamine in the presence of Et_3N and 4-dimethylaminopyridine. The resulting (R),(S)-diamide (6) was purified by the use of HPLC.[12] The (R),(S)-diamide (6)

(2mg) derived from 1 was identical with a synthetic sample.[13] (R),(R)-Diamide (7) (2mg, mp 231-232°C) was derived from 21,22-dihydroteleocidin A-2 (4) in the exactly same procedure as above and this was found by comparison of the mixed mp, ^{1}H-NMR, Mass spectra and retention time in HPLC[12] to be identical with (R),(R)-diamide (7),[14] synthesized from dimethyl R(+)-α-methyl-α-ethylglutarate and R(+)-1-(1-naphtyl)ethylamine. Thus, the above result showed uneqivocally the C-14 absolute configurations of 1 and 2 as R and S, respectively. The absolute configurations at C-9 and C-12 in 1 were elucidated as S, S in the previous paper[15] and 2 has the same configuration on nine-member lactam as evidenced by the same CD spectra.[16]



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8) ODS 5, Mobile Phase, MeOH 78, H_2O 20, $CHCl_3$ 2.
9) TSK-Gel silica 60, n-hexane 85, $CHCl_3$ 10, i-PrOH 5.
10) A. S. C. P. Rao, V. K. Bhalla, U. R. Nayak and S. Dev, Tetrahedron, 29, 1127 (1973).
11) OV-1, 2m, 130°C, N_2 30ml/min, t_R= 14.2min.
12) YMC Pack A-012, 0.8ml/min, 20kg/cm^2, UV_{280}, t_R= 21.5min.
13) Amorphous powder, high mass, Calcd. for $C_{32}H_{36}N_2O_2$: 480.2774, Found. 480.2757, 270MHz ^{1}H-NMR in $CDCl_3$, 50°C, δ, 8.11-7.24 (14H, m, arom. H), 5.99-5.76 (3H, m), 5.46 (1H, m), 2.20-1.24 (6H, m), 1.62 (3H, d, J=6.6Hz), 1.59 (3H, d, J=6.9Hz), 1.07 (3H, s), 0.80 (3H, d, J=7.4Hz).
14) $C_{32}H_{36}N_2O_2$ from elemental analysis and mass spectrum; m/z(%), 480(M^+, 2.4), 170(100), 155 (65), 270MHz ^{1}H-NMR in $CDCl_3$, 50°C, δ, 8.10-7.26 (14H, m, arom. H), 5.96-5.81 (3H, m). 5.52(1H, m), 2.04-1.94(4H, m), 1.80-1.33(2H, m), 1.63(3H, d, J=6.9Hz), 0.98(3H, s), 0.82 (3H, t, J=7.4Hz), t_R= 19.2min.[12]
15) Y. Endo, K. Shudo, K. Furuhata, H. Ogura, S. Sakai, N. Aimi, Y. Hitotsuyanagi and Y. Koyama, Chem. Pharm. Bull. 32, 358 (1984).
16) We considered that the numbering system for teleocidin A-1 and A-2 should be adopted from that for lyngbyatoxin A.[2] Therefore, it is not the same as that of teleocidin B group.[5)6)7)]

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