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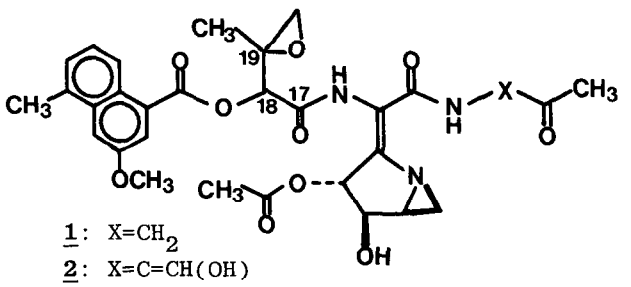
SYNTHETIC STUDIES TOWARD AZINOMYCINS A AND B. SYNTHESIS AND ABSOLUTE STEREOCHEMISTRY OF THE MINOR COMPONENT ISOLATED FROM AZINOMYCINS PRODUCING STRAIN

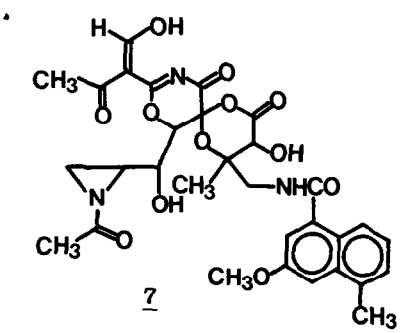
Masayuki Shibuya* and Hideo Terauchi
Faculty of Pharmaceutical Sciences, University of Tokushima,
Sho-machi 1, Tokushima 770, Japan

Abstract: The minor component isolated from *Streptomyces griseofuscus* S42227 was synthesized in optically active form and the absolute configurations of C-18 and C-19 of azinomycins were presumed as 18S, 19S.

Azinomycins A and B are antitumor antibiotics recently isolated from the culture broth of strain *Streptomyces griseofuscus* S42227 by Nagaoka *et al.*[1a] The structures of them, lacking absolute stereochemistry, were deduced as 1 and 2 by spectroscopic methods.[1b] The biologically inactive amide 3 was also isolated along with 4 and 5 from the same strain. By a detailed comparison of spectroscopic data of 3 with those of azinomycins, Yokoi *et al.* concluded that the structure of 3 is the same as that of the left half moiety of azinomycins.[1b]



1: X=CH_2
2: X=C=CH(OH)



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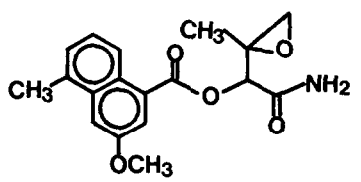
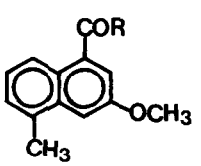
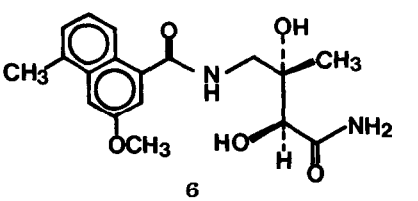


3



4: R=OCH_3
5: R=NH_2



6

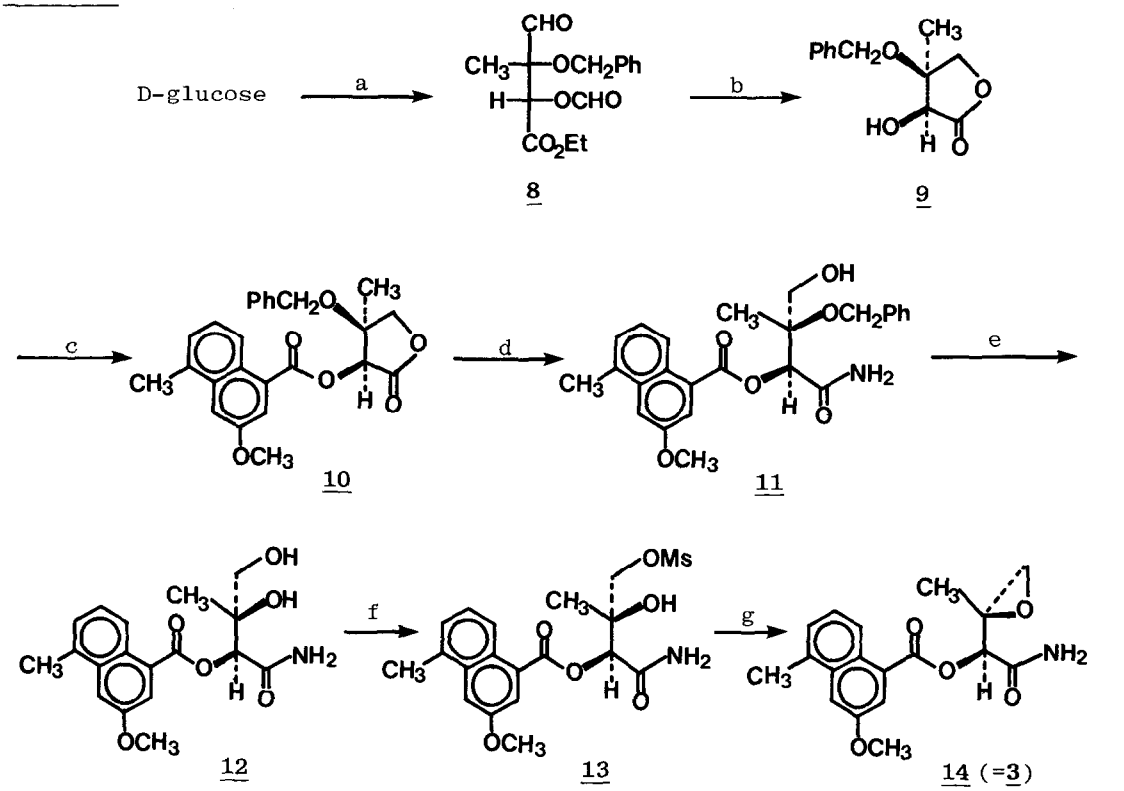
Previously, we synthesized the optically active degradation product **6**[2,3] of antitumor antibiotic carzinophilin, the total structure of which had been first proposed by Lown *et al.*[4] and then revised as **7** by Onda *et al.*[5] Inspection of the gross structures **2** and **7** reveals a close homology and, as Yokoi *et al.* pointed out,[1b] the spectral data for azinomycins are similar to those for carzinophilin **7**. Both compounds, **3** and **6**, are therefore of considerable importance in studying structural relationship of azinomycins and carzinophilin.

We now report that the absolute structure of **3** was established as 18s, 19S (using azinomycin numbering) by the total synthesis starting from the same chiral intermediate **8**[2] as that we have used earlier in the synthesis of **6**. (Scheme 1) Now we are able to prepare the aldehyde **8** from commercially available diacetone-D-glucose in >70% overall yield. Reduction of the aldehyde **8** and then the resultant diol[6] was refluxed with catalytic amount of TsOH under azeotropic removal of EtOH gave the γ-lactone **9** in 92% yield from **8**. Acylation of **9** with 3-methoxy-5-methylnaphthalene-1-carboxylic acid chloride[2] afforded the ester **10** in 84% yield. Aminolysis of the ester **10** was performed with methanolic ammonia at 0°C to give the amide **11** in 91% yield. It was found, as expected, that the ester group was unchanged in this conditions. After hydrogenolysis of **11** to give the diol **12** (73%), selective mesylation of 12 proceeded by using MsCl. The resultant monomesylate **13** was sparingly soluble in many organic solvents. Therefore, without further purification, the final oxirane ring fromation was achieved by heating crude **13** with K_2CO_3 in acetone, and the epoxide **14** was obtained in 89% yield from **12**.[7] This compound was found to be identical (mp, IR, UV, ^1H NMR, ^{13}H NMR, and TLC) with the natural amide **3**. The optical rotation of the synthetic sample ($[\alpha]_D^{23}$ +47.5°(c=0.32, MeOH)) is compatible with that of natural one ($[\alpha]_D^{25}$ +48°(c=0.33, MeOH)).[1b] On the other hand, treatment of **14** with ammonia (5% NH_3 in 1:1 MeOH/H_2O, 80°, 30min) gave **4**, **5**, and **6** in 50%, 6%, and 25% yield, respectively. The formation of **6** is explained as shown in Scheme 2. The absolute configuration of the natural epoxy amide was thus established as shown in **14**. Azinomycins A and B can be presumed to possess the 18S, 19S configurations, respectively, because of the spectroscopic similarity of **1**, **2**, and **3**, and biosynthetic viewpoint.

On account of the highly significant biological activities[1a,c] and unique structural features, azinomycins A and B are attractive synthetic targets. Further, the absolute configurations of two chiral centers of **14** are compatible with those of the host-specific phytotoxins such as AK-toxins[8] and AF-toxins.[9] The γ-lactone **9** must be a promising common precursor for the syntheses of azinomycins and AK- and AF-toxins. These efforts are currently underway in our laboratory.

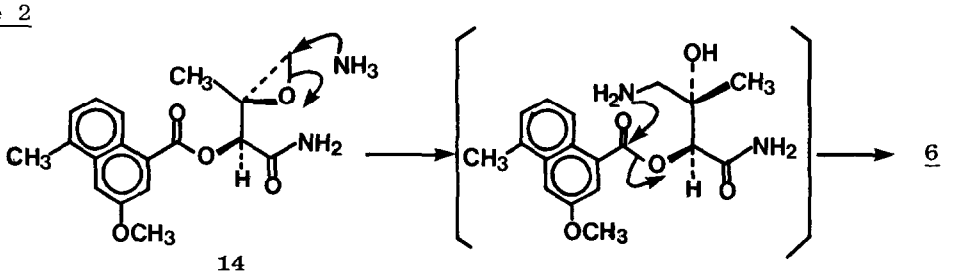
Acknowledgement: The authors are grateful to Dr. Kouichi Yokoi, SS Pharmaceutical Co., Ltd., for generously providing an authentic sample of the natural amide **3** and its spectral data.

Scheme 1



a. See reference 2. b. (i)$NaBH_4$/EtOH-THF(1:1)/0°.(ii)TsOH(cat.)/benzene/reflux. c. 3-methoxy-5-methylnaphthalene-1-carboxylic acid chloride[2]/$Et(i\text{-}Pr)_2N$/DMAP/CH_2Cl_2/0°. d. ca.15% NH_3 in MeOH/0°. e. H_2/10% Pd-C/AcOH. f. MsCl/$Et(i\text{-}Pr)_2N$/CH_2Cl_2/RT. g. K_2CO_3/acetone/reflux.

Scheme 2



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6. This diol was partially transformed into the lactone 9 during purification with silica gel chromatography.
7. Selected data; 9: mp 76-77°; $[\alpha]_D^{23}$ +79.8°(c=0.38, MeOH); ν ($CHCl_3$) 3550 and 1803 cm^{-1}; δ ($CDCl_3$) 1.40 (3H, s), 3.45 (1H, d, J=9.5, OH), 3.86 (1H, d, J=10.5), 4.08 (1H, d, J=9.5), 4.31 (1H, d, J=10.5), 4.40 (1H, d, J=11.5), 4.46 (1H, d, J=11.5), and 7.24 (5H, s). 10: mp 127-128°; $[\alpha]_D^{23}$ +218.2° (c=0.17, $CHCl_3$); ν ($CHCl_3$) 1798 and 1725 cm^{-1}; δ ($CDCl_3$) 1.48, 2.53, 3.75 (3X3H, s), 4.04 (1H, d, J=10.5), 4.41 (1H, d, J=10.5), 4.47 (2H, s), 5.75 (1H, s), 7.24 (5H, s), 7.15-7.30 (2H, m), 7.35 (1H, d, J=2.5), 7.97 (1H, d, J=2.5), and 8.70 (1H, m). 11: ν ($CHCl_3$) 3500, 3400, 1728, and 1692 cm^{-1}; δ ($CDCl_3$) 1.36, 2.55, 3.80 (3X3H, s), 3.30-3.90 (3H, m, $-CH_2-$ and OH), 4.46 (2H, s), 5.53 (1H, s) 6.36, 6.56 (2X1H, br., NH_2), 7.22 (5H, s), 7.10-7.40 (3H, m), 7.85 (1H, d, J=2.5), and 8.62 (1H, m). 12: mp 148-149°; $[\alpha]_D^{23}$ +22.0° (c=0.32, MeOH); ν (KBr) 3440, 3330, 1724, and 1670 cm^{-1}; δ ($CDCl_3$/CD_3OD 3:1) 1.32, 2.63, 3.93 (3X3H, s), 3.51 (1H, d, J=11), 3.65 (1H, d, J=11), 3.58 (1H, s), 7.25-7.40 (2H, m), 7.43 (1H, d, J=2.5), 7.88 (1H, d, J=2.5), and 8.60 (1H, m).
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