

SYNTHETIC APPROACH TOWARD AZINOMYCINS

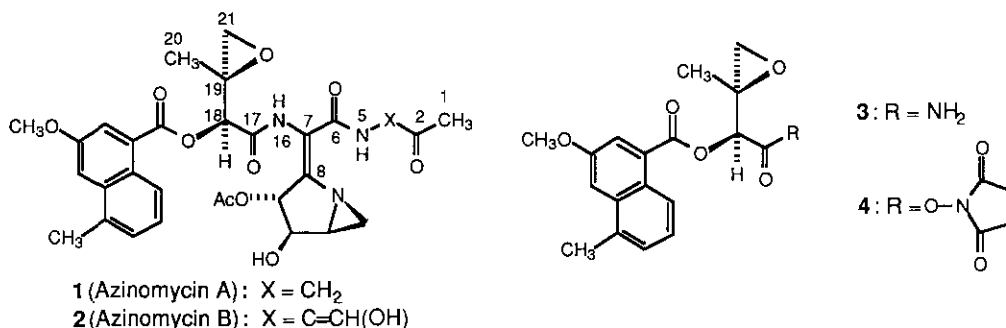
Kenshi Ando, Takae Yamada, and Masayuki Shibuya*

Faculty of Pharmaceutical Sciences, University of Tokushima,

Sho-machi 1, Tokushima 770, Japan

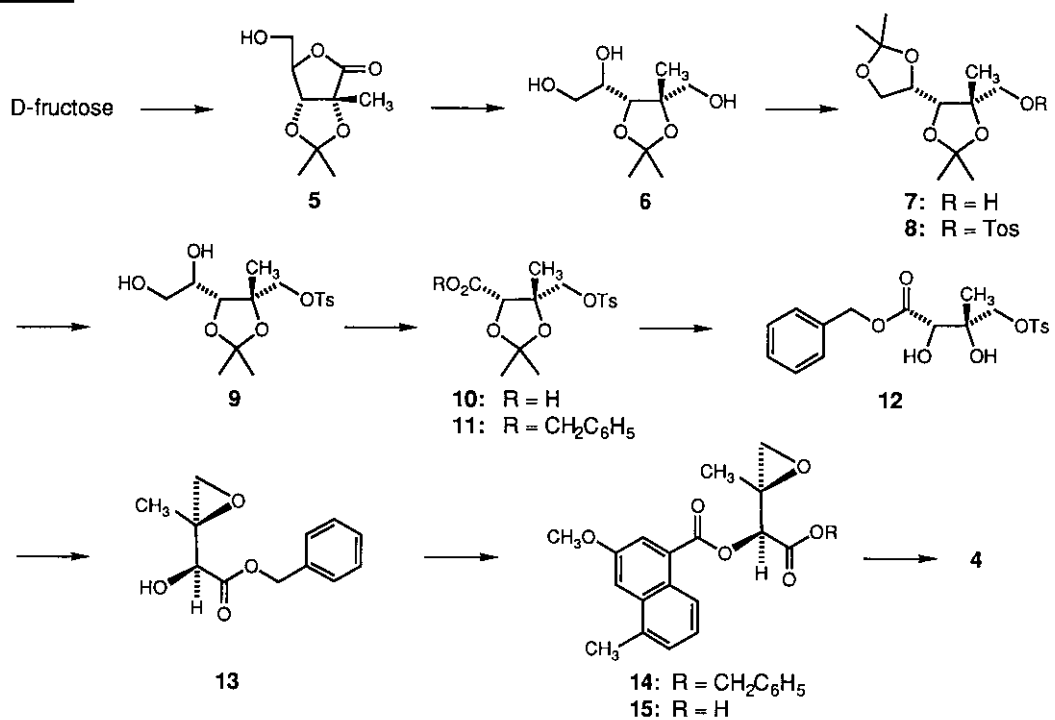
Abstract—The left-half segment **14** of antitumor antibiotics azinomycins A and B was synthesized in optically pure form starting from D-fructose. The dipeptide **18**, equivalent to the azinomycin A top-half, was also synthesized via oxazolidinone intermediates.

Azinomycins A and B are antitumor antibiotics isolated from the culture broth of strain *Streptomyces griseofuscus* S42227 by Nagaoka *et al.* in 1986.¹ Azinomycins were reported to exhibit antitumor activities against P388 leukemia, P815 mastocytoma, B-16 melanoma, and Ehrlich carcinoma.² The structures of them, lacking absolute stereochemistry, were elucidated as **1** and **2** by spectroscopic method.³ Recently, we proposed absolute configurations of C-18 and C-19 as 18*S*, 19*S* by the total synthesis of the minor component **3** isolated from the same strain starting from D-glucose.⁴ Although the amide **3** possesses all structural units for the left-half moiety of azinomycins, it is not necessarily useful for the total synthesis of them. Therefore, from a synthetic point of view, the efficient synthetic method of the other left-half equivalent is required. We describe here an easy access to the N-hydroxysuccinimide ester **4** using D-fructose as a chiral starting material and preparation of some model compounds for the total synthesis of azinomycins.

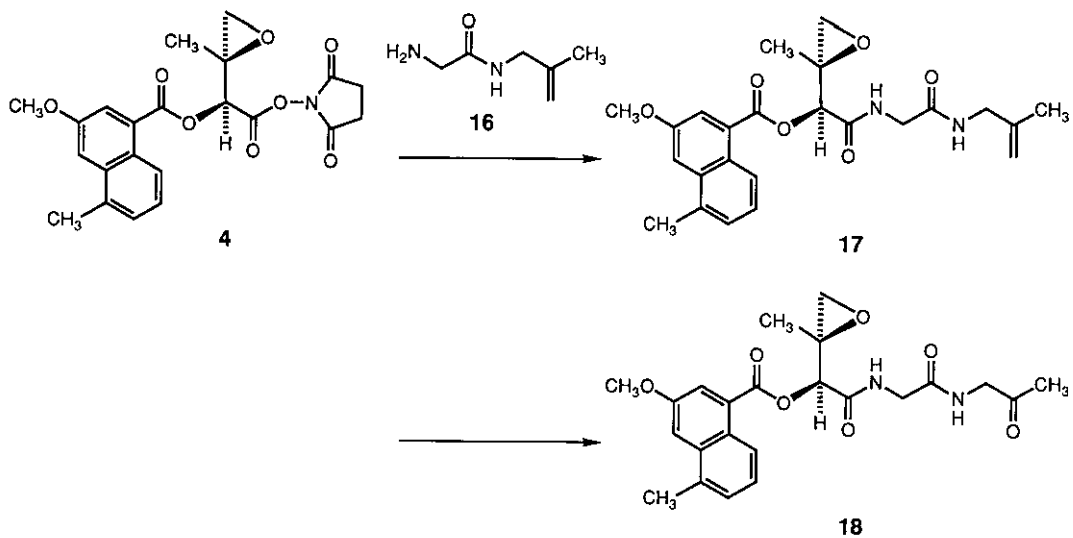


The γ -lactone **5** was available on a large scale from D-fructose by the procedure reported.⁵ Reduction of **5** with lithium aluminum hydride in ether/tetrahydrofuran(1:1) afforded the triol **6** in good yield. The triol **6** was treated with acetone in the presence of a catalytic amount of p-toluenesulfonic acid to give the diacetonide **7**, which was converted into the corresponding tosylate **8** by the usual method in 61% overall yield from **6**. The diacetonide **8** was selectively hydrolyzed with 70% aqueous acetic acid at 55°C to give the diol **9**, which was oxidatively cleaved with sodium periodate and the resultant aldehyde was then oxidized by Jones reagent to give the carboxylic acid **10** in 67% overall yield from **8**. The carboxylic acid **10** was protected as a benzyl

Scheme 1



Scheme 2

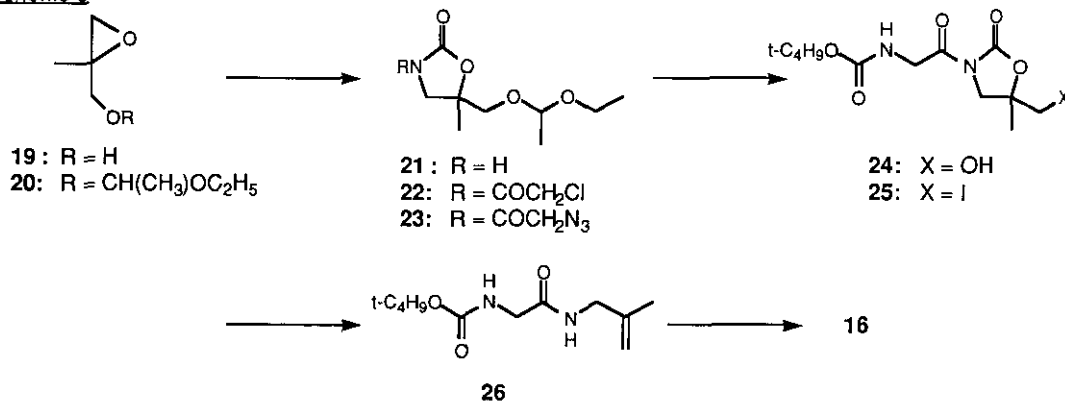


ester by using dicyclohexylcarbodiimide(DCC)/dimethylaminopyridine(DMAP) method⁷ to give **11** in 96% yield. Hydrolysis of the ester **11** with 70% aqueous acetic acid afforded the diol **12**, which was then treated with potassium carbonate in acetone to give the epoxide **13** in 82% overall yield from **11**. Condensation of the epoxide **13** with 3-methoxy-5-methylnaphthalene-1-carboxylic acid⁸ by DCC/DMAP method⁷ afforded the ester **14** in 76% yield. After hydrogenolysis of **14** to the carboxylic acid **15** (95% yield), condensation of **15** with N-hydroxysuccinimide by using DCC afforded the desired ester **4** in 88% yield.(Scheme 1)

The synthesis of the model compound **18** having top-half structure of azinomycin A was achieved as shown in Scheme 2. The N-hydroxysuccinimide ester **4** was condensed with glycyL-2-methylallylamine **16**, which was prepared by the condensation of Boc-glycine N-hydroxysuccinimide ester (Boc-Gly-ONSu) with 2-methylallylamine followed by deprotection, to give the amide **17** in 93% yield. Ozonolysis of **17** followed by reduction with dimethyl sulfide gave the keto amide **18** in 70% yield.

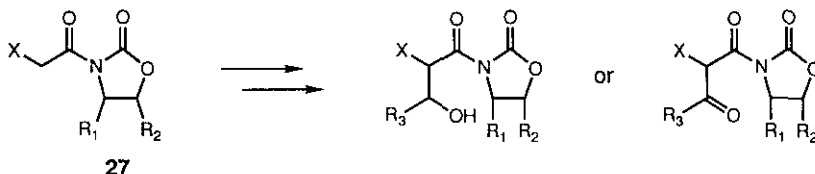
In order to carry out the introduction of 1-azabicyclo[3.1.0]hexane ring system into **18**, it is necessary to modify the synthetic procedure of the amide **16**. As a model study for the synthesis of right-half segment of azinomycins, we synthesized the amide **16** by an alternative route shown in Scheme 3. Thus, the protected epoxy alcohol **20** was prepared from **19**⁹ in 65% yield. The epoxide **20** was converted into the oxazolidinone **21** via two steps sequence in 50% overall yield [(1) NH₃/CH₃OH; (2) (C₂H₅O)₂CO, C₂H₅ONa]. After chloroacetylation of **21** to the carboximide **22** (70% yield), reaction of **22** with sodium azide under phase transfer catalysis afforded the azide **23** in 63% yield. Hydrogenation of the azide **23** over 10% Pd-C in the presence of 1 equiv. of HCl gave the corresponding amine hydrochloride, which was then converted into the t-butoxy-carbonyl derivative. Under these conditions, hydroxy-protective group was removed simultaneously to give the alcohol **24** in 67% overall yield from **23**. The alcohol **24** was converted into the corresponding iodide **25** by using methyltriphenoxyphosphonium iodide¹⁰ in 81% yield. Reductive elimination of **25** with Zn/AcOH afforded the desired amide **26** (43% yield), which was identical with the amide prepared from Boc-Gly-ONSu.

Scheme 3



Efficient C-C bond formation reactions of the carboximides such as **27** (Scheme 4) have been developed recently in the field of the asymmetric synthesis of α amino acids.¹¹ Functionalization of our oxazolidinone intermediates **22** and **23** and subsequent construction of 1-azabicyclo[3.1.0]hexane ring moiety are in progress.

Scheme 4



EXPERIMENTAL

Melting points were determined by the capillary method and uncorrected. Infrared (Ir) spectra were determined with a Perkin-Elmer 1720 FT-IR or a Hitachi 215 spectrophotometer and ¹H-nmr spectra with a JEOL JMS FX-200 spectrometer using tetramethylsilane as an internal reference. Column chromatography was performed on silica gel (K-100-S, from Katayama Chemicals). Optical rotations were measured with a Union Giken PM-201 polarimeter.

2,3-O-Isopropylidene-2-methyl-D-ribitol (6). To a stirred suspension of LiAlH₄ (4.46 g, 117 mmol) in ether (300 ml), a solution of the lactone **5**⁵ (23.63 g, 117 mmol) in ether (300 ml) was added dropwise over 10 min at 0°C. The resulting suspension was stirred overnight at room temperature. After cooling to 0°C, the reaction was quenched with water (8.9 ml) and 10% aqueous NaOH (7.1 ml). After being stirred for 15 min, the suspension was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (10:1 CHCl₃/CH₃OH) to give the triol **6** (19.28 g, 80% yield) as an oil. Ir (CHCl₃): 3392, 1057cm⁻¹; nmr (200 MHz, CDCl₃): δ 1.37-1.38, 1.44 (3X3H, s), 1.91 (1H, br, OH), 2.70 (1H, br, OH), 3.12 (1H, br, OH), 3.42 (1H, d, J=10.5), 3.66 (1H, dd, J=6.4, 11.7), and 3.70-4.00 (4H, m); [α]_D²⁰-10.3°(c=0.10, C₂H₅OH); FAB-MS: m/z 207 (M⁺+H).

2,3:4,5-Di-O-isopropylidene-2-methyl-D-ribitol (7). To a solution of **6** (20 g, 97 mmol) in acetone (300 ml) was added a catalytic amount of TosOH at 0°C, and then the mixture was stirred for 1 h at room temperature. The mixture was neutralized with (C₂H₅)₃N at 0°C, and then evaporated. The residue was chromatographed (15:1 CHCl₃/CH₃OH) to give the diacetonide **7** (20.2g, 84% yield) as an oil. Ir (CHCl₃): 3504, and 1068cm⁻¹; ¹H nmr (200 MHz, CDCl₃): δ 1.35, 1.39, 1.40, 1.41, 1.43 (5X3H, s), 2.35 (1H, t, J=7.1, OH), 3.59 (1H, dd, J=5.9, 7.1), 3.62 (1H, dd, J=5.9, 7.1), 3.74 (1H, d, J=9.0), 3.96 (1H, dd, J=4.4, 8.3), 4.16 (1H, dd, J=6.1, 8.3), and 4.24 (1H, ddd, J=4.4, 6.1, 9.0); [α]_D²⁰-9.7°(c=0.21, C₂H₅OH); FAB-MS: m/z 247 (M⁺+H).

2,3:4,5-Di-O-isopropylidene-2-methyl-1-O-tosyl-D-ribitol (8). To a solution of the diacetonide **7** (15.0 g, 61 mmol) in pyridine (100 ml), were added TosCl (13.9 g, 73 mmol) and dimethylaminopyridine (890 mg, 7.3 mmol) at 0°C. The reaction mixture was stirred for 48 h at room temperature. The solvent was removed *in vacuo*, and the residue was extracted with AcOEt. Organic layer was washed with brine, dried over MgSO₄,

and concentrated *in vacuo*. Purification of the residue with column chromatography (10:1 CHCl₃/acetone) afforded the tosylate **8** (17.8 g, 73% yield) as an oil. ν (CHCl₃): 1358, 1180, 1063, and 836cm⁻¹; nmr (200 MHz, CDCl₃): δ 1.27, 1.29, 1.32, 1.33, 1.40, 2.44 (6X3H, s), 3.68 (1H, dt, J=3.9, 9.0), 3.87 (1H, ddt, J=3.9, 4.2, 7.6), 3.90~4.10 (4H, m), 7.33 (2H, d, J=8.5), and 7.82 (2H, d, J=8.5). $[\alpha]_D^{20}$ - 25.5°(c=0.11, C₂H₅OH); FAB-Ms: m/z 401 (M⁺+H).

2,3-O-isopropylidene-2-methyl-1-O-tosyl-D-ribitol (9). The solution of the tosylate **8** (5.0 g, 12.5 mmol) in 70% aqueous AcOH (10 ml) was stirred for 1 h at 55°C. After cooling to room temperature, the mixture was poured onto ice and extracted with AcOEt. The extract was washed with 5% aqueous Na₂CO₃ and brine, successively, and then dried over MgSO₄, filtered, and concentrated. Residual oil was chromatographed (10:1 CHCl₃/CH₃OH) to give the diol **9** (4.14g, 92% yield) as an oil. ν (CHCl₃): 3401, 1360, 1177, and 1060cm⁻¹; nmr (200 MHz, CDCl₃): δ 1.30, 1.32, 1.35, 2.46 (4X3H, s), 3.60~3.66 (1H, m), 3.76~3.79 (4H, m), 3.90 (1H, d, J=9.5), 4.06 (1H, d, J=9.5), 7.30 (2H, d, J=8.3), and 7.80 (2H, d, J=8.3); $[\alpha]_D^{20}$ - 22.3°(c=0.10, C₂H₅OH); FAB-Ms: m/z 361 (M⁺+H).

2,3-O-isopropylidene-2-methyl-1-O-tosyl-L-erythroic acid (10). To a stirred solution of the diol **9** (5.46 g, 15.2 mmol) in 50% aqueous CH₃OH (100 ml), was added NaIO₄ (3.6 g, 16.7 mmol) at 0°C. The mixture was stirred for 10 min at room temperature, and then the precipitate formed was filtered off. The filtrate was concentrated *in vacuo* and the residue was extracted with AcOEt. The extract was washed with brine, dried over MgSO₄, and evaporated to give crude aldehyde as an oil. This oil was then dissolved in acetone (100 ml). To the stirred solution, Jones reagent (5.7 ml, 2 equiv.) was added dropwise at 0°C. After being stirred for 10 min at 0°C, the reaction was quenched by adding isopropanol (1 ml). The mixture was extracted with AcOEt, washed with 5% aqueous citric acid, dried over MgSO₄, and evaporated. The residual solid was purified by recrystallization from AcOEt to afford the carboxylic acid **10** (3.8 g, 73% yield). mp 122~124°C(decomp); ν (KBr): 3448, 1791, 1364, 1212, and 1098cm⁻¹; nmr (200 MHz, CD₃OD): δ 1.39, 1.45, 1.47, 2.43 (4X3H, s), 3.86 (1H, d, J=9.5), 3.99 (1H, d, J=9.5), 4.44 (1H, s), 7.33 (2H, d, J=8.3), and 7.76 (2H, d, J=8.3); $[\alpha]_D^{20}$ - 6.1°(c=1.14, C₂H₅OH); Anal. Calcd for C₁₅H₂₀O₇S: C,52.31; H,5.85. Found: C,52.48; H,5.55.

Benzyl 2,3-O-isopropylidene-2-methyl-1-O-tosyl-L-erythroate (11). To a stirred solution of the carboxylic acid **10** (3.1 g, 8.7 mmol) in THF (30 ml) were added benzyl alcohol (1.11 ml, 9.6 mmol), DCC (1.88 g, 9.1 mmol), and dimethylaminopyridine (111 mg, 0.9 mmol), successively. The mixture was stirred for 2 h at room temperature. Dicyclohexylurea precipitated was filtered off, and the filtrate was concentrated *in vacuo*. The residual oil was chromatographed (20:1 CHCl₃/acetone) to give the benzyl ester **11** (3.62 g, 96% yield) as an oil. ν (CHCl₃): 1761, 1372, 1178, and 1098cm⁻¹; nmr (200 MHz, CDCl₃): δ 1.34, 1.39, 1.45, 2.44 (4X3H, s), 3.80 (1H, d, J=9.5), 3.89 (1H, d, J=9.5), 4.39 (1H, s), 5.07 (1H, d, J=12.0), 5.26 (1H, d, J=12.0), 7.33 (2H, d, J=9.7), 7.34~7.37 (5H, m), and 7.74 (2H, d, J=9.7); $[\alpha]_D^{20}$ - 18.2°(c=0.10, C₂H₅OH); FAB-Ms: m/z 435 (M⁺+H).

Benzyl 2-methyl-1-O-tosyl-L-erythroate (12). A solution of the benzyl ester **11** (5.0 g, 11.5 mmol) in 80% aqueous AcOH (10 ml) was heated for 2 h at 90°C. After cooling to room temperature, the mixture was

concentrated *in vacuo*, and the residue was extracted with AcOEt. The extract was washed with 5% aqueous Na₂CO₃ and brine successively, and dried over MgSO₄. After evaporation of the solvent, residual oil was purified by chromatography (10:1 CHCl₃/CH₃OH) to give the diol **12** (3.9 g, 84% yield) as an oil. *l*r (CHCl₃): 3467, 1737, 1191, 1360, and 1177cm⁻¹; nmr (200 MHz, CDCl₃): δ 1.18, 2.24 (2X3H, s), 2.94 (1H, br, OH), 3.18 (1H, d, J=6.4, OH), 3.93 (1H, d, J=9.8), 3.96 (1H, d, J=9.8), 4.13 (1H, d, J=6.4), 5.23 (2H, s), 7.32 (2H, d, J=8.3), 7.37 (5H, m), and 7.76 (2H, d, J=8.3); [α]_D²⁰-18.5°(c=0.11, C₂H₅OH); FAB-MS: m/z 395 (M⁺+H).

Benzyl (2S,3S)-3,4-epoxy-2-hydroxy-3-methylbutyrate (13). To a solution of the diol **12** (3.8 g, 9.6 mmol) in acetone (50 ml), was added K₂CO₃ (1.32 g, 9.6 mmol). The suspension was refluxed under stirring for 2 h. After cooling to room temperature, the mixture was diluted with AcOEt, washed, dried over MgSO₄, filtered, and evaporated. The residual oil was chromatographed (40:1 CHCl₃/acetone) to give the epoxide **13** (2.1 g, 98% yield) as an oil. *l*r (CHCl₃): 3461, 1741, 1214, and 1104cm⁻¹; nmr (200 MHz, CDCl₃): δ 1.31 (3H, s), 2.64 (1H, d, J=4.4), 2.86 (1H, d, J=4.4), 3.03 (1H, br, OH), 4.00 (1H, s), 5.24 (1H, d, J=12.0), 5.32 (1H, d, J=12.0), and 7.37 (5H, m); [α]_D²⁰-22.4°(c=0.13, C₂H₅OH); FAB-MS: m/z 223 (M⁺+H).

Esterification of 13. To a stirred solution of **13** (2.0 g, 9.0 mmol) in THF (30 ml) were added 3-methoxy-5-methylnaphthalene-1-carboxylic acid⁸ (2.15 g, 9.1 mmol), DCC (2.04 g, 9.9 mmol), and dimethylaminopyridine (120 mg, 1 mmol), successively. The mixture was stirred for 2 h at room temperature. Dicyclohexylurea precipitated was filtered off, and the filtrate was concentrated *in vacuo*. The residual oil was chromatographed (20:1 CHCl₃/acetone) to give the diester **14** (2.87 g, 76% yield) as an oil. *l*r (CHCl₃): 1726, 1186, 1083, 853, and 808cm⁻¹; nmr (200 MHz, CDCl₃): δ 1.47, 2.66 (2X3H, s), 2.69 (1H, d, J=4.6), 2.98 (1H, d, J=4.6), 3.95 (3H, s), 5.23 (1H, s), 5.24 (1H, d, J=12.2), 5.36 (1H, d, J=12.2), 7.28~7.42 (7H, m), 7.43 (1H, d, J=2.7), 7.89 (1H, d, J=2.7), and 8.58 (1H, dd, J=3.7, 5.9); [α]_D²⁰-12.3°(c=0.16, C₂H₅OH); ms m/z Calcd for C₂₅H₂₄O₆: 420.1573. Found: 420.1535.

(2S,3S)-3,4-Epoxy-3-methyl-2-(3'-methoxy-5'-methylnaphthalenecarbonyloxy)butyric acid (15). A suspension of 10% Pd-C (80 mg) in a solution of the benzyl ester **14** (540 mg, 1.3 mmol) in CH₃OH (40 ml) was stirred for 30 min under a current of H₂ at room temperature. After the catalyst was removed by filtration, the solvent was removed *in vacuo*. Recrystallization of the residue from CH₃OH gave **15** (400 mg, 95% yield) as colorless needles; mp 74~78°C(decomp). *l*r (KBr): 3411, 1719, 1191, 1086, 808, and 752cm⁻¹; nmr (200 MHz, CD₃OD): δ 1.52, 2.65, 3.96 (3X3H, s), 2.74 (1H, d, J=4.9), 3.04 (1H, d, J=4.9), 5.12 (1H, s), 7.23~7.27 (2H, m), 7.32 (1H, d, J=2.7), 7.85 (1H, d, J=2.7), and 8.58 (1H, dd, J=3.0, 6.8); [α]_D²⁰-15.2°(c=0.11, C₂H₅OH). Anal. Calcd for C₁₈H₁₈O₆: C,65.44; H,5.49. Found: C,65.09; H,5.81.

Succinimido (2S,3S)-3,4-epoxy-3-methyl-2-(3'-methoxy-5'-methylnaphthalenecarbonyloxy)butyrate (4). To a solution of the carboxylic acid **15** (150 mg, 0.46 mmol) in AcOEt (3 ml), were added N-hydroxysuccinimide (55 mg, 0.48 mmol) and DCC (0.10 g, 0.48 mmol), successively. After the mixture was stirred for 2 h at room temperature, dicyclohexylurea precipitated was filtered off, and the filtrate was concentrated *in vacuo* to give a crystalline solid. Recrystallization from AcOEt afforded the succinimide ester **4** (70 mg, 88% yield) as colorless

needles; mp 94–96°C(decomp). $\text{Ir}(\text{KBr})$: 1741, 1198, and 1074 cm^{-1} ; nmr (200 MHz, CDCl_3): δ 1.67, 2.67, 3.97 (3X3H, s), 2.79 (1H, d, $J=4.6$), 2.86 (4H, s), 3.13 (1H, d, $J=4.6$), 5.52 (1H, s), 7.36 (2H, m), 7.50 (1H, d, $J=2.7$), 7.93 (1H, d, $J=2.7$), and 8.64 (1H, m); $[\alpha]_D^{20}$ - 9.7°($c=0.10$, $\text{C}_2\text{H}_5\text{OH}$). Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_8$: C,61.82; H,4.95; N,3.28. Found: C,61.46; H,4.99; N,3.32.

Glycyl-2-methylallylamine (16). To a stirred solution of 2-methylallylamine (0.53 g, 4.9 mmol) in DMF (5 ml) were added Boc-Gly-ONSu (1.12 g, 4.1 mmol) and triethylamine (1.6 ml, 11.4 mmol), successively. Stirring was continued for 2 h at room temperature. The mixture was poured onto ice and extracted with AcOEt. The extract was washed with 5% aqueous citric acid, 5% aqueous Na_2CO_3 , and brine, successively, and then dried over MgSO_4 . After evaporation of the filtered solution, the residual oil was chromatographed (15:1 $\text{CHCl}_3/\text{CH}_3\text{OH}$) to give a white solid. Recrystallization from AcOEt afforded **26** (1.2 g, 94% yield) as colorless needles; mp 58–60°C. $\text{Ir}(\text{KBr})$: 3320, 1710, and 890 cm^{-1} ; nmr (200 MHz, CDCl_3): δ 1.46 (9H, s), 1.74 (3H, s), 3.81 (2H, m), 3.83 (2H, m), 4.82 (2H, m), 5.16 (1H, br, NH), and 6.24 (1H, br, NH); Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{N}_2\text{O}_3$: C,57.87; H,8.83; N,12.27. Found: C,57.80; H,9.07; N,12.35. The amide **26** (1.0 g, 4.4 mmol) and anisole (0.5 ml) were dissolved in trifluoroacetic acid (2 ml) and the mixture was stirred for 1 h at room temperature. After the solvent was removed *in vacuo*, the residual oil was washed twice with n-hexane to remove anisole. Purification by column chromatography (100:10:0.5 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/28\%\text{NH}_4\text{OH}$) afforded **16** (410 mg, 82% yield) as an oil. $\text{Ir}(\text{CHCl}_3)$: 3343, 1643, and 898 cm^{-1} ; nmr (200 MHz, CDCl_3): δ 1.53 (2H, s, NH_2), 1.75 (3H, s), 3.40 (2H, s), 3.84 (2H, d, $J=6.1$), 4.84 (2H, s), and 7.40 (1H, br, NH); ms m/z Calcd for $\text{C}_6\text{H}_{12}\text{N}_2\text{O}$: 128.0950. Found: 128.0900.

[[[(2S,3S)-3,4-Epoxy-2-(3'-methoxy-5'-methylnaphthalenecarbonyloxy)butyramido]acetamido]2-methyl-2-propene (17). To the succinimide ester **4** (100 mg, 0.24 mmol), a solution of **16** (40 mg, 0.30 mmol) in THF (2 ml) was added, and the mixture was stirred for 1 hr at room temperature. The mixture was poured onto ice and extracted with AcOEt. The extract was washed with brine, dried over MgSO_4 , filtered, evaporated, and chromatographed (20:1 $\text{CHCl}_3/\text{CH}_3\text{OH}$). Recrystallized from AcOEt to give **17** (95 mg, 93% yield) as colorless needles; mp 72–75°C(decomp). $\text{Ir}(\text{KBr})$: 3290, 1715, 1675, 1090, 905, 890, and 805 cm^{-1} ; nmr (200 MHz, CDCl_3): δ 1.54, 1.70, 2.67, 3.98 (4X3H, s), 2.76 (1H, d, $J=4.4$), 3.05 (1H, d, $J=4.4$), 3.80 (2H, m), 3.89 (1H, dd, $J=6.4$, 16.8), 4.12 (1H, dd, $J=6.4$, 16.8), 4.82 (2H, m), 5.84 (1H, s), 6.67 (1H, br, NH), 7.03 (1H, br, NH), 7.34 (1H, m), 7.35 (1H, m), 7.50 (1H, d, $J=2.7$), 7.95 (1H, d, $J=2.7$), and 8.63 (1H, m); $[\alpha]_D^{20}$ + 23.8°($c=0.38$, $\text{C}_2\text{H}_5\text{OH}$); Anal. Calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_6$: C,65.44; H,6.40; N,6.36. Found: C,65.06; H,6.71; N,6.58.

Ozonolysis of 17. An ozone-oxygen stream was bubbled through a solution of **17** (70 mg, 0.16 mmol) in CH_3OH (10 ml) for 30 min at -78°C. The solution was purged with argon, and dimethyl sulfide (0.1 ml) was added. The cooling bath was removed, and the mixture was stirred for 12 h. The solvent was removed *in vacuo*, and the resulting oil was chromatographed (20:1 $\text{CHCl}_3/\text{CH}_3\text{OH}$) to give the ketone **18** (50 mg, 70% yield) as colorless needles; mp 113–115°C(decomp). $\text{Ir}(\text{KBr})$: 3300, 1715, 1675, 1650, 1090, 850, and 805 cm^{-1} ; nmr (200 MHz, CDCl_3): δ 1.56, 2.17, 2.67 (3X3H, s), 2.79 (1H, d, $J=4.4$), 3.07 (1H, d, $J=4.4$),

3.90–4.20 (2H, m), 3.98 (3H, s), 4.11 (1H, d, J= 5.9), 4.15 (1H, d, J= 5.9), 5.34 (1H, s), 6.94 (1H, br, NH), 7.00 (1H, br, NH), 7.35 (1H, m), 7.36 (1H, m), 7.48 (1H, d, J=2.4), 7.49 (1H, d, J=2.4), and 8.62 (1H, m); $[\alpha]_D^{20} +12.4^\circ$ (c=0.40, C₂H₅OH); Anal. Calcd for C₂₃H₂₆N₂O₇: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.56; H, 6.14; N, 6.11.

2,3-Epoxy-2-methylpropyl 1-ethoxyethyl ether (20). To a stirred solution of 2-methyl-1,2-epoxypropanol⁹ (8.8 g, 100 mmol) in ethyl vinyl ether (24 ml) was added a catalytic amount of TosOH and stirred overnight at room temperature. The mixture was neutralized with (C₂H₅)₃N at 0°C, and then evaporated. The residue was chromatographed (15:1 CHCl₃/acetone) to give **20** (10.4 g, 65% yield) as a diastereomeric mixture. ν (CHCl₃): 2978, 1136, and 1089cm⁻¹; ms m/z Calcd for C₆H₁₁O₂(M⁺-ethoxy): 115.0759. Found: 115.0761.

5-(1-Ethoxyethoxymethyl)-5-methyloxazolidin-2-one (21). A solution of **20** (10.4 g, 65 mmol) in 10N-NH₄OH/CH₃OH (200 ml) was stirred overnight at room temperature. Concentration of the mixture *in vacuo* gave the crude aminoalcohol as an oil. To a stirred solution of the aminoalcohol in diethyl carbonate (16 ml) was added NaOEt (442 mg, 6.5 mmol). The reaction mixture was heated for 2 h at 90°C. After cooling to room temperature, the solvent was removed *in vacuo*, and then the residue was extracted with AcOEt. The extract was washed with brine, dried over MgSO₄, and evaporated. The residue was chromatographed (10:1 CHCl₃/CH₃OH) to afford the oxazolidinone **21** (7.4 g, 50% yield) as a diastereomeric mixture. ν (CHCl₃): 3468, and 1779cm⁻¹; ms m/z Calcd for C₉H₁₃NO₄(M⁺+H): 204.1236. Found: 204.1241.

3-Chloroacetyl-5-(1-ethoxyethoxymethyl)-5-methyloxazolidin-2-one (22). To a stirred solution of the oxazolidinone **21** (1.23 g, 6.0 mmol), was added 1.6M n-C₄H₉Li in hexane (6.0 ml, 10 mmol) at -78°C. After being stirred for 10 min at the same temperature, chloroacetyl chloride (0.53 ml, 6.7 mmol) was added. The mixture was stirred for 15 min at -78°C and then stirred for 30 min at room temperature. The mixture was poured onto ice, and extracted with AcOEt. The extract was washed, dried over MgSO₄, and evaporated. The residual oil was purified by column chromatography (20:1 CHCl₃/CH₃OH) to give **22** (1.15 g, 70% yield) as a diastereomeric mixture. ν (CHCl₃): 3468, 1779, and 1248cm⁻¹; ms m/z Calcd for C₇H₉NO₃Cl (M⁺-ethoxyethyl+H): 190.0271. Found: 190.0272.

3-Azidoacetyl-5-(1-ethoxyethoxymethyl)-5-methyloxazolidin-2-one (23). To a stirred solution of **22** (800 mg, 29 mmol) and tetrabutylammonium hydrogen sulfate (100 mg, 2.9 mmol) in CH₂Cl₂ (3.0 ml) was added a solution of sodium azide (930 mg, 145 mmol) in water (3.0 ml). The biphasic mixture was stirred vigorously for 1 h at room temperature. The mixture was extracted with CH₂Cl₂, and the extract was washed, dried over MgSO₄, and evaporated. Residual oil was purified by column chromatography (20:1 CHCl₃/CH₃OH) to afford **23** (580 mg, 63% yield) as a diastereomeric mixture. ν (CHCl₃): 3435, 1780, and 2109cm⁻¹; ms m/z Calcd for C₁₁H₁₃N₄O₅: 287.1355. Found: 287.1346.

3-N-Boc-glycyl-5-hydroxymethyl-5-methyloxazolidin-2-one (24). A suspension of 10% Pd-C (70 mg) in a solution of **23** (400 mg, 1.4 mmol) and 3N-HCl/C₂H₅OH (0.59 ml, 1.7 mmol) in CH₃OH (20 ml) was stirred for 30 min under a current of H₂ at room temperature. The catalyst was removed by filtration and then the solvent

was removed *in vacuo*. The residual solid was dissolved in DMF (10 ml). To the solution, was added $(C_2H_5)_3N$ (0.46 ml, 3.3 mmol) and $(Boc)_2O$ (295 mg, 1.4 mmol) successively. After being stirred for 2 h at room temperature, the mixture was poured onto ice, and extracted with AcOEt. The extract was washed with 5% aqueous citric acid, 5% aqueous Na_2CO_3 , and brine, successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residual oil was purified by column chromatography (10:1 $CHCl_3/CH_3OH$) to give **24** (260 mg, 67%) as an oil. ν ($CHCl_3$): 3389, 1780, and $1703cm^{-1}$; nmr (200 MHz, $CDCl_3$): δ 1.45 (9H, s), 1.46 (3H, s), 2.70 (1H, br, OH), 3.48 (1H, m), 3.65 (1H, d, $J=11.0$), 3.76 (1H, m), 4.08 (1H, d, $J=11.0$), 4.46 (2H, m), and 5.18 (1H, br, NH); ms m/z Calcd for $C_{12}H_{21}N_2O_6(M^++H)$: 289.1399. Found: 289.1372.

3-N-Boc-glycyl-5-iodomethyl-5-methyloxazolidin-2-one (25). A solution of **24** (250 mg, 0.87 mmol) and $(C_6H_5O)_3P^+CH_3I$ (452 mg, 1.0 mmol) in DMF (3.0 ml) was stirred for 18 h under an argon atmosphere. The solvent was removed *in vacuo*, and the residual oil was extracted with AcOEt. The extract was washed with 5% aqueous $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and evaporated. The residual crude oil was chromatographed (20:1 $CHCl_3/CH_3OH$) to afford the iodide **25** (280 mg, 81% yield) as an oil. ν ($CHCl_3$): 3417, 1783, 1709, and $1168cm^{-1}$; nmr (200 MHz, $CDCl_3$): δ 1.46 (9H, s), 1.73 (3H, s), 3.39 (1H, d, $J=11.1$), 3.42 (1H, d, $J=11.1$), 3.77 (1H, d, $J=11.2$), 4.00 (1H, d, $J=11.2$), 4.49 (2H, m), and 5.10 (1H, br, NH); ms m/z Calcd for $C_8H_{11}N_2O_5I(M^++t-C_4H_9+H)$: 341.9714. Found: 341.9696.

N-Boc-glycyl-2-methylallylamine (26). To a stirred solution of the iodide **25** (60 mg, 0.15 mmol) in AcOH (1.5 ml) was added zinc dust (60 mg) portionwise. The mixture was vigorously stirred for 2 h at room temperature, then the insoluble salt was filtered off. After the solvent was removed *in vacuo*, the residual oil was extracted with AcOEt and the extract was washed with 5% aqueous Na_2CO_3 and brine successively. The organic layer was dried over $MgSO_4$, filtered and evaporated. Residual crude oil was purified by column chromatography (20:1 $CHCl_3/CH_3OH$) to afford **26** (20 mg, 52%) as colorless needles (mp 56~60°C), the spectroscopic data of which were identical with those of the amide prepared from Boc-Gly-ONSu.

REFERENCES AND NOTES

1. K. Nagaoka, M. Matsumoto, J. Oono, K. Yokoi, S. Ishizeki, and T. Nakashima, *J. Antibiot.*, 1986, **39**, 1527.
2. S. Ishizeki, M. Ohtsuka, K. Irinoda, K. Kukita, K. Nagaoka, and T. Nakashima, *J. Antibiot.*, 1987, **40**, 60.
3. K. Yokoi, K. Nagaoka, and T. Nakashima, *Chem. Pharm. Bull.*, 1986, **34**, 4554.
4. M. Shibuya and H. Terauchi, *Tetrahedron Letters*, 1987, **29**, 2619.
5. R. E. Ireland, R. C. Anderson, R. Badoud, B. J. Fitzsimmons, G. J. McGarvey, S. Thaisrivongs, and C. S. Wilcox, *J. Amer. Chem. Soc.*, 1983, **105**, 1988.
6. Recently, we reported the synthesis of AK-toxin II, a host-specific phytotoxic metabolite, starting from compound **6**; K. Ando, T. Yamada, Y. Takaishi, and M. Shibuya, *Heterocycles*, 1989, **29**, 1023.
7. C. Gilon, Y. Klausner, and A. Hassner, *Tetrahedron Letters*, 1979, 3811.
8. M. Shibuya, *Tetrahedron Letters*, 1983, **24**, 1175.

9. A. Bongini, G. Cardillo, M. Orena, G. Porzi, and S. Sandri, *J. Org. Chem.*, 1982, **47**, 4626.
10. S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 1953, 2224.
11. D. A. Evans, M. D. Ennis, and T. Le, *J. Amer. Chem. Soc.*, 1984, **106**, 1154; A. Abdel-Magid, L. N. Pridgen, D. S. Eggleston, and I. Lantos, *J. Amer. Chem. Soc.*, 1986, **108**, 4595; D. A. Evans and A. E. Weber, *J. Amer. Chem. Soc.*, 1986, **108**, 6757; D. A. Evans and A. E. Weber, *J. Amer. Chem. Soc.*, 1987, **109**, 7151; D. A. Evans, E. B. Sjogren, A. E. Weber, and R. E. Conn, *Tetrahedron Letters*, 1987, **28**, 39.

Received, 7th August, 1989