SYNTHETIC APPROACH TOWARD AZINOMYCINS

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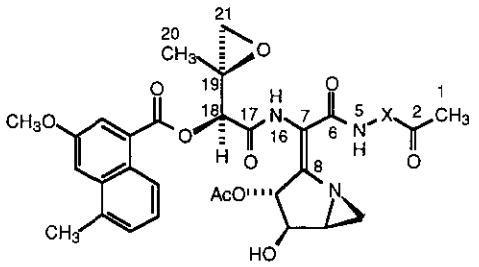
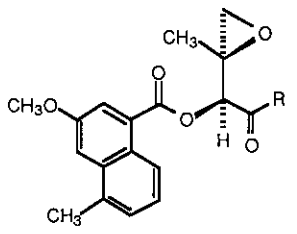
Abstract–The left-half segment **14** of antitumor antibiotics azinomycins A and B was synthesized in optically pure form starting from D-fructose. The dipeptide **18**, equivalent to the azinomycin A top-half, was also synthesized via oxazolidinone intermediates.

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 18S, 19S 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.



1 (Azinomycin A): X = CH_2
2 (Azinomycin B): X = C=CH(OH)

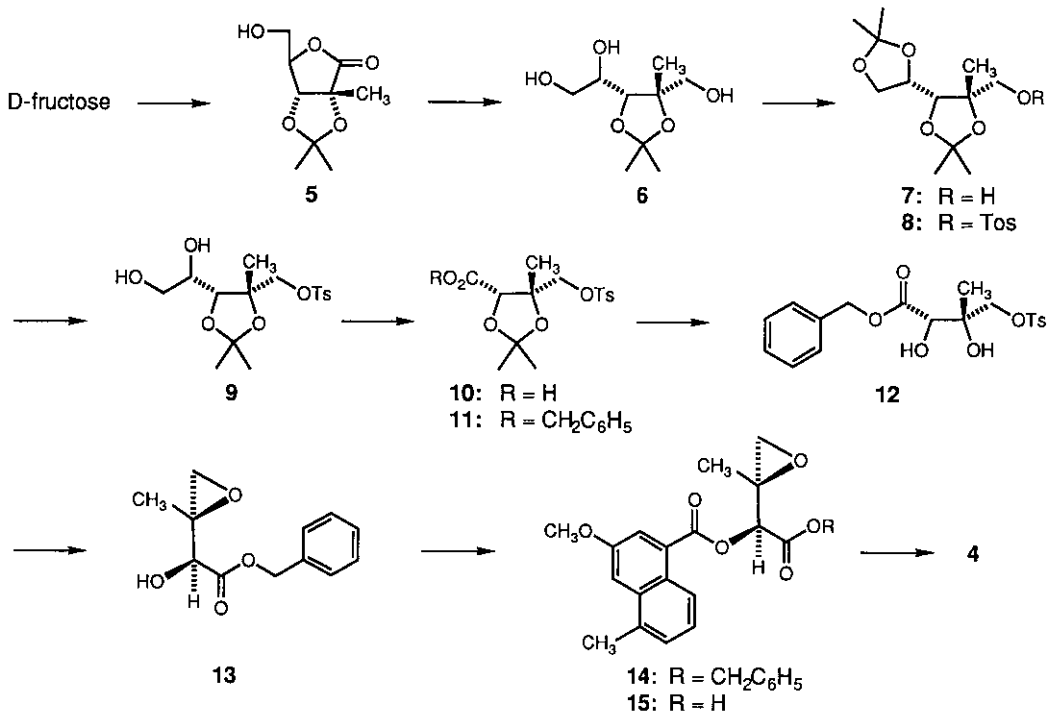


3: R = NH_2

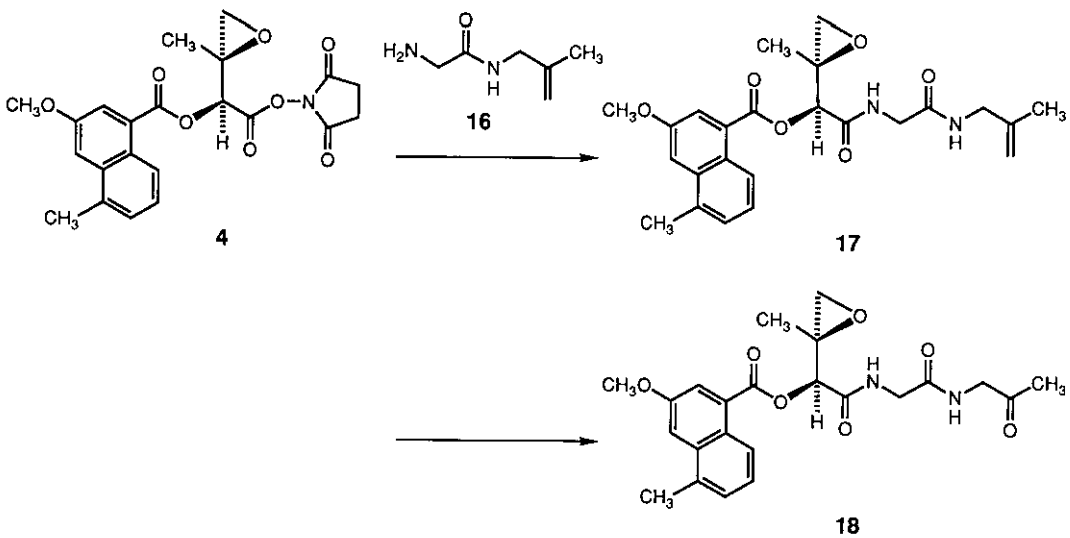
4: R = O–N

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**[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

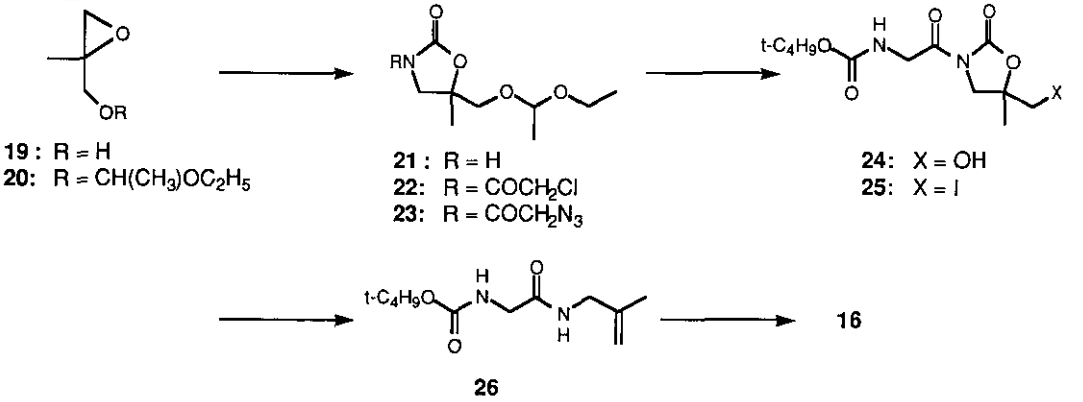


ester by using dicyclohexylcarbodiimide(DCC)/dimethylaminopyridine(DMAP) method[7] to give **11** in 96% yield. Hydrolysis of the ester **11** with 70% aqueous acetic acid afforded the diol **12**, which was then treated with potassium carbonate in acetone to give the epoxide **13** in 82% overall yield from **11**. Condensation of the epoxide **13** with 3-methoxy-5-methylnaphthalene-1-carboxylic acid[8] by DCC/DMAP method[7] 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) NH_3/CH_3OH; (2) $(C_2H_5O)_2CO$, C_2H_5ONa]. 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 iodide[10] 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



19 : R = H
20: R = $CH(CH_3)OC_2H_5$

21 : R = H
22: R = $COCH_2Cl$
23: R = $COCH_2N_3$

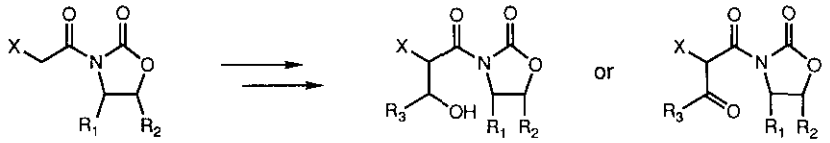
24: X = OH
25: X = I

26

16

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



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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 ^{1}H-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 of $LiAlH_4$ (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 $CHCl_3/CH_3OH$) to give the triol **6** (19.28 g, 80% yield) as an oil. Ir ($CHCl_3$): 3392, 1057cm^{-1}; nmr (200 MHz, $CDCl_3$): 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);. $[\alpha]_D^{20}$ -10.3°(c=0.10, C_2H_5OH); FAB-Ms: m/z 207 (M^++H).

2,3:4,5-Di-*O*-isopropylidene-2-methyl-D-ribitol (7). To a solution of 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 $(C_2H_5)_3N$ at 0°C, and then evaporated. The residue was chromatographed (15:1 $CHCl_3/CH_3OH$) to give the diacetonide **7** (20.2g, 84% yield) as an oil. Ir ($CHCl_3$): 3504, and 1068cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$): 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); $[\alpha]_D^{20}$ - 9.7°(c=0.21, C_2H_5OH); 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 $MgSO_4$,

and concentrated in vacuo. Purification of the residue with column chromatography (10:1 $CHCl_3$/acetone) afforded the tosylate **8** (17.8 g, 73% yield) as an oil. Ir ($CHCl_3$): 1358, 1180, 1063, and 836cm^{-1}; nmr (200 MHz, $CDCl_3$): 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, C_2H_5OH); 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 Na_2CO_3 and brine, successively, and then dried over $MgSO_4$, filtered, and concentrated. Residual oil was chromatographed (10:1 $CHCl_3$/CH_3OH) to give the diol **9** (4.14g, 92% yield) as an oil. Ir ($CHCl_3$): 3401, 1360, 1177, and 1060cm^{-1}; nmr (200 MHz, $CDCl_3$): 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, C_2H_5OH); 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 CH_3OH (100 ml), was added $NaIO_4$ (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 $MgSO_4$, 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 $MgSO_4$, 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); Ir (KBr): 3448, 1791, 1364, 1212, and 1098cm^{-1}; nmr (200 MHz, CD_3OD): 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, C_2H_5OH); Anal. Calcd for $C_{15}H_{20}O_7S$: 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 $CHCl_3$/acetone) to give the benzyl ester **11** (3.62 g, 96% yield) as an oil. Ir ($CHCl_3$): 1761, 1372, 1178, and 1098cm^{-1}; nmr (200 MHz, $CDCl_3$): 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, C_2H_5OH); 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 Na_2CO_3 and brine successively, and dried over $MgSO_4$. After evaporation of the solvent, residual oil was purified by chromatography (10:1 $CHCl_3/CH_3OH$) to give the diol **12** (3.9 g, 84% yield) as an oil. Ir ($CHCl_3$): 3467, 1737, 1191, 1360, and 1177cm^{-1}; nmr (200 MHz, $CDCl_3$): 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); $[\alpha]_D^{20}$-18.5°(c=0.11, C_2H_5OH); 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 K_2CO_3 (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 $MgSO_4$, filtered, and evaporated. The residual oil was chromatographed (40:1 $CHCl_3$/acetone) to give the epoxide **13** (2.1 g, 98% yield) as an oil. Ir ($CHCl_3$): 3461, 1741, 1214, and 1104cm^{-1}; nmr (200 MHz, $CDCl_3$): 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); $[\alpha]_D^{20}$- 22.4°(c=0.13, C_2H_5OH); 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 acid[8] (2.15 g, 9.1mmol), 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 $CHCl_3$/acetone) to give the diester **14** (2.87 g, 76% yield) as an oil. Ir ($CHCl_3$): 1726, 1186, 1083, 853, and 808cm^{-1}; nmr (200 MHz, $CDCl_3$): 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); $[\alpha]_D^{20}$-12.3°(c=0.16, C_2H_5OH); ms m/z Calcd for $C_{25}H_{24}O_6$: 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 CH_3OH (40 ml) was stirred for 30 min under a current of H_2 at room temperature. After the catalyst was removed by filtration, the solvent was removed *in vacuo*. Recrystallization of the residue from CH_3OH gave **15** (400 mg, 95% yield) as colorless needles; mp 74~78°C(decomp). Ir (KBr): 3411, 1719, 1191, 1086, 808, and 752cm^{-1}; nmr (200 MHz, CD_3OD): 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); $[\alpha]_D^{20}$- 15.2°(c=0.11, C_2H_5OH). Anal. Calcd for $C_{18}H_{18}O_6$: 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). Ir(KBr): 1741, 1198, and 1074cm^{-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, C_2H_5OH). Anal. Calcd for $C_{22}H_{21}NO_8$: 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 $CHCl_3/CH_3OH$) to give a white solid. Recrystallization from AcOEt afforded **26** (1.2 g, 94% yield) as colorless needles; mp 58~60°C. Ir (KBr): 3320, 1710, and 890cm^{-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 $C_{11}H_{20}N_2O_3$: 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 $CH_2Cl_2/CH_3OH/28\%NH_4OH$) afforded **16** (410 mg, 82% yield) as an oil. Ir ($CHCl_3$): 3343, 1643, and 898cm^{-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 $C_6H_{12}N_2O$: 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 $CHCl_3/CH_3OH$). Recrystallized from AcOEt to give **17** (95 mg, 93% yield) as colorless needles; mp 72~75°C(decomp). Ir (KBr): 3290, 1715, 1675, 1090, 905, 890, and 805cm^{-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, C_2H_5OH); Anal. Calcd for $C_{24}H_{28}N_2O_6$: 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 $CHCl_3/CH_3OH$) to give the ketone **18** (50 mg, 70% yield) as colorless needles; mp 113~115°C(decomp). Ir (KBr): 3300, 1715, 1675, 1650, 1090, 850, and 805cm^{-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°(c=0.40, C_2H_5OH); Anal. Calcd for $C_{23}H_{26}N_2O_7$: 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-epoxypropanol[9] (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 $(C_2H_5)_3N$ at 0°C, and then evaporated. The residue was chromatographed (15:1 $CHCl_3$/acetone) to give **20** (10.4 g, 65% yield) as a diastereomeric mixture. Ir ($CHCl_3$): 2978, 1136, and 1089cm^{-1}; ms m/z Calcd for $C_6H_{11}O_2$(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-NH_4OH/CH_3OH *(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 $MgSO_4$, and evaporated. The residue was chromatographed (10:1 $CHCl_3/CH_3OH$) to afford the oxazolidinone **21** (7.4 g, 50% yield) as a diastereomeric mixture. Ir ($CHCl_3$): 3468, and 1779cm^{-1}; ms m/z Calcd for $C_9H_{18}NO_4$(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-C_4H_9Li 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 $MgSO_4$, and evaporated. The residual oil was purified by column chromatography (20:1 $CHCl_3/CH_3OH$) to give **22** (1.15 g, 70% yield) as a diastereomeric mixture. Ir ($CHCl_3$): 3468, 1779, and 1248cm^{-1}; ms m/z Calcd for $C_7H_9NO_3Cl$ (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 CH_2Cl_2 (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 CH_2Cl_2, and the extract was washed, dried over $MgSO_4$, and evaporated. Residual oil was purified by column chromatography (20:1 $CHCl_3/CH_3OH$) to afford **23** (580 mg, 63% yield) as a diastereomeric mixture. Ir ($CHCl_3$): 3435, 1780, and 2109cm^{-1}; ms m/z Calcd for $C_{11}H_{19}N_4O_5$: 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/C_2H_5OH (0.59 ml, 1.7 mmol) in CH_3OH (20 ml) was stirred for 30 min under a current of H_2 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. Ir ($CHCl_3$): 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 $(C_6H_5O)_3P{\cdot}CH_3I$ (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. Ir ($CHCl_3$): 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.

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