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Synthesis of a New Amino Acid-Antibiotic, Oxetin and Its Three Stereoisomers

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Oxetin (**1a**), a unique antibiotic having an oxetane ring, and its three stereoisomers (**1b**, **1c**, and **1d**) were synthesized from the known aldehyde (**6**) by utilizing a highly regio- and stereoselective epoxide ring-opening reaction. The biological activities of these oxetin stereoisomers were compared.

Keywords——oxetin; antibiotic; oxetane ring; oxetin stereoisomer; epoxyalcohol; regioselective ring-opening reaction; stereoselective ring-opening reaction

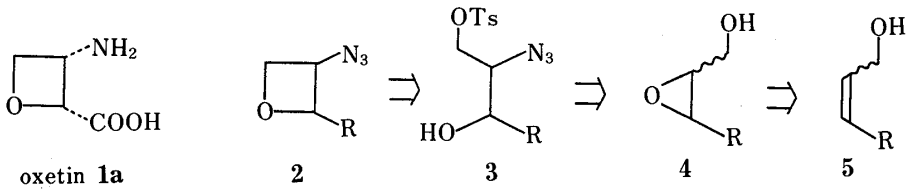
Introduction

Recently, a new amino acid-antibiotic named oxetin (**1a**) was isolated from *Streptomyces* sp. OM-2317 by Ōmura *et al.* and its structure including (2*R*,3*S*) absolute configuration was determined by X-ray crystallography.[1)]

Oxetin (**1a**) is the first amino acid-antibiotic that has an oxetane ring. The antibiotic (**1a**) inhibits *Bacillus subtilis* and *Piricularia oryzae* in minimal media, shows a herbicidal activity, and inhibits glutamine synthetase from spinach leaves.[1)] In order to clarify the structure–activity relationship of oxetin (**1a**) and to search for analogues with higher activity or a narrower spectrum of actions, we focussed our attention initially on the synthesis of oxetin (**1a**) and its analogues. In this paper, we describe the first synthesis of oxetin (**1a**) and its three stereo-isomers (**1b**, **1c**, and **1d**), and the results of preliminary tests of their biological activities.

Synthesis

Our strategy for the synthesis is shown in Chart 1. The oxetane ring (**2**) could be formed by Williamson synthesis from the 1,3-diol monotosylate (**3**), which in turn could be obtained by regio- and stereoselective reaction of the epoxyalcohol (**4**) by the use of azide anion and selective tosylation. The epoxyalcohol (**4**) could be derived from the allylic alcohol (**5**), in which R must be a group that can be easily converted into a carboxyl group.



oxetin **1a** (2*R*, 3*S*) **2** **3** **4** **5**

Chart 1

We employed the known aldehyde (**6**), prepared from D-glucose,[2] as a starting material. Wittig reaction of (**6**) with (ethoxycarbonylmethylene)triphenylphosphorane in benzene gave two separable unsaturated esters, the less polar *cis* ester (**7**) in 55% yield and the more polar *trans* ester (**8**) in 43% yield. Reduction of the *cis* ester (**7**) with diisobutylaluminium hydride in toluene gave the allyl alcohol (**9**) in 88% yield. Epoxidation of **9** with *m*-chloroperbenzoic acid provided, after chromatographic separation, the less polar (5*R*,6*R*)-epoxyalcohol, 5,6-anhydro-α-D-*glycero*-D-*gluco*-heptofuranose (**11a**), in 28% yield, and the more polar (5*S*,6*S*)-epoxyalcohol, the 5,6-anhydro-α-L-*glycero*-L-*ido*- isomer (**11b**), in 52% yield. The stereochemical assignment was made by conversion of these epoxyalcohols (**11a** and **11b**) into oxetin (**1a**) and its enantiomer (**1b**) (*vide infra*).

Similarly, the *trans* ester (**8**) was converted into the less polar (5*R*,6*S*)-epoxyalcohol, the 5,6-anhydro-α-L-*glycero*-D-*gluco*- isomer (**11c**), in 27% yield, and the more polar (5*S*,6*R*)-epoxyalcohol, the 5,6-anhydro-α-D-*glycero*-L-*ido*- isomer (**11d**), in 49% yield *via* the corresponding *trans* allyl alcohol (**10**). The epoxyalcohols (**11c** and **11d**) were tentatively assigned by assuming that preferential attack of the peracid took place from the same direction as in the case of **9**.[3]

Reaction of the epoxyalcohol (**11a**) with sodium azide in aqueous 2-methoxyethanol in the presence of ammonium chloride under reflux provided regio- and stereoselectively the

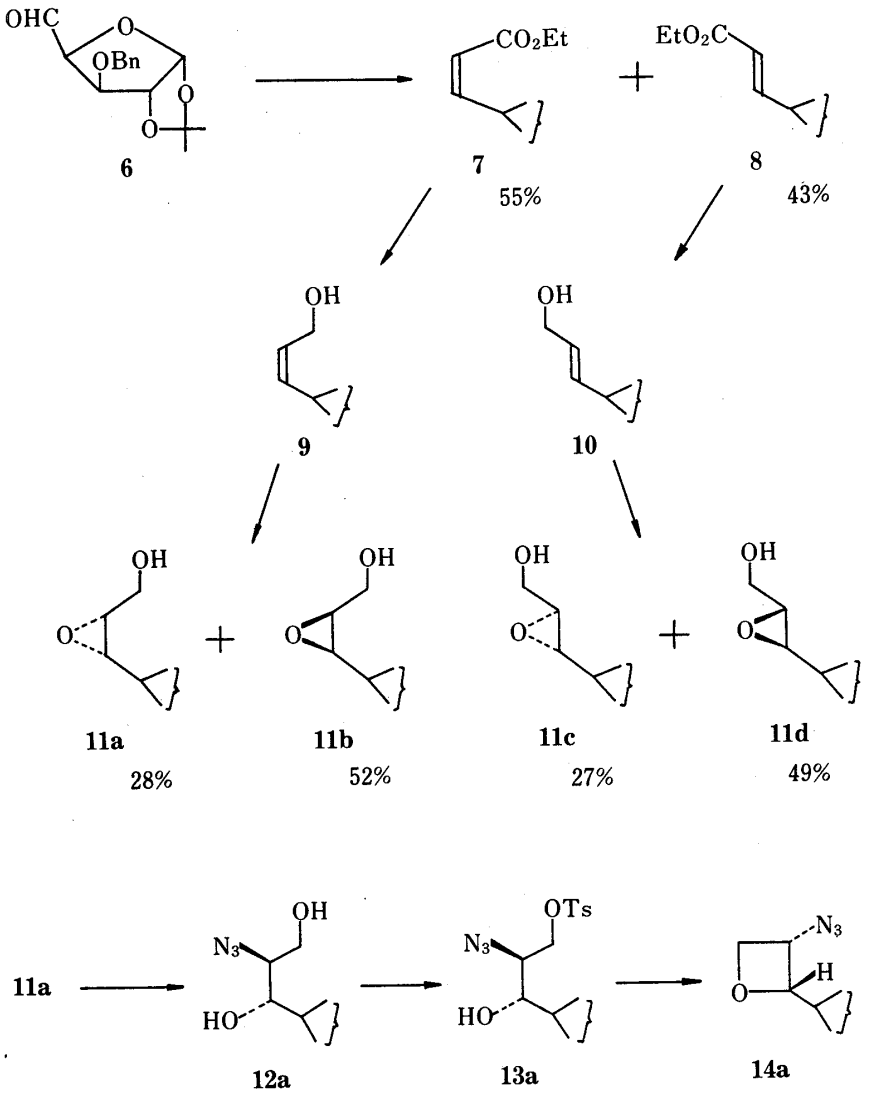


Chart 2

(5*R*,6*S*) azide compound (**12a**) in 81% yield as a single product,[4] whose structure was determined by analysis of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum (200 MHz). Selective tosylation of **12a** with 1.2 eq of *p*-toluenesulfonyl chloride in pyridine gave the monotosylate (**13a**) in 86% yield, and this was cyclized with 1.2 eq of potassium *tert*-butoxide in tetrahydrofuran (THF)–benzene to afford the (5*R*,6*S*)-oxetane compound (**14a**) in 72% yield. Hydrogenation of **14a** with 10% Pd–C in THF–AcOH–H_2O followed by treatment with benzyloxycarbonyl chloride in aqueous methanol in the presence of sodium carbonate gave the amide alcohol (**15a**) in 65% yield. Removal of the isopropylidene group with 0.1 N H_2SO_4 at 67 °C gave the 1,2-deprotected compound (**16a**) in quantitative yield. Then, reduction of **16a** with sodium borohydride in aqueous methanol afforded the tetraol (**17a**) in quantitative yield. Oxidation of **17a** with sodium periodate in aqueous methanol at 0 °C gave the aldehyde hydrate, which was further oxidized with pyridinium dichromate in dimethylformamide to afford the (2*R*,3*S*)-carboxylic acid (**18a**) in 30% yield from (**17a**). However, one-step oxidation of the tetraol (**17a**) with ruthenium trichloride and sodium

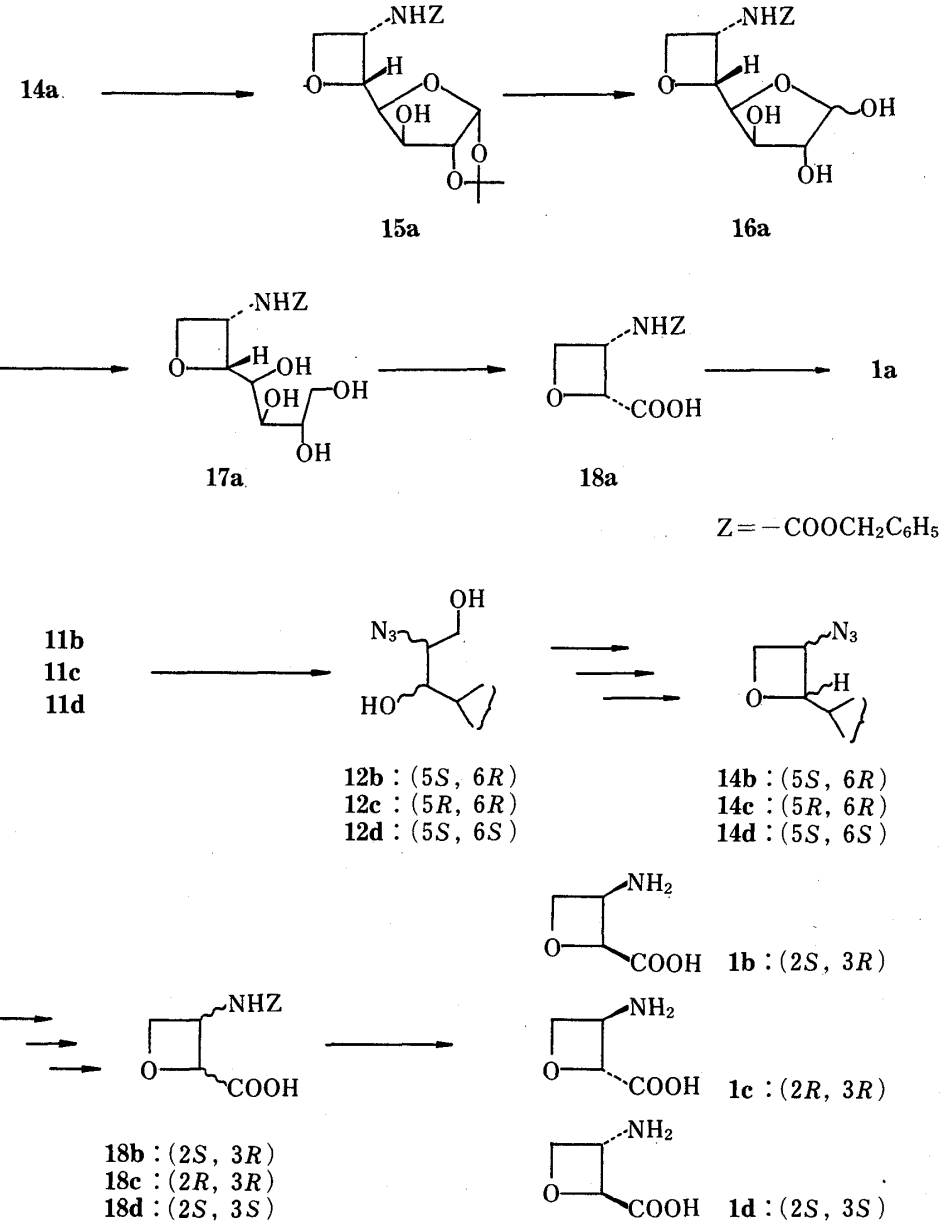


Chart 3

periodate[5] in CCl_4–CH_3CN–H_2O (2 : 2 : 3) at room temperature provided the acid (**18a**) in an improved yield (51%). Removal of the protecting group of **18a** with 10% Pd–C in aqueous methanol under a hydrogen atmosphere afforded, after purification by ion exchange chromatography, oxetin (**1a**) in 80% yield. The chromatographic behavior on thin layer chromatography (TLC) and gas-liquid chromatography (GC) (as the di-trimethylsilyl (TMS) derivative)[6] and the ^{1}H-NMR spectral data of the synthetic oxetin (**1a**) were in good agreement with those of the natural product.[1]

The oxetin enantiomer, the (2*S*,3*R*) compound (**1b**), was prepared by the same procedure from the (5*S*,6*S*)-epoxyalcohol (**11b**) through the (5*S*,6*R*)-azide compound (**12b**), the corresponding monotosylate (**13b**), the (5*S*,6*R*)-oxetane compound (**14b**), the amide alcohol (**15b**), the 1,2-deprotected compound (**16b**), the tetraol (**17b**), and the (2*S*,3*R*)-carboxylic acid (**18b**).

The diastereomers, the (2*R*,3*R*) compound (**1c**) and (2*S*,3*S*) compound (**1d**), were also prepared through the same route from the corresponding epoxyalcohols, the (5*R*,6*S*) (**11c**) and (5*S*,6*R*) (**11d**) compounds, through the oxetane compounds, the (5*R*,6*R*) isomer (**14c**) and the (5*S*,6*S*) isomer (**14d**), and the tetraols (**17c**) and (**17d**), respectively. Thus, syntheses of the four possible stereoisomers were completed.

Biological Activity

The antibacterial activity of oxetin and its three stereoisomers against *Bacillus subtilis* in minimal medium was examined by the paper disk method.[1] Synthetic oxetin (**1a**) showed the same antibacterial activity as the natural product but the other three stereoisomers were inactive against the bacterium.

The inhibitory activity against crude glutamine synthetase from spinach leaves was examined according to the published method.[1] Oxetin and its three stereoisomers inhibited the enzyme activity to similar extents although the activity was relatively weak. The difference between the relative antibacterial activities and the enzyme inhibitory activities may reflect differences of cell permeability of the compounds.

Experimental

Melting points were determined on a hot stage microscope and are uncorrected. ^{1}H-NMR spectra were taken with Hitachi R-24A (60 MHz) and JEOL FX 200 (200 MHz) spectrometers. All ^{1}H-NMR spectra were recorded with tetramethylsilane (TMS) as an internal standard unless otherwise noted. Infrared (IR) spectra were taken with a Hitachi 260-10 spectrometer. Optical rotations were taken with a Jasco DIP-4 digital polarimeter using a 0.5 dm cell. Electron impact-mass spectra (EI-MS) were obtained with a Shimadzu GC-MS 9020 DF mass spectrometer at 70 eV. Column chromatography was done on Silica gel 60 (E. Merck, 70—230 mesh). TLC was performed on precoated Kieselgel 60F_{254} (0.25 mm thickness, E. Merck). The usual work-up refers to dilution with water, extraction with an organic solvent (indicated in parenthesis), washing of the extract to neutrality, drying over $MgSO_4$, filtration, and removal of the solvent under reduced pressure.

Ethyl (5*Z*)-3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-6-enofuranuroate (7) and the (5*E*)- Isomer (8)——A mixture of the aldehyde (**6**) (25.7 g, 92.5 mmol) and (ethoxycarbonylmethylene)-triphenylphosphorane (32.5 g, 93.4 mmol) in benzene (170 ml) was stirred at room temperature for 38 h. Removal of the solvent gave a residue, which was applied to a silica gel column. Elution with hexane–ethyl acetate (25 : 2) gave the *cis* ester (**7**) (17.8 g, 55%), and the *trans* ester (**8**) (13.5 g, 43%).

7: Oil, $[\alpha]_D^{14}$ −34.8° (*c*=4.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.31, 1.49 (3H×2, s×2, acetonide), 1.23 (3H, t, *J*=7 Hz, $-CO_2CH_2C\underline{H}_3$), 4.06 (2H, q, *J*=7 Hz, $-CO_2C\underline{H}_2CH_3$), 4.48 (1H, d, *J*=3 Hz, 2-H), 4.48 (2H, d, *J*=2 Hz, $-C\underline{H}_2-C_6H_5$), 5.58 (1H, ddd, *J*=2, 3, and 6 Hz, 4-H), 5.91 (1H, dd, *J*=2, 11 Hz, 5-H), 6.03 (1H, dd, *J*=6, 11 Hz, 6-H), 6.37 (1H, d, *J*=3 Hz, 1-H), 7.27 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3050—2800 (C–H), 1715 (C=O), 1660, 1455, 1385, 1375, 1305, 1265, 1205, 1180, 1160, 1080, 1025, 885, 860, 720. *Rf* 0.62 (hexane–ethyl acetate=2 : 1, ×1). *Anal.* Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.55; H, 6.84.

8: Oil, $[\alpha]_D^{14}$ −211.1° (*c*=0.6, $CHCl_3$). ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.31, 1.49 (3H×2, s×2, acetonide), 1.29 (3H, t, *J*=7 Hz, $-CO_2CH_2C\underline{H}_3$), 3.95 (1H, d, *J*=3 Hz, 3-H), 4.20 (2H, q, *J*=7 Hz, $-CO_2C\underline{H}_2CH_3$), 4.54 (2H, d, *J*=3 Hz, $-C\underline{H}_2-C_6H_5$), 4.62 (1H, d, *J*=4 Hz, 2-H), 4.76 (1H, ddd, *J*=3, 5, and 6 Hz, 4-H), 5.97 (1H, d, *J*=4 Hz, 1-H),

6.11 (1H, dd, J=3, 16 Hz, 6-H), 6.99 (1H, dd, J=5, 16 Hz, 5-H), 7.32 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3050—2800 (C–H), 1720 (C=O), 1665, 1455, 1385, 1380, 1305, 1210, 1180, 1160, 1080, 1020, 980, 720. *Rf* 0.56 (hexane–ethyl acetate=2:1, ×1). *Anal.* Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.69; H, 7.02.

(5*Z*)-3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enofuranose (9) and the (5*E*)-Isomer (10)——Diisobutylaluminium hydride in hexane (65 ml, 114.4 mmol) was added to a solution of the (*cis*)-α,β-unsaturated ester (**7**) (17.8 g, 51.2 mmol) in toluene (100 ml) at 0 °C, and the mixture was stirred at room temperature for 3 h. The usual work-up (dichloromethane) gave a crude product, which was purified on a column of silica gel. Elution with hexane–ethyl acetate (1 : 1) gave the allyl alcohol (**9**) (13.8 g, 88%). The (5*E*)-isomer (**10**) was obtained in the same manner in 66% yield.

9: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.29, 1.48 (3H×2, s×2, acetonide), 3.84 (1H, d, J=3 Hz, 3-H), 4.13 (2H, m, 7-H_2), 4.53 (1H, d, J=3 Hz, 2-H), 4.57 (2H, s, $-C\underline{H}_2-C_6H_5$), 4.93 (1H, dd, J=3, 6 Hz, 4-H), 5.50—5.95 (2H, m, 5-H, 6-H), 5.86 (1H, d, J=3 Hz, 1-H), 7.31 (5H, s, $-C_6\underline{H}_5$).

10: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.25, 1.46 (3H×2, s×2, acetonide), 3.80 (1H, d, J=3 Hz, 3-H), 4.07 (2H, m, 7-H_2), 4.44—4.68 (4H, m, 2-H, 4-H, $-C\underline{H}_2-C_6H_5$), 5.78—5.98 (3H, m, 1-H, 5-H, 6-H), 7.28 (5H, s, $-C_6\underline{H}_5$).

5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*glycero*-D-*gluco*-heptofuranose (11a), 5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-L-*glycero*-L-*ido*-heptofuranose (11b), 5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-L-*glycero*-D-*gluco*-heptofuranose (11c), and 5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*glycero*-L-*ido*-heptofuranose (11d)——A mixture of the allyl alcohol (**9**) (13.5 g, 44.1 mmol), *m*-chloroperbenzoic acid (9.5 g, 55.1 mmol), and dichloromethane (70 ml) was stirred at room temperature for 16 h. Then calcium hydroxide (20 g, 270.2 mmol) was added to the reaction mixture, and the whole was further stirred at room temperature for 30 min. After filtration, the solvent was removed to give a mixture of the products, which was applied to a column of silica gel. Elution with hexane–ethyl acetate (1 : 1) gave the epoxide (**11a**) (3.9 g, 28%), and the other epoxide (**11b**) (7.4 g, 52%). The other two isomers were obtained from (**10**) in the same manner in 27% (**11c**) and 49% (**11d**) yields.

11a: Oil, $[\alpha]_D^{14}$ −47.8° (c=1.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$ 200 MHz) δ: 1.31, 1.45 (3H×2, s×2, acetonide), 3.33 (1H, dt, J=6, 4 Hz, 6-H), 3.46 (1H, dd, J=4, 7 Hz, 5-H), 3.72—3.96 (2H, m, 7-H_2), 4.05 (1H, dd, J=3, 7 Hz, 4-H), 4.09 (1H, d, J=3 Hz, 3-H), 4.66 (1H, d, J=4 Hz, 2-H), 4.58, 4.79 (1H×2, d×2, J=12 Hz, $-C\underline{H}_2-C_6H_5$), 5.92 (1H, d, J=4 Hz, 1-H), 7.35 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH), 3040—2800 (C–H), 1455, 1395, 1380, 1210, 1160, 1075, 1030, 980, 860, 725. *Rf* 0.39 (hexane–ethyl acetate=2:1, ×2). *Anal.* Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.25; H, 6.81.

11b: Oil, $[\alpha]_D^{14}$ −107.9° (c=1.2, $CHCl_3$). ^{1}H-NMR ($CDCl_3$ 200 MHz) δ: 1.32, 1.45 (3H×2, s×2, acetonide), 3.13 (1H, dt, J=5, 4 Hz, 6-H), 3.33 (1H, dd, J=4, 7 Hz, 5-H), 3.49 (2H, m, 7-H_2), 3.90 (1H, d, J=3 Hz, 4-H), 4.07 (1H, d, J=3 Hz, 3-H), 4.32, 4.87 (1H×2, d×2, J=12 Hz, $-C\underline{H}_2-C_6H_5$), 4.64 (1H, d, J=4 Hz, 2-H), 6.03 (1H, d, J=4 Hz, 1-H), 7.36 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH), 3040—2800 (C–H), 1455, 1390, 1380, 1210, 1165, 1075, 1020, 890, 855, 725. *Rf* 0.35 (hexane–ethyl acetate=2:1, ×2). *Anal.* Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.22; H, 6.88.

11c: Oil, $[\alpha]_D^{14}$ −53.7° (c=1.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$ 200 MHz) δ: 1.31, 1.46 (3H×2, s×2, acetonide), 3.25 (1H, dt, J=4, 2 Hz, 6-H), 3.31 (1H, dd, J=2, 7 Hz, 5-H), 3.55—3.68 (1H, m, 7-H), 3.90—4.02 (1H, m, 7-H), 3.95 (1H, dd, J=3, 7 Hz, 4-H), 4.07 (1H, d, J=3 Hz, 3-H), 4.63 (1H, d, J=3 Hz, 2-H), 4.57, 4.76 (1H×2, d×2, J=12 Hz, $-C\underline{H}_2-C_6H_5$), 5.94 (1H, d, J=4 Hz, 1-H), 7.34 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3150 (–OH), 3050—2800 (C–H), 1720, 1455, 1375, 1205, 1160, 1080, 1020, 910, 885, 860, 720. *Rf* 0.33 (hexane–ethyl acetate=2:1, ×2). *Anal.* Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.33; H, 6.87.

11d: Fine needle crystals (mp 103—104 °C, from hexane–ethyl acetate), $[\alpha]_D^{14}$ −49.4° (c=1.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$ 200 MHz) δ: 1.33, 1.46 (3H×2, s×2, acetonide), 3.02 (1H, dt, J=2, 4 Hz, 6-H), 3.33 (1H, dd, J=2, 6 Hz, 5-H), 3.55—3.67 (1H, m, 7-H), 3.83—3.94 (1H, m, 7-H), 3.93 (1H, dd, J=4, 6 Hz, 4-H), 3.99 (1H, d, J=3 Hz, 3-H), 4.38, 4.86 (1H×2, d×2, $-C\underline{H}_2-C_6H_5$), 4.65 (1H, d, J=4 Hz, 2-H), 6.00 (1H, d, J=4 Hz, 1-H), 7.34 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH), 3050—2800 (C–H), 1720, 1455, 1385, 1375, 1205, 1080, 1020, 900, 885, 720. *Rf* 0.28 (hexane–ethyl acetate=2:1, ×2). *Anal.* Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.39; H, 6.88.

6-Azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-L-*glycero*-D-*gluco*-heptofuranose (12a), 6-Azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-L-*ido*-heptofuranose (12b), 6-Azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-D-*gluco*-heptofuranose (12c), and 6-Azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-L-*glycero*-L-*ido*-heptofuranose (12d)——A mixture of the epoxyalcohol (**11a**) (2.84 g, 8.82 mmol), sodium azide (5.76 g, 87.9 mmol), and ammonium chloride (2.11 g, 39.4 mmol) in 2-methoxyethanol (40 ml) and water (3 ml) was heated at 125 °C for 2 h. The usual work-up and purification by column chromatography with hexane–ethyl acetate (2 : 1) provided the azide compound (**12a**) (2.61 g, 81%). The other three isomers were obtained in the same manner in 88% (**12b**), 73% (**12c**), and 97% (**12d**) yields.

12a: Fine needle crystals (mp 125—126 °C, from hexane–ethyl acetate). ^{1}H-NMR ($CDCl_3$ 200 MHz) δ: 1.33, 1.57 (3H×2, s×2, acetonide), 3.72 (1H, dt, J=5, 3 Hz, 6-H), 3.92 (2H, m, 7-H_2), 4.01—4.13 (1H, m, 5-H), 4.14 (1H, d, J=3 Hz, 3-H), 4.23 (1H, dd, J=3, 9 Hz, 4-H), 4.63 (1H, d, J=4 Hz, 2-H), 4.50, 4.80 (1H×2, d×2, J=12 Hz, $-C\underline{H}_2-C_6H_5$), 5.92 (1H, d, J=4 Hz, 1-H), 7.35 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650—3100 (–OH), 3050—2925 (C–H) 2115 ($-N_3$), 1210, 1080, 1025. *Anal.* Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 55.86; H,

6.43; N, 11.36.

12b: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.32, 1.49 (3H×2, s×2, acetonide), 3.63—4.45 (6H, m), 4.27, 4.93 (1H×2, d×2, J=12 Hz, $-C\underline{H}_2-C_6H_5$), 4.67 (1H, d, J=4 Hz, 2-H), 6.01 (1H, d, J=4 Hz, 1-H), 7.41 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650—3100 (–OH), 3025—2800 (C–H), 2105 ($-N_3$), 1380, 1100. *Anal.* Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 56.18; H, 6.37; N, 11.21.

12c: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.32, 1.48 (3H×2, s×2, acetonide), 3.42—4.32 (6H, m), 4.45, 4.70 (1H×2, d×2, J=11 Hz, $-C\underline{H}_2-C_6H_5$), 4.60 (1H, d, J=4 Hz, 2-H), 5.89 (1H, d, J=4 Hz, 1-H), 7.35 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650—3100 (–OH), 3050—2800 (C–H), 2105 ($-N_3$), 1375, 1070, 1020. *Anal.* Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 56.07; H, 6.30; N, 11.35.

12d: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.32, 1.49 (3H×2, s×2, acetonide), 3.40—4.38 (6H, m), 4.51, 4.81 (1H×2, d×2, J=12 Hz, $-C\underline{H}_2-C_6H_5$), 4.68 (1H, d, J=4 Hz, 2-H), 6.03 (1H, d, J=4 Hz, 1-H), 7.41 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3675—3150 (–OH), 3050—2800 (C–H), 2110 ($-N_3$), 1380, 1210, 1165, 1120, 1080, 1025. *Anal.* Calcd for $C_{17}H_{23}N_3O_6$: C, 55.88; H, 6.34; N, 11.50. Found: C, 56.03; H, 6.28; N, 11.28.

6-Azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-7-*O*-*p*-toluenesulfonyl-α-L-*glycero*-D-*gluco*-heptofuranose (13a), 6-Azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-7-*O*-*p*-toluenesulfonyl-α-D-*glycero*-L-*ido*-heptofuranose (13b), 6-Azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-7-*O*-*p*-toluenesulfonyl-α-D-*glycero*-D-*gluco*-heptofuranose (13c), and 6-Azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-7-*O*-*p*-toluenesulfonyl-α-L-*glycero*-L-*ido*-heptofuranose (13d)——A solution of the azide compound (**12a**) (2.66 g, 7.29 mmol) in pyridine (32 ml) was treated with *p*-toluenesulfonyl chloride (1.63 g, 8.53 mmol) under an argon atmosphere for 10 h. The usual work-up (ether) gave a crude product, which was applied to a column of silica gel. Elution with hexane–ethyl acetate (2 : 1) gave the tosylate (**13a**) (3.24 g, 86%). The other three isomers were obtained in the same manner in 70% (**13b**), 86% (**13c**), and 81% (**13d**) yields.

13a: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.27, 1.42 (3H×2, s×2, acetonide), 2.35 (3H, s, $-C_6H_4-C\underline{H}_3$), 3.60—4.22 (6H, m), 4.23, 4.73 (1H×2, d×2, J=12 Hz, $-C\underline{H}_2-C_6H_5$), 5.72 (1H, d, J=3 Hz, 1-H), 7.12, 7.60 (2H×2, d×2, J=8 Hz, $-SO_2-C_6\underline{H}_4-CH_3$), 7.32 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH), 3050—2800 (C–H), 2125 ($-N_3$) 1180, 730.

13b: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.32, 1.46 (3H×2, s×2, acetonide), 2.42 (3H, s, $-C_6H_4-C\underline{H}_3$), 3.30—3.63 (1H, m), 3.90—4.40 (5H, m), 4.26, 4.92 (1H×2, d×2, J=12 Hz, $-C\underline{H}_2-C_6H_5$), 4.67 (1H, d, J=4 Hz, 2-H), 5.17 (1H, d, J=4 Hz, 1-H), 7.38, 7.86 (2H×2, d×2, J=8 Hz, $-SO_2-C_6\underline{H}_4-CH_3$), 7.42 (5H, s, $-C_6\underline{H}_5$).

13c: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.29, 1.43 (3H×2, s×2, acetonide), 2.41 (3H, s, $-C_6H_4-C\underline{H}_3$), 3.33—4.13 (6H, m), 4.43, 4.73 (1H×2, d×2, J=12 Hz, $-C\underline{H}_2-C_6H_5$), 4.60 (1H, d, J=4 Hz, 2-H), 5.89 (1H, d, J=4 Hz, 1-H), 7.35, 7.84 (2H×2, d×2, J=8 Hz, $-SO_2-C_6\underline{H}_4-CH_3$), 7.37 (5H, s, $-C_6\underline{H}_5$).

13d: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.32, 1.47 (3H×2, s×2, acetonide), 2.43 (3H, s, $-C_6H_4-C\underline{H}_3$), 3.43—4.50 (6H, m), 4.50, 4.80 (1H×2, d×2, J=12 Hz, $-C\underline{H}_2-C_6H_5$), 4.67 (1H, d, J=4 Hz, 2-H), 6.02 (1H, d, J=4 Hz, 1-H), 7.38, 7.91 (2H×2, d×2, J=8 Hz, $-SO_2-C_6\underline{H}_4-CH_3$), 7.44 (5H, s, $-C_6\underline{H}_5$).

5,7-Anhydro-6-azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-L-*glycero*-D-*gluco*-heptofuranose (14a), 5,7-Anhydro-6-azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-L-*ido*-heptofuranose (14b), 5,7-Anhydro-6-azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-D-*gluco*-heptofuranose (14c), and 5,7-Anhydro-6-azide-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-L-*glycero*-L-*ido*-heptofuranose (14d)——Potassium *tert*-butoxide (1.0 g, 8.7 mmol) was added to a solution of the tosylate (**13a**) (3.24 g, 6.24 mmol) in THF (50 ml) and benzene (8.5 ml) at 0 °C, and the mixture was stirred for 20 min. The usual work-up (ethyl acetate) gave the crude product, which was applied to a column of silica gel. Elution with hexane–ethyl acetate (9 : 1) gave the oxetane compound (**14a**) (1.55 g, 72%). The other three isomers were obtained in the same manner in 77% (**14b**), 75% (**14c**), and 88% (**14d**) yields.

14a: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.30, 1.53 (3H×2, s×2, acetonide), 4.07 (1H, d, J=2 Hz, 3-H), 4.25—4.92 (7H, m), 4.95—5.25 (1H, m), 5.91 (1H, d, J=3 Hz, 1-H), 7.32 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3040—2800 (C–H), 2110 ($-N_3$), 1075, 1025, 995 (oxetane). *Anal.* Calcd for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09; N, 12.10. Found: C, 58.70; H, 6.08; N, 12.09.

14b: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.32, 1.52 (3H×2, s×2, acetonide), 4.10—4.41 (1H, m), 4.41—5.24 (8H, m), 6.01 (1H, d, J=4 Hz, 1-H), 7.41 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3050—2800 (C–H), 2110 ($-N_3$), 1075, 1020, 980 (oxetane). *Anal.* Calcd for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09; N, 12.10. Found: C, 58.80; H, 6.07; N, 12.02.

14c: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.33, 1.48 (3H×2, s×2, acetonide), 3.97 (1H, d, J=4 Hz, 3-H), 4.28—4.98 (8H, m), 6.05 (1H, d, J=4 Hz, 1-H), 7.42 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3025—2775 (C–H), 2090 ($-N_3$), 1070, 1010, 985 (oxetane). *Anal.* Calcd for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09; N, 12.10. Found: C, 58.90; H, 6.10; N, 12.05.

14d: Oil. ^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 1.34, 1.49 (3H×2, s×2, acetonide), 4.40—5.11 (9H, m), 6.07 (1H, d, J=4 Hz, 1-H), 7.41 (5H, s, $-C_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3100—2800 (C–H), 2110 ($-N_3$), 1375, 1140, 1080, 1020, 970 (oxetane). *Anal.* Calcd for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09; N, 12.10. Found: C, 58.96; H, 6.09; N, 11.84.

5,7-Anhydro-6-*N*-benzyloxycarbonylamino-6-deoxy-1,2-*O*-isopropylidene-α-L-*glycero*-D-*gluco*-heptofuranose (15a), 5,7-Anhydro-6-*N*-benzyloxycarbonylamino-6-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-L-*ido*-heptofuranose (15b), 5,7-Anhydro-6-*N*-benzyloxycarbonylamino-6-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-D-*gluco*-heptofuranose (15c), and 5,7-Anhydro-6-*N*-benzyloxycarbonylamino-6-deoxy-1,2-*O*-isopropylidene-α-L-*glycero*-L-*ido*-heptofuranose (15d)——A mixture of the oxetane compound (**14a**) (1.0 g, 2.88 mmol), and 10% Pd–C (0.97 g) in THF (5 ml), acetic

acid (2 ml), and water (2 ml) was stirred vigorously under a hydrogen atmosphere for 10 h. Filtration and removal of the solvent gave the crude amino product. It was treated with sodium carbonate (1.85 g, 17.5 mmol) and benzyloxycarbonyl chloride (0.8 ml, 5.60 mmol) in methanol (14 ml) and water (6 ml) at 0 °C. The reaction mixture was stirred for 5 h. The usual work-up (ether) and purification by silica gel column chromatography with hexane–ethyl acetate (1 : 1) gave the amide alcohol (**15a**) (686 mg, 65%). The other three isomers were obtained by the same method in 42% (**15b**), 68% (**15c**), and 57% (**15d**) yields.

15a: Oil. ^{1}H-NMR ($CDCl_3$ 200 MHz) δ: 1.32, 1.49 (3H × 2, s × 2, acetonide), 4.36 (1H, dd, J=3, 5 Hz, 4-H), 4.47—4.56 (2H, m), 4.48 (1H, d, J=4 Hz, 2-H), 4.85—5.16 (3H, m), 5.10 (2H, d, J=1 Hz, $-CH_2-C_6H_5$), 5.84 (1H, m, $-NH$), 5.93 (1H, d, J=3 Hz, 1-H), 7.35 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH), 3050—2800 (C–H), 1715 (C=O), 1510, 1210, 1075, 1020, 980 (oxetane). *Anal.* Calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.34; N, 3.83. Found: C, 59.26; H, 6.34; N, 3.80.

15b: Oil. ^{1}H-NMR ($CDCl_3$ 200 MHz) δ: 1.34, 1.43 (3H × 2, s × 2, acetonide), 4.22 (1H, d, J=3 Hz, 4-H), 4.31 (1H, dd, J=3, 4 Hz, 3-H), 4.54 (1H, dd, J=4, 1 Hz, 2-H), 4.66—4.83 (2H, m), 5.10 (2H, s, $-CH_2-C_6H_5$), 5.26—5.46 (2H, m), 6.24 (1H, d, J=4 Hz, 1-H), 6.07 (1H, m, $-NH$), 7.34 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH), 3025—2800 (C–H), 1710 (C=O), 1515, 1200, 1070, 1010, 970 (oxetane). *Anal.* Calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.37; N, 3.83. Found: C, 59.11; H, 6.40; N, 3.71.

15c: Fine needle crystals (mp 126—127 °C, from hexane–ethanol), ^{1}H-NMR ($CDCl_3$ 200 MHz) δ: 1.32, 1.49 (3H × 2, s × 2, acetonide), 4.15—4.43 (3H, m), 4.51 (1H, d, J=3 Hz, 2-H), 4.70—5.00 (3H, m), 5.05, 5.12 (1H × 2, d × 2, J=12 Hz, $-CH_2-C_6H_5$), 5.58 (1H, m, $-NH$), 6.03 (1H, d, J=3 Hz, 1-H), 7.34 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH), 3050—2825 (C–H), 1700 (C=O), 1510, 1080, 1020, 980 (oxetane). *Anal.* Calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.34; N, 3.83. Found: C, 59.42; H, 6.46; N, 3.72.

15d: Fine needle crystals (mp 164—165 °C, from hexane–ethyl acetate). ^{1}H-NMR ($CDCl_3$ 200 MHz) δ: 1.33, 1.51 (3H × 2, s × 2, acetonide), 4.28—4.46 (3H, m), 4.53 (1H, d, J=4 Hz, 2-H), 4.62—4.78 (1H, m, 6-H), 4.88—4.95 (2H, m), 5.11 (1H, s, $-CH_2-C_6H_5$), 5.38 (1H, m, $-NH$), 6.01 (1H, d, J=4 Hz, 1-H), 7.35 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH), 3100—2800 (C–H), 1700 (C=O), 1500, 1375, 1260, 1200, 1160, 1075, 1015, 980 (oxetane). *Anal.* Calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.34; N, 3.83. Found: C, 59.02; H, 6.38; N, 3.82.

5,7-Anhydro-6-*N*-benzyloxycarbonylamino-6-deoxy-L-*glycero*-D-*gluco*-heptofuranose (16a), 5,7-Anhydro-6-*N*-benzyloxycarbonylamino-6-deoxy-D-*glycero*-L-*ido*-heptofuranose (16b), 5,7-Anhydro-6-*N*-benzyloxycarbonylamino-6-deoxy-D-*glycero*-D-*gluco*-heptofuranose (16c), and 5,7-Anhydro-6-*N*-benzyloxycarbonylamino-6-deoxy-L-*glycero*-L-*ido*-heptofuranose (16d)——A suspension of the amide alcohol (**15a**) (272 mg, 0.75 mmol) in 0.1 N H_2SO_4 (15 ml) was stirred at 68 °C for 4 h. The mixture was cooled and diluted with water (15 ml), and Dowex 1 × 2 was added to neutralize it. Filtration and removal of the solvent gave the 1,2-deprotected compound (**16a**) (240 mg, 99%). The other three isomers were obtained in the same manner in 99% (**16b**), 99% (**16c**), and 90% (**16d**) yields.

16a: Oil. ^{1}H-NMR ($CDCl_3 + CD_3OD$ 60 MHz) δ: 3.52—5.55 (*ca.* 12H, m), 5.11 (2H, s, $-CH_2-C_6H_5$), 7.42 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH), 3025—2800 (C–H), 1700 (C=O), 1200, 1060, 1040, 1010, 980 (oxetane), 720.

16b: Oil. ^{1}H-NMR ($CDCl_3 + CD_3OD$ 60 MHz) δ: 3.36—5.26 (*ca.* 11H, m), 5.01 (2H, s, $-CH_2-C_6H_5$), 5.28—5.40 (1H, m, $-NH$), 7.45 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3050 (–OH), 3050—2800 (C–H), 1710 (C=O), 1515, 1200, 1060, 1040, 1015, 975 (oxetane), 720.

16c: Oil. ^{1}H-NMR ($CDCl_3 + CD_3OD$ 60 MHz) δ: 3.50—5.20 (*ca.* 11H, m), 5.07 (2H, s, $-CH_2-C_6H_5$), 5.20—5.50 (1H, m, $-NH$), 7.33 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3000 (–OH), 3000—2800 (C–H), 1700 (C=O), 1550, 1260, 1065, 1020, 980 (oxetane).

16d: Oil. ^{1}H-NMR ($CDCl_3 + CD_3OD$ 60 MHz) δ: 3.32—5.32 (*ca.* 11H, m), 5.09 (2H, s, $-CH_2-C_6H_5$), 5.39—5.56 (1H, m, $-NH$), 7.39 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH), 3050—2800 (C–H), 1710 (C=O), 1200, 1055, 1030, 975 (oxetane).

1,3-Anhydro-2-*N*-benzyloxycarbonylamino-2-deoxy-L-*glycero*-D-*galacto*-heptitol (17a), 5,7-Anhydro-6-*N*-benzyloxycarbonylamino-6-deoxy-D-*glycero*-L-*ido*-heptitol (17b), 5,7-Anhydro-6-*N*-benzyloxycarbonylamino-6-deoxy-D-*glycero*-D-*gluco*-heptitol (17c), and 1,3-Anhydro-2-*N*-benzyloxycarbonylamino-2-deoxy-L-*glycero*-D-*gluco*-heptitol (17d)——The 1,2-deprotected compound (**16a**) (240 mg, 0.74 mmol) in methanol (8 ml) and water (1 ml) was treated with sodium borohydride (72 mg, 1.89 mmol) at 0 °C, and the mixture was stirred for 4 h. The reaction mixture was diluted with water (15 ml) and Dowex 50W × 2 was added. Then it was filtered off, and the residue was washed with methanol and water (1 : 1). The filtrate and washing were combined, and removal of the solvent gave a crude product. It was dissolved in methanol, and evaporated to give the tetraol (**17a**) (236 mg, 98%). The other isomers were obtained in the same manner in 96% (**17b**), 95% (**17c**), and 90% (**17d**) yields.

17a: Amorphous. ^{1}H-NMR ($CD_3OD + CDCl_3$ 60 MHz) δ: 3.48—5.25 (*ca.* 14H, m), 5.06 (2H, s, $-CH_2-C_6H_5$), 7.32 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3050 (–OH), 3025—2800 (C–H), 1680 (C=O), 1080, 1050, 1020, 985 (oxetane). *Anal.* Calcd for $C_{15}H_{21}NO_7$: 55.04; H, 6.47; N, 4.28. Found: C, 54.87; H, 6.55; N, 4.04.

17b: Amorphous. ^{1}H-NMR ($CD_3OD + CDCl_3$ 60 MHz) δ: 4.15—5.20 (*ca.* 14H, m), 5.06 (2H, s, $-CH_2-C_6H_5$), 7.32 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3750—3000 (–OH), 3000—2750 (C–H), 1680 (C=O), 1540, 1270, 1105, 1095, 985 (oxetane), 745. *Anal.* Calcd for $C_{15}H_{21}NO_7$: C, 55.04; H, 6.47; N, 4.28. Found: C, 54.95; H, 6.60; N, 4.15.

17c: Amorphous. ^{1}H-NMR ($CD_3OD + CDCl_3$ 60 MHz) δ: 3.50—5.17 (*ca.* 14H, m), 5.07 (2H, s, $-CH_2-C_6H_5$), 7.33 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3700—3000 (–OH), 3000—2800 (C–H), 1690 (C=O), 1630, 1615, 1270, 1100, 975 (oxetane), 740. *Anal.* Calcd for $C_{15}H_{21}NO_7$: C, 55.04; H, 6.47; N, 4.28. Found: C, 54.85; H, 6.58; N, 4.10.

17d: Amorphous. ^{1}H-NMR ($CD_3OD + CDCl_3$ 60 MHz) δ: 3.50—5.27 (*ca.* 14H, m), 5.07 (2H, s, $-CH_2-C_6H_5$), 7.33 (5H, s, $-C_6H_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650—3100 (–OH), 3000—2800 (C–H), 1695 (C=O), 1545, 1310, 1275, 1115, 980 (oxetane), 765. *Anal.* Calcd for $C_{15}H_{21}NO_7$: C, 55.04; H, 6.47; N, 4.28. Found: C, 54.91; H, 6.48; N, 4.29.

(2*R*,3*S*)-3-*N*-Benzyloxycarbonylamino-2-oxetanecarboxylic Acid (18a), and the (2*S*,3*R*)-Isomer (18b), (2*R*,3*R*)-Isomer (18c), and (2*S*,3*S*)-Isomer (18d)——Sodium periodate (863 mg, 3.74 mmol) and a catalytic amount of ruthenium trichloride hydrate (5 mg) were added to a suspension of the tetraol (**17a**) (201 mg, 0.61 mmol), carbon tetrachloride (2 ml), acetonitrile (2 ml), and water (3 ml). The mixture was stirred vigorously for 10 h. Work-up (chloroform) gave the crude product, which was applied to a column of silica gel. Elution with acetonitrile–water (19 : 1) gave the carboxylic acid (**18a**) (78 mg, 51%). The other three isomers were obtained in the same manner in 51% (**18b**), 50% (**18c**), and 53% (**18d**) yields.

Another method was also used, as follows. A solution of the tetraol (**17a**) (235 mg, 0.72 mmol) in methanol (10 ml) and water (2 ml) was treated with sodium periodate (555 mg, 2.61 mmol) at 0 °C for 30 min. The usual work-up (ethyl acetate) gave a crude aldehyde hydrate (^{1}H-NMR ($CDCl_3$ 60 MHz) δ: 9.77 (*ca.* 0.1H, s, aldehyde). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3100 (–OH)). Without purification, it was treated with pyridinium dichromate (528 mg, 1.40 mmol) in dimethylformamide (2 ml) at room temperature. After 2 h, the usual work-up (chloroform) and purification by silica gel column chromatography with acetonitrile–water (19 : 1) gave the carboxylic acid (**18a**) (54 mg, 30%).

18a: White solid. ^{1}H-NMR ($CDCl_3$ as a methyl ester derivative 200 MHz) δ: 3.73 (3H, s, $-CO_2CH_3$), 4.65 (1H, t, J=7 Hz, 3-H), 4.91—5.31 (5H, m), 5.41 (1H, m, –NH), 7.35 (5H, s, $-C_6H_5$). IR ν_{max}^{KBr} cm^{-1}: 3650—3200 (–OH), 1700 (C=O), 1635, 1615, 1230, 995 (oxetane). *Anal.* (as a methylester derivative) Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.11; H, 5.90; N, 5.50.

18b: White solid. ^{1}H-NMR ($CDCl_3$ as a methyl ester derivative 200 MHz) δ: 3.73 (3H, s, $-CO_2CH_3$), 4.65 (1H, t, J=7 Hz, 3-H), 4.91—5.31 (5H, m), 5.46 (1H, m, –NH), 7.35 (5H, s, $-C_6H_5$). IR ν_{max}^{KBr} cm^{-1}: 3700—3010 (–OH), 1700 (C=O), 1635, 1615, 1230, 995 (oxetane).

18c: White solid. ^{1}H-NMR ($CDCl_3$ as a methyl ester derivative 200 MHz) δ: 3.82 (3H, s, $-CO_2CH_3$), 4.50—4.61 (1H, m), 4.79—5.08 (3H, m), 5.12 (2H, d, J=1 Hz, $-CH_2-C_6H_5$), 5.34 (1H, m, –NH), 7.36 (5H, s, $-C_6H_5$). IR ν_{max}^{KBr} cm^{-1}: 3700—3100 (–OH), 1700 (C=O), 1635, 1615, 1230, 995 (oxetane).

18d: White solid. ^{1}H-NMR ($CDCl_3$ as a methyl ester derivative 200 MHz) δ: 3.82 (3H, s, $-CO_2CH_3$), 4.51—4.62 (1H, m), 4.78—5.10 (3H, m), 5.12 (2H, d, J=1 Hz, $-CH_2-C_6H_5$), 5.40 (1H, m, –NH), 7.36 (5H, s, $-C_6H_5$). IR ν_{max}^{KBr} cm^{-1}: 3650—3200 (–OH), 1700 (C=O), 1635, 1615, 1230, 995 (oxetane).

(2*R*,3*S*)-3-Amino-2-oxetanecarboxylic Acid (1a), and the (2*S*,3*R*)-Isomer (1b), (2*R*,3*R*)-Isomer (1c), and (2*S*,3*S*)-Isomer (1d)——A mixture of the carboxylic acid (**18a**) (55.5 mg, 0.22 mmol) and 10% Pd–C (8 mg) in methanol (4 ml) and water (4 ml) was stirred vigorously for 20 h under a hydrogen atmosphere. After filtration, the solvent was removed to provide crude oxetin, which was applied to a column of Dowex 50W × 2. The column was washed with water, then elution with 0.5 N aqueous ammonia gave oxetin (**1a**) (21 mg, 80%). The other three isomers were obtained in the same manner in 80% (**1b**), 96% (**1c**), and 97% (**1d**) yields.

1a: Cubic crystals (mp 185—190 °C (dec.), from water–methanol), $[\alpha]_D^{14}$ +53.0° (c=1.0, H_2O) (lit.[1] mp 185—190 °C (dec.), $[\alpha]_D^{25}$ +56.4° (c=1.0, H_2O)). ^{1}H-NMR (D_2O, 1,4-dioxane as an internal standard 200 MHz) δ: 4.27—4.44 (2H, m, 3-H, 4-H), 4.73 (1H, t, J=7 Hz, 4-H), 5.04 (1H, d, J=7 Hz, 2-H). IR ν_{max}^{KBr} cm^{-1}: 3650—3200 (–OH), 3100—2850 (C–H), 1620 (C=O), 1420, 1300, 1220, 980 (oxetane). GC (di-TMS derivative)[6]: 5.2 min. GC-MS (di-TMS derivative)[6] m/z: 261 (M^+), 246, 231, 216, 73. *Rf* 0.29 (acetonitrile–water = 2 : 1, × 1). *Anal.* Calcd for $C_4H_7NO_3$: C, 41.03; H, 6.02; N, 11.96. Found: C, 40.96; H, 6.01; N, 11.86.

1b: Cubic crystals (mp 185—190 °C, from water–methanol), $[\alpha]_D^{21}$ −56.0° (c=1.0, H_2O). ^{1}H-NMR (D_2O, 1,4-dioxane as an internal standard 200 MHz) δ: 4.28—4.43 (2H, m, 3-H, 4-H), 4.72 (1H, t, J=7 Hz, 4-H), 5.04 (1H, d, J=7 Hz, 2-H). IR ν_{max}^{KBr} cm^{-1}: 3600—3100 (–OH), 3100—2850 (C–H), 1620 (C=O), 1420, 1300, 1220, 1120, 980 (oxetane). GC (di-TMS derivative)[6]: 5.2 min. GC-MS (di-TMS derivative)[6] m/z: 261 (M^+), 246, 231, 216, 73. *Rf* 0.29 (acetonitrile–water = 2 : 1, × 1). *Anal.* Calcd for $C_4H_7NO_3$: C, 41.03; H, 6.02; N, 11.96. Found: C, 40.95; H, 6.00; N, 11.90.

1c: Water solid, $[\alpha]_D^{21}$ +13.7° (c=1.0, H_2O). ^{1}H-NMR (D_2O, 1,4-dioxane as an internal standard 200 MHz) δ: 4.15 (1H, dt, J=8, 6 Hz, 3-H), 4.42 (1H, dd, J=6, 8 Hz, 4-H), 4.58 (1H, dd, J=8 Hz, 4-H), 4.84 (1H, d, J=6 Hz, 2-H). IR ν_{max}^{KBr} cm^{-1}: 3700—3100 (–OH), 3050—2900 (C–H), 1635, 1620 (C=O), 1420, 1225, 995 (oxetane). GC (di-TMS derivative)[6]: 6.0 min. GC-MS (di-TMS derivative)[6] m/z: 261 (M^+), 246, 230, 216, 73. *Rf* 0.25 (acetonitrile–water = 2 : 1, × 1).

1d: White solid, $[\alpha]_D^{15}$ −12.0° (c=1.0, H_2O). ^{1}H-NMR (D_2O, 1,4-dioxane as an internal standard 200 MHz) δ: 4.14 (1H, dt, J=8, 6 Hz, 3-H), 4.42 (1H, dd, J=6, 8 Hz, 4-H), 4.58 (1H, dd, J=8 Hz, 4-H), 4.83 (1H, d, J=6 Hz, 2-H). IR ν_{max}^{KBr} cm^{-1}: 3600—3100 (–OH), 3050—2900 (C–H), 1635, 1620 (C=O), 1410, 1225, 955 (oxetane). GC (di-TMS derivative)[6]: 6.0 min. GC-MS (di-TMS derivative)[6] m/z: 261 (M^+), 246, 230, 216, 73. *Rf* 0.25 (acetonitrile–

water = 2 : 1, × 1).

References and Notes

1) S. Omura, M. Murata, N. Imamura, Y. Iwai, and H. Tanaka, *J. Antibiot.*, **37**, 1324 (1984).
2) M. L. Wolfrom and S. Hanessian, *J. Org. Chem.*, **27**, 1800 (1962).
3) An X-ray analysis of **11d** is in progress.
4) C. H. Behrens and K. B. Sharpless, *Aldrichimica Acta*, **16**, 67 (1983).
5) P. H. J. Carlsen, T. Katsuki, W. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).
6) The di-TMS derivatizations of oxetin (**1a**) and its stereoisomers (**1b**, **1c**, and **1d**) were carried out with bis(trimethylsilyl)trifluoroacetamide in acetonitrile at 60 °C for 10 min. GC and GC-MS analysis of the di-TMS derivatives were performed on a glass column packed with 1% OV-17 (2 mm i.d. × 1 m) (oven temperature 130 °C, carrier gas (helium) flow-rate; 50 ml/min).