Synthetic Approach toward Antibiotic Ezomycins. I. Synthesis of 5-Amino-5-deoxyoctofuranose-(1,4) Derivatives by Henry Reaction and Their Stereochemistry

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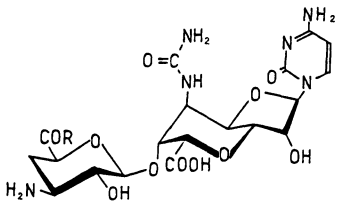
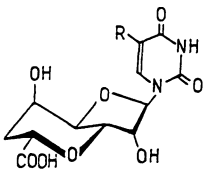
Ezomycins were discovered in a fermentation beer of Streptomyces species as antibiotics, which consisted of aminoocturonic acid, aminoglucuronic acid and base. As a part of a total synthesis of ezomycins, the title compounds have been synthesized. A KF-catalyzed Henry reaction between a nitropentose and a glyceraldehyde derivative gave a nitro alcohols mixture. Hydrogenation of the intact mixture, followed by *N*-acetylation afforded three diastereomers. The absolute configurations of the newly-introduced chiral centers were established by chemical methods and a X-ray crystal structure analysis.

Nucleoside antibiotic ezomycins were found in a fermentation broth of a strain which was very similar to Streptomyces Kitazawaensis.[1] The antibiotics exhibit antimicrobial activity against limited species of phytopathogenic fungi, such as Sclerotinia and Botritis. The molecular structures were established by a degradation study and a spectroscopic analysis.[2-4] A higher-carbon carbohydrate involved in ezomycins A_1, A_2, B_1, B_2, C_1, and C_2 is 5-amino-3,7-anhydro-5-deoxyocturonic acid, in which a furanoid ring is trans-



Ezomycin A_1 R = NHCHCH$_2$CH$_2$SCH$_2$CHNH$_2$ (COOH, COOH)

A_2 R = OH



Octosyl acids A_1 R = COOH

A_2 R = CH$_2$OH

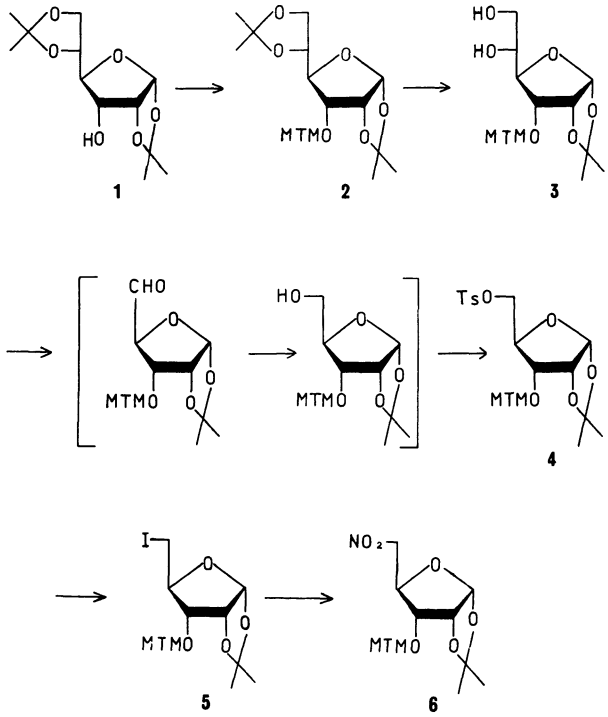
Scheme 1.

fused to a pyranoid ring. This particularly interesting structure was also found in antibiotic octosyl acids.[5] Several synthetic studies toward 3,7-anhydrooctose have been reported.[6-8] However, no derivatives with full function have been synthesized. Now, we have attempted to synthesize 5-amino-5-deoxyoctofuranose as a first step of the synthesis of ezomycins.

In a preceding paper,[9] a generally-applicable facile synthesis of higher-carbon carbohydrates has been developed by a KF-catalyzed Henry reaction between a nitro sugar and a sugar aldehyde, which is applied for the synthesis of 5-amino-5-deoxyoctofuranose-(1,4) derivatives in the present study.

Results and Discussion

In the KF-catalyzed Henry reaction, 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylthiomethyl-5-nitro-α-D-ribofuranose (**6**) was used as a nitro component and 2,3-*O*-isopropylidene-L-glyceraldehyde (**8**) was used as an aldehyde component. Compound **6** was prepared from known 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[10] (**1**) by a **7** steps-reaction. Protection of 3-OH with chloromethyl methyl sulfide and sodium hydride in dioxane gave methylthiomethyl (MTM) ether (**2**) in 62%

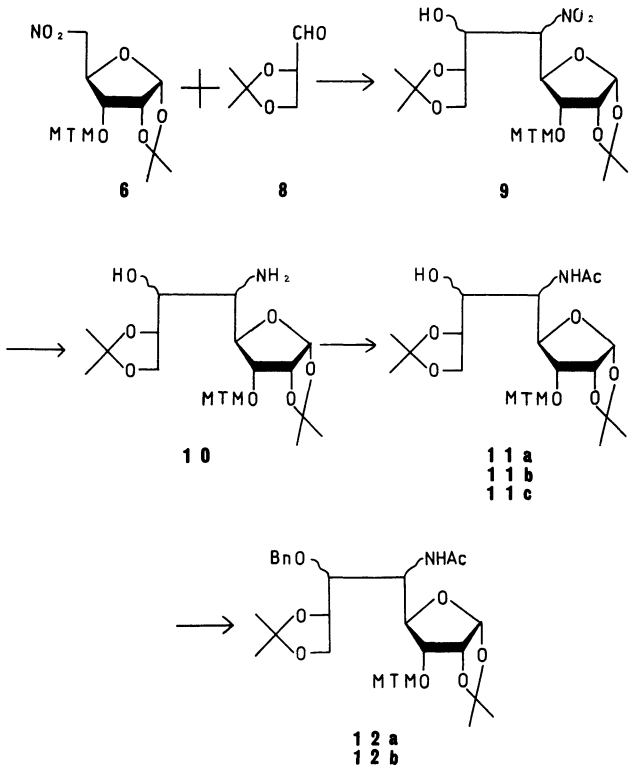


MTM: -CH$_2$SCH$_3$

Scheme 2.

yield. A selective removal of the 5,6-*O*-isopropylidene group by hydrolysis of **2** in aqueous acetic acid afforded the glycol (**3**) in 92% yield. Oxidative cleavage of the 5,6-diol with sodium periodate and successive reduction with sodium borohydride, followed by tosylation with *p*-toluenesulfonyl chloride in pyridine gave the tosylate (**4**) in 79% yield. Displacement of **4** with sodium iodide in 2-butanone afforded the iodide (**5**) in 94% yield. Replacement of **5** with sodium nitrite in dimethyl sulfoxide (DMSO) yielded the nitro compound (**6**) in 54% yield. On the other hand, the aldehyde **8** was prepared by a modified method of a known procedure.[11]

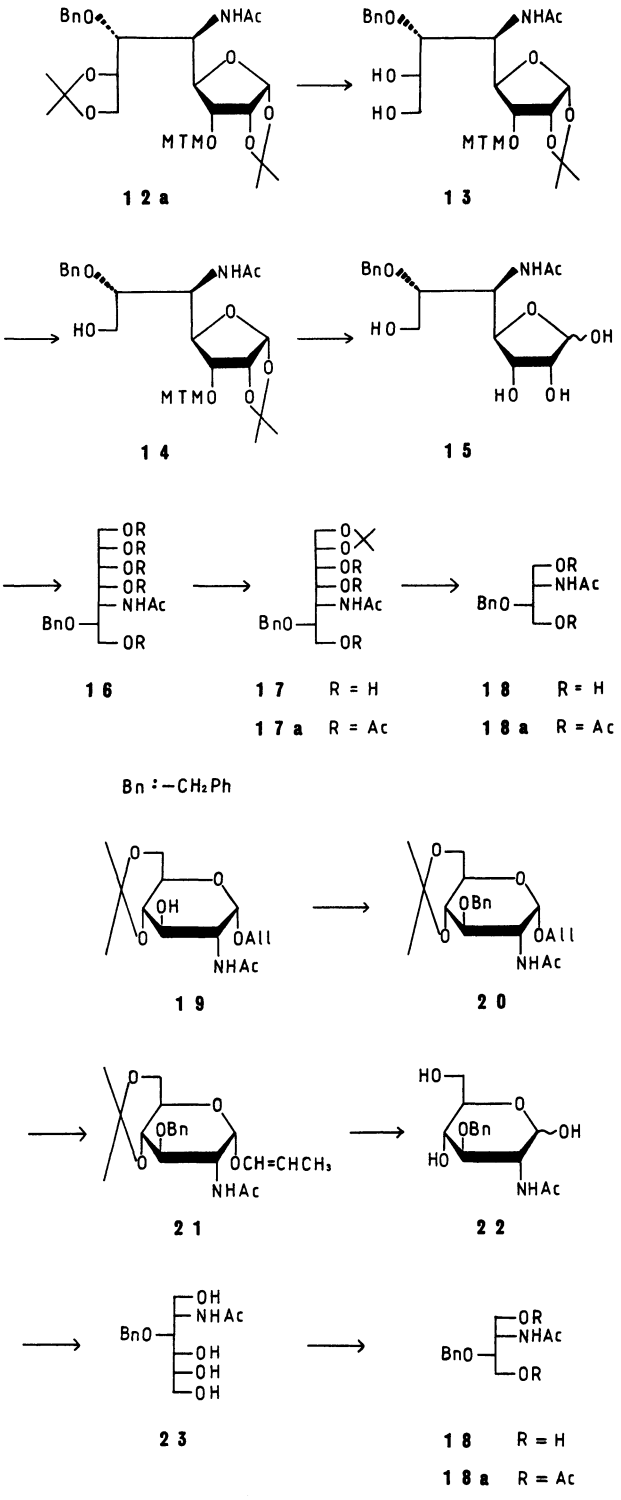
The Henry reaction of **6** and **8** was carried out in a toluene solution under the presence of KF and tetrabutylammonium iodide to give 5-deoxy-5-nitrooctose (**9**) as a mixture of diastereomers. Catalytic hydrogenation of the intact mixture **9** in the presence of Raney Ni, followed by *N*-acetylation afforded a mixture of three 5-acetamido-5-deoxyoctofuranoses (**11a**, **11b**, and **11c**). Compound **11c** was isolated in a homogeneous state by silica-gel chromatography in a poor yield of 5%. Compound **11b** was obtained by repeated fractional



Scheme 3.

recrystallization. But the major product **11a** was contaminated with **11b** which showed the same chromatographic behavior in several solvent systems. *O*-Benzylation of a mixture (67% from **6**) of **11a** and **11b** with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide (DMF) gave the corresponding benzyl ethers (**12a** and **12b**), which were readily isolated in homogeneous states by silica-gel chromatography in 49 and 30% yield, respectively.

A stereochemistry of the newly-introduced chiral centers on C-5 and C-6 of the major product **12a** was established by converting **12a** to 2-acetamido-3-*O*-benzyl-2-deoxy-L-threitol (**18**) as follows. Hydrolysis of **12a** with aqueous acetic acid resulted in a preferential removal of the 7,8-*O*-isopropylidene group giving a diol (**13**). Oxidative cleavage of **13** with sodium

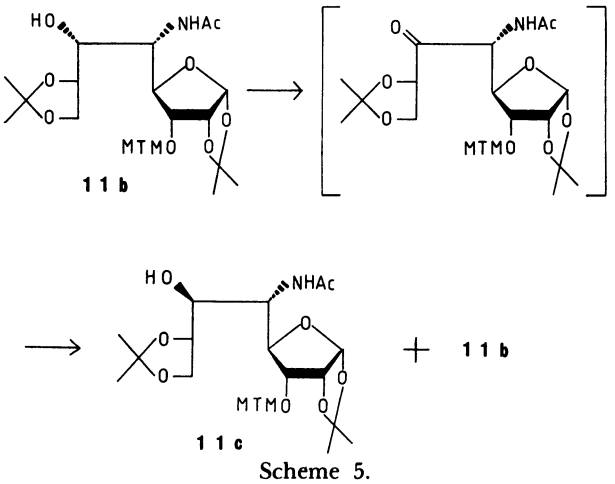


Scheme 4.

periodate and successive reduction with sodium borohydride afforded a heptose derivative (**14**). Removal of protective groups of **14** with aqueous trifluoroacetic acid gave a heptose derivative (**15**). Reduction of **15** with sodium borohydride afforded a heptitol derivative (**16**). Partial protection of **16** with 2-methoxypropene in the presence of *p*-toluenesulfonic acid yielded 1,2-*O*-isopropylidene derivative (**17**). Oxidative cleavage of **17** with sodium periodate and subsequent reduction with sodium borohydride afforded a C_4-alditol (**18**). Compound **18** was found to be identical with an authentic sample prepared as follows. *O*-Benzylation of allyl 2-acetamido-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside[12] (**19**) with benzyl bromide and sodium hydride gave benzyl ether (**20**). Isomerization of the allyl group of **20** with Wilkinson's catalyst[13] afforded 1-propenyl ether (**21**). Hydrolysis of **21** with diluted hydrochloric acid resulted in a removal of the 1-propenyl and 4,6-*O*-isopropylidene groups giving **22**. Reduction of **22** with sodium borohydride yielded a hexitol (**23**). Oxidative cleavage of **23** with sodium periodate and successive reduction with sodium borohydride afforded the same C_4-alditol (**18**). Therefore, the absolute configurations on C-5 and C-6 were established as *R*-configurations. Consequently, **12a** has the same configurations on C-5 and C-6 as those of ezomycins.

A stereochemistry of **11b** was established by means of X-ray crystal structure analysis. Figure 1 shows a perspective drawing of **11b**. The absolute configurations on C-5 and C-6 are S and R, respectively. The torsion angle of both C(4)–C(5)–C(6)–C(7) and N–C(5)–C(6)–O(4) are almost 180°. Interatomic distance O(4)···O(5)($x-1/2, -y+3/2, -z+1$) is 2.722(7), suggesting an existence of an O(4)–H(04)···O(5) hydrogen bond.

The configurations of **11c** were determined by a fact that **11c** was derived from **11b** by oxidation with DMSO



Scheme 5.

and dicyclohexylcarbodiimide (DCC) and successive reduction with sodium borohydride. That is, **11c** was an epimer of **11b** at C-6. Therefore, *S*-configurations were established on C-5 and C-6.

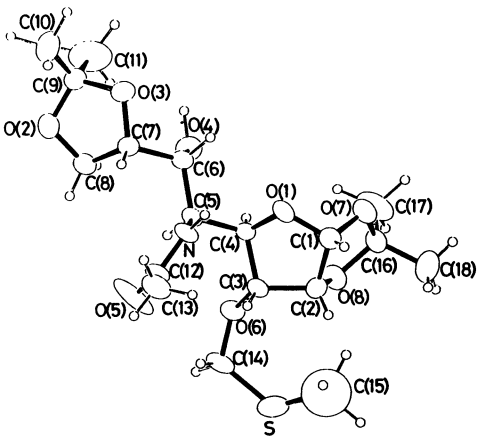


Fig. 1.

In the present case, the KF-catalyzed reaction between **6** and **8** seems to proceed without any predominant stereoselectivity.

Experimental

Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-4 polarimeter. IR spectra were recorded on a Hitachi 225 spectrometer. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer with a reference to tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi M-80 or a Hitachi M-80A mass spectrometer. Solutions were dried over anhydrous sodium sulfate and concentrated below 45 °C. TLC was carried out on glass plates coated with Merck Kieselgel 60 F_{254}, and compounds were detected by spraying with a H_2SO_4 followed by heating. Chromatography was performed on a silica-gel (Merck Kieselgel 60 Art. 7734) column.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-methylthiomethyl-α-D-allofuranose (2). To a stirred solution of **1** (20.0 g) in anhydrous dioxane (200 ml), sodium hydride (60% dispersion in mineral oil, 10.0 g) and chloromethyl methyl sulfide (10.0 ml) were added under ice cooling and the mixture was stirred overnight at room temperature. After addition of methanol, the reaction solution was concentrated and the residue was dissolved in ethyl acetate. The solution was washed with water repeatedly, dried and concentrated to dryness. The oily residue was chromatographed (5:1 (v/v) toluene–ethyl acetate) to give crystals. Recrystallization from hexane afforded 16.0 g (62%) of **2**: R_f=0.27 on TLC (5:1 (v/v) toluene–ethyl acetate); mp 58—60 °C; $[\alpha]_D^{23}$ +123° (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.37, 1.43, 1.55 (total 12H, sX3, CMe_2X2), 2.17 (3H, s, SMe), 4.77 (2H, s, CH_2S), 5.75 (1H, d, *J*=4 Hz, H-1).

Found: C, 52.52; H, 7.45; S, 9.90%. Calcd for $C_{14}H_{24}O_6S$: C, 52.48; H, 7.55; S, 10.01%.

1,2-*O*-Isopropylidene-3-*O*-methylthiomethyl-α-D-allofuranose (3). Compound **2** (6.7 g) was dissolved in 80% aqueous acetic acid (100 ml) and the solution was allowed to stand overnight at room temperature. The solution was coevaporated with toluene and the residue was chromatographed (1:2 (v/v) toluene–ethyl acetate) to give 5.4 g (92%) of **3** as a colorless syrup: R_f=0.41 on TLC (ethyl acetate); $[\alpha]_D^{25}$ +198° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3550 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$)

δ=1.33, 1.57 (total 6H, s×2, CMe_2), 2.20 (3H, s, SMe), 4.77 (2H, s, CH_2S), 5.78 (1H, d, J=4 Hz, H-1).

Found: C, 46.87; H, 6.97; S, 11.40%. Calcd for $C_{11}H_{20}O_6S$: C, 47.13; H, 7.19; S, 11.44%.

1,2-*O*-Isopropylidene-3-*O*-methylthiomethyl-5-*O*-*p*-tolylsulfonyl-α-D-ribofuranose (4). An aqueous solution (560 ml) of sodium periodate (44.9 g) was added dropwise to an aqueous solution (560 ml) of **3** (56.0 g) under ice cooling. After 20 min, sodium borohydride (10.6 g) was added to the solution and the mixture was stirred for 20 min under ice cooling. The mixture was extracted with chloroform and the organic layer was dried and concentrated to dryness. To a solution of the residue in dry pyridine (300 ml) was added *p*-toluenesulfonyl chloride (45.7 g). After 12 h at room temperature, the mixture was concentrated and the residue was partitioned between saturated aqueous sodium hydrogencarbonate and ethyl acetate. The organic layer was washed twice with water, dried and concentrated to dryness. The residue was recrystallized from cyclohexane to afford 63.6 g (79%) of **4**: R_f=0.32 on TLC (5:1 (v/v) toluene–ethyl acetate); mp 80—81 °C; $[\alpha]_D^{23}$ +99° (*c* 1.4, $CHCl_3$); IR (KBr) 1360 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ=1.33, 1.57 (total 6H, s×2, CMe_2), 2.13 (3H, s, SMe), 2.50 (3H, s, $SO_2C_6H_4Me$), 4.73 (2H, s, CH_2S), 5.67 (1H, d, J=4 Hz, H-1), 7.38 (2H, d, J=9 Hz, C_6H_4), 7.85 (2H, d, J=9 Hz, C_6H_4).

Found: C, 50.51; H, 5.95; S, 15.57%. Calcd for $C_{17}H_{24}O_7S_2$: C, 50.48; H, 5.95; S, 15.85%.

5-Deoxy-5-iodo-1,2-*O*-isopropylidene-3-*O*-methylthiomethyl-α-D-ribofuranose (5). To a solution of **4** (45.1 g) in 2-butanone (450 ml) was added sodium iodide (58.5 g) and the mixture was heated for 2 h under reflux. The solution was concentrated and the residue was partitioned between water and ethyl acetate. The organic layer was washed twice with water, dried and concentrated to dryness to give 37.7 g (93.9%) of **5** as an almost homogeneous syrup: R_f=0.55 on TLC (5:1 (v/v) toluene–ethyl acetate); ^1H NMR ($CDCl_3$) δ=1.37, 1.57 (total 6H, s×2, CMe_2), 2.20 (3H, s, SMe), 4.73 (2H, s, CH_2S), 5.80 (1H, d, J=4 Hz, H-1).

The product was used in the next step without any purification.

5-Deoxy-1,2-*O*-isopropylidene-3-*O*-methylthiomethyl-5-nitro-α-D-ribofuranose (6). To a solution of **5** (37.7 g) in DMSO (370 ml) were added phloroglucinol monohydrate (28.9 g) and sodium nitrite (14.5 g). After stirring for 4 d at ambient temperature, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water repeatedly, dried and concentrated to dryness. The residue was chromatographed (10:1 (v/v) toluene–ethyl acetate) to yield crystalline solids. Recrystallization from cyclohexane–toluene (2:1 v/v) afforded 15.8 g (54.2%) of **6**: R_f=0.36 on TLC (5:1 (v/v) toluene–ethyl acetate); mp 89—90 °C; $[\alpha]_D^{25}$ +167° (*c* 1.5, $CHCl_3$); IR (KBr) 1560, 1380 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ=1.37, 1.57 (total 6H, s×2, CMe_2), 2.17 (3H, s, SMe), 4.78 (2H, s, CH_2S), 5.80 (1H, d, J=4 Hz, H-1).

Found: C, 43.14; H, 6.09; N, 5.10; S, 11.61%. Calcd for $C_{10}H_{17}NO_6S$: C, 43.00; H, 6.13; N, 5.01; S, 11.48%.

2,3-*O*-Isopropylidene-L-glyceraldehyde (8). To an ice-cooled solution of 4,5-*O*-isopropylidene-L-arabinose diethyl thioacetal[14] (**7**, 10.0 g) in ethyl acetate (100 ml) was added lead tetraacetate (20.0 g) and the mixture was vigorously stirred for 5 min. To the mixture was added sodium carbonate (30 g) and the mixture was vigorously stirred for 2 h under ice cooling. After the salts were filtered off, the filtrate was concentrated to give a pale yellow syrup. It was rapidly chromatographed (3:2 (v/v) hexane–ethyl acetate) to afford 3.1 g (70%) of **8** as a colorless syrup: $[\alpha]_D^{29}$ −48.9° (*c* 1.02, C_6H_6) (lit,[15] $[\alpha]_D^{22}$ −67.9° (C_6H_6)). The IR and ^1H NMR spectra were superimposable on those of D-isomer, prepared by oxidative cleavage of 1,2:5,6-di-*O*-isopropylidene-D-mannitol.

The product was used in the successive reaction without further purification.

5-Acetamido-5-deoxy-1,2:7,8-di-*O*-isopropylidene-3-*O*-methylthiomethyl-β-L-erythro-L-talooctofuranose-(1,4) (11b) and 5-Acetamido-5-deoxy-1,2:7,8-di-*O*-isopropylidene-3-*O*-methylthiomethyl-β-L-threo-L-talooctofuranose-(1,4) (11c). To a solution of **6** (1.0 g) in toluene (3 ml) were added **8** (0.75 g), anhydrous potassium fluoride (0.25 g) and tetrabutylammonium iodide (0.75 g). The total mixture was stirred for 2 h 30 min at room temperature. The mixture was diluted with ethyl acetate, washed with water repeatedly, dried and concentrated to dryness. The residue was dissolved in a mixture of ethyl acetate (20 ml) and acetic acid (1 ml), and hydrogenated in the presence of Raney Nickel T-4[16] (ca. 2.5 g) under a pressure of 5.5 kg cm^{-2} for 20 h. After the catalyst was filtered off, the filtrate was added with sodium carbonate (5 g) and the mixture was stirred for 1 h at room temperature. The precipitates were filtered off, and the filtrate was concentrated to give a syrup. The residue was dissolved in a mixture of methanol (20 ml) and acetic anhydride (1 ml), and the mixture was allowed to stand for 10 min at room temperature. Coevaporation with toluene gave a syrup, which was chromatographed (ethyl acetate) to afford 1.01 g (67.0%) of a mixture of **11a** and **11b**, and 72 mg (4.7%) of **11c** as a colorless syrup. The mixture of **11a** and **11b** was dissolved in toluene (10 ml), and the solution was stored at −20 °C overnight. The crystals of **11b** were collected by filtration and washed with toluene. Recrystallization from toluene yielded an analytical sample. Furthermore, recrystallization from ethyl acetate–cyclohexane afforded nice single crystals for X-ray structure analysis.

11b: R_f=0.36 on TLC (ethyl acetate); mp 138—139 °C; $[\alpha]_D^{23}$ +25.9° (*c* 1.0, $CHCl_3$); IR (KBr) 1660 cm^{-1} (NHCO); ^1H NMR ($CDCl_3$) δ=1.33, 1.36, 1.42, 1.58 (total 12H, s×4, CMe_2×2), 2.04 (3H, s, NHAc), 2.18 (3H, s, SMe), 2.65 (1H, d, J=8 Hz, OH), 4.78 (2H, s, CH_2S), 5.72 (1H, d, J=4 Hz, H-1), 5.93 (1H, d, J=13 Hz, NH).

Found: C, 51.49; H, 7.29; N, 3.19%. Calcd for $C_{18}H_{31}NO_8S$: C, 51.29; H, 7.41; N, 3.32%.

11c: R_f=0.21 on TLC (ethyl acetate); $[\alpha]_D^{25}$ +40.0° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 1680 cm^{-1} (NHCO); ^1H NMR ($CDCl_3$) δ=1.36, 1.43, 1.56 (total 12H, s×3, CMe_2×2), 2.04 (3H, s, NHAc), 2.20 (3H, s, SMe), 2.92 (1H, d, J=4 Hz, OH), 4.70 (1H, dd, J=4, 4 Hz, H-2), 4.80 (2H, s, CH_2S), 5.79 (1H, d, J=4 Hz, H-1), 6.20 (1H, d, J=9 Hz, NH).

Found: C, 50.79; H, 7.23; N, 3.04%; M+H, 422.1823. Calcd for $C_{18}H_{31}NO_8S$: C, 51.29; H, 7.41; N, 3.32%. Calcd for $C_{18}H_{32}NO_8S$: *m/z*, 422.1846.

5-Acetamido-6-*O*-benzyl-5-deoxy-1,2:7,8-di-*O*-isopropylidene-3-*O*-methylthiomethyl-β-L-erythro-D-allooctofuranose-(1,4) (12a) and 5-Acetamido-6-*O*-benzyl-5-deoxy-1,2:7,8-di-*O*-isopropylidene-3-*O*-methylthiomethyl-β-L-erythro-L-talooctofuranose-(1,4) (12b). To a stirred solution of the intact mixture (6.19 g) of **11a** and **11b** in anhydrous DMF (60 ml) were added benzyl bromide (2.1 ml) and sodium hydride

(0.88 g) under ice cooling. After 95 min, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with water repeatedly, dried and concentrated to dryness. The residue was chromatographed (1:1 (v/v) toluene–ethyl acetate) to give 3.64 g (48.5%) of **12a** and 2.26 g (30.1%) of **12b**. Recrystallization from toluene–cyclohexane (1:2 v/v) and cyclohexane yielded analytical samples, respectively.

12a: R_f=0.58 on TLC (ethyl acetate); mp 144—145 °C; $[\alpha]_D^{22}$ +17.7° (*c*, 1.04, $CHCl_3$); IR (KBr) 3330 (NH), 1680 (NHCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.32, 1.36, 1.41, 1.54 (total 12H, s×4, CMe_2×2), 1.97 (3H, s, NHAc), 2.20 (3H, s, SMe), 5.66 (1H, d, J=10 Hz, NH), 5.79 (1H, d, J=4 Hz, H-1), 7.38 (5H, s, Ph).

Found: C, 58.75; H, 7.25; N, 2.47; S, 6.32%. Calcd for $C_{25}H_{37}NO_8S$: C, 58.69; H, 7.29; N, 2.74; S, 6.27%.

12b: R_f=0.53 on TLC (ethyl acetate); mp 108—109 °C; $[\alpha]_D^{20}$ +15.2° (*c* 1.57, $CHCl_3$); IR (KBr) 3310 (NH), 1680 (NHCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.32, 1.37, 1.41 (total 12H, s×3, CMe_2×2), 1.98 (3H, s, NHAc), 2.14 (3H, s, SMe), 5.57 (1H, d, J=4 Hz, H-1), 5.59 (1H, d, J=11 Hz, NH), 7.36 (5H, bs, Ph).

Found: C, 58.75; H, 7.17; N, 2.75; S, 6.24%. Calcd for $C_{25}H_{37}NO_8S$: C, 58.69; H, 7.29; N, 2.74; S, 6.27%.

5-Acetamido-6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylthiomethyl-β-L-erythro-D-allooctofuranose-(1,4) (13). Compound **12a** (2.0 g) was dissolved in 70% aqueous acetic acid (20 ml), and the solution was allowed to stand for 12 h at room temperature. The reaction solution was coevaporated with toluene to dryness, and the residue was chromatographed (ethyl acetate) to afford 1.68 g (90.7%) of **13** as crystals: R_f=0.42 on TLC (ethyl acetate); mp 147 °C; $[\alpha]_D^{22}$ +21.0° (*c* 1.03, $CHCl_3$); IR (KBr) 1650 cm^{-1} (NHCO); ^1H NMR ($CDCl_3$) δ=1.37, 1.55 (total 6H, s×2, CMe_2), 2.02 (3H, s, NHAc), 2.19 (3H, s, SMe), 5.84 (1H, d, J=4 Hz, H-1), 5.94 (1H, d, J=9 Hz, NH), 7.39 (5H, s, Ph).

Found: C, 56.07; H, 6.95; N, 3.04; S, 6.88%. Calcd for $C_{22}H_{33}NO_8S$: C, 56.03; H, 7.05; N, 2.97; S, 6.80%.

5-Acetamido-6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylthiomethyl-β-L-glycero-D-alloheptofuranose-(1,4) (14). To a stirred solution of **13** (103 mg) in 50% aqueous ethanol (2 ml) was added a solution of sodium periodate (49 mg) in 50% aqueous ethanol (2 ml) under ice cooling. After 60 min, the solution was diluted with water and extracted with dichloromethane repeatedly. The combined extract was dried and concentrated to dryness. The residue was dissolved in 50% aqueous ethanol (3 ml). To the stirred solution was added sodium borohydride (17 mg) under ice cooling. After 30 min, the reaction mixture was diluted with water and extracted with dichloromethane repeatedly. The extract was dried and concentrated to dryness. The residue was chromatographed (1:1 (v/v) toluene–ethyl acetate) to give 84 mg (87%) of **14** as crystals: R_f=0.44 on TLC (ethyl acetate); mp 148—150 °C; $[\alpha]_D^{26}$ +37.2° (*c* 1.02, $CHCl_3$); IR (KBr) 1665 cm^{-1} (NHCO); ^1H NMR ($CDCl_3$) δ=1.35, 1.55 (total 6H, s×2, CMe_2), 1.97 (3H, s, NHAc), 2.16 (3H, s, SMe), 5.77 (1H, d, J=4 Hz, H-1), 5.89 (1H, d, J=8 Hz, NH), 7.34 (5H, s, Ph).

Found: C, 57.21; H, 6.90; N, 2.92%. Calcd for $C_{21}H_{31}NO_7S$: C, 57.13; H, 7.08; N, 3.17%.

5-Acetamido-6-*O*-benzyl-5-deoxy-L-glycero-D-alloheptose (15). Compound **14** (83 mg) was dissolved in 90% aqueous trifluoroacetic acid (1.7 ml), and the solution was allowed to stand for 55 min under ice cooling. The reaction solution was concentrated to dryness, and the residue was chromatographed (10:1 (v/v) dichloromethane–methanol) rapidly to afford 58 mg (90%) of **15** as an amorphous solid. The compound was unstable and was not characterized.

3-Acetamido-2-*O*-benzyl-3-deoxy-L-glycero-L-altroheptitol (16). To an ice-cooled solution of **15** (70 mg) in 50% aqueous ethanol (4 ml) was added sodium borohydride (62 mg), and the solution was stirred for 2 h under ice cooling. After deionized with Amberlite IR-120 (H^+), the solution was concentrated to dryness. The residue was chromatographed (8:1 (v/v) dichloromethane–methanol) to yield 54 mg (78%) of **16** as a pale yellow syrup: R_f=0.44 on TLC (5:1 (v/v) dichloromethane–methanol); $[\alpha]_D^{30}$ −36.7° (*c* 1.25, MeOH); IR (neat) 1645 cm^{-1} (NHCO); ^1H NMR (CD_3OD) δ=1.99 (3H, s, NHAc), 7.32 (5H, bs, Ph).

Found: M+H, 344. Calcd for $C_{16}H_{26}NO_7$: *m/z*, 344.

3-Acetamido-1,4,5-tri-*O*-acetyl-2-*O*-benzyl-3-deoxy-6,7-*O*-isopropylidene-L-glycero-L-altroheptitol (17a). To a stirred solution of **16** (146 mg) in anhydrous DMF (2 ml) were added 2-methoxypropene (0.24 ml) and *p*-toluenesulfonic acid monohydrate (7 mg). After 5 h at room temperature, the solution was added with dry pyridine (6 ml) and acetic anhydride (6 ml) under ice cooling. After 1 h 45 min at room temperature, the solution was concentrated to dryness. The residue was dissolved in ethyl acetate, and the solution was washed three times with water. The organic layer was dried and concentrated to dryness. The residue was chromatographed (3:2 (v/v) toluene–ethyl acetate) to give 64 mg (30%) of **17a** as a colorless syrup: R_f=0.65 on TLC (ethyl acetate); $[\alpha]_D^{28}$ −27.6° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 1735 (OAc), 1675 (NHCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.35 (6H, s, CMe_2), 2.00 (3H, s, NHAc), 2.04, 2.07 (total 9H, s×2, OAc×3), 6.36 (1H, d, J=10 Hz, NH), 7.33 (5H, s, Ph).

Found: M+H, 510. Calcd for $C_{25}H_{36}NO_{10}$: *m/z*, 510.

5-Acetamido-6-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-L-glycero-D-alloheptitol (17). Compound **17a** (64 mg) was dissolved in ice-cooled 0.1 M methanolic sodium methoxide (2 ml (1 M=1 mol dm^{-3})). After 45 min under ice cooling, the solution was deionized with Amberlite IR-120 (H^+) and concentrated to dryness. The residue was chromatographed (1:8 (v/v) toluene–ethyl acetate) to afford 40 mg (83%) of **17** as a colorless syrup: R_f=0.16 on TLC (ethyl acetate); $[\alpha]_D^{29}$ −20.2° (*c* 1.98, $CHCl_3$); IR ($CHCl_3$) 1655 cm^{-1} (NHCO); ^1H NMR ($CDCl_3$) δ=1.34, 1.40 (total 6H, s×2, CMe_2), 2.00 (3H, s, NHAc), 6.41 (1H, d, J=9 Hz, NH), 7.34 (5H, s, Ph).

Found: M+H, 384. Calcd for $C_{19}H_{30}NO_7$: *m/z*, 384.

Allyl 2-Acetamido-3-*O*-benzyl-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside (20). To a stirred solution of **19** (2.91 g) in anhydrous DMF (30 ml) were added benzyl bromide (1.35 ml) and sodium hydride (580 mg) under ice cooling. After 1 h under ice cooling, the solution was partitioned between water and ethyl acetate. The organic layer was washed twice with water, dried and concentrated to dryness. The residue was chromatographed (2:1 (v/v) toluene–ethyl acetate) to give 3.01 g (79.6%) of **20** as an amorphous solid: R_f=0.31 on TLC (1:1 (v/v) toluene–ethyl acetate); $[\alpha]_D^{20}$ +107° (*c* 0.62, $CHCl_3$); IR (KBr) 3290 (NH), 1640 (NHCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.42, 1.48 (total 6H, s×2, CMe_2), 1.89 (3H, s, NHAc), 5.47 (1H, d, J=8 Hz, NH), 5.72 (1H, m, $CH_2\underline{CH}{=}CH_2$), 7.32 (5H, m, Ph).

Found: M+H, 392. Calcd for $C_{21}H_{30}NO_6$: *m/z*, 392.

1-Propenyl 2-Acetamido-3-*O*-benzyl-2-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranoside (21). To a solution of

20 (81 mg) in 75% aqueous ethanol (1.6 ml) were added 1,4-diazabicyclo[2.2.2]octane (12mg) and chlorotris(triphenylphosphine) rhodium(I) (38 mg). After refluxing for 20 min, the reaction mixture was filtered to remove the catalyst. The filtrate was concentrated and the residue was chromatographed (3:1 (v/v) toluene–ethyl acetate) to yield 70 mg (86%) of **21** as a colorless syrup: R_f=0.38 on TLC (1:1 (v/v) toluene–ethyl acetate); $[\alpha]_D^{29}$+134° (*c* 3.49, $CHCl_3$); IR ($CHCl_3$) 1670 cm^{-1} (NHCO); ^1H NMR ($CDCl_3$) δ=1.42—1.69 (total 9H, CMe_2, CH=CHC$\underline{H}_3$), 1.87 (3H, s, NHAc), 4.58 (1H, d, *J*= 12 Hz, CH_2Ph), 4.83 (1H, d, *J*=12 Hz, CH_2Ph), 4.99 (1H, d, *J*=3 Hz, H-1), 7.32 (5H, s, Ph).

Found: M+H, 392. Calcd for $C_{21}H_{30}NO_6$: *m/z*, 392.

2-Acetamido-3-*O*-benzyl-2-deoxy-D-glucose (22). A solution of **21** (40 mg) in 0.2 M HCl in 70% aqueous dioxane (4 ml) was allowed to stand for 20 h at room temperature. After neutralized with silver carbonate, the reaction mixture was filtered to remove the precipitates and the filtrate was concentrated to dryness. The residue was chromatographed (5:1 (v/v) dichloromethane–methanol) to give 29 mg (91%) of **22**: R_f=0.43—0.51 on TLC (5:1 (v/v) dichloromethane–methanol; $[\alpha]_D^{30}$ +2.7° (*c* 1.43, H_2O); IR (KBr) 1645 cm^{-1} (NHCO); ^1H NMR (CD_3OD) δ=1.93 (3H, s, NHAc), 5.08 (1H, d, *J*=3 Hz, H-1), 7.34 (5H, bs, Ph).

Found: M+Na, 334. Calcd for $C_{15}H_{21}NO_6Na$: *m/z*, 334.

2-Acetamido-3-*O*-benzyl-2-deoxy-D-sorbitol (23). To a stirred solution of **22** (37 mg) in water (2 ml) was added sodium borohydride (46 mg). After 12 h, the solution was deionized with Amberlite IR-120 (H^+) and concentrated to dryness. The residue was chromatographed (5:1 (v/v) dichloromethane–methanol) to give 28 mg (75%) of **23** as crystals. Recrystallization from 2-propanol yielded an analytical sample: R_f=0.38 on TLC (5:1 (v/v) dichloromethane–methanol); mp 125—127 °C; $[\alpha]_D^{30}$ −16.5° (*c* 1.19, MeOH); IR (KBr) 1635 cm^{-1} (NHCO); ^1H NMR (CD_3OD) δ=1.94 (3H, s, NHAc), 7.42 (5H, bs, Ph).

Found: C, 57.73; H, 7.32; N, 4.18%. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47%.

2-Acetamido-1,4-di-*O*-acetyl-3-*O*-benzyl-2-deoxy-L-threitol (18a) and 2-Acetamido-3-*O*-benzyl-2-deoxy-L-threitol (18). (A) from 17: To a stirred solution of **17** (21 mg) in methanol (0.5 ml) was added a solution of sodium periodate (47 mg) in water (1.0 ml) under ice cooling. After 1 h 35 min, sodium borohydride (21 mg) was added to the reaction solution under ice cooling. After 35 min, the reaction mixture was deionized with Amberlite IR-120 (H^+). The resin was filtered off, and the filtrate was concentrated to dryness. The residue was dissolved in a mixture of dry pyridine (1 ml) and acetic anhydride (0.5 ml) and the solution was allowed to stand for 1 h 10 min at room temperature. Coevaporation with toluene gave a syrupy residue, which was chromatographed (1:1 (v/v) toluene–ethyl acetate) to yield 12 mg (66%) of **18a** as a syrup: R_f=0.44 on TLC (ethyl acetate); $[\alpha]_D^{30}$ +14.7° (*c* 0.72, $CHCl_3$); IR ($CHCl_3$) 1735 (OAc), 1670 (NHCO) cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.98, 2.06 (total 9H, s×2, NHAc, OAc×2), 4.52 (1H, d, *J*=12 Hz, CH_2Ph), 4.74 (1H, d, *J*=12 Hz, CH_2Ph), 5.79 (1H, d, *J*=9 Hz, NH), 7.36 (5H, s, Ph).

Found: M+H, 338. Calcd for $C_{17}H_{24}NO_6$: *m/z*, 338.

Compound **18a** (11.4 mg) was dissolved in ice-cooled 0.1 M methanolic sodium methoxide (1 ml), and the solution was stirred for 1 h under ice cooling. The reaction mixture was deionized with Amberlite IR-120 (H^+). The resin was filtered off, and the filtrate was concentrated to dryness. The residue was chromatographed (20:1 (v/v) dichloromethane–methanol) to give 8.5 mg (99%) of **18** as crystals: R_f=0.48 on TLC (5:1 (v/v) dichloromethane–methanol); mp 133—135 °C; $[\alpha]_D^{27}$ −46.5° (*c* 0.76, MeOH); IR (KBr) 1655 cm^{-1} (NHCO); ^1H NMR (CD_3OD) δ=1.96 (3H, s, NHAc), 7.37 (5H, bs, Ph).

Found: M+H, 254.1366. Calcd for $C_{13}H_{20}NO_4$: *m/z*, 254.1390.

(B) from 23: To a stirred solution of **23** (28 mg) in water (1.5 ml) was added a solution of sodium periodate (96 mg) in water (1.5 ml) dropwise under ice cooling. After 2 h, the reaction solution was added with sodium borohydride (17 mg) under ice cooling. After 40 min, the reaction solution was deionized with Amberlite IR-120 (H^+). The resin was filtered off, and the filtrate was concentrated to dryness. The residue was dissolved in a mixture of dry pyridine (4 ml) and acetic anhydride (3 ml), and the mixture was allowed to stand overnight at room temperature. The solution was coevaporated with toluene to dryness to give a pale brown syrup. The residue was chromatographed (1:1 (v/v) toluene–ethyl acetate) to afford 27 mg (89%) of **18a** as a colorless syrup: $[\alpha]_D^{30}$+14.7° (*c* 1.25, $CHCl_3$). IR, ^1H NMR and MS spectra were superimposable on those of the product derived from **17**.

The product was deacylated by the same procedure described in the preparation (A) to yield **18** (quantitative yield): mp 134—135 °C; $[\alpha]_D^{28}$ −46.3° (*c* 1.91, MeOH). IR, ^1H NMR and MS spectra were superimposable on those of the product derived from **17**.

Treatment of 11b with DMSO–DCC Followed by Sodium Borohydride. To a stirred solution of **11b** (300 mg), toluene (0.1 ml), phosphoric acid (0.02 ml) and pyridine (0.04 ml) in DMSO (1.5 ml) was added DCC (440 mg). After 3 h at room temperature, to the mixture was added a solution of oxalic acid (250 mg) in methanol (1 ml) under ice cooling. After 30 min under ice cooling, the mixture was diluted with ethyl acetate and the insoluble materials were filtered off. The filtrate was washed with aqueous sodium hydrogencarbonate and water, and concentrated to dryness. The residue was dissolved in 50% aqueous ethanol (6 ml), and to the solution was added sodium borohydride (40 mg). After 30 min at room temperature, the reaction mixture was deionized with Amberlite IR-120 (H^+). The resin was filtered off, and the filtrate was concentrated to dryness. The residue was chromatographed (ethyl acetate) to give 86 mg (29%) of **11c** and 126 mg (42%) of **11b**.

X-Ray Crystal Structure Analysis of 11b. A crystal of 0.4×0.4×0.6 mm^3 was mounted on an automated Rigaku AFC-5 four-circle diffractometer. The cell dimensions were refined from 25 2θ values (60°<2θ<70°) with λ(Cu $K\alpha_1$)= 1.54056 Å. The crystal data are: $C_{18}H_{31}NO_8S$, FW 421.5; orthorhombic, space group $P2_12_12_1$, *a*=13.938(1), *b*=27.866(2), *c*=5.5524(5) Å, *V*=2156.5(3) $Å^3$, *Z*=4, D_m(benzene/tetrachloromethane)=1.29(1), D_x=1.30 $Mg\,m^{-3}$, μ=1.66 mm^{-1}. Intensity measurement was performed to 2θ=120° by θ—2θ scan technique with scan speed 6° min^{-1} (θ). 2523 reflections were measured and 2322 reflections were observed [$|F_o|>3\sigma(|F_o|)$]. Absorption correction was neglected. The structure was solved by direct methods,[17] and refined by block-diagonal least square.[18] The minimized function is $\sum w||F_o|-|F_c||^2$, where $w=[\sigma^2(|F_o|)+0.025|F_o|^2]^{-1}$. The position of a methyl C(15) atom bonded to S was difficult to be found on Fourier synthesis, suggesting positional disorder. Only one possible position of C(15) was found on difference

Table 1. Positional Parameters ($\times 10^4$) and Equivalent Isotropic Thermal Parameters

Atom	x	y	z	B_{eq}/Å^2	Atom	x	y	z	B_{eq}/Å^2
S	8658(2)	9362(1)	−1241(5)	4.5	C(5)	7162(4)	7532(2)	571(12)	2.4
O(1)	6101(3)	8095(2)	2503(10)	3.2	C(6)	6435(4)	7119(2)	269(13)	2.5
O(2)	7442(4)	6022(2)	−2143(13)	4.1	C(7)	6936(4)	6639(2)	253(14)	2.6
O(3)	6227(4)	6265(2)	233(12)	3.7	C(8)	7527(5)	6515(2)	−2005(16)	3.4
O(4)	5972(3)	7188(2)	−1988(11)	3.5	C(9)	6496(6)	5900(3)	−1429(16)	3.6
O(5)	9114(4)	7567(4)	1117(12)	6.7	C(10)	6537(9)	5435(3)	165(34)	8.4
O(6)	7735(4)	8506(2)	−1944(10)	3.3	C(11)	5767(10)	5951(5)	−3480(23)	7.0
O(7)	5003(3)	8712(2)	1931(11)	3.6	C(12)	8645(4)	7525(2)	2946(13)	2.7
O(8)	6056(4)	9007(2)	−830(11)	3.5	C(13)	9092(5)	7503(3)	5379(15)	3.7
N	7685(3)	7498(2)	2819(10)	2.6	C(14)	8645(5)	8738(3)	−1950(22)	4.7
C(1)	5920(5)	8589(2)	2784(14)	3.0	C(15)	8009(20)	9578(7)	1034(48)	13.7
C(2)	6640(5)	8855(2)	1199(16)	3.1	C(16)	5094(5)	9053(2)	43(16)	3.2
C(3)	7315(4)	8457(2)	377(13)	2.7	C(17)	4411(7)	8914(4)	−1985(21)	5.6
C(4)	6664(4)	8026(2)	347(13)	2.5	C(18)	4896(8)	9545(3)	989(27)	6.2

synthesis. However, its thermal parameter became greater than 20Å^2 when anisotropic thermal parameters were introduced. In the last three cycles of least square calculation, the anisotropic thermal parameters of the C(15) atom were refined with damping factor 0.1. The positional parameters for all the hydrogen atoms were calculated and refined with damping factor 0.1 because only four hydrogen atoms among 31 hydrogen atoms could be found on difference synthesis. Final R=0.108, wR=0.169, and S=6.2.[19] Rather large R value may be attributed to the positional disorder of the MTM group. Any molecules of mother liquor, ethyl acetate and cyclohexane, will not exist judging from its density and the difference synthesis. Complex neutral-atom scattering factors were taken from International Tables for X-ray Crystallography.[20] The final atomic parameters are listed in Table 1. The absolute structure was determined with reference to the known absolute configuration of D-glucose.[21]

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