Stereoselective Reactions. XX.¹⁾ Synthetic Studies on Optically Active β -Lactams. III.²⁾ Stereocontrolled Synthesis of Chiral Intermediate to (+)-Thienamycin from D-Glucose³⁾

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A chiral key intermediate (19a) for the synthesis of (+)-thienamycin was synthesized starting from D-glucose. The enol ether 13, obtained from the ketone 11 by Horner–Wittig reaction, was transformed to the corresponding methyl ester 16 by pyridinium chlorochromate oxidation or by employing the Wacker process. The ester 16 was further converted to the β -lactam 19a, which is a useful chiral precursor to (+)-thienamycin.

Keywords β -lactam; thienamycin; chiral synthesis; D-glucose; Horner–Wittig reaction; pyridinium chlorochromate; Wacker process

Thienamycin (1),⁵⁾ a β -lactam antibiotic having a 1-carbapen-2-em ring system and three contiguous chiral centers at C-5, 6 and 8, is reported to exhibit a desirable antibacterial activity as well as stability to β -lactamase. A number of syntheses of (+)-1 and the key intermediates for (+)-1 have been reported from a variety of starting materials such as (*S*)-aspartic acid,^{6a)} penicillin,^{6b)} (*S*)-threonine,^{6c)} D-glucose derivatives,^{3,6d–f)} (*S*)-3-hydroxybutanoate derivatives,^{6g)} and by asymmetric induction.^{6h–j)}

As shown in Chart 1, retrosynthetic analysis of thienamycin has led to the recognition of a hidden D-glucose skeleton within the thienamycin molecule. Thus, successive bond disconnection of thienamycin at the double bond (C-2–C-3) and β -lactam function (N-4–C-7) generates a β -amino acid 2, which can be related to the δ -lactone 3. Since racemic 3 has already been converted into ($\pm$)-thienamycin,⁷⁾ optically pure 3 was selected as the target for the chiral synthesis of 1. The δ -lactone 3 could be obtained by functionalization of the 3- and 4-hydroxy groups of 2,6-dideoxy- α -D-arabino-pyranose (4), which in turn can be prepared from D-glucose. The details are presented in this paper.

The synthetic scheme for the preparation of (+)-thienamycin is illustrated in Charts 2 and 3. The starting

material, methyl 3-azido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy- α -D-arabino-hexopyranoside (6), which already contains a 2-deoxy function and the potential amino group at C-3, was obtained from D-glucose.^{8,9)} Hydrogenation of the azido group, reductive dehalogenation and debenzoylation were effected in a single step by treatment of 6 with Raney nickel under hydrogen in the presence of triethylamine (TEA) in methanol to furnish the corresponding amino alcohol, which, without purification, was converted into various *N*-protected derivatives (7a, c, d) by treatment with acetic anhydride, trifluoroacetic anhydride, and benzyloxy-carbonyl (Z) chloride, respectively, in 48–57% yields. The next stage of the synthesis was to introduce a carboxyl group or its equivalent at C-4 of 7a–d. First, the introduction of the cyano group as a carboxyl equivalent was examined using potassium cyanide. Since the attempt to convert the equatorial 4-*O*-methanesulfonate 7b into the corresponding nitrile 7e with potassium cyanide in *N,N*-dimethylformamide (DMF) at 100 °C by a double-inversion process via the oxazolinium intermediate, involving participation of the neighboring acetamide group, resulted in the formation of the corresponding 1,3-oxazoline as the sole product, the axial 4-hydroxy derivatives (8a and 8d) were prepared from 7a and 7c, and converted to 4-*O*-

Chart 1

Chart 2

methanesulfonyl and 4-*O*-*p*-bromobenzenesulfonyl derivatives (**8b**, **c**, **e**) according to the reported procedure,^{9,10} and then the introduction of a cyano group in an *S*_N2 fashion was examined. However, the reaction of **8b** and **8c** with potassium cyanide in the presence of 18-crown-6 in acetonitrile at reflux temperature afforded the olefinic compound (**9**) and the *N*-*p*-bromobenzenesulfonyl derivative (**8f**), respectively. Interestingly, the 3-cyano derivative (**10**) was obtained by the reaction of **8e** with potassium cyanide in the presence of 18-crown-6 in dimethyl sulfoxide (DMSO) at 60–80 °C in 66% yield.¹¹

Since one of the efficient sequences for the one-carbon homologation of ketone to carboxylic acid or its equivalent is the Horner–Wittig reaction, the preparation of the enol ether **13** from the ketone **11** derived from the alcohol **7d** and its conversion to a carboxyl compound were examined by employing the Horner–Wittig reaction. Oxidation of **7d** with trifluoroacetic anhydride and DMSO in methylene dichloride¹² afforded the corresponding ketone **11** in 95% yield, and **11** was treated with the anion derived from methoxymethyldiphenylphosphine oxide¹³ and lithium diisopropylamide (LDA) in tetrahydrofuran (THF) to give the adducts **12** as a mixture of two diastereomers in a ratio of 2.8:1 in 92% yield. The isomers were separated

by column chromatography and treated with potassium hydride in DMF to provide the enol ethers **13a** and **13b** in 54–75% yields. The major diastereomer **12a** was converted to **13a**. Regiochemistry of **13a** and **13b** was tentatively determined by means of proton nuclear Overhauser effect (NOE) experiments. Upon irradiation of the vinyl proton of **13a**, significant enhancement (about 15%) of the C-6 methyl proton signal was observed, while no such enhancement was observed for **13b**. The conversion of the enol ether **13a** to the corresponding aldehyde **15** by acid hydrolysis resulted in the formation of the undesired enedialdehyde **14** by β -elimination. However, oxidation of the enol ethers **13a** and **13b** with pyridinium chlorochromate (PCC) in methylene dichloride¹⁴ gave the corresponding methyl ester **16** (mp 128 °C, [α]_D²⁰ +79.6° (CHCl₃)) in 30 and 15% yields, respectively. Stable equatorial orientation of the methoxycarbonyl group at C-4 is supported by the nuclear magnetic resonance (NMR) coupling constant (10 Hz) between H-4 and H-5, and no epimer at C-4 could be detected. A possible reaction mechanism is shown in Fig. 1. Initial electrophilic attack on the olefin by PCC from the less-hindered α -side gave an unstable intermediate **23**, in which heterolytic cleavage of the Cr–O bond, accompanied by a 1,2-hydride shift on the β -side gave the

TABLE I. Conversion of the Enol Ether (**13a**) to the Methyl Ester (**16**) with Various Reagents

Oxidant (eq)	Solvent	Temperature	Time (h)	Yield of 16 (%)
PCC (3)	CH ₂ Cl ₂	r.t.	24	30
PDC (2)	DMF	r.t.	48	7
Collins reagent (7.5)	CH ₂ Cl ₂	r.t.	48	No reaction
Jones reagent (2)	Acetone	0 °C	2	Many products
PdCl ₂ (0.1)	DMF-H ₂ O	r.t.	24	No reaction
CuCl ₂ (1)	(10:1)			
PdCl ₂ (0.5)	DMF-H ₂ O	r.t.	20	25
CuCl (1)	(10:1)			
PdCl ₂ (0.5)	DMF-H ₂ O	70 °C	19	53
CuCl (5)	(10:1)			

r.t. = room temperature.

Fig. 2

methoxycarbonyl compound with equatorial orientation. The use of other chromium oxidants such as pyridinium dichromate (PDC), Collins reagent, and Jones reagent did not improve the conversion yield of **13a** to **16**. However, by employing the Wacker process¹⁵⁾ using 0.5 eq of palladium chloride and 5 eq of cuprous chloride in DMF-H₂O (10:1) at 70 °C for 19 h, **16** was obtained in 53% yield from **13a**. In this reaction too, no epimer at C-4 was detected. The results on the conversion of **13a** to **16** are summarized in Table I. Figure 2 shows a possible reaction mechanism *via* the Wacker process. The palladium reagent approaches the olefin from the less-hindered α -side to form the π -complex **24**. Addition of water to the double bond forms the unstable σ -alkyl derivative (**25**), which was converted to the methyl ester **16** by a 1,2-hydride shift and cleavage of the Pd-C bond.

The ester **16** was treated with aqueous HCl in THF followed by Jones oxidation to provide the δ -lactone **17a** in 65% yield. The δ -lactone **17a** was further converted to the chiral thienamycin derivative (**22**) *via* the β -lactam **19** by employing Merck's procedure.⁷⁾ Removal of the Z group by catalytic hydrogenation followed by acid hydrolysis of the methyl ester gave the lactone acid **17b**, which was heated in benzyl alcohol to afford an equilibrium mixture of the acyclic β -amino acid hydrochloride **18** and starting lactone acid **17b**. This was used, without isolation, for β -lactam ring formation with *N,N'*-dicyclohexylcarbodiimide to give the β -lactam **19a** having the requisite chirality in 64% yield from **17a** after purification by column chromatography. After removal of the benzyl group of **19a**, the resulting acid **19b** was treated with *N,N'*-carbonyldiimidazole, followed by addition of the magnesium salt of *p*-nitrobenzyl hydrogen malonate¹⁶⁾ to afford the β -ketoester **20a** in 74% yield from **19a**. The construction of the carbapenam ring system by carbene insertion reaction of the diazo keto ester **20b** with a catalytic amount of rhodium acetate in benzene gave the bicyclic ketone **21**. Then, the ketone **21** was treated with diphenyl phosphorochloridate and *N,N*-diisopropylethylamine in acetonitrile

to provide the corresponding enol phosphate, which was reacted with *N-p*-nitrobenzyloxycarbonylaminoethanthiol to afford the bis-protected thienamycin **22** (mp 173.5–175 °C, $[\alpha]_D^{20} + 59.5^\circ$ (DMF)), which was precipitated directly from the reaction mixture in 48% yield from **20a**. Its spectral data are identical with those reported for racemic **22**.⁷⁾ The bis-protected thienamycin **22** was previously transformed into (+)-thienamycin by catalytic hydrogenation.^{6a,7,18)}

The presently described synthesis should be totally stereoselective and provide optically pure thienamycin. Further synthetic studies on optically active thienamycin derivatives are in progress in our laboratory.

Experimental

All melting temperatures are uncorrected. Infrared (IR) spectral measurements were performed with a JASCO DS-402G or a JASCO IRA-1 grating IR spectrometer. ¹H-NMR spectra were measured with JEOL JNM-FX 100 (100 MHz), JEOL JNM-PS (100 MHz) and Hitachi R-24 (60 MHz) spectrometers. ¹³C-NMR spectra were measured with a JNM-FX 100 (100 MHz) spectrometer. Data are recorded in parts per million (ppm) downfield from internal tetramethylsilane. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were determined with a JASCO DIP-181 polarimeter. Mass spectra (MS) were recorded with a JEOL JMS-01 5G-Z mass spectrometer. The organic solvents were dried over MgSO₄ before vacuum evaporation.

Methyl 3-Azido-4-O-benzoyl-6-bromo-2,3,6-trideoxy- α -D-arabino-hexopyranoside (6) This sample was obtained from methyl 3-azido-4,6-benzylidene-2-deoxy- α -D-ribo-hexopyranoside by the reported procedure,⁸⁾ mp 65–65.5 °C (2-propanol), $[\alpha]_D^{20} + 41.9^\circ$ ($c = 1.0$, CHCl₃), (lit.⁸⁾ syrup, $[\alpha]_D^{25} + 52.7^\circ$ ($c = 0.53$, CHCl₃).

Reaction of Methyl 3-Acetamido-4-O-methanesulfonyl-2,3,6-trideoxy- α -D-lyxo-hexopyranoside (8b) with Potassium Cyanide A mixture of methyl 3-acetamido-2,3,6-trideoxy- α -D-lyxo-hexopyranoside (**8a**, 60 mg, 0.3 mmol, mp 176.5–178 °C; $[\alpha]_D^{20} + 219^\circ$ ($c = 1.88$, MeOH), lit.⁹⁾ mp 176–178 °C; $[\alpha]_D^{20} + 220^\circ$ ($c = 1.45$, MeOH)) and methanesulfonyl chloride (44 mg, 0.38 mmol) in pyridine (1 ml) was stirred at –20 °C overnight. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (silica gel, CHCl₃:acetone = 20:1) to afford **8b** (42 mg, yield 51%) as crystals, mp 173–174.5 °C (2-propanol). ¹H-NMR (CDCl₃): 1.22 (3H, d, $J = 7$ Hz, C₆-CH₃), 1.6–2.34 (2H, m, C₂-H), 1.96 (3H, s, COCH₃), 3.12 (3H, s, SO₂CH₃), 3.31 (3H, s, OCH₃), 3.76–4.92 (4H, m, C₁-, C₃-, C₄-, and C₅-H), 6.27 (1H, s, NH). MS m/z : 281 (M⁺).

A mixture of **8b** (20 mg, 0.07 mmol), potassium cyanide (23 mg, 0.35 mmol), and 18-crown-6 (9.4 mg, 0.035 mmol) in acetonitrile (1 ml) was heated under reflux for 10.5 h. After removal of the solvent *in vacuo*, an oily residue was purified by column chromatography (silica gel, CHCl_3 :acetone=30:1) to afford **9** (5 mg, yield 39%) and starting **8b** (11 mg, 55% recovery). **9**: oil, IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1620. $^1\text{H-NMR}$ (CDCl_3): 1.76 (3H, s, $\text{C}_6\text{-CH}_3$), 1.95 (3H, s, COCH_3), 1.6–2.15 (2H, m, $\text{C}_2\text{-H}$), 3.69 (3H, s, OCH_3), 4.40–5.70 (3H, m, $\text{C}_1\text{-}$, $\text{C}_3\text{-}$, and $\text{C}_4\text{-H}$). MS m/z : 185 (M^+).

Reaction of Methyl 3-Acetamido-4-O-*p*-bromobenzenesulfonyl-2,3,6-trideoxy- α -D-lyxo-hexopyranoside (8c**) with Potassium Cyanide** A mixture of **8c** (41 mg, 0.096 mmol, mp 182–184 °C; $[\alpha]_{\text{D}}^{20} + 217^\circ$ ($c=1$, MeOH)), potassium cyanide (39 mg, 0.6 mmol), and 18-crown-6 (16 mg, 0.06 mmol) in acetonitrile (1 ml) was heated under reflux for 4.5 h. After removal of the solvent *in vacuo*, the resulting residue was dissolved in CHCl_3 . The insoluble materials were filtered off and the filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography (silica gel, benzene:acetone=5:1) to afford **8f** (35 mg, yield 95%) as crystals, mp 176 °C (2-propanol). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3320, 3300, 1575. $^1\text{H-NMR}$ (CDCl_3): 1.21 (3H, d, $J=7\text{ Hz}$, $\text{C}_6\text{-CH}_3$), 1.4–1.9 (2H, m, $\text{C}_2\text{-H}_{\text{ab}}$), 2.55 (1H, br s, OH), 3.29 (3H, s, OCH_3), 3.1–4.05 (3H, m, $\text{C}_3\text{-}$, $\text{C}_4\text{-}$, $\text{C}_5\text{-H}$), 4.5–4.74 (1H, m, $\text{C}_1\text{-H}$), 6.08 (1H, br s, NH), 7.4–7.9 (4H, m, aromatic protons). Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{BrNO}_5\text{S}$: C, 41.07; H, 4.77; N, 3.68. Found: C, 41.00; H, 4.71; N, 3.81.

Reaction of Methyl 4-O-*p*-Bromobenzenesulfonyl-3-trifluoroacetamido-2,3,6-trideoxy- α -D-lyxo-hexopyranoside (8e**) with Potassium Cyanide** A mixture of **8e** (150 mg, 0.32 mmol, prepared from **7c**^{10b}) in the same manner as described above for the preparation of **8c**, mp 177–179 °C, $[\alpha]_{\text{D}}^{20} + 115^\circ$ ($c=1.1$, CHCl_3), potassium cyanide (103 mg, 1.58 mmol), and 18-crown-6 (40 mg, 0.15 mmol) in DMSO (1 ml) was heated at 60 °C for 19 h, then at 80 °C for 13 h. After removal of the solvent *in vacuo*, the residue was dissolved in acetone and CHCl_3 (1:1). The insoluble materials were filtered off and the filtrate was concentrated *in vacuo* to give an oily residue, which was purified by column chromatography (silica gel, hexane:ether=2:1) to afford **10** (55 mg, yield 66%) as an oil. IR: $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3350, 2250 (CN), 1738. $^1\text{H-NMR}$ (CDCl_3): 1.22 (3H, d, $J=6\text{ Hz}$, $\text{C}_6\text{-CH}_3$), 1.71 (1H, dd, $J=12$, 15 Hz, $\text{C}_4\text{-H}_a$), 2.25 (2H, m, $\text{C}_2\text{-H}_{\text{ab}}$), 2.59 (1H, dd, $J=2$, 15 Hz, $\text{C}_4\text{-H}_b$), 3.34 (3H, s, OCH_3), 3.78 (1H, ddq, $J=2$, 6, 12 Hz, $\text{C}_5\text{-H}$), 4.83 (1H, m, $\text{C}_1\text{-H}$), 8.02 (1H, br s, NH). $^{13}\text{C-NMR}$ (CDCl_3): 20.4 (q, C_6), 36.7 (t), 37.7 (t), 47.6 (s, C_3), 55.4 (q, OCH_3), 59.7 (d, C_5), 96.9 (d, C_1), 115.4 (q, CF_3), 117.5 (s, CN), 115.9 (q, CO). High-resolution MS m/z ($(\text{M}+1)^+$): Calcd for $\text{C}_{10}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_3$: 265.0799. Found: 265.0799.

Methyl 3-(Benzyloxycarbonyl)amino-2,3,6-trideoxy- α -D-arabino-hexopyranoside (7d**)** A mixture of **6** (10 g, 27 mmol), Raney nickel (W-4, 20 g), and TEA (2.76 g, 27.3 mmol) in MeOH (80 ml) was shaken under hydrogen at 3.6 kg/cm² for 8 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give a residue, which was treated with benzyloxycarbonyl chloride (4.2 ml, 29.4 mmol) and TEA (4.3 ml, 30.9 mmol) in CH_2Cl_2 (100 ml) at room temperature for 4 h. After successive washing with saturated aqueous NaHCO_3 , H_2O , and saturated aqueous NaCl, drying followed by evaporation gave a residue, which was purified by column chromatography (silica gel, benzene:AcOEt=3:1) to afford **7d** (4.3 g, yield 55%) as crystals, mp 132–135 °C (benzene), $[\alpha]_{\text{D}}^{22} + 117.4^\circ$ ($c=1.4$, CHCl_3). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3410, 3305, 1680. $^1\text{H-NMR}$ (CDCl_3): 1.27 (3H, d, $J=6\text{ Hz}$, $\text{C}_6\text{-CH}_3$), 1.63 (1H, ddd, $J=3$, 13, 13 Hz, $\text{C}_2\text{-H}_a$), 2.01 (1H, dd, $J=4$, 13 Hz, $\text{C}_2\text{-H}_b$), 3.30 (3H, s, OCH_3), 2.70–4.22 (4H, m, $\text{C}_3\text{-}$, $\text{C}_4\text{-}$, and $\text{C}_5\text{-H}$, OH), 4.64 (1H, d, $J=3\text{ Hz}$, $\text{C}_1\text{-H}$), 5.04 (2H, s, OCH_2Ph), 5.32 (1H, d, $J=7\text{ Hz}$, NH), 7.28 (5H, s, aromatic protons). Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.14; H, 7.30; N, 4.63.

Methyl 3-(Benzyloxycarbonyl)amino-2,3,6-trideoxy- α -arabino-hexopyranoside-4-ulose (11**)** A solution of trifluoroacetic anhydride (5.7 ml, 40.6 mmol) in CH_2Cl_2 (13 ml) was added at -78°C to a solution of DMSO (3.84 ml, 49 mmol) in CH_2Cl_2 (95 ml) over a period of 10 min. The mixture was stirred at -78°C for 15 min, then a solution of **7d** (8.0 g, 27.1 mmol) in CH_2Cl_2 (95 ml) was added below -65°C over a period of 20 min. The mixture was stirred below -65°C for 1.5 h, followed by addition of TEA (11.3 ml, 81.2 mmol). After warming to room temperature, the mixture was washed with H_2O (100 ml). The aqueous layer was back-washed with CH_2Cl_2 . The combined organic solutions were washed with saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (silica gel, benzene:AcOEt=20:1) to give a solid. Recrystallization from isopropyl ether–hexane provided **11** (7.5 g, yield 95%) as prisms, mp

82–83 °C, $[\alpha]_{\text{D}}^{20} + 91.2^\circ$ ($c=1$, CHCl_3). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3290, 1730, 1650. $^1\text{H-NMR}$ (CDCl_3): 1.20 (3H, d, $J=6\text{ Hz}$, $\text{C}_6\text{-CH}_3$), 1.86 (1H, ddd, $J=4$, 14, 15 Hz, $\text{C}_2\text{-H}_a$), 2.64 (1H, ddd, $J=7$, 7, 15 Hz, $\text{C}_2\text{-H}_b$), 3.34 (3H, s, OCH_3), 4.28 (1H, q, $J=7\text{ Hz}$, $\text{C}_5\text{-H}$), 4.43–5.23 (2H, m, $\text{C}_1\text{-}$ and $\text{C}_3\text{-H}$), 5.01 (2H, s, OCH_2Ph), 5.83 (1H, d, $J=7\text{ Hz}$, NH), 7.20 (5H, s, aromatic protons). Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.35; H, 6.52; N, 4.60.

Methyl 3-(Benzyloxycarbonyl)amino-4-(diphenylphosphino)methoxy-methyl-2,3,6-trideoxy- α -D-arabino-hexopyranoside (12**)** A solution of methoxymethyldiphenylphosphine oxide (12 g, 48.8 mmol) in anhydrous THF (140 ml) was added to LDA in anhydrous THF (140 ml) prepared from diisopropylamine (6.9 ml, 49.3 mmol) and butyllithium (32.2 ml of a 1.52 M solution in hexane) below -65°C over a period of 10 min, and the mixture was stirred below -65°C for 20 min. Then, a solution of **11** (7.0 g, 23.9 mmol) in THF (60 ml) was added below -65°C over a period of 20 min. After being stirred below -65°C for 1.5 h, the mixture was allowed to warm to -10°C , then the reaction was quenched with 10% aqueous citric acid (100 ml). The organic layer was separated, and the aqueous layer was extracted with AcOEt (100 ml $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (silica gel, AcOEt) to provide **12** (11.9 g, yield 92%) as a mixture of two diastereomers. They were separated by medium-pressure liquid chromatography (silica gel, AcOEt). Less polar isomer (**12a**, oil, 7.84 g): $[\alpha]_{\text{D}}^{20} + 60.6^\circ$ ($c=1.04$, CHCl_3). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3300, 1705, 1125, 1110. $^1\text{H-NMR}$ (CDCl_3): 1.15 (3H, d, $J=7\text{ Hz}$, $\text{C}_6\text{-CH}_3$), 1.67–2.1 (2H, m, $\text{C}_2\text{-H}$), 3.23 (3H, s, POCHOCH_3), 3.26 (3H, s, OCH_3), 3.78–4.72 (4H, m, $\text{C}_1\text{-}$, $\text{C}_3\text{-}$, and $\text{C}_5\text{-H}$, POCH), 5.06 (2H, s, OCH_2), 5.22 (1H, br s, OH), 5.50 (1H, d, $J=10\text{ Hz}$, NH), 7.0–8.20 (15H, m, aromatic protons). MS m/z : 539 (M^+). Polar isomer (**12b**, oil, 2.8 g): $[\alpha]_{\text{D}}^{20} + 72.2^\circ$ ($c=1$, CHCl_3). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3300, 1708, 1127, 1111. $^1\text{H-NMR}$ (CDCl_3): 1.19 (3H, d, $\text{C}_6\text{-CH}_3$), 1.70–2.10 (2H, m, $\text{C}_2\text{-H}$), 3.15 (3H, s, POCHOCH_3), 3.20 (3H, s, OCH_3), 3.70–5.20 (6H, m, $\text{C}_1\text{-}$, $\text{C}_3\text{-}$, and $\text{C}_5\text{-H}$, POCH, OCH_2), 5.75 (1H, d, $J=8\text{ Hz}$, NH), 6.90–8.20 (15H, m, aromatic protons). MS m/z : 539 (M^+).

Methyl 3-(Benzyloxycarbonyl)amino-4-(*E*)-methoxymethylene-2,3,4,6-tetradeoxy- α -D-arabino-hexopyranoside (13a**)** A solution of **12a** (747 mg, 1.38 mmol) in DMF (5 ml) was added to a solution of potassium hydride (480 mg, 4.2 mmol, 35% oil suspension, washed with hexane) in DMF (10 ml) at -10°C over a period of 20 min. The mixture was stirred at 0°C for 1 h, then 10% aqueous citric acid (20 ml) was added, and the whole was extracted with AcOEt (50 ml $\times$ 4). The combined organic extracts were washed with saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (silica gel, benzene:AcOEt=30:1) to afford a solid (390 mg). Recrystallization from hexane gave **13a** (333 mg, yield 75%) as colorless needles, mp 66–67 °C, $[\alpha]_{\text{D}}^{20} + 86.9^\circ$ ($c=1.0$, CHCl_3). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3325, 1700. $^1\text{H-NMR}$ (CDCl_3): 1.39 (3H, d, $J=6\text{ Hz}$, $\text{C}_6\text{-CH}_3$), 1.7–1.85 (1H, m, $\text{C}_2\text{-H}_a$), 2.12–2.45 (1H, ddd, $J=4.9$, 14 Hz, $\text{C}_2\text{-H}_b$), 3.36 (3H, s, $\text{C}_1\text{-OCH}_3$), 3.57 (3H, s, OCH_3), 4.12–4.38 (1H, m, $\text{C}_3\text{-H}$), 4.66 (1H, dq, $J=2$, 7 Hz, $\text{C}_5\text{-H}$), 4.87 (1H, dd, $J=4$, 8 Hz, $\text{C}_1\text{-H}$), 5.09 (2H, s, OCH_2), 5.33 (1H, d, $J=8\text{ Hz}$, NH), 6.01 (1H, m, CHOCH_3), 7.35 (5H, s, aromatic protons). $^{13}\text{C-NMR}$ (CDCl_3): 20.7 (q, C_6), 37.2 (t, C_2), 46.9 (d, C_3), 55.2 (q, OCH_3), 60.0 (d, C_5), 63.8 (q, CHOCH_3), 66.6 (t, OCH_2), 97.1 (d, C_1), 116.4 (s, C_4), 128.0, 128.4, and 136.6 (aromatic carbons), 143.0 (d, $=\text{CHOCH}_3$), 155.4 (s, CO). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.49; H, 7.26; N, 4.34.

Methyl 3-(Benzyloxycarbonyl)amino-4-(*Z*)-methoxymethylene-2,3,4,6-tetradeoxy- α -D-arabino-hexopyranoside (13b**)** This sample was obtained from **12b** as an oil in 54% yield in the same manner as described for the preparation of **13a**, $[\alpha]_{\text{D}}^{20} + 97.4^\circ$ ($c=2.9$, CHCl_3). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3340, 1715. $^1\text{H-NMR}$ (CDCl_3): 1.25 (3H, d, $J=7\text{ Hz}$, $\text{C}_6\text{-CH}_3$), 1.5–2.3 (2H, m, $\text{C}_2\text{-H}$), 3.35 (3H, s, $\text{C}_1\text{-OCH}_3$), 3.54 (3H, s, $=\text{CHOCH}_3$), 4.15–4.50 (1H, m, $\text{C}_3\text{-H}$), 4.58–4.95 (2H, m, $\text{C}_1\text{-}$ and $\text{C}_5\text{-H}$), 5.09 (2H, s, OCH_2), 5.90 (1H, s, $=\text{CHO}$), 7.32 (5H, s, aromatic protons). $^{13}\text{C-NMR}$ (CDCl_3): 17.9 (q, C_6), 36.1 (t, C_2), 45.5 (d, C_3), 54.6 (q, OCH_3), 60.1 (d, C_5), 63.8 (q, $=\text{CHOCH}_3$), 66.2 (t, OCH_2), 98.2 (d, C_1), 117.2 (s, C_4), 127.9, 128.3, and 136.8 (aromatic carbons), 142.7 (d, $=\text{CHOMe}$), 155.6 (s, CO). MS m/z : 321 (M^+).

Acid Hydrolysis of **13a** A mixture of **13a** (23 mg, 0.072 mmol), 5 N aqueous H_2SO_4 (0.075 ml), and THF (0.3 ml) was stirred at room temperature for 3.5 h, then 0.075 ml of 5 N aqueous H_2SO_4 was added, and the mixture was stirred at room temperature for 4.5 h. After dilution with AcOEt, the mixture was washed with saturated aqueous NaHCO_3 and saturated aqueous NaCl. Drying followed by evaporation gave an

oily residue, which was purified by column chromatography (silica gel, benzene:AcOEt=20:1) to afford **14** (7.5 mg, yield 40%) as an oil. $^1\text{H-NMR}$ (CDCl_3): 2.20 (3H, d, $J=6$ Hz, CH_3), 2.93 (2H, dd, $J=2$ and 7 Hz, CH_2CHO), 5.0–5.25 (1H, m, CHNHZ), 5.06 (2H, s, $\text{CH}_2\text{C}_6\text{H}_5$), 5.82 (1H, d, $J=8$ Hz, NH), 6.72 (1H, q, $J=6$ Hz, CH_3CH), 7.33 (5H, s, C_6H_5), 9.29 (1H, d, $J=2$ Hz, CHO), 9.67 (1H, t, $J=1$ Hz, CHO). MS m/z : 275 (M^+).

Methyl 3-(Benzyloxycarbonyl)amino-4-methoxycarbonyl-2,3,4,6-tetra-deoxy- α -D-arabino-hexopyranoside (16) A PCC Oxidation: A mixture of **13a** (250 mg, 0.78 mmol) and pyridinium chlorochromate (503 mg, 2.34 mmol) in CH_2Cl_2 (2.5 ml) was stirred at room temperature for 24 h. After addition of ether (10 ml), the mixture was stirred at room temperature for 15 min, then the insoluble materials were filtered off and washed with ether. The combined organic layers were concentrated *in vacuo* to give a residue, which was purified by column chromatography (silica gel, benzene:AcOEt=15:1) to afford **16** (78.6 mg, yield 30%) as crystals, mp 128 °C (isopropyl ether), $[\alpha]_D^{20} + 79.6^\circ$ ($c=1.1$, CHCl_3). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3320, 1718, 1680. $^1\text{H-NMR}$ (CDCl_3): 1.17 (3H, d, $J=6$ Hz, $\text{C}_6\text{-CH}_3$), 1.65 (1H, ddd, $J=3, 13, 13$ Hz, $\text{C}_2\text{-H}_a$), 1.93–2.40 (2H, m, $\text{C}_2\text{-H}_e$, $\text{C}_4\text{-H}$), 3.32 (3H, s, OCH_3), 3.60 (3H, s, COOCH_3), 3.8–4.46 (2H, m, $\text{C}_3\text{-H}$ and $\text{C}_5\text{-H}$), 4.75 (1H, d, $J=3$ Hz, $\text{C}_1\text{-H}$), 4.93 (1H, d, $J=10$ Hz, NH), 5.02 (2H, s, OCH_2), 7.30 (5H, s, aromatic protons). $^{13}\text{C-NMR}$ (CDCl_3): 19.5 (q, C_6), 35.7 (t, C_2), 46.4 (d, C_3), 51.9 (q), 54.6 (q), 55.8 (d), 65.1 (d), 66.6 (t, CH_2Ph), 97.9 (d, C_1), 128.0, 128.4, and 136.5 (aromatic carbons), 155.3 (s, NHCO), 172.1 (s, COOCH_3). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.61; H, 6.93; N, 4.39.

B) Wacker Process: A mixture of PdCl_2 (28 mg, 0.155 mmol) and CuCl (154 mg, 1.56 mmol) in DMF (1 ml) and H_2O (0.1 ml) was stirred at room temperature for 1 h under an oxygen atmosphere, then **13a** (100 mg, 0.31 mmol) was added. The mixture was stirred at 70 °C for 19 h, and the insoluble material was removed by filtration using Celite. After addition of H_2O (3 ml) to the filtrate, the mixture was extracted with AcOEt, and the organic extracts were washed with saturated aqueous NaHCO_3 . Drying followed by evaporation gave a residue, which was purified by column chromatography (silica gel, benzene:AcOEt=15:1) to afford **16** (55.6 mg, yield 53%) as crystals, whose spectral data were identical with those of the sample obtained by PCC oxidation.

(3R,4S,5R)-3-(Benzyloxycarbonyl)amino-4-methoxycarbonyl-5-hexano-lide (17a) A mixture of **16** (370 mg, 1.1 mmol), 0.6N aqueous HCl (7 ml), and THF (7 ml) was heated under reflux for 3 h. After cooling to room temperature, the mixture was neutralized with aqueous NaHCO_3 , then extracted with AcOEt ($\times 4$). The combined organic extracts were washed with saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was oxidized with Jones reagent (0.41 ml) in acetone (18.5 ml) at 0 °C for 40 min. After addition of 2-propanol (0.24 ml), the mixture was neutralized with NaHCO_3 , then the organic layer was removed *in vacuo* to give a residue, to which AcOEt (30 ml) and H_2O (5 ml) were added. After removal of the insoluble materials by filtration, the organic layer was separated and washed with saturated aqueous NaCl. Drying followed by evaporation gave a solid, which was recrystallized from benzene-isopropyl ether to give **17a** (228 mg, yield 65%) as colorless needles, mp 118.5–119 °C, $[\alpha]_D^{20} + 2.2^\circ$ ($c=1.2$, CHCl_3). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3365, 1720. $^1\text{H-NMR}$ (CDCl_3): 1.38 (3H, d, $J=6$ Hz, $\text{C}_6\text{-CH}_3$), 2.38–2.79 (2H, m, $\text{C}_3\text{-H}_a$, $\text{C}_5\text{-H}$), 3.0 (1H, dd, $J=7, 15$ Hz, $\text{C}_3\text{-H}_e$), 3.69 (3H, s, COOCH_3), 4.13–4.62 (2H, m, $\text{C}_4\text{-H}$ and $\text{C}_6\text{-H}$), 5.08 (2H, s, OCH_2Ph), 5.22 (1H, d, $J=8$ Hz, NH), 7.33 (5H, s, aromatic protons). $^{13}\text{C-NMR}$ (CDCl_3): 19.6 (q, C_7), 35.4 (t, C_3), 47.3 (d, C_4), 52.4 (d, C_5), 52.8 (q, COOCH_3), 66.8 (t, OCH_2Ph), 74.8 (d, C_6), 127.9, 128.4, and 136.0 (aromatic carbons), 155.3 (s, NHCO), 169.3 (s), 170.8 (s). Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.88; H, 6.01; N, 4.26.

(3S,4R)-3-[(R)-1-Hydroxyethyl]-4-[(benzyloxycarbonyl)methyl]-2-azetidinone (19a) **17a** (195 mg, 0.6 mmol) was catalytically hydrogenated with 5% Pd-C (75 mg) in MeOH (9 ml) for 1 h. After removal of the catalyst, the filtrate was concentrated *in vacuo* to give a residue, to which 3 ml of concentrated HCl was added. The mixture was heated under reflux for 40 min, then the HCl was removed *in vacuo*. After repeated evaporation from benzene, a mixture of the crude hydrochloride of **17b** (126 mg, yield quant.) and benzyl alcohol (0.9 ml) was stirred at 70 °C for 7 h, then allowed to cool to room temperature. Benzyl alcohol (0.9 ml), N,N' -dicyclohexylcarbodiimide (126 mg, 0.6 mmol) and TEA (0.063 ml, 0.62 mmol) were added, and the reaction mixture was stirred at 55 °C for 5.5 h. Then, the precipitate was removed by filtration. The filtrate was subjected to column chromatography (silica gel, benzene:AcOEt=1:3)

to give the β -lactam, **19a** (102 mg, yield 64%) as an oil, $[\alpha]_D^{20} + 9.9^\circ$ ($c=2.3$, CHCl_3), (lit.^{6a}) $[\alpha]_D^{20} + 9.84^\circ$ ($c=2.1$, CHCl_3). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3305, 1755. $^1\text{H-NMR}$ (CDCl_3): 1.27 (3H, d, $J=6.3$ Hz, CH_3), 2.74 (2H, d, $J=6.8$ Hz, CH_2COOBn), 2.86 (1H, dd, $J=2.2, 6.6$ Hz, $\text{C}_3\text{-H}$), 3.09 (1H, brs, OH), 3.94 (1H, dt, $J=2.2, 6.8$ Hz, $\text{C}_4\text{-H}$), 4.14 (1H, dq, $J=6.3, 6.6$ Hz, CH_3CH), 5.13 (2H, s, CH_2Ph), 6.52 (1H, brs, NH), 7.35 (5H, s, aromatic protons). $^{13}\text{C-NMR}$ (CDCl_3): 21.3 (q, CH_3), 39.4 (t, CH_2COO), 47.6 (d, C_4), 64.0 (d, C_3), 65.3 (d, CH_3CH), 66.9 (t, CH_2Ph), 128.4, 129.1, and 135.3 (aromatic carbons), 168.0 (s), 171.2 (s). MS m/z : 263 (M^+).

(3S,4R)-3-[(R)-1-Hydroxyethyl]-4-[3-(p-nitrobenzyloxycarbonyl)-2-oxopropyl]-2-azetidinone (20a) A solution of **19a** (85 mg, 0.325 mmol) in MeOH (2.5 ml) was catalytically hydrogenated using 5% Pd-C (25 mg) at room temperature for 1 h. After removal of the catalyst, the filtrate was concentrated *in vacuo* to afford **19b**, which was dissolved in DMF (0.25 ml) and CH_3CN (1 ml), then N,N' -carbonyldiimidazole (55 mg, 0.34 mmol) was added. After stirring of the mixture at room temperature for 1.5 h, the magnesium salt of *p*-nitrobenzyl hydrogen malonate (97.5 mg, 0.37 mmol) was added, then the whole was stirred at room temperature overnight. After addition of AcOEt (10 ml) and water (5 ml), the mixture was acidified (pH 2) with 2N aqueous HCl, followed by extraction with AcOEt ($\times 5$). The combined organic extracts were washed with saturated aqueous NaCl and saturated aqueous NaHCO_3 . The aqueous washings were back-washed with AcOEt. The combined organic solutions were washed with saturated aqueous NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography to give **20a** (83.8 mg, yield 74%) as crystals, mp 126–127.5 °C (AcOEt), $[\alpha]_D^{20} + 25.7^\circ$ ($c=1.13$, MeOH), (lit.^{6b}) mp 121 °C, $[\alpha]_D^{22} + 21.3^\circ$ ($c=0.31$, CHCl_3). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3420, 3315, 1758, 1727, 1710. $^1\text{H-NMR}$ (CDCl_3): 1.31 (3H, d, $J=6.3$ Hz, CH_3), 2.29 (1H, d, $J=4.1$ Hz, OH), 2.83 (1H, dd, $J=2.3, 7.1$ Hz, $\text{C}_3\text{-H}$), centered at 2.96 (2H, ABX, $J=5.6, 7.7$ Hz, CHCH_2CO), 3.59 (2H, s, COCH_2COO), 3.95 (1H, ABX, $\text{C}_4\text{-H}$), 4.16 (1H, ddq, $J=4.1, 6.3, 7.0$ Hz, CHCH_3), 5.27 (2H, s, COOCH_2), 6.03 (1H, brs, NH), 7.53 (2H, d, $J=9$ Hz, aromatic protons), 8.24 (2H, d, $J=9$ Hz, aromatic protons). High-resolution MS m/z ($(\text{M}+1)^+$): Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_7$: 351.1508. Found: 351.1148.

p-Nitrobenzyl (3R,5R,6S)-6-[(R)-1-Hydroxyethyl]-1-carba-2-oxopenam-3-carboxylate (21) A mixture of **20a** (80 mg, 0.22 mmol), *p*-carboxy-benzenesulfonyl azide (58 mg, 0.25 mmol), and TEA (0.1 ml, 0.72 mmol) in AcOEt (0.8 ml) was stirred at room temperature for 30 min. After addition of H_2O , the precipitate was collected, and washed with H_2O and ether. Drying over P_2O_5 *in vacuo* gave the diazo derivative (**20b**) (63.6 mg, yield 74%) as a pale yellow powder, mp 157–159.5 °C, $[\alpha]_D^{20} + 39.6^\circ$ ($c=0.56$, MeOH), (lit.¹⁷) mp 151–152 °C, $[\alpha]_D^{22} + 21.8^\circ$ ($c=0.23$, CH_3CN). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3390, 2130, 1736, 1708, 1657. $^1\text{H-NMR}$ (CDCl_3): 1.33 (3H, d, $J=6.4$ Hz, CH_3), 2.58 (1H, brs, OH), 2.58 (1H, dd, $J=2.2, 7.6$ Hz, $\text{C}_3\text{-H}$), centered at 3.27 (2H, ABX, $J=6.1, 7.3, 18.1$ Hz, CHCH_2CO), 3.98 (1H, ABX, $\text{C}_4\text{-H}$), 4.18 (1H, dq, $J=6.1, 6.7$ Hz, CHCH_3), 5.36 (2H, s, COOCH_2), 5.96 (1H, brs, NH), 7.54 (2H, d, $J=9$ Hz, aromatic protons), 8.24 (2H, d, $J=9$ Hz, aromatic protons). MS m/z : 330 $[(\text{M}-(\text{N}_2 \text{ and OH}))^+]$. A solution of **20b** (56 mg, 0.15 mmol) and $\text{Rh}_2(\text{OAc})_4$ (3 mg) in benzene (2 ml) was heated under reflux for 3 min, then allowed to cool to room temperature. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give **21** (38.5 mg, yield 74%) as crystals, mp 104–106 °C, $[\alpha]_D^{20} + 155.6^\circ$ ($c=0.46$, CH_3CN), (lit.¹⁸) mp 110–111 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3460, 3400, 1749. $^1\text{H-NMR}$ (CDCl_3): 1.41 (3H, d, $J=6$ Hz, CH_3), 1.78 (1H, d, $J=5$ Hz, OH), 2.46 (1H, dd, $J=8, 19$ Hz, $\text{C}_1\text{-H}_a$), 1.97 (1H, dd, $J=7, 19$ Hz, $\text{C}_1\text{-H}_b$), 3.21 (1H, dd, $J=2.5, 7$ Hz, $\text{C}_6\text{-H}$), 4.17 (1H, ddd, $J=2.5, 7$ Hz, $\text{C}_5\text{-H}$), 4.32 (1H, dq, $J=6, 7$ Hz, CH_3CH), 4.77 (1H, s, $\text{C}_3\text{-H}$), 5.30 (2H, s, COOCH_2), 7.52 (2H, d, $J=8$ Hz, aromatic protons), 8.24 (2H, d, $J=8$ Hz, aromatic protons). High-resolution MS m/z (M^+): Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_7$: 348.0955. Found: 348.0927.

p-Nitrobenzyl (5R,6S)-6-[(R)-1-Hydroxyethyl]-2-[(p-nitrobenzyloxycarbonyl)aminoethylthio]-1-carbapen-2-em-3-carboxylate (22) A solution of N,N -diisopropylethylamine (13 mg, 0.1 mmol) in CH_3CN (0.2 ml) was added to a solution of **21** (30 mg, 0.086 mmol) in CH_3CN (0.75 ml) at -20°C over a period of 2 min, then a solution of diphenyl phosphorochloridate (26 mg, 0.095 mmol) in CH_3CN (0.2 ml) was added at -20°C over a period of 2 min. The mixture was stirred at -20°C for 1.5 h, then *N-p*-nitrobenzyloxycarbonylaminoethanthiol (24.3 mg, 0.095 mmol) was added and stirring was continued at -20°C for 2.5 h. After addition of ether (3 ml), the precipitate was collected and dried *in vacuo* to afford **22** (32.7 mg, yield 65%) as a powder, mp 173.5–175 °C, $[\alpha]_D^{20} + 59.5^\circ$ ($c=0.3$, DMF), (lit.¹⁸) mp 167–169 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} :

3410, 3300, 1775, 1690. $^1\text{H-NMR}$ (CDCl_3): 1.26 (3H, d, $J=6$ Hz, CH_3), 3.08 (2H, m, SCH_2), 3.32 (1H, dd, $J=2, 6$ Hz, $\text{C}_6\text{-H}$), 3.20–3.60 (4H, m, CH_2N , $\text{C}_1\text{-H}_{\text{ab}}$), 4.12 (1H, dq, $J=6, 6.5$ Hz, CH_3CH), 4.27 (1H, ABX, $\text{C}_5\text{-H}$), 5.24 (2H, s, CH_2Ph), 5.30 and 5.55 (2H, AB, $J=13.8$ Hz, CH_2Ph), 6.92 (1H, brs, NH), 7.66, 7.83 and 8.21 ($4\times 2\text{H}$, each d, $J=8.5$ Hz, aromatic protons). MS m/z : 581 ($(\text{M}+1)^+$).

References and Notes

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