

Chiral Syntheses of Dihydroxyamino Acid Moieties of AI-77-B and Calyculins from D-Glucosamine

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Manipulation of *cis* (4*S*,5*S*)-4,5-disubstituted 2-oxazolidinones (4, 5), derived easily from D-glucosamine (1) as a chiral pool, including degradation of the C6-carbon and/or one-carbon homologation at the C1-position allowed chiral syntheses of (2*S*,3*S*)-dihydroxy-(4*S*)-amino acid moieties (6—8), which are important structural components of a gastroprotective substance, AI-77-B, and a group of antitumor substances, calyculins.

Key words D-glucosamine; chiral pool; (2*S*,3*S*,4*S*)-2,3-dihydroxy-4-amino hexanedioic acid; (2*S*,3*S*,4*S*)-2,3-dihydroxy-4-dimethylamino-5-methoxypentanoic acid; synthesis

Unusual amino acids and their congeners, including aminoalcohols, are widely distributed in biologically important molecules and often play important roles in biological activities.²⁾ Much attention has been paid to the development of efficient synthetic methods for those unusual amino acids.³⁾ Amino acids with contiguously

hydroxylated functionalities, such as 1,2-hydroxyamino and 1,2-dihydroxy-3-amino systems, are of special interest, since those amino acids and their derivatives with multiple stereogenic centers are key building blocks in pepstatin⁴⁾ and alipatinin,⁵⁾ which are inhibitors of the aspartic proteases pepsin and renin, and in inhibitors of aspartic

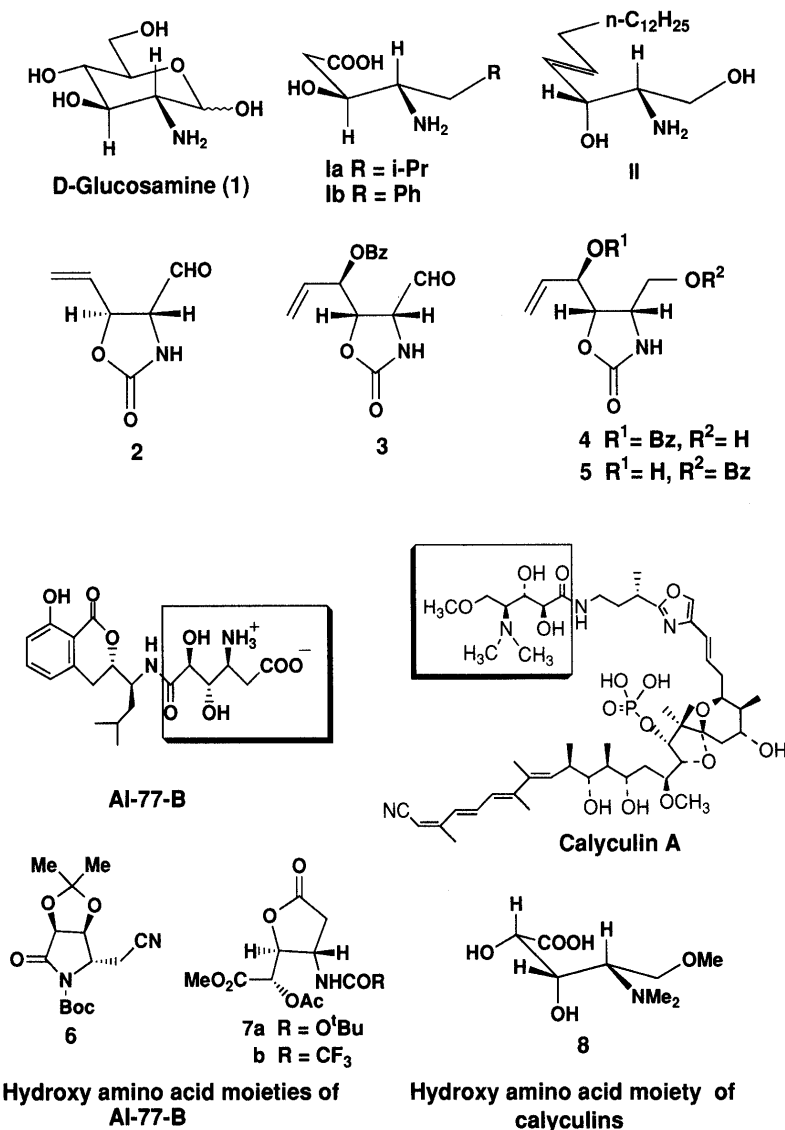


Fig. 1

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proteases of human immunodeficiency virus type-1 (HIV-1),⁶⁾ as well as in ceramides, which constitute the hydrophobic part of glycosphingolipids and sphingophospholipids,⁷⁾ a gastroprotective substance, AI-77-B,⁸⁾ and antitumor substances, calyculins.⁹⁾

We have employed D-glucosamine (**1**), which is a readily available aminosugar and a chiral polyhydroxyamine source,¹⁰⁾ to the chiral synthesis of (3*S*,4*S*)-statine (**1a**) and (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) (**1b**) by way of (4*R*,5*S*)-4-formyl-5-vinyl-2-oxazolidinone (**2**),¹¹⁾ and also to D-erythro-C18-sphingosine (**II**) via protected (4*S*,5*S*)-4-formyl-5-((1*R*)-1-hydroxy-2-propen-1-yl)oxazolidin-2-one (**3**)^{12,13)} (Fig. 1). In our synthetic studies on **II**, we have found a method for selective preparation of mono-protected diols (**4**, **5**) from the aldehyde (**3**).^{12,13)}

An antiulcer substance AI-77-B isolated from the culture broth of *Bacillus pumilus* AI-77 has 3,4-dihydro-8-hydroxyisocoumarin and (2*S*,3*S*,4*S*)-2,3-dihydroxy-4-aminohexanedioic acid moieties.⁸⁾ Calyculins isolated from the marine sponge *Discoderma calyx* exhibit potent inhibitory activities against protein phosphatases 1 and 2A as well as antitumor activities, and contain a (2*S*,3*S*,4*S*)-2,3-dihydroxy-4-dimethylamino-5-methoxypentanoic acid moiety in the structures as a common building block.⁹⁾ Much effort has been devoted to the synthesis of those dihydroxyamino acids utilizing various chiral pools: for the former, D-glutamic acid,^{14a)} L-aspartic acid,^{14b)}

D-glyceric acid,^{14c)} and D-mannose,^{14d)} and for the latter, L-serine,^{15a)} L-glutamic acid,^{15b)} D-isoascorbic acid,^{15c)} and D-gulonolactone.^{15d)}

In this paper we report the synthesis of Shioiri's intermediate (**6**)^{14a)} for AI-77-B and we also present full details of our synthesis of the (2*S*,3*S*)-dihydroxy-(4*S*)-amino acid moiety (**7**), which is recognized to be the synthetic equivalent of the hydroxyamino acid moiety of AI-77-B and the amino acid component (**8**) of calyculins, utilizing oxazolidinone chirons (**4**, **5**) derived from D-glucosamine (**1**).¹²⁾ The syntheses described here involve one-carbon homologation and one-carbon degradation of the partially protected oxazolidinone (**4**), providing the known lactam (**6**)^{14a)} and lactones (**7**), and one-carbon degradation of the other protected oxazolidinone (**5**), yielding the known dihydroxyamino acid (**8**).^{9b)}

Results and Discussion

Synthesis of the γ -Lactam (6**), Shioiri's Intermediate for AI-77-B (Chart 1)** In the total synthesis of AI-77-B, Shioiri and coworkers utilized a γ -lactam (**6**) as an intermediate with full functionalities for the dihydroxyamino acid moiety of AI-77-B.^{14a)} We have achieved transformation of the primary alcohol (**4**) to the γ -lactam (**6**) in seven steps. The primary alcohol (**4**) was obtained by mild reduction of the aldehyde (**3**), which was prepared from D-glucosamine (**1**) by way of C3-stereo-inversion.^{12,13)} The alcohol (**4**) was converted into the nitrile

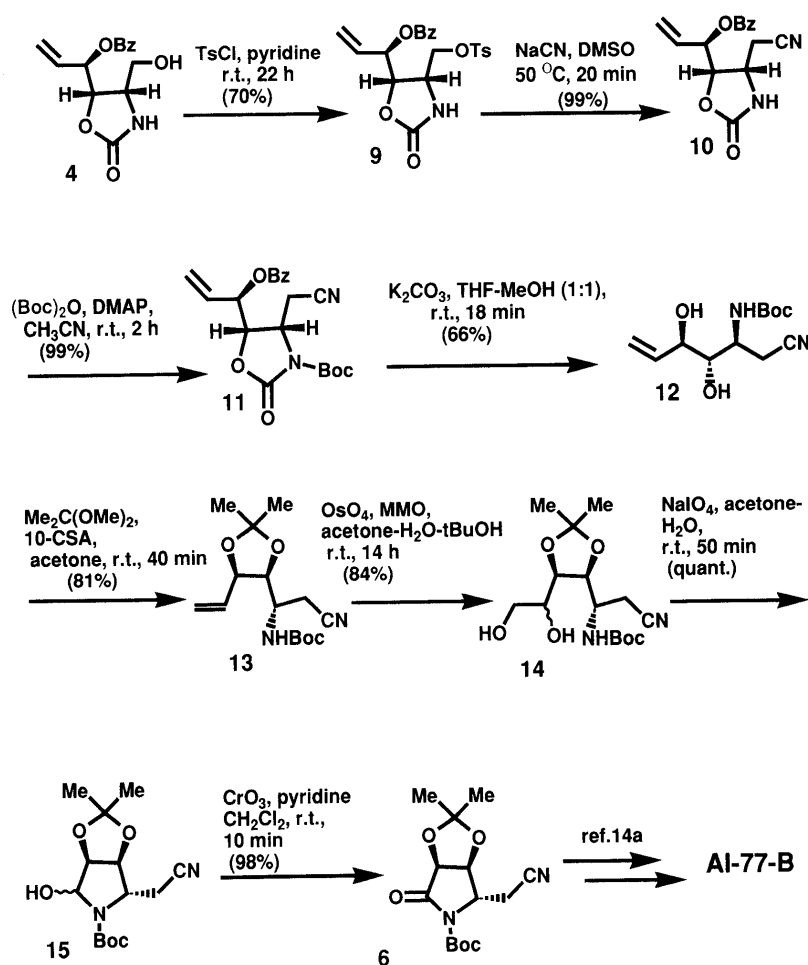


Chart 1

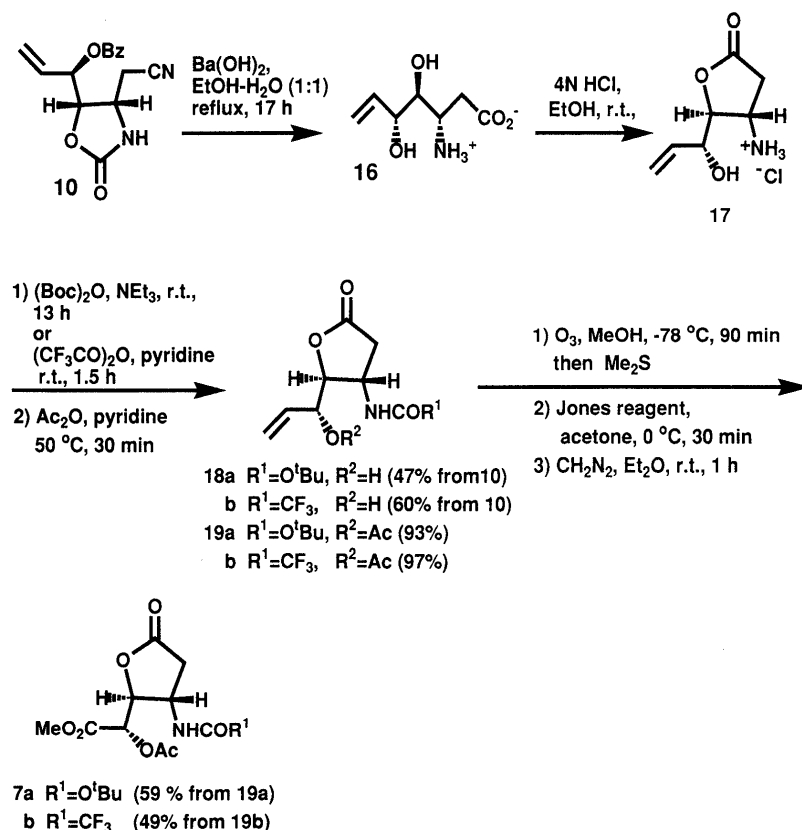


Chart 2

(10) in 69% overall yield *via* the corresponding tosylate (9). Treatment of 10 with (*tert*-BuOCO)₂O [(Boc)₂O] in the presence of dimethylaminopyridine (DMAP) afforded the *N*-Boc derivative (11), which was converted into a diol (12) in 65% overall yield by mild alkaline methanolysis using K₂CO₃. Successive transformation including protection of the vicinal diol functionality of 12 as the acetonide (13), catalytic dihydroxylation of the olefin with OsO₄ in the presence of *N*-methylmorpholine *N*-oxide (MMO), and one-carbon degradation of the glycol (14) with NaIO₄ gave a diastereomeric mixture of cyclic amins (15) in a high overall yield (68%). Finally, Collins oxidation of 15 furnished quantitatively the protected γ -lactam (6), the structure of which was verified by spectral comparison with an authentic sample.^{14a)}

Synthesis of the Dihydroxyamino Acid Moiety (7) of AI-77-B (Chart 2) Treatment of the nitrile (10) with Ba(OH)₂ in aqueous EtOH gave a linear dihydroxyamino acid (16), which, without purification, was converted into the corresponding *N*-protected γ -lactones (18a, b) by usual *tert*-butoxycarbonylation and trifluoroacetylation of the crude γ -lactone (17), derived from 16 by acid treatment, in 47% and 60% overall yields from 10, respectively. After protection of the alcohols to the corresponding acetates (19a, b), one-carbon degradation was carried out through ozonolysis, Jones oxidation, and esterification with CH₂N₂ to provide crystalline γ -lactones (7a, b) in 59% and 49% overall yields from 19a and 19b, respectively. The structures of the esters (7a, b) were characterized by elemental analysis, and IR, ¹H-NMR, and MS analyses.

Synthesis of the Dihydroxyamino Acid (8) for Calyculins (Chart 3) The secondary alcohol (5),^{12,13)} prepared easily from the aldehyde (3) by NaBH₄ reduction involving acyl migration, was treated with methylal¹⁶⁾ to give the *N,O*-dimethoxymethyl (MOM) derivative (20) in 83% yield. Compound 20 was converted into the terminal methylether (22) in a high overall yield (90%) *via* the primary alcohol (21) through debenzoylation and methylation. Treatment of 22 with LiAlH₄ in tetrahydrofuran (THF) directly afforded the 1-hexene derivative (23) with the *N,N*-dimethylamino functionality in 82% yield. After benzylation of 23, one-carbon degradation of the olefin (24) was carried out to afford the functionalized pentanoic acid Na salt (26) in 55% overall yield *via* usual procedures including catalytic dihydroxylation using OsO₄, oxidation with NaIO₄, and Jones oxidation through the terminal glycol (25). The structure of 26 was established by spectral analysis and also by characterization of the derived methyl ester (27). Final deprotection of vicinal diol function of 26 was achieved by successive treatments with 4N HCl and 28% aqueous NH₃, followed by purification using ion-exchange resin Amberlite IR-120B to give the crystalline carboxylic acid (8), whose structure was verified by ¹H-NMR spectral comparison with the corresponding authentic enantiomer (+)-(8), synthesized by Shioiri *et al.*^{15b)}

In addition to our recent synthesis of *D*-erythro-C18-sphingosine (II) starting with *D*-glucosamine (1),¹²⁾ the present work has led to the functionalized oxazolidinones (4, 5) as useful chiral auxiliaries for unusual and biologically important dihydroxyamino acids and their congeners.

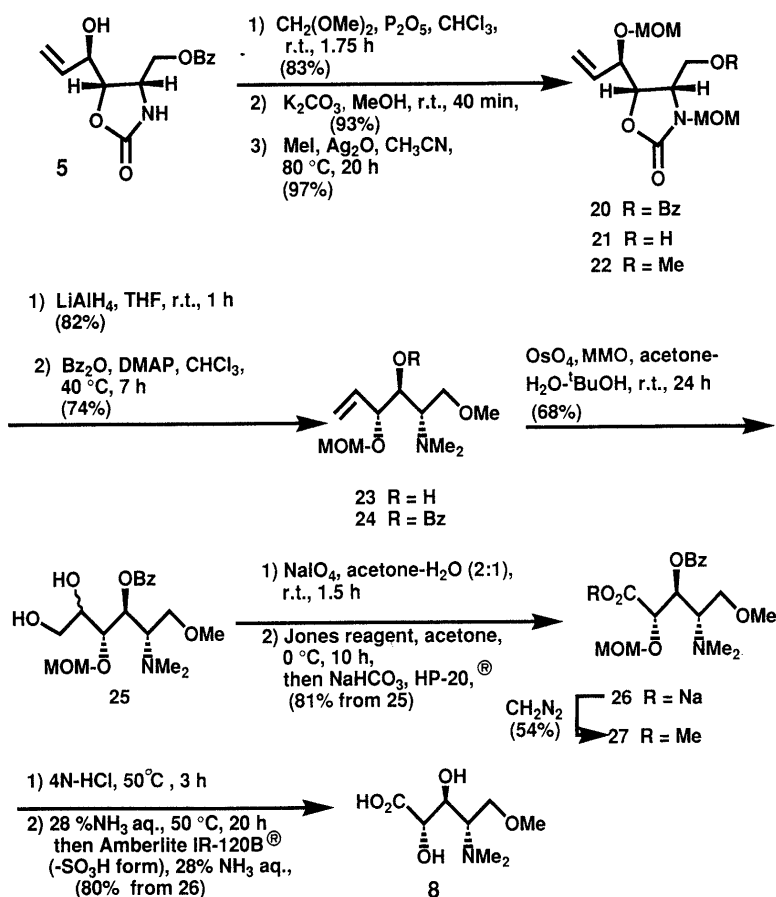


Chart 3

Experimental

All melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined in CHCl_3 solutions at 20°C by using a JASCO-DIP-360 digital polarimeter. IR absorption spectra were recorded on a JASCO-IRA-1, JASCO-IRA-100, or Shimadzu FTIR-8100 spectrometer in CHCl_3 solutions and are indicated in ν (cm^{-1}). ^1H -NMR spectra were taken on a JEOL-GX-270 (270 MHz), JEOL-GSX-270 (270 MHz), or JEOL-EX-400 (400 MHz) instrument in CDCl_3 with SiMe_4 as an internal standard. Chemical shifts are indicated in δ and coupling constants (J) in hertz (Hz) (s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; br: broad). Mass spectra (MS) and high-resolution MS (HR-MS) were recorded on a JEOL JMS-D-300, JMS-DX-300, or JMS-SX-102A spectrometer and peaks are indicated as m/z . Reactions were carried out under an argon atmosphere using distilled anhydrous solvents: THF and Et_2O were distilled from sodium/benzophenone; toluene, MeOH, and EtOH from sodium; pyridine, N,N -dimethylformamide (DMF), CH_3CN , CHCl_3 , CH_2Cl_2 from CaH_2 ; and acetone from K_2CO_3 . After extraction of the products with an appropriate solvent, drying over anhydrous MgSO_4 , and evaporation of the solvent *in vacuo*, products were purified by column chromatography on silica gel (Merck, Kieselgel 60, 70–230 mesh or 230–400 mesh) or alumina (Nacalai Tesque, Alumina Activated 300, 300 mesh), unless otherwise noted.

(4S,5S)-5-[(1R)-1-Benzoyloxy-2-propen-1-yl]-4-(*p*-toluenesulfonyl-methyl-2-oxazolidinone) (9) A solution of the alcohol 4 (28.4 mg, 0.1 mmol), p -toluenesulfonyl chloride (29.9 mg, 0.15 mmol), pyridine (0.2 ml) and CH_2Cl_2 (0.2 ml) was stirred for 22 h at room temperature. The reaction mixture was diluted with AcOEt, washed with 1 N HCl, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (AcOEt–hexane (1:1)) followed by recrystallization from hexane–AcOEt to afford the tosylate (9) (31.0 mg, 70%) as a colorless solid. mp 149°C . $[\alpha]_D^{20} -11.4^\circ$ ($c=0.38$, CHCl_3). Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_7\text{S}$: C, 58.46; H, 4.91; N, 3.25. Found: C, 58.39; H, 5.01; N, 3.29. IR (KBr): 3400, 1780, 1770 cm^{-1} . MS (EI): 432 ($M+1$)⁺, 431 (M)⁺, 105 (base). ^1H -NMR: 2.42 (3H, s, CH_3), 4.09–4.16 (1H, m, CH_2OTs), 4.22–4.29 (2H, m, CH_2OTs , 4-H), 4.85 (1H, dd, $J=7.8$, 6.8, 5-H), 5.38–5.46 (3H, m, NH, $\text{CH}_2=\text{CH}$), 5.72

(1H, t, $J=5.9$, CHOBz), 5.92 (1H, ddd, $J=17.5$, 10.3, 5.9, $\text{CH}_2=\text{CH}$), 7.28 (2H, d, arom-H), 7.46–7.52 (2H, m, arom-H), 7.61–7.65 (2H, m, arom-H), 7.69 (2H, d, $J=8.3$, arom-H), 7.98 (2H, dd, $J=8.3$, 1.5, arom-H).

(4S,5S)-5-[(1R)-1-Benzoyloxy-2-propen-1-yl]-4-cyanomethyl-2-oxazolidinone (10) A solution of the tosylate (9) (699 mg, 1.62 mmol) and NaCN (103 mg, 2.11 mmol) in dimethyl sulfoxide (DMSO, 7 ml) was stirred for 20 min at 50°C under an argon atmosphere. The reaction mixture was poured into brine (80 ml) and extracted with AcOEt. The combined extracts were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (AcOEt–hexane (2:1)) to give the nitrile (10) (462 mg, quant.) as an amorphous solid. $[\alpha]_D^{20} -18.4^\circ$ ($c=0.98$, CHCl_3). IR (CHCl_3): 2130, $1710\text{--}1785\text{ cm}^{-1}$. MS (EI): 286 (M)⁺, 105 (base); HR-MS (EI) Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4$ (M)⁺: 286.0953; Found: 286.0936. ^1H -NMR: 2.66–2.83 (2H, m, CH_2CN), 4.23–4.31 (1H, m, 4-H), 4.89 (1H, dd, $J=7.3$, 7.3, 5-H), 5.47 (1H, d, $J=10.3$, $\text{CH}_2=\text{CH}$), 5.53 (1H, d, $J=17.6$, $\text{CH}_2=\text{CH}$), 5.48 (1H, d, $J=17.1$, $\text{CH}_2=\text{CH}$), 5.69 (1H, brs, NH), 5.77 (1H, dd, $J=7.3$, 5.9, CHOBz), 6.00 (1H, ddd, $J=17.6$, 10.3, 5.9, $\text{CH}_2=\text{CH}$), 7.46–7.52 (2H, m, arom-H), 7.61–7.67 (1H, m, arom-H), 8.02 (1H, d, $J=6.8$, arom-H).

(4S,5S)-5-[(1R)-1-Benzoyloxy-2-propen-1-yl]-3-*tert*-butoxycarbonyl-4-cyanomethyl-2-oxazolidinone (11) A solution of the oxazolidinone (10) (299 mg, 1.05 mmol), (Boc) $_2\text{O}$ (263 mg, 1.20 mmol), and DMAP (6 mg, 0.05 mmol) in CH_3CN (4.0 ml) was stirred for 2 h at room temperature. The reaction mixture was diluted with AcOEt (40 ml) and washed with 0.002 N HCl (40 ml). The aqueous layer was extracted with AcOEt. The combined extracts were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane (1:1)) to afford the *N*-Boc-oxazolidinone (11) (401 mg, 99%) as a colorless amorphous powder. $[\alpha]_D^{20} +53.0^\circ$ ($c=0.78$, CHCl_3). Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_6$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.39; H, 6.00; N, 7.05. IR (KBr): 2240, 1815, 1720 cm^{-1} . MS (EI): 386 (M)⁺, 105 (base). HR-MS (EI) Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_6$ (M)⁺: 386.1476; Found: 386.1470. ^1H -NMR: 1.57 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.77 (1H, dd, $J=17.6$, 3.9, CH_2CN), 3.05 (1H, dd, $J=17.6$, 5.9, CH_2CN), 4.60–4.68 (1H, m, 4-H), 4.77 (1H, dd, $J=7.3$,

8.3, 5-H), 5.50 (1H, d, $J=10.3$, $\text{CH}_2=\text{CH}$), 5.61 (1H, d, $J=19.1$, $\text{CH}_2=\text{CH}$), 5.88 (1H, dd, $J=7.3$, 5.9, CH_2OBz), 6.04 (1H, ddd, $J=17.1$, 10.3, 5.9, $\text{CH}_2=\text{CH}$), 7.42–7.55 (2H, m, arom-H), 7.60–7.70 (1H, m, arom-H), 8.04 (2H, d, $J=6.8$, arom-H).

(3S,4S,5R)-3-tert-Butoxycarbonylamino-4,5-dihydroxy-6-heptenenitrile (12) To a solution of the *N*-Boc-oxazolidinone (**11**) (119.1 mg, 0.308 mmol) in THF (1.5 ml)–MeOH (1.5 ml) was added K_2CO_3 (powder, 16.6 mg, 0.120 mmol). The mixture was stirred for 18 min at room temperature, poured into brine (15 ml) and extracted with AcOEt. The combined extracts were dried over MgSO_4 , concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane (1:1)) and recrystallization from hexane–AcOEt to afford the diol (**12**) (52.2 mg, 66%) as colorless needles. mp 135–136 °C. $[\alpha]_D^{20} + 36.3^\circ$ ($c=0.64$, CHCl_3). Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_4$: C, 56.23; H, 7.87; N, 10.93. Found: C, 56.45; H, 7.66; N, 10.70. IR (KBr): 3500, 3350, 2260, 1690 cm^{-1} . MS (EI): 256 (M^+), 57 (base). $^1\text{H-NMR}$: 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.26 (1H, d, $J=4.4$, OH), 2.70–2.98 (3H, m, OH, 2- H_2), 3.72–3.82 (1H, m, 4-H), 3.88–4.00 (1H, m, 3-H), 4.25–4.35 (1H, m, 5-H), 5.08 (1H, d, $J=7.8$, NH), 5.32 (1H, d, $J=10.7$, $\text{CH}_2=\text{CH}$), 5.40 (1H, d, $J=17.1$, $\text{CH}_2=\text{CH}$), 5.93 (1H, ddd, $J=17.1$, 10.7, 5.8, $\text{CH}_2=\text{CH}$).

(3S,4S,5R)-3-tert-Butoxycarbonylamino-4,5-isopropylidenedioxy-6-heptenenitrile (13) Dimethoxypropane (250 μl) and 10-camphorsulfonic acid (10-CSA) (9.5 mg, 0.041 mmol) were added to a solution of the diol (**12**) (52.4 mg, 0.205 mmol) in acetone (0.95 ml). The mixture was stirred for 40 min at room temperature, then poured into 5% aqueous solution of NaHCO_3 (2 ml)–brine (7 ml) and extracted with AcOEt. The combined extracts were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2 –AcOEt–hexane (2:2:1)) and recrystallization from hexane–AcOEt to afford the acetonide (**13**) (49.4 mg, 81%) as colorless needles. mp 180–181 °C. $[\alpha]_D^{20} + 16.3^\circ$ ($c=0.47$, CHCl_3). IR (KBr): 3360, 2250, 1690, 1535 cm^{-1} . MS (EI): 295 ($\text{M}-1$) $^+$, 251 ($\text{M}-45$) $^+$, 57 (base). $^1\text{H-NMR}$: 1.38 (3H, s, CH_3), 1.43 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.49 (3H, s, CH_3), 2.68–2.84 (2H, m, 2- H_2), 3.80–3.95 (1H, m, 3-H), 4.15–4.20 (1H, m, 4-H), 4.60–4.75 (2H, m, 5-H, NH), 5.29 (1H, d, $J=10.3$, $\text{CH}_2=\text{CH}$), 5.41 (1H, d, $J=17.1$, $\text{CH}_2=\text{CH}$), 5.84 (1H, ddd, $J=17.1$, 10.3, 6.9, $\text{CH}_2=\text{CH}$).

Epimeric Mixture of (3S,4S,5R)-3-tert-Butoxycarbonylamino-6,7-dihydroxy-4,5-isopropylidenedioxyheptanenitrile (14) MMO (50% aqueous solution, 34.58 mg, 0.148 mmol) and OsO_4 (5% (w/v) solution in *tert*-BuOH, 0.33 ml, 0.006 mmol) were added to a solution of the acetonide (**13**) (38.29 mg, 0.129 mmol) in acetone (0.5 ml)– H_2O (0.2 ml). The mixture was stirred for 14 h at room temperature under an argon atmosphere. After addition of NaHSO_3 (11.18 mg, 0.107 mmol), the whole was stirred for an additional 40 min to obtain a heterogeneous mixture. This was diluted with acetone (10 ml) and the resultant precipitate was removed by filtration through Celite. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt) to afford a mixture of epimers of the diol (**14**) (36.01 mg, 84%) as a colorless powder. The $^1\text{H-NMR}$ spectrum revealed that **14** was composed of epimers in a ratio of 5.5:1. Anal. Calcd for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_6$: C, 54.53; H, 7.93; N, 8.48. Found: C, 56.40; H, 7.93; N, 8.36. IR (KBr): 3360, 2250, 1675 cm^{-1} . MS (EI): 275 ($\text{M}-55$) $^+$, 259 ($\text{M}-71$) $^+$, 59 (base). $^1\text{H-NMR}$: 1.35, 1.37, 1.40, 1.50 (6H, 4 $\times$ s, 2 $\times$ CH_3), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.88 (2H, d, 2- H_2), 2.99 (1H, br s, OH), 3.60–3.93 (3H, m, 6-H, 7- H_2 , 3.94–4.08 (1H, m, 3-H), 4.08–4.17 (1H, m, 5-H), 4.20–4.30 (1H, m, 4-H), 5.29 (1H, d, $J=7.8$, NH).

Epimeric Mixture of (3S,4S,5S)-N-(tert-Butoxycarbonyl)-5-cyano-methyl-3,4-isopropylidenedioxy-2-hydroxypyrrolidine (15) A solution of NaIO_4 (8.74 mg, 0.041 mmol) in H_2O (40 ml) was added to a solution of the epimeric mixture of glycol (**14**) (10.31 mg, 0.031 mmol) in acetone (80 ml). The mixture was stirred for 50 min at room temperature, diluted with AcOEt (2 ml), and washed with brine (1 ml). The aqueous layer was extracted with AcOEt. The combined extracts were dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt) to afford an epimeric mixture of pyrrolidine (**15**) (9.23 mg, quant.) as a colorless oil. The $^1\text{H-NMR}$ spectrum revealed that **15** was composed of epimers in a ratio of 1:1. IR (CHCl_3): 2250, 1700 cm^{-1} . MS (EI): 283 ($\text{M}-15$) $^+$, 42 (base). HR-MS (EI) Calcd for $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_5$ ($\text{M}-\text{CH}_3$) $^+$: 283.1296; Found: 283.1279. $^1\text{H-NMR}$: 1.41 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.51 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.58–2.92 (2H, m, CH_2CN), 3.23–3.45 (1H, m, OH), 4.15–4.30 (1H, m, 5-H), 4.60–4.90 (2H, m, 3-H, 4-H), 5.35–5.58 (1H, m, 2-H).

(3S,4S,5S)-N-(tert-Butoxycarbonyl)-3,4-isopropylidenedioxy-5-cyano-methylpyrrolidin-2-one (6) Pyridine (20 μl) was dissolved in CH_2Cl_2 (0.2 ml), and CrO_3 (13.54 mg, 0.136 mmol) was added under an argon atmosphere. The mixture was stirred for 10 min, then a solution of **15** (9.23 mg, 0.0312 mmol) in CH_2Cl_2 was added dropwise, and Ac_2O (13 μl , 0.13 mmol) was added. The reaction mixture was stirred for an additional 1 h, then chromatographed on silica gel (AcOEt–hexane (1:1)) to afford the lactam (**6**) (9.09 mg, 98%) as a colorless oil. $[\alpha]_D^{20} + 105.4^\circ$ ($c=0.45$, CHCl_3). IR (CHCl_3): 2250, 1800, 1770, 1720, 1310, 1150 cm^{-1} . MS (EI): 296 (M^+), 281 ($\text{M}-15$) $^+$, 44 (base). HR-MS (EI) Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_5$ (M^+): 296.1372; Found: 296.1414. $^1\text{H-NMR}$: 1.40 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.57 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.85 (1H, dd, $J=17.1$, 3.4, CH_2CN), 3.01 (1H, dd, $J=17.1$, 5.9, CH_2CN), 4.39 (1H, dd, $J=5.9$, 3.4, 5-H), 4.56 (1H, d, $J=5.9$, 4-H), 4.90 (1H, d, $J=5.9$, 3-H).

(3S,4S,5R)-3-Amino-4,5-dihydroxy-6-heptenoic Acid (16) Saturated $\text{Ba}(\text{OH})_2$ aqueous solution was added to a solution of the nitrile (**10**) (408 mg, 1.43 mmol) in EtOH (40 ml), and the mixture was heated under reflux for 17 h under an argon atmosphere. After cooling of the reaction mixture, CO_2 gas was bubbled into it. The resulting solution was heterogeneous. The precipitate thus obtained was removed through Celite, and rinsed with EtOH. The combined filtrates were concentrated *in vacuo* to afford a mixture of the amino acid (**16**) and benzoic acid (450 mg) as a solid. The mixture was used in the next step without further purification. IR (KBr): 3300, 2600 cm^{-1} . $^1\text{H-NMR}$ (CD_3OD): 2.49 (1H, dd, $J=17.0$, 10.4, 2- H_2), 2.63 (1H, dd, $J=17.0$, 3.4, 2- H_2), 3.50–3.82 (2H, m, 3-H, 4-H), 3.92–3.98 (1H, m, 5-H), 5.22 (1H, d, $J=10.7$, $\text{CH}_2=\text{CH}$), 5.35 (1H, d, $J=17.1$, $\text{CH}_2=\text{CH}$), 5.99 (1H, ddd, $J=17.1$, 10.7, 5.9, $\text{CH}_2=\text{CH}$), 7.30–7.50 (3H, m, arom-H), 7.97 (2H, d, $J=6.8$, arom-H).

(3S,4S)-3-Amino-4-[(1R)-1-hydroxy-2-propen-1-yl]-4-butanolide HCl Salt (17) The crude amino acid (**16**) was dissolved in EtOH, and a small amount of 4N HCl was added. The resulting solution was stirred at room temperature, concentrated *in vacuo*, and then dried over P_2O_5 under reduced pressure for 8 h to give a mixture of the butanolide HCl salt (**17**) and benzoic acid as a colorless solid. The mixture was used in the next step without further purification. IR (KBr): 1780 cm^{-1} ; $^1\text{H-NMR}$ (CD_3OD): 2.55 (1H, dd, $J=18.6$, 2.4, 2- H_2), 3.14 (1H, dd, $J=18.6$, 8.8, 2- H_2), 4.00–4.08 (1H, m, 3-H), 4.40–4.45 (1H, m, $\text{CH}(\text{OH})$), 4.54 (1H, dd, $J=3.4$, 2.0, 4-H), 5.37 (1H, d, $J=10.7$, $\text{CH}_2=\text{CH}$), 5.55 (1H, d, $J=17.1$, $\text{CH}_2=\text{CH}$), 5.97 (1H, ddd, $J=17.1$, 10.8, 4.4, $\text{CH}_2=\text{CH}$), 7.40–7.50 (2H, m, arom-H), 7.50–7.60 (1H, m, arom-H), 7.97 (2H, d, $J=7.3$, arom-H).

(3S,4S)-3-tert-Butoxycarbonylamino-4-[(1R)-1-hydroxy-2-propen-1-yl]-4-butanolide (18a) A suspension of the crude 3-amino-4-butanolide HCl salt (**17**) (30.1 mg) was prepared from **10** (28.7 mg, 0.1 mmol), then $(\text{Boc})_2\text{O}$ (34.9 mg, 0.16 mmol) and NEt_3 (56 μl , 0.4 mmol) were added to it. The mixture was stirred for 13 h at room temperature, diluted with AcOEt, washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane– CH_2Cl_2 (1:2:2)) followed by recrystallization from hexane–AcOEt to afford the *N*-Boc-3-aminobutanolide (**18a**) (12.2 mg, 47% from **10**) as colorless crystals. mp 86–88 °C. $[\alpha]_D^{20} + 3.5^\circ$ ($c=0.23$, CHCl_3). Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.24; H, 7.31; N, 5.45. MS (FAB): 280 ($\text{M}+\text{Na}$) $^+$, 258 ($\text{M}+\text{H}$) $^+$, 202 ($(\text{M}+\text{H}-\text{CH}_2=\text{C}(\text{CH}_3)_2$) $^+$, base). HR-MS (FAB) Calcd for $\text{C}_8\text{H}_{12}\text{NO}_5$ ($\text{M}+\text{H}-\text{CH}_2=\text{C}(\text{CH}_3)_2$) $^+$: 202.0715; Found: 202.0749. IR (KBr): 3445, 3320, 1770, 1695, 1560 cm^{-1} . MS (EI): 201 ($\text{M}-56$) $^+$, 200 ($\text{M}-57$) $^+$, 57 (base). $^1\text{H-NMR}$ (CD_3OD): 1.44 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.47 (1H, dd, $J=18.1$, 4.4, 2- H_2), 3.01 (1H, dd, $J=18.1$, 8.4, 2- H_2), 4.32–4.35 (2H, m, 3-H, 4-H), 4.41–4.46 (1H, m, $\text{CH}(\text{OH})$), 5.35 (1H, dd, $J=10.7$, 2.9, $\text{CH}_2=\text{CH}$), 5.48 (1H, dd, $J=17.1$, 2.9, $\text{CH}_2=\text{CH}$), 5.93 (1H, ddd, $J=17.1$, 10.7, 6.4, $\text{CH}_2=\text{CH}$).

(3S,4S)-4-[(1R)-1-Hydroxy-2-propen-1-yl]-3-trifluoroacetyl-amino-4-butanolide (18b) A solution of trifluoroacetic anhydride (558 mg, 2.66 mmol) in CH_2Cl_2 (1 ml) was added to a stirred mixture of the crude product **17** (127 mg), which had been prepared from **10** (126 mg, 0.44 mmol), and pyridine (218 mg, 2.66 mmol) in CH_2Cl_2 (2.0 ml) on an ice bath. After the addition, the ice bath was removed, and the mixture was stirred for an additional 3 h at room temperature. It was diluted with AcOEt, washed with 1N HCl and brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was dissolved in MeOH, and a few drops of triethylamine were added to the solution. The reaction mixture was allowed to stand for 11 h at room temperature and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography

(AcOEt–hexane (1 : 1)) followed by recrystallization from hexane–AcOEt to afford the trifluoroacetamide (**18b**) (67 mg, 66% from the nitrile (**10**)) as a colorless solid. mp 130–131 °C. $[\alpha]_D^{20} + 1.8^\circ$ ($c=0.93$, CHCl₃). Anal. Calcd for C₉H₁₀F₃NO₄: C, 42.69; H, 3.98; N, 5.53. Found: C, 42.41; H, 3.95; N, 5.50. IR (KBr): 3510, 3400, 1765, 1700, 1550 cm⁻¹. MS (EI): 254 (M + 1)⁺, 83 (base). ¹H-NMR (CDCl₃ and small amount of CD₃OD): 2.51 (1H, dd, $J=18.6$, 3.4, 2-H₂), 3.09 (1H, dd, $J=18.6$, 9.3, 2-H₂), 4.40–4.52 (2H, m, 4-H, CH(OH)), 4.62–4.72 (1H, m, 3-H), 5.37 (1H, d, $J=10.3$, CH₂=CH), 5.51 (1H, d, $J=17.1$, CH₂=CH), 5.91 (1H, ddd, $J=17.1$, 10.3, 4.9, CH₂=CH).

(3S,4S)-4-[(1R)-1-Acetoxy-2-propen-1-yl]-3-tert-butoxycarbonylamino-4-butanolide (19a) A stirred mixture of the butanolide (**18a**) (10.6 mg, 0.041 mmol), acetic anhydride (83.7 mg, 0.82 mmol) and pyridine (64.8 mg, 0.82 mmol) was heated at 50 °C for 0.5 h, then diluted with AcOEt. The resulting solution was washed with 1 N HCl and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane (2 : 3)) followed by recrystallization from hexane–AcOEt to afford the acetate (**19a**) (11.5 mg, 93%) as colorless needles. mp 120–123 °C. $[\alpha]_D^{20} + 7.7^\circ$ ($c=0.27$, CHCl₃). IR (KBr): 3480, 1780, 1750, 1680, 1530 cm⁻¹. MS (FAB): 322 (M + Na)⁺, 300 (M + H)⁺, 244 (M + H – CH₂=C(CH₃)₂)⁺, 184 (base). HR-MS (FAB) Calcd for C₁₀H₁₄NO₆ (M + H – CH₂=C(CH₃)₂)⁺: 244.0821; Found: 244.0793. ¹H-NMR: 1.45 (6H, s, C(CH₃)₃), 2.10 (3H, s, COCH₃), 2.45 (1H, dd, $J=18.1$, 4.9, 2-H₂), 2.95 (1H, dd, $J=18.1$, 8.7, 2-H₂), 4.30–4.43 (1H, m, 3-H), 4.46 (1H, t, $J=3.7$, 4-H), 4.90 (1H, d, $J=7.3$, NH), 5.42 (1H, d, $J=10.7$, CH₂=CH), 5.46 (1H, d, $J=18.1$, CH₂=CH), 5.50–5.53 (1H, m, CH₂OAc), 5.85 (1H, ddd, $J=18.1$, 10.8, 6.3, CH₂=CH).

(3S,4S)-4-[(1R)-1-Acetoxy-2-propen-1-yl]-3-trifluoroacetylaminobutanolide (19b) The same procedure as for **18a**, but using the trifluoroacetamide (**18b**) (18.4 mg, 0.073 mmol), Ac₂O (155.2 mg, 1.52 mmol), and pyridine (117.5 mg, 1.487 mmol) in CH₂Cl₂ (0.5 ml), afforded the acetate **19b** (20.9 mg, 97%) as a colorless solid. mp 106–109 °C. $[\alpha]_D^{20} - 8.6^\circ$ ($c=1.06$, CHCl₃). Anal. Calcd for C₁₁H₁₂F₃NO₅: C, 44.75; H, 4.10; N, 4.75. Found: C, 44.24; H, 4.13; N, 4.67. IR (KBr): 3320, 1790, 1755, 1705 cm⁻¹. MS (EI): 296 (M + 1)⁺, 253 (M – 42)⁺, 239 (M – 56)⁺, 43 (base). ¹H-NMR: 2.08 (3H, s, COCH₃), 2.55 (1H, dd, $J=18.6$, 3.9, 2-H₂), 3.06 (1H, dd, $J=18.6$, 9.3, 2-H₂), 4.55 (1H, dd, $J=3.4$, 2.9, 4-H), 4.70–4.78 (1H, m, 3-H), 5.44–5.55 (3H, m, CH₂=CH, CH₂OAc), 5.85 (1H, ddd, $J=17.1$, 10.8, 6.4, CH₂=CH), 7.79 (1H, d, $J=7.3$, NH).

(R)-Methyl 2-Acetoxy-2-[(3S,4S)-3-tert-butoxycarbonylamino-4-butanolide-4-yl]acetate (7a) The acetate **19a** (46 mg, 0.15 mmol) was dissolved in MeOH (4.0 ml). This solution was cooled to –78 °C with stirring, and O₃ was bubbled into it. Nitrogen was passed through the solution to remove the excess O₃, then Me₂S (0.8 ml) was added and the solution was allowed to warm to room temperature. The reaction mixture was concentrated *in vacuo* to afford a residue, which was dissolved in acetone (4.0 ml). This solution was cooled on an ice bath, and Jones reagent (240 mg, 0.2 mmol) was added with stirring. The excess Jones reagent was quenched with 2-propanol. The resulting solution was heterogeneous. The insoluble solid was removed by filtration through Celite, and rinsed with acetone. The combined filtrates were concentrated *in vacuo*. The residue was dissolved in ether, and the resulting solution was treated with CH₂N₂ in ether. The mixture was left standing for 1 h at room temperature, then the excess CH₂N₂ was quenched with AcOH. The whole was concentrated *in vacuo*. The residue was purified by alumina column chromatography (AcOEt) followed by recrystallization from hexane–AcOEt to afford the ester (**7a**) (30 mg, 59%) as a colorless solid. mp 136–138 °C. $[\alpha]_D^{20} - 15^\circ$ ($c=0.1$, CHCl₃). IR (KBr): 3350, 1795, 1760, 1750, 1685 cm⁻¹. MS (FAB): 354 (M + Na)⁺, 332 (M + H)⁺, 276 ((M + H – CH₂=C(CH₃)₂)⁺, base). HR-MS (FAB) Calcd for C₁₀H₁₄NO₈ (M + H – CH₂=C(CH₃)₂)⁺: 276.0719; Found: 276.0760. ¹H-NMR: 1.43 (6H, s, C(CH₃)₃), 2.17 (3H, s, COCH₃), 2.50 (1H, dd, $J=18.6$, 3.9, 2-H₂), 3.02 (1H, dd, $J=18.6$, 8.8, 2-H₂), 3.83 (3H, s, COOCH₃), 4.35–4.47 (1H, m, 3-H), 4.75–4.87 (2H, m, 4-H, NH), 5.38 (1H, d, $J=2.4$, CHOAc).

(R)-Methyl 2-Acetoxy-2-[(3S,4S)-3-trifluoroacetylaminobutanolide-4-yl]acetate (7b) The same procedure as used for **19a**, but with the acetate (**19b**) (29.4 mg, 0.1 mmol), afforded the ester **7b** (14 mg, 43%) as a colorless solid. mp 165–168 °C. $[\alpha]_D^{20} - 74.7^\circ$ ($c=0.35$, CHCl₃). Anal. Calcd for C₁₁H₁₂F₃NO₇: C, 40.37; H, 3.70; N, 4.28. Found: C, 40.45; H, 3.86; N, 4.25. IR (KBr): 3320, 1795, 1755, 1740, 1705, 1555, 1065 cm⁻¹. MS (EI): 328 (M + 1)⁺, 239 (M – 88)⁺, 43 (base). ¹H-NMR (CD₃OD):

2.18 (3H, s, OCOCH₃), 2.60 (1H, dd, $J=18.6$, 3.4, 2-H₂), 3.18 (1H, dd, $J=18.6$, 9.3, 2-H₂), 3.85 (3H, s, CO₂CH₃), 4.68–4.75 (1H, m, 3-H), 4.88 (1H, dd, $J=2.9$, 4-H), 5.41 (1H, d, $J=2.9$, CH₂OAc), 7.20 (1H, d, $J=5.68$, NH).

(4S,5S)-4-Benzoyloxymethyl-3-methoxymethyl-5-[(1R)-1-methoxymethoxy-2-propen-1-yl]-2-oxazolidinone (20) A solution of the primary benzoate (**5**)^{12,13} (287 mg, 1.035 mmol) and dimethoxymethane (3.5 ml) in CHCl₃ (4 ml) was added to P₂O₅ (1.59 g, 11.27 mmol). The mixture was stirred for 2 h at room temperature, then diluted with CHCl₃ (30 ml), and the organic layer was neutralized with a cold aqueous solution (*ca.* 50 ml) of NaHCO₃ (6.31 g, 75.1 mmol) on an ice bath. The organic layer was washed with brine (20 ml), dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane (1 : 1)) to afford the di-MOM-protected oxazolidinone (**20**) (314 mg, 83%) as a colorless oil. $[\alpha]_D^{20} - 36.8^\circ$ ($c=1.16$, CHCl₃). IR (CHCl₃): 1765, 1725 cm⁻¹. MS (EI): 365 (M)⁺, 350 (M – 15)⁺, 320 (M – 45)⁺, 45 (base). HR-MS (EI) Calcd for C₁₇H₂₀NO₇ (M – 15)⁺: 350.1240; Found: 350.12640. ¹H-NMR: 3.32 (3H, s, OCH₃), 3.38 (3H, s, OCH₃), 4.23–4.31 (1H, m, 4-H), 4.45–4.65 (3H, m, CH₂OBz, CH₂=CHCH₂ (OMOM), 5-H), 4.72 (1H, d, $J=10.4$, NCH₂OCH₃), 4.74 (1H, d, $J=10.4$, NCH₂OCH₃), 4.80–4.86 (4H, m, CH₂OBz, OCH₂OCH₃), 5.42 (1H, d, $J=17.6$, CH₂=CH), 5.45 (1H, d, $J=10.3$, CH₂=CH), 5.86 (1H, ddd, $J=17.6$, 10.3, 6.8, CH₂=CH), 7.40–7.50 (2H, m, arom-H), 7.52–7.65 (1H, m, arom-H), 8.01 (2H, d, $J=6.8$, arom-H).

(4S,5S)-4-Hydroxymethyl-3-methoxymethyl-5-[(1R)-1-methoxymethoxy-2-propen-1-yl]-2-oxazolidinone (21) A solution of di-MOM-protected oxazolidinone (**20**) (490 mg, 1.34 mmol) in MeOH (3.0 ml) was treated with K₂CO₃ (31 mg). This suspension was ultrasonicated for a few minutes, and stirred for 50 min at room temperature. It was poured into brine (30 ml), and extracted with CHCl₃. The combined extracts were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane (1 : 1)–AcOEt) to afford the alcohol (**21**) (325 mg, 93%) as a colorless oil. $[\alpha]_D^{20} - 47.0^\circ$ ($c=1.14$, CHCl₃). IR (CHCl₃): 3400, 1750 cm⁻¹. MS (EI): 262 (M + 1)⁺, 230 (M – 31)⁺, 45 (base). HR-MS (EI) Calcd for C₁₀H₁₆NO₅ (M – 31)⁺: 230.1029; Found: 230.1034. ¹H-NMR: 3.43 (3H, s, OCH₃), 3.44 (3H, s, OCH₃), 3.45 (1H, br s, OH), 3.83–4.40 (3H, m, 4-H, CH₂OH), 4.48–4.58 (2H, m, CH(OMOM), 5-H), 4.64 (1H, d, $J=6.4$, OCH₂OCH₃), 4.65 (1H, d, $J=10.8$, NCH₂OCH₃), 4.76 (1H, d, $J=6.4$, OCH₂OCH₃), 4.89 (1H, d, $J=10.8$, NCH₂OCH₃), 5.45 (1H, d, $J=10.8$, CH₂=CH), 5.46 (1H, d, $J=17.7$, CH₂=CH), 5.70–5.84 (1H, m, CH₂=CH).

(4S,5S)-3,4-Bis(methoxymethyl)-5-[(1R)-1-methoxymethoxy-2-propen-1-yl]-2-oxazolidinone (22) The primary alcohol (**21**) (245 mg, 0.94 mmol) and MeI (2.5 ml, 40.0 mmol) were dissolved in CH₃CN (2.5 ml), and Ag₂O (412 mg, 1.78 mmol) was added. The suspension was heated at 80 °C for 14 h in a sealed tube, and filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane (2 : 1)) to afford the methylether (**22**) (250 mg, 97%) as a colorless oil. $[\alpha]_D^{20} - 6.1^\circ$ ($c=1.02$, CHCl₃). IR (CHCl₃): 1755 cm⁻¹. MS (EI): 260 (M – 15)⁺, 45 (base). ¹H-NMR: 3.36 (3H, s, OCH₃), 3.37 (3H, s, OCH₃), 3.41 (3H, s, OCH₃), 3.68–3.80 (2H, m, CH₂OCH₃), 4.00–4.08 (1H, m, 4-H), 4.40–4.55 (2H, m, CH(OMOM), 5-H), 4.59 (1H, d, $J=6.4$, CH(OCH₂OCH₃)), 4.76 (1H, d, $J=6.4$, CH(OCH₂OCH₃)), 4.79 (2H, s, NCH₂OCH₃), 5.42 (1H, d, $J=11.2$, CH₂=CH), 5.43 (1H, d, $J=16.1$, CH₂=CH), 5.70–5.85 (1H, m, CH₂=CH).

(2S,3S,4R)-2-Dimethylamino-1-methoxy-4-methoxymethoxy-5-hexen-3-ol (23) A solution of the methylether (**22**) (121.0 mg, 0.440 mmol) in THF (5 ml) was added dropwise to a cooled and stirred suspension of LiAlH₄ (37.5 mg, 0.988 mmol) in THF (3 ml) under an argon atmosphere. After the addition, the ice bath was removed, and the reaction mixture was allowed to come to room temperature, and stirred for an additional 1 h. The reaction was quenched by addition of H₂O (38 μ l) in an ice bath, followed by addition of a 15% aqueous solution of NaOH (69.6 mg) and H₂O (111 μ l). The resulting solution was diluted with EtOH (8 ml) and filtered through a Celite pad, which was rinsed with THF–EtOH (1 : 1, 20 ml). The combined filtrates were concentrated *in vacuo*. The residue was purified by alumina column chromatography (AcOEt–MeOH (10 : 1)) to afford the dimethylaminoalcohol (**23**) (83.8 mg, 82%) as a colorless oil. $[\alpha]_D^{20} - 95.3^\circ$ ($c=1.22$, CHCl₃). IR (CHCl₃): 3400 cm⁻¹. MS (EI): 233 (M)⁺, 218 (M – 15)⁺, 102 (base). HR-MS (EI) Calcd for C₁₀H₂₀NO₄ (M – 15)⁺: 218.1393; Found:

218.1408. $^1\text{H-NMR}$: 2.34 (6H, s, $\text{N}(\text{CH}_3)_2$), 2.58–2.69 (1H, m, 3-H), 3.35 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 3.60–3.70 (2H, m, 1-H₂), 3.95 (1H, dd, $J=6.8, 4.4$, 3-H), 4.28 (1H, dd, $J=7.8, 4.4$, 4-H), 4.59 (1H, d, $J=6.8$, OCH_2CH_3), 4.73 (1H, d, $J=6.8$, OCH_2CH_3), 5.33 (1H, d, $J=17.1$, $\text{CH}_2=\text{CH}$), 5.36 (1H, d, $J=11.0$, $\text{CH}_2=\text{CH}$), 5.85 (1H, ddd, $J=17.1, 10.1, 7.9$, $\text{CH}_2=\text{CH}$).

(2S,3S,4R)-3-Benzoyloxy-2-dimethylamino-1-methoxy-4-methoxy-methyloxy-5-hexene (24) Benzoic anhydride (272.4 mg, 1.20 mmol) and DMAP (154.0 mg) were added to a solution of the alcohol (**23**) (91.2 mg, 0.391 mmol) in CHCl_3 (2 ml). The reaction mixture was stirred for 7 h at 40 °C under an argon atmosphere, then diluted with AcOEt (30 ml). The whole was washed with 5% aqueous solution of NaHCO_3 and brine, dried over MgSO_4 , and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt –hexane (1:1)) to afford the benzoate (**24**) (98.1 mg, 74%) as a colorless oil. $[\alpha]_D^{20} -23.6^\circ$ ($c=1.21$, CHCl_3). IR (CHCl_3): 1710 cm^{-1} . MS (EI): 338 ($\text{M}+1$)⁺, 337 (M)⁺, 336 ($\text{M}-1$)⁺, 292 ($\text{M}-45$)⁺, 102 (base). HR-MS (EI) Calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4$ ($\text{M}-45$)⁺: 292.1548; Found: 292.1538. $^1\text{H-NMR}$: 2.35 (6H, s, $\text{N}(\text{CH}_3)_2$), 3.09–3.18 (1H, m, 2-H), 3.30 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.60 (1H, dd, $J=10.3, 3.9$, 1-H₂), 3.66 (1H, dd, $J=10.3, 7.8$, 1-H₂), 4.48 (1H, dd, $J=7.8, 4.4$, 4-H), 4.58 (1H, d, $J=6.8$, OCH_2OCH_3), 4.67 (1H, d, $J=6.8$, OCH_2OCH_3), 5.33 (1H, d, $J=10.7$, $\text{CH}_2=\text{CH}$), 5.35 (1H, d, $J=20.0$, $\text{CH}_2=\text{CH}$), 5.47 (1H, dd, $J=5.9, 4.4$, 3-H), 5.87 (1H, ddd, $J=20.0, 10.7, 7.8$, $\text{CH}_2=\text{CH}$), 7.40–7.45 (2H, m, arom-H), 7.50–7.60 (1H, m, 1H, arom-H), 8.04 (2H, d, $J=7.8$, arom-H).

Epimeric Mixture of (3R,4S,5S)-4-Benzoyloxy-5-dimethylamino-6-methoxy-3-methoxymethyloxyhexane-1,2-diol (25) MMO (50% aqueous solution, 70.0 mg, 0.299 mmol) and OsO_4 (5%, w/v solution in *tert*-BuOH, 0.63 ml, 0.012 mmol) were added to a cooled and stirred solution of the terminal olefin (**24**) (87.9 mg, 0.261 mmol) in acetone (0.50 ml)– H_2O (0.25 ml) on an ice bath under an argon atmosphere. The mixture was stirred for 24 h at room temperature, then the reaction was quenched by NaHSO_3 (39.99 mg, 0.396 mmol). The whole was stirred for 1 h, then diluted with acetone (10 ml), and the precipitate was removed by filtration through Celite. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt – MeOH (1:1)) to afford a mixture of the epimers of the diol (**25**) (66.3 mg, 68%) as a colorless powder. The $^1\text{H-NMR}$ spectrum revealed that **25** was composed of the epimers in a ratio of 7:1. IR (CHCl_3): 3400, 1710 cm^{-1} . MS (EI): 372 ($\text{M}+1$)⁺, 370 ($\text{M}-1$)⁺, 340 ($\text{M}-31$)⁺, 102 (base). HR-MS (EI) Calcd for $\text{C}_{17}\text{H}_{26}\text{NO}_6$ ($\text{M}-31$)⁺: 340.1760; Found: 340.1786. $^1\text{H-NMR}$: 2.45 (6H, s, $\text{N}(\text{CH}_3)_2$), 3.15, 3.21 (3H, s, OCH_3), 3.38, 3.43 (3H, s, OCH_3), 3.40–3.52 (1H, m, 5-H), 3.53–3.65 (2H, m, 6-H₂), 3.70–3.83 (2H, m, 1-H₂), 3.85–3.94 (1H, m, 2-H), 4.05–4.11 (1H, m, 3-H), 4.74 (2H, s, OCH_2OCH_3), 5.43 (1H, dd, $J=9.3, 1.0$, 4-H), 7.40–7.50 (2H, m, arom-H), 7.50–7.60 (1H, m, arom-H), 8.03 (2H, m, arom-H).

Sodium (2S,3S,4S)-3-Benzoyloxy-4-dimethylamino-5-methoxy-2-methoxymethyloxy-pentanoate (26) A solution of NaIO_4 (14.3 mg, 0.067 mmol) in H_2O (0.28 ml) was added to a solution of the diol (**25**) (21.0 mg, 0.057 mmol) in acetone (0.40 ml). The mixture was stirred for 1.5 h at room temperature, then diluted with acetone (8 ml). The resulting solution was filtered through a Celite pad. The filtrate was concentrated *in vacuo* to give the aldehyde as a colorless oil, which was used in the next step without purification. The $^1\text{H-NMR}$ spectrum of the crude product indicated an aldehyde structure. $^1\text{H-NMR}$: 2.29 (6H, s, $\text{N}(\text{CH}_3)_2$), 3.26 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.28–3.40 (1H, m, 4-H), 3.44–3.67 (2H, m, 5-H), 4.22 (1H, d, $J=2.4$, 2-H), 4.76 (1H, d, $J=6.8$, OCH_2OCH_3), 4.81 (1H, d, $J=6.8$, OCH_2OCH_3), 5.41 (1H, dd, $J=10.7, 2.4$, 3-H), 7.40–7.50 (2H, m, arom-H), 7.50–7.60 (1H, m, arom-H), 8.05 (2H, d, $J=7.3$, arom-H), 8.96 (1H, s, CHO).

The residue was dissolved in acetone (0.80 ml) and cooled on an ice bath, and Jones reagent (307.5 mg, 0.615 mmol) in acetone (0.40 ml) was added dropwise. The mixture was stirred for 10 h on an ice bath, the reaction was quenched with 2-propanol (0.10 ml) and the whole was filtered through a Celite pad. The filtrate was neutralized with NaHCO_3 (229 mg, 2.73 mmol) and concentrated *in vacuo*. The residue was applied to a column of absorbent HP-20 (H_2O – MeOH), followed by recrystallization from Et_2O – MeOH to afford the sodium salt (**26**) (17.19 g, 81%) as a hygroscopic colorless solid. MS (FAB): 378 ($\text{M}+1$)⁺, 102 (base). HR-MS (FAB) Calcd for $\text{C}_{17}\text{H}_{25}\text{NNaO}_7$ ($\text{M}+1$)⁺: 378.1529; Found: 378.1508. $^1\text{H-NMR}$: 2.39 (6H, s, $\text{N}(\text{CH}_3)_2$), 3.23 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.40–3.85 (3H, m, 4-H, 5-H₂), 4.30–4.35 (1H, m, 2-H), 4.60–4.85 (2H, m, OCH_2OCH_3), 5.60–5.85 (1H, m, 3-H),

7.30–7.65 (3H, m, arom-H), 8.00 (2H, d, $J=6.8$, arom-H).

Methyl (2S,3S,4S)-3-Benzoyloxy-4-dimethylamino-5-methoxy-2-methoxymethyloxy-pentanoate (27) One drop of AcOH was added to a solution of **26** (8.4 mg, 0.022 mmol), and a solution of diazomethane in ether was added dropwise. The mixture was left standing for 1 h at room temperature, then carefully quenched with AcOH . These operations were repeated twice and the reaction mixture was concentrated *in vacuo*. The residue was purified by alumina column chromatography (AcOEt –hexane (1:1)) to afford the ester (**27**) (4.4 mg, 54%) as a colorless oil. $[\alpha]_D^{20} -32.4^\circ$ ($c=0.59$, CHCl_3). IR (CHCl_3): 1740, 1715 cm^{-1} . MS (EI): 369 (M)⁺, 338 ($\text{M}-31$)⁺, 102 (base). HR-MS (EI) Calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_6$ ($\text{M}-\text{CH}_3\text{O}$)⁺: 338.1603; Found: 338.1616. $^1\text{H-NMR}$: 2.30 (6H, s, $\text{N}(\text{CH}_3)_2$), 3.23 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 3.35–3.45 (1H, m, 4-H), 3.52–3.60 (2H, m, 5-H₂), 3.73 (3H, s, CO_2CH_3), 4.54 (1H, d, $J=2.4$, 2-H), 4.71 (1H, d, $J=6.8$, OCH_2OCH_3), 4.78 (1H, d, $J=6.8$, OCH_2OCH_3), 5.58 (1H, dd, $J=10.3, 3.0$, 3-H), 7.40–7.50 (2H, m, arom-H), 7.50–7.60 (1H, m, arom-H), 8.05 (2H, d, $J=8.3$, arom-H).

(2S,3S,4S)-2,3-Dihydroxy-4-dimethylamino-5-methoxy-pentanoic Acid (8) The sodium salt (**26**) (8.76 mg, 0.0232 mmol) was dissolved in 4 N HCl (4.0 ml) and heated at 50 °C for 3 h with stirring. The solution was concentrated *in vacuo*, and the residue was dissolved in a 28% aqueous solution of NH_3 (4.0 ml). The resultant solution was heated at 50 °C for 20 h with stirring, then concentrated *in vacuo*. The residue was dissolved in dilute HCl and this solution was washed with AcOEt and concentrated *in vacuo*. The residue was dissolved in H_2O and applied to a column of ion-exchange resin Amberlite IR-120B- SO_3H form (28% aqueous solution of NH_3) to afford the amino acid (**8**) (3.86 mg, 80%) as a colorless solid. $[\alpha]_D^{20} -39^\circ$ ($c=0.07$, $\text{EtOH}-\text{H}_2\text{O}$ (1:1)). MS (FAB): 208 ($\text{M}+1$)⁺, 115 (base). HR-MS (FAB) Calcd for $\text{C}_8\text{H}_{18}\text{NO}_5$ ($\text{M}+1$)⁺: 208.1185; Found: 208.1194. $^1\text{H-NMR}$ (D_2O , internal standard: sodium-*d*₄-3-trimethylsilylpropionate): 2.88 (6H, s, $\text{N}(\text{CH}_3)_2$), 3.43 (3H, s, OCH_3), 3.42–3.52 (1H, m, 4-H), 3.88 (1H, dd, $J=12.2, 8.8$, 5-H₂), 3.99 (1H, dd, $J=12.2, 4.0$, 5-H₂), 4.13 (1H, d, $J=5.4$, 2-H), 4.36 (1H, dd, $J=5.4, 2.0$, 3-H).

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