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Synthesis of (3*S*,4*S*)-Statine and a Related Compound, (3*S*,4*S*)-AHPPA, from D-Glucosamine as a Chiral Pool

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Biologically important *threo*-β-hydroxy-γ-amino acids, (3*S*,4*S*)-statine ((3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid) (**1**) and (3*S*,4*S*)-AHPPA (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid) (**2**), were synthesized starting from D-glucosamine (**3**) as a chiral pool. Two routes for the transformation of D-glucosamine to key intermediates, which are applicable to the synthesis of *threo*-β-hydroxy-γ-amino acids, were investigated. The successful route involved C(6)-carbon degradation and elimination of the C(4)-hydroxy group of D-glucosamine in 8 steps and 30% overall yield to furnish (4*R*,5*S*)-2-oxo-5-vinyloxazolidine-4-carbaldehyde dimethyl acetal (**17**), which has been utilized as a versatile intermediate for synthesizing the target compounds.

Pepstatin[1)] was first isolated from culture filtrates of various species of actinomycetes as a potent inhibitor of aspartic protease pepsin, renin and cathepsin in 1970. Ahpatinins[2,3)] were found from a culture broth of streptomyces sp. WK-142, and found to show similar pepsin-inhibiting activities, but more potent renin-inhibiting activities than that of pepstatin. The key components of these natural oligopeptides are novel β-hydroxy-γ-amino acids, statine ((3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid) (**1**) and AHPPA ((3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid) (**2**), which along with its analogues are important constituent parts of renin inhibitors (CGP-29287 and U-71038)[4)] and HIV protease inhibitors.[5)] In view of the development of new antihypertensive drugs involving the renin-angiotensin-aldosterone pressor system,[6)] and for therapeutic agents for acquired immunodeficiency syndrome (AIDS),[7)] an efficient synthesis of natural statine (**1**), AHPPA (**2**), and their analogues has been one of the most attractive decoys for synthetic chemists.

All of the synthetic methods for these compounds reported to date have been concerned with construction of the one or two chiral centers involved in **1** and **2** by asymmetric induction, mainly starting from α-amino acid, (*S*)-leucine,[8)] and (*S*)-phenylalanine,[8b,9)] and in a few cases from malic acid[10)] and sugar derivatives,[11)] and by asymmetric synthesis using (−)-3-ketopinoyl-2-oxazolone[12a)] and applying Sharpless oxidation.[12b)] These hydroxy amino acids (**1** and **2**) have (3*S*,4*S*)-4-amino-3-hydroxypentanoic acid as a common structure. We were concerned with the design and development of a strategy for the enantiospecific synthesis of **1** and **2** via routes **a** and **b** from a common intermediate (**II** or **VI**) obtainable from D-glucosamine (**3**), as shown in Chart 1. Route **a** implies the preparation of C6-bromide (**I**) of N-protected D-glucosamine, followed by a reductive elimination of the C5-oxygen functionality, thus providing a furanoid (**II**), to which the requisite carbon chain is introduced to lead to terminal olefin (**III**). Another route **b** involves the oxidative fission of the C6-carbon of the N-protected glycol (**IV**), followed by iodination of the terminal position, thus furnishing an iodide (**V**), which is transformed via a reductive elimination of iodine and the C4-oxygen to a key intermediate, *trans*-4,5-disubstituted oxazolidinone, of type (**VI**). Eventually, a successful methodology was found involving the latter process (**b**), including preparation of a protected chiral amino alcohol synthon of type (**VI**) which is adaptable to various *threo*-aminoalcohol syntheses and is suitable for the introduction of alkyl or aryl groups at the C(1)-carbon. In this paper we give a detailed account of our preliminary communication concerning the synthesis of **1** and **2** from **3**.[13)]

Results and Discussion

Attempted Approach Including a Carbon-Chain Extension at the C(1)-Position of the Derived Furanose (Route a). First of all, a transformation of the known N,O-protected D-glucosamine (**4**) to 2,5,6-trideoxy-2-methoxycarbonylamino-5,6-dehydro-D-glucofuranose derivatives (**9**) and a subsequent elongation of the requisite carbon chains at the C(1)-position for the target compounds (**1** and **2**) was attempted, as illustrated in Scheme 1. Methyl 2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside (**4**), easily available from D-glucosamine (**3**),[14)] was smoothly converted into the C(6)-bromide (**5**) with NBS in the presence of Ph_3P.[15)] The structure of **5** was characterized by itself and the corresponding diacetate (**6**). Dehydrobromination of the bromide (**5**) with Zn powder[16)] in aqueous 2-propanol afforded a 5,6-deoxygenated furanose derivative (**7**) in excellent yield. Protection of the secondary alcohol of **7** as acetate (**9a**) and

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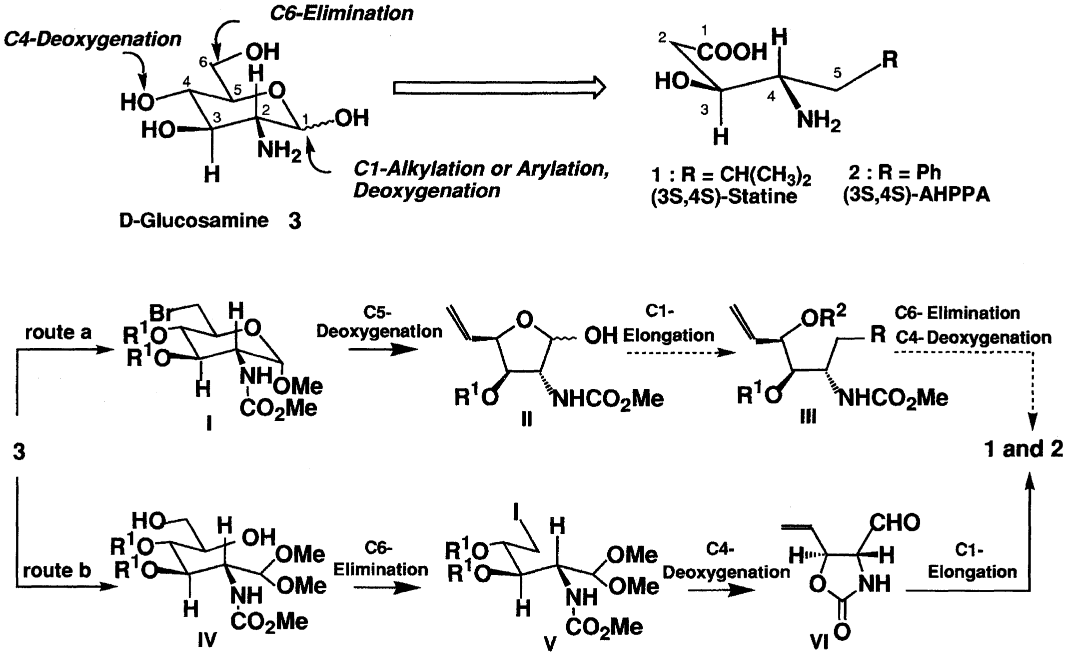
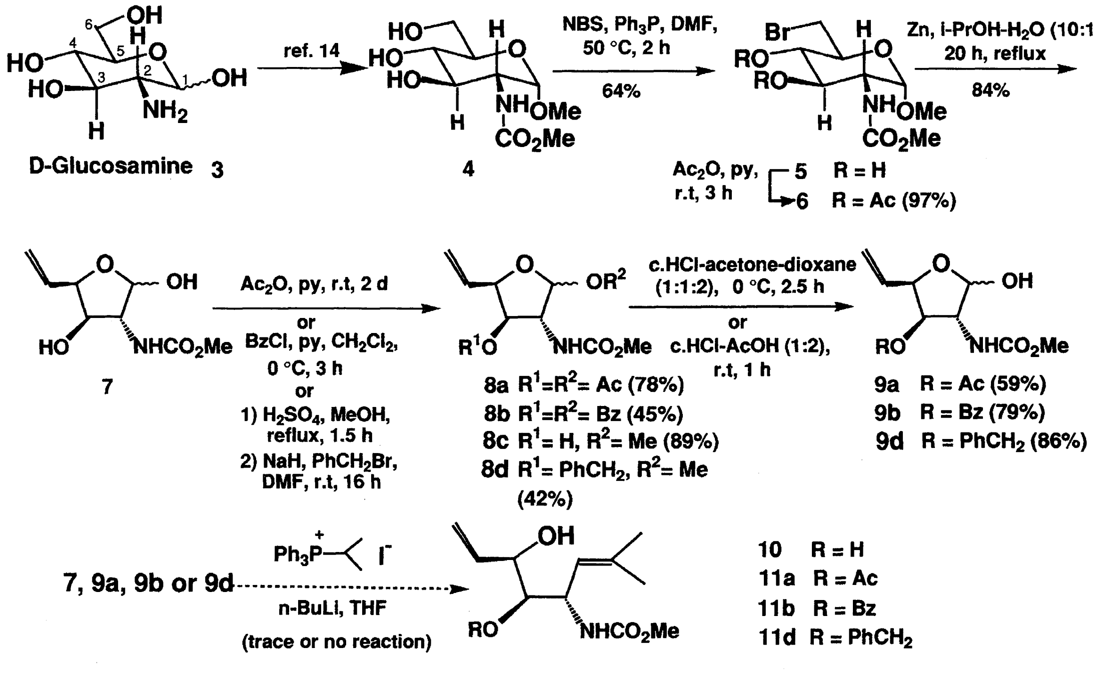


Chart 1.

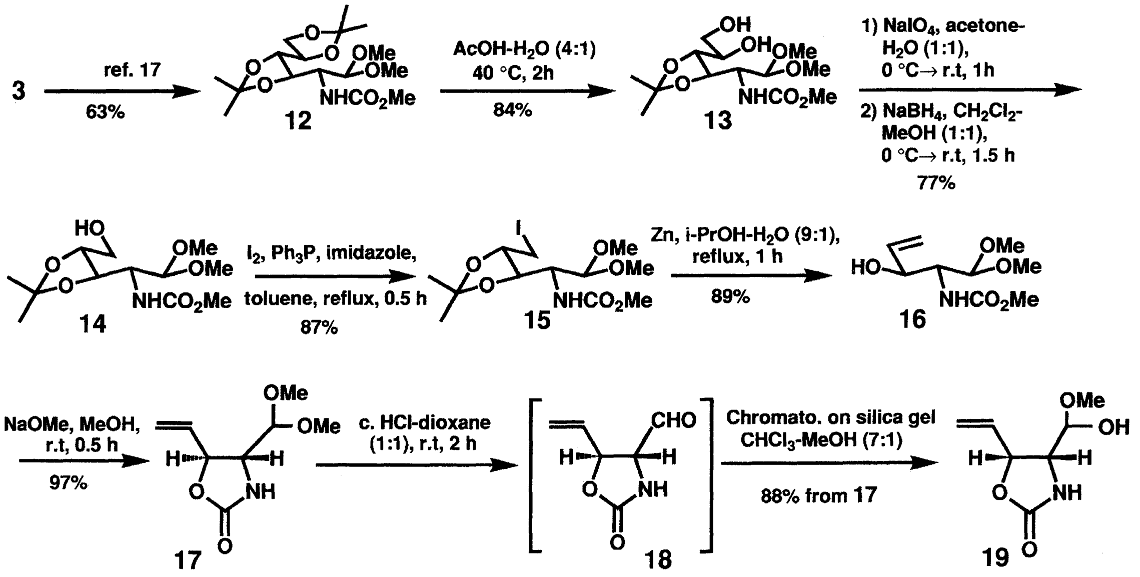


Scheme 1.

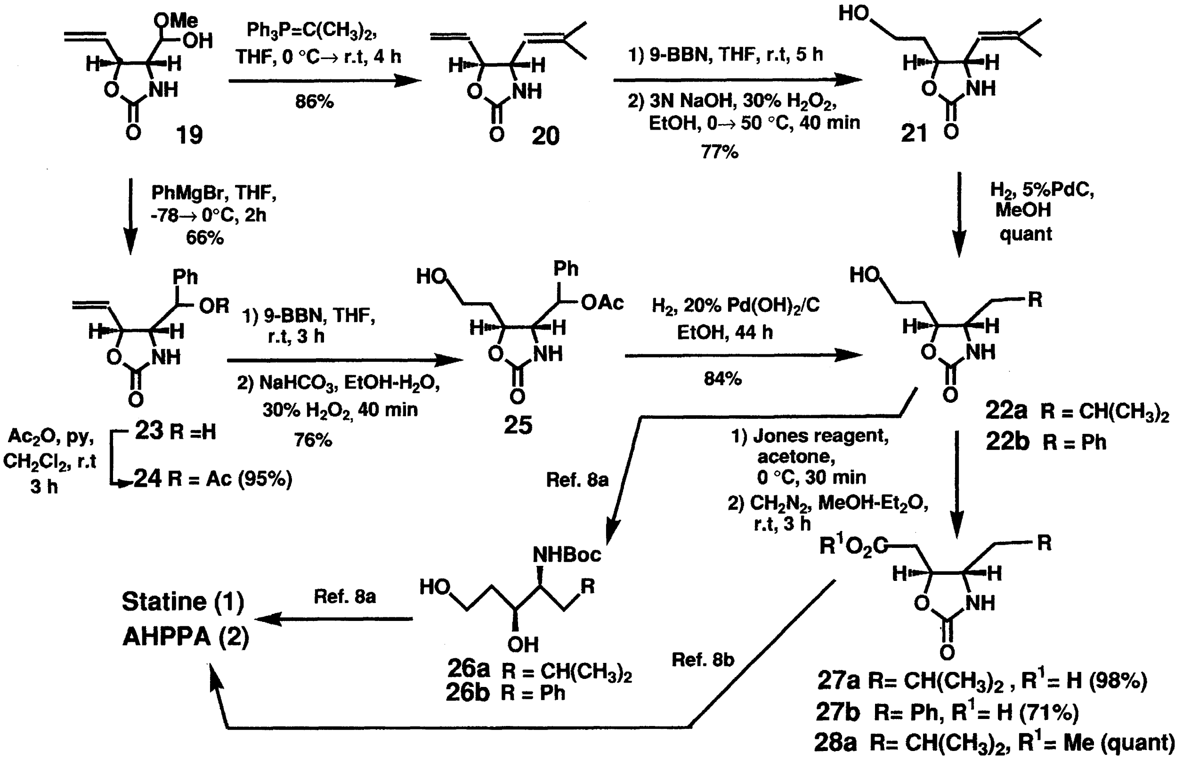
benzoate (**9b**) was carried out by esterification followed by a partial hydrolysis of the anomeric acyloxy groups of the resulting diesters (**8a** and **8b**). Monobenzyl ether (**9d**) of **7** was prepared by a three step sequence of reactions, including glycosidation, benzylation, and hydrolysis through the methyl glycoside (**8c**) and the corresponding secondary benzyl ether (**8d**).

Attempts to elongate the carbon chains requisite for the target compounds **1** at the anomeric position of hemiacetals (**7**), (**9a**), (**9b**), and (**9d**) by the Wittig reaction with isopropylidenetriphenylphosphorane ($Ph_3P=C(CH_3)_2$) were in vain, and gave only a trace of the desired compound (**10** or **11d**) when **7** or **9d** was used as a substrate.

Successful Approach to the Natural Statine (1) and AHPPA (2) by Way of 2-Oxo-5-vinyloxazolidine-4-carbaldehyde (Route b). Preparation of the Key Chiron, (4*R*, 5*S*)-2-Oxo-5-vinyloxazolidine-4-carbaldehyde Dimethyl Acetal (17) (Scheme 2). The elimination of the C(6)-carbon to form a C5-primary alcohol (**14**) was achieved through four steps from D-glucosamine (**3**) by way of the known urethane derivative (**12**), which was easily prepared from D-glucosamine (**3**) in 63% yield through protection of the amino



Scheme 2.



Scheme 3.

group by methoxycarbonylation and acetalization according to the literature.[17] Thus, a selective removal of the 5,6-O-isopropylidene group of **12** with aqueous acetic acid at 40 °C[17] gave the diol **13** in a good yield. Degradation of the C(6)-carbon of **13** was carried out by oxidation with $NaIO_4$ to provide an unstable aldehyde, which was immediately reduced to an alcohol (**14**) in 85% yield from **13**. The next C(4)-deoxygenation to lead to the key intermediate, (4*R*,5*S*)-2-oxo-5-vinyloxazolidine-4-carbaldehyde dimethyl acetal (**17**), in a high overall yield (84%) was achieved by a three-step consecutive procedure, including the iodonation[18] of **14** with iodine in the presence of Ph_3P and imidazole, affording the iodide (**15**), reductive β-elimination upon a treatment of **15** with zinc powder, producing the terminal olefin (**16**), followed by C(3)–OH protection by the formation of a 2-oxazolidinone ring upon a treatment of **16** with NaOMe in MeOH. Thus, a versatile protected chiral *threo*-amino alcohol (**17**) bearing vinyl and aldehyde functionalities was prepared from D-glucosamine (**3**) in 8 steps and 30% overall yield.

Synthesis of (3*S*,4*S*)-Statine (1) and (3*S*,4*S*)-AHPPA

(2) by Elongation of the Carbon Chains on the Aldehyde Analogue (17) (Scheme 3). The 2-oxazolidinone (**17**) served as the key intermediate for the synthesis of statine (**1**) and AHPPA (**2**). The acidic hydrolysis of **17**, followed by a treatment of the product with MeOH on a silica-gel column chromatograph, gave methyl hemiacetal (**19**). Attempts to obtain the corresponding free aldehyde (**18**) were in vain because the aldehyde was found to be susceptible to hydration through the work up and chromatography on silica gel. The Wittig reaction of **19** with $Ph_3P{=}C(CH_3)_2$ in THF afforded the crystalline diene (**20**) in 76% overall yield from **17**. Site-selective hydroboration-oxidation of diene (**20**) was attained by using 9-borabicyclo[3.3.0]nonane (9-BBN) to give the primary alcohol (**21**) in 77% yield. Hydrogenation of the unsaturated alcohol (**21**) gave the known saturated alcohol (**22a**), which had been used as a synthetic precursor for (3*S*,4*S*)-statine (**1**)[8a] and was characterized by a spectral comparison with the derived known (*t*-butoxycarbonylamino)alkanediol (**26a**).[8a] The alcohol (**22a**) was also converted into the known carboxylic acid (**27a**)[19] and methyl ester (**28a**).[8b] For a derivation of **17** to (3*S*,4*S*)-AHPPA (**2**), phenyl Grignard reagent was adopted to start with the formation of the hemiacetal (**19**). A Grignard reaction of **19** with phenylmagnesium bromide in THF afforded in 66% yield the phenylcarbinol (**23**). The resulting alcohol (**23**) was converted into its acetate (**24**) in order to enhance the reactivity for hydrogenolysis. The hydroboration-oxidation of **24** using the diborane afforded a mixture of regioisomers of alcohol, while hydroboration using 9-BBN afforded regioselectivity in 76% yield the terminal alcohol (**25**). Hydrogenolysis of the acetoxy group in **25** proceeded smoothly, leading to the known synthetic precursor (**22b**) for (3*S*,4*S*)-AHPPA (**2**).[8a] The structure of **22b** was verified by a conversion into the known (*t*-butoxycarbonylamino)alkanediol (**26b**).[8a] The carboxylic acid (**27b**) and its ester (**28b**) were derived analogously from the alcohol (**22b**), and were identified with the corresponding known compounds by spectral comparisons.[19,8b] The methyl esters (**28a** and **28b**) have also been utilized as precursors for synthesis of (3*S*,4*S*)-statine (**1**) and (3*S*,4*S*)-AHPPA (**2**), respectively.[8b]

The synthesis of the alcohols (**22a,b**) and carboxylic acids (**27a,b**) described here implies not only the synthesis of natural statine (**1**) and AHPPA (**2**), starting from an easily available *threo*-amino alcohol chiral pool, D-glucosamine (**3**), but also the versatility of the chiral oxazolidinone (**17**) as a chiron for the synthesis of biologically important *threo*-aminoalcohols and their analogues.

Experimental

The melting points (mp) were measured with a Yanagimoto micro-melting point-apparatus, and are uncorrected. The optical rotations ($[\alpha]_D$) were determined in $CHCl_3$ solutions at 20 °C by using a JASCO-DIP-360 digital polarimeter. Infrared (IR) absorption spectra were recorded on a JASCO-IRA-1, JASCO-IRA-100, or a Shimadzu FTIR-8100 spectrometer in $CHCl_3$ solutions, and are indicated in ν (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a JOEL EX-400 (400 MHz) or a JOEL GX-270 (270 MHz) spectrometer in $CDCl_3$ solutions with $SiMe_4$ used as an internal standard. The chemical shifts are given in δ (ppm) and the coupling constants (*J*) in hertz (Hz) (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). The mass spectra (MS) and high-resolution MS (HRMS) were recorded on a JMS-DX-300 or a JMS-D-300, and are indicated at *m*/*z*. All of the reactions were run under a positive pressure of dry nitrogen unless otherwise noted. Anhydrous solvents were distilled before use: tetrahydrofuran (THF) from sodium benzophenone ketyl; toluene, MeOH, and EtOH from sodium; CH_2Cl_2, *N*,*N*-dimethylformamide (DMF), pyridine, and dioxane from CaH_2; acetone from K_2CO_3; diethyl ether (Et_2O) from $LiAlH_4$. Column chromatography was done with Merk Kieselgel 60 (70—230 mesh or 230—400 mesh).

Methyl 6-Bromo-2,6-dideoxy-2-methoxycarbonylamino-D-glucopyranoside (5): To an ice-cold solution of **4** (15.09 g, 60 mmol), prepared from D-glucosamine hydrocloride (**3** HCl salt) according to the literature,[14] and *N*-bromosuccinimide (21.08 g, 120 mmol) in anhydrous DMF (120 ml) was added portionwise triphenylphosphine (31.20 g, 120 mmol); the reaction mixture was then warmed to 50 °C. After stirring the mixture for 2.5 h at 50 °C, MeOH (8 ml) was added, and the whole was stirred for 0.5 h at 50 °C. The resulting solution was poured into brine and extracted with AcOEt. The extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed ($CHCl_3$–$CHCl_3$/MeOH (7/1)) on silica gel to give a bromide (**5**) (12.00 g, 64%) as pale brown crystals. Mp 129—132 °C. $[\alpha]_D^{20}$ +92.6° (*c* 0.65, $CHCl_3$). IR (KBr) 3590, 3322, 1691, 1545 cm^{-1}. MS (FAB) *m*/*z* 338 $(M(^{81}Br)+Na)^+$, 336 $(M(^{79}Br)+Na)^+$, 316 $(M(^{81}Br)+H)^+$, 314 $(M(^{79}Br)+H)^+$, 136 (base). HRMS (FAB) Calcd for $C_9H_{17}BrNO_6$: $(M+H)^+$, 314.0240. Found: *m*/*z* 314.0182. ^1H NMR ($CDCl_3$) $\delta = 3.41$ (3H, s, OCH_3), 3.71 (3H, s, CO_2CH_3), 3.39—3.82 (8H, m, C2,3,4,5,6-H, C3-OH, C4-OH), 4.73 (1H, d, $J = 3.7$ Hz, C1-H), 5.28 (1H, d, $J = 8.8$ Hz, NH). Anal. Calcd for $C_9H_{16}BrNO_6$: C, 34.41; H, 5.19; N, 4.46%. Found: C, 34.82; H, 4.89; N, 4.43%.

Methyl 6-Bromo-3,4-*O*-diacetyl-2,6-dideoxy-2-methoxycarbonylamino-D-glucopyranoside (6): A solution of **5** (13 mg, 0.04 mmol) and acetic anhydride (108 mg, 1.41 mmol) in pyridine (119 mg, 1.41 mmol) was stirred for 5 h at room temperature. The reaction mixture was concentrated in vacuo. The residue was chromatographed (AcOEt–hexane (1/1)) on silica gel to afford a diacetate (**6**) (16 mg, 97%) as a white solid. $[\alpha]_D^{20}$ +93.7° (*c* 0.75, $CHCl_3$). IR (neat) 3350, 1750, 1725, 1525, 1377 cm^{-1}. MS (FAB) *m*/*z* 422 $(M(^{81}Br)+Na)^+$, 420 $(M(^{79}Br)+Na)^+$, 400 $(M(^{81}Br)+H)^+$, 398 $(M(^{79}Br)+H)^+$, 368 $(M(^{81}Br)-31)^+$, 366 $(M(^{79}Br)-31)^+$, 137 (base). HRMS (FAB) Calcd for $C_{13}H_{21}BrNO_8$: $(M+H)^+$, 398.0451. Found: *m*/*z* 398.0405. ^1H NMR ($CDCl_3$) $\delta = 2.02$ (3H, s, $COCH_3$), 2.05 (3H, s, $COCH_3$), 3.30—3.50 (2H, m, CH_2Br), 3.45 (3H, s, OCH_3), 3.66 (3H, s, CO_2CH_3), 3.90—4.10 (2H, m, C2,5-H), 4.76 (1H, d, $J = 3.7$ Hz, C1-H), 4.90 (1H, d, $J = 9.9$ Hz, NH), 4.97 (1H, dd, $J = 9.9$, 9.6 Hz, C4-H), 5.20 (1H, dd, $J = 9.3$, 10.6 Hz, C3-H).

2,5-Dideoxy-2-methoxycarbonylamino-5-methylene-D-xylofuranose (7): A mixture of **5** (5.61 g, 17.8 mmol) and Zn powder (23.29 mg, 360 mg atom) in 2-propanol–H_2O (10/1, 220 ml) was heated under reflux for 20 h under vigorous stirring. After cooling, the precipitate was removed by filtration through celite and rinsed with EtOH. The filtrate was concentrated in vacuo. The residue was chromatographed (AcOEt) on silica gel to afford an olefin (**7**) (3.05 g, 84%) as a pale-brown oil. The ^1H NMR spectrum indicated **7** to be a 2 : 1 mixture of epimers. IR 3605, 3435, 1713, 1514 cm^{-1}. MS (FAB) *m*/*z* 204 $(M+H)^+$, 186 $(M+H-18)^+$, 136 (base). HRMS (FAB) Calcd for $C_8H_{12}NO_4$: $(M+H-H_2O)^+$, 186.0766. Found: *m*/*z* 186.0800. Major epimer: ^1H NMR ($CDCl_3$) $\delta = 3.00$ (1H, brs, OH), 3.35 (1H, brs, OH), 3.72 (3H, s, CO_2CH_3), 4.02—4.10 (1H, m, C2-H), 4.28—4.40 (1H, m, C3-H), 4.77 (1H, dd, $J=6.2$, 6.2 Hz, C4-H), 5.40—5.55 (4H, m, C1-H, NH, $CH=C\underline{H}_2$), 5.96 (1H, ddd, $J=17.2$, 10.6, 6.6 Hz, $C\underline{H}=CH_2$).

2,5-Dideoxy-1,3-*O*-diacetyl-2-methoxycarbonylamino-5-methylene-D-xylofuranose (8a): To a mixture of **7** (50 mg, 0.25 mmol) and pyridine (160 mg, 2.03 mmol) was added acetic anhydride (210 mg, 2.06 mmol) at room temperature. After stirring for 2 d, 1 M-HCl (4ml)–Brine (4ml) was added to the reaction mixture (M=mol dm^{-3}). The resulting mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane–AcOEt (1/2)) to afford an epimeric mixture of diacetate **8a** (55 mg, 78%) as a colorless oil. The ^{1}H NMR spectrum revealed **8a** to be a 4.5 : 1 ratio of epimers. MS (EI) m/z 244 (M−43)$^+$, 43 (base). Major epimer: ^{1}H NMR ($CDCl_3$) $\delta=2.07$ (3H, s, $COCH_3$), 2.12 (3H, s, $COCH_3$), 3.71 (3H, s, OCH_3), 4.50—4.65 (1H, m, C2-H), 4.82 (1H, dd, $J=7.3$, 7.3 Hz, C4-H), 4.90—5.05 (1H, m, C3-H), 5.22—5.40 (3H, m, NH, $CH=C\underline{H}_2$), 5.65—5.92 (1H, m, $C\underline{H}=CH_2$), 6.29 (1H, d, $J=4.9$ Hz, C1-H).

2,5-Dideoxy-1,3-*O*-dibenzoyl-2-methoxycarbonylamino-5-methylene-D-xylofuranose (8b): To an ice-cold solution of **7** (430 mg, 2.12 mmol) and pyridine (421 mg, 5.30 mmol) in CH_2Cl_2 (5 ml) was added dropwise benzoyl chloride (0.51 ml, 4.40 mmol). After stirring for 3 h, the reaction mixture was poured into 0.5 M-HCl aq, and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$–hexane–AcOEt (4/2/1)) to afford a pair of epimeric dibenzoate (**8b$_1$**) (276 mg, 32%) and (**8b$_2$**) (116 mg, 13%) as a colorless oil.

8b$_1$: TLC (silica gel, $CHCl_3$/hexane/AcOEt, $R_f=0.53$). MS (EI) m/z 411 (M)$^+$, 306, 185, 105 (base). ^{1}H NMR ($CDCl_3$) $\delta=3.66$ (3H, s, CO_2CH_3), 4.80—4.90 (1H, m, C2-H), 5.06 (1H, dd, $J=7.4$, 6.8 Hz, C4-H), 5.19 (1H, d, $J=8.3$ Hz, NH), 5.26 (1H, d, $J=10.2$ Hz, $CH=C\underline{H}_2$), 5.41 (1H, d, $J=17.1$ Hz, $CH=C\underline{H}_2$), 5.66 (1H, dd, $J=7.3$, 7.8 Hz, C3-H), 5.84 (1H, ddd, $J=17.6$, 10.7, 7.3 Hz, $C\underline{H}=CH_2$), 6.65 (1H, d, $J=4.4$ Hz, C1-H), 7.42—7.57 (4H, m, arom-H), 7.59—7.68 (2H, m, arom-H), 8.00—8.07 (4H, m, arom-H).

8b$_2$: TLC (silica gel, $CHCl_3$/hexane/AcOEt, $R_f=0.38$). MS (EI) m/z 411 (M)$^+$, 306, 185, 105 (base). ^{1}H NMR ($CDCl_3$) $\delta=3.73$ (3H, s, CO_2CH_3), 4.62—4.71 (1H, m, C2-H), 5.08 (1H, dd, $J=5.9$, 6.4 Hz, C4-H), 5.20—5.30 (1H, brs, NH), 5.23 (1H, d, $J=10.3$ Hz, $CH=C\underline{H}_2$), 5.41 (1H, d, $J=17.1$ Hz, $CH=C\underline{H}_2$), 5.62 (1H, dd, $J=5.4$, 2.0 Hz, C3-H), 5.93 (1H, ddd, $J=17.1$, 10.3, 6.8 Hz, $C\underline{H}=CH_2$), 6.46 (1H, s, C1-H), 7.35—7.50 (4H, m, arom-H), 7.50—7.60 (2H, m, arom-H), 8.02—8.11 (4H, m, arom-H).

Methyl 2,5-Dideoxy-2-methoxycarbonylamino-5-methylene-D-xylofuranoside (8c): To a solution of **7** (2.37 g, 11.7 mmol) and anhydrous MeOH (100 ml) was added dropwise H_2SO_4 (0.17 g, 1.7 mmol) at room temperature; the mixture was then heated at a reflux for 1.5 h. After cooling, the reaction mixture was neutralized with $BaCO_3$ (0.67 g, 3.4 mmol), and the resulting salt was filtered off. The filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt) to afford a mixture of epimers of methyl glycoside (**8c**) (2.26 g, 89%) as a pale-brown oil. The ^{1}H NMR spectrum revealed **8c** to be a 4.5 : 1 ratio of epimers. IR (neat) 3350, 1700, 1540 cm^{-1}. MS (FAB) m/z 218 (M+H)$^+$, 200 (M+H−18)$^+$, 186 (M+H−32)$^+$, 91 (base). HRMS (FAB) Calcd for $C_8H_{12}NO_4$: (M+H−CH_3OH)$^+$, 186.0766. Found: m/z 186.0766. Major epimer: ^{1}H NMR ($CDCl_3$) $\delta=3.11$ (1H, brs, OH), 3.41 (3H, s, CO_2CH_3), 3.70 (3H, s, CO_2CH_3), 4.02—4.15 (1H, m, C3-H), 4.20—4.30 (1H, m, C2-H), 4.60—4.70 (1H, m, C4-H), 5.00 (1H, d, $J=5.4$ Hz, C1-H), 5.30—5.50 (3H, m, NH, $CH=C\underline{H}_2$), 5.97 (1H, ddd, $J=17.1$, 10.3, 6.8 Hz, $C\underline{H}=CH_2$).

Methyl 2,5-Dideoxy-3-*O*-benzyl-2-methoxycarbonylamino-5-methylene-D-xylofuranoside (8d): To a stirred suspension of NaH (173 mg, 60% in mineral oil, 4.32 mmol) in DMF (2 ml) was added dropwise a solution of **8c** (727 mg, 3.34 mmol) in DMF (3 ml) and then a solution of benzyl bromide (675 mg, 3.95 mmol) in DMF (1 ml) in the same manner. After stirring for 16 h at room temperature, the reaction mixture was poured into H_2O, and extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt–hexane(1/2)) to give a benzyl ether (**8d**) (434 mg, 42%) as colorless needles. The ^{1}H NMR spectrum revealed **8d** to be a 50 : 1 ratio of epimers. Major epimer: Mp 80.4—81.7 °C (AcOEt–hexane). IR (KBr) 3335, 1693, 1545 cm^{-1}. MS (FAB) m/z 308 (M+H)$^+$, 276 (M+H−32)$^+$, 91 (base). HRMS (FAB) Calcd for $C_{15}H_{18}NO_4$: (M+H−CH_3OH), 276.1236. Found: m/z 276.1241. ^{1}H NMR ($CDCl_3$) $\delta=3.41$ (3H, s, OCH_3), 3.71 (3H, s, CO_2CH_3), 3.92 (1H, dd, $J=4.4$, 5.1 Hz, C3-H), 4.35—4.40 (1H, m, C2-H), 4.48 (1H, dd, $J=7.0$, 5.9 Hz, C4-H), 4.62 (1H, d, $J=12.5$ Hz, $C\underline{H}_2Ph$), 4.72 (1H, d, $J=12.5$ Hz, $C\underline{H}_2Ph$), 5.02 (1H, d, $J=5.1$ Hz, C1-H), 5.27—5.40 (3H, m, $CH=C\underline{H}_2$, NH), 6.03 (1H, ddd, $J=17.6$, 10.3, 7.7 Hz, $C\underline{H}=CH_2$), 7.22—7.38 (5H, m, arom-H). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56%. Found: C, 62.82; H, 7.10; N, 4.53%.

2,5-Dideoxy-3-*O*-acetyl-2-methoxycarbonylamino-5-methylene-D-xylofuranose (9a): A solution of **8a** (259 mg, 0.09 mmol) in dioxane–acetone–12 M-HCl (2/1/1, 4.0 ml) was stirred for 2.5 h on an ice bath. The reaction was diluted with $CHCl_3$ (50 ml), and then washed with brine, saturated $NaHCO_3$ aq, and again brine. The extract was dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane–AcOEt (1/1)) to give **9a** (131 mg, 59%) as colorless needles. The ^{1}H NMR spectrum of **9a** indicated the compound to be a 20 : 1 mixture of epimers. MS (EI) m/z 185 (M−60)$^+$, 43 (base). Major epimer: ^{1}H NMR ($CDCl_3$) $\delta=2.06$ (3H, s, $COCH_3$), 3.15 (1H, d, $J=2.9$ Hz, OH), 3.69 (3H, s, CO_2CH_3), 4.30—4.42 (1H, m, C2-H), 4.85 (1H, dd, $J=6.8$, 6.8 Hz, C4-H), 5.22—5.40 (4H, m, NH, C3-H, $CH=C\underline{H}_2$), 5.49 (1H, dd, $J=4.9$, 3.4 Hz, C1-H), 5.55 (1H, ddd, $J=17.1$, 10.3, 6.8 Hz, $C\underline{H}=CH_2$).

2,5-Dideoxy-3-*O*-benzoyl-2-methoxycarbonylamino-5-methylene-D-xylofuranose (9b): A suspension of an epimeric mixture of **8b$_1$** and **8b$_2$** (132 mg, 0.32 mmol) in dioxane–acetone–12 M-HCl (2/1/1, 1.5 ml) was stirred for 2.5 h on an ice bath. The reaction was diluted with AcOEt (50 ml), and then washed with brine (20 ml), saturated $NaHCO_3$ aq (10 ml) and again brine (10 ml). The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (d$CHCl_3$–hexane–AcOEt (1/1/1)) to give a benzoate (**9b**) (80 mg, 79%) as colorless oil. The ^{1}H NMR spectrum indicated **9b** to be a 50 : 1 mixture of epimers. Major epimer: ^{1}H NMR ($CDCl_3$) $\delta=3.68$ (3H, s, CO_2CH_3), 3.80 (1H, brs, OH), 4.50—4.60 (1H, m, C2-H), 4.98 (1H, dd, $J=6.8$, 6.8 Hz, C4-H), 5.20 (1H, d, $J=10.7$, $CH=C\underline{H}_2$), 5.36 (1H, d, $J=17.1$ $CH=C\underline{H}_2$), 5.45—5.60 (3H, m, NH, C1-H, C3-H), 5.81 (1H, ddd, $J=17.6$, 10.3, 7.3 Hz, $C\underline{H}=CH_2$), 7.40—7.50 (4H, m, arom-H), 7.50—7.62 (2H, m, arom-H), 8.00—8.10 (4H, m, arom-H).

2,5-Dideoxy-3-*O*-benzyl-2-methoxycarbonylamino-5-methylene-D-xylofuranose (9d): A solution of **8d** (47.1 mg, 0.15 mmol) in AcOH–12 M-HCl (2/1, 0.4 ml) was stirred for 1 h at room temperature and poured into H_2O (10 ml). The resulting solution was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt–hexane, 1/1) to give a hemiacetal (**9d**) (38.6 mg, 86%) as colorless solid. The ^{1}H NMR spectrum revealed **9d** to be a 5 : 3 ratio of epimers. Mp 82—87 °C. IR (KBr) 3400, 3315, 1698, 1545 cm^{-1}. MS (FAB) *m*/*z* 294 $(\mathrm{M+H})^+$, 276 $(\mathrm{M+H}-18)^+$, 91 (base). HRMS (FAB) Calcd for $\mathrm{C_{15}H_{18}NO_4}$: $(\mathrm{M+H-H_2O})^+$, 276.1236. Found: *m*/*z* 276.1288. ^{1}H NMR (CDCl$_3$) $\delta = 3.18$ (1H, brs, OH), 3.70, 3.71 (3H, s, CO$_2$CH$_3$), 3.98—4.05 (1H, m, C3-H), 4.20—4.35 (1H, m, C2-H), 4.55—4.80 (3H, m, C4-H, CH$_2$Ph), 5.15 (1H, d, $J = 11.2$ Hz, C1-H of one of the epimers) and 5.25—5.55 (4H, m, CH=C$\underline{\mathrm{H}}_2$ C1-H of the other of epimers, NH), 5.95—6.08 (1H, m, C$\underline{\mathrm{H}}$=CH$_2$), 7.26—7.40 (5H, m, arom-H).

Trials for Wittig Olefination of Xylofuranoses (7, 9a, 9b, 9d). i) Wittig Reaction of 7. Formation of (3*S*, 4*R*, 5*S*)-5-Methoxycarbonylamino-7-methyl-1,6-octadiene-3,4-diol (10): To an ice-cold suspension of isopropyltriphenylphosphonium iodide (950 mg, 2.20 mmol) in THF (2 ml) was added dropwise butyllithium in hexane (1.65 mol dm^{-3}, 1.20 ml, 1.98 mmol) under an argon atmosphere. After stirring for 20 min, to the reaction mixture was added dropwise a solution of **7** (100 mg, 0.50 mmol) in THF (3 ml); the mixture was then stirred for 20 h at 0 °C. The mixture was quenched with saturated aqueous solution of NH$_4$Cl and diluted with AcOEt (20 ml) and brine (20 ml). The resulting heterogeneous solution was filtered off and rinsed with AcOEt. The organic layer was washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt) to afforded a diol (**10**) (5 mg, 4%) as a colorless oil. $[\alpha]_{\mathrm{D}}^{20} - 23.0°$ (*c* 0.38, CHCl$_3$). IR (neat) 3360, 1710, 1520 cm^{-1}. MS (FAB) *m*/*z* 252 $(\mathrm{M+Na})^+$, 230 $(\mathrm{M+H})^+$, 142 (base). HRMS (FAB) Calcd for $\mathrm{C_{11}H_{20}NO_4}$: $(\mathrm{M+H})^+$, 230.1392. Found: *m*/*z* 230.1430. ^{1}H NMR (CDCl$_3$) $\delta = 1.72$ (3H, d, $J = 0.9$ Hz, CH$_3$), 1.73 (3H, d, $J = 1.0$ Hz, CH$_3$), 2.28 (1H, d, $J = 5.4$ Hz, OH), 3.05 (1H, brs, OH), 3.38—3.47 (1H, m, C4-H), 3.67 (3H, s, CO$_2$CH$_3$), 4.08 (1H, dd, $J = 11.2$, 5.9 Hz, C3-H), 4.42—4.45 (1H, m, C5-H), 4.99 (1H, d, $J = 8.3$ Hz, NH), 5.18 (1H, d, $J = 9.3$ Hz, C$\underline{\mathrm{H}}$=C(CH$_3$)$_2$), 5.28 (1H, d, $J = 10.3$ Hz, CH=C$\underline{\mathrm{H}}_2$), 5.38 (1H, d, $J = 17.1$ Hz, CH=C$\underline{\mathrm{H}}_2$), 5.94 (1H, ddd, $J = 17.1$, 11.2, 6.4 Hz, C$\underline{\mathrm{H}}$=CH$_2$).

ii) Wittig Reaction of 9a: To an ice-cold suspension of isopropyltriphenylphosphonium iodide (391 mg, 0.91 mmol) in THF (2 ml) was added dropwise butyllithium in hexane (1.65 mol dm^{-3}, 0.48 ml, 0.79 mmol) under an argon atmosphere. After stirring for 20 min, to the reaction mixture was added dropwise a solution of **9a** (50 mg, 0.20 mmol) in THF (2 ml); the mixture was then stirred for 5.0 h. The mixture was quenched with saturated aqueous solution of NH$_4$Cl. The resulting heterogeneous solution was filtered off and rinsed with Et$_2$O. The filtrate was dried over MgSO$_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt–hexane, (1/1)) but no desired compound (**11a**) was detected.

iii) Wittig Reaction of 9b: To an ice-cold suspension of isopropyltriphenylphosphonium iodide (522 mg, 0.98 mmol) in THF (1 ml) was added dropwise butyllithium in hexane (1.65 mol dm^{-3}, 0.66 ml, 1.09 mmol) on an ice bath under an argon atmosphere. After stirring for 1 h, to the reaction mixture was added dropwise a solution of **9b** (69.8 mg, 0.23 mmol) in THF (1 ml); the mixture was then stirred for 5.0 h at 0 °C. The mixture was quenched with a saturated aqueous solution of NH$_4$Cl and diluted with AcOEt. The resulting heterogeneous solution was filtered off and rinsed with AcOEt. The filtrate was dried over MgSO$_4$, and concentrated in vacuo. The separation of the crude oil by chromatography on silica gel afforded the starting substance (**9b**) (32 mg), but gave no desired compound (**11b**).

iv) Wittig Reaction of 9d. Formation of (3*S*,4*R*,5*S*)-4-Benzyloxy-5-methoxycarbonylamino-7-methyl-1,6-octadien-3-ol (11d): To an ice-cold suspension of isopropyltriphenylphosphonium iodide (289.1 mg, 0.66 mmol) in THF (1 ml) was added dropwise butyllithium in hexane (1.62 mol dm^{-3}, 0.36 ml, 0.59 mmol) at −50 °C under an argon atmosphere. After stirring for 30 min, to the reaction mixture was added dropwise a solution of **9d** (17.3 mg, 0.06 mmol) in THF (1 ml) at the temperature; the whole was stirred for 1.5 h at −50 °C. Then, the mixture was allowed to warm to room temperature, and stirred for 4.5 h. The mixture was quenched with saturated aqueous solution of NH$_4$Cl and diluted with AcOEt. The resulting heterogeneous solution was filtered off and rinsed with AcOEt. The filtrate was washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane–AcOEt, 1/1) to afforded a diene (**11d**) (2.8 mg, 15%) as a colorless oil. $[\alpha]_{\mathrm{D}}^{20} - 12.5°$ (*c* 0.24, CHCl$_3$). IR (neat) 3300, 1722, 1510 cm^{-1}. MS (FAB) *m*/*z* 320 $(\mathrm{M+H})^+$, 289 $(\mathrm{M+H}-31)^+$, 91 (base). ^{1}H NMR (CDCl$_3$) $\delta = 1.69$ (3H, s, CH$_3$), 1.70 (3H, s, CH$_3$), 2.49 (1H, d, $J = 3.9$ Hz, OH), 3.36 (1H, dd, $J = 2.4$, 6.3 Hz, C4-H), 3.64 (3H, s, CO$_2$CH$_3$), 4.13—4.22 (1H, m, C$\underline{\mathrm{H}}$(OH)), 4.55—4.70 (1H, m, C5-H), 4.68 (2H, s, C$\underline{\mathrm{H}}_2$Ph), 5.01 (1H, d, $J = 9.3$ Hz, NH), 5.16 (1H, d, $J = 9.3$ Hz, C$\underline{\mathrm{H}}$=C(CH$_3$)$_2$), 5.26 (1H, d, $J = 10.7$ Hz, CH=C$\underline{\mathrm{H}}_2$), 5.40 (1H, d, $J = 17.1$ Hz, CH=C$\underline{\mathrm{H}}_2$), 6.00 (1H, ddd, $J = 17.1$, 10.3, 5.3 Hz, C$\underline{\mathrm{H}}$=CH$_2$) 7.20–7.40 (5H, m, arom-H).

2-Deoxy-3,4 : 5,6-*O*-diisopropylidene-2-methoxycarbonylamino-D-glucose Dimethyl Acetal (12): This compound was prepared according to the literature.[17] To an ice-cold solution of D-glucosamine HCl salt (**3 · HCl salt**) (64.51 g, 0.30 mol) and Na$_2$CO$_3$ (34.95 g, 0.33 mol) in acetone–H$_2$O (1/1, 1000 ml) was added ClCO$_2$CH$_3$ (29 ml, 0.37 mol) dropwise over a 30 min period on an ice bath. After stirring for 2 h, the ice bath was removed and the mixture was allowed to warm up to room temperature, and was then stirred for an additional 18 h. To the mixture was added dioxane and concentrated in vacuo to give a residue (118 g) as a pale-brown powder. To a solution of the obtained product and 2,2-dimethoxypropane (240 ml) in dioxane (500 ml) was added TsOH · H$_2$O (9.5 g, 50 mmol), which was stirred for 3.5 h at 70 °C. The mixture was cooled on an ice bath, and then neutralized with NaHCO$_3$ (30 g) to give a heterogeneous mixture. The thus obtained insoluble solids were removed by filtration through celite and washed with dioxane. The combined filtrates were concentrated in vacuo and chromatographed on silica gel (hexane–AcOEt 2/1) to afford the dimethyl acetal (**12**) (69.1 mg, 63% from **3 · HCl**) as a colorless oil. $[\alpha]_{\mathrm{D}}^{20} + 6.3°$ (*c* 1.36, CHCl$_3$). IR 3400, 1720 cm^{-1}. MS (EI) *m*/*z* 348 $(\mathrm{M}-15)^+$, 149, 75 (base). HRMS (EI) Calcd for $\mathrm{C_{15}H_{26}NO_8}$: $(\mathrm{M-CH_3})^+$, 348.1658. Found: *m*/*z* 348.1670. ^{1}H NMR (CDCl$_3$) $\delta = 1.34$, 1.36, 1.39, 1.47 (each 3H, s, 4×CH$_3$), 3.41, 3.68 (each 3H, s, 2×OCH$_3$), 3.37 (3H, s, CO$_2$CH$_3$), 3.25—4.30 (6H, m, C2,3,4,5,6-H), 4.34 (1H, d, $J = 6.4$ Hz, C$\underline{\mathrm{H}}$(OCH$_3$)$_2$), 5.06 (1H, d, $J = 10.3$ Hz, NH).

2-Deoxy-3,4-*O*-isopropylidene-2-methoxycarbonylamino-D-glucose Dimethyl Acetal (13): A solution of **12** (9.46 g, 26.1 mmol) in AcOH–H$_2$O (4/1, 100 ml) was stirred for 2 h at 40 °C. To the mixture was added dioxane (50 ml) and concentrated in vacuo; this operation was repeated 3 times, and the resulting oil was chromatographed on silica gel (AcOEt) to afford the diol **13** (7.07 g, 84%) as colorless crystals. Mp 97—98 °C (hexane–AcOEt). $[\alpha]_{\mathrm{D}}^{20} - 6.2°$ (*c* 1.02, CHCl$_3$). IR 3400, 1700 cm^{-1}. ^{1}H NMR (CDCl$_3$) $\delta = 1.37$ (6H, s, 2×CH$_3$), 3.17 (2H, brs, 2×OH), 3.35 (3H, s, OCH$_3$), 3.41 (3H, s, OCH$_3$), 3.70 (3H, s, CO$_2$CH$_3$), 3.70—3.85 (4H, m, 4,5,6-H), 4.04—4.18 (1H, m, 2-H), 4.25—4.30 (1H, m, 3-H), 4.40 (1H, d, $J = 7.3$ Hz, 1-H), 5.22 (1H, d, $J = 10.3$ Hz, NH). Anal. Calcd for $C_{13}H_{25}NO_8$: C, 48.29; H, 7.79; N, 4.33%. Found: C, 48.11; H, 7.71; N, 4.37%.

2-Deoxy-3,4-*O*-isopropylidene-2-methoxycarbonylamino-D-xylose Dimethyl Acetal (14): To an ice-cold solution of **13** (6.12 g, 18.9 mmol) in acetone (50 ml) was added a solution of $NaIO_4$ (4.45 g, 20.8 mmol) in H_2O (33 ml) dropwise over a 1 h period. After stirring for 1 h the mixture was diluted with brine and extracted with $CHCl_3$. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo to give a residue (5.78 g) as an oil. To an ice-cold solution of the product obtained above in MeOH–$CHCl_3$ (1/1, 50 ml) was added $NaBH_4$ (0.58 g, 15.3 mmol) in small portions. After stirring for 1.5 h the mixture was poured into brine and extracted with $CHCl_3$. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Column chromatography of the residue on silica gel (AcOEt) afforded the primary alcohol **14** (4.30 g, 77%) as colorless crystals. Mp 76—77 °C (hexane–AcOEt). $[\alpha]_{\mathrm{D}}^{20}+9.3°$ (*c* 1.04, $CHCl_3$). IR 3400, 1715 cm^{-1}. ^1HNMR ($CDCl_3$) $\delta = 1.41$ (6H, s, $2\times CH_3$), 2.33 (1H, brs, OH), 3.35 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.69 (3H, s, CO_2CH_3), 3.65—3.95 (4H, m, C2,3,4-H), 4.18 (1H, d, J=8.8 Hz, C3-H), 4.39 (1H, d, J=6.8 Hz, $C\underline{H}(OCH_3)_2$), 5.15 (1H, d, J=9.8 Hz, NH). Anal. Calcd for $C_{12}H_{23}NO_7$: C, 49.14; H, 7.90; N, 4.78%. Found: C, 49.18; H, 8.03; N, 4.81%.

(2*R*,3*R*,4*S*)-5-Iodo-3,4-isopropylidenedioxy-2-methoxycarbonylaminopentanal Dimethyl Acetal (15): Iodine (I_2) (5.04 g, 19.9 mmol) was added in portions to a stirred solution of **14** (4.04 g, 13.8 mmol), Ph_3P (10.83 g, 41.3 mmol) and imidazole (2.91 g, 42.7 mmol) in toluene (55 ml). After the addition of I_2, the mixture was heated at reflux for 0.5 h under an argon atmosphere. After cooling, the solution was decanted and a residual brown oil was washed with toluene by decantation. The combined solution was concentrated in vacuo and chromatographed on silica gel (hexane–AcOEt–CH_2Cl_2 6/3/1) to give the iodide **15** (4.82 g, 87%) as colorless crystals. Mp 117—118 °C (hexane–AcOEt). $[\alpha]_{\mathrm{D}}^{20}+20.0$ °C (*c* 1.07, $CHCl_3$). IR 3400, 1715 cm^{-1}. ^1HNMR ($CDCl_3$) $\delta = 1.41$ (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.25—3.45 (2H, m, CH_2I), 3.37 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 3.70 (3H, s, CO_2CH_3), 3.65—3.75 (1H, m, C4-H), 3.95—4.10 (2H, m, C2,3-H), 4.36 (1H, d, J = 6.8 Hz, $C\underline{H}(OCH_3)_2$), 5.05 (1H, d, J = 9.8 Hz, NH). Anal. Calcd for $C_{12}H_{22}INO_6$: C, 35.74; H, 5.50; N, 3.47%. Found: C, 35.50; H, 5.52; N, 3.48%.

(2*R*,3*S*)-3-Hydroxy-2-methoxycarbonylamino-4-pentenal Dimethyl Acetal (16): To a solution of **15** (8.75 g, 21.7 mmol) in *i*-PrOH–H_2O (9/1, 100 ml) was added Zn powder (7.17 g, 109 mg-atom); the mixture was then heated at reflux for 1 h. After cooling, the precipitate was removed by filtration through celite and washed with EtOH (50 ml). The combined filtrates were concentrated in vacuo. The residue was dissolved in AcOEt and washed with aqueous $NaHCO_3$ solution, aqueous $Na_2S_2O_3$ solution, and brine. The AcOEt layer was dried over $MgSO_4$ and concentrated in vacuo. Column chromatography of the residue on silica gel (hexane–AcOEt 1/2) afforded olefine **16** (4.23 g, 89%) as a pale-yellow oil. $[\alpha]_{\mathrm{D}}^{20}-21.7°$ (*c* 1.03, $CHCl_3$). IR 3400, 1700 cm^{-1}. ^1HNMR ($CDCl_3$) $\delta = 1.75$ (1H, brs, OH), 3.48 (3H, s, OCH_3), 3.49 (3H, s, OCH_3), 3.68 (3H, s, CO_2CH_3), 3.70—3.80 (1H, m, C2-H), 4.45 (1H, d, J = 2.9 Hz, $C\underline{H}(OCH_3)_2$), 4.60—4.65 (1H, m, C3-H), 5.15—5.40 (3H, m, $CH{=}C\underline{H}_2$, NH), 5.81 (1H, ddd, J=17.1, 10.3, 4.9 Hz, $C\underline{H}{=}CH_2$). Anal. Calcd for $C_9H_{17}NO_5$: C, 49.30; H, 7.82; N, 6.39%. Found: C, 49.12; H, 7.87; N, 6.31%.

(4*R*,5*S*)-2-Oxo-5-vinyl-oxazolidine-4-carbaldehyde Dimethyl Acetal (17): The olefin (**16**) (4.80 g, 21.9 mmol) was dissolved in a solution of CH_3ONa in MeOH (1.2 mol dm^{-3}, 55 ml). After stirring for 0.5 h at room temperature, the mixture was cooled on an ice bath, and then adjusted to pH 6—7 with concd HCl. After the resulting solution was concentrated in vacuo, the residue was dissolved in $CHCl_3$, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Column chromatography on silica gel (ethyl ether) afforded oxazolidinone **17** (3.97 g, 97%) as a pale yellow oil. $[\alpha]_{\mathrm{D}}^{20}-67.4°$ (*c* 1.38, $CHCl_3$). IR (neat) 3060, 1750 cm^{-1}. ^1HNMR ($CDCl_3$) $\delta = 3.40$ (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 3.55—3.64 (1H, m, C4-H), 4.32 (1H, d, J = 6.8 Hz, $C\underline{H}(OCH_3)_2$), 4.80—4.87 (1H, m, C5-H), 5.31 (1H, dd, J=9.3, 1.0 Hz, $CH{=}C\underline{H}_2$), 5.41 (1H, dd, J = 17.1, 1.0 Hz, $CH{=}C\underline{H}_2$), 5.53 (1H, brs, NH), 5.91 (1H, ddd, J = 17.1, 9.3, 6.4 Hz, $C\underline{H}{=}CH_2$). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48%. Found: C, 51.21; H, 6.85; N, 7.55%.

(4*R*,5*S*)-4-(Hydroxymethoxymethyl)-5-vinyl-2-oxazolidinone (19): To a solution of **17** (703 mg, 3.77 mmol) in dioxane (5 ml) was added concd HCl (5 ml); the solution was then stirred for 2 h at room temperature. To the reaction mixture was added dioxane; the mixture was then concentrated in vacuo. This operation was repeated 3 times, and the resulting oil was chromatographed on silica gel ($CHCl_3$–MeOH, 7/1) to give methyl hemiacetal **19** (563 mg, 88%) as a diastereomeric mixture. IR 3420, 3300, 1750 cm^{-1}. MS (EI) *m/z* 142 $(M-31)^+$, 112, 68 (base). ^1HNMR ($CDCl_3$) $\delta = 3.43$ and 3.45 (3H, s, OCH_3), 3.52—3.60 (1H, m, C4-H), 4.47—4.64 (1H, m, $C\underline{H}(OH)(OMe)$), 4.80—4.90 and 4.95—5.04 (1H, m, C5-H), 5.29 and 5.30 (1H, m, $CH{=}C\underline{H}_2$), 5.44 (1H, d, J = 17.1 Hz, $CH{=}C\underline{H}_2$), 6.52 and 6.66 (1H, s, NH), 5.84—5.98 (1H, m, $C\underline{H}{=}CH_2$).

(4*S*,5*S*)-4-(2-Methyl-1-propenyl)-5-vinyl-2-oxazolidinone (20): To an ice-cold suspension of isopropyltriphenylphosphonium iodide (7.777 g, 17.95 mmol) in THF (40 ml) under an argon atmosphere was added dropwise butyllithium in hexane (1.62 mol dm^{-3}, 10.0 ml, 16.2 mmol). After 20 min stirring, to the reaction mixture was added dropwise a solution of **19** (550 mg, 3.18 mmol) in THF (30 ml); the mixture was then stirred for 1 h on an ice bath and then for an additional 3 h at room temperature. The mixture was diluted with diethyl ether (200 ml), quenched with a saturated aqueous solution of NH_4Cl, poured into brine, and extracted with diethyl ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a pale-brown oil. The oil was chromatographed on silica gel (hexane–AcOEt, 1/1) to afforded the diene (**20**) (456 mg, 86%) as needles. Mp 48.5—49.5 °C. $[\alpha]_{\mathrm{D}}^{20}-51.0°$ (*c* 1.05, $CHCl_3$). IR 3430, 1750 cm^{-1}. MS (EI) *m/z* 167 $(M)^+$, 110 (base). ^1HNMR ($CDCl_3$) $\delta = 1.65$ (3H, d, J = 1.5 Hz, CH_3), 1.47 (3H, d, J = 1.5 Hz, CH_3), 4.34 (1H, dd, J = 8.3, 8.3 Hz, C4-H), 4.54 (1H, dd, J = 6.8, 7.8, C5-H), 5.10—5.18 (1H, m, $C\underline{H}{=}C(CH_3)_2$), 5.29 (1H, dd, J = 9.3, 1.0 Hz, $CH{=}C\underline{H}_2$), 5.40 (1H, dd, J = 17.1, 1.0 Hz $CH{=}C\underline{H}_2$), 5.91 (1H, ddd, J = 17.1, 9.3, 1.0 Hz, $C\underline{H}{=}CH_2$), 6.57 (1H, brs, NH). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.83; N, 8.39%. Found: C, 64.41; H, 7.73; N, 8.37%.

(4*S*,5S)-5-(2-Hydroxyethyl)-4-(2-methyl-1-propenyl)-2-oxazolidinone (21): To a stirred suspension of 9-BBN (95 mg, 0.74 mmol) in THF (1 ml) under an argon atmosphere was added a solution of **20** (106 mg, 0.63 mmol) in THF (2 ml) at room temperature. After stirring for 5 h the reaction mixture was cooled on an ice bath; EtOH (2 ml), 3 M-NaOH aq (1.0 ml), and 30 % H_2O_2 (359 mg, 3.16 mmol) were then added. The resulting mixture was stirred for 40 min at 50 °C, and then diluted with EtOH (10 ml), adjusted to pH 5—6 with concd HCl to give a heterogeneous mixture. The thus-obtained precipitates were removed by filtration and rinsed with AcOEt. The combined filtrates were concentrated in vacuo and flash chromatographed on silica gel (AcOEt) to afford the primary alcohol **21** (90 mg, 77%) as a colorless oil. $[\alpha]_{\mathrm{D}}^{20}-86.2°$ (*c* 0.94,

$CHCl_3$). IR 1750 cm^{-1}. MS (EI) *m*/*z* 170 $(M-15)^+$, 83 (base). HRMS (EI) Calcd for $C_8H_{12}NO_3$: $(M-CH_3)^+$, 170.0837. Found: *m*/*z* 170.0827. ^1H NMR ($CDCl_3$) $\delta = 1.70$ (3H, d, $J = 1.0$ Hz, CH_3), 1.76 (3H, d, $J = 1.0$ Hz, CH_3), 1.85—2.05 (2H, m, $C\underline{H}_2CH_2OH$), 3.84 (2H, t, $J = 6.4$ Hz, $C\underline{H}_2OH$), 4.25—4.40 (2H, m, C4,5-H), 5.00 (1H, brs, NH), 5.10—5.20 (1H, m, $C\underline{H}{=}C(CH_3)_2$).

(4*S*,5*S*)-5-(2-Hydroxyethyl)-4-isobutyl-2-oxazolidinone (22a): A solution of **21** (18.5 mg, 0.10 mmol) and 5% Pd/C (10.7 mg) in EtOH (2 ml) was stirred at room temperature under 1 atm H_2 for 15 h. The catalyst was removed by filtration through celite. Evaporation of the solvent afforded an oil. The residue was chromatographed on silica gel (AcOEt) to give **22a** (18.6 mg, quant) as a colorless oil. $[\alpha]_D^{20} -75.2°$ (*c* 1.76, $CHCl_3$). IR 1745 cm^{-1}. MS (EI) *m*/*z* 188 $(M+1)^+$, 130 $(M-57)^+$, 112 (base). HRMS (EI) Calcd for $C_9H_{18}NO_3$: $(M+H)^+$, 188.1286. Found: *m*/*z* 188.1303. ^1H NMR ($CDCl_3$) $\delta = 0.92$ (3H, d, $J = 5.9$ Hz, CH_3), 0.94 (3H, d, $J = 5.9$ Hz, CH_3), 1.32—1.45 (1H, m, $C\underline{H}_2CH(CH_3)_2$), 1.45—1.58 (1H, m, $C\underline{H}_2CH(CH_3)_2$), 1.58—1.75 (1H, m, $CH_2C\underline{H}(CH_3)_2$), 1.82—2.05 (2H, m, $C\underline{H}_2CH_2OH$), 2.22 (1H, brs, OH), 3.50—3.65 (1H, m, C4-H), 3.83 (2H, t, $J = 6.8$ Hz, $C\underline{H}_2OH$), 4.30—4.40 (1H, m, C5-H), 6.50 (1H, brs, NH).

(4*S*, 5*S*)- 4- (1- Hydroxy- 1- phenylmethyl)- 5- vinyl- 2- oxazolidinone (23): A solution of PhMgBr, prepared from Mg (249 mg, 10.25 mgatom) and PhBr (1.365 g, 8.4 mmol)) in THF (7 ml) under an argon atmosphere, was cooled to −78 °C. To this solution was added dropwise methyl hemiacetal (**19**) (360 mg, 2.10 mmol) in THF (3 ml). The reaction temperature was held at −78 °C for 1 h, and then allowed to rise to 0 °C, and maintained at this temperature for an additional 1 h. The mixture was quenched by the addition of a saturated aqueous solution of NH_4Cl (5 ml) and poured into brine (80 ml). The resulting mixture was extracted with $CHCl_3$. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give an oil. Chromatography on silica gel (AcOEt) afforded a diastereomeric mixture of alcohols **23** (300 mg, 66%) as a colorless oil. IR 3420, 1750 cm^{-1}. MS (EI) *m*/*z* 220 $(M+1)^+$, 113 (base). HRMS (EI) Calcd for $C_{12}H_{14}NO_3$: $(M+H)^+$, 220.0973. Found: *m*/*z* 220.0993. ^1H NMR ($CDCl_3$) $\delta = 3.41$ and 3.52 (1H, brs, OH), 3.70—3.80 (1H, m, C4-H), 4.61 and 4.81 (1H, d, $J = 7.3$ Hz and d, $J = 4.9$ Hz, respectively, $C\underline{H}(OH)Ph$), 4.65—4.70 (1H, m, C5-H (one of the diastereomers)),), 4.95—5.20 (3H, m, $CH{=}C\underline{H}_2$, and C5-H (the other of the diastereomers)), 5.45—5.75 (1H, m, $C\underline{H}{=}CH_2$), 5.89 and 6.22 (1H, brs, NH), 7.30—7.40 (5H, m, arom-H).

(4*S*, 5*S*)- 4- (1- Acetoxy- 1- phenylmethyl)- 5- vinyl- 2- oxazolidinone (24): A solution of mixture of **23** (216 mg, 0.98 mmol), pyridine (97 mg, 1.2 mmol) and acetic anhydride (205 mg, 2.0 mmol) in CH_2Cl_2 (0.4 ml) was stirred under an argon atmosphere at room temperature for 3 h. The mixture was diluted with diethyl ether (40 ml) and then washed well with 4 M-HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Column chromatography of the residue on silica gel (AcOEt–hexane 1/1) afforded a diastereomeric mixture of acetates **24** (245 mg, 95%) as a colorless oil. IR 1760, 1750 cm^{-1}. MS (EI) *m*/*z* 262 $(M+1)^+$, 113, 107. HRMS (EI) Calcd for $C_{14}H_{16}NO_4$: $(M+H)^+$, 262.1078. Found: *m*/*z* 262.1074. Major epimer: ^1H NMR ($CDCl_3$) $\delta = 2.14$ (3H, s, $COCH_3$), 3.83—3.90 (1H, m, C4-H), 4.63—4.70 (1H, m, C5-H), 5.05—5.32 (2H, m, $CH{=}C\underline{H}_2$), 5.50—5.85 (1H, m, $C\underline{H}{=}CH_2$), 5.70 (1H, d, $J = 7.3$ Hz, CH(OAc)Ph), 7.30—7.45 (5H, m, arom-H).

(4*S*,5*S*)-4-(1-Acetoxy-1-phenylmethyl)-5-(2-hydroxyethyl)-2-oxazolidinone (25): A solution of **24** (98 mg, 0.38 mmol) in THF (2 ml) was added dropwise to a solution of 9-BBN (110 mg, 0.43 mmol) in THF (3 ml) under an argon atmosphere at room temperature. After stirring for 3 h the reaction mixture was cooled on an ice bath; then $NaHCO_3$ (290 mg, 3.45 mmol), H_2O (5.6 ml), EtOH (3ml), and 30% H_2O_2 (484 mg, 4.27 mmol) were added successively. The resulting solution was stirred for 40 min at room temperature and concentrated in vacuo. The residue was diluted with brine and extracted with $CHCl_3$. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (AcOEt) to afford a diastereomeric mixture of primary alcohols **25** (80 mg, 76%) as a colorless oil. IR 3410, 1750 cm^{-1}. MS (EI) *m*/*z* 280 $(M+1)^+$, 130 (base). HRMS (EI) Calcd for $C_{14}H_{18}NO_5$: $(M+H)^+$, 280.1184. Found: *m*/*z* 280.1161. ^1H NMR ($CDCl_3$) $\delta = 1.40$—1.55 and 1.65—1.95 (2H, m, $C\underline{H}_2CH_2OH$), 2.13 and 2.15 (3H, each s, $COCH_3$), 3.59 and 3.69 (2H, each t, $J = 6.5$ and 5.4 Hz, respectively, $C\underline{H}_2OH$), 3.85—3.95 (1H, m, C4-H), 4.40—4.50 and 4.64—4.71 (1H, each m, C5-H), 5.69 and 5.83 (1H, each d, $J = 7.3$ and 5.9 Hz, respectively, CH(OAc)Ph), 5.78 and 6.52 (1H, each brs, NH), 7.30—7.45 (5H, m, arom-H).

(4*S*,5*S*)-4-Benzyl-5-(2-hydroxyethyl)-2-oxazolidinone (22b): A solution of **25** (137 mg, 0.49 mmol) and 20% $Pd(OH)_2/C$ (91 mg) in EtOH (3 ml) was stirred at room temperature under 1 atm H_2 for 44 h. The catalyst was removed by filtration through celite. Evaporation of the solvent afforded an oil. The oil was flash chromatographed on silica gel ($CHCl_3$–MeOH 10/1) to give **22b** (91 mg, 84%) as a colorless oil. $[\alpha]_D^{20} -86.2°$ (*c* 1.22, $CHCl_3$). IR 1750 cm^{-1}. MS (EI) *m*/*z* 222 $(M+1)^+$, 130 (base). HRMS (EI) Calcd for $C_{12}H_{16}NO_3$: $(M+H)^+$, 222.1129. Found: *m*/*z* 222.1118. ^1H NMR ($CDCl_3$) $\delta = 1.70$—2.00 (3H, m, $C\underline{H}_2CH_2OH$), 2.75—2.96 (2H, m, CH_2Ph), 3.70—3.85 (3H, m, $C\underline{H}_2OH$, C4-H), 4.45—4.55 (1H, m, C5-H), 5.44 (1H, brs, NH), 7.15—7.40 (5H, m, arom-H).

(4*S*,5*S*)-4-Isobutyl-2-oxooxazolidine-5-acetic Acid (27a): To a stirred solution of **22a** (45.1 mg, 0.24 mmol) in acetone (6 ml) was added dropwise Jones reagent (0.30 ml, 0.63 mmol) on an ice-bath. After stirring for 20 min, to the mixture was added dropwise *i*-PrOH (0.2 ml); the whole was then stirred for an additional 10 min to turn heterogeneous. The generated insoluble solids were removed by filtration through celite and washed with acetone. The combined filtrates were concentrated in vacuo and chromatographed on silica gel (AcOEt—$CHCl_3$–MeOH–AcOH 32/3/0.5) to afford the carboxylic acid **27a** (46 mg, 96%) as a colorless oil. $[\alpha]_D^{20} -48.1°$ (*c* 1.41, $CHCl_3$). IR 1760, 1730 cm^{-1}. MS (FAB) *m*/*z* 202 $(M+1)^+$, 188, 158. ^1H NMR(CD_3OD) $\delta = 0.93$ (3H, d, $J = 5.9$ Hz, CH_3), 0.95 (3H, d, $J = 5.9$ Hz, CH_3), 1.37—1.55 (2H, m, $C\underline{H}_2CH(CH_3)_2$), 1.65—1.80 (1H, m, $CH_2C\underline{H}(CH_3)_2$), 2.70 (2H, d, $J = 6.4$ Hz, 2H, $C\underline{H}_2CO_2H$), 3.60—3.70 (1H, m, C4-H), 4.50—4.58 (1H, m, C5-H).

Methyl (4*S*,5*S*)-4-Isobutyl-2-oxooxazolidine-5-acetate (28a): To a solution of **27a** (9.0 mg, 0.04 mmol) in MeOH (0.1 ml) was added a solution of CH_2N_2 in Et_2O at room temperature. After standing the mixture for 3 h, the reaction was quenched with AcOH. The mixture was concentrated in vacuo and chromatographed on silica gel (AcOEt–hexane 1/1—AcOEt) to give the methyl ester **28a** (9.5 mg, 99%) as a colorless oil. $[\alpha]_D^{20} -43.3°$ (*c* 0.98, $CHCl_3$). IR 3420, 1750 cm^{-1}. MS (EI) *m*/*z* 216 $(M)^+$, 142 (base). HRMS (EI) Calcd for $C_{10}H_{18}NO_4$ $(M)^+$, 216.1235. Found: *m*/*z* 216.1245. ^1H NMR ($CDCl_3$) $\delta = 0.92$ (3H, d, $J = 6.4$ Hz, CH_3), 0.95 (3H, d, $J = 6.8$ Hz, CH_3), 1.40—1.49 (1H, m, $C\underline{H}_2CH(CH_3)_2$), 1.50—1.60 (1H, m, $C\underline{H}_2CH(CH_3)_2$), 1.60—1.74 (1H, m, $CH_2C\underline{H}(CH_3)_2$), 2.69 (1H, dd, $J = 16.1$, 6.4 Hz, $C\underline{H}_2CO_2Me$), 2.82 (1H, dd, $J = 16.1$, 6.4 Hz, $C\underline{H}_2CO_2Me$), 3.57—3.65 (1H, m, C4-H), 3.72 (3H, s,

$COOCH_3$), 4.54—4.60 (1H, m, C5-H), 6.26 (1H, brs, NH).

(4*S*,5*S*)-(4-Benzyl-2-oxooxazolidine-5-acetic Acid (27b): To a stirred solution of **22b** (82 mg, 0.37 mmol) in acetone (10 ml) was added dropwise Jones reagent (0.45 ml, 0.95 mmol) on an ice bath. After stirring for 40 min, to the mixture was added dropwise *i*-PrOH (0.2 ml); the mixture was then stirred for an additional 10 min. The resulting insoluble solids were removed by filtration through celite and washed with acetone. The combined filtrates were concentrated in vacuo and chromatographed on a silica gel ($CHCl_3$–MeOH–AcOH 32/2/0.5) to afford the carboxylic acid **27b** (62 mg, 71%) as a colorless oil. $[\alpha]_D^{20} -62.5°$ (*c* 1.18, $CHCl_3$). IR 1760, 1750 cm^{-1}. MS (EI) *m*/*z* 236 $(M+1)^+$, 100 (base). HRMS (EI) Calcd for $C_{12}H_{14}NO_4$ $(M+H)^+$, 236.0923. Found: *m*/*z* 236.0945. ^1HNMR (CD_3OD) $\delta = 2.40$—2.80 (2H, m, $C\underline{H}_2CO_2H$), 2.90 (2H, d, $J = 5.9$ Hz, CH_2Ph), 3.83—3.93 (1H, m, C4-H), 4.60—4.70 (1H, m, C5-H), 7.20—7.40 (5H, m, arom-H).

Methyl (4*S*,5*S*)-4-Benzyl-2-oxooxazolidine-5-acetate (28b): To a solution of **27b** (57 mg, 0.242 mmol) in MeOH (0.5 ml) was added a solution of CH_2N_2 in Et_2O at room temperature. After standing for 3 h, the reaction was quenched with AcOH. The mixture was concentrated in vacuo and chromatographed on silica gel (AcOEt) to give the methyl ester **28b** (60 mg, quant.) as a colorless oil. $[\alpha]_D^{20} -53.1°$ (*c* 1.24, $CHCl_3$). IR 1760, 1750 cm^{-1}. MS (EI) *m*/*z* 250 $(M+1)^+$, 249 $(M)^+$, 158 (base). HRMS (EI) Calcd for $C_{13}H_{16}NO_4$ $(M+H)^+$, 250.1078. Found: *m*/*z* 250.1062. ^1HNMR ($CDCl_3$) $\delta = 2.61$ (1H, dd, $J = 16.1$, 6.8 Hz, $C\underline{H}_2CO_2CH_3$), 2.78 (1H, dd, $J = 16.1$, 6.3 Hz, $C\underline{H}_2CO_2CH_3$), 2.84 (1H, dd, $J = 13.7$, 8.8 Hz, CH_2Ph), 2.99 (1H, dd, $J = 13.7$, 5.4 Hz, CH_2Ph), 3.69 (1H, s, CO_2CH_3), 3.70—3.85 (1H, m, C4-H), 4.65—4.75 (1H, m, C5-H), 5.25 (1H, brs, NH), 7.15—7.40 (1H, m, arom-H).

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