Synthesis of D-*erythro*-Sphingosine from D-Glucosamine

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D-*erythro*-Sphingosine (1) was synthesized from D-glucosamine (2) as a chiral pool through stereoinversion of the C(3)-hydroxyl group *via* an oxidation–reduction sequence, transformation to the *erythro*-amino-alcohol chiron (9) protected as the oxazolidinone, and elongation of the side chain at the C(6)-position of the derived chloride (12).

Key words D-*erythro*-sphingosine; enantiospecific synthesis; D-glucosamine; chiral pool

Sphingosines are important components of ceramides, which constitute the hydrophobic part of glycosphingolipids such as cerebroside and ganglioside, and sphingophospholipids such as sphingomyelin and ceramide ciliatin.[2] D-*erythro*-Sphingosine ((2*S*,3*R*,4*E*)-2-aminooctadec-4-ene-1,3-diol) (**1**) is the most frequently occurring stereoisomer in nature and has recently been found to be a potent inhibitor of protein kinase C.[3] Owing to the biological importance and inaccessibility from natural sources, a great deal of effort has been devoted to the synthesis of optically active sphingosines starting from readily available chiral pools. A number of methods are available for the synthesis of sphingosines, particularly D-*erythro*-sphingosine, utilizing chiral pools which contain no chiral amino group, such as (*S*,*S*)-tartaric acid,[4a] (*R*)-glycidol,[4b] and sugars (D-glucose,[4c] D-galactose,[4d] and D-xylose,[4e]), chiral alcohols[4f] and epoxy alcohols[4g] prepared by chemical and enzymatic asymmetric synthesis, and chiral amino acids (L-serine).[4h] However, syntheses starting from chiral 1,2-aminoalcohol building blocks have been limited to only a few cases in which D-glucosamine (**2**) was used.[5]

In our study on the utilization of D-glucosamine as a chiral poly-hydroxylated amine source, we have recently achieved chiral synthesis of (3*S*,4*S*)-statine, a key component of inhibitory peptides of the aspartic proteases pepsin and renin.[6] We wish to report herein a new chiral synthesis of D-*erythro*-sphingosine (**1**) starting from D-glucosamine (**2**) *via* elongation of the side chain of the terminal allylic chloride (**12**), which was obtained by facile derivation from the protected *erythro*-aminoalcohol (**9**). The key intermediate (**9**) was prepared from **2** through stereoinversion of the C3-hydroxyl group by reduction of the corresponding C3-keto-derivative (**3**), providing the allosamine derivative (**4**) followed by C6-bromination and reductive opening of the pyranose ring (Chart 1).

Preparation of the Protected *erythro*-Aminoalcohol (9) The key intermediate (**9**) was derived from D-glucosamine *via* a nine-step sequence of reactions illustrated in Chart 2. Among the known methods for inversion of the C3-hydroxyl group of the D-glucosamine skeleton,[7] we selected a procedure including oxidation to the corresponding ketone followed by hydride-reduction as the most reliable process.[7a] Thus, methyl 4,6-*O*-benzylidene-2-methoxycarbonylamino-2-deoxy-α-D-*ribo*-hexopyranosid-3-ulose (**3**), prepared in 54% overall yield from **1** *via* four steps according to the literature,[8] was reduced with $NaBH_4$ to give in high yield (90%) the crystalline D-allopyranoside (**4**), along with a trace amount of the C3-epimer (**4'**), which could be removed by recrystallization. The crystalline 6-bromo-pyranoside (**6**) was obtained in 61% overall yield from **4** through a two-step sequence of reactions including formation of an oxazolidinone derivative (**5**) and oxidative bromination of the benzylidene acetal functionality using *N*-bromosuccinimide (NBS) according to the reported method.[7a,9] The structure of **6** including the stereochemistry at the C3-carbon atom was established by X-ray crystallography and a

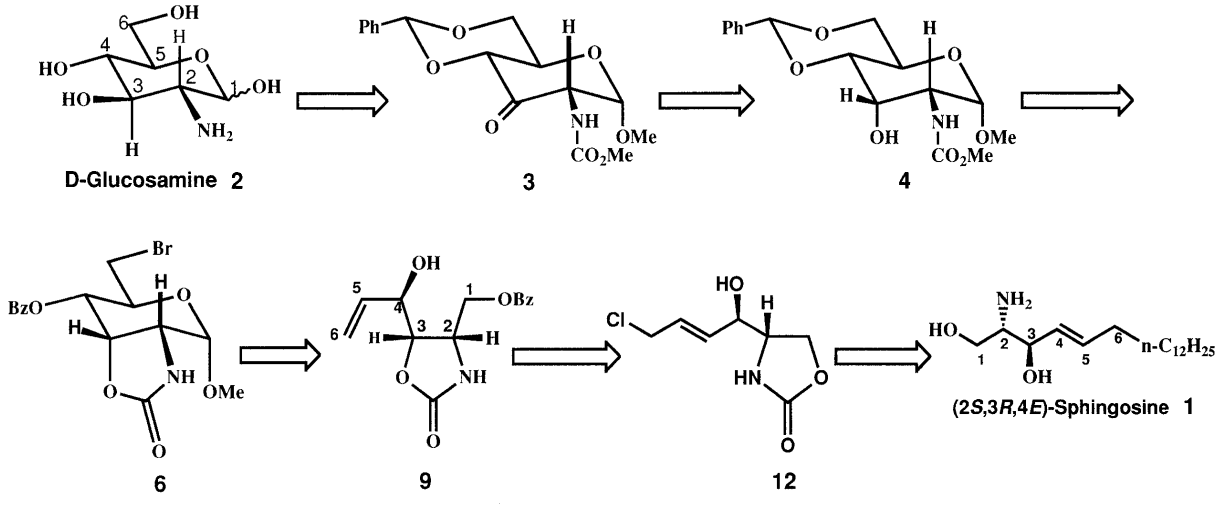

Chart 1

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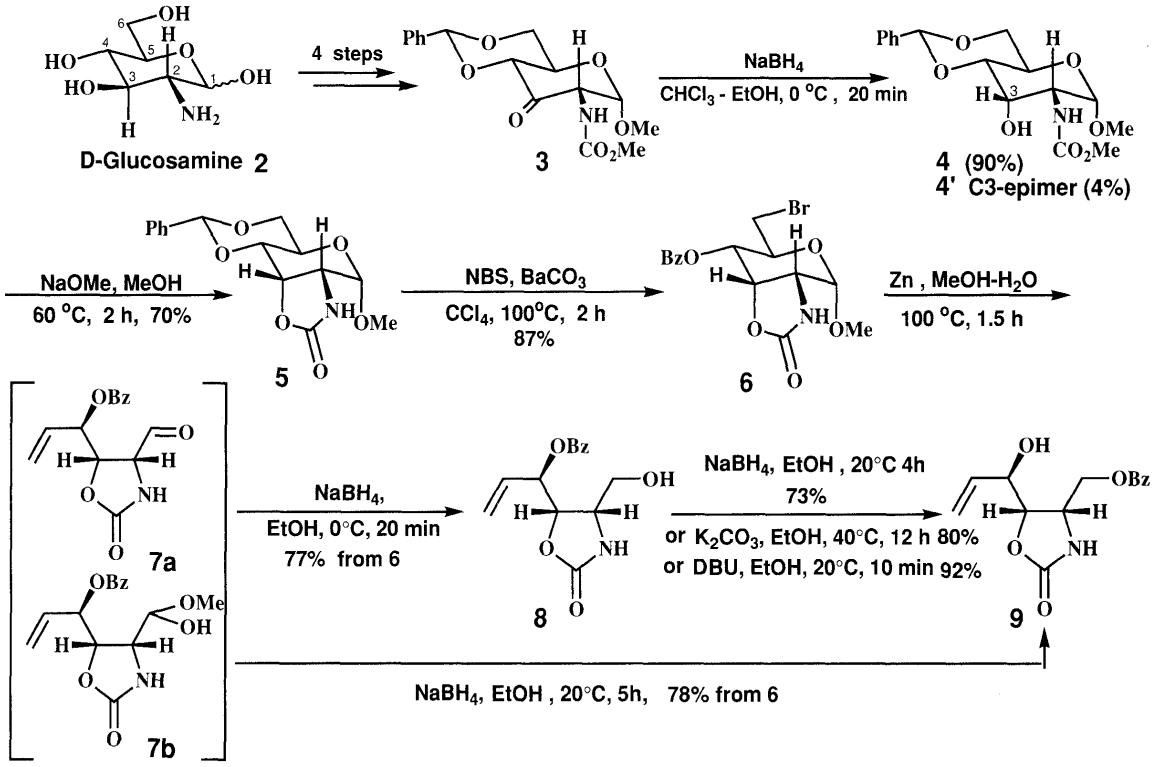

Chart 2

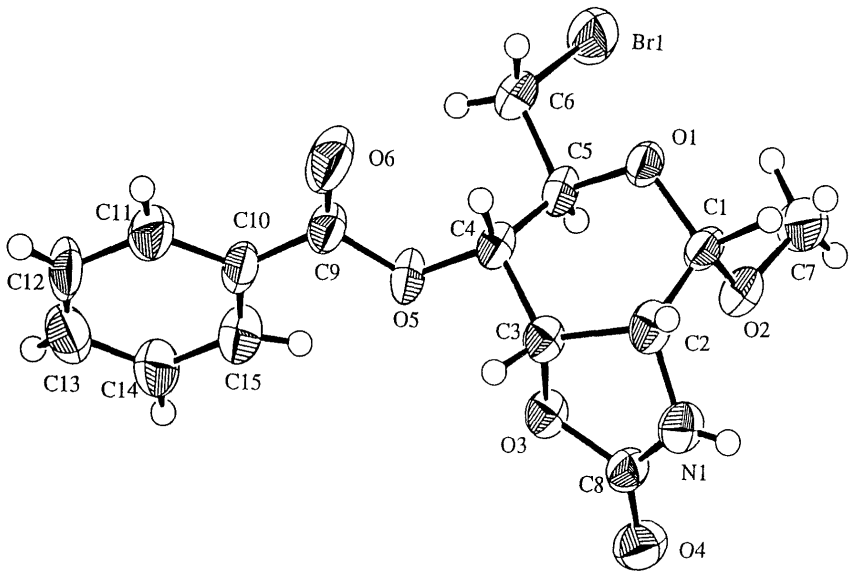

Fig. 1. Perspective View of the Crystal Structure of the Bromide (**6**)

perspective view is shown in Fig. 1. Debrominative ring fission[10] of the bromide (**6**) was realized by heating with Zn in aqueous MeOH to afford an inseparable mixture of an aldehyde (**7a**) and its methyl hemiacetal (**7b**), which, without purification, was treated with $NaBH_4$ in EtOH at 0 °C for 20 min to give the secondary benzoate (**8**) as an oil in 77% overall yield from **6**. Prolonged exposure of the aldehyde (**7**) to room temperature for 12 h gave a rearranged primary benzoate (**9**) as crystals in 78% overall yield from **6**. Smooth isomerization of the secondary benzoate (**8**) to the primary one (**9**) was achieved with $NaBH_4$, K_2CO_3, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in EtOH at 20 to 40 °C.

Preparation of Terminal *trans*-Allylic Chloride (12) Chlorination of the secondary allylic alcohol (**9**) with an excess amount of $SOCl_2$ in ether under reflux for 15 h gave exclusively the desired terminal allylic chloride in 83% yield. The *E*-stereochemistry of the allylic chloride (**10**) was supported by the coupling constant ($J_{1',2'} = 15.1$ Hz) of the olefinic protons in ^{1}H-NMR. Using *N*,*N*-dimethyl formamide (DMF) as a solvent, the reaction proceeded smoothly to afford **10** in 79% yield in 3 h at room temperature, while prolonged reaction (15 h) provided a 6:5-mixture of **10** and the *N*-formylated derivative (**11**) in 89% yield. Compound **11** was derived from **10** under the same conditions, as shown in Chart 3.[11] Both compounds (**10** and **11**) were transformed to a rearranged oxazolidinone derivative (**12**) in excellent yield by a basic

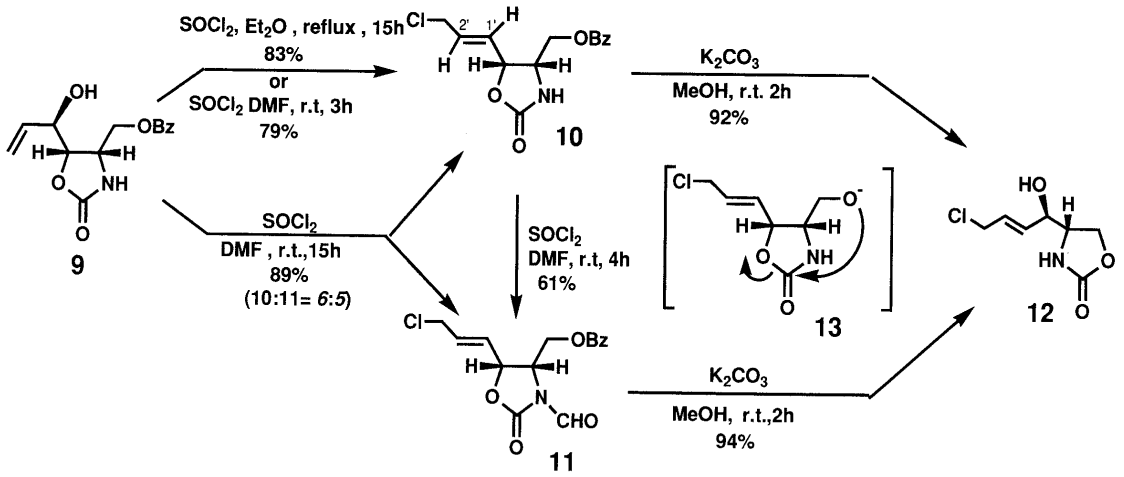

Chart 3

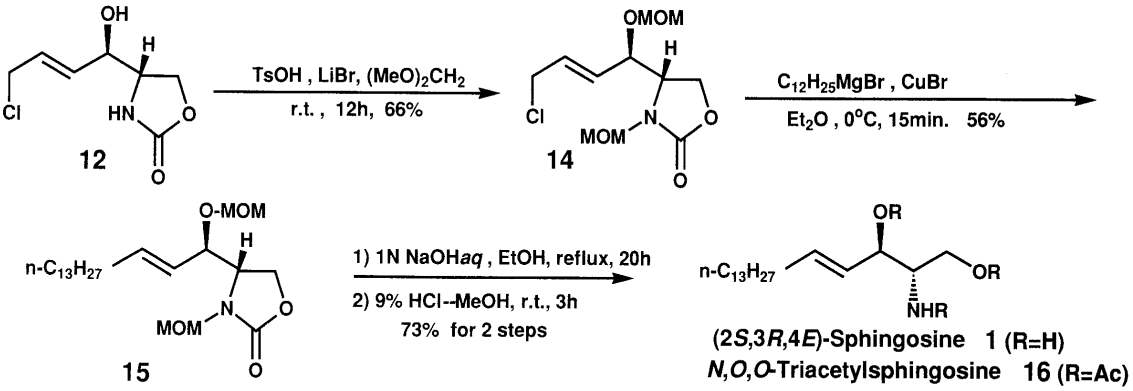

Chart 4

treatment using K_2CO_3 in MeOH. The process is supposed to involve transesterification, yielding a primary alkoxide (**13**) followed by cyclization as illustrated, which took place easily owing to the driving force of release from the 1,2-*cis*-strain of the substituents on the oxazolidinone skeleton. Similar oxazolidinone equilibration of 4,5-*cis*-5-substituted 4-hydroxymethyloxazolidinones has been reported to give isomerized 4-substituted oxazolidinones.[12]

Synthesis of D-*erythro*-Sphingosine (1) Having the terminal allylic chloride (**12**) with consecutive olefinic aminoalcohol functionalities of the requisite stereochemistry in hand, synthesis of D-*erythro*-sphingosine (**1**) was completed according to the scheme shown in Chart 4. After *N,O*-protection of **12** with a methoxymethyl (MOM) group, elongation of the side chain of the oxazolidinone derivative (**14**) to construct the whole carbon chain of D-*erythro*-sphingosine (**1**) was achieved in 56% yield by reaction with a Grignard reagent prepared from dodecyl bromide in the presence of CuBr. The *N,O*-MOM protecting groups were removed *via* successive treatments of **15** with 1 N NaOH in refluxing EtOH and 9% aqueous HCl in MeOH at room temperature to give D-*erythro*-sphingosine (**1**) as crystals in 73% overall yield. The structure of the synthetic compound (**1**) was confirmed by comparison of the physicochemical data of the product and its crystalline *N,O,O*-triacetyl derivative (**16**) with those for the corresponding authentic compounds.[4g]

Thus, a total synthesis of D-*erythro*-sphingosine (**1**) has been accomplished starting from D-glucosamine (**2**) in 14 steps by way of the key protected *erythro*-aminoalcohol (**9**). It is worth noting that the intermediates **8** and **9** appear to have potential for syntheses of phytosphingosines[13] and unusual hydroxy-amino acid moieties of biologically active compounds such as AI-77-B and calyculins.[14]

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 spectrometer in $CHCl_3$ solutions and are indicated in $\nu(cm^{-1})$. ^{1}H-NMR spectra were taken on JEOL GX-270 (270 MHz) and JEOL JNM-EX-400 (400 MHz) instruments in $CDCl_3$ solutions 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 (HRMS) were recorded on JEOL JMS-SX102A spectrometer and are indicated as *m/z*. Reactions were carried out under an argon atmosphere using distilled anhydrous solvents, and after extraction 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), unless otherwise noted.

Starting methyl 4,6-*O*-benzylidene-2-desoxy-2-methoxycarbonylamino-α-D-*ribo*-hexopyranosid-3-ulose (**3**) was prepared in 89% yield with CrO_3 and pyridine in CH_2Cl_2 according to the literature procedure from methyl 4,6-*O*-benzylidene-2-desoxy-2-(methoxycarbonylamino)-α-D-glucopyranoside (**4'**).[8]

Methyl 4,6-*O*-Benzylidene-2-deoxy-2-(methoxycarbonylamino)-α-D-glucopyranoside (4') A mixture of methyl 2-desoxy-2-(methoxycarbonylamino)-α-D-glucopyranoside (25.6 g, 102 mmol), which was prepared from D-glucosamine (**2**)·HCl (24.0 g, 114 mmol) according to the litera-

ture,[8] benzaldehyde (184 ml, 1.81 mol), and $ZnCl_2$ (61.7 g, 450 mmol) was stirred for 5 h at 60 °C. The reaction mixture was poured into ice-water (800 ml) and the product was extracted with $CHCl_3$. The extract was washed, dried, and evaporated to give a crude mass, which was washed with hexane and recrystallized from MeOH to afford the 4,6-*O*-benzylidene acetal (**4'**) (27.7 g, 61% overall yield from D-glucosamine (**2**)) as colorless needles, mp 229 °C, $[\alpha]_D^{20}$ +41.0 (c=1.13, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{21}NO_7$: C, 56.63; H, 6.24; N, 4.13. Found: C, 56.41; H, 6.24; N, 4.18. IR (KBr): 3440, 3330, 1685, 1545. ^{1}H-NMR: 2.27 (1H, br s, OH), 3.40 (3H, s, OCH_3), 3.54 (1H, m, 4-H), 3.71 (3H, s, CO_2CH_3), 3.40—3.75 (4H, m, 2-H, 5-H, 6-H_2), 4.28 (1H, dd, J=5.37, 3.17, 3-H), 4.72 (1H, d, J=2.93, 1-H), 5.07 (1H, d, J=7.81, NH), 5.56 (1H, s, 7-H), 7.40 (5H, br, arom.-H).

Methyl 4,6-*O*-Benzylidene-2-deoxy-2-(methoxycarbonylamino)-α-D-allopyranoside (4) $NaBH_4$ (540 mg, 14.5 mmol) was added in portions to an ice-cooled solution of **3** (13.3 g, 39.4 mmol) in EtOH (200 ml)–$CHCl_3$ (500 ml). The reaction temperature was held below 0 °C for 1.5 h, and the reaction mixture was poured into a mixture of brine (1200 ml) and 4 N HCl (6 ml). The resulting solution was extracted with $CHCl_3$. The combined extracts were washed with brine, dried, and concentrated *in vacuo* to give a crude alcohol (13.94 g). Recrystallization of the crude alcohol from isopropyl ether afforded the pure alcohol (**4**) (9.6 g, 72%) as colorless needles, mp 141 °C, $[\alpha]_D^{20}$ +82.7° (c=1.02, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{21}NO_7$: C, 56.63; H, 6.24; N, 4.13. Found: C, 56.39; H, 6.23; N, 4.18. IR (KBr): 3540, 3410, 1695. MS (EI): 340 $(M+1)^+$, 339 $(M)^+$, 308 $(M-31(CH_3O))^+$, 130 (base). ^{1}H-NMR: 2.69 (1H, s, OH), 3.44 (3H, s, OCH_3), 3.63 (1H, dd, J=9.8, 2.4, 4-H), 3.70 (3H, s, COOMe), 3.79 (1H, dd, J=10.3, 10.3, 6-H_{ax}), 3.95—4.01 (1H, m, 2-H), 4.07—4.06 (1H, m, 5-H), 4.19—4.23 (1H, m, 3-H), 4.37 (1H, dd, J=10.3, 6.4, 6-H_{eq}), 4.75 (1H, d, J=3.9, 1-H), 5.53—5.57 (1H, m, NH), 5.60 (1H, s, Ph-CH), 7.34—7.39 (3H, m, arom.-H), 7.46—7.51 (2H, m, arom.-H).

Column chromatography of the mother liquor of recrystallization on silica gel ($CHCl_3$–MeOH 40/1) gave another crop of **4** (2.2 g, 18%) and the C(3)-epimer (**4'**) (450 mg, 4%).

Methyl 2-Amino-4,6-*O*-benzylidene-2,3-*N*,*O*-carbonyl-2-deoxy-α-D-allopyranoside (5) The alcohol **4** (13.09 g, 38.5 mmol) was added to a solution of MeONa in MeOH (4.34 mol/l, 185 ml) and the mixture was heated at 60 °C under stirring for 2 h. The reaction mixture was poured into cold water (1200 ml) and extracted with $CHCl_3$. The organic solution was washed with brine, dried, and concentrated *in vacuo*. The residue was recrystallized from EtOH to afford the oxazolidinone (**5**) (8.30 g, 70%) as colorless crystals, mp 233 °C, $[\alpha]_D^{20}$ +216.3° (c=0.95, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{17}NO_6$: C, 58.62; H, 5.58; N, 4.56. Found: C, 58.44; H, 5.60; N, 4.59. IR (KBr): 3400, 2950, 2870, 1770, 1730. MS (EI): 308 $(M+1)^+$, 307 $(M)^+$, 276 $(M-31)^+$, 105 (base). ^{1}H-NMR: 3.42 (3H, s, OCH_3), 3.76 (1H, dd, J=10.3, 10.3, 6-H_{ax}), 3.80 (1H, dd, J=9.8, 3.4, 4-H), 3.93 (1H, dd, J=4.9, 5.9, 2-H), 4.16 (1H, ddd, J=10.3, 9.8, 4.9, 5-H), 4.38 (1H, dd, J=10.3, 4.9, 6-H_{eq}), 4.75 (1H, d, J=4.9, 1-H), 4.88 (1H, dd, J=5.9, 3.4, 3-H), 5.32 (1H, s, NH), 5.59 (1H, s, Ph-CH), 7.34—7.38 (3H, m, arom.-H), 7.47—7.52 (2H, m, arom.-H).

Methyl 2-Amino-4-*O*-benzoyl-6-bromo-2,3-*N*,*O*-carbonyl-2,6-dideoxy-α-D-allopyranoside (6) A suspension of the oxazolidinone (**5**) (3.70 g, 12.0 mmol), *N*-bromosuccimide (2.35 g, 12.6 mmol) and $BaCO_3$ (7.10 g, 36.1 mmol) in CCl_4 (240 ml) was heated under reflux for 2 h in an argon atmosphere. After the mixture had cooled, $CHCl_3$ (100 ml) and H_2O (100 ml) were added to it and the whole was stirred for 30 min. The insoluble precipitate was removed by filtration through Celite. The filtrate was extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2–Et_2O to afford the bromide (**6**) (3.85 g, 83.2%) as colorless prisms, mp 178—180 °C, $[\alpha]_D^{20}$ +207.5° (c=0.38, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{16}BrNO_6$: C, 46.65; H, 4.18; N, 3.63. Found: C, 46.72; H, 4.29; N, 3.67. IR (KBr): 3425, 2900, 1780, 1725. MS (EI): 325 $(M-59)^+$, 323 $(M-61)^+$, 105 (base). ^{1}H-NMR: 3.53 (3H, s, OCH_3), 3.55 (1H, dd, J=11.4, 5.9, 6-H_A), 3.69 (1H, dd, J=11.4, 2.9, 6-H_B), 3.99 (1H, dd, J=6.6, 4.0, 2-H), 4.47 (1H, ddd, J=8.4, 5.9, 2.6, 5-H), 4.94 (1H, d, J=4.4, 1-H), 5.11 (1H, dd, J=7.0, 3.7, 3-H), 5.15 (1H, br s, NH), 5.31 (1H, dd, J=10.3, 3.7, 4-H), 7.42—7.50 (2H, m, arom.-H), 7.55—7.66 (2H, m, arom.-H), 8.06 (1H, dd, J=7.7, 0.7, arom.-H (p)).

X-Ray Structure Analysis of the Bromide (6) Crystals of **6** were grown from a mixed solution of CH_2Cl_2–Et_2O to yield colorless prisms. Crystal data: $C_{15}H_{16}BrNO_6$; M.W.=386.20; monoclinic; $P2_1$(#4); a=9.2395(8), b=9.395(2), c=9.4074(9) Å; β=104.008(7)°; V=792.3(1) Å^3; Z=2; D_c=1.619 g/cm^3. The diffraction intensities were collected from a crystal with dimensions of 0.300×0.300×0.100 mm on a Rigaku AFC-5R diffractometer with graphite-monochromated CuK_α radiation and a 12 kW rotating anode generator. Of the total 1358 reflections observed within a 2θ range of 120.1°, 1272 were unique ($R_{int.}$=0.079). The final cycle of full-matrix least-squares refinement was based on 1254 observed reflections ($I>3.00\sigma(I)$) and 208 variable parameters. The final R value was 0.034 (R_w=0.050).

(4*R*,5*S*)-5-[(1*R*)-1-Benzoyloxy-2-propen-1-yl]-2-oxooxazolidin-4-carboxaldehyde (7a) and the Methylhemiacetal (7b) Zn powder (7.85 g, 120 mgatom) was added to a solution of **6** (1.54 g, 4.0 mmol) in EtOH–H_2O (10:1, 220 ml) and the mixture was heated under reflux for 3 h. After cooling, the precipitate was removed by filtration through Celite and rinsed with EtOH. The combined filtrates were concentrated *in vacuo*. The residue was dissolved in AcOEt. The solution was dried over $MgSO_4$ and concentrated *in vacuo* to give a crude aldehyde (**7**) (980 mg) as an oil, which was used in the next step without purification. An analytical sample of the aldehyde was prepared by silica gel column chromatography ($CHCl_3$–MeOH (10:1)) to afford a mixture of the aldehyde **7a** (minor) and methyl hemiacetal **7b** (major) as a colorless oil. IR: 3690, 3330, 1767, 1724. MS (FAB) 330 [M (hemiacetal)+23]$^+$, 308 [M (hemiacetal)+1]$^+$, 276 [M (aldehyde)+1)]$^+$ 105 (base). Methyl hemiacetal (**7b**): HRMS Calcd for $C_{15}H_{18}NO_6$ $(M+H)^+$: 308.1134. Found: 308.1141. ^{1}H-NMR 3.32, 3.42 (3H, s, OCH_3), 3.45 (1H, br s, OH), 3.80—3.97 (1H, m, 4-H), 4.65—4.75 (1H, m, C<u>H</u>(OH)OCH_3), 4.86 (1H, dd, J=7.7, 7.3, 5-H), 5.42 (1H, d, J=10.1, C<u>H</u>$_2$=CH), 5.51 (1H, d, J=17.2, C<u>H</u>$_2$=CH), 5.90—6.24 (3H, m, C<u>H</u>OBz, CH_2=C<u>H</u>, NH), 7.42—7.58 (2H, m, arom.-H), 7.59 (1H, d, J=6, arom.-H), 8.45 (2H, dd, J=6.5, 1.8, arom.-H), Aldehyde (**7a**): ^{1}H-NMR: 4.82 (1H, m), 5.21 (1H, dd, J=9.16, 4.03), 9.85 (1H, s, CHO).

2,4-Dinitrophenylhydrazone of 7a 2,4-Dinitrophenylhydrazine (20 mg, 0.1 mmol) was added to a mixture of the aldehyde **7a** and the methyl hemiacetal **7b** (33 mg) in EtOH (1 ml). The resulting suspension was treated with 4 N HCl dioxane (11 mg), and the whole was stirred for 7 h at room temperature. It was concentrated *in vacuo* and the resulted solid was dispersed in aqueous 1 N $NaHCO_3$ (2 ml), filtered, and washed with H_2O and EtOH. The pale brown solid obtained was recrystallized from EtOH to give the hydrazone (19 mg, 42%) as pale brown prisms, mp 210.6—211.5 °C (dec.). *Anal.* Calcd for $C_{20}H_{17}N_5O_8 \cdot 1/5H_2O$: C, 52.34; H, 3.82; N, 15.26. Found: C, 52.15; H, 3.49; N, 15.00. IR (KBr): 3474, 1801, 1761, 1716, 1618, 1587, 1522, 1340, 1267. MS (FAB): 456 $[M+1]^+$, 307, 154, 107 (base). HRMS Calcd for $C_{20}H_{18}N_5O_8$ $(M+H)^+$: 456.1156. Found: 456.1219. ^{1}H-NMR (DMSO-d_6): 4.81 (1H, dd, J=8.6, 6.9, 4-H), 5.12 (1H, dd, J=8.6, 6.6, 5-H), 5.36 (1H, d, J=10.6, C<u>H</u>$_2$=CH), 5.41 (1H, d, J=17.1, C<u>H</u>$_2$=CH), 5.68 (1H, dd, J=5.9, 5.9, C<u>H</u>OBz), 5.99 (1H, ddd, J=17.2, 10.6, 5.9, CH_2=C<u>H</u>), 7.38 (2H, dd, J=7.9, 7.9, arom.-H), 7.56 (1H, dd, J=7.6, 7.2, arom.-H), 7.65 (1H, d, J=9.6, arom.-H), 7.89 (2H, d, J=6.9, arom.-H), 8.12—8.22 (2H, m, CH=N, CONH), 8.35 (1H, s, arom.-H), 8.79 (1H, d, J=2.6, arom.-H), 11.5 (1H, s, C=NNH).

(4*S*,5*S*)-5-[(1*R*)-1-Benzoyloxy-2-propen-1-yl]-4-hydroxymethyloxazolidin-2-one (8) $NaBH_4$ (154 mg, 4.0 mmol) was added *in portions* to an ice-cold solution of the mixture of products **7a** and **7b** (980 mg) in EtOH (20 ml). After having been stirred for 20 min, the reaction mixture was adjusted to neutral with 4 N HCl and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (AcOEt–Hexane (2:1) to afford the alcohol (**8**) (850 mg, 77% from the bromide (**6**)) as a pale yellow oil, $[\alpha]_D^{20}$ +10.3° (c=1.67, $CHCl_3$). IR: 3240—3250, 1720—1775. MS (EI): 278 $(M+1)^+$, 246 $(M-31(CH_2OH))^+$, 105 (base). HRMS Calcd for $C_{13}H_{12}NO_4$ $(M-CH_2OH)^+$: 246.07658. Found: 246.07648. ^{1}H-NMR: 2.62 (1H, br s, OH), 3.79 (2H, m, 4-C<u>H</u>$_2$OH), 4.01—4.10 (1H, m, 4-H), 4.86 (1H, dd, J=7.8, 7.8, 5-H), 5.40 (1H, d, J=10.3, C<u>H</u>$_2$=CH), 5.48 (1H, d, J=17.1, C<u>H</u>$_2$=CH), 5.83 (1H, t, J=7.62, 5-CHOBz), 5.93—6.06 (2H, m, NH, CH_2=C<u>H</u>), 7.44—7.63 (3H, m, arom.-H_3), 8.01—8.08 (2H, m, arom.-H_2).

Benzoyl Migration of 8, Providing (4*S*,5*S*)-4-Benzoyloxymethyl-5-[(1*R*)-1-hydroxy-2-propen-1-yl]oxazolidin-2-one (9) a) With $NaBH_4$: A mixture of **8** (293 mg, 1.06 mmol) and $NaBH_4$ (69 mg, 1.8 mmol) in EtOH (4.0 ml) was stirred for 4 h at room temperature and the reaction was quenched by addition of ice-water. The whole was shaken with AcOEt and the extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (230—400 mesh, AcOEt) to give the *sec*-alcohol (**9**) (215 mg, 73%) as colorless neeedles, mp 150—152 °C, $[\alpha]_D^{20}$ −65.1° (c=0.29, $CHCl_3$). IR (KBr): 3470, 3300, 1770, 1765, 1700. MS (EI): 279

$(M+2)^+$, 278 $(M+1)^+$, 277 $(M)^+$, 105 (base). ^{1}H-NMR: 2.47 (1H, br s, OH), 4.20—4.30 (1H, m, 4-H), 4.45—4.60 (3H, m, C$\underline{H}_2$OBz, CH_2=CHC$\underline{H}$(OH), 5-H), 4.75 (1H, dd, J=11.2, 3.4, C$\underline{H}_2$OBz), 5.34 (1H, d, J=10.3, C$\underline{H}_2$=CH), 5.47 (1H, d, J=17.6, C$\underline{H}_2$=CH), 5.88 (1H, br s, NH), 6.01 (1H, ddd, J=17.6, 10.3, 4.9, CH_2=C$\underline{H}$), 7.40—7.49 (2H, m, arom.-H), 7.53—7.61 (1H, m, arom.-H), 8.00 (1H, d, J=6.9, arom.-H).

b) With K_2CO_3: K_2CO_3 powder (119.5 mg, 0.87 mmol) was added to a solution of **8** (121.2 mg, 0.44 mmol) in EtOH (2 ml). After having been stirred for 12 h at 40 °C under an argon atmosphere, the reaction mixture was added to H_2O and the whole was extracted with AcOEt. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified to give the *sec*-alcohol (**9**) (96.5 mg, 80%).

c) With DBU: DBU (54.0 mg, 0.35 mmol) was added to a solution of **8** (102.7 mg, 0.37 mmol) in EtOH (2 ml). After having been stirred for 10 min at room temperature, the reaction mixture was diluted with AcOEt (30 ml), washed with brine (20 ml)–aqueous 1 N HCl (2 ml), and brine (10 ml × 2), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified to afford the *sec*-alcohol (**9**) (94.1 mg, 92%).

Reduction of 7 with Concomitant Benzoyl Migration, Yielding 9 A solution of $NaBH_4$ (6.9 mg, 0.182 mmol) in EtOH was stirred for 0.5 h at room temperature. Then a solution of **7a** and **7b** (29.3 mg), obtained from the bromide (**6**) (38.5 mg, 0.1 mmol), in EtOH (0.2 ml) was added. The reaction mixture was stirred for an additional 5 h at room temperature, diluted with AcOEt, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography (AcOEt) to give the *sec*-alcohol (**9**) (21.5 mg, 78% from the bromide **6**) as colorless needles.

Chlorination of 9, Yielding (4*S*,5*R*)-4-Benzoyloxymethyl-5[(*E*)-3-chloro-1-propen-1-yl]oxazolidin-2-one (10) a) A solution of the alcohol (**9**) (689 mg, 2.5 mmol) in Et_2O (120 ml) was treated with $SOCl_2$ (5.44 ml, 74.5 mmol) at room temperature and the mixture was refluxed for 15 h. The reaction was quenched by addition of ice and the whole was extracted with EtOAc, washed with brine, dried, and evaporated to give a crude crystalline product. Purification of the crude mass by chromatography with EtOAc–hexane (1 : 1) followed by recrystallization from Et_2O afforded a terminal allylic chloride (**10**) (602 mg, 83%), mp 132—134 °C, $[\alpha]_D^{20}$ −76.4° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{14}H_{14}ClNO_4$: C, 56.86; H, 4.77; N, 4.74. Found: C, 56.60; H, 4.89; N, 4.58. IR: 1760, 1720, 1270, 970. ^{1}H-NMR: 4.06 (2H, d, J=6.34, 3′-H_2), 4.16—4.25 (2H, m, 4-H, 4-CH_2OBz), 4.44 (1H, m, 4-CH_2OBz), 5.24 (1H, dd, J=7.08, 6.84, 5-H), 5.92 (1H, dd, J=6.84, 15.14, 1′-H), 6.07—6.16 (2H, m, 2′-H, NH), 7.45 (2H, dd, J=7.57, 8.55, arom.-H_2 (m)), 7.59 (1H, dd, J=1.22, 7.57, arom.-H (*p*)), 8.01 (2H, dd, J=1.22, 8.55, arom.-H_2(*o*)).

b) A solution of **9** (231 mg, 0.8 mmol) in DMF (8.0 ml) was treated with $SOCl_2$ (496 mg, 4.2 mmol) and the mixture was stirred at room temperature for 3 h. After work-up as in procedure a), a terminal allylic chloride (**10**) (196 mg, 79%) was obtained.

c) A solution of **9** (500 mg, 1.8 mmol) in DMF (10.0 ml) was treated with $SOCl_2$ (1.20 g, 10.0 mmol) and the mixture was stirred at room temperature for 15 h. Work-up as in procedure a) and chromatography of the product afforded compound **10** (259 mg, 48.6%) and the *N*-formyl derivative (**11**) as an oil (236 mg, 40.4%). **11**: IR: 1785, 1710, 1260, 960. ^{1}H-NMR: 4.03 (2H, d, J=6.35, 3′-H_2), 4.42 (1H, m, 4-CH_2OBz), 4.70—4.76 (2H, m, 4-CH_2OBz, 4-H), 5.27 (1H, dd, J=7.57, 7.08, 5-H), 5.95 (1H, dd, J=7.08, 15.38, 1′-H), 6.16 (1H, m, 2′-H), 7.47 (2H, m, arom.-H_2(*m*)), 7.61 (1H, m, arom.-H(*p*)), 7.98 (2H, m, arom.-H_2(*o*)), 9.01 (1H, s, N-CHO). MS (FAB): 324 (M+1), 326 (M+3), 296 (M−CHO), 298 (M+1−CO).

***N*-Formylation of 10, Providing 11** A mixture of **10** (300 mg, 1.0 mmol) and $SOCl_2$ (480 mg, 4.0 mmol) in DMF (5.0 ml) was stirred for 4 h at room temperature and the whole was worked up as above to give oily **11** (195 mg, 61%) and recovered the starting material **10** (97 mg).

Recyclization of 10 and 11, Leading to (4*S*,1′*R*)-4[(*E*)-4-Chloro-1-hydroxy-2-buten-1-yl]oxazolidin-2-one (12) a) A mixture of **10** (1.06 g, 3.6 mmol) and K_2CO_3 (249 mg, 1.8 mmol) in MeOH (14 ml) was stirred for 2 h at room temperature. The mixture was extracted with EtOAc, washed with brine, dried, and concentrated *in vacuo* to give a crude mass, which was purified by chromatography with EtOAc–hexane (3 : 1) followed by recrystallization from $CHCl_3$ to give a terminal allylic chloride (**12**) (632 mg, 92%), mp 98—100 °C, $[\alpha]_D^{20}$ +11.1° (c=0.44, $CHCl_3$). *Anal.* Calcd for $C_7H_{10}ClNO_3$: C, 43.88; H, 5.26; N, 7.31. Found: C, 43.73; H, 5.26; N, 7.33. IR (KBr): 3360, 3290, 1750, 1250, 980. ^{1}H-NMR: 3.25 (1H, d, J=3.90, OH), 3.92 (1H, m, 4-H), 4.08 (2H, d, J=6.35, 4′-H), 4.27—4.44 (3H, m, 5-H_2, 1′-H), 5.73 (1H, dd, J=5.86, 15.13, 2′-H), 6.05 (1H, m, 3′-H), 6.24 (1H, s, NH).

b) A mixture of **11** (300 mg, 0.93 mmol) and K_2CO_3 (55 mg, 0.4 mmol) in MeOH (3.0 ml) was stirred for 2 h at room temperature. Work-up of the mixture and purification of the product gave crystalline **12** (167 mg, 94%).

***N,O*-Protection of 12, Affording the *N,O*-Di-Methoxymethyl Derivative (14)** A solution of **12** (240 mg, 1.3 mmol) in methylal (5.0 ml) was treated with LiBr (43.6 mg, 0.5 mmol) and *p*-TsOH (43.2 mg, 0.3 mmol) and the mixture was stirred for 12 h at room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc, washed with brine, dried, and evaporated *in vacuo* to give a crude oil, which was purified by chromatography with EtOAc–hexane (1 : 2) to give **14** (230 mg, 66%) as an oil, $[\alpha]_D^{20}$ −141.2° (c=0.71, $CHCl_3$). IR: 1755, 1155, 1120, 970. ^{1}H-NMR: 3.35 (6H, s, 2 × OCH_3), 4.01 (1H, m, 4-H), 4.07 (2H, d, J=6.34, 4′-H_2), 4.31—4.37 (3H, m, 5-H_2, 1′-H), 4.57, 4.68 (2H, ABq, J=7.08, OCH_2O), 4.74, 4.88 (2H, ABq, J=10.99, OCH_2O), 5.64 (1H, dd, J=6.84, 15.14, 2′-H), 6.02 (1H, m, 3′-H). MS (EI): 218 (M−61(OCH_2OCH_3)), 149, 130, 114. HRMS Calcd for $C_9H_{13}ClNO_3$ (M−OCH_2OCH_3)$^+$: 218.0584. Found: 218.0596.

Elongation of the Side Chain of 14, Providing (4*S*,1′*R*)-*N*-Methoxymethyl-4[(*E*)-1-(methoxymethyl)oxy-2-hexadecen-1-yl]oxazolidin-2-one (15) An ethereal solution of $C_{12}H_{25}MgBr$ (0.43 ml of mol/l in Et_2O), prepared from dodecyl bromide and Mg in Et_2O, was added to an ice-cold suspension of CuBr (49.6 mg, 0.35 mmol) in Et_2O. After 10-min stirring of the mixture at 0 °C, a solution of **14** (44 mg, 0.16 mmol) in Et_2O (1.0 ml) was added and the whole was stirred for 15 min at 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl and the product was extracted with EtOAc, washed with brine, dried, and concentrated *in vacuo* to give a crude oil. Purification of the crude product by chromatography with EtOAc–hexane (1 : 5) afforded **15** as an oil (36 mg, 56%). $[\alpha]_D^{20}$ −100.8° (c=0.77, $CHCl_3$). NMR: 0.88 (3H, t, J=6.59, C–CH_3), 1.26 (22H, br s, 11 × CH_2), 2.06 (2H, dd, J=6.84, 13.19, 4′-H_2), 3.33 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 4.00 (1H, m, 4-H), 4.22 (1H, dd, J=2.69, 7.57, 1′-H), 4.32 (2H, d, J=8.30, 5-H_2), 4.51, 4.69 (2H, ABq, J=6.84, OCH_2O), 4.75, 4.88 (2H, ABq, J=10.75, OCH_2O), 5.23 (1H, dd, J=7.57, 15.38, 2′-H), 5.82 (1H, m, 3′-H). IR: 1745, 1115, 960. MS (EI): 382 (M−31 (OCH_3)), 352 (M−61(OCH_2-OCH_3)), 238, 149, 130. HRMS Calcd for $C_{21}H_{38}O_3N$ (M−OCH_2-OCH_3)$^+$: 352.2852. Found: 352.2856.

Synthesis of D-*erythro*-Sphingosine (1) A mixture of **15** (132 mg, 0.32 mmol) and aqueous 1 N NaOH (6.0 ml) in EtOH (6.0 ml) was heated under reflux for 20 h. After concentration of the reaction mixture *in vacuo*, the residue was extracted with EtOAc. The organic solution was washed with brine, dried, and evaporated *in vacuo* to give a crude mass. The crude product was stirred with 9% HCl–MeOH (3.0 ml) at room temperature for 3 h, then neutralized with $NaHCO_3$ and concentrated *in vacuo* to give a crude mass, which was purified by extraction with $CHCl_3$ followed by chromatography with $CHCl_3$–MeOH–H_2O (13 : 6 : 1) to yield a crystalline mass. Recrystallization of the product from $CHCl_3$–MeOH gave pure **1** (69 mg, 73%), mp 80—82 °C, $[\alpha]_D^{20}$ −2.5° (c=1.3, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.32; H, 12.18; N, 4.50. IR: 3460, 970. ^{1}H-NMR (400 MHz): 0.83 (3H, t, J=7.02, C–CH_3), 1.23 (22H, br s, 11 × CH_2), 2.00—2.10 (2H, m, 6-H_2), 3.5—3.6 (1H, m, 2-H), 4.23 (1H, dd, J=7.03, 10.97, 1-H), 4.28 (1H, dd, J=4.02, 10.97, 1-H), 4.75 (1H, dd, J=5.10, 5.06, 3-H), 5.91—6.00 (2H, m, 4-H, 5-H).

***N,O,O*-Triacetyl-D-*erythro*-Sphingosine (16)** A mixture of **1** (30 mg, 0.1 mmol), Ac_2O (102 mg, 1.0 mmol), and pyridine (120 mg, 1.5 mmol) in CH_2Cl_2 (3.0 ml) was stirred at room temperature for 15 h, then concentrated *in vacuo*. The residue was extracted with EtOAc. The organic solution was washed with brine, dried, and evaporated *in vacuo* to give a crude mass, which was purified by chromatography with EtOAc–hexane (1 : 1) followed by recrystallization from EtOAc–hexane to afford **16** as crystals (33 mg, 78%), mp 103—105 °C, $[\alpha]_D^{20}$ −13.3° (c=1.11, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{43}NO_5$: C, 67.73; H, 10.18; N, 3.29. Found: C, 67.53; H, 10.23; N, 3.35. IR: 1735, 1670, 965. ^{1}H-NMR (400 MHz): 0.88 (3H, t, J=6.84, C–CH_3), 1.25 (22H, br s, 11 × CH_2), 1.98 (3H, s, $COCH_3$), 2.06 (3H, s, $COCH_3$), 2.07 (3H, s, $COCH_3$), 2.00—2.10 (2H, m, 6-H_2), 4.05 (1H, dd, J=3.91, 11.23, 1-H), 4.30 (1H, dd, J=6.11, 11.23, 1-H), 4.43 (1H, m, 2-H), 5.28 (1H, dd, J=6.60, 7.32, 3-H), 5.39 (1H, dd, J=7.32, 15.14, 4-H), 5.71 (1H, d, J=9.28, NH),

5.79 (1H, m, 5-H).

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References and Notes

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