(fixed) hydrogens have converged to a conventional crystallographic residual of 0.073 (R_w = 0.090) for the observed reflections. Crystallographic results are available as supplementary material.

Single-Crystal X-ray Analysis of 7-Isocyano-11-cycloamphilectene (2). Crystals were grown from a hexane solution by slow evaporation. Preliminary X-ray photographs showed orthorhombic symmetry, and accurate lattice constants of a = 8.1169 (7), b = 13.299 (2), and c = 16.962 (2) Å were determined from a least-squares fit of 15 diffractometer-measured 2θ values. The systematic extinctions, crystal density (~1.08 g/cm^3), and optical activity were uniquely accommodated by space group $P2_12_12_1$ with 1 molecule of $C_{21}H_{31}N$ forming the asymmetric unit. All diffraction maxima with $2\theta \leq 114°$ plus a subset of maxima with $2\theta \leq 156°$ were collected on a computer-controlled diffractometer using variable-speed, 1° ω scans and graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.541 78 Å). Of the 1821 reflections measured in this fashion, 1170 (64%) were judged observed ($F_o \geq 3\sigma(F_o)$) after correcting for background, Lorentz, and polarization effects.[6] The structure was solved uneventfully by using a multisolution tangent formula approach, and hydrogens were located on a ΔF synthesis after partial refinement. Block-diagonal least-squares refinements with anisotropic non-hydrogen atoms and isotropic (fixed) hydrogens have converged to a conventional crystallographic residual of 0.054 (R_w = 0.061) for the observed reflections. Additional crystallographic results are described in the supplementary material.

Preparation of Formamide from Isonitrile. General Procedure. The isonitrile (ca. 2–10 mg) was dissolved in a mixture of glacial acetic acid (0.5 mL) and water (two drops) and left at 30 °C for 24 h. Solvent was removed under vacuum and the residue dissolved in toluene (0.5 mL) and reevaporated. The residue was then dissolved in warm hexane and left standing at a temperature of −20 °C until crystals of formamide appeared.

Formamide 6: colorless prisms, mp 78–80 °C; IR ($CHCl_3$) 3440, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.87 (d, 3 H, J = 6.2 Hz), 0.88 (d, 3 H, J = 6.5 Hz), 1.57 (br s, 3 H), 1.64 (br s, 3 H), 1.68 (br s, 3 H), 2.25 (m, 1 H), 2.50 (m, 1 H), 5.07 (br d, 1 H, J = 9 Hz), 5.30 (m, 1 H), 5.61 (br d, 1 H, J = 12 Hz), 7.99 (d, 1 H, J = 12 Hz); EIMS, m/z 315 (M^+, 2%), 270 (45), 186 (49), 159 (100); exact-mass EIMS measured 315.2652, $C_{21}H_{33}NO$ requires 315.2562.

Formamide 7: colorless needles, mp 165–166 °C; IR ($CHCl_3$) 3380, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.84 (s, 3 H), 0.90, 0.91, 0.92 (2 d, s overlapping, 9 H), 2.28 (m, 3 H), 5.47 (br d, 1 H, J = 12 Hz), 8.37 (d, 1 H, J = 12 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.0 (q), 19.1 (q), 26.1 (t), 26.5 (q), 29.2 (t), 29.3 (s), 29.8 (t), 29.8 (q), 33.0 (d), 34.7 (d), 39.9 (t), 40.1 (d), 43.8 (t), 44.3 (d), 44.7 (t), 47.5 (d), 56.2 (s), 127.8 (s), 129.3 (s), 164.2 (d); exact-mass EIMS measured 315.2573, $C_{21}H_{33}NO$ requires 315.2562.

Single-Crystal X-ray Analysis of Formamide 7. The formamide 7 crystallized as stout rods and a crystal of approximate dimensions 0.4 × 0.4 × 0.6 mm was selected for further analysis. Preliminary X-ray diffraction photographs displayed orthorhombic symmetry, and precise lattice constants of a = 8.785 (2), b = 9.480 (2), and c = 22.521 (4) Å were determined from a least-squares fit of 15 diffractometer-measured 2θ values. The systematic extinctions, crystal density, and optical activity were uniquely accommodated by space group $P2_12_12_1$ with 1 molecule of composition $C_{21}H_{33}NO$ forming the asymmetric unit. All unique diffraction maxima with $2\theta < 114°$ were collected with graphite-monochromated Cu K$\bar{\alpha}$ radiation (1.541 78 Å) and variable-speed, 1° ω scans. Of the 1483 reflections measured in this way, 1242 (84%) were judged observed after correction for Lorentz, polarization, and background effects.[6] No absorption (μ = 4.8 cm^{-1}) or decomposition corrections were made. The structure was solved with the MULTAN family of programs. Hydrogens were located on a ΔF synthesis or, in a few instances, calculated. Block-diagonal least-squares refinements with anisotropic non-hydrogen atoms and isotropic hydrogens have converged to a crystallographic residual of 0.077 for the observed data. Additional crystallographic details are available as supplementary material.

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Registry No. 1, 108695-79-0; 2, 108695-80-3; 3, 108695-81-4; 4, 108695-82-5; 5, 74799-57-8; 6, 108695-83-6; 7, 108695-84-7.

Supplementary Material Available: Lists of crystal data and data collection parameters and tables of fractional coordinates, thermal parameters, interatomic distances, interatomic angles, and torsional angles for 7-isocyano-1-cycloamphilectene (1), 7-isocyano-11-cycloamphilectene (2), and formamide 7 (15 pages). Ordering information is given on any current masthead page.

Total Synthesis of (+)-Nojirimycin and (+)-1-Deoxynojirimycin

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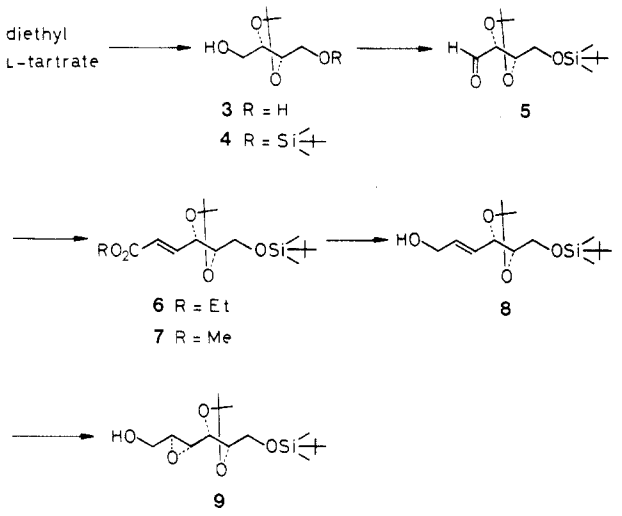
An efficient chiral total synthesis of (+)-nojirimycin (1) and (+)-1-deoxynojirimycin (2) has been achieved in optically pure form via the common intermediate 11 derived from the nonsugar chiral pool. The monosilyl derivative 4 of 2,3-*O*-isopropylidene-L-threitol (3) was converted to the (*E*)-allyl alcohol 8, which upon asymmetric epoxidation provided the syn epoxide 9. Regio- and stereoselective epoxide opening reaction of 9 followed by methoxymethylation yielded the azide 11, which afforded in five steps (+)-1-deoxynojirimycin (2). The azide 11 could also serve as the intermediate for the synthesis of (+)-nojirimycin (1), which was thus derived from 11 in six steps.

The antibiotic nojirimycin (1) was first isolated from several strains of Streptomyces[1,2] and then from Bacillus.[3] Nojirimycin was the first member of the "heterose" discovered in nature and has remarkable biological activity against drug-resistant strains of *Sarcina lutea*, *Shigella flexneri*, and *Xanthomonas oryzae*.[1] 1-Deoxynojirimycin

(1) Ishida, N.; Kumagai, K.; Niida, T.; Tsuruoka, T.; Yumoto, H. *J. Antibiot., Ser. A* **1967**, *20*, 66.
(2) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *24*, 2125.
(3) Schmidt, D. D.; Frommer, W.; Müller, L.; Truscheit, E. *Naturwissenschaften* **1979**, *66*, 584.

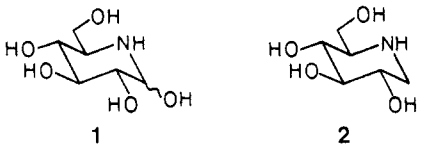
0022-3263/87/1952-3337$01.50/0

Scheme I



(2) initially obtained by chemical transformation of nojirimycin[2] and L-sorvofuranose[20] was first isolated from plants of genus Morus (*Mori cortex*)[4] as an alkaloidal component named moranoline and later also from strains of Bacillus[3] and a mulberry tree (*Morus bombycis*).[5] These antibiotics inhibit various glucosidases, including a processing glucosidases of glycoprotein synthesis.

With one exception,[6] the previously reported syntheses of **1**[2,7] and **2**[2,7a,8,20] started with natural aldohexoses (and

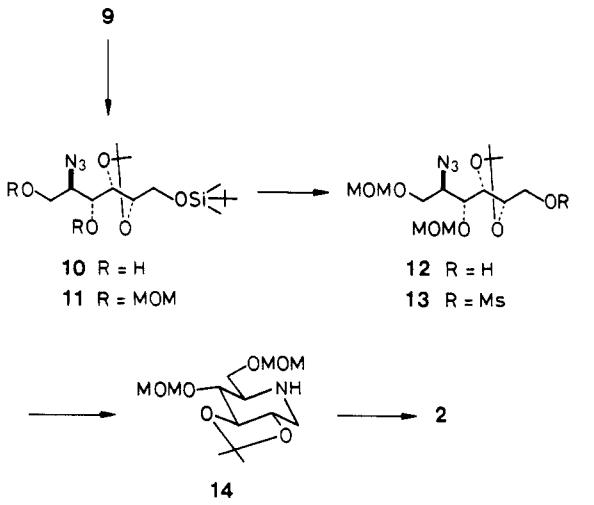


a ketohexose), D-glucose in most cases, and proceeded through the synthetic modification of existing functional groups. We here report an efficient new approach for the synthesis of **1** and **2** in enantiomerically pure natural form via a common intermediate derived from a nonsugar precursor.

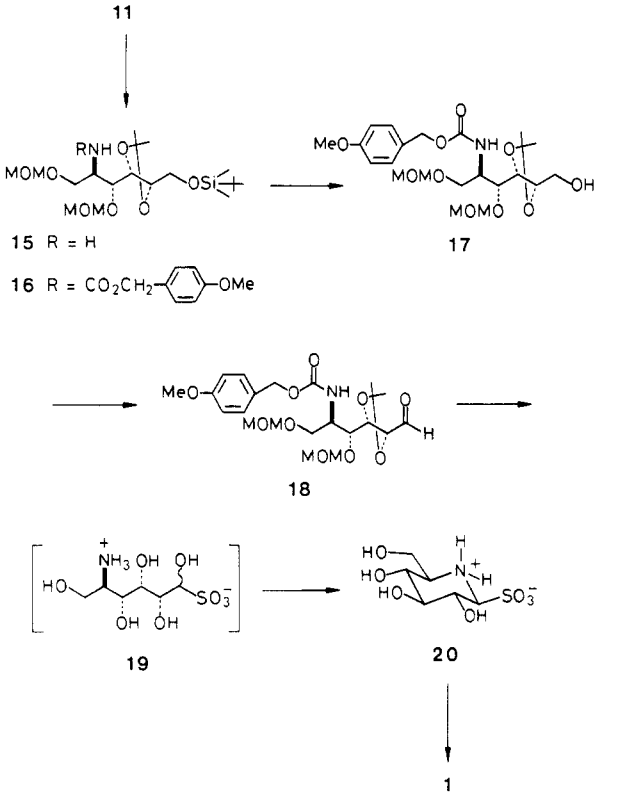
We chose to start with the chiral C_2-symmetrical diol **3**,[9] readily available from diethyl L-tartrate, monoreaction[9] of which was virtually perfectly accomplished by using 1 equiv of *tert*-butyldimethylsilyl chloride and sodium hydride to give the silylate **4** in 99.7% yield (Scheme I). Swern oxidation of **4** afforded somewhat unstable aldehyde **5** in 85% yield. The Wittig reaction of **5** gave the α,β-unsaturated ester **6** in an E/Z ratio of 68:32 (by 400-MHz ^{1}H NMR) in 87% yield. Application of Horner–Emmons condensation using trimethyl phosphonoacetate to **5** resulted in a dramatic improvement in both the selectivity and yield (95%), providing the E ester **7** as a single reaction product.

Dibal reduction of **7** gave the allylic alcohol **8** (81% yield) which was subjected to Sharpless asymmetric epoxidation[10] with diethyl L-tartrate to afford the syn epoxide **9** exclusively in 78% yield.[11] Epoxide-opening reaction of **9** with nucleophiles was expected to occur with high selectivity for C-2 on the basis of both steric and inductive effects of the acetal oxygen atoms.[15] Treatment of **9** with NaN_3 and

Scheme II



Scheme III



(4) Yagi, M.; Kouno, T.; Aoyagi, Y.; Murai, H. *Nippon Nogei Kagaku Kaishi* **1976**, *50*, 571.

(5) Daigo, K.; Inamori, Y.; Takemoto, T. *Chem. Pharm. Bull.* **1986**, *34*, 2243.

(6) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134.

(7) (a) Saeki, H.; Ohki, E. *Chem. Pharm. Bull.* **1968**, *16*, 2477. (b) Klemer, A.; Hofmeister, U.; Lemmes, R. *Carbohydr. Res.* **1979**, *68*, 391.

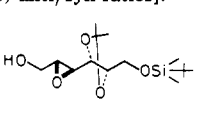
(8) (a) Paulsen, H.; Tadt, K. *Adv. Carbohydr. Chem.* **1968**, *23*, 115. (b) Kinast, G.; Schedel, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 805. (c) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165. (d) Bernotas, R. C.; Ganem, B. *Ibid.* **1985**, *26*, 1123. (e) Setoi, H.; Takeno, H.; Hashimoto, M. *Chem. Pharm. Bull.* **1986**, *34*, 2642.

(9) Seebach, D.; Hungerbühler *Modern Synthetic Methods, 1980*; Scheffold, R., Ed.; Salle and Sauerländer-Verlag: Frankfurt and Aarau, 1980; Vol. 2, pp 91–171.

(10) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

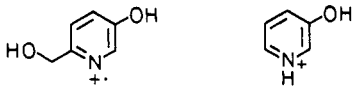
(11) In published studies[12] on stereoselective epoxidation of allylic alcohols with *m*-chloroperbenzoic acid (MCPBA), alkoxy groups exert the pronounced syn directive effect based on secondary interaction between the ether oxygen atom and the incoming peracid (cooperative effect), though in the case of the nor series of allylic alcohols the degree of the stereoselectivity is low.[13]

In our hands, when **8** was treated with MCPBA in dichloromethane, however, the undesired anti epoxide **i** was formed predominantly [65:35 (0 °C) and 70:30 (−20 °C) anti/syn ratios].[14]



NH_4Cl in 1,2-dimethoxyethane/2-methoxyethanol/H_2O indeed furnished the azide **10** with the requisite stereochemical framework in 75% yield on the basis of recovered **9** (37%) (Scheme II). Compound **10** was transformed to the bis(methoxymethyl) ether **11**, which underwent desilylation (n-Bu_4NF, THF), followed by mesylation to provide **13** in 89% overall yield from **10**. The cyclization of **13** to **14** was accomplished in 92% yield by catalytic reduction of the azide to the corresponding amine followed by exposure of the amine to triethylamine in methanol at reflux. Hydrolytic removal of the protecting groups with hydrochloric acid led to 1-deoxynojirimycin (**2**) in 90% yield, which was identical by physical data (melting point and optical rotation) and the ^1H NMR spectrum with naturally derived **2**.[2]

We turned next to elaborate **11**, utilized as the key intermediate for the synthesis of 1-deoxynojirimycin in the above sequence (Scheme II), to nojirimycin (**1**) as outlined in Scheme III. Thus **11** was hydrogenolyzed to give **15**, which was converted to the alcohol **17** via a sequence of reactions including N-[p-(methoxybenzyl)oxy]-carbonylation[16] and desilylation of the resultant carbamate **16** by fluoride ion in 76% overall yield from **11**. Swern oxidation of **17** generated the aldehyde **18**, deprotection of which was smoothly accomplished by exposure to aqueous sulforous acid at room temperature for 60 h, providing 1-deoxynojirimycin-1-sulfonic acid (**20**) (63% yield from **18**) via the formation of the bisulfite adduct **19**. The 400-MHz ^1H NMR spectrum of this substance was superimposable on that of an authentic sample[17] derived from natural nojirimycin. Evidence for the structure **20** in a "piperidinose" form was obtained by the mass spectrum,[2,18] which showed intense 2-pyridinemethanol and hydroxypyridinium ions at m/e 125 (75%) and 96 (base), respectively. Further evidence for the structure of **20** was



125 (75%) 96 (base)

supplied by the 400-MHz ^1H NMR spectrum, which showed the well-resolved signal pattern and the large values of J (9.0 to 10.4 Hz) for the all ring protons proving their all trans axial relationship.

Finally, nojirimycin (**1**) was generated by treatment with Dowex 1-X2 (OH^-) resin in 92% yield.

In summary, the synthesis of (+)-nojirimycin (**1**) and (+)-1-deoxynojirimycin (**2**) achieved in this work has permitted readily utilization of the nonsugar chiral pool and developing efficient, highly stereoselective routes to these antibiotics in enantiomerically pure form via the common intermediate **11**.

Experimental Section

General Procedures. Melting points were determined by using a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-360 digital polarimeter in a 1-dm cell. IR spectra were determiend on a Hitachi 260-30 spectrophotometer. ^1H NMR spectra were recorded on either Varian EM-390 (90 MHz) or Bruker AM-400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer at 100.6 MHz, with $CDCl_3$ used as an internal standard unless otherwise noted, and the degree of substitution of each carbon atom was determined by complete decoupling and DEPT composed 90° and 135° pulse sequence experiments. Mass spectra were obtained with a Hitachi RMU-7L double-focusing mass spectrometer equipped with a Hitachi M-003 data processing system at an ionizing potential of 70 eV. TLC was run on Wako precoated silica gel 70 FM plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography.

4(S)-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-5(S)-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane (4). To a cold (0 °C) solution of 1.0 g (6.2 mmol) of 4(S),5(S)-bis(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane (**3**)[19] 1,2-dimethoxyethane (10 mL) was added in portions sodium hydride (250 mg of a 60% mineral oil dispersion, 6.2 mmol) and the mixture was stirred for 5 min under nitrogen. To this was added dropwise a solution of *tert*-butyldimethylsilyl chloride (930 mg, 6.2 mmol) in 1,2-dimethoxyethane (10 mL) during 10 min at 0 °C, and the mixture was stirred for 3.5 h at room temperature under nitrogen. The reaction mixture was poured into water (10 mL) and the layers were separated. The aqueous layer was extracted with benzene (3 × 10 mL), and the combined organic layers were washed with water, dried ($MgSO_4$), and evaporated in vacuo. The residue was passed through a short column of silica gel with ethyl acetate–hexane (1:10 then 1:5) to give **4** (1.70 g, 99.7%) as a colorless oil: $[\alpha]^{20}_D$ −5.4° (c 1.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.07 (6 H, s), 0.89 (9 H, s), 1.39 (3 H, s), 1.40 (3H, s), 2.44 (1 H, unresolved), 3.61–3.80 (3 H, m), 3.82–3.90 (2 H, m), 3.98 (1 H, dt, J = 7.8, 4.6 Hz); ^{13}C NMR ($CDCl_3$) carbons with 0 proton attached δ 18.45, 109.19, carbons with 1 proton attached δ 78.21, 80.25, carbons with 2 protons attached δ 62.85, 63.81, carbons with 3 protons attached δ −5.42 (2 carbons), 25.93 (3 carbons), 26.99, 27.11; mass spectrum, m/e (relative intensity) 261 ($M^+ - CH_3$, 9), 219 (5), 161, (20), 131 (63), 117 (30), 75 (100). An analytical sample was prepared by distillation in a Kugelrohr: bp 95–100 °C (0.1 mm).

Anal. Calcd for $C_{13}H_{28}O_4Si$: C, 56.48; H, 10.21. Found: C, 56.73; H, 10.29.

4-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-L-threose (5). To a stirred −78 °C solution of oxalyl chloride (0.97 g, 7.6 mmol) in dichloromethane (5 mL) was added dropwise a solution of dimethyl sulfoxide (1.20 g, 15.4 mmol) in dichloromethane (5 mL) over a period of 5 min, and the mixture was stirred for another 15 min at −78 °C. To this mixture was added dropwise a solution of **4** (1.06 g, 3.8 mmol) in dichloromethane (5 mL) over 5 min, and stirring was continued at −78 °C. After 1 h, triethylamine (2.33 g, 23.0 mmol) was added to the reaction mixture, and the reaction was allowed to warm to ambient temperature. After addition water (10 mL) the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined extracts were washed with water, dried ($MgSO_4$), and evaporated. Rapid chromatography of the resulting residue on silica gel with ethyl acetate–hexane (1:5) gave **5** (870 mg, 85%) as a colorless oil; IR ($CHCl_3$) 1728, 1250, 1072, 830; ^1H NMR (90 MHz, $CDCl_3$) δ Me_4Si 0.87 (9 H, s), 1.40 (3 H, s), 1.45 (3 H, s), 3.60–4.50 (4 H, m), 9.75 (1 H, d, J = 1.5 Hz). This material deteriorated upon storage and was used directly in the next reactions.

Ethyl 6-[(*tert*-Butyldimethylsilyl)oxy]-4(S),5(S)-(isopropylidenedioxy)hex-2-enoate (Mixture of *E* and *Z* Isomers of 6). To a stirred mixture of **5** (883 mg, 3.22 mmol) and [(ethoxycarbonyl)methylene]triphenylphosphorane (1.345 g, 3.86 mmol) in dichloromethane (10 mL) at room temperature. The mixture was stirred for 14 h at room temperature and condensed in vacuo. Purification of the oily residue by silica gel chromatography with ethyl acetate–hexane (1:10) gave **6** (960 mg, 87%) as a colorless oil, which ^1H NMR indicated was a 68:32 mixture of the E and Z isomers: ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ limiting with

(12) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347. Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S. *Ibid.* **1985**, *26*, 6485.
(13) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343. Hasan, I.; Kishi, Y. *Ibid.* **1980**, *21*, 4229.
(14) Details will be reported elsewhere.
(15) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67.
(16) Nagasawa, T.; Kuroiwa, K.; Narita, K.; Isowa, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1269.
(17) We are grateful to Dr. T. Tsuruoka, Central Research Laboratories, Meiji Seika Kaisha, Ltd., for generously providing with an authentic sample of **20**.
(18) Inouye, S.; Omoto, S.; Tsuruoka, T.; Niida, T. *Meiji Seika Kenkyu Nenpo* **1972**, *96*.
(19) Feit, P. W. *J. Med. Chem.* **1964**, *7*, 14.
(20) Paulsen, H.; Sangster, I.; Heyns, K. *Chem. Ber.* **1967**, *100*, 802.

an olefinic region 5.92 and 6.12 (total 1 H, with a ratio 32:68, dd each, J = 11.6, 1.2 Hz and J = 15.7, 1.6 Hz, respectively), 6.18 and 6.94 (total 1 H, with a ratio 32:68, dd each, J = 11.6, 8.6 Hz and J = 15.7, 5.1 Hz, respectively).

Ethyl 6-[(*tert*-Butyldimethylsilyl)oxy]-4(*S*),5(*S*)-(isopropylidenedioxy)-2(*E*)-hexenoate (7). To a cold (0 °C) stirred suspension of sodium hydride (182 mg of a 60% mineral oil dispersion, 4.55 mmol) in benzene (10 mL) was added a solution of trimethyl phosphonoacetate (827 mg, 4.54 mmol) in benzene (2 mL). Stirring was continued for 1 h at room temperature and a solution of **5** (1.245 g, 4.54 mmol) in benzene (4 mL) was added dropwise to this mixture over 5 min. After being stirred for another 1 h, the mixture was poured into ice–water (50 mL). The layers were separated and the aqueous layer was extracted with benzene (3 × 50 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Silica gel chromatography of the residue with ethyl acetate–hexane (1:8) gave 1.43 g (95%) of a nearly pure sample of **7** as a colorless oil containing below 1% of the Z isomer as indicated by ^1H NMR analysis: $[\alpha]^{20}_D$ −12.7° (c 2.3, MeOH). The following are spectral data for the E isomer **7**: ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.069 (3 H, s), 0.074 (3 H, s), 0.90 (9 H, s), 1.42 (3 H, s), 1.43 (3 H, s), 3.70–3.84 (3 H, m, including 3 H, s at δ 3.74), 4.51 (1 H, ddd, J = 7.6, 5.1, 1.6 Hz), 6.13 (1 H, dd, J = 15.7, 1.6 Hz), 6.95 (1 H, dd, J = 15.7, 5.1 Hz); ^{13}C NMR ($CDCl_3$) carbons with 0 proton attached δ 18.36, 110.01, 166.62, carbons with 1 proton attached 77.83, 80.92, 121.53, 145.20, carbon with 2 protons attached δ 62.83, carbons with 3 protons attached δ −5.38, −5.31, 25.92 (3 carbons), 26.87, 27.01, 51.69; mass spectrum, m/e (relative intensity) 315 (M^+ − CH_3, 11), 215 (90), 185 (35), 155 (20), 117 (28), 109 (37), 97 (44), 89 (100); exact mass calcd for $C_{15}H_{27}O_5Si$ (M^+ − CH_3), m/e 315.1626, found 315.1618.

6-[(*tert*-Butyldimethylsilyl)oxy]-4(*S*),5(*S*)-(isopropylidenedioxy)-2(*E*)-hexen-1-ol (8). To a solution of **7** (6.0 g, 18.2 mmol) in dichloromethane (100 mL) under nitrogen was added 37 mL of a 1.0 M solution of DIBAL in toluene (37 mmol). After being stirred at room temperature for 14 h, the mixture was cooled and quenched by the dropwise addition of water (5 mL). The solid that separated was filtered, and the filtrate was washed with water and dried ($MgSO_4$). After removal of the solvent, the reaction residue was chromatographed on silica gel with ethyl acetate–hexane (1:5 then 1:4) to give **8** (4.45 g, 81%) as a colorless oil: $[\alpha]^{20}_D$ −18.5° (c 1.6, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.025 (3 H, s), 0.029 (3 H, s), 0.86 (9 H, s), 1.37 (3 H, s), 1.38 (3 H, s), 2.31 (1 H, br s), 3.62–3.79 (3 H, m), 4.10 (2 H, br s), 4.34 (1 H, t, J = 7.3 Hz), 5.70 (1 H, ddt, J = 15.6, 7.3, 1.5 Hz), 5.91 (1 H, dt, J = 15.6, 5.1 Hz); ^{13}C NMR ($CDCl_3$) carbons with 0 proton attached δ 18.33, 109.03, carbons with 1 proton attached δ 78.36, 81.39, 128.20, 133.55, carbons with 2 protons attached δ 62.38, 62.56, carbons with 3 protons attached δ −5.43, −5.32, 25.89 (3 carbons), 26.92, 27.09; mass spectrum, m/e (relative intensity) 303 (M^+ + 1, 0.5), 287 (M^+ − CH_3, 10), 187 (100), 169 (45), 157 (45).

Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.73; H, 10.08.

(2*S*,3*R*,4*S*,5*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-4,5-(isopropylidenedioxy)hexan-1-ol (9). To a cooled (−20 °C) mixture of 4A molecular sieves (300 mg) and dichloromethane (10 mL) was sequentially added titanium(IV) isopropoxide (378 mg, 1.33 mmol) and diethyl L-tartrate (274 mg, 1.33 mmol) under nitrogen, and the mixture was stirred for 10 min. With vigorous stirring, a solution of **8** (288 mg, 0.952 mmol) in dichloromethane (1 mL) was added dropwise via syringe at −20 °C over about 5 min. To this was added *tert*-butyl hydroperoxide (635 μL, 1.91 mmol, 3.0 M in toluene) via syringe, and the reaction was stirred at −20 °C for 14 h under nitrogen. To this cold reaction mixture was added 10% aqueous tartaric acid (5 mL), and the mixture was allowed to warm to room temperature with stirring and passed through a Celite pad. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The dichloromethane solution was concentrated in vacuo and the residue was chromatographed on silica gel with ethyl acetate–hexane (1:5 to 1:4) to give **9** (236 mg, 78%) as a colorless oil: $[\alpha]^{20}_D$ −22.4° (c 0.11, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.04 (6, H, s), 0.86 (9 H, s), 1.35 (3 H, s), 1.36 (3 H, s), 2.27 (1 H, br s), 3.10 (1 H, dd, J = 4.7, 2.3 Hz), 3.15 (1 H, dt, J = 4.0, 2.3 Hz), 3.61 (1 H, dd, J = 12.8, 4.0 Hz), 3.69 (1 H, dd, J = 10.7, 5.8 Hz), 3.80 (1 H, dd, J = 10.7, 4.0 Hz), 3.83–3.94 (2 H, m, unresolved), 3.99 (1 H, ddd, J = 7.9, 5.8, 4.0 Hz); ^{13}C NMR ($CDCl_3$) carbons with 0 proton attached δ 18.38, 109.86, carbons with 1 proton attached δ 54.92, 55.76, 78.12, 78.20, carbons with 2 protons attached δ 60.88, 63.49, carbons with 3 protons attached δ −5.40, −5.35, 25.92 (3 carbons), 26.68, 27.02; mass spectrum, m/e (relative intensity) 303 (M^+ − CH_3, 13), 173 (10), 159 (12), 143 (20), 131 (22), 129 (39), 117 (55), 75 (100), 73 (50).

Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.49. Found: C, 56.66; H, 9.48.

(2*R*,3*R*,4*S*,5*S*)-2-Azido-6-[(*tert*-butyldimethylsilyl)oxy]-4,5-(isopropylidenedioxy)hexane-1,3-diol (10). A solution of **9** (3.38 g, 10.6 mmol), sodium azide (2.76 g, 42.5 mmol), and ammonium chloride (2.27 g, 42.5 mmol) of a solvent mixture of 1.2-dimethoxyethane (10 mL), 2-methoxyethanol (20 mL), and water (10 mL) was refluxed for 6 h. The reaction mixture was diluted with water (10 mL) and extracted with ether (3 × 50 mL). The ether extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel with ethyl acetate–hexane (1:5 then 1:4). The first fraction was found to consist of unchanged **9** (1.25 g, 37%) and the second fraction contained **10** (1.82 g, 47% or 75% based on recovered **9**) as a colorless oil: $[\alpha]^{22}_D$ −26.6° (c 1.6, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.08 (6 H, s), 0.90 (9 H, s), 1.42 (3 H, s), 1.44 (3 H, s), 2.33 (1 H, br t, J = 6.0 Hz), 2.54 (1 H, d, J = 9.8 Hz), 3.50 (1 H, ddd, J = 8.3, 5.2, 4.3 Hz), 3.67 (1 H, ddd, J = 9.8, 8.3, 1.4 Hz), 3.72 (1 H, dd, J = 10.7, 6.0 Hz), 3.83 (1 H, dd, J = 10.7, 3.9 Hz), 3.83–3.91 (1 H, m), 3.96–4.04 (1 H, m), 4.07 (1 H, ddd, J 25.91 8.1, 6.0, 3.9 Hz), 4.18 (1 H, dd, J = 8.1, 1.4 Hz); ^{13}C NMR ($CDCl_3$) carbons with 0 proton attached δ 18.35, 109.78, carbons with 1 proton attached δ 64.91, 69.53, 76.92, 78.08, carbons with 2 protons attached 62.87, 63.37, carbons with 3 protons attached δ −5.48, −5.40, 25.91 (3 carbons), 27.02, 27.11.

(2*S*,3*S*,4*R*,5*R*)-5-Azido-1-[(*tert*-butyldimethylsilyl)oxy]-2,3-(isopropylidenedioxy)-4,6-bis(methoxymethoxy)hexane (11). A solution containing **10** (1.46 g, 4.04 mmol), *N*,*N*-diisopropylethylamine (2.61 g, 20.2 mmol), and chloromethyl methyl ether (1.63 g, 20.2 mmol) in chloroform (20 mL) was refluxed for 3 h. The mixture was cooled and diluted with chloroform (20 mL). The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel chromatography with ethyl acetate–hexane (1:7) to give **11** (1.65 g, 91%) as a colorless oil: $[\alpha]^{22}_D$ −23.4° (c 1.7, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.050 (3 H, s), 0.054 (3 H, s), 0.88 (9 H, s), 1.37 (3 H, s), 1.40 (3 H, s), 3.37 (3 H, s), 3.40 (3 H, s), 3.65–3.79 (4 H, m), 3.82 (1 H, dd, J = 10.5, 4.0 Hz), 3.91 (1 H, dd, J = 10.2, 2.4 Hz), 4.04 (1 H, ddd, J = 7.9, 6.1, 4.0 Hz), 4.11 (1 H, dd, J = 7.9, 2.4 Hz), 4.64 (2 H, s), 4.69 (1 H, 1/2 AB q, J = 6.6 Hz), 4.70 (1 H, 1/2 AB q, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) carbons with 0 proton attached δ 18.35, 109.20, carbons with 1 proton attached δ 62.60, 76.60, 76.64, 78.85, carbons with 2 protons attached δ 63.87, 67.35, 96.83, 98.33, carbons with 3 protons attached δ −5.49, −5.43, 25.93 (3 carbons), 26.96, 27.16, 55.52, 56.48; mass spectrum, m/e (relative intensity) 434 (M^+ − CH_3, 3), 245 (10), 199 (14), 187 (24), 131 (30), 129 (48), 117 (96), 115 (30), 89 (79), 75 (64), 73 (100); exact mass calcd for $C_{18}H_{36}N_3O_7Si$ (M^+ − CH_3), m/e 434.2320, found 434.2291.

(2*S*,3*S*,4*R*,5*R*)-5-Azido-2,3-(isopropylidenedioxy)-4,6-bis(methoxymethoxy)hexan-1-ol (12). To a solution of **11** (1.05 g, 2.34 mmol) in THF (30 mL) was added tetra-*n*-butylammonium fluoride (4.67 mL, 4.67 mmol, 1 M in THF), and the mixture was stirred at room temperature for 30 min. After evaporation of the solvent below 30 °C, the residue was purifed by silica gel chromatography with ethyl acetate–hexane (1:3 then 1:2) to give **12** (767 mg, 98%) as a colorless oil: $[\alpha]^{21}_D$ −39.2° (c 2.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.41 (3 H, s), 1.43 (3 H, s), 2.26 (1 H, t, J = 6.2 Hz), 3.38 (3 H, s), 3.41 (3 H, s), 3.66–3.75 (3 H, m), 3.75–3.82 (2 H, m), 3.90 (1 H, dd, J = 10.4, 2.8 Hz), 4.08–4.17 (2 H, m), 4.65 (1 H, $^1/_2$ AB q, J = 6.5 Hz), 4.66 (1 H, $^1/_2$ AB q, J = 6.5 Hz), 4.68 (1 H, $^1/_2$ AB q, J = 6.6 Hz, 4.73 (1 H, $^1/_2$ AB q, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) carbon wtih 0 proton attached δ 109.25, carbons with 1 proton attached δ 62.51, 76.31, 77.02, 77.41, carbons with 2 protons attached δ 62.20, 67.09, 96.85, 98.37; carbons

with 3 protons attached δ 26.95, 27.19, 55.62, 56.58; mass spectrum, *m/e* (relative intensity) 320 ($M^+ - CH_3$, 8), 131 (100), 87 (55), 86 (48).

Anal. Calcd for $C_{13}H_{25}N_3O_7$: C, 46.56; H, 7.51; N, 12.53. Found: C, 46.79; H, 7.71; N, 12.28.

(2*S*,3*S*,4*R*,5*R*)-5-Azido-2,3-(isopropylidenedioxy)-4,6-bis(methoxymethoxy)-1-[(methylsulfonyl)oxy]hexane (13). To a stirred cold (0 °C) solution containing **12** (271 mg, 0.808 mmol) and triethylamine (327 mg, 3.23 mmol) in dichloromethane (4 mL) was added methanesulfonyl chloride (185 mg, 1.62 mmol). The mixture was stirred for 10 min at 0 °C and diluted with dichloromethane (10 mL). The resulting solution was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on silica gel with ethyl acetate–hexane (1:3 then 1:2) to give **13** (315 mg, 94%) as a colorless oil: $[\alpha]^{24}_D$ −43.8° (*c* 2.2, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.43 (3 H, s), 1.45 (3 H, s), 3.07 (3 H, s), 3.40 (3 H, s), 3.41 (3 H, s), 3.67 (1 H, dd, *J* = 7.3, 2.7 Hz), 3.74 (1 H, dd, *J* = 10.3, 6.1 Hz), 3.80 (1 H, ddd, *J* = 7.3, 6.1, 2.7 Hz), 3.90 (1 H, dd, *J* = 10.3, 2.7 Hz), 4.12 (1 H, dd, *J* = 7.6, 2.7 Hz), 4.29–4.43 (3 H, m), 4.66 (1 H, $^1/_2$ AB q, *J* = 6.7 Hz), 4.68 (1 H, $^1/_2$ AB q, *J* = 6.7 Hz), 4.68 (1 H, $^1/_2$ AB q, *J* = 6.6 Hz), 4.72 (1 H, $^1/_2$ AB q, *J* = 6.6 Hz).

Anal. Calcd for $C_{14}H_{27}N_3O_9S$: C, 40.67; H, 6.58; N, 10.16. Found: C, 40.90; H, 6.54; N. 9.87.

(2*R*,3*R*,4*S*,5*S*)-4,5-(Isopropylidenedioxy)-3-(methoxymethoxy)-2-[(methoxymethoxy)methyl]piperidine (14). A mixture of **13** (322.5 mg, 0.780 mmol), 10% palladium on carbon (320 mg), and methanol (10 mL) was hydrogenated at atomospheric pressure for 2 h. After filtration, triethylamine (ca. 200 mg) was added to the filtrate and the mixture was refluxed for 2 h. Evaporation and silica gel chromatography with ammoniac methanol–chloroform (1:20) gave **14** (209 mg, 92%) as a colorless oil: $[\alpha]^{24}_D$ +98.2° (*c* 1.3, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.42 (6 H, s), 1.76 (1 H, br s), 2.64 (1 H, ddd, *J* = 9.0, 4.8, 2.9 Hz), 2.65–2.74 (1 H, unresolved), 3.27–3.45 (3 H, m, including 3 H, s at δ 3.37 and 3 H, s, at δ 3.40), 3.65–3.84 (3 H, m), 4.63 (1 H, d, *J* = 6.5 Hz), 4.64 (1 H, $^1/_2$ AB q, *J* = 6.6 Hz), 4.65 (1 H, $^1/_2$ AB *J* = 6.6 Hz), 4.98 (1 H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) carbon with 0 proton attached δ 110.24; carbons with 1 proton attached δ 59.10, 74.81, 76.28, 84.38, carbons with 2 protons attached δ 46.83, 67.35, 96.12, 97.04, carbons with 3 protons attached δ 26.81, 27.04, 55.54, 56.03; mass spectrum, *m/e* (relative intensity) 292 (M^+ + 1, 2), 291 (M^+, 2), 246 (20), 230 (10), 216 (100), 140 (30), 118 (20); exact mass calcd for $C_{11}H_{20}NO_5$ ($M^+ - CH_2OCH_3$), *m/e* 246.1340, found 246.1354.

(+)-1-Deoxynojirimycin (2). A solution of **14** (119 mg, 0.41 mmol) in a 1:2 mixture of concentrated HCl–methanol (2 mL) was refluxed for 1 h. Evaporation of the mixture at reduced pressure left a solid that was purified by silica gel chromatography with ammoniac methanol–chloroform (1:1) to give **2** (60 mg, 90%) as colorless prisms: mp 202–204 °C (lit.[2] mp 196 °C); $[\alpha]^{24}_D$ +47.1° (*c* 0.17, H_2O) [lit.[2] $[\alpha]^{21}_D$ +47° (H_2O)]; ^1H NMR (400 MHz, D_2O) δ $Me_3Si(CH_2)_3SO_3Na$ (0.015 ppm) 2.47 (1 H, t, *J* = 11.0 Hz), 2.56 (1 H, ddd, *J* = 9.5, 6.2, 2.8 Hz), 3.13 (1 H, dd, *J* = 11.0, 5.1 Hz), 3.24 (1 H, t, *J* = 9.5 Hz), 3.33 (1 H, t, *J* = 9.5 Hz), 3.50 (1 H, ddd, *J* = 11.0, 9.5, 5.1 Hz), 3.64 (1 H, dd, *J* = 11.7, 6.2 Hz), 3.83 (1 H, dd, *J* = 11.7, 2.8 Hz); ^{13}C NMR [D_2O with $Me_3Si(CH_2)_3SO_3Na$ (0 ppm) as internal standard] carbons with 1 proton attached δ 63.09, 73.45, 74.12, 81.00, carbons with 2 protons attached δ 51.24, 63.99; mass spectrum, *m/e* (relative intensity) 164 (M^+ + 1, 3), 146 (2), 132 (100), 114 (6), 73 (15), 72 (30).

(2*S*,3*S*,4*R*,5*R*)-5-Amino-1-[(*tert*-butyldimethylsilyl)oxy]-2,3-(isopropylidenedioxy)-4,6-bis(methoxymethoxy)hexane (15). A solution of **11** (1.6 g, 3.6 mmol) in methanol (40 mL) including 10% palladium on carbon (1 g) was hydrogenated at atmospheric pressure for 4 h. After filtration the solvent was removed in vacuo and the residue was chromatographed on silica gel with ethyl acetate–hexane (1:1 then 1:0) to give **15** (1.29 g, 86%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.03 (6 H, s), 0.85 (9 H, s), 1.34 (3 H, s), 1.38 (3 H, s), 1.64 (2 H, br s), 3.15 (1 H, td, *J* = 6.3, 4.5 Hz), 3.33 (3 H, s), 3.38 (3 H, s), 3.53 (1 H, dd, *J* = 9.7, 6.7 Hz), 3.56 (1 H, dd, *J* = 6.0, 2.9 Hz), 3.64 (1 H, dd, *J* = 9.7, 4.5 Hz), 3.69 (1 H, dd, *J* = 10.7, 5.4 Hz), 3.77 (1 H, dd, *J* = 10.7, 4.1 Hz), 4.00–4.08 (1 H, m), 4.15 (1 H, dd, *J* = 7.9, 2.9 Hz), 4.60 (2 H, s), 4.69 (2 H, s); ^{13}C NMR ($CDCl_3$) carbons with 0 proton attached δ 18.36, 108.93, carbons with 1 proton attached δ 53.09, 77.07, 78.63, 78.81, carbons with 2 protons attached δ 63.80, 70.12, 96.89, 97.95, carbons with 3 protons attached δ −5.47, −5.40, 25.93 (3 carbons), 26.98, 27.16, 55.37, 56.20.

(2*S*,3*S*,4*R*,5*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,3-(isopropylidenedioxy)-5-[[[*p*-(methoxybenzyl)oxy]carbonyl]amino]-4,6-bis(methoxymethoxy)hexane (16). To a solution containing **15** (175 mg, 0.413 mmol) and triethylamine (63 mg, 0.62 mmol) in dioxane (1 mL) was added a solution of *p*-methoxybenzyl *S*-(4,6-dimethylpyrimidin-2-yl)thiocarbonate[16] (138 mg, 0.453 mmol) in dioxane (0.5 mL) via syringe, and the mixture was stirred at room temperature. After 6 h the mixture was diluted with water (3 mL) and extracted with chloroform (3 × 10 mL). The extract was washed with water, dried ($MgSO_4$), and evaporated in vacuo. Silica gel chromatography of the residue gave **16** (222 mg, 91%) as a colorless oil: $[\alpha]^{24}_D$ −8.9° (*c* 1.1, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.04 (6 H, s), 0.87 (9 H, s), 1.36 (3 H, s), 1.40 (3 H, s), 3.31 (3 H, s), 3.37 (3 H, s), 3.56 (1 H, dd, *J* = 9.9, 7.8 Hz), 3.60–3.71 (2 H, m), 3.77 (3 H, s), 3.79 (1 H, dd, *J* = 10.7, 3.8 Hz), 3.85 (1 H, dd, *J* = 4.3, 2.3 Hz), 4.05–4.20 (2 H, m), 4.20–4.31 (1 H, unresolved), 4.58 (2 H, s), 4.62 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.73 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.98 (1 H, $^1/_2$ AB q, *J* = 11.9 Hz), 5.04 (1 H, $^1/_2$ AB q, *J* = 11.9 Hz), 5.80 (1 H, d, *J* = 8.8 Hz), 6.85 (2 H, d, *J* = 8.6 Hz), 7.28 (2 H, d, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$) carbons with 0 proton attached δ 18.31, 109.39, 128.98, 156.57, 159.50, carbons with 1 proton attached δ 52.28, 74.14, 76.68, 78.59, 113.83 (2 carbons), 129.83 (2 carbons), carbons with 2 protons attached δ 63.51, 66.32, 67.09, 96.70 (2 carbons), carbons with 3 protons attached δ −5.54, −5.47, 25.87 (3 carbons), 26.76, 27.15, 55.23, 55.39, 56.16; mass spectrum, *m/e* (relative intensity) 572 ($M^+ - CH_3$, 5), 544 (3), 528 (5), 512 (7), 486 (11), 468 (15), 434 (68), 392 (30), 316 (50), 258 (100), 245 (45), 228 (57).

Anal. Calcd for $C_{28}H_{49}NO_{10}Si$: C, 57.22; H, 8.40; N, 2.38. Found: C, 57.48; H, 8.57; N, 2.29.

(2*S*,3*S*,4*R*,5*R*)-2,3-(Isopropylidenedioxy)-5-[[[*p*-(methoxybenzyl)oxy]carbonyl]amino]-4,6-bis(methoxymethoxy)-hexan-1-ol (17). To a stirred solution of **16** (169 mg, 0.288 mmol) in THF (2 mL) was added tetra-*n*-butylammonium fluoride (575 μL, 0.575 mmol, 1 M in THF) via syringe at room temperature. After 1 h the mixture was diluted with water (2 mL) and extracted with chloroform (3 × 5 mL). The extract was washed with water, dried ($MgSO_4$), and evaporated. Silica gel chromatography of the residue with ethyl acetate–hexane (1:1 then 1:0) gave **17** (133 mg, 98%) as a colorless oil: $[\alpha]^{24}_D$ −17.4° (*c* 0.86, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.38 (3 H, s), 1.40 (3 H, s), 2.57 (1 H, t, *J* = 6.1 Hz), 3.31 (3 H, s), 3.36 (3 H, s), 3.50–3.85 (5 H, unresolved, including 3 H, s at δ 3.77), 4.04–4.25 (3 H, unresolved), 4.57 (2 H, s), 4.61 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.73 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.97 (1 H, $^1/_2$ AB q, *J* = 12.0 Hz), 5.03 (1 H, $^1/_2$ AB q, *J* = 12.0 Hz), 5.76 (1 H, d, *J* = 8.7 Hz), 6.85 (2 H, d, *J* = 8.7 Hz), 7.27 (2 H, d, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$) carbons with 0 proton attached δ 109.40, 128.81, 156.51, 159.52, carbons with 1 proton attached δ 51.88, 74.84, 77.18 (2 carbons), 113.85 (2 carbons), 129.83 (2 carbons), carbons with 2 protons attached δ 61.87, 66.44, 66.85, 96.73, 96.94; carbons with 3 protons attached δ 26.75, 27.13, 55.24, 55.49, 56.19; mass spectrum, *m/e* (relative intensity) 473 (M^+, 11), 458 ($M^+ - CH_3$, 4), 398 (10), 354 (50), 320 (70), 292 (70), 258 (79), 224 (100); exact mass calcd for $C_{22}H_{35}NO_{10}(M^3)$, *m/e* 473.2258, found 473.2234.

(2*R*,3*S*,4*R*,5*R*)-2,3-(Isopropylidenedioxy)-5-[[[*p*-(methoxybenzyl)oxy]carbonyl]amino]-4,6-bis(methoxymethoxy)-hexanal (18). Swern oxidation was run similar to that of **4** by using **17** (932 mg, 1.97 mmol), oxalyl chloride (500 mg, 3.94 mmol), dimethyl sulfoxide (615 mg, 7.87 mmol), and triethylamine (1.196 g, 11.82 mmol). After workup the crude material was chromatographed on silica gel with ethyl acetate–hexane (1:1 then 1:0) to give **18** (763 mg, 82%) as a colorless oil: IR ($CHCl_3$) 1702, 1500, 1238, 1024 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ Me_4Si 1.35 (3 H, s), 1.40 (3 H, s), 3.26 (3 H, s), 3.32 (3 H, s), 3.40–4.85 (10 H, m, containing 3 H, s at δ 3.76), 4.90 (2 H, s), 5.30–5.85 (1 H, unresolved), 6.82 (2 H, $^1/_2$ AB q, *J* = 9.0 Hz), 7.22 (2 H, $^1/_2$ AB q, *J* = 9.0 Hz), 9.74 (1 H, s). This material deteriorated upon strage and was used immediately in the next reaction.

1-Deoxynojirimycin-1-sulfonic Acid (20). A stirred solution of **18** (124 mg, 0.263 mmol) and water (1.5 mL) was saturated with SO_2 and the resulting homogeneous aqueous solution was stirred

at room temperature. After 60 h the mixture was diluted with methanol (10 mL) and saturated again with SO_2 to generate a white precipitate that was collected by centrifuging (2000 rpm × 10 min). The white solid obtained was suspended in 10 mL of methanol–ether (1:10), recentrifuged, and dried in vacuo to give crystals of **20** (43 mg, 63%): mp 140–145 °C dec (lit.[2] mp 145–147 °C dec); ^{1}H NMR (400 MHz, D_2O) δ $Me_3Si(CH_2)_3SO_3Na$ (0.015 ppm) 3.29 (1 H, ddd, J = 9.6, 4.6, 3.0 Hz, H-5), 3.61 (1 H, dd, J = 9.3, 9.0 Hz, H-3), 3.72 (1 H, dd, J = 9.6, 9.3 Hz, H-4), 3.94 (1 H, dd, J = 10.4, 9.0 Hz, H-2), 3.95 (1 H, dd, J = 12.9, 4.6 Hz, H-6), 4.03 (1 H, dd, J = 12.9, 3.0 Hz, H-6), 4.19 (1 H, d, J = 10.4 Hz, H-1); ^{13}C NMR [D_2O with $Me_3Si(CH_2)_3SO_3Na$ as internal standard] carbons with 1 proton attached δ 63.04, 69.99, 72.11, 73.20, 78.62, carbon with 2 protons attached δ 60.27; mass spectrum, m/e (relative intensity) 227 (5), 143 (24), 125 (75), 124 (85), 96 (100).

(+)-Nojirimycin (1). A solution of **20** (30 mg, 0.115 mmol) in water (1 mL) was applied to a column of 10 mL of Dowex 1×2 (OH^-) resin (100–200 mesh) and eluted with water (200 mL). The elute was lyophilized to give 1 (20 mg, 90%) as a white crystalline product: mp 124–131 °C dec (lit.[2] mp 125–131 °C dec); $[\alpha]^{24}_D$ +71.2° (c 0.17, H_2O, equilibrium) [lit.[2] $[\alpha]^5_D$ +73.5° (H_2O, 20 h)].

Registry No. 1, 15218-38-9; 2, 19130-96-2; 3, 50622-09-8; 4, 108817-96-5; 5, 108817-97-6; (*E*)-6, 108817-98-7; (*Z*)-6, 108818-11-7; 7, 108817-99-8; 8, 108818-00-4; 9, 108818-01-5; 10, 108818-02-6; 11, 108818-03-7; 12, 108818-04-8; 13, 108818-05-9; 14, 108818-06-0; 15, 108818-07-1; 16, 108818-08-2; 17, 108818-09-3; 18, 108818-10-6; 20, 81703-56-2; [(ethoxycarbonyl)methylene]triphenylphosphorane, 1099-45-2; trimethyl phosphonoacetate, 5927-18-4; *p*-methoxybenzyl *S*-(4,6-dimethylpyrimidin-2-yl)thiocarbonate, 41840-29-3.

Stereodivergent Total Synthesis of *N*-Acetylacosamine and *N*-Benzoylristosamine

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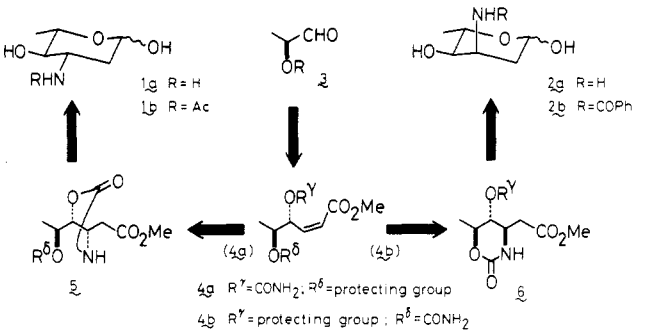
Highly diastereoselective syntheses of L-*N*-acetylacosamine (**1b**) and L-*N*-benzoylristosamine (**2b**), two isomeric L-3-amino-2,3,6-trideoxyhexoses, were achieved by utilizing the intramolecular conjugate addition of carbamate group in the *Z*-α,β-unsaturated esters **4a** and **4b**, respectively. **4a** and **4b** were prepared from the common intermediate, 4,5-dihydroxy-2-hexynoate derivative **7a**, readily available by the non-chelation-controlled addition of methyl propiolate to *O*-(*tert*-butyldimethylsilyl)lactaldehyde **3**.

The 3-amino-2,3,6-trideoxyhexoses are distributed in nature as the glycosidic moiety of important antibiotics. Daunosamine is found in anthracycline antibiotics such as adriamycin and daunorubicin,[1] used clinically in antitumor therapy. A clinically important modification of adriamycin is the replacement of daunosamine for its C-4 epimer, acosamine (**1a**), and it is reported to reduce the relative cardiotoxicity.[2] The acosamine was originally isolated as one of the sugar constituents of actinoidin,[3] a member of the important vancomycin group of glycopeptide antibiotics. Another naturally occurring isomer is ristosamine (**2a**), which is also a carbohydrate constituent of vancomycin group antibiotics such as ristomycin.[4] Although a variety of efforts[5] to synthesize these amino sugars have been reported, to our knowledge, there is not a stereocontrolled divergent synthesis of these isomeric sugars from common intermediate without the aid of stereochemical inversion procedures. Recently we have developed a new amination methodology using the intramolecular conjugate additions of γ- or δ-carbamoyloxy-α,β-unsaturated esters.[6] They provide a good way to achieve diastereoselective amination of acyclic olefinic systems, since complementary diastereofacial selection can be accomplished by changing the site of carbamoyloxy group between γ- and δ-positions. Its synthetic utility has been demonstrated by the stereoselective syntheses of all four possible diastereomers of racemic *N*-acyl-3-amino-2,3,6-trideoxyhexose.[7,8] The relatively low selectivity in the conjugate addition of the homoallylic carbamate in the synthesis of (±)-*N*-benzoyldaunosamine[8] was dramatically improved by using *Z*-α,β-unsaturated ester instead of the *E* isomer (eq 1), and hence L-*N*-benzoyldaunosamine was synthesized under high stereocontrol.[9,10] In this paper we

Scheme I



(1) Arcamone, F.; Franceschi, G.; Orezzi, P.; Babier, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334. Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondelli, R. *Ibid.* **1964**, *86*, 5335; Arcamore, F.; Franceschi, G.; Penco, S.; Selva, A. *Tetrahedron Lett.* **1969**, 1007.

(2) Marco, A. D.; Casazza, A. M.; Dasdia, T.; Formelli, F.; Necco, A.; Soranzo, C. *J. Med. Chem.* **1975**, *18*, 703.

(3) Sztaricskai, F.; Harris, C. M.; Harris, T. M. *Tetrahedron Lett.* **1979**, 2861.

(4) Bognar, R.; Sztaricskai, F.; Munk, M. E.; Tamas, J. *J. Org. Chem.* **1974**, *39*, 2971. Hunt, A. H.; Debono, M.; Merkel, K. E.; Barnhart, M. *Ibid.* **1984**, *49*, 635.

(5) For comprehensive review on syntheses of 2,3,6-trideoxy-3-aminohexoses, see: Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35.

(6) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Itô, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797.

(7) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Itô, S. *Tetrahedron Lett.* **1985**, *26*, 4133.

(8) Hirama, M.; Shigemoto, T.; Itô, S. *Tetrahedron Lett.* **1985**, *26*, 4137.

0022-3263/87/1952-3342$01.50/0