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TOTAL SYNTHESIS OF ANTIBIOTIC A23187 (CALCIMYCIN) FROM D-GLUCOSE

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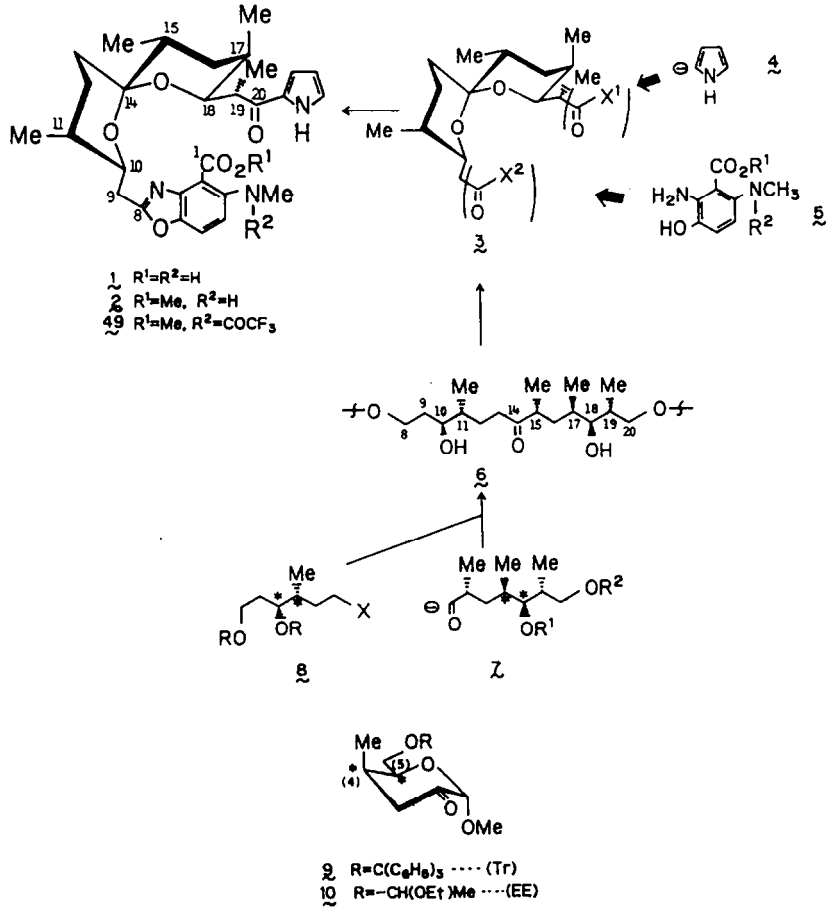
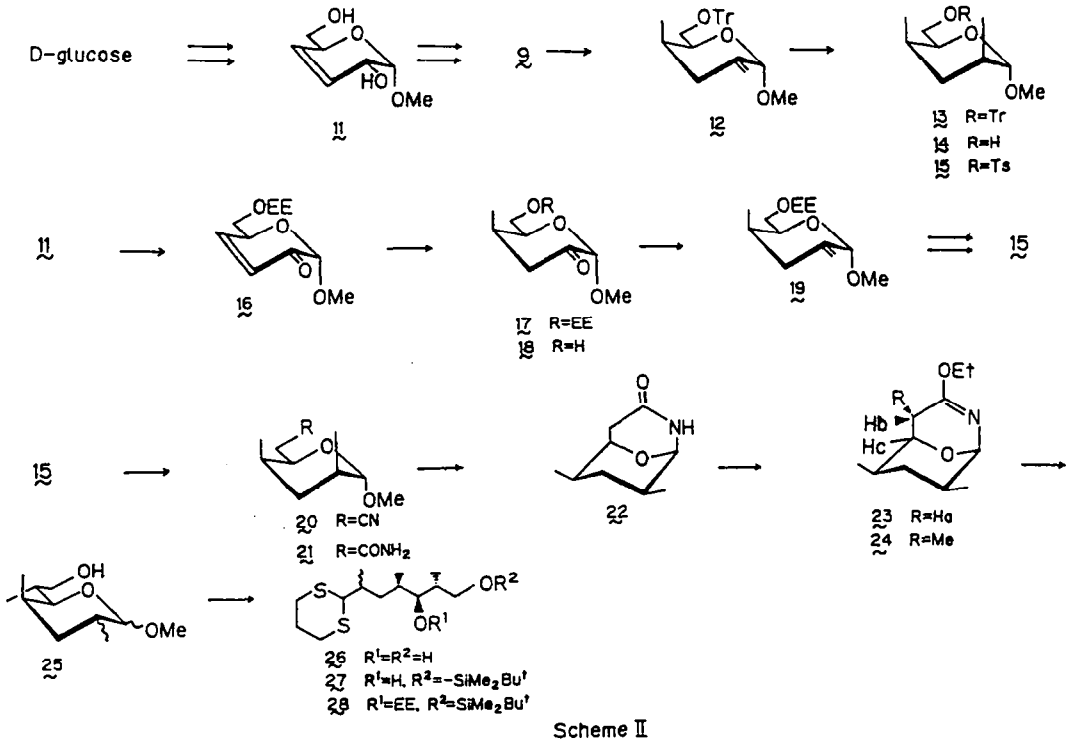
Abstract: The fully stereocontrolled synthesis of A23187 by using the chirons derived from D-glucose is described.

Use of carbohydrates as chiral pool is a widely accepted strategy in stereocontrolled total synthesis.[1] Complex molecules bearing polyoxo type carbon chain with multiple asymmetric centers such as macrolides or polyethers have often been synthesized through application of this strategy. As part of our project[2] on the synthesis of natural products based on carbohydrate template concept, we describe herein a total synthesis of divalent cation ionophore antibiotic A23187 (calcimycin) 1 in detail.[3] The antibiotic A23187, produced in the cultures of Streptomyces chartreusensis,[4] has high ionophoric specificity for Ca^{++} [5] and is one of the most frequently cited molecules in biochemical studies.[6]



Scheme I

The unique dioxaspiro structure[7] as well as specific biological functions have attracted much attention of synthetic chemists. Not only total synthesis of **1**[8] but also preparation of its analogs has been studied by several groups.[9] Retrosynthetic consideration led us to design a convergent approach to the synthesis of **1** (scheme I) as follows. A unique dioxaspiro system **3** with suitable functionalities, a pyrrole carbanion equivalent **4**, and benzoxazole precursor **5** are designed to be connected. The dioxaspiro segment **3**, which involves all asymmetric carbons of **1**, would be derived from a open-chain precursor **6** by acid catalized thermodynamic ring-closure process[10], so that stereochemistry of the spiro center (C-14) can be controlled by well known anomeric effect. The ketodiol **6** may, in turn, be prepared by coupling of chiral synthons **7** and **8**. Based on the concept of carbohydrate template,[1a] both synthons may be obtained starting from a common hexopyranosidulose **9**,[11] since the (4R,5S)configurations (*) of **9** are identical with those at C-10,11 and C-17,18 positions of **1**. Stereoselective introduction of methyl groups at 15 and 19 position and efficient coupling of segments **3**, **4**, and **5** are prerequisit to establish a synthetic route to **1**. The dithioacetal **28** was designed as a chiron[12] equivalent to **7**, and a synthesis of **28** from D-glucose is shown in Scheme II.



Scheme II

The compound **9** has been prepared from D-glucose via **11** by Fraser-Reid et al.[11)13] Wittig methylenation of **9** gave **12**, which was hydrogenated (H_2, Pd-C) to afford cis-dimethyl compound **13** as a predominant product.[14] Isolation of **13** was carried out by column chromatography followed by recrystallization. Minor fraction contained other stereoisomers. The stereochemistry of **13** was confirmed by comparison of its ^{1}H- and ^{13}C-NMR spectra with those of the authentic sample,[15] obtainable from D-glucose via an alternative way.[16] The configuration of the newly incorporated methyl group disagreed with that required for the C-15 methyl group of **1**. However, it was expected that the methyl group could be epimerized later because it was located at α-position of masked carbonyl group. Evans et al have reported their observation of acid-catalyzed equilibration at this position in **1**.[8a)17]

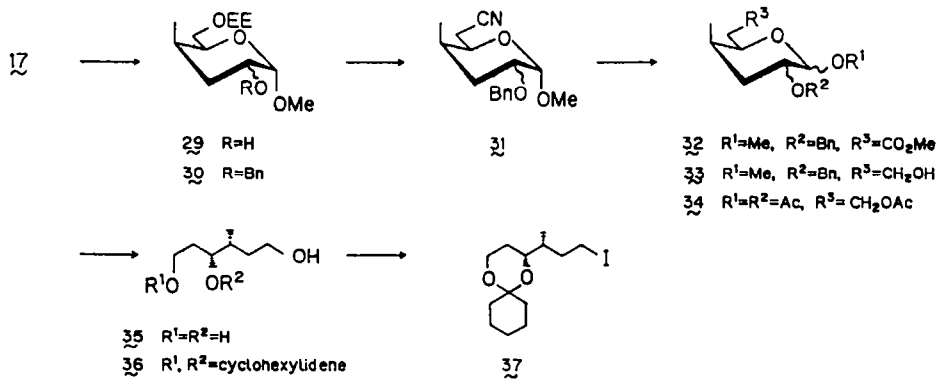
Detritylation of **13** was effected under the condition of metal reduction to afford **14**, which was then converted to a tosylate **15**, suitable substrate for carbon chain elongation. In order to

avoid the tedious process of detritylation and to allow larger scale preparation, it was examined to protect the primary alcohol of 11 with α-ethoxyethyl group instead of trityl group.

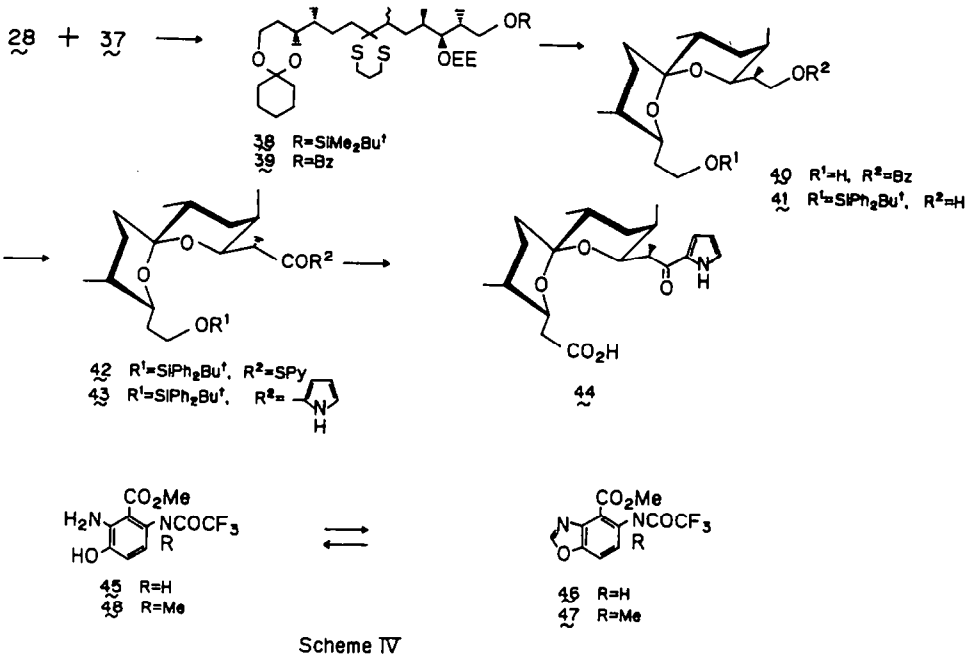
Allylic oxidation of 11 with MnO_2 was followed by treatment with ethyl vinyl ether and pyridinium p-toluenesulfonate (PPTS)[18] to give 16 in good yield. Addition of lithium dimethylcuprate to the enone system of 16 was performed in high stereoselectivity (>95 %), which was ascertained by a direct comparison of the deprotected sample 18 with that derived from 9. Upon Wittig reaction and hydrogenation, 17 was converted to a dimethyl compound via 19. The α-ethoxyethyl protecting group was readily removed under the mild condition (p-TsOH, MeOH). The resulting alcohol 14 was contaminated with minor diastereomers which was produced in the hydrogenation process, and was tosylated. By taking advantage of medium pressure column chromatography, the major isomer 15 was separated from the minor products (58 % from 19).

The tosylate 15 was then converted to 20 with NaCN and $n\text{-}Bu_4NBr$ in DMF at 85°C. The presence of the ammonium salt in the reaction effected the smooth displacement of tosylate by cyanide, otherwise decomposition of 20 competed with the formation of 20.

The labile nitrile 20, without purification, was hydrolyzed under a mildly basic condition (30 % H_2O_2, aq. Na_2CO_3, acetone)[19] to the amide 21. Stereocontrolled introduction of methyl group (C-19 Me in 1) was accomplished by the use of rigid bicyclic system as follows. Heating of 21 in toluene with either p-TsOH or $CuSO_4 \cdot 5H_2O$ afforded a bicyclic lactam 22 in high yield. Treatment of 22 with Meerwein reagent ($Et_3O^+BF_4^-$) gave 23, which was methylated (LDA, MeI, THF, -78°~-40°C) to give 24 as a sole product quantitatively. The methylating agent approached exclusively from the convex face of the anion of 23 as expected. The disappearance of Hα-proton in the NMR spectrum of 24 reasonably explains the stereochemical course of the methylation. The imino-linkage of 24 was cleaved under a hydrolytic condition (5 % H_2SO_4 - 80 % MeOH, 60°, 11 h) to give a diastereomeric mixture of esters, which, upon reduction ($LiAlH_4$), afforded 25 as a mixture of isomers. NMR spectrum of the mixture 25 showed nearly equal magnitude of two doublets due to anomeric protons at δ 3.90 (J=8Hz) and at δ 4.45 (J=3Hz). The existence of an axial proton at C(2), supported by the coupling constant of the higher field signal (δ 3.90), indicates that epimerization of C(2) methyl group took place at least in 50 % of the substrate during the above transformation. The exact proportion of the epimerized product was determined in the following step. The mixture 25 was treated with 1,3-propanedithiol and BF_3·etherate to give 26 in 55 % overall yield from 24. VPC-MS Analysis of the bistrimethylsilyl derivative of 26 showed the sample being a 3:1 mixture of two diastereomers. The primary hydroxyl group of 26 was selectively protected with a bulky silyl group to give 27, which was then converted to the α-ethoxyethyl ether 28.



Scheme III



Scheme IV

The other chiron **37**, a synthetic equivalent to **8**, was also synthesized from **17** as shown in Scheme III. Reduction of **17** with $NaBH_4$ gave a diastereomeric mixture of **29**, which was benzylated to give **30** (72 %). After removing the ethoxyethyl group (p-TsOH, MeOH), the resulting alcohol was converted to a nitrile **31** via a trifluoromethanesulfonate. An attempt to convert the corresponding p-toluenesulfonate to **31** under the same condition used for **15** was unsuccessful.

Methanolysis of **31** gave a methyl ester **32**, which was reduced with $LiAlH_4$ to **33** (84 % from **31**). Hydrogenation of **33** was followed by acetolysis to give **34**. Hydrolysis, periodate oxidation and $NaBH_4$ reduction eliminated one carbon unit from **34** to afford a triol **35**. Selective protection of 1,3-diol with cyclohexylidene group and chromatographic purification gave a homogeneous monoalchohol **36** (29.3 % from **33**). Conversion of **36** to **37** was achieved by treatment with 2,4,5-triiodoimidazole and Ph_3P (69 %).[20] The coupling of two chirons **28** and **37**, synthesized as above, and the further transformation are depicted in Scheme IV.

The anion generated from **28** with t-BuLi in n-hexane was treated with **37** in the presence of HMPA to give a coupling product **38** in 69.8 % yield. After replacing the protecting group through de-silylation and benzoylation (71.2 %), the thioketal **39** was hydrolyzed to a ketone, which, without purification, was heated in 10 % aq. H_3PO_4 - THF to give a spiroketal **40** as a sole product (66.3 %). No contamination with stereoisomers was observed in its HPLC and NMR (400 MHz) spectrum. Therefore, equilibration of **40** with the diastereomer at C-15 must have occured during the cyclization process in favor to **40**. Since in our preliminary work[21] we failed in the introduction of the pyrrole moiety to a spiroketal system with benzoxazole ring, we intended to build up the pyrrolyl ketone system before attaching the benzoxazole. The hydroxyl group of **40** was protected as an acid-stable silylether and the benzoyl group was removed to give **41**. Oxidation of **41** with chromic acid afforded a carboxylic acid, which was then converted to a 2-pyridylthiol ester **42** according to the procedure reported by Mukaiyama et al.[22] Regioselective acylation of pyrrole with **42** was carried out by an efficient method developed by our group.[23] The ester **42** was treated with a mixture of pyrrolylmagnesium bromide (3 eq) and CuI (1.5 eq) in THF-ether (1:1) at 0°C to give **43** in 80 % yield.

In order to construct the benzoxazole system, we condensed an appropriately substituted aminophenol **48** with **44**, derived from **43** through desilylation and oxidation. The aminophenol **48** was prepared from known **45**[8a)24] in three steps. (i) Selective protection of the adjacent

aminophenolic function as an oxazole ring to give **46** (94 %), (ii) methylation of **46** to give **47** (94 %), and (iii) hydrolysis of the oxazole ring (68 %).

Coupling of **44** and **48** was achieved by means of mixed anhydride method. The initial acylation took place at the phenolic oxygen but during chromatography on silica gel the acyl group migrated to give an amide, which afforded the benzoxazole **49** (Scheme I) by heating with PPTS in dichloroethane. Finally, the trifluoroacetyl group was removed by treatment with n-Bu_4NF to produce A23187 methyl ester **2** in 24 % overall yield from **44**. The synthetic **2** was identical in all respects (IR 400MHz-NMR, MS, CD, HPLC) with the authentic sample prepared from the natural antibiotic **1**. Hydrolysis of **2** to the free acid **1** has already described.[8a)]

In summary, we achieved a fully stereocontrolled synthesis of A23187 by using two chirons **28** and **37** derived from D-glucose. This convergant approach, involving three heterocyclic intermediate **3**, **4** and **5**, offers an advantage of permitting independent modification of each heterocyclic intermediates for synthesis of various analogs of A23187.[25)]

EXPERIMENTAL

All melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Varian EM-360, JEOL JNM FX90Q, FX400 or GX400 spectrometer for solutions in $CDCl_3$, unless noted otherwise. IR spectra were recorded on a Shimadzu IR-430 spectrophotometer. Optical rotations and C.D were measured for solutions in $CHCl_3$, unless noted otherwise, with a Perkin-Elmer 141 polarimeter or a Jasco J-20A automatic recording spectropolarimeter. Low and high-resolution mass spectra were taken on a Hitachi RMU-6MG or Hitachi M-80 mass spectrometer.

Methyl 2,3,4-trideoxy-4-C-methyl-2-C-methylene-6-O-triphenylmethyl-α-D-threo-hexopyranoside **12**. To a suspension of methyltriphenylphosphonium bromide (15 g, 42 mmol) in dry THF (100 mℓ) was added 1.34N n-BuLi/n-hexane (26.2 mℓ, 35 mmol) in an ice-MeOH bath under N_2. After stirring stirred for 30 min, a solution of **9** (6.0 g, 14.4 mmol) in dry THF (60 mℓ) was added to the mixture. The cooling bath was removed and the mixture was allowed to come to room temperature. Stirring was continued overnight. Then most of the solvent was evaporated *in vacuo* and the residue was extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting crude product was chromatographed on silica gel (400 g) in n-hexane-EtOAc-Et_3N (85:15:1) to give crystalline compound **12** (5.6 g, 93.8 %) mp. 166°C (recrystallized from toluene). $[\alpha]_D^{22}$ +35.0° (c=1.3). (lit.[14] mp. 137~139°C; $[\alpha]_D^{23}$ +48.2°). ^{1}H-NMR; δ 0.66 (3 H, d, J=7Hz), 3.44 (3 H, s), 4.24 (1 H, m), 4.85 (1 H, s), 4.89 (1 H, d, J=9Hz), 7.20~7.55 (15 H, m). Anal Found: C, 80.68; H, 7.30 %. Calcd. for $C_{28}H_{30}O_3$: C, 81.12; H, 7.30 %.

Methyl 2,3,4-trideoxy-2,4-C-dimethyl-6-O-triphenylmethyl-α-D-lyxo-hexopyranoside **13**. A solution of **12** (7.02 g, 16.9 mmol) in EtOAc (200 mℓ) was hydrogenated overnight in the presence of 10% Pd-C (3 g) under a medium pressure (3.5 kg/cm^2) of H_2. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel (1 kg) in n-hexane-EtOAc-Et_3N (90:10:1) to give cis dimethyl compound **13** as a more polar fraction (5.12 g, 72.6%) and the less polar isomers (1.62 g). The cis dimethyl compound **13** was recrystallized from n-hexane-EtOAc. mp. 143~143.5°C $[\alpha]_D^{22}$ +30.4° (lit mp. 140~142°C[15], 138~140°C[14], $[\alpha]_D$ +27.0°[15], +29.1°[14]). (c=1.6). ^{1}H-NMR δ 0.70 (3 H, d, J=7Hz), 0.94 (3H, d, J=7Hz), 3.46 (3 H, s), 4.08 (1 H, m), 4.26 (1 H, d, J=6Hz), 7.20~7.55 (15 H, m). ^{13}C-NMR 15.9, 18.3, 30.6, 33.7, 34.6, 55.3, 63.0, 71.9, 86.6, 104.2, 126.8, 127.7, 128.7, 144.0.

Methyl 2,3,4-trideoxy-2,4-C-dimethyl-α-D-lyxo-hexopyranoside **14**. A solution of the tritylether **13** (2.07 g, 4.97 mmol) in dry THF (80 mℓ) was added to liq. NH_3 (150 mℓ) in a dry ice-acetone bath. The mixture was vigorously stirred while Na (1.6 g) was added by portions to the mixture. After stirring for 2 h, pulverized NH_4Cl was added portionwise to the mixture until excess Na was destroyed. The bath was removed and NH_3 was allowed to evaporate slowly. The residue was dissolved in water and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was chromatographed on silica gel (100 g) with n-hexane-EtOAc (1:1) as eluant to afford **14** as a volatile solid (0.72 g, 83.2 %), which was sublimed to give needles. mp. 45~46.5°C. $[\alpha]_D^{25}$ +101.7° (c=7.2), IR (KBr) νmax 3430 cm^{-1}. ^{1}H-NMR δ 0.88 (3 H, d, J=7Hz), 0.98 (3 H, d, J=7Hz), 3.40 (3 H, s), 4.25 (1 H, d, J=6Hz).

Methyl 3,4-dideoxy-6-O-(1-ethoxyethyl)-α-D-glycero-hex-3-enopyranosid-2-ulose **16**. The diol **11** was oxidized with active MnO_2 according to the reported manner. Minor modification (running the reaction in CH_2Cl_2 instead of $CHCl_3$) efficiently converted **11** to enone (91.3 %). A mixture of the oxidized compound (50 g, 0.32 mmol) and ethyl vinyl ether (91 g, 1.3 mol) was stirred with pyridinium p-toluenesulfonate (5 g) in dry CH_2Cl_2 (750 mℓ) at room temperature for 4 h. Then the mixture was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved in a mixture of n-hexane-EtOAc-Et_3N (70:30:1, 300 mℓ) and filtered through silica gel (200 g) with suction. The silica gel was washed with the same mixed-solvent (1 ℓ) and the filtrate was concentrated *in vacuo* to give **16** (70.2 g, 96.4 %), which was used for the next reaction without further purification. IR (neat) νmax 1695, 1610 cm^{-1}. ^{1}H-NMR δ 1.22, 1.23 (3 H, t, J=7Hz), 1.33, 1.35 (3 H, d, J=6Hz), 3.5~3.9 (4 H, m), 3.56 (3 H, s), 4.66 (1 H, m), 4.78 (1 H, s), 4.79 (1 H, m), 6.16 (1 H, dd, J=11, 4Hz), 7.07 (1 H, dt, J=11, 2.5Hz).

Methyl 3,4-dideoxy-6-O-(1-ethoxyethyl)-4-C-methyl-α-D-threo-hexopyranosid-2-ulose **17**. To a solution of $LiMe_2Cu$, prepared from 1.5N ethereal MeLi (346 mℓ, 0.52 mol) and CuI (49.5 g, 0.26 mol) in dry ether (1.5 ℓ) was added a solution of **16** (30 g, 0.13 mol) in dry ether (200 mℓ) with stirring in a dry ice-acetone bath under Ar. After 20 min, the mixture was poured into aq. $NaHCO_3$ (1 l) and stirred at room temperature for 1 h. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with water and brine, dried (Na_2SO_4) and evaporated in vacuo. The resulting product **17** (28.1 g, 87.6 %) was used for the next reaction without purification. IR (neat) νmax 1730cm^{-1}. ^{1}H-NMR δ 0.97 (3 H, d, J=7Hz), 1.23 (3 H, t, J=7Hz), 1.34 (3 H, d, J=5.5Hz), 2.20 (1 H, dm, J=14Hz), 2.43 (1 H, m), 2.98 (1 H, dd, J=14, 6Hz), 3.47 (3 H, s), 3.4~3.7 (4 H, m), 4.45 (1 H, m), 4.49 (1 H, s), 4.76 (1 H, q, J=5.5Hz).

Methyl 3,4-dideoxy-4-C-methyl-α-D-threo-hexopyranosid-2-ulose **18**. According to the reported procedure for detritylation of **9**,[13] the ethoxyethyl ether **17** was treated with HCl/$CHCl_3$ at 0°C for 4 h. The mixture was neutralized with Na_2CO_3, filtered and evaporated in vacuo. The residue was chromatographed on silica gel in $CHCl_3$-EtOAc (9:1) to give **18**, which was identical with the sample derived from **9**. IR (neat) νmax 3400, 1730 cm^{-1}. ^{1}H-NMR δ 0.96 (3 H, d, J=7Hz), 2.05 (1 H, brs), 2.20 (1 H, m), 3.01 (1 H, dd, J=6, 14Hz), 3.48 (3 H, s), 4.42 (1 H, m), 4.52 (1 H, s).

Methyl 2,3,4-trideoxy-6-O-(1-ethoxyethyl)-4-C-methyl-2-C-methylene-α-D-threo-hexopyranoside **19**. To a suspension of methyltriphenylphosphonium bromide (16.8 g, 50.5 mmol) in dry THF (170 mℓ) was added 1.46N n-BuLi/n-hexane (26.6 mℓ, 38.9 mmol) in an ice-MeOH bath under Ar. After stirring for 30 min, a solution of **17** (4.25 g, 17.3 mmol) in dry THF (80 mℓ) was added to the mixture. The cooling bath was removed and the mixture was allowed to come to room temperature. Stirring was continued overnight. Then the solvent was evaporated in vacuo. The residue was dissolved in 70 % aq. MeOH (200 mℓ) and extracted with n-hexane. The extract was washed successively with 70 % MeOH, water and brine, and dried (Na_2SO_4). Evaporation of the solvent gave a crude product, which was chromatographed on silica gel in n-hexane-EtOAc-Et_3N (90:10:1) to give **19** (2.38 g, 80%). $[\alpha]_D^{26}$ +103.4° (c=0.58). IR (neat) νmax 1645 cm^{-1}. ^{1}H-NMR δ 0.86 (3 H, d, J=7Hz), 1.22 (3 H, t, J=7Hz), 1.32 (3 H, d, J=5Hz), 2.00 (1 H, m), 2.78 (1 H, m), 3.21 (3 H, s), 3.43~3.72 (2 H, m), 4.18 (1 H, m), 4.74 (1 H, q, J=10Hz), 4.82 (1 H, s), 4.88 (1 H, s), 4.97 (1 H, s). Anal. Found: C, 64.25; H, 9.85 %. Calcd. for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90 %.

Methyl 2,3,4-trideoxy-2,4-C-dimethyl-6-O-(p-toluenesulfonyl)-α-D-lyxo-hexopyranoside **15**. (A): from **14**. A mixture of **14** (1.31 g, 7.52 mmol) and p-toluenesulfonyl chloride (2.0 g, 10.5 mmol) in dry pyridine (15 mℓ) was stirred overnight at room temperature. The mixture was diluted with ether (200 mℓ), washed with water and brine, and dried (Na_2SO_4). After evaporating the solvent in vacuo, the residue was chromatographed on silica gel (100 g) in n-hexane-EtOAc (4:1) to give **15** (2.43 g, 98.4%) as a volatile oil. $[\alpha]_D^{22}$ +57.0° (c=1.5), IR (neat) νmax 1600, 1450, 1360 cm^{-1}. ^{1}H-NMR δ 0.84 (3 H, d, J=6Hz), 0.95 (3 H, d, J=7Hz), 1.58~2.00 (3 H, m), 2.43 (3 H, s), 3.31 (3 H, s), 4.02~4.18 (4 H, m), 4.20 (1 H, d, J=6Hz), 7.30 (2 H, d, J=9Hz), 7.78 (2 H, d, J=9Hz). (B): from **19**. The olefin **19** (5.0 g, 20.5 mmol) was hydrogenated with 10% Pd-C (2.0 g) in EtOAc (150 mℓ) in a medium pressure apparatus (3.8 kg/cm^2). The catalyst was filtered off and evaporation of the solvent gave a diastereomeric mixtue of 2,4-C-dimethyl compounds (4.95 g), which, without separation, was treated with p-toluenesulfonic acid (50 mg) in MeOH (130 mℓ) at 0~5°C. After stirring for 1.5 h excess Et_3N (2 mℓ) was added to the mixture, which was then evaporated in vacuo. The residue was dissolved in ether, washed with water and brine, and dried (K_2CO_3). Evaporation of the solvent gave crude **14** (3.70 g), which was stirred overnight with p-toluenesulfonyl chloride (5.4 g, 28.3 mmol) in dry pyridine (40 mℓ). Working up and chromatography of the crude tosylate by a medium pressure column packed with silica gel (Wako-gel C-300, 500 g) in toluene-EtOAc (9:1) afforded **15** (4.99 g, 78% from **19**) as a more polar fraction. As a less polar fraction, a mixture of its stereoisomers (0.40 g) was obtained.

Methyl 6-C-cyano-2,3,4,6-tetradeoxy-2,4-C-dimethyl-α-D-lyxo-hexopyranoside **20**. A mixture of **15** (14.3 g, 45.8 mmol), NaCN (21.5 g, 438 mmol) and n-Bu_4NBr (28.6 g, 88.8 mmol) in dry DMF (200 mℓ) was stirred for 7 h at 80°C under N_2. After cooling, the resulting mixture was diluted with water and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and evaporated in vacuo to give a crude solid of **20** (7.65 g). The product was used for the next reaction without purification because of its instability. Analytical sample was prepared by passing a short column of silica gel. IR (Nujol) νmax 2260 cm^{-1}. ^{1}H-NMR δ 0.92 (3 H, d, J=7Hz), 1.02 (3 H, d, J=7Hz), 1.64~2.67 (5 H, m), 3.43 (3 H, s), 4.24 (1 H, d, J=6Hz), 4.27 (1 H, m).

Methyl 6-C-carbamoyl-2,3,4,6-tetradeoxy-2,4-C-dimethyl-α-D-lyxo-hexopyranoside **21**. To a mixture of crude **20** (6.95 g) and 30 % H_2O_2 (185 mℓ, 1.63 mol) in acetone (320 mℓ) was added dropwise 1N aq. Na_2CO_3 (51 mℓ, 51 mmol) in an ice-water bath with stirring. The mixture was stirred for 3 days at room temperature, diluted with water (320 mℓ), and concentrated in vacuo to remove acetone. The resulting aqueous mixture was extracted with $CHCl_3$. The extract was washed successively with water, aq. $Na_2S_2O_3$ and brine, dried (Na_2SO_4), and evaporated in vacuo to give a crude solid, which was washed with n-hexane-EtOAc (1:1) to give **21** (4.78 g, 57.1 % from **15**). mp. 162~163°C (recrystallized from n-hexane-EtOAc). $[\alpha]_D^{23}$ +123.5°C (c=0.5). IR (KBr) νmax 3200, 1650 cm^{-1}. ^{1}H-NMR δ 0.90 (3 H, d, J=6.5Hz), 0.98 (3 H, d, J=6Hz), 1.3~2.6 (6 H, m), 3.40 (3 H, s), 3.64~3.75 (1 H, m), 4.26 (1 H, d, J=6Hz), 5.8~6.2 (2 H, br). Anal. Found: C, 59.45; H, 9.44; N, 6.84 %. Calcd. for $C_{10}H_{19}O_3N$: C, 59.67; H, 9.52; N, 6.96 %.

[1R,5R,6R,8S]-6,8-Dimethyl-2-aza-9-oxabicyclo[3,3,1]nonan-3-one **22**. A solution of **21** (3.2 g, 15.9 mmol) in dry toluene (40 mℓ) was heated under reflux with p-toluenesulfonic acid (320 mg) for 6 h. After cooling, the mixture was washed with aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated in vacuo. The resulting crude product was chromatographed on silica gel (250 g) in $CHCl_3$-acetone (4:1) to give **22** (2.19 g, 81.3%). mp. 144°C. (Crystallized from n-hexane-benzene-EtOAc), $[\alpha]_D^{20}$ -

117.7° (c=0.062). IR (KBr) νmax 3200, 1670 cm^{-1}. ^{1}H-NMR δ 0.86 (3 H x 2, d, J=7Hz), 2.29 (1 H, d, J=18Hz), 2.65 (1 H, dd, J=18, 8Hz), 4.08 (1 H, dd, J=8, 5Hz), 4.82 (1 H, t, J=3Hz), 7.60 (1 H, br s). Anal. Found: C, 63.67; H, 8.93; N, 8.24 %. Calcd. for $C_9H_{15}O_2N$: C, 63.88; H, 8.94; N, 8.28 %. Instead of p-toluenesalfonic acid, $CuSO_4 \cdot 5H_2O$ was usable as the catalyst in the above reaction. (**21**/$CuSO_4 \cdot 5H_2O$/toluene = 1/10/200 w/w/v, 1~2d).

[1R,5R,6R,8S]-3-Ethoxy-6,8-dimethyl-2-aza-9-oxabicyclo[3,3,1]non-2-ene **23**. A mixture of **22** (1.0 g, 6.1 mmol) and triethyloxonium tetrafluoroborate (1.5 g, 7.9 mmol) in dry CH_2Cl_2 (30 mℓ) was stirred overnight at room temperature under Ar. Then 50 % aq. K_2CO_3 (11 mℓ) was added and the resulting mixture was stirred for 10 min. The organic layer was separated by decantation and the aqueous layer was extracted with CH_2Cl_2. The combined organic extract was dried (K_2CO_3) and evaporated in vacuo. The residue was chromatographed on silica gel (80 g) in n-hexane-EtOAc-Et_3N (60:40:1) to give **23** (871 mg, 74.7 %) as a volatile oil. $[\alpha]_D^{22}$ -78.4°C (c=1.19). IR (neat) νmax 1670 cm^{-1}. ^{1}H-NMR δ 0.83 (3 H, d, J=7Hz), 0.90 (3 H, d, J=7Hz), 1.30 (3 H, t, J=7Hz), 1.98 (Hb, d, J_{ab}=18Hz), 2.53 (Ha, dd, J_{ab}=18, J_{ac}=7Hz), 4.10 (2 H, q, J=7Hz), 5.13 (1 H, d, J=3.5Hz).

[1R,4S,5S,6R,8S]-3-Ethoxy-4,6,8-trimethyl-2-aza-9-oxabicyclo[3,3,1]non-2-ene **24**. To a solution of **23** (870 mg, 4.4 mmol) in dry THF (18 mℓ) was added 0.5N LDA/THF (17.7 mℓ, 8.85 mmol) with stirring in a dry ice-acetone bath under Ar. After stirring for 2 h, freshly distilled MeI (2.2 mℓ, 35.2 mmol) was added to the mixture. Stirring was continued for 2 h at -78°. Then the reaction mixture was diluted with ether-CH_2Cl_2 (1:1, 250 mℓ) and stirred with 50 % aq. K_2CO_3 (25.5 mℓ) at room temperature for 15 min. The organic layer was separated, dried (K_2CO_3), and evaporated in vacuo to give a crude product (1.15 g), which was used for further synthesis without purification. A sample for characterization was prepared by column chromatography on silica gel. $[\alpha]_D^{22}$ -90.5° (c=2.5). IR (neat) νmax 1670 cm^{-1}. ^{1}H-NMR δ 0.83 (3 H, d, J=7Hz), 0.88 (3 H, d, J=7Hz), 1.27 (3 H, t, J=7Hz), 1.29 (3 H, d, J=7Hz), 3.55 (Hc, d, J=4.5Hz), 4.08 (2 H, q, J=7Hz), 5.10 (1 H, d, J=3.5Hz).

Methyl 2,3,4,6-tetradeoxy-2,4,6-trimethyl-α(& β)-D-gluco(& manno)-heptopyranoside **25**. A solution of crude **24** (1.10 g) in MeOH-H_2O-H_2SO_4 (76:19:5, 21.4 mℓ) was heated with stirring at 60°C for 11 h. After cooling, the mixture was diluted with ether-EtOAc (1:1, 220 mℓ), washed with satd. $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated in vacuo to give a crude oil (856 mg), which was heated under reflux with $LiAlH_4$ (620 mg, 16.3 mmol) in dry ether (70 mℓ) for 3 h. The excess reducing agent was destroyed by an addition of water. The mixture was diluted with ether-EtOAc (1:1, 200 mℓ) and the organic layer was separated by decantation. The organic extract was washed successively with aq. potassium sodium tartrate, water and brine, dried (Na_2SO_4), and evaporated in vacuo to give a diastereomeric mixture of **25** (684 mg). The crude product **25** was used for the next reaction without purification. ^{1}H-NMR spectrum of **25** showed two doublet signals of nearly equal magnitude at δ 3.90 (J=8Hz) and 4.45 (J=3Hz).

2,3,4,6-Tetradeoxy-2,4,6-trimethyl-D-gluco(& manno)-heptose trimethylene dithioacetal **26**. A mixture of **25** (684 mg), 1,3-propanedithiol (3.4 mℓ, 33.9 mmol) and BF_3·etherate (0.5 mℓ) in dry CH_2Cl_2 (28 mℓ) was stirred overnight ar room temperature. The mixture was diluted with EtOAc (200 ml), washed with satd. $NaHCO_3$, and dried (Na_2SO_4). After removing the solvent, the residue was chromatographed on silica gel (45 g) in n-hexane-EtOAc (1:1) to give **26** (565 mg, 45.9 % from **23**) as an oil. $[\alpha]_D^{26}$ -1.36° (c=0.33). IR (neat) νmax 3450 cm^{-1}. ^{1}H-NMR δ 0.83 (3 H, d, J=6Hz), 0.86 (3 H, d, J=6Hz), 1.03 (3 H, d, J=6Hz), 1.4~2.2 (6 H, m), 2.60 (1 H, br s), 2.80~2.95 (4 H, m), 3.4~3.8 (5 H, m), 4.11 (1 H, d, J=4Hz). Anal. Found: C, 56.08; H, 9.33 %. Calcd. for $C_{13}H_{26}O_2S_2$: C, 56.07; H, 9.41 %. A sample for GC-MS analysis was obtained by bistrimethylsilylation of **26** with TMSCl and pyridine. The analysis was carried out on a column of 2 m length packed with 5 % SE-30 at 250° in a stream of N_2 (1.2 kg/cm^2). The sample split into two peaks (retention time, 6.9 min and 7.4 min, magnitude 1:3), both of which showed m/z 422 (M^+).

7-O-t-Butyldimethylsilyl-2,3,4,6-tetradeoxy-2,4,6-trimethyl-D-gluco(& manno)-heptose trimethylene dithioacetal **27**. A mixture of **26** (548 mg, 1.97 mmol), t-butylchlorodimethylsilane (297 mg, 1.97 mmol) and imidazole (308 mg, 4.52 mmol) in dry DMF (10 mℓ) was stirred for 2 h in an ice-water bath. The resulting mixture was diluted with ether, washed with water and brine, and dried (Na_2SO_4). After removing the solvent, the residue was chromatographed on silica gel (75 g) in n-hexane-EtOAc (85:15) to give **27** (741 mg, 95.8 %). $[\alpha]_D^{28}$ -10.7° (c=2.0). IR (neat) νmax 3500 cm^{-1}. ^{1}H-NMR δ 0.08 (6 H, s), 0.88 (9 H, s), 0.8~0.9 (3 H x 2), 1.06 (3 H, d, J=7Hz), 1.51 (1 H, br s), 1.4~2.0 (6 H, m), 2.9 (4 H, m), 3.2~3.8 (4 H, m), 4.10 (1 H, J, J=4Hz).

7-O-t-Butyldimethylsilyl-2,3,4,6-tetradeoxy-5-O-(1-ethoxyethyl)-2,4,6-trimethyl-D-gluco(& manno)-heptose trimethylene dithioacetal **28**. A solution of **27** (480 mg, 1.2 mmol) and ethyl vinyl ether (380 mg, 5.3 mmol) in dry CH_2Cl_2 (5 mℓ) was stirred with pyridinium p-toluenesulfonate (30 mg) at room temperature for 6 h. The resulting mixture was diluted with CH_2Cl_2, washed with brine, and dried (K_2CO_3). Evaporation and chromatography on silica gel (65 g) in n-hexane-EtOAc-Et_3N (95:5:1) gave **28** (541 mg, 95.5 %) as an oil. $[\alpha]_D^{28}$ +27.6° (c=0.76). ^{1}H-NMR δ 0.08 (6 H, s), 0.8~0.91 (3 H x 2, m), 0.86 (9 H, s), 1.02 (3 H, m), 1.15 (3 H, m), 1.26 (3 H, m), 1.64~1.84 (4 H, m), 1.84~2.10 (3 H, m), 2.75~2.90 (4 H, m), 3.2~3.6 (5 H, m), 4.05~4.15 (1 H, m), 4.55~4.70 (1 H, m). Anal. Found: C, 59.48; H, 10.38 %. Calcd. for $C_{23}H_{48}O_3S_2Si$: C, 59.43; H, 10.41 %.

Methyl 3,4-dideoxy-6-O-(1-ethoxyethyl)-4-C-methyl-α-D-xylo(& lyxo)-hexopyranoside **29**. A solution of $NaBH_4$ (4.56 g, 120 mmol) in 99 % EtOH (480 mℓ) was added dropwise to a solution of **17** (30 g, 120 mmol) in THF-99 % EtOH (1:1, 720 mℓ) with stirring in an ice-water bath, over a period of 30 min. The mixture was stirred at room temperature for 2 h and then concentrated in vacuo. The residue was extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo to give crude **29** (27.9 g), which was used for the next reaction without

purification. ^{1}H-NMR δ 0.99 (3 H, d, J=7Hz), 1.21 (3 H, t, J=7Hz), 1.31 (3 H, d, J=5.5Hz), 3.44 (3 H, s).

Methyl 2-O-benzyl-3,4-dideoxy-6-O-(1-ethoxyethyl)-4-C-methyl-α-D-xylo(& lyxo)-hexopyranoside 30. To a suspension of 60 % NaH/mineral oil (4.62 g, 120 mmol) in dry DMF (167 mℓ) was added dropwise a solution of crude 29 (16.74 g, 67.5 mmol) in dry DMF (30 mℓ) over a period of 20 min with stirring in an ice-water bath, and the mixture was stirred for 2 h. Then benzyl bromide (9.6 mℓ, 80.9 mmol) was carefully added to the mixture. The cooling bath was removed and stirring was continued overnight at room temperature. Excess NaH was destroyed by an addition of water and most of DMF was distilled off in vacuo. The residue was diluted with water and extracted with ether. The ethereal extract was washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo to give a crude product, which was chromatographed on silica gel (1 kg) in n-hexane-EtOAc-Et_3N (85:15:1) to afford 30 (15.34 g, 62.1 % from 17). $[\alpha]_D^{27}$ +48.2° (c=1.7), IR (neat) νmax 3030, 1590, 730, 690 cm^{-1}. ^{1}H-NMR δ 0.93 (3 H, d, J=7Hz), 1.20 (3 H, t, J=7Hz), 1.29 (3 H, d, J=5Hz), 3.42 (3 H, s), 3.50 (2 H, m), 4.55 (1 H, d, J=12Hz), 4.61 (1 H, d, J=12Hz), 4.69 (1 H, d, J=4Hz), 4.71 (1 H, q, J=5Hz), 7.35 (5 H, m). Anal. Found: C, 67.56; H, 8.89 %. Calcd. for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93%.

Methyl 2-O-benzyl-6-C-cyano-3,4,6-trideoxy-4-C-methyl-α-D-xylo(& lyxo)-hexopyranoside 31. A mixture of 30 (11.8 g, 34.9 mmol) and p-toluenesulfonic acid (1.18 g) in MeOH (236 mℓ) was stirred for 1.5 h in an ice-water bath. Excess Et_3N was added to neutralize the acidic mixture and most of MeOH was evaporated in vacuo. The residue was dissolved in ether, washed with water and brine, and dried (Na_2SO_4). After evaporating the solvent in vacuo, the crude product was chromatographed on silica gel (500 g) in n-hexane-EtOAc (85:15) to give an alcohol (7.98 g, 85.9 %). $[\alpha]_D^{25}$ +73.5° (c=1.1). IR (neat) νmax 3450 cm^{-1}. ^{1}H-NMR δ 0.91 (3 H, d, J=7Hz), 1.62~2.40 (3 H, m), 2.44 (1 H, br s), 3.43 (3 H, s), 3.44~3.7 (3 H, m), 3.96 (1 H, m), 4.54 (1 H, d, J=12Hz), 4.61 (1 H, d, J=12Hz), 4.69 (1 H, d, J=4Hz), 7.34 (3 H, br), 7.35 (2 H, br). To a mixture of above alcohol (7.95 g, 29.9 mmol) and N,N-diisopropylethylamine (11.6 g, 89.7 mmol) in dry CH_2Cl_2 (67.5 mℓ) was added trifluoromethanesulfonic anhydride (6 mℓ, 36 mmol) with stirring in an ice-MeOH bath. After stirring for 30 min, the mixture was diluted with n-hexane-EtOAc (9:1, 500 mℓ) and filtered through silica gel (200 g) with suction. The filtrate was concentrated at <10°C in vacuo to give a crude triflate (11.5 g), which was dissolved in dry DMF (115 mℓ) and stirred with NaCN (7.0 g, 144 mmol) at room temperature for 1.5 h. The resulting mixture was poured into ice-water and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel (500 g) in n-hexane-EtOAc (85:15) to give 31 (6.59 g, 68.9 % from 30) as an oil. $[\alpha]_D^{26}$ +72.3° (c=0.7). IR (neat) νmax 2200, 1480, 730 cm^{-1}. ^{1}H-NMR δ 0.96 (3 H, d, J=7Hz), 1.7~2.1 (3 H, m), 2.33 (1 H, dd, J=6, 16Hz), 2.47 (1 H, dd, J=9, 16Hz), 3.46 (3 H, s), 3.64 (1 H, m), 4.19 (1 H, m), 4.54 (1 H, d, J=12Hz), 4.61 (1 H, d, J=12Hz), 4.68 (1 H, d, J=4Hz), 7.34 (3 H, br), 7.35 (2 H, br). Anal Found: C, 69.41; H, 7.68 %. Calcd. for $C_{16}H_{21}O_3N$: C, 69.41; H, 7.68 %.

Methyl 2-O-benzyl-3,4,6-trideoxy-4-C-methyl-α(& β)-D-xylo(& lyxo)-heptopyranoside 33. A solution of 31 (6.57 g, 23.9 mmol) in satd. methanolic HCl (40 mℓ) was kept at 0°C for 4 days. The mixture was concentrated in vacuo. The residue was heated under reflux in MeOH-ether (1:1, 80 mℓ) for 4 h. The mixture was concentrated in vacuo and the resulting product was dissolved in ether. The ethereal solution was washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo to give crude 32 (6.86 g) as an oil. ^{1}H-NMR δ 0.95 (3H, d, J=7Hz), 3.40 (3 H, s), 3.68 (3 H, s). To a suspension of $LiAlH_4$ (632 mg, 16.6 mmol) in dry ether (50 mℓ) was added dropwise a solution of 32 (6.83 g) in dry ether (6 mℓ) with stirring in an ice-water bath. After stirring for 1 h, excess reducing agent was destroyed with water and the mixture was extracted with ether. The ethereal extract was washed successively with aq. potassium sodium tartrate, water and brine, and dried (Na_2SO_4). Evaporation of the solvent gave a crude product, which was chromatographed on silica gel (500 g) in n-hexane-EtOAc (4:1) to afford 33 (5.63 g, 84.2 %) as a colorless oil. $[\alpha]_D^{25}$ +49.8°C (c=1.0). IR (neat) νmax 3450, 1490, 730 cm^{-1}. ^{1}H-NMR δ 0.96 & 0.97 (3 H, d, J=7Hz), 1.4~2.4 (6 H, m), 2.48 (1 H, br s), 3.42 & 3.54 (3 H, s), 3.64 & 4.04 (1 H, m), 3.78 (2 H, m), 4.25 & 4.66 (1 H, d, J=7 & 4Hz), 4.5~4.8 (2 H, d x 4, J=12Hz), 7.30~7.35 (5 H, m). Anal. Found: C, 68.17; H, 8.76%. Calcd. for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63 %.

2,3,5-Trideoxy-3-C-methyl-D-threo-hexose 35. A mixture of 33 (5.45 g, 19.5 mmol) and 10% Pd-C (1.0 g) in EtOAc (50 mℓ) was shaken overnight under H_2 at an initial pressure of 4 kg/cm^2. The catalyst was filtered off and the filtrate was concentrated in vacuo to give debenzylated compound (3.94 g) as an oil. The oil (1.0 g) was stirred in a mixture of acetic anhydride (15 mℓ) and BF_3•etherate (0.5 mℓ) at room temperature for 1 h. Most of acetic anhydride was evaporated in vacuo and the residue was extracted with EtOAc. The extract was washed with water and brine, and dried (Na_2SO_4) and evaporated to give crude 34, which was then stirred in 1 % methanolic NaOMe at room temperature for 30 min. The resulting mixture was neutralized with conc. HCl and concentrated in vacuo. The residue was dissolved in 99 % EtOH (30 mℓ) and the insoluble material was filtered off. To the stirred filtrate was added $NaIO_4$ (2.5 g) by portions with an ice-water cooling. After 15 min, the bath was removed and stirring was continued for 1 h. The resulting precipitate was filtered off and the filtrate was again cooled in an ice-water bath. Then a solution of $NaBH_4$ (680 mg) in 99 % EtOH (10 mℓ) was added dropwise to the cooled mixture with stirring. After completing the addition, the bath was removed and the mixture was stirred at room temperature for 1 h. The insoluble material in the mixture was filtered off. AcOH was added to the mixture to destroy excess $NaBH_4$ and the mixture was evaporated to dryness in vacuo. The residue was dissolved in ether and the precipitate was filtered off. Evaporation of ether gave crude 35 (567 mg), which was used for the next reaction without purification. IR (neat) νmax 3150 cm^{-1}.

4,6-O-Cyclohexylidene-2,3,5-trideoxy-3-C-methyl-D-threo-hexose **36**. A mixture of crude **35** (302 mg), 1,1-dimethoxycyclohexane (1.23 g, 8.6 mmol) and camphorsulfonic acid (31 mg, 0.13 mmol) in dry DMF (1.5 mℓ) was stirred at 40°C under reduced pressure (25 mmHg) for 5 h. The acid catalyst was neutralized with Et_3N. The mixture was diluted with water and extracted with n-hexane. The extract was washed with water and evaporated in vacuo. The residue was dissolved in ether (10 mℓ) and stirred with 50 % aq. AcOH (5 mℓ) at room temperature for 3 h. Then the mixture was extracted with ether. The ethereal extract was washed successively with water, satd. $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated in vacuo. The resulting crude product was chromatographed on silica gel (25 g) in n-hexane-EtOAc (4:1) to give **36** (232 mg, 42.8 % from **33**) as a colorless oil. $[\alpha]_D^{26}$ +6.2° (c=0.7). IR (neat) νmax 3450 cm^{-1}. ^{1}H-NMR δ 0.95 (3 H, d, J=7Hz), 1.34~1.82 (12 H, m), 2.50 (1 H, brs), 3.59~4.02 (5 H, m). Anal. Found: C, 67.99; H, 10.46 %. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59 %.

4,6-O-Cyclohexylidene-1,2,3,5-tetradeoxy-1-iodo-3-C-methyl-D-threo-hexose **37**. A mixture of **36** (100 mg, 0.35 mmol), 2,4,5-triiodoimidazole (357 mg, 0.81 mmol) and triphenylphosphine (420 mg, 1.60 mmol) in dry toluene (20 mℓ) was heated under reflux for 4 h. After cooling, the mixture was poured into satd. $NaHCO_3$ (60 mℓ) with stirring. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed successively with aq. Na_2SO_3, water, satd. $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation of the solvent gave a crude oil, which was chromatographed on silica gel (10 g) in h-hexane-EtOAc (95:5) to afford **37** (101 mg, 68 %) as an oil. $[\alpha]_D^{25}$ +18.4° (c=0.6). IR (neat) νmax 1440, 1360, 1280, 1150, 1100, 970 cm^{-1}. ^{1}H-NMR δ 0.92 (3 H, d, J=6.4Hz), 1.3~2.4 (15 H, m), 3.20 (1 H, m), 3.32 (1 H, m), 3.70 (1 H, m), 3.82 (1 H, m), 3.98 (1 H, m).

13-O-t-Butyldimethylsilyl-1,3-O-cyclohexylidene-2,4,5,6,8,9,10,12-octadeoxy-11-O-(1-ethoxyethyl)-4,8,10,12-C-tetramethyl-D-gluco(& D-manno)-D-threo-7-trideculose trimethylene dithioacetal **38**. To a solution of **28** (600 mg, 1.29 mmol) in dry n-hexane (0.76 mℓ) was added 0.7N t-BuLi/n-pentane (2.4 mℓ, 1.68 mmol) with stirring at -20°C under Ar. After stirring for 4 h at -20°C, dry HMPA (2.4 mℓ) was added to the mixture. The mixture was stirred for 15 min and to this was added a solution of **37** (567 mg, 1.68 mmol) in dry n-hexane (2.4 mℓ). Stirring was continued for 1 h at -20°C. Then the mixture was left overnight in a freezer (-25°C). The resulting mixture was diluted with ether, washed with water and brine, dried (K_2CO_3), and evaporated in vacuo. The residue was chromatographed on silica gel (90 g) in h-hexane-EtOAc-Et_3N (95:5:1). The fraction corresponding to Rf 0.4~0.54 [TLC on silica gel, n-hexane-EtOAc (9:1)] was collected and evaporated in vacuo to give **38** (609 mg, 69.8 %) as an oil. ^{1}H-NMR δ 0.85 (9 H, s), 0.80~1.0 (3 H x 8, m), 2.4~2.6 (10 H, m), 2.6~2.9 (4 H, m).

13-O-Benzoyl-1,3-O-cyclohexylidene-2,4,5,6,8,9,10,12-octadeoxy-11-O-(1-ethoxyethyl)-4,8,10,12-C-tetramethyl-D-gluco(& D-manno)-D-threo-7-trideculose trimethylene dithioacetal **39**. A mixture of **38** (140 mg, 0.2 mmol) and 0.5N n-Bu_4NF/THF (3 mℓ, 1.5 mmol) was stirred at room temperature for 5 h. The mixture was diluted with ether, washed with water and brine, and dried (K_2CO_3). After removing the solvent, the residue was chromatographed on silica gel (14 g) in h-hexane-EtOAc-Et_3N (70:30:0.5) to afford an alcohol (87 mg, 75 %) as an oil. IR (neat) νmax 3450 cm^{-1}. ^{1}H-NMR 0.9~1.0 (3 H x 6, m), 1.1~1.9 (24 H, m), 2.3~2.9 (4 H, m), 3.3~4.2 (9 H, m), 4.65 (1 H, m). To a solution of the alcohol (111 mg, 0.2 mmol) in dry pyridine (2.6 mℓ), was added benzoyl chloride (105 μℓ, 0.9 mmol). The mixture was stirred overnight at room temperature, poured into aq. $NaHCO_3$, and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel (19 g) in n-hexane-EtOAc-Et_3N (90:10:3) to give **39** (125 mg, 71.2 % overall from **38**) as an oil. $[\alpha]_D^{22}$ +21.8° (c=0.3). IR (neat) νmax 1720, 1270, 1160, 720 cm^{-1}. ^{1}H-NMR δ 0.85~1.25 (3 H x 6), 1.25~1.73 (16 H, m), 1.95~2.25 (4 H, m), 2.5~2.7 (4 H, m), 3.35~4.05 (8 H, m), 4.25 (1 H, m), 4.65 (1 H, m), 5.05 (1 H, m), 5.67 (1 H, m), 7.47 (2 H, m), 7.56 (1 H, m), 8.05 (2 H, m).

[2R,3R,6S,8S,9R,11R,1"R]-8-(2"-Benzoyloxy-1"-methylethyl)-2-(2'-hydroxyethyl)-3,9,11-trimethyl-1,7-dioxaspiro[5,5]undecane **40**. A mixture of **39** (57 mg, 0.086 mmol), $HgCl_2$ (114 mg, 0.42 mmol) and $CaCO_3$ (57 mg, 0.57 mmol) in 80 % aq. CH_3CN (5.5 mℓ) was stirred overnight at room temperature. The mixture was diluted with ether and the insoluble material was filtered off through celite. The filtrate was washed successively with satd. $NaHCO_3$, water and brine, dried (Na_2SO_4), and evaporated in vacuo. The residue (52 mg) was heated under reflux overnight in a mixture of 10 % H_3PO_4 (4 mℓ) and THF (4 mℓ). Most of THF was evaporated in vacuo and the resulting mixture was extracted with ether. The ethereal extract was washed with water, satd. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (4.5 g) in n-hexane-EtOAc (4:1) to give **40** (23 mg, 66.3 %) as an oil. $[\alpha]_D^{26}$ +44.9° (c=0.5). IR (neat) νmax 3450, 1710, 1280 cm^{-1}. ^{1}H-NMR δ 0.90 (3 H x 2, d, J=7Hz), 0.98 (3 H, d, J=7Hz), 1.04 (3 H, d, J=7Hz), 1.19~2.24 (12 H, m), 2.86 (1 H, br s), 3.51 (1 H, m), 3.56 (1 H, dd, J=2.1, 10.4Hz), 3.63 (1 H, m), 3.82 (1 H, m), 4.49 (2 H, m), 7.46 (2 H, m), 7.56 (1 H, m), 8.04 (2 H, m). MS Found: 404.25646. Calcd. for $C_{24}H_{36}O_5$: 404.25627.

[2R,3R,6S,8S,9R,11R,1"R]-2-(2'-t-Butyldiphenylsilyloxyethyl)-8-(2"-hydroxy-1"-methylethyl)-3,9,11-trimethyl-1,7-dioxaspiro[5,5]undecane **41**. To a mixture of **40** (83 mg, 0.21 mmol), imidazole (20.9 mg, 0.32 mmol) in dry DMF (1.7 mℓ) was added t-butylchlorodiphenylsilane (62.1 mg, 0.23 mmol) with stirring in an ice-water bath. The mixture was stirred at 0~5°C for 1.5 h, diluted with water, and extracted with ether. The extract was washed with water and brine, and dried (Na_2SO_4). After evaporating the solvent, the residue was chromatographed on silica gel (8.5 g) in n-hexane-EtOAc (95:5) to give a silyl ether (112 mg, 85 %) as an oil. $[\alpha]_D^{26}$ +29.8° (c=0.5). ^{1}H-NMR δ 0.80 (3 H, d, J=6.7Hz), 0.84 (3 H, d, J=6.1Hz), 0.85 (3 H, d, J=6.7Hz), 0.90 (3 H, d, J=6.7Hz), 1.03 (9 H, s), 1.06~2.01 (14 H, m), 3.25 (1 H, dd, J=2.4, 10.4Hz), 3.58 (1 H, m), 3.68 (1 H, dt, J=5.5, 9.5Hz), 4.01 (1 H, dd, J=7.9, 10.4Hz), 4.67 (1 H, dd, J=3.5, 10.4Hz), 7.37 (8 H, m), 7.50 (1 H,

m), 7.63 (4 H, m), 7.98 (2 H, m). A mixture of above silylated compound (103 mg, 0.16 mmol) and satd. methanolic K_2CO_3 (10 mℓ) was stirred at room temperature for 2 h. The resulting mixture was concentrated in vacuo and the residue was extracted with ether. The ethereal extract was washed with water and brine, and dried (Na_2SO_4). After removing the solvent, the residue was chromatographed on silica gel (10 g) in n-hexane-EtOAc (85:15) to give **41** (68 mg, 70 % overall from **40**) as an oil. $[\alpha]_D^{26}$ +37.7° (c=0.7). IR (neat) νmax 3450 cm^{-1}. ^{1}H-NMR δ 0.59 (3 H, d, J=6.8Hz), 0.85 (3 H x 2, d, J=7.1Hz), 0.90 (3 H, d, J=7.1Hz), 1.06 (9 H, s), 1.10~1.92 (13 H, m), 3.34 (1 H, m), 3.40 (1 H, dd, J=2.9, 10.3Hz), 3.55 (1 H, m), 3.64 (1 H, m), 3.70~3.82 (2 H, m), 7.36 (6 H, m), 7.65 (4 H, m).

[2R,3R,6S,8S,9R,11R,1"R]-2-(2'-t-Butyldiphenylsilyloxyethyl)-8-[1"-methyl-2"-oxo-2"-(pyrid-2-ylthio)ethyl]-1,7-dioxaspiro[5,5]undecane **42**. To a solution of **41** (68 mg, 0.13 mmol) in acetone (16 mℓ) was added 8N Jones' reagent[26] (0.16 mℓ, 1.28 mmol) with stirring in an ice-MeOH bath (-10~-15°C). After stirring for 20 min, excess oxidant was destroyed with MeOH (1.6 mℓ). Then the mixture was diluted with water (25 mℓ) and adjusted to pH 4 by an addition of aq. $NaHCO_3$. After evaporating most of acetone in vacuo, the mixture was extracted with EtOAc-ether (1:1). The extract was washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo to give a crude carboxylic acid (69 mg), which was stirred with 2,2'-dipyridyl disulfide (93 mg, 0.42 mmol) and triphenylphosphine (111 mg, 0.42 mmol) in CH_2Cl_2 (4 mℓ) at room temperature for 3 h. The resulting mixture was concentrated in vacuo and the residue was chromatographed on silica gel (25 g) in n-hexane-EtOAc (9:1) to afford **42** (62 mg, 72 %) as an oil. $[\alpha]_D^{26}$ +49.7° (c=0.6). IR (neat) νmax 1690, 1560, 1540, 1430, 1410 cm^{-1}. ^{1}H-NMR δ 0.82 (3 H, d, J=6.1Hz), 0.82 (3 H, d, J=6.8Hz), 0.89 (3 H, d, J=7.1Hz), 0.99 (3 H, d, J=6.8Hz), 1.05 (9 H, s), 1.16~1.83 (10 H, m), 2.01~2.12 (1 H, m), 2.75 (1 H, m), 3.56 (1 H, m), 3.61 (1 H, dd, J=2.4, 10.5Hz), 3.77~3.89 (2 H, m), 7.21 (1 H, m), 7.33 (6 H, m), 7.51 (1 H, m), 7.59 (1 H, m), 7.66 (4 H, m), 8.57 (1 H, m).

[2R,3R,6S,8S,9R,11R,1"R]-2-(2'-t-Butyldiphenylsilyloxyethyl)-8-[1"-methyl-2"-oxo-2"-(1H-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5,5]undecane **43**. A solution of 0.5N pyrrolylmagnesium bromide/ether-THF (1:1) (0.56 mℓ, 0.28 mmol) was added to a suspension of CuI (28 mg, 0.14 mmol) in dry THF (0.2 mℓ) with stirring in an ice-water bath under Ar. After stirring for 30 min, a solution of **42** (62 mg, 0.10 mmol) in dry THF (0.8 mℓ) was added to the mixture. Stirring was continued for 1 h at 0~5°C. Then the mixture was diluted with ether and stirred with satd. NH_4Cl (2 mℓ) for 15 min. The insoluble material was filtered off. The filtrate was washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel (6 g) in n-hexane-EtOAc (9:1) to give **43** (46 mg, 80 %) as crystals. mp. 102~103°C (recrystallized from n-hexane-EtOAc). $[\alpha]_D^{26}$ +57.4° (c=0.2). IR (KBr) νmax 3500, 1620 cm^{-1}. ^{1}H-NMR δ 0.73 (3 H, d, J=7.1Hz), 0.78 (3 H, d, J=6.1Hz), 0.93 (3 H, d, J=6.8Hz), 0.95 (3 H, d, J=7.1Hz), 1.09 (9 H, s), 1.12~1.76 (11 H, m), 3.14 (1 H, m), 3.32 (1 H, dq, J=4, 10Hz), 3.58 (1 H, dd, J=2.4, 10.3Hz), 3.82~3.94 (2 H, m), 6.21 (1 H, m), 6.87 (1 H, m), 6.93 (1 H, m), 7.39 (6 H, m), 7.72 (4 H, m), 9.15 (1 H, br s).

[2R,3R,6S,8S,9R,11R,1'R]-2-Carboxymethyl-8-[1'-methyl-2'-oxo-2'-(1H-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5,5]undecane **44**. A mixture of **43** (46 mg, 0.076 mmol) and 0.5N n-Bu_4NF/THF (1.2 mℓ) was stirred at room temperature for 40 min. The mixture was diluted with ether, washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent gave a crude product, which was chromatographed on silica gel (4.6 g) in n-hexane-EtOAc (4:1) to afford a desilylated product (25.6 mg, 92 %) as an oil. $[\alpha]_D^{26}$ +138.0° (c=0.3). IR (neat) νmax 3450, 3250, 1620, 1540 cm^{-1}. ^{1}H-NMR δ 0.79 (3 H, d, J=7.1Hz), 0.86 (3 H, d, J=6.6Hz), 1.02 (3 H, d, J=7.1Hz), 1.06 (3 H, d, J=6.8Hz), 1.26~1.49 (4 H, m), 1.57~1.91 (6 H, m), 2.36 (1 H, br s), 3.18~3.31 (2 H, m), 3.66~3.75 (2 H, m), 3.89~3.97 (2 H, m), 6.28 (1 H, m), 7.01 (1 H, m), 7.05 (1 H, m), 9.53 (1 H, br s). ^{13}C-NMR 10.8, 11.3, 13.5, 16.3, 25.9, 26.3, 28.5, 30.7, 32.7, 35.7, 36.8, 42.7, 59.9, 67.7, 73.1, 98.3, 110.7, 117.3, 124.8, 133.1, 195.2. MS. Found: 363.24152, Calcd. for $C_{21}H_{33}O_4N$: 363.24095. To a solution of the above product (20 mg, 0.055 mmol) in acetone (10 mℓ) was added 8N Jones' reagent (0.1 mℓ) with stirring in a dry ice-CCl_4 bath (≃-20°C). After stirring for 1 h, excess oxidant was destroyed with MeOH (0.8 mℓ). The mixture was diluted with water (16 mℓ) and ajusted to pH 4 by an addition of aq. $NaHCO_3$. After evaporating most of acetone in vacuo, the mixture was extracted with EtOAc-ether (1:1). The extract was washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel (2 g) in EtOAc-i-PrOH-AcOH (85:5:10) to give **44** (17 mg, 75.3 % from **43**). $[\alpha]_D^{26}$ +120.9° (c=0.9). IR (neat) νmax 3200, 1710, 1620, 1410, 980 cm^{-1}. ^{1}H-NMR δ 0.79 (3 H, d, J=6.8Hz), 0.84 (3 H, d, J=6.6Hz), 0.90 (3 H, d, J=6.1Hz), 0.97 (3 H, d, J=6.8Hz), 1.19~1.32 (2 H, m), 1.55~1.81 (6 H, m), 2.32~2.51 (3 H, m), 3.17~3.28 (1 H, m), 3.84~3.94 (2 H, m), 6.24 (1 H, m), 6.99 (1 H, m), 7.08 (1 H, m), 10.93 (1 H, br s). MS. Found: 377.22138, Calcd. for $C_{21}H_{31}O_5N$: 377.22021.

Methyl 5-trifluoroacetamido-4-benzoxazolecarboxylate **46**. A mixture of **45**[8a),24] (200 mg, 0.72 mmol) and trimethyl orthoformate (4 mℓ) was stirred with a catalytic amount of p-toluenesulfonic acid in dry DMF (25 mℓ) at room temperature for 1.5 h. The mixture was diluted with water and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo to give a solid, which was washed with n-hexane to afford **46** (195 mg, 94 %), mp. 147-148°C (recrystallized from n-hexane-EtOAc). IR (KBr) νmax 3400, 1715, 1680, 1620, 1595, 1550, 1510 cm^{-1}. ^{1}H-NMR δ 4.17 (3 H, s), 7.87 (1 H, d, J=9Hz), 8.30 (1 H, s), 8.83 (1 H, d, J=9Hz), 12.4 (1 H, br). Anal. Found: C, 45.81; H, 2.43; N, 9.63 %. Calcd. for $C_{11}H_7O_4N_2F_3$: C, 45.84; H, 2.45; N, 9.72 %.

Methyl 5-(N-methyltrifluoroacetamido)-4-benzoxazolecarboxylate **47**. A mixture of **46** (167 mg, 0.56 mmol), methyl iodide (0.8 mℓ) and K_2CO_3 (400 mg) in acetone (20 mℓ) was heated under reflux for 1 h. After cooling, the mixture was evaporated in vacuo. Water was added to the residue and the mixture was extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4),

and evaporated in vacuo. The residue was chromatographed on silica gel (20 g) in n-hexane-EtOAc (1:1) to give **47** (164 mg, 93.7 %) as crystals. mp. 98-98.5°C (recrystallized from n-hexane-ether). IR (KBr) νmax 3400, 1730, 1685, 1620 cm^{-1}. ^{1}H-NMR δ 3.40 (3 H, s), 4.03 (3 H, s), 7.40 (1 H, d, J=8Hz), 7.85 (1 H, d, J=8Hz), 8.37 (1 H, s). Anal. Found: C, 47.73; H, 2.99; 9.26 %. Calcd. for $C_{12}H_9O_4N_2F_3$: C, 47.69; H, 3.00; N, 9.27 %.

Methyl 3-hydroxy-6-(N-methyltrifluoroacetamido)-anthranilate **48**. A mixture of **47** (309 mg, 1.0 mmol), 2N HCl (13 mℓ) and MeOH (2 mℓ) was heated with stirring at 90°C for 30 min. After cooling, the mixture was neutralized with 10 % aq. Na_2CO_3 and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel (20 g) in benzene-EtOAc (2:1) to give **48** (203 mg, 67.9 %) as crystals. mp. 121~121.5°C (recrystallized from n-hexane-EtOAc). IR (KBr) νmax 3500, 3370, 3300, 1660, 1610 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ 3.23 (3 H, s), 3.86 (3 H, s), 6.16 (1 H, br), 6.53 (1 H, d, J=8Hz), 6.97 (1 H, d, J=8Hz). Anal. Found: C, 45.37; H, 3.81; N, 9.46 %. Calcd. for $C_{11}H_{11}O_4N_2F_3$: C, 45.21; H, 3.80; N, 9.58 %.

A23187 methyl ester **2**. To a mixture of **44** (20 mg, 0.053 mmol) and Et_3N (29.4 μℓ, 0.21 mmol) in dry CH_2Cl_2 (1 mℓ) was added ethyl chloroformate (11.8 μℓ, 0.12 mmol) with stirring in an ice-MeOH bath under Ar. After stirring for 30 min, a solution of **48** (35 mg, 0.12 mmol) in dry THF (1.2 mℓ) was added to the mixture. Stirring was continued for 1.5 h at -5°~-10°C and overnight at room temperature. Then most of the solvent was evaporated in vacuo and the residue was extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4), and evaporated in vacuo. A column chromatography of the residue on silica gel (8 g) in n-hexane-EtOAc (3:2) afforded an oily product, Rf 0.78~0.86 in n-hexane-EtOAc (1:1), which was heated under reflux with pyridinium p-toluenesulfonate (20 mg) in 1,2-dichloroethane (5 mℓ) for 9 h. After cooling, the mixture was diluted with CH_2Cl_2, washed with satd. $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel (4 g) in n-hexane-EtOAc (65:35) to give crude **49** (15.4 mg). Rf 0.43~0.57 in n-hexane-EtOAc (1:1). A part of the sample (5.9 mg) was stirred with 0.5N n-Bu_4NF/THF (0.6 mℓ) at room temperature for 1 h. The resulting mixture was diluted with ether, washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent gave a crude product, which was chromatographed on silica gel (0.5 g) in n-hexane-EtOAc (7:3) to give **2** (2.6 mg, 23.9 % overall from **44**). The following physical properties were all identical with those of the authentic sample, prepared from natural **1** (CH_2N_2). IR ($CHCl_3$) νmax 3440, 3350, 1665, 1640, 1400, 1250, 980 cm^{-1}. ^{1}H-NMR δ 0.86 (3 H, d, J=6.6Hz), 0.87 (3 H, d, J=7.1Hz), 0.94 (3 H, d, J=6.8Hz), 0.96 (3 H, d, J=7.1Hz), 1.0 (2 H, m), 1.08~1.20 (2 H, m), 1.20~1.30 (4 H, m), 1.65~1.75 (2 H, m), 2.84 (1 H, dd, J=6.8, 14.4Hz), 2.97 (3 H, d, J=4.6Hz), 3.09 (1 H, dd, J=8.1, 14.4Hz), 3.67 (1 H, dd, J=2.4, 10.3Hz), 3.98 (3 H, s), 6.21 (1 H, m), 6.66 (1 H, d, J=9.3Hz), 6.90 (2 H, m), 7.62 (1 H, d, J=9.0Hz), 7.85 (1 H, br s). MS. Found: 537.28191. Calcd. for $C_{30}H_{39}O_6N_3$: 537.28388. m/z 538 (M^++1, 35), 537 (M^+, 100), 333 (9), 332 (25), 319 (16), 318 (68), 260 (13), 220 (40), 188 (23), 94 (50), CD (MeOH, 0.00006 g/ml), $[\theta]_{292}$ +5290, $[\theta]_{282}$ 0, $[\theta]_{267}$ -5740, $[\theta]_{252}$ 0.

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