Total Synthesis of Antibiotic Hygromycin A

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The first total synthesis of the antibiotic (−)-hygromycin A (1) has been achieved by a coupling reaction of the sugar moiety (2) and the cyclitol moiety (3). Both components were synthesized in homochiral forms starting from D-glucose. This synthesis fully confirmed the unique structure of 1, which is much different from other usual aminocyclitol antibiotics.

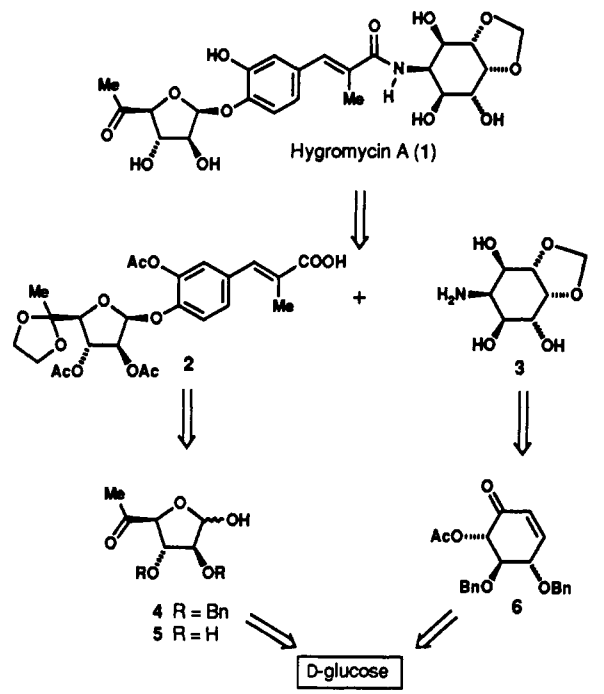
Introduction

Hygromycin A (1) is an antibiotic produced by several strains of *Streptomyces*[1] and was first isolated in 1953. It has been reported that 1 has a relatively broad spectrum of activity against Gram-positive and Gram-negative bacteria.[1a,b] Recently, 1 has attracted renewed interest due to the discovery of its hemagglutination inactivation activity[2] as well as its high antitreponemal activity.[3] The structural studies of 1, using a degradation method by Mann[4] and careful spectral analyses by Kakinuma,[5] revealed that it has a quite unique structure among the aminocyclitol antibiotic family represented by streptomycin and kanamycin. Namely, the anomeric configuration of 1 was assigned as β-cis,[5] which is unusual among naturally occurring furanosides, and the cyclitol structure of 1, assigned as 1L-4,5-*O*-methylene-2-amino-2-deoxy-*neo*-inositol (3),[5] is much different from that of 2-deoxystreptamine or streptamine, common and general cyclitols found in other usual aminocyclitol antibiotics.[6] The presence of the methyl ketone function and the 2-methylcaffeic acid moiety is also rare among the antibiotics in this class.

In spite of the unique structure and interesting biological activity of 1, only a few reports have appeared on the synthesis of the structure components of 1,[7,8] and no report on a total synthesis of 1 has been described. In this article, we document a total synthesis of hygromycin A (1) with full experimental detail.[9]

Our synthetic plan is based on a coupling of the sugar component containing 2-methylcaffeic acid (2) and the optically active aminocyclitol (3; Scheme I), 2 was planned to result from a glycosidation of a furanose derivative (4) with an appropriate aglycon, and 3 was envisioned to result from D-glucose utilizing a Ferrier rearrangement.[10]

Scheme I



Results and Discussion

Synthesis of the Sugar Component (2). In 1967, Takahashi and Nakajima reported the efficient synthesis of 6-deoxy-D-*arabino*-5-hexulofuranose (5) starting from methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-α-D-altroside.[8] We began our synthesis following their methodology with some modification (Scheme II). Thus, treatment of the known methyl 4,6-*O*-benzylidene-2,3-anhydro-α-D-allopyranoside (7)[11] with aqueous base and a successive one-pot benzylation gave the di-*O*-benzyl derivative (8) in 68% yield. A benzyl group was chosen as the protecting group because of its nonparticipating character in the glycosidation step, which would be one of the crucial steps in this synthesis. Removal of the benzylidene group in 8 gave 9 (100%), whose primary hydroxyl group was selectively displaced by iodide with a Mitsunobu reaction[12] to give 10 in 74% yield. Dehydroiodination of 10 was accom-

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(2) Yoshida, M.; Takahashi, E.; Uozumi, T.; Beppu, T. *Agric. Biol. Chem.* **1986**, *50*, 143.

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(12) Mitsunobu, O. *Synthesis* **1981**, 1.

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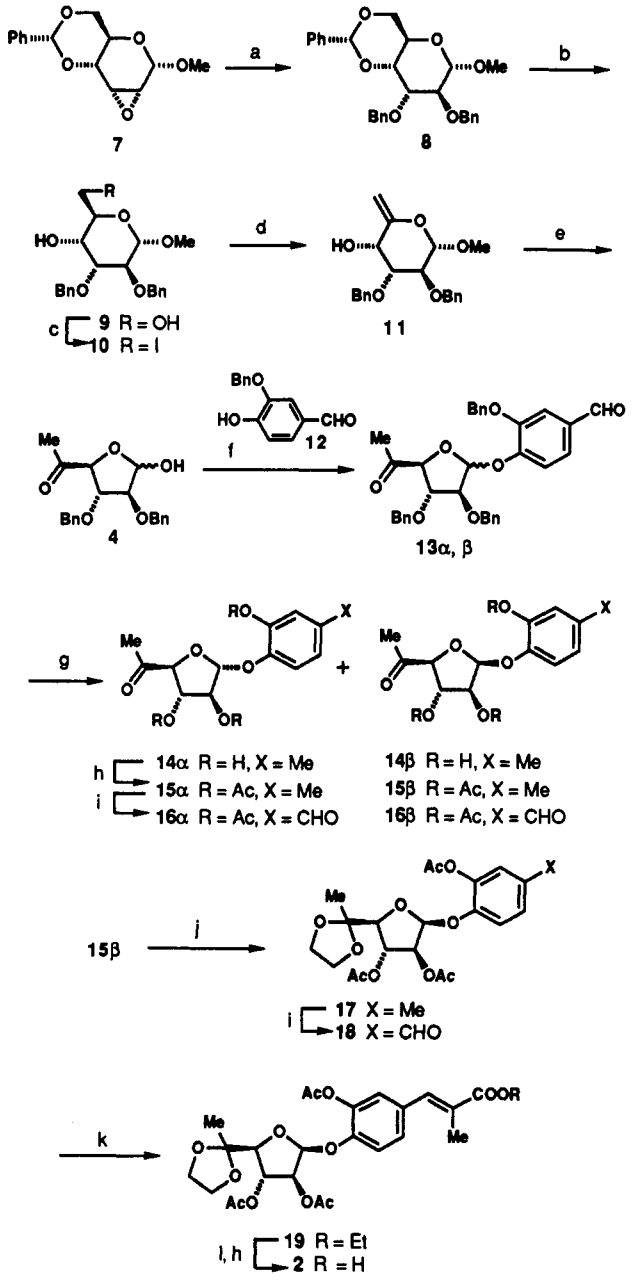
Scheme II[a]



[a] Key: a KOH, H_2O, reflux, then BnCl, DMSO; b aq AcOH; c MeI, Ph_3P, DEAD, THF; d DBU, toluene 80 °C; e IR-120B resin (H^+ form), THF–H_2O; f **12**, Ph_3P, DEAD, THF, rt; g H_2, $Pd(OH)_2$, EtOAc; h Ac_2O, pyridine; i CAN, CH_3CN–H_2O, j $(CH_2OTMS)_2$, TMSOTf, CH_2Cl_2; k $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, rt; l 1 M aqueous NaOH, MeOH.

plished by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford 5-enopyranoside **11**, which was then hydrolyzed with Amberlite IR-120B resin (H^+ type) in aqueous tetrahydrofuran (THF) to give the desired furanose **4** as an anomeric mixture (α:β = 2:1 in $CDCl_3$–D_2O, 67% yield from **11**).

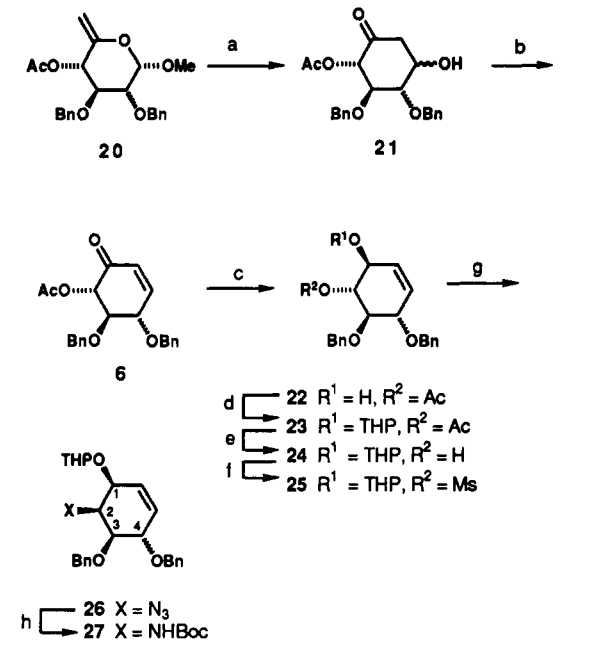
Condensation of **4** with **12**[13] was achieved under the conditions of Mitsunobu's protocol (Ph_3P, diethyl azodicarboxylate, THF).[12,14] The condensates **13α** and **13β** were obtained in 77% yield as an inseparable mixture (**13α**:**13β** = 4:5). Hydrogenolysis of a mixture of **13α** and **13β** (H_2, $Pd(OH)_2$, EtOAc) caused debenzylation, as well as undesired reduction of a formyl group to give **14α** and **14β**, which were easily and cleanly separated by a chromatography on silica gel in 39 and 46% isolated yields, respectively. Many attempts to prevent the formyl group from reducing under various hydrogenolytic conditions were made, but no satisfactory result was obtained. The structures of **14α** and **14β** were established from their ^1H and ^{13}C NMR spectra. Stevens and Fletcher reported that the anomeric protons of arabinofuranose derivatives, in which the vicinal protons at C-1 and C-2 have a cis relationship, are observed as doublets (J = ca. 4 Hz) in their ^1H NMR spectra, whereas those having a trans relationship appear as singlets (J < 1 Hz).[15] The signal of H-1 in **14β** was observed at δ 5.38 as a doublet (J = 4.3 Hz) in its ^1H NMR spectrum. On the other hand, the signal of H-1 in **14α** was observed at δ 5.64 as a sharp singlet. From these observations, it was expected that **14β** had a 1,2-cis linkage (β-glycoside) and **14α** had a 1,2-trans linkage (α-glycoside). The ^{13}C NMR spectra of **14α** and **14β** (resonance of anomeric carbon: **14α**, δ 107.7 ppm; **14β**, 103.6) also supported these structures.[16]

To complete the synthesis of the sugar moiety (**2**), we then made efforts to regenerate the formyl function in **14β**. Acetylation of **14β** gave triacetate **15β** in 96% yield. Oxidation of **15β** with ceric ammonium nitrate (CAN) in acetonitrile–water (1:2) gave aldehyde **16β** in 35% yield. On the other hand, epimeric **15α** was oxidized with CAN similarly as in the preparation of **16β** to afford **16α** in 25% yield. The physical and spectral properties of **16β** were completely identical with those of an authentic sample prepared from natural hygomycin A (see Experimental Section for a preparation of authentic samples). From this synthesis, we could confirm the anomeric configuration of hygromycin A to be β (1,2-cis linkage); however, the low yield of the CAN oxidation of **15β** and the chemical instability of **15β** and **16β** led us to explore alternative paths to a total synthesis. Since it was anticipated that the presence of the methyl ketone function might make **15β** and **16β** relatively unstable,[17] protection of the ketone carbonyl in **15β** was first attempted. Although treatment of **15β** with ethylene glycol in the presence of acid catalyst resulted in degradation of the substrate, ketalization under Noyori's condition[18] gave a good result and the ketal **17** was obtained in 86% yield. Oxidation of **17** with CAN in acetonitrile–water gave a better result than did **15β**, and the compound **18** was obtained in 66% yield. Wittig olefination of **18** with $Ph_3P{=}C(Me)CO_2Et$ in toluene smoothly afforded the only E-olefin **19** in 95% yield. Saponification and successive acetylation of **19** gave the desired product **2** in 66% overall yield from **19**.

Synthesis of the Aminocyclitol (3). The major structural feature of the cyclitol moiety in hygromycin A should be the presence of the methylene ketal group located at the C-4,5 position, which makes **3** optically active. To confirm the absolute stereochemistry of **3**, we planned to synthesize **3** from D-glucose utilizing the Ferrier rear-

(13) Hansson, C.; Wickberg, B. *Synthesis* **1976**, 191.
(14) (a) Grynkiewicz, G. *Carbohydr. Res.* **1977**, *53*, C11. (b) Garegg, P. J.; Iversen, T.; Norberg, T. *Carbohydr. Res.* **1979**, *73*, 313.
(15) Stevens, J. D.; Fletcher, H. G., Jr. *J. Org. Chem.* **1968**, *33*, 1799.
(16) It has been reported that the signals of the anomeric carbon atoms of furanoses, in which the substituents at C-1 and C-2 are trans oriented, are observed at lower field than those of the corresponding cis isomer in their ^{13}C NMR spectra: Bock, K.; Pederson, C. *Advances in Carbohydrate Chemistry and Biochemistry*; Tipson, R. S.; Horton, D., Ed.; Academic Press: New York, **1983**; Vol. *41*, pp 27. See also ref 5.
(17) Treatment of **15β** or **16β** with mild base such as pyridine; or silica gel for purification caused partial elimination of C-3 acetoxyl group to give corresponding enone and/or epimerization at C-4. It has been also reported[18] that hygromycin A in an alkaline solution at room temperature afforded a mixture (1:1) of hygromycin A and its 4''-epimer.
(18) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. (b) Yoshimura, J.; Horito, S.; Hashimoto, H. *Chem. Lett.* **1981**, 375.

Scheme III[a]



[a] Key: a $(CF_3CO_2)_2Hg$, acetone–H_2O, rt; b MsCl, Et_3N, CH_2Cl_2; c $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; d dihydropyran, pyridinium *p*-toluenesulfonate (PPTS), CH_2Cl_2; e MeONa, MeOH; f MsCl, pyridine; g NaN_3, HMPA, 100 °C; h $LiAlH_4$, ether, then $(Boc)_2O$, Et_3N, CH_2Cl_2; i see Table I and text; j Ac_2O, pyridine; k NaH, CH_2Br_2, DMF; l H_2, $Pd(OH)_2$, EtOH; m TFA–$CHCl_3$ (1:1), rt.

rangement.[10] The known 5-enopyranoside **20**,[19] prepared from D-glucose in 7 steps, was chosen as the starting material (Scheme III). Ferrier rearrangement of **20** using a catalytic amount of mercuric trifluoroacetate in acetone–water[20] afforded cyclohexanone **21** (α-alcohol: β-alcohol = 8:1). Without isolation, elimination of the β-hydroxyl group in **21** was effected by the action of methanesulfonyl chloride (MsCl) and triethylamine to give **6** in 87% yield from **20**. Reduction of the ketone carbonyl in **6** with $NaBH_4$ in the presence of $CeCl_3$[21] proceeded highly stereoselectively, and **22** was obtained in 86% yield as a single product. The hydroxyl group was protected as a tetrahydropyranyl (THP) ether to give **23** (99%), whose *O*-acetyl group was removed by sodium methoxide in methanol to afford **24**. At this stage, two diastereoisomers arising from the presence of the THP ether were cleanly separated to give diastereomers **24a** and **24b** in 36 and 41% yields, respectively.[22] Compound **24a** was mesylated to give **25a**, quantitatively (**25b**, 94%). Azidolysis of **25a** with sodium azide in hexamethylphosphoramide (HMPA) at 100 °C proceeded in S_N2 fashion, and the product having an axial azido group (**26a**) was obtained in 73% yield (**26b**, 84%). The ^1H NMR spectra of **26a**, in which the proton at C-2 appeared as a doublet of doublets with small coupling constants ($J_{1,2}$ = 3.7 and $J_{2,3}$ = 2.2 Hz), strongly supported the structure of **26a**. Upon OsO_4 oxidation of **26a**, it was expected that the reagent would approach the double bond from the less hindered α-face, due to the presence of the axial-oriented azido group, to give neo isomer **28a** predominantly. However, contrary to our expectation, OsO_4 oxidation of **26a**,[23] followed by acetylation, afforded epi isomer **29a** as the main product (**28a**:**29a** = 1:2, 76% combined yield). To enhance the neo stereoselectivity in the OsO_4 oxidation step, the azido group in **26a** was converted into the more bulky (*tert*-butoxycarbonyl)amino group ($LiAlH_4$ in ether, then di-*tert*-butyl dicarbonate (Boc_2O)) to afford **27a** in 84% yield (**27b**, 81%). The results of oxidation of **27a** with OsO_4 under various conditions are shown in Table I. Among the conditions attempted, Sharpless's protocol[24] using chiral amine (hydroquinine 4-chlorobenzoate, run 12) gave the highest yield (83%) with modest stereoselectivity (**30a**:**31a** = 62:38). With the same procedure, **27b** was converted into a mixture of **30b** and **31b** (60:40, 82% combined yield). The neo configuration in **30** and epi configuration in **31** were confirmed by the ^1H NMR spectra of their corresponding diacetates **32b** and **33b**. Coupling constants in **32b** ($J_{1,6} = J_{3,4}$ = 10.3 Hz, $J_{4,5} = J_{5,6}$ = 2.9 Hz, and $J_{1,2} = J_{2,3}$ = 4.4 Hz) and **33b** ($J_{3,4} = J_{4,5}$ = 2.9 Hz, $J_{5,6} = J_{1,6}$ = 9.9 Hz, and $J_{1,2} = J_{2,3}$ = 4.4 Hz) as well as the chemical shifts of H-4 and 5 in **32b** and **33b** (H-4, δ 5.00 for **32b** and δ 5.60 for **33b**; H-5, δ 5.70 for **32b** and δ 4.89 for **33b**) clearly showed that **32b** had a neo configuration with hydroxyl groups at C-4 and 5 and **33b** had an epi configuration with hydroxyl groups at C-4 and 5. Introduction of a methylene acetal group into **30a** was accomplished by treatment of **30a** with methylene bromide and sodium hydride in *N*,*N*-dimethylformamide (DMF)[25] to afford **34a** in 60% yield (**34b**, 51%). Debenzylation of **34a** (H_2, $Pd(OH)_2$, EtOH) gave **35a** in 96% yield (**35b**, 100%), which was then treated with trifluoroacetic acid (TFA) to afford **3** isolated in 70% yield. From **35b**, **3** was also obtained in 83% yield. Conventional acetylation of **3** gave the corresponding tetra-*N*,*O*-acetate **36**. The spectral properties (IR, ^1H and ^{13}C NMR) of **36**, $[\alpha]^{21}_D$ −46° (*c* 1.62, $CHCl_3$), were fully identical with those of the authentic sample, $[\alpha]^{24}_D$ −49° (*c* 1.68, $CHCl_3$), prepared from natural hygromycin A. From these results it was concluded that the absolute configuration of the aminocyclitol in hygromycin A was

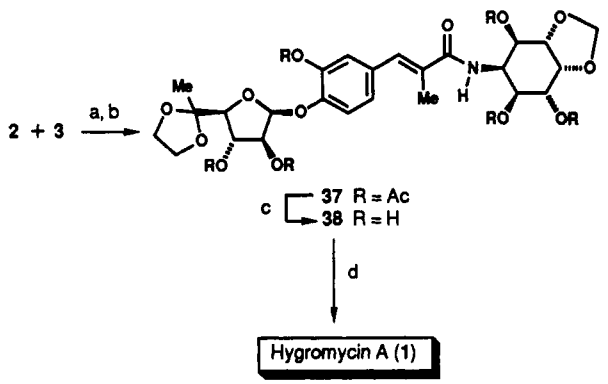
(19) Köhn, A.; Schmidt, R. R. *Liebigs Ann. Chem.* **1987**, 1045.
(20) During this synthetic study, we have found that Ferrier rearrangement proceeded efficiently with a catalytic amount (less than 10 mol %) of mercuric trifluoroacetate in acetone–water, without acidic solvent such as aqueous sulfuric acid. The detailed communication is under preparation.
(21) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(22) Since these two diastereoisomers showed almost same reactivities toward reaction conditions we have employed, a detailed property of only one isomer is discussed in the text. The yields of another diastereoisomer were shown in parentheses in the text.
(23) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(24) Jakobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
(25) Brimacombe, J. S.; Foster, A. B.; Jones, B. D.; Willard, J. J. *J. Chem. Soc. (C)* **1967**, 2404.

Table I. OsO_4 Oxidation of *N*-Boc Derivative 27a

run	solvent (ratio)	amt of OsO_4 (equiv)	amt of NMO (equiv)	additive[a] (equiv)	time	temp (°C)	yield[b] (%)	neo:epi[c] (30a:31a)
1	THF–H_2O (3:2)	0.06	3.0	A (5.0)	9 d	rt	58	57:43
2	*t*-BuOH–H_2O (4:1)	0.05	1.4	A (0.5)	3 h	reflux	59	49:51
3	1,4-dioxane–H_2O (4:1)	0.10	2.0	A (0.5)	3 d	reflux	42 (53)	52:48
4	pyridine–H_2O (4:1)	0.05	1.4		2 h	70	0 (95)	
5	CH_3CN–H_2O (4:1)	0.05	1.4	A (0.5)	1 d	reflux	17 (67)	57:43
6	MeOH–H_2O (4:1)	0.05	1.4	A (0.5)	7 h	reflux	0 (93)	
7	HMPA–H_2O (4:1)	0.15	2.5	A (1.5)	1 d	70	48 (22)	59:41
8	DMF–H_2O (4:1)	0.05	1.4	A (0.5)	1 d	100	53 (41)	66:34
9	DMF–H_2O (4:1)	0.25	3.5	A (2.0)	4 d	70	66 (19)	62:38
10	DMF–H_2O (4:1)	0.02	1.2	B (0.13)	3 d	80	52 (32)	58:42
11	DMF–H_2O (4:1)	0.15	1.2	B (0.5)	3 d	80	42	60:40
12	DMF–H_2O (4:1)	0.12	1.5	B (0.15)	7 d	rt	83	62:38
13	DMF–H_2O (4:1)	0.02	1.5	C (0.15)	10 d	rt	74	57:43

[a] Key: A, pyridine; B, hydroquinine 4-chlorobenzoate; C, hydroquinidine 4-chlorobenzoate. [b] Combined yield of **30a** and **31a**, yields in parenthesis are recovery of starting material (**27a**). [c] Ratios were determined from 270-MHz ^1H NMR.

Scheme IV[a]



[a] Key: a $(EtO)_2P(O)CN$, Et_3N, DMF; b Ac_2O, pyridine; c MeONa, MeOH; d TFA–H_2O (3:2), rt.

the same as that proposed by Kakinuma[5] and should be 1L-4,5-*O*-methylene-2-amino-2-deoxy-*neo*-inositol.

Total Synthesis of Hygromycin A (1). With optically active sugar moiety **2** and aminocyclitol **3** in hand, the central issue became a coupling of these two moieties that would complete the total synthesis (Scheme IV). Toward this end, attempts were made to condense **2** and **3** under various reaction conditions. Although the yield of condensation of **3** with activated ester of **2** prepared from DCC and *N*-hydroxysuccinimide was low (21%), Shioiri's protocol[26] worked very well and the condensate **37** was obtained in 75% yield based on **3**, after acetylation. Deacylation of **37** with NaOMe in MeOH afforded **38** in 94% yield. Finally, **38** was treated with aqueous TFA (rt, 1 h) to give **1** in 45% yield after purification with Sephadex LH-20 and G-10. The synthetic **1** (mp 110–112 °C, $[\alpha]^{28}_D$ −148° (*c* 0.46, water)) was identical in all respects with natural hygromycin A (mp 113–115 °C, $[\alpha]^{23}_D$ −136° (*c* 1, water)).

In summary, the first total synthesis of hygromycin A in a homochiral form has been achieved. This synthesis fully confirmed the assigned structure and absolute stereochemistry, and provided a procedure for the preparation of new derivatives of hygromycin A.[27]

Experimental Section

Melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. ^1H and ^{13}C NMR spectra were measured on a JEOL JNM-GX 400 FT (400-MHz), JEOL GX 270 (270-MHz), or JEOL EX 90 (90-MHz) spectrometer in chloroform-*d* with tetramethylsilane as an internal standard, unless otherwise noted. Specific rotations were measured in a 0.1-dm tube with a JASCO DIP-370 digital polarimeter. Mass spectra were taken on a JEOL JMS-DX302 mass spectrometer with EI mode. IR spectra were recorded with a JASCO Model A-202 spectrometer. Column chromatography was performed with Wakogel C-300 (Wako Pure Chemical, Osaka, Japan) or Katayama 60 (Katayama Chemical, Osaka, Japan). Analytical and preparative TLC were carried out on glass plates coated with Merck Kieselgel 60 Art 7734.

Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C under reduced pressure.

Solvents for reactions were dried and distilled before use (THF (from sodium benzophenone ketyl), CH_2Cl_2, HMPA, benzene, toluene, and DMF (from CaH_2), pyridine and triethylamine (from NaOH)).

Methyl 4,6-*O*-Benzylidene-2,3-di-*O*-benzyl-α-D-altropyranoside (8). A mixture of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**7**)[11] (5.0 g, 19 mmol) and sodium hydroxide (6.64 g, 118 mmol) in water (170 mL) was heated under reflux for 48 h. After being cooled, this was concentrated and the residual water was removed azeotropically (codistilled with ethanol and toluene several times) to give a residue, which was then dissolved in DMSO (60 mL). To this solution, a solution of benzyl chloride (13.5 mL, 118 mmol) in DMSO (40 mL) was added dropwise over 1 h at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was poured into ice–water and extracted with CH_2Cl_2 (500 mL × 2). The extracts were combined and dried. Concentration of the solvent left a residue that was purified on a column of silica gel (150 g) with toluene and EtOAc–toluene (1:20) to give an oil, which was crystallized and recrystallized from ethanol to afford **9** (5.97 g, 68%) as plates: mp 86–87.5 °C; $[\alpha]^{23}_D$ −1° (*c* 2.5, $CHCl_3$); IR (KBr) 2900, 1450 cm^{-1}; ^1H NMR (90 MHz) δ 7.36 (m, 15 H), 5.55 (s, 1 H), 4.75 (d, 1 H, *J* = 3.0 Hz), 4.68–3.56 (m, 10 H), 3.42 (s, 3 H). Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.37; H, 6.51.

Methyl 2,3-Di-*O*-benzyl-α-D-altropyranoside (9). A solution of **8** (7.0 g, 15 mmol) in 80% aqueous acetic acid (40 mL) was heated at 80 °C for 30 min. After being cooled, the mixture was concentrated to give a syrup, which was purified on a column of silica gel (100 g) with acetone–toluene (1:5) to afford **9** (5.67 g, 100%) as a colorless syrup: $[\alpha]^{24}_D$ +59° (*c* 1.6, $CHCl_3$); IR (neat) 3450 cm^{-1}; ^1H NMR (90 MHz) δ 7.30 (s, 10 H), 4.78–4.36 (m, 5 H), 3.88–3.56 (m, 6 H), 3.39 (s, 3 H), 2.84 (b s, 2 H). Anal. Calcd for $C_{21}H_{26}O_6 \cdot {}^1/_4H_2O$: C, 66.56; H, 7.05. Found: C, 66.93; H, 6.91.

Methyl 2,3-Di-*O*-benzyl-6-iodo-α-D-altropyranoside (10). To a stirred solution of **9** (4.39 g, 11.7 mmol) and Ph_3P (3.69 g, 14.1 mmol) in THF (25 mL) at 0 °C under N_2 was added diethyl azodicarboxylate (2.22 mL, 14.1 mmol). After the solution was stirred at 0 °C for 5 min, methyl iodide (0.88 mL, 14.1 mmol) was added, and the resulting mixture was stirred at room temperature for 19 h. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution and brine and dried. Evaporation of the solvent left a syrup, which was purified on a column of silica gel (150 g) with EtOAc–toluene (1:20) to afford

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10 (4.19 g, 74%) as a colorless syrup: $[\alpha]^{27}_D$ +51° (c 1, $CHCl_3$); IR (neat) 3500 cm^{-1}; ^1H NMR (90 MHz) δ 7.43–7.24 (m, 10 H), 4.78–4.26 (m, 6 H), 3.88–3.10 (m, 5 H), 3.49 (s, 3 H). Anal. Calcd for $C_{21}H_{25}O_5I$: C, 52.08; H, 5.20. Found: C, 51.77; H, 5.11.

2,3-Di-*O*-benzyl-6-deoxy-D-*arabino*-5-hexulofuranose (4). A mixture of 10 (5.01 g, 10.3 mmol) and DBU (3.10 mL, 20.7 mmol) in toluene (30 mL) was stirred at 80 °C for 23 h. The mixture was diluted with EtOAc (200 mL) and successively washed with 1 M aqueous H_2SO_4 solution, saturated aqueous $NaHCO_3$ solution, and water and dried. Removal of the solvent gave crude 11, which was dissolved in 5:2 THF–water (40 mL). To this solution was added Amberlite IR 120B resin (H^+ form, ca. 5 g), and the mixture was stirred at room temperature for 22 h. The resin was removed by filtration, and the filtrate was concentrated to give a residue, which was purified on a column of silica gel (100 g) with EtOAc–toluene (1:10) to give 4 (2.36 g, 67% from 10) as a colorless syrup: $[\alpha]^{24}_D$ −12° (c 0.72, $CHCl_3$, 30 min) and −20° (12 h); IR (neat) 3450 and 1718 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$ and one drop of D_2O) δ 7.46–7.14 (m, 10 H), 5.51 (d, $^1/_3$H, J = 3.9 Hz), 5.41 (s, $^2/_3$H), 4.68–3.56 (m, 4 H), 2.23 (s, 3 H × $^1/_3$), 2.16 (s, 3 H × $^2/_3$); HRMS calcd for $C_{20}H_{22}O_5$ 342.1467, found 342.1472. Anal. Calcd for $C_{20}H_{22}O_5 \cdot {}^1/_2H_2O$: C, 68.36; H, 6.48. Found: C, 68.16; H, 6.27.

Condensation of 4 and 12. To a stirred mixture of 4 (1.79 g, 5.24 mmol), 12[13] (1.32 g, 5.76 mmol), and Ph_3P (1.65 g, 6.29 mmol) in THF (15 mL) under Ar at room temperature was added a THF solution (5 mL) of diethyl azodicarboxylate (0.99 mL, 6.29 mmol) dropwise over 20 min. After being stirred at room temperature for 2.5 h, the mixture was concentrated to give a residue, which was purified on a column of silica gel (150 g) with EtOAc–hexane (1:4) to afford a mixture of 13α and 13β (2.22 g, 77% from 4) as a colorless syrup; IR (neat) 1720 and 1690 cm^{-1}; ^1H NMR (90 MHz) δ 9.87 (s, 1 H), 7.57–6.61 (m, 18 H), 5.98 (s, $^4/_9$H), 5.81 (d, $^5/_9$H, J = 4.5 Hz), 5.15–5.42 (m, 9 H), 2.15 (s, 3 H × $^4/_9$), 2.03 (3 H × $^5/_9$); HRMS calcd for $C_{34}H_{32}O_7$ 552.2148, found 552.2152. Anal. Calcd for $C_{34}H_{32}O_7$: C, 73.90; H, 5.84. Found: C, 73.50; H, 5.78%.

2-Hydroxy-4-methylphenyl 6′-Deoxy-β-D-*arabino*-5′-hexulofuranoside (14β) and Its α-Anomer (14α). A mixture of 13α and 13β (192 mg, 0.347 mmol) in EtOAc (2 mL) was hydrogenolyzed in the presence of 20% $Pd(OH)_2$ on carbon (40 mg) under an atmospheric pressure of H_2 at room temperature for 30 min. The catalyst was removed by filtration, and the filtrate was concentrated to give a residue, which was chromatogrpahed on a column of silica gel (5 g) with EtOAc–toluene (1:1) to give, first, 14α (36 mg, 39%) as a colorless syrup: $[\alpha]^{25}_D$ +80° (c 1.2, $CHCl_3$); IR (neat) 3350 and 1710 cm^{-1}; ^1H NMR ($CDCl_3$–D_2O, 400 MHz) δ 6.91 (d, 1 H, J = 8.3 Hz), 6.69 (d, 1 H, J = 1.8 Hz), 6.57 (dd, 1 H, J = 1.8 and 8.3 Hz), 5.64 (s, 1 H), 4.53 (d, 1 H, J = 2.9 Hz), 4.38 (b m, 1 H), 4.28 (b m, 1 H), 2.19 (s, 3 H), 2.18 (s, 3 H); ^{13}C NMR δ 210.4, 146.7, 140.5, 134.0, 120.9, 117.0, 116.9, 107.7, 90.8, 79.4, 77.3, 26.6, 20.8; HRMS calcd for $C_{13}H_{16}O_6$ 268.0947, found 268.0930.

Further elution gave 14β (43 mg, 46%) as a colorless syrup: $[\alpha]^{26}_D$ −141° (c 1.2, $CHCl_3$); IR (neat) 3350 and 1710 cm^{-1}; ^1H NMR ($CDCl_3$–D_2O, 400 MHz) δ 6.90 (d, 1 H, J = 8.5 Hz), 6.74 (d, 1 H, J = 1.8 Hz), 6.58 (dd, 1 H, J = 8.5 and 1.8 Hz), 5.38 (d, 1 H, J = 4.3 Hz), 4.44 (dd, 1 H, J = 7.3 and 7.3 Hz), 4.35 (d, 1 H, J = 7.3 Hz), 4.27 (dd, 1 H, J = 7.3 and 4.3 Hz), 2.22 (s, 3 H), 2.16 (s, 3 H); ^{13}C NMR δ 210.2, 147.1, 142.3, 134.7, 120.8, 118.0, 117.5, 103.6, 86.0, 76.6, 76.6, 26.5, 20.8; HRMS calcd for $C_{13}H_{16}O_6$ 268.0947, found 268.0931.

2-Acetoxy-4-methylphenyl 2′,3′-Di-*O*-acetyl-6′-deoxy-α-D-*arabino*-5′-hexulofuranoside (15α). A mixture of 14α (74 mg, 0.28 mmol) in pyridine (1 mL) and Ac_2O (1 mL) was stirred at room temperature for 30 min, and this was concentrated to give a residue, which was purified by a flash chromatography (silica gel 12 g) with EtOAc–toluene (1:10) to afford 15α (92 mg, 85%) as a colorless syrup: $[\alpha]^{22}_D$ +80° (c 0.7, $CHCl_3$); IR (neat) 1750 and 1725 cm^{-1}; ^1H NMR (90 MHz) δ 7.32–6.83 (m, 3 H), 5.70 (s, 1 H), 5.41–5.21 (m, 2 H), 4.68 (d, 1 H, J = 4.5 Hz), 2.33 (s, 3 H), 2.30 (s, 3 H), 2.15 (s, 3 H), 2.10 (s, 3 H); HRMS calcd for $C_{19}H_{22}O_9$ 394.1264, found 394.1254.

2-Acetoxy-4-methylphenyl 2′,3′-Di-*O*-acetyl-6′-deoxy-β-D-*arabino*-5′-hexulofuranoside (15β). Similar treatment of 14β (275 mg, 1.03 mmol) as described for a preparation of 15α gave 15β (386 mg, 96%) as a plate (recrystallized from EtOAc–hexane): mp 74–77 °C; $[\alpha]^{22}_D$ −133° (c 1.4, $CHCl_3$); IR (KBr) 1750 and 1720 cm^{-1}; ^1H NMR (90 MHz) δ 7.34–6.85 (m, 3 H), 6.04–5.78 (m, 2 H), 5.20 (dd, 1 H, J = 6.0 and 4.5 Hz), 4.33 (d, 1 H, J = 4.8 Hz), 2.31 (s, 6 H), 2.11 (s, 6 H); HRMS calcd for $C_{19}H_{22}O_9$ 394.1264, found 394.1267. Anal. Calcd for $C_{19}H_{22}O_9$: C, 57.87; H, 5.62. Found: C, 57.70; H, 5.56.

2-Acetoxy-4-formylphenyl 2′,3′-Di-*O*-acetyl-6′-deoxy-α-D-*arabino*-5′-hexulofuranoside (16α). To a solution of 15α (67 mg, 0.17 mmol) in CH_3CN (0.7 mL) at 0 °C was added an aqueous solution (0.7 mL) of ceric ammonium nitrate (CAN, 413 mg, 1.01 mmol) dropwise over 15 min. After being stirred at 5 °C for 3.5 h, the mixture was diluted with EtOAc and washed successively with 5% aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution, and water and dried. Removal of the solvent afforded a residue, which was purified by flash chromatography on silica gel (3 g) with EtOAc–hexane (1:2) to give 16α (19 mg, 28%) as a colorless syrup: $[\alpha]^{24}_D$ +52° (c 0.95, $CHCl_3$); IR (neat) 1740 and 1690 cm^{-1}; ^1H NMR (400 MHz) δ 9.90 (s, 1 H), 7.76 (dd, 1 H, J = 8.6 and 1.8 Hz), 7.62 (d, 1 H, J = 1.8 Hz), 7.40 (d, 1 H, J = 8.6 Hz), 5.87 (s, 1 H), 5.31 (m, 2 H), 4.66 (d, 1 H, J = 4.3 Hz), 2.34 (s, 3 H), 2.31 (s, 3 H), 2.18 (s, 3 H), 2.13 (s, 3 H); ^{13}C NMR δ 203.3, 189.9, 169.7, 169.3, 168.2, 152.4, 141.1, 131.8, 129.6, 123.8, 116.4, 104.3, 87.6, 80.1, 76.9, 26.6, 20.7, 20.6, 20.5; HRMS calcd for $C_{19}H_{21}O_{10}$ (M + H) 409.1133, found (M + H) 409.1135.

2-Acetoxy-4-formylphenyl 2′,3′-Di-*O*-acetyl-6′-deoxy-β-D-*arabino*-5′-hexulofuranoside (16β). A similar treatment of 15β (46 mg, 0.12 mmol) with CAN (256 mg, 0.486 mmol) afforded 16β (17 mg, 35%) as a colorless syrup. An analytical sample was prepared by recrystallization from ether–EtOAc–hexane: mp 114–116 °C; $[\alpha]^{22}_D$ −240° (c 0.54, $CHCl_3$); IR (neat) 1740 and 1690 cm^{-1}; ^1H NMR (400 MHz) δ 9.90 (s, 1 H), 7.77 (dd, 1 H, J = 8.6 and 1.8 Hz), 7.60 (d, 1 H, J = 1.8 Hz), 7.36 (d, 1 H, J = 8.6 Hz), 6.05 (d, 1 H, J = 4.3 Hz), 5.85 (dd, 1 H, J = 6.1 and 4.9 Hz), 5.22 (dd, 1 H, J = 6.1 and 4.3 Hz), 4.38 (d, 1 H, J = 4.9 Hz), 2.34 (s, 3 H), 2.13 (s, 3 H), 2.13 (s, 3 H), 2.07 (s, 3 H); ^{13}C NMR δ 204.6, 189.8, 170.1, 169.6, 168.2, 152.5, 140.8, 131.7, 129.6, 123.9, 115.0, 98.5, 84.9, 76.4, 74.2, 25.8, 20.8, 20.3, 20.3; HRMS calcd for $C_{19}H_{20}O_{10}$ 408.1057, found 408.1039. The spectral data (IR, ^1H and ^{13}C NMR) were in good accordance with those of the authentic sample prepared from natural hygromycin A (vide infra).

2-Acetoxy-4-methylphenyl 2′,3′-Di-*O*-acetyl-6′-deoxy-β-D-*arabino*-5′-hexulofuranoside Ethylene Acetal (17). To a stirred solution of 15β (475 mg, 1.20 mmol) and 1,2-bis[(trimethylsilyl)oxy]ethane (746 mg, 3.61 mmol) in CH_2Cl_2 (10 mL) under N_2 at −5 °C was added trimethylsilyl trifluoromethanesulfonate (24 μL, 0.12 mmol). After being stirred at −5 °C for 8 h, the reaction was quenched by adding pyridine (2 mL). The mixture was poured into saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, and dried. Evaporation of the solvent left a residue, which was chromatographed on a column of silica gel (15 g) with EtOAc–toluene (1:10) containing 1% Et_3N to give 17 as a colorless syrup (453 mg, 86%): $[\alpha]^{26}_D$ −116° (c 0.89, $CHCl_3$); IR (neat) 1740 cm^{-1}; ^1H NMR (90 MHz) δ 7.50–7.00 (m, 3 H), 6.13 (dd, 1 H, J = 8.7 and 8.7 Hz), 5.93 (d, 1 H, J = 5.3 Hz), 5.32 (dd, 1 H, J = 8.7 and 5.3 Hz), 4.20–3.90 (m, 5 H), 2.40 (s, 6 H), 2.16 (s, 6 H), 1.27 (s, 3 H). Anal. Calcd for $C_{21}H_{26}O_{10}$: C, 57.53; H, 5.98. Found: C, 57.23; H, 5.83.

2-Acetoxy-4-formylphenyl 2′,3′-Di-*O*-acetyl-6′-deoxy-β-D-*arabino*-5′-hexulofuranoside Ethylene Acetal (18). To a stirred solution of 17 (27 mg, 0.062 mmol) in CH_3CN (1 mL) at 0 °C was added an aqueous solution (2 mL) of CAN (204 mg, 0.372 mmol) dropwise over 10 min. After being stirred at 5 °C for 14 h, the reaction mixture was worked up similarly as described for a preparation of 16α to give 18 (19 mg, 66%) as a colorless syrup: $[\alpha]^{25}_D$ −167° (c 0.73, $CHCl_3$); IR (neat) 1740 and 1690 cm^{-1}; ^1H NMR (400 MHz) δ 9.87 (s, 1 H), 7.71 (dd, 1 H, J = 8.6 and 1.8 Hz), 7.60 (d, 1 H, J = 1.8 Hz), 7.27 (d, 1 H, J = 8.6 Hz), 5.96 (dd, 1 H, J = 8.2 and 8.2 Hz), 5.93 (d, 1 H, J = 4.9 Hz), 5.19 (dd, 1 H, J = 8.2 and 4.9 Hz), 4.12 (m, 1 H), 4.06 (d, 1 H, J = 8.2 Hz), 3.89–3.65 (m, 3 H), 2.38 (s, 3 H), 2.13 (s, 3 H), 2.11 (s, 3 H), 1.20 (s, 3 H); HRMS calcd for $C_{21}H_{24}O_{11}$ 452.1319, found 452.1322. Anal. Calcd for $C_{21}H_{24}O_{11}$: C, 55.75; H, 5.35. Found: C, 55.56; H, 5.44.

2-Acetoxy-4-[(*E*)-2-(ethoxycarbonyl)-1-propen-1-yl]phenyl 2′,3′-Di-*O*-acetyl-6′-deoxy-β-D-*arabino*-5′-hexulofuranoside

Ethylene Acetal (19). To a stirred solution of **18** (263 mg, 0.581 mmol) in CH_2Cl_2 (5 mL) was added a solution of $Ph_3P{=}C(Me)COOEt$ (274 mg, 0.756 mmol) in CH_2Cl_2 (5 mL) dropwise over 10 min at room temperature. After stirring at room temperature for 14 h, the mixture was concentrated and chromatographed on a column of silica gel (15 g) with EtOAc–toluene (1:4) containing 1% Et_3N to give **19** (293 mg, 94%) as a crystalline residue: mp 64–66 °C (from ether–hexane); $[\alpha]^{27}_D$ −137° (*c* 1.4, $CHCl_3$); IR (neat) 1750 and 1700 cm^{-1}; ^1H NMR (400 MHz) δ 7.57 (b s, 1 H), 7.22 (dd, 1 H, *J* = 8.3 and 2.0 Hz), 7.16 (d, 1 H, *J* = 8.3 Hz), 7.13 (d, 1 H, *J* = 2.0 Hz), 5.95 (dd, 1 H, *J* = 8.1 and 8.1 Hz), 5.84 (d, 1 H, *J* = 4.4 Hz), 5.17 (dd, 1 H, *J* = 8.1 and 4.4 Hz), 4.25 (q, 2 H, *J* = 7.3 Hz), 4.03 (d, 1 H, *J* = 8.1 Hz), 3.92–3.70 (m, 4 H), 2.36 (s, 3 H), 2.13 (s, 3 H), 2.11 (s, 3 H), 2.10 (d, 3 H, *J* = 1.5 Hz), 1.34 (t, 3 H, *J* = 7.3 Hz), 1.24 (s, 3 H); ^{13}C NMR δ 170.4, 169.6, 168.6, 168.6, 147.8, 140.1, 137.2, 130.5, 128.6, 128.0, 124.2, 115.2, 108.2, 96.9, 82.1, 76.1, 72.2, 65.8, 65.3, 60.9, 20.9, 20.6, 20.5, 20.5, 14.3, 14.0; HRMS calcd for $C_{26}H_{32}O_{12}$ 536.1894, found 536.1890. Anal. Calcd for $C_{26}H_{32}O_{12}$: C, 58.20; H, 6.01. Found: C, 57.79, 5.79.

2-Acetoxy-4-[(*E*)-2-carboxy-1-propen-1-yl]phenyl 2′,3′-Di-*O*-acetyl-6′-deoxy-β-D-*arabino*-5′-hexulofuranoside Ethylene Acetal (2). To a stirred solution of **19** (336 mg, 0.631 mmol) in MeOH (6 mL) at 50 °C under Ar was added aqueous 1 M NaOH solution (3.79 mL, 3.79 mmol). After being stirred at 50 °C overnight, the reaction mixture was neutralized with AcOH (0.217 mL) and concentrated to give a residue, which was then treated with pyridine (5 mL) and Ac_2O (5 mL) overnight. To this mixture was added MeOH (5 mL) at 0 °C to destroy excess reagent, and the resulting mixture was concentrated to give an oil, which was dissolved in EtOAc and washed with 0.5 M aqueous HCl solution and brine. The carboxylic acid was extracted three times from this EtOAc layer with aqueous $NaHCO_3$ solution. These aqueous extracts were combined and then acidified with 3 M HCl. The product was reextracted with EtOAc, and the organic layer was dried. Removal of the solvent gave **2** (243 mg, 76%) as a colorless syrup: $[\alpha]^{29}_D$ −115° (*c* 1.0, $CHCl_3$); IR (neat) 3450, 1750, and 1715 cm^{-1}; ^1H NMR (400 MHz) δ 7.69 (b s, 1 H), 7.25 (dd, 1 H, *J* = 9.2 and 1.8 Hz), 7.22 (d, 1 H, *J* = 9.2 Hz), 7.17 (d, 1 H, *J* = 1.8 Hz), 5.96 (dd, 1 H, *J* = 8.0 and 8.0 Hz), 5.86 (d, 1 H, *J* = 4.3 Hz), 5.18 (dd, 1 H, *J* = 8.0 and 4.3 Hz), 4.04 (d, *J* = 8.0 Hz), 3.90–3.70 (m, 4 H), 2.37 (s, 3 H), 2.13 (s, 6 H), 2.11 (s, 3 H), 1.24 (s, 3 H). This compound was used in the next step without further purification.

2L-(2,4/3)-2-*O*-Acetyl-3,4-di-*O*-benzyl-2,3,4-trihydroxy-5-cyclohexen-1-one (6). A mixture of methyl 4-*O*-acetyl-2,3-di-*O*-benzyl-α-D-*xylo*-5-enopyranoside (**20**)[19] (500 mg, 1.25 mmol) and mercuric trifluoroacetate (27 mg, 0.063 mmol) in acetone–water (2:1, 15 mL) was stirred at room temperature for 18 h. The mixture was partially concentrated to remove acetone and extracted with EtOAc. The extract was washed successively with 10% aqueous KI solution, 20% aqueous $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution and dried. Removal of the solvent gave crude **21** as an oil, which existed as a mixture of diastereoisomers (α-OH:β-OH ≒ 8:1). This crude **21** was dissolved in CH_2Cl_2 (15 mL). To this solution at 0 °C were added MsCl (0.39 mL, 5.0 mmol) and Et_3N (1.34 mL, 9.62 mmol), and the resulting mixture was stirred at room temperature for 1.5 h. The mixture was diluted with CH_2Cl_2, washed with 0.5 M aqueous sulfuric acid solution, and water and dried. Removal of the solvent gave an oil, which was purified on a column of silica gel (18 g) with EtOAc–toluene (1:10) to give **6** (397 mg, 87%) as a colorless syrup: $[\alpha]^{30}_D$ +86° (*c* 1.3, $CHCl_3$); IR (neat) 1740 and 1690 cm^{-1}; ^1H NMR (270 MHz) δ 7.45–7.20 (m, 10 H), 6.86 (dd, 1 H, *J* = 10.1 and 2.0 Hz), 6.06 (dd, 1 H, *J* = 10.1 and 2.3 Hz), 5.42 (d, 1 H, *J* = 11.0 Hz), 5.10–4.54 (m, 4 H), 4.45 (ddd, 1 H, *J* = 8.2, 2.3 and 2.0 Hz), 4.02 (dd, 1 H, *J* = 11.0 and 8.2 Hz), 2.10 (s, 3 H). Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.11; H, 6.05. Found: C, 71.82; H, 6.03.

1D-(1,3/2,4)-3-*O*-Acetyl-1,2-di-*O*-benzyl-5-cyclohexene-1,2,3,4-tetrol (22). To a stirred mixture of **6** (2.79 g, 7.61 mmol) in MeOH (60 mL) at 0 °C was added $CeCl_3{\cdot}7H_2O$ (4.26 g, 11.4 mmol). After the mixture was stirred at 0 °C for 5 min, $NaBH_4$ (317 mg, 8.38 mmol) was added the the mixture was stirred at 0 °C for 30 min. To the reaction mixture was added AcOH (0.48 mL, 8.5 mmol), and the mixture was concentrated to give a residue, which was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution and brine, and dried. Removal of the solvent left a syrup, which was purified on a column of silica gel (80 g) with EtOAc–toluene (1:4) to afford **22** (2.42 g, 86%) as a colorless syrup: $[\alpha]^{28}_D$ +79° (*c* 0.75, $CHCl_3$); IR (neat) 3450 and 1740 cm^{-1}; ^1H NMR (400 MHz) δ 7.35–7.26 (m, 10 H), 5.76 (ddd, 1 H, *J* = 10.3, 2.0 and 2.0 Hz), 5.70 (ddd, 1 H, *J* = 10.3, 2.0 and 2.0 Hz), 4.99 (dd, 1 H, *J* = 10.3 and 7.3 Hz), 4.84 (d, 1 H, *J* = 11.5 Hz), 4.74 (d, 1 H, *J* = 11.5 Hz), 4.67 (s, 2 H), 4.31 (ddd, 1 H, *J* = 7.3, 2.0 and 2.0 Hz), 4.23 (ddd, 1 H, *J* = 7.3, 2.0 and 2.0 Hz), 3.76 (dd, 1 H, *J* = 10.3 and 7.3 Hz), 2.05 (s, 3 H); HRMS calcd for $C_{22}H_{24}O_5$ 368.1623, found 368.1624. Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.36; H, 6.56.

1D-(1,3/2,4)-3-*O*-Acetyl-1,2-di-*O*-benzyl-4-*O*-tetrahydropyranyl-5-cyclohexene-1,2,3,4-tetrol (23). A mixture of **22** (13 mg, 0.035 mmol), dihydropyrane (16 μL, 0.17 mmol), and PPTS (2.6 mg, 0.0104 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 20 h. The mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution and brine, and dried. Evaporation of the solvent left a syrup, which was purified by preparative TLC (EtOAc–toluene (1:6)) to afford **23** (16 mg, 99%) as a colorless syrup, which is a mixture of diastereomers of THP groups: ^1H NMR (270 MHz) δ 7.34–7.26 (m, 10 H), 5.76–5.72 (m, 2 H), 5.25 and 5.21 (dd, total 1 H, ca. 1:1 ratio, *J* = 7.9 and 4.4 Hz), 4.87–4.67 (m, 4 H), 4.42–4.32 (m, 1 H), 4.31–4.26 (m, 1 H), 4.29 (m, 1 H), 3.88 (m, 1 H), 3.72 and 3.68 (dd, total 1 H, ca. 1:1 ratio, *J* = 7.9 and 7.9 Hz), 3.50 (m, 1 H), 1.90–1.50 (m, 6 H). Anal. Calcd for $C_{27}H_{32}O_6$: C, 71.65; H, 7.13. Found: C, 71.23; H, 6.97.

1D-(1,3/2,4)-1,2-Di-*O*-benzyl-4-*O*-tetrahydropyranyl-5-cyclohexene-1,2,3,4-tetrol (24). To a stirred solution of **23** (2.80 g, 6.19 mmol) in MeOH (30 mL) at room temperature was added 1 M NaOMe in MeOH (12.4 mL, 12.4 mmol). After being stirred at room temperature for 5 h, the reaction mixture was neutralized with Amberlite IR-120 B resin (H^+ form). The resin was removed by filtration and the filtrate was concentrated to give a syrup, which was chromatographed on a column of silica gel (120 g) with EtOAc–toluene (1:15) to give, first, one of diastereomers of **24**, **24a** (920 mg, 36%), as a crystaline residue; R_f 0.43 (EtOAc–toluene (1:6)); mp 81 °C (from EtOH); $[\alpha]^{26}_D$ +159° (*c* 0.76, $CHCl_3$); IR (KBr) 3400 cm^{-1}; ^1H NMR (270 MHz) δ 7.33 (m, 10 H), 5.73 (ddd, 1 H, *J* = 10.3, 1.8 and 1.8 Hz), 5.60 (ddd, 1 H, *J* = 10.3, 1.8 and 1.8 Hz), 5.01–4.68 (m, 4 H), 4.64 (dd, 1 H, *J* = 2.6 and 5.9 Hz), 4.21–4.03 (m, 3 H), 3.80–3.54 (m, 3 H), 1.90–1.50 (m, 6 H). Anal. Calcd for $C_{25}H_{30}O_5$: C, 73.14; H, 7.34. Found: C, 73.10; H, 7.18. Further elution gave another diastereomer, **24b** (1.03 g, 41%), as a colorless syrup: R_f 0.34 (EtOAc–toluene (1:6)); $[\alpha]^{27}_D$ +35° (*c* 1.51, $CHCl_3$); IR (neat) 3450 cm^{-1}; ^1H NMR (270 MHz) δ 7.36–7.26 (m, 10 H), 5.74 (s, 2 H), 5.01–4.62 (m, 4 H), 4.93 (dd, 1 H, *J* = 5.1 and 2.6 Hz), 4.30 (dd, 1 H, *J* = 7.6 and 2.9 Hz), 4.19 (dd, 1 H, *J* = 7.6 and 2.9 Hz), 3.94–3.87 (m, 1 H), 3.74 (dd, 1 H, *J* = 10.3 and 7.6 Hz), 3.58 (dd, 1 H, *J* = 10.3 and 7.6 Hz), 3.56–3.48 (m, 1 H), 1.90–1.50 (m, 6 H). Anal. Found: C, 72.85; H, 7.34.

1D-(1,3/2,4)-1,2-Di-*O*-benzyl-3-*O*-(methanesulfonyl)-4-*O*-tetrahydropyranyl-5-cyclohexene-1,2,3,4-tetrol (25). To a stirred solution of **24a** (903 mg, 2.20 mmol) in pyridine (20 mL) was added methanesulfonyl chloride (MsCl, 1.02 mL, 13.2 mmol), and the mixture was heated at 50 °C for 1.5 h. After the solution was cooled, water was added at 0 °C to this mixture and the product was extracted twice with EtOAc. The extracts were combined, washed with saturated $NaHCO_3$ solution and brine, and dried. Evaporation of the solvent left a syrup, which was chromatographed on a column of silica gel (30 g) with EtOAc–toluene (1:15) to give **25a** (1.06 g, 99%) as a colorless syrup: $[\alpha]^{26}_D$ +154° (*c* 1.14, $CHCl_3$); IR (neat) 1350 cm^{-1}; ^1H NMR (90 MHz) δ 7.35 (m, 10 H), 5.76 (s, 2 H), 4.88–3.30 (m, 11 H), 3.01 (s, 3 H), 2.00–1.30 (m, 6 H). Similar treatment of the diastereomer **24b** (114 mg, 0.278 mmol) afforded **25b** (128 mg, 94%): $[\alpha]^{26}_D$ +57° (*c* 1.71, $CHCl_3$); IR (neat) 1350 cm^{-1}; ^1H NMR (90 MHz) δ 7.31 (s, 10 H), 5.78 (m, 2 H), 4.90–3.40 (m, 11 H), 2.84 (s, 3 H), 1.84–1.40 (m, 6 H).

1D-(1,2,3/4)-2-Azido-3,4-di-*O*-benzyl-1-*O*-tetrahydropyranyl-5-cyclohexene-1,3,4-triol (26). A mixture of **25a** (1.04 g, 2.13 mmol) and sodium azide (2.07 g, 31.8 mmol) in HMPA (20 mL) was heated at 100 °C for 39 h. After being cooled, the reaction mixture was poured into ice–water and extracted twice with EtOAc. The combined extracts were washed with brine and dried. Removal of the solvent left a syrup, which was purified

on a column of silica gel (40 g) with EtOAc–toluene (1:15) to give **26a** (676 mg, 73%) as a colorless syrup; $[\alpha]^{26}_D$ +165° (*c* 1.23, $CHCl_3$); IR (neat) 2100 cm^{-1}; ^1H NMR (270 MHz) δ 7.38–7.26 (m, 10 H), 5.76 (ddd, 1 H, *J* = 10.6, 2.2 and 2.2 Hz), 5.61 (dddd, 1 H, *J* = 10.6, 1.8, 1.8 and 1.8 Hz), 4.79–4.65 (m, 5 H), 4.43 (ddd, 1 H, *J* = 3.7, 2.2 and 1.8 Hz), 4.32 (ddd, 1 H, *J* = 8.1, 2.2 and 1.8 Hz), 4.27 (ddd, 1 H, *J* = 3.7, 2.2 and 1.8 Hz), 3.90 (m, 1 H), 3.67 (dd, *J* = 8.1 and 2.2 Hz), 3.55 (m, 1 H), 2.00–1.42 (m, 6 H); HRMS calcd for $C_{25}H_{29}N_3O_4$ 435.2158, found 435.2173. Anal. Calcd for $C_{25}H_{29}N_3O_4$: C, 68.94; H, 6.71; N, 9.65. Found: C, 68.82; H, 6.70; N, 9.43. From **25b** (1.03 g, 2.10 mmol), 774 mg (84%) of **26b** was obtained as a colorless syrup: $[\alpha]^{24}_D$ +60° (*c* 1.45, $CHCl_3$); IR (neat) 2100 cm^{-1}; ^1H NMR (90 MHz) δ 7.34–7.25 (m, 10 H), 5.24 (m, 2 H), 4.87–4.13 (m, 8 H), 3.83 (m, 1 H), 3.66 (dd, 1 H, *J* = 8.0 and 2.5 Hz), 3.50 (m, 1 H), 1.82–1.40 (m, 6 H); HRMS calcd for $C_{25}H_{29}N_3O_4$ 435.2158, found 435.2157. Anal. Calcd for $C_{25}N_{29}N_3O_4$: C, 68.94; H, 6.71; N, 9.65. Found: C, 68.69; H, 6.59; N, 9.50.

1D-(1,2,3/4)-3,4-Di-*O*-benzyl-2-[(*tert*-butoxycarbonyl)-amino]-1-*O*-tetrahydropyranyl-5-cyclohexene-1,3,4-triol (27). To a stirred mixture of $LiAlH_4$ (174 mg, 4.58 mmol) in ether (10 mL) at 0 °C under Ar was added an etheral solution (10 mL) of **26a** (665 mg, 1.53 mmol) dropwise. After being stirred at 0 °C for 1 h, the reaction was quenched by adding water and the product was extracted with EtOAc. The extract was dried and concentrated to give a residue (570 mg), which was dissolved in CH_2Cl_2 (10 mL). To this solution, Et_3N (0.388 mL, 2.79 mmol) and a solution of Boc_2O (608 mg, 2.79 mmol) in CH_2Cl_2 (5 mL) were added and the mixture was stirred at room temperature for 4.5 h. Evaporation of the solvent left a syrup, which was chromatographed on a column of silica gel (25 g) with EtOAc–hexane (1:6) to give **27a** (652 mg, 84%) as a colorless syrup: $[\alpha]^{24}_D$ +151° (*c* 0.94, $CHCl_3$); IR (neat) 3450 and 1710 cm^{-1}; ^1H NMR (90 MHz) δ 7.41–7.22 (m, 10 H), 5.80 (s, 2 H), 4.91–4.27 (m, 8 H), 4.10 (m, 1 H), 3.95 (m, 1 H), 3.77 (dd, 1 H, *J* = 6.8 and 2.8 Hz), 3.60 (m, 1 H), 1.90–1.32 (m, 6 H), 1.47 (s, 9 H). Anal. Calcd for $C_{30}H_{39}NO_6$: C, 70.70; H, 7.71; N, 2.75. Found: C, 70.42; H, 7.61; N, 2.63. By a similar treatment, **26b** (794 mg, 1.82 mmol) was converted into **27b** (753 mg, 81%): $[\alpha]^{24}_D$ +57° (*c* 0.69, $CHCl_3$); IR (neat) 3450 and 1710 cm^{-1}; ^1H NMR (90 MHz) δ 7.60–7.20 (m, 10 H), 5.77 (s, 2 H), 4.90–4.39 (m, 8 H), 4.13 (m, 1 H), 4.03–3.41 (m, 3 H), 1.93–1.37 (m, 6 H), 1.45 (s, 9 H). Anal. Found: C, 70.35; H, 7.57; N, 2.63.

OsO_4 Oxidation of 26. A mixture of **26a** (7.9 mg, 0.018 mmol), 4-methylmorpholine *N*-oxide monohydrate (2.9 mg, 0.022 mmol), and 0.05 M solution of OsO_4 in *t*-BuOH (109 μL, 0.0054 mmol) in THF–water (10:1, 1 mL) was stirred at room temperature for 4 days. After addition of solid $NaHSO_3$ (10 mg), the mixture was diluted with EtOAc, washed with brine, and dried. Evaporation of the solvent left a syrup, which was acetylated with pyridine (0.5 mL) and Ac_2O (0.5 mL) at room temperature overnight. Evaporation of the solvent gave a residue, which was purified by preparative TLC (EtOAc–toluene (1:2)) to give **29a** (4.7 mg, 51%) and **28a** (2.3 mg, 25%): ^1H NMR (270 MHz, for **29a**) δ 7.36–7.26 (m, 10 H), 5.61 (ddd, 1 H, *J* = 3.4, 3.4 and 1.2 Hz), 4.88 (d, 1 H, *J* = 11.5 Hz), 4.86 (dd, 1 H, *J* = 9.8 and 1.2 Hz), 4.83 (m, 1 H), 4.72 (s, 2 H), 4.67 (d, 1 H, *J* = 11.5 Hz), 4.22 (dd, 1 H, *J* = 3.4 and 3.4 Hz), 4.06 (dd, 1 H, *J* = 9.8 and 9.8 Hz), 3.91 (dd, 1 H, *J* = 3.4 and 3.4 Hz), 3.77 (m, 1 H), 3.52 (m, 1 H), 3.43 (dd, 1 H, *J* = 9.7 and 3.4 Hz), 2.19 (s, 3 H), 2.18 (s, 3 H), 1.80–1.47 (m, 6 H); (for **28a**) 7.36–7.26 (m, 10 H), 5.71 (dd, 1 H, *J* = 3.4 and 3.4 Hz), 5.20 (dd, 1 H, *J* = 9.8 and 3.4 Hz), 4.85 (m, 1 H), 4.83 (d, 1 H, *J* = 11.2 Hz), 4.68 (d, 1 H, *J* = 11.2 Hz), 4.66 (d, 1 H, *J* = 11.2 Hz), 4.54 (d, 1 H, *J* = 11.2 Hz), 4.16 (dd, 1 H, *J* = 3.4 and 3.4 Hz), 4.13 (dd, 1 H, *J* = 9.8 and 3.4 Hz), 3.90 (dd, 1 H, *J* = 9.8 and 3.4 Hz), 3.79 (dd, 1 H, *J* = 9.8 and 3.4 Hz), 3.56–3.53 (m, 2 H), 2.10 (s, 3 H), 2.04 (s, 3 H), 1.78–1.45 (m, 6 H).

OsO_4 Oxidation of 27. A mixture of **27a** (130 mg, 0.255 mmol), hydroquinine 4-chlorobenzoate (18 mg, 0.038 mmol), 4-methylmorpholine *N*-oxide monohydrate (51.7 mg, 0.383 mmol), and 0.05 M solution of OsO_4 in *t*-BuOH (0.102 mL, 0.0051 mmol) in DMF–water (4:1, 3 mL) was stirred at room temperature for 7 days. After addition of solid $NaHSO_3$ (15 mg), the mixture was diluted with EtOAc, washed with brine, and dried. Removal of the solvent left a syrup, which was chromatographed on a column of silica gel (8 g) with EtOAc–toluene (1:4) to give, first, **31a** (44.5 mg, 32%) as a colorless syrup: R_f 0.31 (EtOAc–toluene 1:1); $[\alpha]^{26}_D$ +13° (*c* 0.71, $CHCl_3$); IR (neat) 3400 and 1710 cm^{-1}; ^1H NMR (90 MHz) δ 7.28 (m, 10 H), 6.09 (d, 1 H, *J* = 9.1 Hz), 4.95–3.30 (m, 13 H), 3.10 (b s, 2 H), 1.84–1.08 (m, 6 H), 1.48 (s, 9 H). Anal. Calcd for $C_{30}H_{41}NO_8$: C, 66.28; H, 7.60; N, 2.58. Found: C, 66.14; H, 7.32; N, 2.41. Further elution afforded **30a** (71 mg, 51%) as a colorless syrup; R_f 0.24 (EtOAc–toluene (1:1)); $[\alpha]^{26}_D$ +10° (*c* 0.92, $CHCl_3$); IR (neat) 3400 and 1700 cm^{-1}; ^1H NMR (90 MHz) δ 7.30 (m, 10 H), 5.45 (d, 1 H, *J* = 8.9 Hz), 4.74 (d, 1 H, *J* = 12.3 Hz), 4.63 (d, 1 H, *J* = 11.3 Hz), 4.60 (m, 1 H), 4.48 (d, 1 H, *J* = 11.3 Hz), 4.46 (d, 1 H, *J* = 12.3 Hz), 4.36–3.32 (m, 7 H), 3.99 (dd, 1 H, *J* = 4.0 and 4.0 Hz), 1.75–1.17 (m, 6 H), 1.43 (s, 9 H). Anal. Calcd for $C_{30}H_{41}NO_8 \cdot {}^1/_2H_2O$: C, 65.20; H, 7.66; N, 2.53. Found: C, 65.58; H, 7.43; N, 2.56.

By a similar treatment, **27b** (692 mg, 1.36 mmol) was converted into **31b** (240 mg, 33%) and **30b** (359 mg, 49%). **31b**: $[\alpha]^{24}_D$ −24° (*c* 1.08, $CHCl_3$); IR (neat) 3430 and 1710 cm^{-1}; ^1H NMR (90 MHz) δ 7.40–7.10 (m, 10 H), 5.61 (d, 1 H, *J* = 10.0 Hz), 4.89 (d, 1 H, *J* = 11.0 Hz), 4.73 (d, 1 H, *J* = 8.5 Hz), 4.60 (d, 1 H, *J* = 8.5 Hz), 4.51 (d, 1 H, *J* = 11.0 Hz). 4.70–4.50 (m, 2 H), 4.18–3.40 (m, 7 H), 1.90–1.20 (m, 6 H), 1.40 (s, 9 H). **30b**: $[\alpha]^{26}_D$ −28° (*c* 1.21, $CHCl_3$); IR (neat) 3450 and 1700 cm^{-1}; ^1H NMR (90 MHz) δ 7.42–7.12 (m, 10 H), 4.94–4.40 (m, 6 H), 4.20 (dd, 1 H, *J* = 2.9 and 2.9 Hz), 4.08–3.32 (m, 6 H), 1.90–1.20 (m, 6 H), 1.42 (s, 9 H). Anal. Calcd for $C_{30}H_{41}NO_8 \cdot {}^1/_2H_2O$: C, 65.20; H, 7.66; N, 2.53. Found for **31b**: C, 65.11; H, 7.51; N, 2.47. Found for **30b**: C, 65.93; H, 7.58; N, 2.48.

Acetylation of **30b** and **31b** (pyridine, Ac_2O, room temperature, overnight) afforded **32b** and **33b**, respectively. ^1H NMR (270 MHz, for **32b**) δ 7.30 (m, 10 H), 5.70 (dd, 1 H, *J* = 2.9 and 2.9 Hz), 5.11–4.97 (m, 2 H), 4.70 (d, 1 H, *J* = 4.9 Hz), 4.66 (d, 1 H, *J* = 4.9 Hz), 4.69 (m, 1 H), 4.58 (d, 1 H, *J* = 7.9 Hz), 4.55 (m, 1 H), 4.54 (d, 1 H, *J* = 7.9 Hz), 4.15 (dd, 1 H, *J* = 10.3 and 4.4 Hz), 3.93 (m, 1 H), 3.86 (dd, 1 H, *J* = 10.3 and 4.4 Hz), 3.60 (dd, 1 H, *J* = 10.3 and 2.9 Hz), 3.54 (m, 1 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.80–1.50 (m, 6 H), 1.44 (s, 9 H); (for **33b**) δ 7.28 (m, 10 H), 5.60 (dd, 1 H, *J* = 2.9 and 2.9 Hz), 5.30 (b d, 1 H, *J* = 11.0 Hz), 4.92 (d, 1 H, *J* = 10.6 Hz), 4.89 (dd, 1 H, *J* = 9.9 and 2.9 Hz), 4.84 (m, 1 H), 4.81 (d, 1 H, *J* = 10.6 Hz), 4.75 (ddd, 1 H, 11.0, 4.4, and 4.4 Hz), 4.63 (d, 1 H, *J* = 11.0 Hz), 4.51 (d, 1 H, *J* = 11.0 Hz), 3.86 (dd, 1 H, *J* = 4.4 and 2.9 Hz), 3.80 (dd, 1 H, *J* = 9.9 and 9.9 Hz), 3.80 (m, 1 H), 3.55 (dd, 1 H, *J* = 9.9 and 4.4 Hz), 3.51 (m, 1 H), 2.16 (s, 3 H), 2.16 (s, 3 H), 1.80–1.42 (m, 6 H), 1.56 (s, 9 H).

1L-1,6-Di-*O*-benzyl-2-[(*tert*-butoxycarbonyl)amino]-2-deoxy-4,5-*O*-methylene-3-*O*-tetrahydropyranyl-*neo*-inositol (34). To a stirred mixture of 60% NaH (20 mg, 0.50 mmol) in DMF (1 mL) was added a solution of **30a** (68 mg, 0.13 mmol) in DMF (2 mL) at 0 °C. After the solution was stirred at 0 °C for 45 min, CH_2Br_2 (31 μL, 0.44 mmol) was added and the mixture was stirred at room temperature for 3 h. MeOH was added to this mixture, which was concentrated to give a residue. This was diluted with EtOAc, washed with water, and dried. Removal of the solvent gave a syrup, which was purified by preparative TLC (EtOAc–toluene (1:3)) to afford **34a** (42 mg, 60%) as a colorless syrup: $[\alpha]^{26}_D$ +1° (*c* 1.68, $CHCl_3$); IR (neat) 3370 and 1710 cm^{-1}; ^1H NMR (270 MHz) δ 7.30 (m, 10 H), 5.21 (s, 1 H), 5.04 (b d, 1 H, *J* = 9.2 Hz), 4.78 (s, 1 H), 4.76 (d, 1 H, *J* = 11.4 Hz), 4.75 (d, 1 H, *J* = 7.7 Hz), 4.73 (d, 1 H, *J* = 7.7 Hz), 4.68 (m, 1 H), 4.64 (d, 1 H, *J* = 11.4 Hz), 4.38 (m, 1 H), 4.33 (dd, 1 H, *J* = 7.0 and 3.3 Hz), 4.26 (dd, 1 H, *J* = 7.0 and 2.6 Hz), 4.09 (dd, 1 H, *J* = 7.3 and 2.6 Hz), 4.02 (dd, *J* = 7.3 and 7.3 Hz), 3.78 (dd, 1 H, *J* = 3.3 and 3.3 Hz), 3.76 (m, 1 H), 3.47 (m, 1 H), 2.32 (m, 1 H), 2.02 (m, 1 H), 1.80–1.50 (m, 4 H), 1.43 (s, 9 H). Anal. Calcd for $C_{31}H_{41}NO_8$: C, 67.01; H, 7.44; N, 2.52. Found: C, 67.12; H, 7.26; N, 2.54. By a similar treatment, **30b** (167 mg, 0.31 mmol) was converted into **34b** (93 mg, 51%): $[\alpha]^{18}_D$ −28° (*c* 0.91, $CHCl_3$); IR (neat) 3370 and 1710 cm^{-1}; ^1H NMR (270 MHz) δ 7.32 (m, 10 H), 5.21 (s, 1 H), 5.04 (b d, 1 H, *J* = 9.5 Hz), 4.81–4.62 (m, 5 H), 4.37 (m, 1 H), 4.33 (dd, 1 H, *J* = 7.0 and 3.4 Hz), 4.26 (dd, 1 H, *J* = 7.0 and 2.6 Hz), 4.08 (dd, 1 H, *J* = 7.5 and 2.6 Hz), 4.02 (dd, 1 H, *J* = 7.5 and 7.5 Hz), 3.77 (dd, 1 H, *J* = 3.4 and 3.4 Hz), 3.77 (m, 1 H), 3.45 (m, 1 H), 1.80–1.40 (m, 6 H), 1.43 (s, 9 H).

1L-2-[(*tert*-Butoxycarbonyl)amino]-2-deoxy-4,5-*O*-methylene-3-*O*-tetrahydropyranyl-*neo*-inositol (35). A mixture of **34a** (131 mg, 0.236 mmol) and 20% $Pd(OH)_2$ (13 mg) in EtOH (2 mL) was hydrogenolyzed under an atmospheric

pressure of H_2 at room temperature for 21 h. The catalyst was removed by filtration, and the filtrate was concentrated to give analytically pure **35a** (85 mg, 96%) as a colorless syrup: $[\alpha]^{23}_D$ 0° (*c* 1.52, $CHCl_3$); IR (neat) 3400 and 1690 cm^{-1}; ^1H NMR (90 MHz) δ 5.52 (b d, 1 H, *J* = 6.0 Hz), 5.24 (s, 1 H), 4.83 (s, 1 H), 4.65 (m, 1 H), 4.32–3.36 (m, 10 H), 1.79–1.09 (m, 6 H), 1.47 (s, 9 H). Anal. Calcd for $C_{17}H_{29}NO_8$: C, 54.39; H, 7.79; N, 3.73. Found: C, 54.22; H, 7.37; N, 3.54. By a similar treatment, **34b** (46 mg, 0.82 mmol) was converted into **35b** (31 mg, 100%); $[\alpha]^{23}_D$ −43° (*c* 1.2, $CHCl_3$); IR (neat) 3370 and 1690 cm^{-1}; ^1H NMR (90 MHz) δ 5.22 (s, 1 H), 5.09 (b d, 1 H, *J* = 9.2 Hz), 4.88 (s, 1 H), 4.69 (m, 1 H), 4.43–3.43 (m, 10 H), 1.90–0.70 (m, 6 H), 1.45 (s, 9 H). Anal. Found: C, 54.66; H, 7.41; N, 3.28.

1L-2-Amino-2-deoxy-4,5-*O*-methylene-*neo*-inositol (3). A solution of **35a** (27 mg, 0.073 mmol) in TFA–$CHCl_3$ (1:1, 1.5 mL) was stirred at room temperature for 1 h. This mixture was concentrated and codistilled with $CHCl_3$ several times to give a residue, which was purified first by a column of resin (Amberlite IR-120 B, H^+ form, 2 mL) with water and 1 M aqueous NH_4OH to give a residue. This was further purified on a column of Sephadex LH-20 (1 g) with MeOH–EtOAc (1:3) to afford **3** (9.7 mg, 70%) as an amorphous solid: mp 151–156 °C dec (lit.[5] mp 155–159 °C dec); $[\alpha]^{21}_D$ −36° (*c* 0.49, H_2O) (lit.[5] $[\alpha]^{22}_{574}$ −33° (*c* 1.97, H_2O)); IR (KBr) 3450 cm^{-1}; ^1H NMR (D_2O, acetone as an internal standard at δ 2.08, 270 MHz) δ 5.07 (s, 1 H), 4.83 (s, 1 H), 4.17 (dd, 1 H, *J* = 7.7 and 4.6 Hz), 4.06 (dd, 1 H, *J* = 4.6 and 4.6 Hz), 4.00 (dd, 1 H, *J* = 9.3 and 4.6 Hz), 3.73 (dd, 1 H, *J* = 9.3 and 3.3 Hz), 3.60 (dd, 1 H, *J* = 7.7 and 3.3 Hz), 3.25 (t, 1 H, *J* = 3.3 and 3.3 Hz). By a similar treatment, **35b** (64 mg, 0.17 mmol) was also converted into **3** (27 mg, 83%). Anal. Calcd for $C_7H_{13}NO_5$: C, 43.98; H, 6.85; N, 7.33. Found: C, 44.03; H, 6.72; N, 6.94.

1D-1,3,4-Tri-*O*-acetyl-2-deoxy-2-acetamido-5,6-*O*-methylene-*neo*-inositol (36). A mixture of **3** (93 mg, 0.48 mmol) and 4-(dimethylamino)pyridine (4-DMAP, 5 mg) in pyridine (1 mL) and Ac_2O (1 mL) were stirred at room temperature overnight. The mixture was concentrated to give a residue, which was purified on a column of silica gel (8 g) with acetone–toluene (1:2) to afford **36** (109 mg, 63%) as a colorless syrup: $[\alpha]^{23}_D$ −49° (*c* 1.7, $CHCl_3$); IR (neat) 3300, 1660, 1540 cm^{-1}; ^1H NMR (270 MHz) δ 6.25 (b d, 1 H, *J* = 8.4 Hz), 5.52 (dd, 1 H, *J* = 7.7 and 6.6 Hz), 5.43 (ddd, 1 H, *J* = 7.7, 1.5 and 1.5 Hz), 5.32 (s, 1 H), 4.91 (m, 1 H), 4.87 (m, 1 H), 4.82 (s, 1 H), 4.29 (m, 2 H), 2.15 (s, 3 H), 2.12 (s, 3 H), 2.05 (s, 3 H), 1.98 (s, 3 H); ^{13}C NMR δ 170.5, 170.5, 169.8, 169.5, 95.7, 74.1, 74.0, 71.4, 70.5, 69.0, 45.7, 23.0, 21.0, 20.9, 20.6. The ^1H and ^{13}C NMR and IR spectra of synthetic **36** were identical with those of the authentic sample prepared from natural hygromycin A (vide infra). Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.14; H, 5.89; N, 3.90. Found: C, 49.85; H, 5.95; N, 3.82.

Condensation of 2 and 3. To a stirred mixture of **2** (48 mg, 0.094 mmol) and **3** (20 mg, 0.10 mmol) in DMF (1 mL) at 0 °C were added diethyl cyanophosphonate (17.1 μL, 0.113 mmol) and Et_3N (27.5 μL, 0.197 mmol), and the mixture was stirred at 0 °C for 2.5 h. The mixture was diluted with EtOAc, washed with brine, and dried. Evaporation of the solvent left a residue (69 mg), which was treated with pyridine (2 mL) and Ac_2O (1 mL) at room temperature for 2 h. This mixture was evaporated to give a residue, which was purified by preparative TLC (acetone–$CHCl_3$ (1:5)) to afford **37** (57 mg, 75%) as a colorless syrup: $[\alpha]^{26}_D$ −91° (*c* 0.96, $CHCl_3$); IR (neat) 1750, 1660, 1510 cm^{-1}; ^1H NMR (270 MHz) δ 7.17 (m, 3 H), 7.05 (b s, 1 H), 6.67 (b d, 1 H, *J* = 8.0 Hz), 5.96 (dd, 1 H, *J* = 8.1 and 8.1 Hz), 5.86 (d, 1 H, *J* = 4.8 Hz), 5.64 (dd, 1 H, *J* = 6.6 and 6.6 Hz), 5.49 (dd, 1 H, *J* = 6.6 and 2.9 Hz), 5.37 (s, 1 H), 5.18 (dd, 1 H, *J* = 8.1 and 4.8 Hz), 5.00–4.93 (m, 2 H), 4.80 (s, 1 H), 4.33 (dd, 1 H, *J* = 6.6 and 2.9 Hz), 4.03 (1 H, d, *J* = 8.1 Hz), 3.93–3.71 (m, 4 H), 2.36 (s, 3 H), 2.18 (s, 3 H), 2.14 (s, 3 H), 2.12 (s, 3 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 2.03 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR δ 171.0, 170.5, 170.4, 169.6, 169.3, 168.6, 168.6, 147.5, 140.1, 133.1, 130.9, 130.4, 128.1, 124.0, 115.2, 108.1, 96.9, 95.8, 82.0, 76.1, 74.2, 73.9, 72.3, 71.2, 69.5, 65.8, 65.3, 45.9, 21.0, 20.9, 20.9, 20.6, 20.5, 20.5, 20.4, 14.1. Anal. Calcd for $C_{37}H_{45}NO_{19}$: C, 55.01; H, 5.61; N, 1.73. Found: C, 54.61; H, 5.61; N, 1.58.

Hygromycin A Ethylene Acetal (38). To a stirred solution of **37** (51 mg, 0.063 mmol) in MeOH (1 mL) at 0 °C was added 1 M NaOMe solution in MeOH (63 μL, 0.063 mmol). After being stirred at the same temperature for 30 min, the reaction was neutralized with acidic resin (Amberlite IR120-B, H^+ type). The resin was removed by filtration, and the filtrate was concentrated to give **38** (33 mg, 94%) as an amorphous solid: mp 109–114 °C dec; $[\alpha]^{22}_D$ −103° (*c* 0.84, MeOH); IR (KBr) 3420, 1610, 1510 cm^{-1}; ^1H NMR (MeOH-d_4, 270 MHz) δ 7.25 (b s, 1 H), 7.10 (d, 1 H, *J* = 8.4 Hz), 6.92 (d, 1 H, *J* = 2.2 Hz), 6.85 (dd, 1 H, *J* = 8.4 and 2.2 Hz), 5.56 (d, 1 H, *J* = 4.8 Hz), 5.23 (s, 1 H), 4.79 (s, 1 H), 4.50 (dd, 1 H, *J* = 6.6 and 2.6 Hz), 4.32 (dd, 1 H, *J* = 8.3 and 8.3 Hz), 4.23–4.14 (m, 3 H), 3.97 (dd, 1 H, *J* = 6.6 and 6.6 Hz), 3.88–3.59 (m, 7 H), 2.12 (b d, 3 H, *J* = 0.7 Hz), 1.27 (s, 3 H). Anal. Calcd for $C_{25}H_{33}NO_{13}\cdot{}^1/_2H_2O$: C, 53.19; H, 6.07; N, 2.48. Found: C, 52.97; H, 6.20; N, 2.17.

Hygromycin A (1). A mixture of **38** (57 mg, 0.10 mmol) in TFA–water (6:4, 1 mL) was stirred at room temperature for 1 h. The mixture was concentrated and codistilled several times with $CHCl_3$ and EtOH to give a residue, which was chromatographed first on a column of Sephadex LH-20 (7 g) with MeOH–EtOAc (1:3) and further purified by Sephadex G-10 (7 g) with water to afford **1** (24 mg, 45%) as an amorphous solid: mp 110–112 °C; $[\alpha]^{22}_D$ −148° (*c* 0.46, H_2O) (natural product mp 113–115 °C; $[\alpha]^{22}_D$ −136° (*c* 0.96, H_2O)); IR (KBr) 3420, 1710, 1610, 1510 cm^{-1}; ^1H NMR (MeOH-d_4, 270 MHz) δ 7.26 (b s, 1 H), 7.22 (d, 1 H, *J* = 8.4 Hz), 6.93 (d, 1 H, *J* = 1.8 Hz), 6.88 (dd, 1 H, *J* = 8.4 and 1.8 Hz), 5.62 (d, 1 H, *J* = 4.4 Hz), 5.23 (s, 1 H), 4.79 (s, 1 H), 4.50 (dd, 1 H, *J* = 6.5 and 2.6 Hz), 4.35 (dd, 1 H, *J* = 6.4 and 6.4 Hz), 4.27 (d, 1 H, *J* = 6.4 Hz), 4.24–4.16 (m, 4 H), 3.97 (dd, 1 H, *J* = 6.5 and 6.5 Hz), 3.81 (dd, 1 H, *J* = 2.9 and 2.9 Hz), 2.13 (s, 6 H); ^{13}C NMR (MeOH-d_4) δ 210.0, 172.6, 148.4, 146.0, 134.9, 132.9, 132.2, 122.6, 118.3, 117.8, 103.7, 96.2, 88.5, 78.6, 78.2, 78.2, 77.6, 72.6, 71.6, 71.3, 50.2, 26.2, 14.6. The ^1H and ^{13}C NMR spectra were fully identical with those of the natural product.

Preparation of 16β and 36 from Hygromycin A. A mixture of natural hygromycin A (containing some inorganic salts, 500 mg), pyridine (10 mL), and Ac_2O (10 mL) was stirred at room temperature for 2 h. The mixture was concentrated to give crude hexa-*O*-acetylhygromycin A, which was dissolved in CH_2Cl_2 (10 mL). To this solution was bubbled O_3 at −78 °C for 20 min, and then Me_2S (2 mL) was added. The resultant mixture was stirred at room temperature for 15 h and concentrated to give a residue, which was purified by flash chromatography of silica gel (35 g) with acetone–toluene (1:10) to afford **16β** (285 mg) and *N*-pyruvyl derivative of **36** (239 mg): **16β**; mp 110–114 °C (from ether–EtOAc–hexane); $[\alpha]^{22}_D$ −220° (*c* 0.55, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}O_{10}$: C, 55.88; H, 4.94. Found: C, 55.67; H, 4.92.

A mixture of *N*-pyruvyl derivative of **36** (239 mg, 0.617 mmol), 1 M aqueous NaOH solution (2.5 mL), and MeOH (5 mL) was heated under reflux for 2 h. After being cooled, this mixture was chromatographed on a column of acidic resin (IR-120B, H^+ form, 10 mL) with water and 1 M aqueous NH_4OH to give a residue, which was acetylated with pyridine (1 mL), Ac_2O (1 mL), and 4-DMAP (5 mg) at room temperature overnight. The mixture was concentrated to give a residue, which was purified on a column of silica gel (2 g) with acetone–toluene (1:2) to afford **36** (69 mg) as a colorless syrup: $[\alpha]^{27}_D$ −49° (*c* 1.68, $CHCl_3$). Anal. Calcd for $C_{15}H_{21}NO_9$: C, 50.14; H, 5.89; N, 3.90. Found: C, 49.98; H, 6.11; N, 3.50.

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