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SYNTHETIC STUDIES ON NOGALAMYCIN CONGENERS [1][1]
CHIRAL SYNTHESIS OF THE DEF-RING SYSTEM OF NOGALAMYCIN

Motoji Kawasaki, Fuyuhiko Matsuda, and Shiro Terashima*

Sagami Chemical Research Center,
Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

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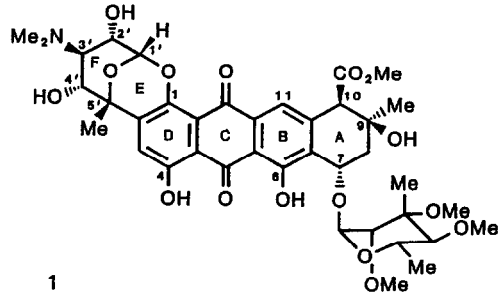
Abstract: From the retrosynthetic perspective on nogalamycin congeners, the potent antitumor antibiotics of the anthracycline family, the regioselective Diels-Alder reaction employing the naphthoquinone (**4**), the CDEF-ring system of nogalamycin congeners, as a dienophile was anticipated to constitute the key step of one of the most convenient and flexible synthetic routes to their 11-deoxyanthracyclinone frameworks (**3**). As a model study to explore an efficient and reliable synthetic scheme to produce the characteristic bicyclic acetal structure of **4** in an optically active form, the preparation of the DEF-ring system (**6**) was first examined prior to the chiral synthesis of **4**. The chiral synthesis of **6** accomplished starting from readily available (-)-D-arabinose (**11**), involves the following novel aspects: (1) synthesis of the suitably functionalized (-)-methylketone (**18**) from **11** through (-)-β-D-gentosaminide (**14**) which carries the stereochemistries at the $C_{2'}$-, $C_{3'}$-, and $C_{4'}$-positions, (2) stereoselective construction of the $C_{5'}$-asymmetric center by chelation-controlled addition of the aryllithium [**9** (M=Li)] to **18**, (3) formation of the bicyclic acetal by treating the hydroquinone (**28**) with trimethylsilyl bromide.

Nogalamycin (**1**) and its congeners are notable members of the anthracycline family.[2] Nogalamycin (**1**) isolated from *Streptomyces nogalater* var. *nogalater* sp.n. by Wiley *et al.* in 1968,[3] showed high inhibitory activity against gram-positive bacteria and prominent cytotoxicity against L1210 and KB cell lines *in vitro*. Although **1** was found to exhibit antitumor activity against two types of solid tumors *in vivo*, its relatively poor activity accompanied by unacceptable toxicity in large animals caused cessation of testing.[2] As the results of the synthesis and testing of numerous semisynthetic derivatives of **1**, it was found that 7-con-*O*-methylnogarol (**2**) showed superior antitumor activity to that of the parent compound (**1**).[2] Recently, **2** was chosen for clinical trials based on broad spectrum activity against a panel of murine tumors, lower cardiotoxicity than that

of adriamycin, and differences in biochemical effects from those of other anthracyclines.[4]

These novel compounds carry the characteristic C-glycoside moiety (the DEF-ring system) in which the amino sugar (F-ring) is fused to the 11-deoxyanthracycline D-ring to form the new E-ring.[5,6] Their promising antitumor activity and unique structures definitely distinguish these compounds as unusually attractive targets for total synthesis and a number of synthetic studies on nogalamycin congeners have been reported.[7]



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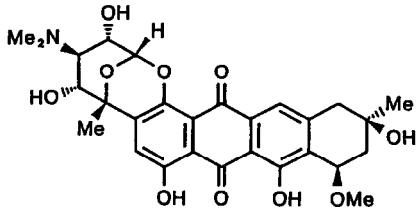

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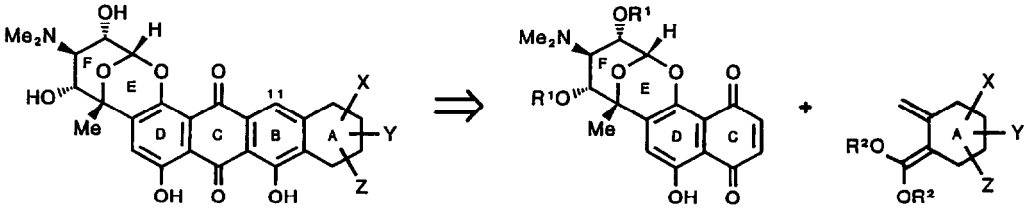
We started the program directed toward the total syntheses of nogalamycin congeners with an aim to explore the general and flexible synthetic route to these novel anthracyclines. Our effort culminated in the first total syntheses of nogalamycin congeners including **2**, in optically active forms. This series of papers concerns with full details of the total syntheses and antitumor activity of various structural types of nogalamycin congeners. These studies also disclosed novel aspects of the structural-activity relationships of nogalamycin congeners.[1]

Synthetic Strategy

From the retrosynthetic perspective on nogalamycin congeners, the construction of their 11-deoxyanthracyclinone frameworks (**3**) by the regioselective Diels-Alder reaction of the diene (**5**) with the naphthoquinone (**4**), the CDEF-ring system of **3**, as a dienophile, was anticipated to hold promise as one of the most convenient and flexible synthetic routes. This is because the 11-deoxyanthracyclinone frameworks had been successfully produced by employing the regioselective Diels-Alder reaction with juglone.[8]



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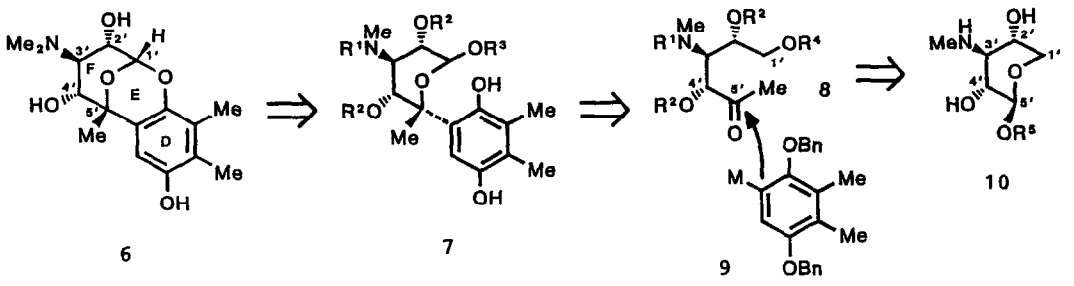
For the chiral synthesis of **4**, it is indispensable to explore an efficient and reliable synthetic scheme to produce the characteristic bicyclic acetal structure (the DEF-ring system) in an optically active form. Thus, prior to the synthesis of **4**, the preparation of the DEF-ring system (**6**) was first examined as a model study.[1a] Our synthetic plan involves (1) preparation of the suitably functionalized methyl ketone (**8**), the glycoside moiety, from the β-D-gentosaminide (**10**), which carries desired stereochemistries at the $C_{2'}$-, $C_{3'}$-, and $C_{4'}$-positions

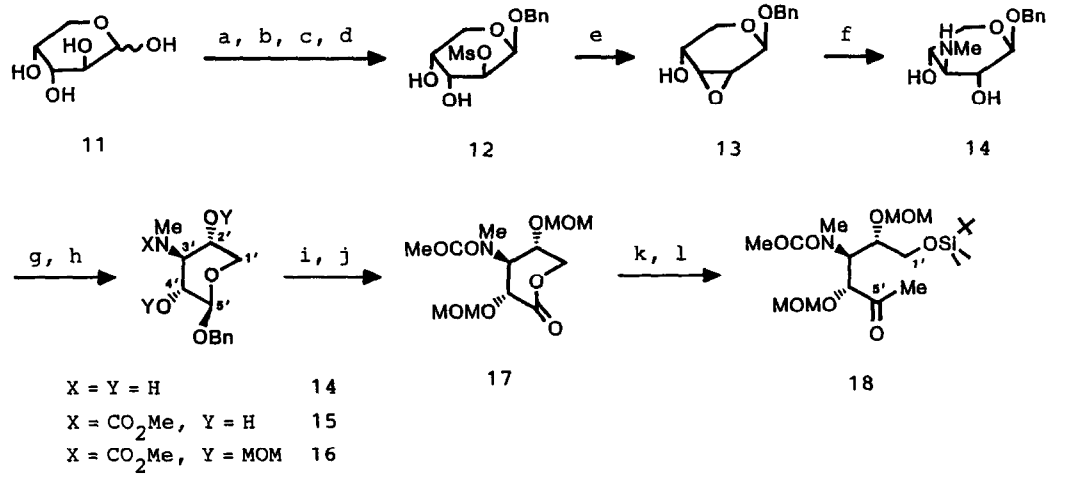


(nogalamycin numbering),[9] (2) stereoselective construction of the $C_{5'}$-asymmetric center based on the chelation-controlled addition of the arylmetal (**9**) to **8** under influence of the $C_{4'}$-alkoxyl group adjacent to the carbonyl group, and (3) formation of the bicyclic acetal through the hydroquinone (**7**). As mentioned below, the synthesis of **6** has been completed according to this synthetic plan. The first part of this series of papers concerns full details of this model study.[1a]

Results and Discussion

Synthesis of the (-)-Methyl Ketone (18), the Glycoside Moiety, from (-)-D-Arabinose. As shown in **Scheme 1**, (-)-benzyl β-D-gentosaminide (**14**), mp 151-152 °C and $[\alpha]_D^{20}$ -76.9° (c 0.450, EtOH), was produced in 8 steps from (-)-D-arabinose (**11**) by way of benzyl 2-*O*-methanesulfonyl-β-D-arabinopyranoside (**12**)[9] and benzyl 2,3-anhydro-β-D-ribopyranside (**13**)[10] according to the method reported for the corresponding methyl gentosaminide.[11] Taking into account the subsequent synthetic scheme, the methylamino and two hydroxyl groups of **14** were sequentially protected in forms of methyl carbamate and methoxylmethyl ethers, respectively,

Scheme 1



X = Y = H 14
X = CO_2Me, Y = H 15
X = CO_2Me, Y = MOM 16

a) HCl, BnOH, rt, 18 h, 90% b) $(MeO)_2CMe_2$, p-TsOH·H_2O, reflux, 20 min, 95% c) MsCl, Et_3N, THF, rt, 30 min d) 0.5M H_2SO_4, Me_2CO, reflux, 5 min, 87% (2 steps) e) NaOMe, MeOH, 50 °C, 2 h, 99% f) $MeNH_2$, MeOH, 60 °C, 24 h, 100% g) MeOCOCl, K_2CO_3, Me_2CO, reflux, 1 h, 85% h) MOMCl, $^iPr_2NEt$, THF, reflux, 30 min, 87% i) H_2, 10% Pd-C, EtOH, rt, 10 h, 99% j) 1) $(COCl)_2$-DMSO, CH_2Cl_2, -60 °C, 10 min 2) Et_3N, -60 → -20 °C, 30 min, 88% k) MeLi, THF, -78 °C, 2 h, 94% l) $^tBuMe_2SiCl$, $C_3H_4N_2$, DMF, rt, 20 h, 84%.

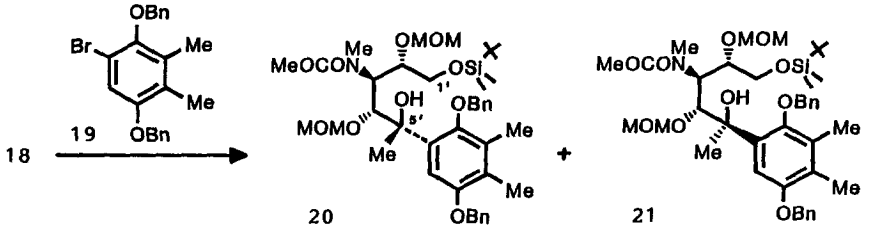
affording the glycoside (**16**) by way of the methyl carbamate (**15**). Successive debenzylation of **16** and Swern oxidation of the formed lactol gave the lactone (**17**). Addition of methyllithium to **17** followed by the usual silylation, gave rise to the open-chain (-)-methyl ketone (**18**), $[\alpha]_D^{20}$ -28.8° (c 1.10, $CHCl_3$).

Construction of the $C_{5'}$-Asymmetric Center. For stereocontrolled formation of the $C_{5'}$-asymmetic center which constitutes one of the key steps of our synthetic scheme, nucleophilic addition of the aryllithium [**9** (M=Li)] genarated from 1,4-dibenzyloxy-5-bromo-2,3-dimethylbenzene (**19**) was first examined. Results of the addition reaction are summarized in **Table I.**

Interestingly, the stereoselectivity and chemical yields of the resulting $C_{5'}$-epimeric alcohols (**20** and **21**) were found to highly depend upon reaction solvents (**Table I, Run 1-4**). Thus, when tetrahydrofuran was employed as a solvent, **20** and **21** were obtained in a 7:1 ratio and a significant amount of unreacted **18** was recovered (**Run 1**). On the other hand, the reaction in ether afforded **20** and **21** in a high combined yield and with recovery of a small amount of **18** (**Run 2**). In this case, the ratio of **20** to **21** was 2:1. The reaction in a mixture of ether-tetrahydrofuran (4:1) was found to proceed in a stereoselective manner (**20:21** = 8:1) to yield **20** and **21** in a fairly good combined yield (**Run 3**). Finally, the most satisfactory result (**20:21** = 8:1) was obtained by adding of a tetrahydrofuran solution of **18** to an ethereal solution of **9** (M=Li) (**Run 4**). These epimeric products (**20** and **21**) and the starting material (**18**) could be readily separated by column chromatography, **20**: $[\alpha]_D^{20}$ -30.1° (c 1.20, $CHCl_3$), and **21**: mp 84-86 °C; $[\alpha]_D^{20}$ -37.0° (c 1.50, $CHCl_3$). Although stereochemistries at the $C_{5'}$-positions of **20** and **21** could not be determined at this stage, the major epimer (**20**) was assumed to have the desired configuration since it is well known that addition of an organolithium reagent to an α-alkoxy ketone generally affords a chelation-controlled product as a major isomer.[12] This assignment was obviously confirmed by successful conversion of **20** into the objective compound (**6**) (*vide infra*).

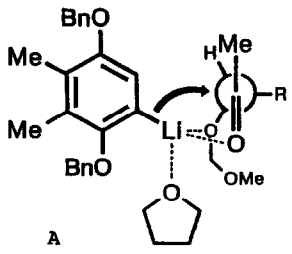
In contrast to the aryllithium [**9** (M=Li)], treatment of **18** with the aryl-

Table I. Addition Reaction of the Arylmetal (**9**) to the Methyl Ketone (**18**)

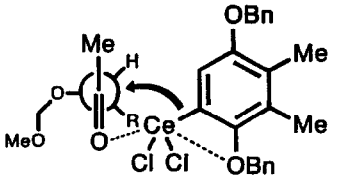


Run	Conditions	Yield (%)		
		20	**21**	**18**
1	**19**, ^{n}BuLi, THF, 0 °C, 10 min	49	7	32
2	**19**, ^{n}BuLi, Et_2O, 0 °C, 1 min	51	26	7
3	**19**, ^{n}BuLi, THF-Et_2O (1:4), 0 °C, 1 min	55	7	20
4	**19**, ^{n}BuLi, THF (1) + Et_2O (4), 0 °C, 1 min	66	8	18
5	**19**, ^{n}BuLi, then $CeCl_3$, THF, -78 °C, 1 h	6	89	0

dichlorocerium [9 (M=$CeCl_2$)] genarated by treating 9 (M=Li) with anhydrous cerium(III) chloride,[13] selectively produced undesired 21 (20:21 = 1:15) in an almost quantitative yield (Run 5). Efficient formation of the addition products (20 and 21) is probably due to low basicity of the cerium(III) reagents.[13]



A



B

These notable selectivity could be nicely explained by assuming that intramolecular interaction between metal cation and oxygen atom of the adjacent benzyl ether is stronger in 9 (M=$CeCl_2$) than in 9 (M=Li). Thus, in the reaction of 9 (M=Li), the lithium cation interacts with oxygen atom of the methoxymethyl ether group adjacent to the carbonyl group of 18 more preferentially than with oxygen atom of the benzyl ether involved in the aromatic ring. Especially, in the presence of tetrahydrofuran which can readily solvate a lithium cation, the intramolecular interaction should be much weaker. Therefore, the usual chelation model (A) seems to be well consistent with the transition state of addition reaction with 9 (M=Li). On the other hand, the cerium(III) cation chelates with oxygen atom of the adjacent benzyl ether more strongly than the lithium cation probably due to its increased steric bulkiness. Accordingly, the addition reaction with 9 (M=$CeCl_2$) seems to proceed through the transition state corresponding to Felkin-Anh model (B).[14]

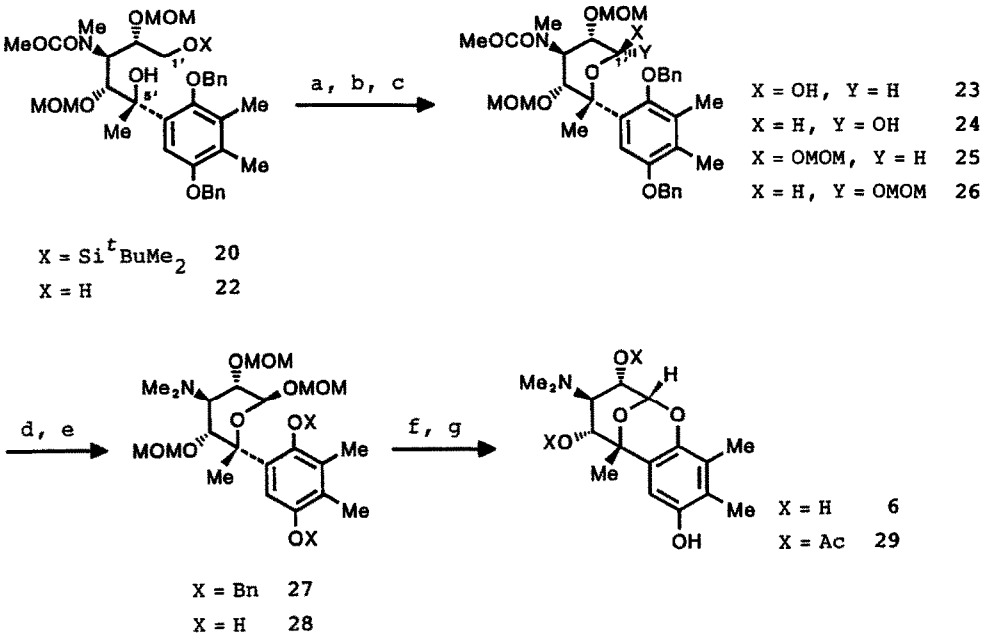
Synthesis and Structure Elucidation of the (-)-DEF-Ring System (6). After desilylation of the desired (-)-alcohol (20), oxidation of the resulting diol (22) and protection of the formed hemiacetals (23 and 24) afforded a mixture of the $C_{1'}$-epimeric acetals (25 and 26) as shown in Scheme 2. While separation of the mixture by chromatography gave the β-acetal (25) along with a small amount of the α-acetal (25) (25:26 = 14:1),[15] the main product (25) was only converted into 6 simply from practical reasons.

Reduction of 25 with lithium aluminum hydride underwent smoothly to afford the dimethylamine (27). Debenzylation of 27 yielded the unstable *p*-hydroquinone (28), which was immediately subjected to the next reaction without purification. Brief exposure of 28 to trimethylsilyl bromide[16] effected simultaneous clean cleavage of the three methoxymethyl ethers and intramolecular acetal formation, furnishing the (+)-bicylic acetal (6), $[\alpha]_D^{20}$ -35.6° (c 0.500, MeOH).[17]

On the other hand, the undesired (-)-alcohol (21) was derived to the isomeric (-)-bicyclic acetal (35), $[\alpha]_D^{20}$ -50,1° (c 1.40, MeOH), by way of the diol (30), the β-acetal (31), the dimethylamine (33), and the *p*-hydroquinone (34), following exactly the same procedure as that described for 20 (Scheme 3).

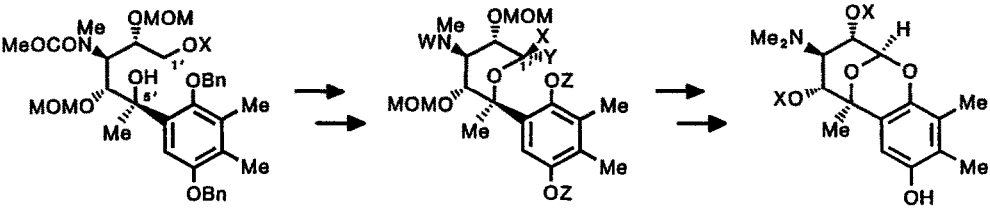
With the two isomeric DEF-ring systems (6 and 35) in hand, ^{1}H NMR spectral data of 6 and 35 were compared with those of 7-dis-nogalarol (37)[5a] and the racemic model compound (38), the latter of which had already been synthesized by Sammes *et al.*[7a] As shown in Table II, the chemical shifts and coupling constants exhibited by the protons of the C-glycoside parts cleanly disclosed the structures of 6 and 35 as depicted in Scheme 2 and 3. Selective acetylation of the $C_{2'}$- and $C_{4'}$-hydroxyl groups[3c,d] of 6 and 35 readily produced the well-crystalline deacetates

Scheme 2



a) ^{n}Bu$_4$NF, THF, rt, 1 h, 94% b) SO$_3$Py, DMSO, Et$_3$N, THF, rt, 2 h, 88% c) MOMCl, ^{i}Pr$_2$NEt, THF, reflux, 9 h, 85% (25), 6% (26) d) LiAlH$_4$, Et$_2$O, reflux, 30 min, 94% e) H$_2$, 10% Pd-C, rt, 3 h f) TMSBr, CH$_2$Cl$_2$, reflux, 15 min, 82% (2 steps) g) Ac$_2$O, MeOH, 40 °C, 3 h, 93%.

Scheme 3



X = Si^{t}BuMe$_2$ 21
X = H 30

W = CO$_2$Me, X = OMOM, Y = H, Z = Bn 31
W = CO$_2$Me, X = H, Y = OMOM, Z = Bn 32
W = Me, X = OMOM, Y = H, Z = Bn 33
W = Me, X = OMOM, Y = Z = H 34

X = H 35
X = Ac 36

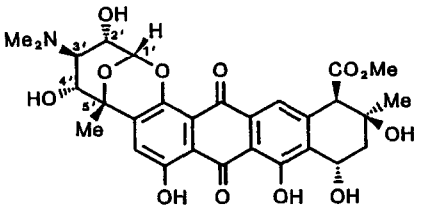
(**29** and **36**), respectively, **29**: mp 216-218 °C; $[\alpha]_D^{20}$ -57.6° (0.500, CHCl$_3$), and **36**: mp 174-175 °C; $[\alpha]_D^{20}$ -69.1° (c 0.540, CHCl$_3$). X-Ray crystallographic analyses of **29** and **36** unambiguously established the structures of **6** and **35** assigned above.[18]

Conclusion

As described above, the chiral synthesis of **6** was successfully accomplished in excellent overall yield starting from readily available **11**. Based on the information accumulated in this model study, the stereocontrolled construction of **4**, the key intermediate of our synthetic plan, was next attempted. This is the subject of the accompanying paper.[20]

Table II. ^{1}H NMR Spectral Data of 37, 38, 6, and 35

Compound (solvent)	Chemical Shifts (δ: ppm)				Coupling Constants (Hz)		
	1'	2'	3'	4'	1'2'	2'3'	3'4'
37 (CD_3COCD_3)	5.87	4.16	2.86	3.66	3.3	10.5	10.5
38 ($CDCl_3$)	5.47	4.00	2.17	3.48	3.5	10.4	10.4
6 (CD_3COCD_3)	5.41	3.92	2.31	3.47	3.5	10.3	10.3
35 (CD_3COCD_3)	5.33	3.59	2.56	3.91	3.1	11.3	8.1



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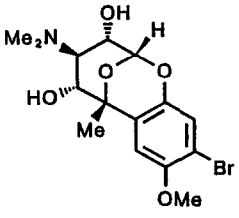

38

Experimental

General. All melting points were determined with a Yamato MP-21 melting point apparatus and are uncorrected. Measurements of optical rotations were carried out using a Horiba SEPA-200 automatic digital polarimeter. IR spectra measurements were performed with a JASCO A-200 IR spectrometer. ^{1}H NMR spectra were measured with a Hitachi R-90H spectrometer (90 MHz) and a Bruker AM 400 spectrometer (400 MHz). All signals are expressed as ppm down field from tetramethylsilane used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), broad (br). Assignments of peaks are indicated according to the numbering of IUPAC nomenclature to avoid confusion. Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Unless otherwise noted, all reactions were performed using anhydrous solvents. Especially, tetrahydrofuran and ether freshly distilled from sodium benzophenone ketyl were used. Wako Gel C-200 was used as an adsorbent for column chromatography. The following abbreviations are used for solvents and reagents: acetic anhydride (Ac_2O), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethanol (EtOH), ethyl acetate (AcOEt), methanol (MeOH), sulfur trioxide pyridine complex (SO_3Py), tetrabutylammonium fluoride (Bu_4NF), tetrahydrofuran (THF), trimethylsilyl bromide (TMSBr).

(-)-Benzyl β-D-Arabinopyranoside. This was prepared from (-)-D-arabinose (11), mp 161-162 and $[\alpha]_D^{20}$ -98.2° (c 3.00, H_2O), by the treatment with HCl in benzyl alcohol according to the reported procedure (90%).[19] The glycoside obtained as colorless crystals, showed mp 167-169 °C [lit. mp 169-171 °C[19]] and $[\alpha]_D^{20}$ -217° (c 0.400, H_2O).

(-)-Benzyl 2-*O*-Methanesulfonyl-β-D-arabinopyranoside (12). A solution of (-)-benzyl β-D-arabinopyranoside (32 g, 0.13 mol) and *p*-toluenesulfonic acid monohydrate (1.0 g, 5.3 mmol) in 2,2-dimethoxypropane (200 ml) was heated at reflux for 20 min. After being cooled to room temperature, the reaction mixture was poured onto saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic extracts were combined, washed with brine, and dried ($MgSO_4$). Filtration and con-

centration *in vacuo*, followed by purification by column chromatography (SiO_2, AcOEt-$CHCl_3$), gave pure benzyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside as a pale yellow caramel (35 g, 95%). ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.35 and 1.52 (6H, two s, CMe_2), 2.34 (1H, d, J = 7 Hz, OH), 3.6-4.3 (5H, m, C_2-H, C_3-H, C_4-H, C_5-H_2), 4.50 and 4.77 (2H, two d, each J = 6 Hz, $C\underline{H}_2Ph$), 4.88 (1H, d, J = 4 Hz, C_1-H), 7.33 (5H, s, $CH_2\underline{Ph}$); IR (neat) 3480, 1220, 1065 cm^{-1}.

Methanesulfonyl chloride (16 g, 0.14 mol) was added to a solution of the benzyl isopropylidenearabinoside (20 g, 71 mmol) and triethylamine (43 g, 0.42 mol) in THF (140 ml) cooled in an ice bath. The reaction mixture was warmed up to ambient temperature. After stirring was continued for 30 min, the reaction was quenched by the addition of MeOH (20 ml) and the mixture was diluted with AcOEt. The ethyl acetate solution was washed with saturated aqueous $NaHCO_3$, and dried ($MgSO_4$). Filtration and concentration *in vacuo* gave benzyl 3,4-*O*-isopropylidene-2-*O*-methanesulfonyl-β-D-arabinopyranoside as a pale yellow caramel (25 g). ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.36 and 1.57 (6H, two s, CMe_2), 3.10 (3H, s, SO_3Me), 3.9-4.1 (2H, m, C_5-H_2), 4.2-4.8 (5H, m, C_2-H, C_3-H, C_4-H, $C\underline{H}_2Ph$), 5.03 (1H, d, C_1-H), 7.33 (5H, s, $CH_2\underline{Ph}$); IR (neat) 1360, 1175, 1070, 1020, 835, 520 cm^{-1}.

A solution of the methanesulfonate (25 g) in acetone (40 ml) was added to 0.5M H_2SO_4 (500 ml) heated at 100 °C and the mixture was further heated at reflux for 5 min. After being cooled at 0 °C, the mixture was extracted with AcOEt. The combined extracts were washed with brine and dried ($MgSO_4$). Filtration and concentration *in vacuo* gave pure **12** as a colorless solid (20 g, 87%, 2 steps). Recrystallization from MeOH-ether gave colorless crystals, mp 126-127 °C [lit. mp 129-130 °C[9]] and $[\alpha]_D^{20}$ -184° [c 2.30, EtOH-$CHCl_3$ (1:5)] [lit. $[\alpha]_D^{20}$ -189.5° [c 3.2, EtOH-$CHCl_3$ (1:5)][9]]. ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.01 (3H, s, SO_3Me), 2.9-3.1 (1H, m, OH), 3.2-4.3 (4H, m, C_3-H, C_4-H, C_5-H_2), 3.24 (1H, d, J = 6 Hz, OH), 4.4-4.9 (3H, m, $C\underline{H}_2Ph$, C_2-H), 5.08 (1H, d, J = 4 Hz, C_1-H), 7.33 (5H, s, $CH_2\underline{Ph}$); IR (KBr) 3470, 3420, 1355, 1170, 1010, 970 cm^{-1}.

(-)-Benzyl 2,3-Anhydro-β-D-ribopyranoside (13). Sodium methoxide (6.8 g, 0.13 mmol) was added to a solution of **12** (10 g, 31 mmol) in MeOH (80 ml) at room temperature. The reaction mixture was heated at 50 °C for 2 h, cooled to ambient temperature, and diluted with AcOEt. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate *in vacuo* gave pure **13** as a colorless solid (6.9 g, 99%). Recrystallization from ether gave colorless crystals, mp 76-77 °C [lit. mp 76-77 °C[10]] and $[\alpha]_D^{20}$ -64.3° (c 0.830, $CHCl_3$) [lit. $[\alpha]_D^{20}$ -67° (c 0.8, $CHCl_3$)[10]]. ^{1}H NMR (90 HMz, $CDCl_3$) δ 2.77 (1H, d, J = 11 Hz, OH), 3.20 (1H, d, J = 4 Hz, C_2-H), 3.3-4.0 (4H, m, C_3-H, C_4-H, C_5-H_2), 4.53 and 4.77 (2H, two d, each J = 12 Hz, $C\underline{H}_2Ph$), 5.00 (1H, s, C_1-H), 7.34 (5H, s, $CH_2\underline{Ph}$); IR (KBr) 3480, 1085, 1065, 725 cm^{-1}.

(-)-Benzyl 3-Deoxy-3-methylamino-β-D-xylopyranoside [(-)-Benzyl β-D-Gentosaminide] (14). Methylamine (20 ml) was added to a solution of **13** (9.5 g, 43 mmol) in MeOH (3.0 ml) cooled at -30 °C. The reaction mixture was heated at 60 °C in a sealed tube for 24 h, cooled to room temperature, and concentrated *in vacuo*, affording pure **14** as a colorless solid (11 g, 100%). Recrystallization from $CHCl_3$ gave colorless crystals, mp 151-152 °C and $[\alpha]_D^{20}$ -76.9° (0.450, EtOH). ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.3-3.0 (4H, m, C_3-H, OH x 2, NH), 2.42 (3H, s, NMe), 3.1-3.8 (3H, m, C_2-H, C_4-H, $C_{5\text{-}ax}$-H), 4.02 (1H, dd, J = 4 and 11 Hz, $C_{5\text{-}eq}$-H), 4.37 (1H, d, J = 6 Hz, C_1-H), 4.53 and 4.86 (2H, two d, each J = 12 Hz, $C\underline{H}_2Ph$), 7.32 (5H, s, $CH_2\underline{Ph}$); IR (KBr) 3400, 1140, 1070, 750, 700 cm^{-1}; MS m/z 254 (M^+H); High-resolution MS (M^+H) 254.1390 (254.1387 calcd. for $C_{13}H_{20}NO_4$).

(-)-Benzyl 3-Deoxy-3-(*N*-methoxycarbonyl-*N*-methylamino)-β-D-xylopyranoside (15). Methyl chloroformate (0.47 g, 5.0 mmol) and **14** (0.50 g, 2.0 mmol) was added to a

suspension of anhydrous K_2CO_3 (1.4 g, 10 mmol) in acetone (20 ml) at room temperature under an argon atmosphere. The reaction mixture was heated at reflux for 1 h, cooled to room temperature, and filtered. The filtrate was concentrated *in vacuo* and recrystallization of the residue from $CHCl_3$-hexane gave pure **15** as colorless crystals (0.52 g, 85%), mp 175-178 °C and $[\alpha]_D^{20}$ -70.7° (c 2.10, MeOH). ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.88 (3H, s, NMe), 3.1-4.1 (10H, C_2-H, C_3-H, C_4-H, C_5-H_2, CO_2Me, OH x 2), 4.34 (1H, d, J = 7 Hz, C_1-H), 4.59 and 4.84 (2H, two d, each J = 12 Hz, C$\underline{H}_2$Ph), 7.1-7.5 (5H, m, $CH_2\underline{Ph}$); IR (KBr) 3470, 1700, 1075, 765 cm^{-1}. *Anal.* Calcd. for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50%. Found: C, 57.60; H, 6.76; N, 4.38%.

(-)-Benzyl 3-Deoxy-2,4-bis-(*O*-methoxymethyl)-3-(*N*-methoxycarbonyl-*N*-methylamino)-β-D-xylopyranoside (16). Chloromethyl methyl ether (12 g, 0.15 mol) was added to a solution of **15** (3.9 g, 13 mmol) and ethyldiisopropylamine (19 g, 0.15 mol) in THF (20 ml) at room temperature under an argon atmosphere. The reaction mixture was heated at reflux for 30 min and cooled in an ice bath. After successive addition of triethylamine (10 ml) and MeOH (10 ml), the mixture was diluted with AcOEt. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, AcOEt-$CHCl_3$) of the residual oil afforded pure **16** as a colorless caramel (4.8 g, 97%), $[\alpha]_D^{20}$ -23.7° (c 1.10, EtOH). ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.87 and 2.93 (3H, two s, NMe), 3.26 (6H, s, $CH_2O\underline{Me}$ x 2), 3.70 (3H, s, CO_2Me), 3.1-5.0 (12H, m, C_1-H, C_2-H, C_3-H, C_4-H, C_5-H_2, C$\underline{H}_2$Ph, C$\underline{H}_2$OMe x 2, NH), 7.30 (5H, s, $CH_2\underline{Ph}$); IR (neat) 1700, 1100, 1030 cm^{-1}. *Anal.* Calcd. for $C_{19}H_{29}NO_8$: C, 57.13; H, 7.32; N, 3.51%. Found: C, 57.13; H, 7.37; N, 3.43%.

(3R,4S,5S)-(+)-3,5-Bis(methoxymethyloxy)-4-(*N*-methoxycarbonyl-*N*-methylamino)-tetrahydro-2-pyranone (17). A mixture of **16** (4.8 g, 12 mmol), 10% Pd-C (0.50 g), and 12M HCl (0.10 ml) in EtOH (100 ml) was stirred at room temperature for 10 h under a hydrogen atmosphere. After the reaction mixture was neutralized with triethylamine, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO_2, AcOEt) to give pure 3-deoxy-2,4-bis-(*O*-methoxymethyl)-3-(*N*-methoxycarbonyl-*N*-methylamino)-D-xylopyranose as a colorless caramel (3.7 g, 99%). ^{1}H NMR ($CDCl_3$) δ 2.92 (3H, s, NMe), 3.1-4.3 (6H, m, C_2-H, C_3-H, C_4-H, C_5-H_2, OH), 3.31 and 3.36 (6H, two s, $CH_2O\underline{Me}$ x 2), 4.3-5.4 (5H, m, C$\underline{H}_2$OMe x 2, C_1-H); IR (neat) 3450, 1700, 1030 cm^{-1}. *Anal.* Calcd. for $C_{12}H_{23}NO_8$: C, 46.60; H, 7.50; N, 4.53%. Found: C, 46.44; H, 7.52; N, 4.32%.

A solution of DMSO (23 g, 0.30 mol) in CH_2Cl_2 (50 ml) was added to a solution of oxalyl chloride (17 g, 0.14 mol) in CH_2Cl_2 (500 ml) cooled at -60 °C under an argon atmosphere. After the reaction mixture was stirred at the same temperature for 2 min, a solution of the hemiacetal (21 g, 68 mmol) in CH_2Cl_2 (50 ml) was added and stirring was continued for 10 min. Triethyamine (70 g, 0.70 mmol) was added and the mixture was allowed to warm up to -20 °C over 30 min. 3M HCl was added, and the lower methylene chloroide layer was separated. The upper aqueous layer was further extracted with $CHCl_3$. The combined extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate *in vacuo* gave a residue, which was chromatographed (SiO_2, AcOEt) to yield crude **17** as a solid. The solid was further triturated with ether-hexane, affording pure **17** as a colorless solid (18 g, 88%). Recrystallization from benzene gave an analytical sample of **17** as colorless crystals, mp 85-86 °C and $[\alpha]_D^{20}$ +67.1° (c 2.00, $CHCl_3$). ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.09 (3H, s, NMe), 3.3-3.6 (1H, m, C_4-H), 3.35 and 3.37 (6H, two s, $CH_2O\underline{Me}$ x 2), 4.2-5.2 (8H, m, C_3-H, C_5-H, C_6-H_2, C$\underline{H}_2$OMe x 2); IR (KBr) 1770, 1700, 1025 cm^{-1}. *Anal.* Calcd. for $C_{12}H_{21}NO_8$: C, 46.90; H, 6.89; N, 4.56%. Found: C, 46.73; H, 6.84; N, 4.43%.

(2S,3S,4R)-(-)-1-(*tert*-Butyldimethylsilyloxy)-3-(*N*-methoxycarbonyl-*N*-methylamino)-2,4-bis(methoxymethyloxy)-5-henanone (18). Methyllithium (4.2 ml, 1.2M hexane solution, 5.0 mmol) was added to a solution of **17** (0.40 g, 5.0 mmol) in THF (30 ml) cooled at -78 °C under an argon atmosphere. After stirring was continued for 2h at the same temperature, the reaction mixture was quenched by the addition of MeOH (0.50 ml). The mixture was warmed up to 0 °C and saturated aqueous NH_4Cl (0.30 ml) was added. After stirring for 5 min at room temperature, the solution was dired ($MgSO_4$), filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, AcOEt) of the residue afforded pure (3R,4S,5S)-2-hydroxy-4-(*N*-methoxycarbonyl-*N*-methylamino)-3,5-bis(methoxymethyloxy)-2-methyltatrahydropyran as a colorless caramel (0.39 g, 94%). ^{1}H NMR (90 MHz, C_5D_5N) δ 1.72 (3H, s, C_2-Me), 3.03 and 3.13 (3H, two s, NMe), 3.23, 3.26, 3.34, and 3.37 (6H, four s, $CH_2O\underline{Me}$ x 2), 3.5-5.0 (6H, m, C_3-H, C_4-H, C_5-H, C_6-H_2, OH), 3.70 (3H, s, CO_2Me); IR (neat) 3400, 1690, 1020 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{25}NO_8$: C, 48,29; H, 7.79; N, 4.33%. Found: C, 48.13; H, 8.04; N, 4.16%.

tert-Butyldimethylsilyl chloride (0.75 g, 5.0 mmol) was added to a solution of the hemiketal (0.39 g, 1.2 mmol) and imidazole (0.88 g, 13 mmol) in DMF (10 ml) at room temperature under an argon atmosphere. After being stirred for 20 h at room temperature, the mixture was diluted with ether, washed successively with water and brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by separation by column chromatography (SiO_2, AcOEt-$CHCl_3$), afforded pure **18** as a pale yellow caramel (0.45 g, 84%), $[\alpha]_D^{20}$ -28.8° (c 1.10, $CHCl_3$). ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.07 (6H, s, $SiMe_2$), 0.93 (9H, s, Si^{t}Bu), 2.14 and 2.19 (3H, two s, COMe), 2.88 and 2.91 (3H, two s, NMe), 3.33 and 3.35 (6H, two s, $CH_2O\underline{Me}$ x 2), 3.65 (3H, s, CO_2Me), 3.5-3.9 (3H, m, C_1-H_2, C_3-H), 4.2-5.1 (6H, m, C_2-H, C_4-H, $C\underline{H}_2$OMe x 2); IR (neat) 1730, 1705, 1030, 840, 780 cm^{-1}. *Anal.* Calcd. for $C_{19}H_{39}NO_8Si$: C, 52.15; H, 8.98; N, 3.20%. Found: C, 52.04; H, 8.97; N, 3.10%.

1,4-Dibenzyloxy-5-bromo-2,3-dimethylbenzene (19). A solution of 2,3-dimethylphenol (5.1 g, 42 mmol) and $KON(SO_3)_2$ (Fremy's salt) (22 g, 82 mmol) in acetone (10 ml) was added to a aqueous solution (300 ml) of KH_2PO_4 (3.0 g, 22 mmol) in a 1 l separatory funnel at room temperature. After vigorous shaking for 20 min, another portion of Fremy's salt (5 g, 19 mmol, total 0.10 mol) was added to the reaction mixture and shaking was further continued for 20 min. The reaction mixture was extracted with AcOEt, and combined extracts were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Filtration and concentration *in vacuo* gave crude 2,3-dimethyl-1,4-benzoquinone as a brown solid (6.5 g).

47% Aqueous HBr (25 ml) was added to a solution of the quinone (6.5 g) in acetic acid (50 ml) in an ice bath. After stirring for 10 h at 10 °C, the reaction mixture was diluted with ether, washed with brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo* gave crude 5-bromo-2,3-dimethyl-1,4-benzenediol as a brown solid (6.5 g).

A solution of the hydroquinone (6.5 g) in DMF (20 ml) was added to a stirred suspension of NaH (4.0 g, 50% dispersion in oil, 83 mmol) and benzyl chloride (13 g, 10 mmol) in DMF (50 ml) cooled at 0 °C under an argon atmosphere. After stirring was continued for 1 h at room temperature, the reaction mixture was diluted with ether. The ethereal solution was washed successively with 15% aqueous NaOH and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chormatographed (SiO_2, $CHCl_3$-hexane) to give crude **19** as a pale yellow solid. Recerystallization from hexane gave pure **19** as colorless crystals (7.1 g, 43%, 3 steps, from 2,3-dimethylphenol), mp 97-98 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.16 and 2.24 (6H, two s, C_2-Me, C_3-Me), 4.85 and 5.01 (4H, two s, $C\underline{H}_2$Ph x 2), 7.00 (1H, s, C_6-H), 7.3-7.7 (10H, m, $CH_2\underline{Ph}$ x 2); IR (KBr) 1450, 1375, 1235, 1105,

1020, 750, 530 cm^{-1}. *Anal.* Calcd. for $C_{21}H_{21}O_2Br$: C, 66.51; H, 5.33; Br, 20.11%. Found: C, 66.67; H, 5.48; Br, 19.98%.

(2R,3R,4S,5S)-(-)-2-(2,5-dibenzyloxy-3,4-dimethylphenyl)-6-(*tert*-butyldimethylsilyloxy)-4-(*N*-methoxycarbonyl-*N*-methylamino)-2,4-bis(methoxymethyloxy)-2-hexanol (20) and Its (2S,3R,4S,5S)-(-)-Isomer (21).

a) Table I, Run 1. Butyllithium (0.13 ml, 1.5M hexane solution, 0.20 mmol) was added to a solution of **19** (80 mg, 0.20 mmol) in THF (2.5 ml) cooled at -78 °C under an argon atmosphere. After stirring for 10 min at the same temperature, the reaction mixture was allowed to warm up to 0 °C and stirring was continued for 3 min. A solution of **18** (44 mg, 0.10 mmol) in THF (0.50 ml) was added to the reaction mixture at 0 °C. After stirring was continued for 10 min at the same temperature, the reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with ether. The ethereal extracts were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, AcOEt-hexane) gave pure **20** as a colorless caramel (37 mg, 49% from **18**), pure **21** as a colorless caramel (5 mg, 7% from **18**), and pure **18** as a colorless caramel (14 mg, 32% from **18**).

b) Table I, Run 2. Butyllithium (0.13 ml, 1.5M hexane solution, 0.20 mmol) was added to a solution of **19** (80 mg, 0.20 mmol) in ether (2.5 ml) cooled at -20 °C under an argon atmosphere. After stirring for 10 min at 0 °C, a solution of **18** (44 mg, 0.10 mmol) in ether (0.50 ml) was added to the reaction mixture and stirring was continued for 1 min at 0 °C. The same treatments of the reaction mixture as those described in a) afforded pure **20** as a colorless caramel (39 mg, 51%) and a mixture of **21** and **18** (**21**:**18** ≈ 83:17 by ^1H NMR) as a colorless caramel [23 mg, 26% (**21**), 7% (**18**)] after separation by column chromatography (SiO_2, AcOEt-hexane).

c) Table I, Run 3. Butyllithium (0.13 ml, 1.5M hexane solution, 0.24 mmol) was added to a solution of **19** (80 mg, 0.20 mmol) in a mixture of THF (0.50 ml) and ether (2.0 ml) cooled at -20 °C under an argon atmosphere. After stirring for 10 min at 0 °C, a solution of **18** (44 mg, 0.10 mmol) in a mixture of THF (0.10 ml) and ether (0.40 ml) was added to the reaction mixture and stirring was continued for 1 min at 0 °C. Treatments of the reaction mixture in the same manner as that described in a), followed by purification by column chromatography (SiO_2, AcOEt-hexane), gave pure **20** as a colorless caramel (42 mg, 55%) and a mixture of **21** and **18** (**21**:**18** ≈ 26:74 by ^1H NMR) as a pale yellow caramel [14 mg, 7% (**21**), 20% (**18**)].

d) Table I, Run 4. Butyllithium (0.13 ml, 1.5M hexane solution, 0.20 mmol) was added to a solution of **19** (80 mg, 0.20 mmol) in ether (2.5 ml) cooled at -20 °C under an argon atmosphere. After stirring for 10 min at 0 °C, a solution of **18** (44 mg, 0.10 mmol) in THF (0.50 ml) was added to the reaction mixture and stirring was continued for 1 min at 0 °C. The same treatments of the reaction mixture as those described in a), followed by separation by column chromatography (SiO_2, AcOEt-hexane), afforded pure **20** as a pale yellow caramel (50 mg, 66%) and a mixture of **21** and **18** (**21**:**18** = 31:69 by ^1H NMR) as a pale yellow caramel [14 mg, 8% (**21**), 18% (**18**)].

e) Table I, Run 5. Butyllithium (0.33 ml, 1.5M hexane solution, 0.50 mmol) was added to a solution of **19** (0.20 g, 0.50 mmol) in THF (4.0 ml) cooled at -60 °C under an argon atmosphere. After being stirred for 5 min at the same temperature, the reaction mixture was cooled at -78 °C. The cooled solution was added by using a cannula to a stirred suspension of anhydrous $CeCl_3$ (0.25 g, 1.0 mmol)[13] in THF (6.0 ml) cooled at -78 °C. After stirring for 10 min at -78 °C, a solution of **18** (0.11 g, 0.25 mmol) was added to the reaction mixture and stirring was continued for 1 h at -78 °C. The reaction mixture was worked up in a similar manner to that

described in a), giving pure **20** as a pale yellow caramel (11 mg, 6%) and pure **21** as a pale yellow solid (170 mg, 89%) after purification by column chromatography (SiO_2, AcOEt-hexane). The latter solid (**21**) was recrystallized from hexane to afford colorless crystals.

20: $[\alpha]_D^{20}$ -30.1° (c 1.20, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ -0.07 (6H, s, $SiMe_2$), 0.82 (9H, s, Si^tBu), 1.63 and 1.65 (3H, two s, C_2-Me), 2.19 and 2.27 (6H, two s, $ArMe_2$), 2.93 (3H, s, NMe), 3.21, 3.25, 3.36, and 3.40 (6H, four s, $CH_2O\underline{Me}$ x 2), 3.52 and 3.65 (3H, two s, CO_2Me), 3.9-5.2 (11H, C_3-H, C_5-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x 2, OH), 6.88 and 7.03 (1H, two s, ArH), 7.2-7.7 (10H, m, $CH_2\underline{Ph}$ x 2); IR (neat) 3470, 1740, 1700, 1455, 1220, 1150, 1105, 1030, 840, 780 cm^{-1}; MS m/z 698 (M^+-^{t}Bu), 516, 394, 361, 360, 320. *Anal.* Calcd. for $C_{41}H_{61}NO_{16}Si$: C, 65.14; H, 8.13; N, 1.85%. Found: C, 65.03; H, 8.05; N, 1.84%.

21: mp 84-86 °C and $[\alpha]_D^{20}$ -37.0° (c 1.50, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ -0.28 (6H, s, $SiMe_2$), 0.71 (9H, s, Si^tBu), 1.72 (3H, s, C_2-Me), 2.16 and 2.25 (6H, two s, $ArMe_2$), 2.92 (3H, s, NMe), 3.15 and 3.36 (6H, two s, $CH_2O\underline{Me}$ x 2), 3.65 (3H, s, CO_2Me), 4.1-5.4 (11H, m, C_3-H, C_5-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x 2, OH), 7.0-7.7 (11H, ArH, $CH_2\underline{Ph}$ x 2); IR (KBr) 3400, 1740, 1700, 1680, 1470, 1450, 1150, 1100, 1030, 840, 780, cm^{-1}; MS m/z 698 (M^+-^{t}Bu), 516, 394, 361, 360, 320. *Anal.* Calcd. for $C_{41}H_{61}NO_{10}Si$: C, 65.14; H, 8.13; N, 1.85%. Found: C, 65.13; H, 7.96; N, 1.79%.

(2R,3S,4R,5R)-(-)-5-(2,5-Dibenzyloxy-3,4-dimethylphenyl)-3-(*N*-methoxycarbonyl-*N*-methylamino)-2,4-bis(methoxymethyloxy)-1,5-hexanediol (22). Bu_4NF (2.1 ml, 1.0M THF solution, 2.1 mmol) was added to a solution of **20** (0.54 g, 0.71 mol) in THF (5.0 ml) at room temperature under an argon atmosphere. After stirring for 1 h at the same temperature, the reaction mixture was concentrated *in vacuo*. The residue was chromatographed (SiO_2, AcOEt-hexane) to give pure **21** as a colorless caramel (0.43 g, 94%), $[\alpha]_D^{20}$ -15.6° (0.750, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.62 (3H, s, C_5-Me), 2.19 (3H, s, ArMe), 2.26 and 2.30 (3H, two s, ArMe), 2.86 (3H, s, NMe), 3.29 (6H, s, $CH_2O\underline{Me}$ x 2), 3.39 and 3.66 (3H, two s, CO_2Me), 4.0-5.2 (12H, m, C_2-H, C_4-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x 2, OH x 2), 6.86 and 6.98 (1H, two s, ArH), 7.2-7.6 (10H, $CH_2\underline{Ph}$ x 2); IR (neat) 3480, 1690, 1450, 1215, 1150, 1100, 1020, 750, 700 cm^{-1}. *Anal.* Calcd. for $C_{35}H_{47}NO_{10}$: C, 65.51; H, 7.38; N, 2.18%. Found: C, 65.23; H, 7.41; N, 2.13%.

(2R,3R,4R,5S,6S)-2-(2,5-Dibenzyloxy-3,4-dimethylphenyl)-6-hydroxy-4-(*N*-methoxycarbonyl-*N*-methylamino)-3,5-bis(methoxymethyloxy)-2-methyltetrahydropyran (23) and Its (2R,3R,4R,5S,6R)-Isomer (24). SO_3Py (80 mg, 0.50 mmol) was added to a solution of **22** (0.15 g, 0.23 mmol), DMSO (0.55 g, 7.0 mmol), and triethylamine (0.36 g, 3.6 mmol) in THF (0.50 ml) at room temperature under an argon atmosphere. Further amounts of SO_3Py (20 mg, 0.13 mmol, and 20 mg, 0.13 mmol, total 0.67 mmol) were added to the reaction mixture after 0.5 and 1 hs' reactions, respectively, and stirring was continued for total 2 h at room temperature. The mixture was diluted with ether, washed successively with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by purification by column chromatography (SiO_2, AcOEt-$CHCl_3$), afforded a mixture of **23** and **24** as a colorless caramel (0.13 g, 88%). ^1H NMR (90 MHz, $CDCl_3$) δ 1.86 (3H, s, C_2-Me), 2.23 and 2.28 (6H, two s, $ArMe_2$), 2.90 and 2.95 (3H, two s, NMe), 3.32 and 3.35 (6H, two s, $CH_2O\underline{Me}$ x 2), 3.69 and 3.74 (3H, two s, CO_2Me), 4.3-5.3 (10H, m, C_6-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x 2, OH), 7.2-7.7 (11H, ArH, $CH_2\underline{Ph}$ x 2); IR (neat) 3420, 1705, 1690, 1500, 1460, 1415, 1380, 1335, 1230, 1040, 820, 740 cm^{-1}; MS m/z 639 (M^+), 531, 426; High-resolution MS (M^+) 639.3020 (639.3040 calcd. for $C_{35}H_{45}NO_{10}$).

(2R,3R,4R,5S,6R)-(+)-2-(2,5-Dibenzyloxy-3,4-dimethylphenyl)-4-(*N*-methoxycarbonyl-*N*-methylamino)-3,5,6-tris(methoxymethyloxy)-2-methyltetrahydropyran (25) and Its (2R,3R,4R,5S,6S)-(+)-Isomer (26). Chloromethyl methyl ether (0.32 g, 4.0

mmol) was added to a solution of the mixture of **23** and **24** (0.15 g, 0.23 mmol) and ethyldiisopropylamine (0.74 g, 5.7 mmol) in THF (1.0 ml) at room temperature under an argon atmosphere. The reaction mixture was heated at reflux for 3 h and cooled to ambient temperature. Another portion of chloromethyl methyl ether (0.32 g, 4.0 mmol, total 8.0 mmol) was added to the reaction mixture and heating under reflux was further continued for 9 h. After cooling to 0 °C, MeOH (1.0 ml) was added to the reaction mixture. After stirring for 5 min, the mixture was diluted with AcOEt. The ethyl acetate solution was washed successively with 1M HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed (SiO_2, AcOEt-hexane) to give pure **25** as a colorless caramel (0.14 g, 85%) and pure **26** as a colorless caramel (10 mg, 6%).

25: $[\alpha]_D^{20}$ +32.0° (c 5.20, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.80 and 1.82 (3H, two s, C_2-Me), 2.22 and 2.28 (6H, two s, $ArMe_2$), 2.92 and 2.98 (3H, two s, NMe), 3.19, 3.20, 3.25, 3.28, and 3.33 (9H, five s, $CH_2O\underline{Me}$ x 3), 3.69 and 3.74 (3H, two s, CO_2Me), 4.3-5.4 (11H, m, C_6-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x 3), 7.2-7.8 (11H, m, ArH, $CH_2\underline{Ph}$ x 2); IR (neat) 1740, 1705, 1490, 1450, 1370, 1320, 1220, 1100, 1020, 990, 920, 730, 700 cm^{-1}; MS m/z 683 (M^+), 531, 470, 440; High-resloution MS (M^+) 683.3329 (683.3303 calcd. for $C_{37}H_{49}NO_{11}$).

26: $[\alpha]_D^{20}$ +9.00° (c 3.00, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.85 (3H, s, C_2-Me), 2.22 and 2.28 (6H, two s, $ArMe_2$), 2.90 and 2.95 (3H, two s, NMe), 3.27, 3.30, 3.31, and 3.32 (9H, four s, $CH_2O\underline{Me}$ x 3), 3.70 and 3.75 (3H, two s, CO_2Me), 4.2-5.4 (11H, m, C_6-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x 3), 7.2-7.8 (11H, m, ArH, $CH_2\underline{Ph}$ x 2); IR (neat) 1740, 1700, 1690, 1450, 1370, 1320, 1220, 1100, 1020, 915, 700 cm^{-1}.

(2R,3R,4R,5S,6R)-(+)-2-(2,5-Dibenzyloxy-3,4-dimethylphenyl)-4-dimethylamino-3,5,6-tris(methoxymethyloxy)-2-methyltetrahydropyran (27). $LiAlH_4$ (50 mg, 1.3 mmol) was added to a solution of **25** (20 mg, 0.18 mmol) in ether (3.0 ml) at room temperature under an argon atmosphere. The reaction mixture was heated at reflux for 30 min and cooled to ambient temperature. After the excess hydride was decomposed by the addition of MeOH (0.50 ml), the mixture was diluted with brine and extracted with AcOEt. The combined extracts were washed with brine, dried (K_2CO_3), filtered, and concentrated *in vacuo*. The residual oil was chromatographed (SiO_2, AcOEt-hexane) to give pure **27** as a colorless caramel (0.11 g, 94%), $[\alpha]_D^{20}$ +23.8° (c 0.660, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.81 (3H, s, C_2-Me), 2.21 and 2.27 (6H, two s, $ArMe_2$), 2.47 (6H, s, NMe_2), 3.09 (1H, t, J = 9 Hz, C_4-H), 3.26, 3.31, and 3.39 (9H, three s, $CH_2O\underline{Me}$ x 3), 3.63 (1H, dd, J = 8 and 9 Hz, C_5-H), 3.75 (1H, d, J = 9 Hz, C_3-H), 4.4-5.1 (11H, m, C_6-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x 3), 7.3-7.7 (11H, m, ArH, $CH_2\underline{Ph}$ x 2); IR (neat) 1455, 1370, 1220, 1100, 1025, 920, 735, 700 cm^{-1}; MS m/z 639 (M^+), 608, 581, 418; High-resolution MS (M^+) 639.3404 (639.3404 calcd. for $C_{36}H_{49}NO_9$).

(2R,3R,4R,5S,6R)-2-(2,5-Dihydroxy-3,5-dimethylphenyl)-4-dimethylamino-3,5,6-tris(methoxymethyloxy)-2-methyltetrahydropyran (28). A mixture of **27** (93 mg, 0.15 mmol) and 10% Pd-C (30 mg) in EtOH (2.0 ml) was stirred for 3 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered and concentrated *in vacuo*, giving **28** as a pale yellow caramel (66 mg, 99%). ^1H NMR (90 MHz, $CDCl_3$) δ 1.67 (3H, s, C_2-Me), 2.16 (6H, s, $ArMe_2$), 2.54 (6H, s, NMe_2), 3.38, 3.41, and 3.43 (9H, three s, $CH_2O\underline{Me}$ x 3), 3.0-3.8 (3H, m, C_3-H, C_4-H, C_5-H), 4.4-5.0 (9H, m, C_6-H, $C\underline{H}_2OMe$ x 3, OH x 2), 7.12 (1H, s, ArH); IR (neat) 3450, 1440, 1250, 1160, 1035 cm^{-1}. Since this compound (**28**) was found to be unstable to air, it was directly used for the next step without further purification.

(2R,3S,4R,5R,6R)-(-)-4-Dimethylamino-6,9,10-trimethyl-2,6-epoxy-3,4,5,6-tetrahydro-2H-1-benzoxocine-3,5,8-triol (6). TMSBr (0.23 g, 1.5 mmol) was added to a

solution of **28** (50 mg, 0.11 mmol) in CH_2Cl_2 (0.50 ml) at room temperature under an argon atmosphere. The mixture was heated at 50 °C for 15 min, cooled to ambient temperature, and concentrated *in vacuo*. The residue was dissolved in MeOH (2.0 ml) and the methanol solution was concentrated *in vacuo*. Successive addition of MeOH (2.0 ml) to the residue and concentration of the methanolic solution *in vacuo* were repeated two more times. Then, the residue was diluted with a mixture of MeOH (2.0 ml) and toluene (2.0 ml), and the solution was concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, triethylamine-EtOH-AcOEt) afforded pure **6** as a pale yellow amorphous powder (28 mg, 82%, 2 steps from **27**), $[\alpha]_D^{20}$ -35.6° (c 0.500, MeOH). ^1H NMR (400 MHz, $CDCl_3$-D_2O) δ 1.63 (3H, s, C_6-Me), 2.17 and 2.18 (6H, two s, C_9-Me, C_{10}-Me), 2.18 (1H, t, J = 10.3 Hz, C_4-H), 2.44 (6H, s, NMe_2), 3.47 (1H, d, J = 10.3 Hz, C_5-H), 3.98 (1H, dd, J = 3.8 and 10.3 Hz, C_3-H), 5.53 (1H, d, J = 3.8 Hz, C_2-H), 6.46 (1H, s, C_7-H); ^1H NMR (400 MHz, CD_3COCD_3-D_2O) δ 1.51 (3H, s, C_6-Me), 2.10 and 2.11 (6H, two s, C_9-Me, C_{10}-Me), 2.31 (1H, t, J = 10.3 Hz, C_4-H), 2.41 (6H, s, NMe_2), 3.47 (1H, d, J = 10.3 Hz, C_5-H), 3.92 (1H, dd, J = 3.5 and 10.3 Hz, C_3-H), 5.41 (1H, d, J = 3.5 Hz, C_2-H), 6.49 (1H, s, C_7-H); IR (KBr) 3450, 1450, 1425, 1230, 1085, 1050, cm^{-1}; MS m/z 310 (M^+H), 205; High-resolution MS (M^+) 310.1634 (310.1653 calcd. for $C_{16}H_{24}NO_5$).

(2R,3S,4R,5R,6R)-(-)-2,5-Diacetoxy-4-dimethylamino-6,9,10-trimethyl-2,6-epoxy-3,4,5,6-tetrahydro-2H-1-benzoxocin-10-ol (29). A solution of **6** (22 mg, 70 μmol) and Ac_2O (0.22 g, 2.2 mmol) in MeOH (0.50 ml) was heated at 40 °C for 3 h, cooled to ambient temperature, and concentrated *in vacuo*. The residue was diluted with toluene and the toluene solution was concentrated *in vacuo*. The residual oil was chromatographed (SiO_2, AcOEt-$CHCl_3$) to give pure **29** as a colorless solid (26 mg, 93%). Recrystallization from $CHCl_3$-hexane gave an analytical sample of **29** as colorless crystals, mp 216-218 °C and $[\alpha]_D^{20}$ -57.6° (c 0.500, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (3H, s, C_6-Me), 2.09 and 2.10 (6H, two s, COMe x 2), 2.16 and 2.18 (6H, two s, C_9-Me, C_{10}-Me), 2.67 (1H, t, J = 10.5 Hz, C_4-H), 4.36 (1H, s, OH), 5.05 (1H, d, J = 10.5 Hz, C_5-H), 5.11 (1H, dd, J = 4.2 and 10.5 Hz, C_3-H), 5.67 (1H, d, J = 4.2 Hz, C_2-H), 6.36 (1H, s, C_7-H); IR (KBr) 3450, 1750, 1725, 1230, 1050 cm^{-1}; MS m/z 393 (M^+), 333, 205. *Anal.* Calcd. for $C_{20}H_{27}NO_7$: C, 61.06; H, 6.92; N, 3.56%. Found: C, 61.29; H, 7.20; N, 3.47%.

(2S,3S,4R,5S)-(+)-5-(2,5-Dibenzyloxy-3,4-dimethylphenyl)-3-(*N*-methoxycarbonyl-*N*-methylamino)-2,4-bis(methoxymethyloxy)-1,5-hexanediol (30). Desilylation of **21** (0.30 g, 0.39 mmol) in the same manner as that described for **20** gave crude **30** after concentration of the reaction mixture *in vacuo*. This was purified by column chromatography (SiO_2, AcOEt-hexane) to afford pure **30** as a colorless caramel (0.24 g, 96%), $[\alpha]_D^{20}$ +0.20° (c 1.80, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.56 and 1.64 (3H, two s, C_5-Me), 2.20 and 2.27 (6H, s, $ArMe_2$), 2.90 and 2.92 (3H, two s, NMe), 3.22 (6H, s, $CH_2O\underline{Me}$ x 2), 3.3-3.6 (2H, m, C_1-H_2), 3.68 (3H, s, CO_2Me), 3.9-4.5 (7H, m, $C\underline{H}_2Ph$ x 2, C_2-H, C_3-H, C_4-H), 4.5-5.1 (6H, m, $C\underline{H}_2OMe$ x 2, OH x 2), 6.94 and 6.99 (1H, two s, ArH), 7.2-7.7 (10H, m, $CH_2\underline{Ph}$ x 2); IR (neat) 3470, 2950, 1680, 1460, 1100, 1020, 740 cm^{-1}. *Anal.* Calcd. for $C_{35}H_{47}NO_{10}$: C, 65.51; H, 7.38; N, 2.18%. Found: C, 65.31; H, 7.31; N, 2.10%.

(2S,3R,4R,5S,6RS)-2-(2,5-Dibenzyloxy-3,4-dimethylphenyl)-6-hydroxy-4-(*N*-methoxycarbonyl-*N*-methylamino)-3,5-bis(methoxymethyloxy)-2-methyltetrahydropyran. The same oxidation of **30** (0.22 g, 0.34 mmol) as that described for **22** gave the crude product after concentration of the combined ethereal extracts *in vacuo*. This was chromatographed (SiO_2, AcOEt-$ChCl_3$) to give an epimeric mixture of the hemiacetals as a colorless caramel (0.19 g, 87%). ^1H NMR (90 MHz, $CDCl_3$) δ 1.65 (3H, s, C_2-Me), 2.21 and 2.28 (6H, two s, $ArMe_2$), 2.60 (3H, NMe), 2.95 and 3.24 (6H, two s, $CH_2O\underline{Me}$ x 2), 3.66 (3H, s, CO_2Me), 3.8-5.2 (11H, m, C_3-H, C_5-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x

2, OH), 6.79 (1H, s, ArH), 7.2-7.7 (10H, m, $CH_2\underline{Ph}$ x 2); IR (neat) 3450, 1705, 1690, 1490, 1460, 1415, 1380, 1325, 1230, 1110, 1035 cm^{-1}; MS m/z 639 (M^+), 531, 245; High-resolution MS (M^+) 639.3043 (639.3041 calcd. for $C_{35}H_{45}NO_{10}$).

(2S,3R,4R,5S,6R)-(+)-2-(2,5-Dibenzyloxy-3,4-dimethylphenyl)-4-(*N*-methoxycarbonyl-*N*-methylamino)-3,5,6-tris(methoxymethyloxy)-2-methyltetrahydropyran (31) and Its (2S,3R,4R,5S,6S)-(-)-Isomer (32). Methoxymethylation of the epimeric mixture of the hemiacetals (0.17 g, 0.26 mmol) in a similar manner to that described for the mixture of **23** and **24** gave a crude mixture of **31** and **32** after concentration of the combined ethyl acetate extracts *in vacuo*. This was chromatographed (SiO_2, AcOEt-hexane) to afford pure **31** as a colorless caramel (0.16 g, 74%) and pure **32** as a colorless caramel (20 mg, 10%).

31: $[\alpha]_D^{20}$ +11.6° (c 2.65, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.67 (3H, s, C_2-Me), 2.22 and 2.31 (6H, two s, $ArMe_2$), 2.56 (3H, s, NMe), 2.93, 2.94, 3.19, 3.20, 3.36, and 3.38 (9H, six s, $CH_2O\underline{Me}$ x 3), 3.65 and 3.68 (3H two s, CO_2Me), 3.1-4.0 (3H, m, C_3-H, C_4-H, C_5-H), 4.2-5.4 (11H, m, C_6-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x 3), 6.82 (1H, s, ArH), 7.2-7.8 (10H, m, $CH_2\underline{Ph}$ x 2); IR (neat) 1700, 1450, 1370, 1320, 1220, 1150, 1100, 1020, 990, 920, 730 cm^{-1}; MS m/z 683 (M^+), 561, 531, 440; High-resloution MS (M^+) 683.3331 (683.3303 calcd. for $C_{37}H_{49}NO_{11}$).

32: $[\alpha]_D^{20}$ -69.1° (c 0.230, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.78 (3H, s, C_2-Me), 2.21 and 2.29 (6H, two s, $ArMe_2$), 2.67 and 2.68 (3H, two s, NMe), 2.94, 2.98, 3.17, 3.19, 3.38, and 3.40 (9H, six s, $CH_2O\underline{Me}$ x 3), 3.67 and 3.68 (3H, two s, CO_2Me), 3.0-4.0 (3H, m, C_3-H, C_4-H, C_5-H), 4.0-5.2 (11H, m, C_6-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x 3), 6.81 (1H, s, ArH), 7.2-7.7 (10H, m, $CH_2\underline{Ph}$ x 2); IR (neat) 1700, 1480, 1450, 1370, 1320, 1220, 1120, 920, 740, 700 cm^{-1}; MS m/z 683 (M^+), 561, 531, 440; High-resolution MS (M^+) 683.3300 (683.3301 calcd. for $C_{37}H_{49}NO_{11}$).

(2S,3R,4R,5S,6R)-(+)-2-(2,5-Dibenzyloxy-3,4-dimethylphenyl)-4-dimethylamino-3,5,6-tris(methoxymethyloxy)-2-methyltetrahydropyran (33). The same reduction of **31** (0.32 g, 0.47 mmol) as that described for **25** afforded crude **33** after concentration of the combined ethyl acetate extracts *in vacuo*. This was purified by column chromatography (SiO_2, AcOEt-hexane) to give pure **33** as a colorless caramel (0.29 g 95%), $[\alpha]_D^{20}$ +10.3° (c 0.800, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.62 (3H, s, C_2-Me), 2.20 and 2.29 (6H, two s, $ArMe_2$), 2.33 (6H, s, NMe_2), 2.6-3.5 (3H, m, C_3-H, C_4-H, C_5-H), 2.81, 3.36, and 3.38 (9H, three s, $CH_2O\underline{Me}$ x 3), 3.9-5.2 (11H, m, C_6-H, $C\underline{H}_2Ph$ x 2, $C\underline{H}_2OMe$ x 3), 6.83 (1H, s, ArH), 7.2-7.7 (10H, m, $CH_2\underline{Ph}$ x 2); IR (neat) 1455, 1370, 1220, 1155, 1100, 1025, 920, 735, 700 cm^{-1}; MS m/z 639 (M^+), 608, 581, 418; High-resolution MS (M^+) 639.3422 (639.3404 calcd. for $C_{36}H_{49}NO_9$).

(2S,3R,4R,5S,6R)-2-(2,5-Dihydroxy-3,4-dimethylphenyl)-4-dimethylamino-3,5,6-tris(methoxymethyloxy)-2-methyltetrahydropyran (34). Hydrogenolysis of **33** (94 mg, 0.15 mmol) in the same manner as that described for **27** afforded **34** (86 mg, 100%) after concentration of filtrate *in vacuo*. ^1H NMR (90 MHz, $CDCl_3$) δ 1.67 (3H, s, C_2-Me), 2.14 and 2.17 (6H, two s, $ArMe_2$), 2.57 (6H, s, NMe_2), 2.8-3.8 (3H, m, C_3-H, C_4-H, C_5-H), 3.14, 3.42, and 3.50 (9H, three s, $CH_2O\underline{Me}$ x 3), 4.0-5.1 (7H, m, C_6-H, $C\underline{H}_2OMe$ x 3), 6.56 (1H, s, ArH); IR (neat) 3400, 1450, 1220, 1155, 1080, 1020, 980, 920 cm^{-1}. Since, this compound was found to be unstable to air, it was directly used for the next step without further purification.

(2S,3S,4R,5R,6S)-(-)-4-Dimethylamino-3,5-dihydroxy-6,9,10-trimethyl-2,6-epoxy-3,4,5,6-tetrahydro-2H-1-benzoxocine-3,5,8-triol (35). The same treatments of **34** (54 mg, 0.12 mmol) with TMSBr as those described for **28** gave crude **35** after concentration of the solution in a mixture of MeOH and toluene *in vacuo*. Column chromatography (SiO_2, triethylyamine-EtOH-AcOEt) of this sample afforded pure **35** as a pale yellow caramel (30 mg, 83%, 2 steps, from **33**), $[\alpha]_D^{20}$ -50.1° (c 1.40, MeOH). ^1H NMR (400 MHz, CD_3COCD_3-D_2O) δ 1.45 (3H, s, C_6-Me), 2.07 and 2.10 (6H,

two s, C_9-Me, C_{10}-Me), 2.33 (6H, s, NMe_2), 2.56 (1H, dd, J = 8.1 and 11.3 Hz, C_4-H), 3.59 (1H, dd, J = 3.1 and 11.3 Hz, C_3-H), 3.91 (1H, d, J = 8.1 Hz, C_5-H), 5.33 (1H, d, J = 3.1 Hz, C_2-H), 6.47 (1H, s, C_7-H); IR (neat) 3400, 1440, 1010, 980, 855, 790 cm^{-1}; MS m/z 310 (M^+H), 205, 189; High-resolution MS (M^+H) 310.1629 (310.1653 calcd. for $C_{16}H_{24}NO_5$).

(2S,3S,4R,5R,6S)-(-)-3,5-Diacetoxy-4-dimethylamino-6,9,10-trimethyl-2,6-epoxy-3,4,5,6-tetrahydro-2H-1-benzoxocin-8-ol (36). Acetylation of **35** (28 mg, 90 μmol) in the same manner as that described for **6** gave crude **36** after concentration of the toluene solution *in vacuo*. This was purified by column chromatography (SiO_2, AcOEt-$CHCl_3$) to give pure **36** as a colorless solid (32 mg, 88%). Recrystallization from ether-hexane afforded an analytical sample of **36** as colorless crystals, mp 174-175 °C and $[\alpha]_D^{20}$ -69.1° (c 0.540, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, s, C_6-Me), 2.10 and 2.11 (6H, two s, C_9-Me, C_{10}-Me), 2.16 and 2.18 (12H, two s, COMe x 2, NMe_2), 3.01 (1H, dd, J = 7.7 and 11.7 Hz, C_4-H), 4.57 (1H, s, OH), 5.05 (1H, dd, J = 3.1 and 11.7 Hz, C_3-H), 5.24 (1H, d, J = 7.7 Hz, C_5-H), 5.43 (1H, d, J = 3.1 Hz, C_2-H), 6.48 (1H, s, C_7-H); IR (KBr) 1760, 1750, 1225, 1010 cm^{-1}; MS m/z 393 (M^+), 333, 289. *Anal.* Calcd. for $C_{20}H_{27}NO_7$: C, 61.06; H, 6.92; N, 3.56%. Found: C, 61.02; H, 7.04; N, 3.46%.

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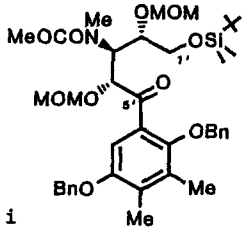

i

15) Stereochemistries of the C$_{1'}$-positions of **23**, **24**, **25**, and **26** were assigned based on the ^{1}H NMR spectrum of **27**, obtainable from **23** by way of **25**. The coupling constants of the protons of the C-glycoside moiety involved in **27** are follows. ^{1}H NMR (90 MHz, CDCl$_3$) $J_{1'2'}$ = 8 Hz, $J_{2'3'} = J_{3'4'}$ = 9 Hz.

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