Tetrahedron Vol. 44, No. 18, pp. 5713 to 5725, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

SYNTHETIC STUDIES ON NOGALAMYCIN CONGENERS [2][1,2] CHIRAL SYNTHESIS OF THE CDEF-RING SYSTEM OF NOGALAMYCIN

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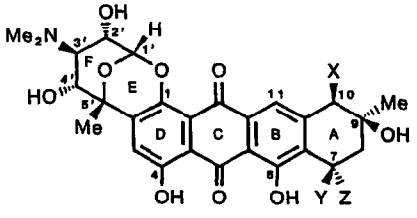
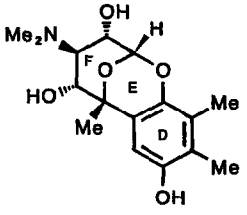
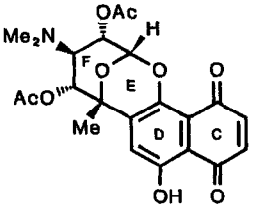
(*Received in Japan* 2 *May* 1988)

Abstract: The chiral synthesis of the (+)-naphthoquinone (**4**), the CDEF-ring system of nogalamycin congeners, has been accomplished following the synthetic scheme developed for the model (-)-DEF-ring system (**3**) in the preceding paper. This synthesis features (1) stereoselective construction of the $C_{5'}$-asymmetric center by introducing the naphthalene moiety into the (-)-methyl ketone (**5**), the glycoside part, (2) regioselective oxidation of the 1,4,5,8-tetramethoxynaphthalene moiety with cerium(III) ammonium nitrate , and (3) efficient formation of bicyclic acetal system.

Nogalamycin (**1**) and its congeners are notable members of the anthracycline family because of their unique structures and prominent antitumor activity. Especially, 7-con-*O*-methylnogarol (**2**), a semisynthetic derivative of **1**, has been reported to exhibit more promising anticancer activity than the parent compounds (**1**).[2]



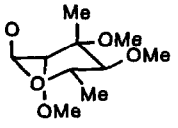




3

4

X = CO_2Me, Y = H, Z =



1

X = H, Y = OMe, Z = H 2

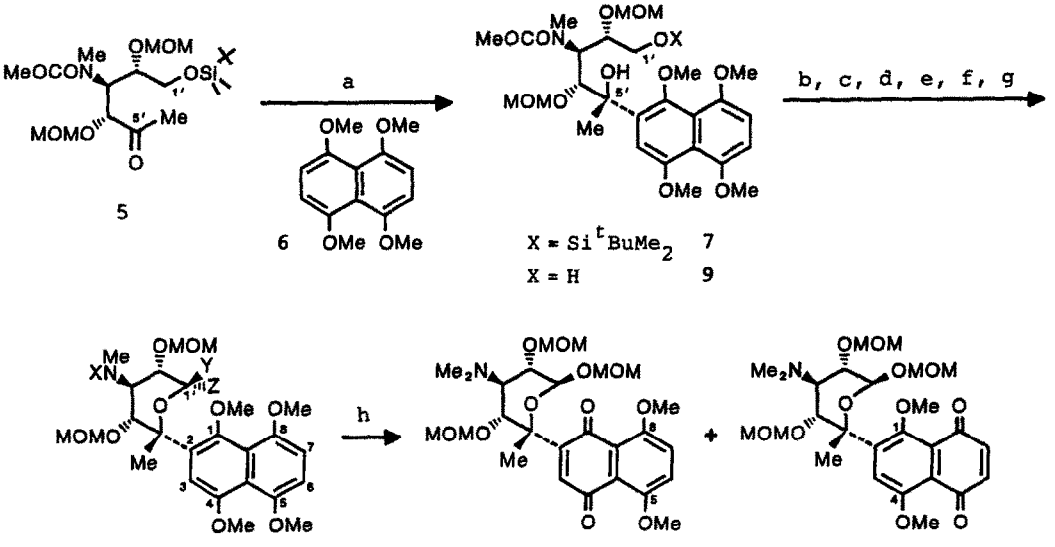
As described in the preceding paper,[1a,2] we have already achieved the chiral synthesis of the (-)-bicyclic acetal (**3**), the DEF-ring system of nogalamycin congeners, from readily available (-)-D-arabinose. This model study explored an efficient synthetic scheme to construct the DEF-ring system stereoselectively in

an optically active form. Based on the results accumulated in this model study, we next examined the stereocontrolled synthesis of the (+)-naphthoquinone (**4**), the CDEF-ring system of nogalamycin congeners which had been supposed to be the key intermediate of our synthetic plan.[2] In the second part of this series of papers, we wish to disclose full details of the stereoselective synthesis of **4** in an optically active form.[1b]

Results and Discussion.

Stereocontrolled Synthesis of the (-)-Dimethylamine (15), the Substrate for Regioselective Oxidation with Cerium(III) Ammonium Nitrate (CAN). For the synthesis of **4** according to the previously explored synthetic scheme, introduction of a suitably protected 1,4,5,8-tetraalkoxynaphthalene moiety into the (-)-methyl ketone (**5**) was required to construct the bicyclic acetal system at the later stage of the synthesis. After several preliminary experiments employing various types of tetraalkoxynaphthalene derivatives,[3,4] it was finally found that 1,4,5,8-tetramethoxynaphthalene (**6**) prepared from 1,4-dimethoxybenzene by way of 5,8-dihydroxy-1,2,3,4-tetrahydronaphthalene-1,4-dione,[5,6] was only usable for this purpose. As shown in **Scheme 1**, addition of the 2-lithio-1,4,5,8-tetramethoxy-

Scheme 1



X = CO_2Me, Y = Z = O **10**
X = CO_2Me, Y = OH, Z = H **11**
X = CO_2Me, Y = H, Z = OH **12**
X = CO_2Me, Y = OMOM, Z = H **13**
X = CO_2Me, Y = H, Z = OMOM **14**
X = Me, Y = OMOM, Z = H **15**
X = Me, Y = H, Z = OMOM **16**

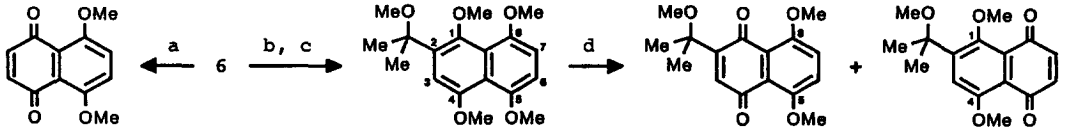
a) **6**, ^{n}BuLi, THF, 30 min, 57% (**7**, from **5**), 4% (**8**, from **5**), 10% (**5**, from **5**) b) $^n Bu_4NF$, THF, rt, 1 h, 98% c) 1) $(COCl)_2$-DMSO, CH_2Cl_2, -60 °C, 20 min 2) Et_3N, -60 → 0 °C, 30 min, 95% d) DIBAL, PhMe, -78 °C, 20 min e) K_2CO_3, MeOH, reflux, 30 min, 82% (**11**, 2 steps) f) MOMCl, $^i Pr_2NEt$, THF, reflux, 3 h, 91% (**13**) g) $LiAlH_4$, Et_2O, reflux, 1 h, 95% h) CAN, H_2O-EtOH, -78 → -10 °C, 2.5 h, 74% (**21**), 16% (**22**).

naphthalene generated from **6** and butyllithium, to **5** took place in a highly stereoselective manner in tetrahydrofuran, giving the desired (-)-alcohol (**7**), $[\alpha]_D^{20}$ -35.5° (c 1.00, $CHCl_3$), and its $C_{5'}$-epimer (**8**) (nogalamycin numbering) in 14:1 ratio and in a good combined yield. Although the reaction was carried out in tetrahydrofuran, recovery of a small amount of **5** was only observed in contrast to the model study reported in the preceding paper.[2] Stereochemistries at the $C_{5'}$-positions of the separable isomers (**7** and **8**) could not be rigorously determined at this stage. However, the major alcohol (**7**) was assumed to have the desired stereochemistry by taking into account the previous result which had clearly disclosed that the addition of an aryllithium to **5** proceeds under the usual chelation control.[2]

After desilylation of **7**, oxidation of the resulting diol (**9**) followed by reduction of the formed lactone (**10**),[7] afforded the hemiacetals (**11** and **12**) as an epimeric mixture at the $C_{1'}$-position (**11**:**12** = 4:1). This was equilibrated under the basic conditions, resulting in exclusive formation of the thermodynamically more stable β-hemiacetal (**11**). After protecting the hemiacetal functionality in a form of methoxymethyl ether, the major β-acetal (**13**) was subjected to reduction to produce the (-)-dimethylamine (**15**), mp 109-110 °C and $[\alpha]_{435}^{20}$ -10.3° (c 1.08, $CHCl_3$). Similarly, the minor α-hemiacetal (**12**) could be derived to the epimeric dimethylamine (**16**) by way of the α-acetal (**14**). Stereochemistries of the $C_{1'}$-positions of **11**-**16** were assigned based on the ^1H NMR spectral data of **15** and **16**.[8]

Regioselective Oxidation of the 1,4,5,8-Tertramethoxynaphthalene (15) with CAN. The preliminary experiments obviously suggested that, for constructing bicyclic acetal structure of **4**, the C_1- and C_4-methoxy groups of the 2-alkyl-1,4,5,8-tetramethoxynaphthalene moiety of 15 should be regioselectively cleaved prior to the intramolecular acetalization.[4] As shown in **Scheme 2**, the model studies examined on some tetramethoxynaphthalenes (**6** and **18**) revealed that oxidative cleavage

Scheme 2



17 18 19 20

a) CAN, H_2O-MeCN, 0 °C, 40 min, 97% b) 1) ^nBuLi, THF, 0 °C, 30 min 2) Me_2CO, 0 °C, 1 min, 62% c) MeI, NaH, DMF, 40 °C, 1 h, 96% d) CAN, H_2O-MeCN, 0 °C, 15 min, 86% (**19**), 11% (**20**).

of the aryl methyl ethers by CAN[9] was quite suitable for this purpose. Thus, the treatments of 1,4,5,8-tetramethoxynaphthalene (**6**) with CAN at 0 °C was found to afford 5,8-dimethoxy-1,4-naphthoquinone (**17**) as a sole product in an almost quantitative yield. On the other hand, the oxidation of 2-(1-methoxy-1-methylethyl)-1,4,5,8-tetramethoxynaphthalene (**18**) prepared from **6**,[3] with CAN at 0 °C underwent regioselectively, affording a mixture of the regioisomeric naphthoquinones (**19** and **20**) in 8:1 ratio and in a high combined yield. Structures of these regioisomers (**19** and **20**) were determined based on their ^1H NMR spectra. As summarized in **Table I**, the signals due to the two aryl methyl ethers of **19** appeared as overlapped singlets at δ 3.98. In contrast, probably due to influence of the 1-methoxy-1-methylethyl group, two singlets assignable to two aryl methyl ethers were observed

Table I. ^{1}H NMR Spectral Data of **15**, **18-22**

Compound	Chemical Shifts (δ: ppm, in $CDCl_3$)			
	C_1- and C_4-OMe	C_5- and C_8-OMe	C_3-H	C_6- and C_7-H
18	(3.71, 3.93, 3.96, 3.96)[a]		7.16	6.86
19	-	3.98, 3.98	6.96	7.33
20	3.82, 4.02	-	7.65	6.82
15	(3.74, 3.87, 3.93, 3.95)[a]		7.73	6.83
21	-	3.92, 3.96	7.27	7.27
22	3.85, 4.01	-	8.08	6.80

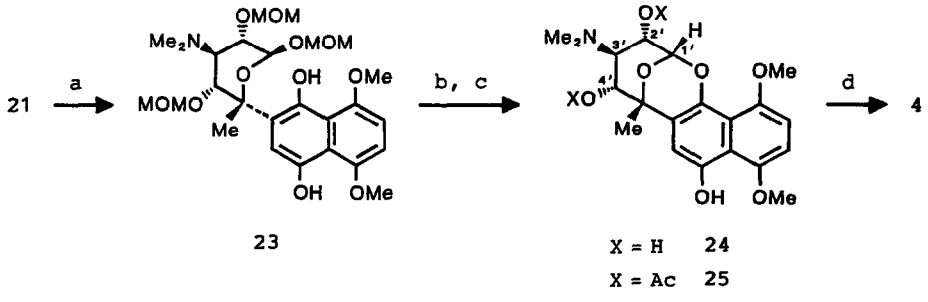
a) These four singlets could not be rigorously assigned.

at δ 3.82 and 4.03 in the NMR spectrum of **20**. It is noteworthy that the oxidation took place preferentially at the more sterically hindered C_1- and C_4-positions of the 2-alkyl-1,4,5,8-tetramethoxynaphthalene ring rather than at the less hindered C_5- and C_8-positions. This remarkable regioselectivity may be accounted for by the electron density of naphthalene ring affected by the electrondonating 1-methoxy-1-methylethyl group.

As expected from the results of the model study, when **15** was oxidized with CAN at a lower temperature (-78 → 0 °C),[10] the desired (+)-naphthoquinone (**21**), mp 147-148 °C and $[\alpha]_D^{20}$ +14.3° (c 0.280, $CHCl_3$), was found to be produced as a major product along with the minor regioisomer (**22**) in 5:1 ratio and in a high combined yield. These regioisomers (**21** and **22**) could be readily separated by column chromatography. Structure assignments of **21** and **22** were achieved by comparing the ^{1}H NMR spectra of these compounds with those of **19** and **20** as shown in **Table I.**

Synthesis of the (+)-CDEF-Ring System (4). After reduction of the 1,4-naphthoquinone (**21**) with sodium hydrosulfite, brief exposure of the formed unstable hydroquinone (**23**) to trimethylsilyl bromide effected simultaneous cleavage of the three methoxymethyl ethers and intramolecular acetalization. Selective acetylation of the $C_{2'}$- and $C_{4'}$-hydroxyl groups of the resulting bicyclic acetal (**24**) readily gave the (+)-diacetate (**25**), mp 182-183 °C and $[\alpha]_D^{20}$ +79.7° (c 0.310, $CHCl_3$). The protons involved in the C-glycoside moiety of **25** showed similar

Scheme 3



a) $Na_2S_2O_4$, H_2O-$CHCl_3$, rt b) 1) TMSBr, CH_2Cl_2, reflux, 10 min 2) MeOH, -78 °C → rt c) KOAc, Ac_2O, MeOH, rt, 1 h, 78% (3 steps) d) 1) BBr_3, CH_2Cl_2, 0 °C, 30 min 2) Et_3N, MeOH, -78 °C → rt 3) CAN, H_2O-EtOH, -78 °C, 10 min, 71%.

chemical shifts and coupling constants to those observed for the protons of the F-ring of the 2',4'-diacetate of **3**.[11] Thus, the structure of **25** was definitely established as depicted in **Scheme 3**. Cleavage of the two methyl ethers of **25** with boron tribromide followed by quenching with triethylamine gave rise to the demethylated product in a form of the triethylamine complex. This was further subjected to oxidation with CAN,[12] furnishing the (+)-naphthoquinone (**4**), mp 153-155 °C and $[\alpha]_D^{20}$ +420° (0.050, $CHCl_3$).

Conclusion

As mentioned above, the efficient chiral synthesis of **4** was acheived following the synthetic scheme previously explored for **3**. With **4** in hand, the regioselective Diels-Alder reaction employing **4** as a dienophile, the key step of our synthetic plan, was next examined to construct the 11-deoxyanthracylinone skeletons of nogalamycin congeners. This is the subject of the accompanying paper.[13]

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 measurement were performed with a JACSO A-200 IR spectrometer. ^1H 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), cerium(III) ammonium nitrate (CAN), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), diisobutylaluminumhydride (DIBAL), N,N,-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethanol (EtOH), ethyl acetate (AcOEt), methanol (MeOH), tetrabutylammonium fluoride (Bu_4NF), tetrahydrofuran (THF), Trimethylsilyl bromide (TMSBr).

5,8-Dihydroxy-1,2,3,4-tetrahydronaphthalene-1,4-dione. The Friedel-Crafts reaction of 1,4-dimethoxybenzene with 2,3-dichloromaleic anhydride in fused NaCl-$AlCl_3$,[5] followed by reduction of crude 2,3-dichloro-5,8-dihydroxy-1,4-naphthoquinone with $SnCl_2$ under acidic condition (30%, 2 steps),[6] gave the product as yellow crystals, mp 145-148 °C (recrystallized from EtOH) [lit. mp 152 °C[6a]]. ^1H NMR (90 MHz, $CDCl_3$) δ 2.06 (4H, s, C_2-H_2, C_3-H_2), 4.88 (2H, s, OH x 2), 8.01 (2H, s, C_6-H, C_7-H).

1,4,5,8-Tetramethoxynaphthalene (6). A suspension of NaH (12 g, 50% dispersion in oil, 0.25 mol) was added to a stirred solution of 5,8-dihydroxy-1,2,3,4-tetrahydronaphthalene-1,4-dione (6.0 g, 31 mmol) and dimethyl sulfate (32 g, 0.25 mol) in DMF (300 ml) cooled at -35 °C under an argon atmosphere. The reaction mixture was heated at 40 °C for 1 h. After cooling to ambient temperature, another portion of dimethyl sulfate (13 g, 0.11 mol, total 0.36 mol) was added to the reaction mixture and stirring was further continued for 30 min. KOH (30 g) and water (2.5 l) were successively added to the reaction mixture cooled in an ice bath. The precipitate was collected by filtration, washed with water, and dried over P_2O_5 *in vacuo*. The crude product was chromatographed (SiO_2, AcOEt-$CHCl_3$) to

give crude **6** as a yellow solid. Recrystallization from EtOH afforded pure **6** as colorless crystals (6.1 g, 79%), 167-169 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.90 (12H, s, OMe x 4), 6.84 (4H, s, ArH_4); IR (KBr) 1600, 1380, 1270, 1075, 1050, 795 cm^{-1}; MS m/z 248 (M^+), 233, 205, 202, 190. *Anal.* Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%. Found: C, 67.87; H, 6.54%.

(2R,3R,4S,5S)-(-)-6-(*tert*-Butyldimethylsilyloxy)-4-(*N*-methoxycarbonyl-*N*-methylamino)-3,5-bis(methoxymethyloxy)-2-(1,4,5,8-tetramethoxy-2-naphthalenyl)-2-hexanol (7) and Its (2S,3R,4S,5S)-(-)-Isomer (8). Butyllithium (4.6 ml, 1.5M hexane solution, 7.0 mmol) was added to a solution of **6** (1.7 g, 7.0 mmol) in THF (180 ml) in an ice bath under an argon atmosphere. After stirring for 20 min, a solution of **5** (2.1 g, 4.9 mmol) in THF (10 ml) was added to the reaction mixture and stirring was further continued for 3 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with toluene and the combined extracts were washed with brine and dried (MgSO4). Filtration and concentration *in vacuo* gave a crude mixture of **5-8**. This was triturated with ether and the solid was colleced by filtration. The solid was recrystallized from dioxane to give pure **6** (0.73 g, 43% from **6**) as pale yellow crystals. Mother liquor from the trituration was concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, AcOEt-hexane and AcOEt-$CHCl_3$), affording **5** as a pale yellow caramel (0.21 g, 10% from **5**), pure **7** as a pale yellow caramel (1.9 g, 57% from **5**), and pure **8** as a pale yellow caramel (0.13 g, 4% from **5**).

7: $[\alpha]_D^{20}$ -35.5° (c 1.00, $CHCl_3$). ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.03 and 0.05 (6H, two s, $SiMe_2$), 0.86 and 0.90 (9H, two s, Si^tBu), 1.74 and 1.76 (3H, two s, C_2-Me), 2.9-5.0 (10H, C_3-H, C_4-H, C_5-H, C_6-H_2, C$\underline{H}_2$OMe x 2, OH), 3.00 and 3.02 (3H, two s, NMe), 3.10, 3.29, 3.33, 3.37, 3.55, 3.64, 3.70, 3.81, 3.84, 3.86, and 3.89 (21H, eleven s, $CH_2O\underline{Me}$ x 2, ArOMe x 4, CO_2Me), 6.84 (2H, s, $C_{6'}$-H, $C_{7'}$-H), 7.13 and 7.25 (1H, two s, $C_{3'}$-H); IR (neat) 3450, 1690, 1600 cm^{-1}; MS m/z 685 (M^+), 653, 628. *Anal.* Calcd. for $C_{33}H_{55}NO_{12}Si$: C, 57.79; H, 8.08; N, 2.04%. Found: C, 57.76; H, 7.93; N, 1.99%.

8: $[\alpha]_D^{20}$ -105° (c 1.15 $CHCl_3$). ^{1}H NMR (90 MHz, $CDCl_3$) δ -0.31, -0.25. and 0.06 (6H, three s, $SiMe_2$), 0.68 and 0.91 (9H, two s, Si^tBu), 1.65 and 1.69 (3H, two s, C_2-Me), 3.00 and 3.04 (3H, two s, NMe), 3.1-5.0 (10H, m, C_3-H, C_4-H, C_5-H, C_6-H_2, C$\underline{H}_2$OMe x 2, OH), 3.42, 3.71, 3.75, 3.90, and 3.98 (21H, five s, $CH_2O\underline{Me}$ x 2, ArOMe x 4, CO_2Me), 6.80 and 6.84 (2H, two s, $C_{6'}$-H, $C_{7'}$-H), 7.07 and 7.31 (1H, two s, $C_{3'}$-H); IR (neat) 3450, 1690, 1600 cm^{-1}; MS m/z 685 (M^+) 653, 628, 394. *Anal.* Calcd. for $C_{33}H_{55}NO_{12}Si$: C, 57.79; H, 8.08; N, 2.04%. Found: C, 57.51; H, 7.85; N, 1.91%.

(2S,3S,4R,5R)-(-)-3-(*N*-Methoxycarbonyl-*N*-methylamino)-2,4-bis(methoxymethyloxy)-5-(1,4,5,8-tetramethoxy-2-naphthalenyl)-1,5-hexanediol (9). Bu_4NF (5.0 ml, 1.0M THF solution, 5.0 mmol) was added to a solution of **7** (1.5 g, 2.2 mmol) in THF (50 ml) at room temperature under an argon atmosphere. After stirring for 1 h, the reaction mixture was concentrated *in vacuo*. Column chromatography (SiO_2, AcOEt) of the residue gave pure **9** as a colorless caramel (1.2 g, 98%), $[\alpha]_D^{20}$ -31.4° (c 1.25, $CHCl_3$). ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.73 (3H, s, C_5-Me), 2.96 (3H, s, NMe), 3.2-4.1 (28H, m, C_1-H_2, C_2-H, C_3-H, C_4-H, OMe x 7, OH x 2), 4.4-5.0 (4H, m, C$\underline{H}_2$OMe x 2), 6.81 (2H, s, $C_{6'}$-H, $C_{7'}$-H), 7.05 and 7.22 (1H, two s, $C_{3'}$-H); IR (neat) 3450, 1680, 1600 cm^{-1}; MS m/z 571 (M^+).

(3S,4R,5R,6R)-4-(*N*-Methoxycarbonyl-*N*-methylamino)-3,5-bis(methoxymethyloxy)-6-methyl-6-(1,4,5,8-tetramethoxy-2-naphthalenyl)tetrahydro-2-pyranone (10). A solution of DMSO (0.20 g, 2.6 mmol) in CH_2Cl_2 (0.50 ml) was added to a solution of oxalyl chloride (0.15 g, 1.2 mmol) in CH_2Cl_2 (3.0 ml) cooled at -60 °C under an argon atmosphere. After stirring for 2 min at the same temperature, a solution of

9 (0.29 g, 0.50 mmol) in CH_2Cl_2 (1.0 ml) was added to the reaction mixture and stirring was further continued for 20 min. After triethylamine (0.61 g, 6.0 mmol) was added, the reaction mixture was allowed to warm up to 0 °C over 30 min and diluted with AcOEt. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Column chromatography (SiO_2, AcOEt-hexane) of the residual oil gave pure **10** as a colorless caramel (0.27 g, 95%). ^1H NMR (90 MHz, $CDCl_3$) δ 2.04 (3H, s, C_6-Me), 2.97 (3H, s, NMe), 3.20 and 3.36 (6H, two s, $CH_2O\underline{Me}$ x 2), 3.66, 3.70, 3.86, 3.90, and 3.92 (15H, five s, ArOMe x 4, CO_2Me), 4.51 and 4.60 (2H, two d, each J = 8 Hz, $C\underline{H}_2OMe$), 4.73 and 5.13 (2H, two d, each J = 7 Hz, $C\underline{H}_2OMe$), 6.84 (2H, s, C_6'-H, C_7'-H), 7.00 (1H, s, C_3'-H); IR (neat) 1740, 1695, 1600, 1025 cm^{-1}; MS m/z 567 (M^+), 491.

(2R,3R,4R,5S,6S)-(+)-6-Hydroxy-4-(*N*-methoxycarbonyl-*N*-methylamino)-3,5-bis-(methoxymethyloxy)-2-methyl-2-(1,4,5,8-tetramethoxy-2-naphthalenyl)tetrahydropyran (11) and Its (2R,3R,4R,5S,6R)-Isomer (12).

a) Preparation of 11. DIBAL (0.92 ml, 1.0M hexane solution, 0.92 mmol) was added to a solution of **10** (0.44 g, 0.77 mmol) in toluene (30 ml) cooled at -78 °C under an argon atmosphere. After stirring was continued for 20 min at the same temperature, the reaction was quenched by the addition of MeOH (0.50 ml). The mixture was diluted with saturated aqueous NH_4Cl and extracted with AcOEt. The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (30 ml) and anhydrous K_2CO_3 (2.0 g, 11 mmol) was added to the methanolic solution at room temperature. The mixture was heated at reflux for 30 min, cooled to ambient temperature, filtered, and concentrated *in vacuo*. The residual oil was chromatographed (SiO_2, AcOEt-hexane) to give pure **11** as a colorless caramel (0.35 g, 82%), $[\alpha]_D^{20}$ +12.2° (c 1.05, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.83 and 1.91 (3H, two s, C_6-Me), 2.96 and 2.99 (3H, two s, NMe), 3.28 and 3.37 (6H, two s, $CH_2O\underline{Me}$ x 2), 3.4-4.3 (19H, m, C_3-H, C_4-H, C_5-H, ArOMe x 4, CO_2Me, OH), 4.4-4.9 (5H, m, C_6-H, $C\underline{H}_2OMe$ x 2), 6.80 (2H, s, C_6'-H, C_7'-H), 7.72 (1H, s, C_3'-H); IR (neat) 3450, 1690, 1600, 1070, 1030 cm^{-1}; MS m/z 569 (M^+).

b) Preparation of a Mixture of 11 and 12. DIBAL (8.0 ml, 1.0M hexane solution, 8.0 mmol) was added to a solution of **10** (0.82 g, 1.5 mmol) in toluene (50 ml) cooled at -78 °C under an argon atmosphere. After stirring for 20 min at the same temperature, the reaction was quenched by the addition of MeOH (5.0 ml). After addition of $CHCl_3$ and water, the mixture was neutralized to pH 7 with 1M HCl. The lower chloroform layer was separated and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by separation by column chromatography (SiO_2, AcOEt), gave a mixture of **11** and **12** as a colorless caramel (0.57 g, 70%). This was immediately used for the next step.

(2R,3R,4R,5S,6R)-(-)-4-(*N*-Methoxycarbonyl-*N*-methylamino)-3,5,6-tris(methoxy-methyloxy)-2-methyl-2-(1,4,5,8-tetramethoxy-2-naphthalenyl)tetrahydropyran (13) and Its (2R,3R,4R,5S,6S)-(-)-Isomer (14).

a) Preparation of 13. Chloromethyl methyl ether (3.2 g, 39 mmol) was added to a solution of **11** (0.35 g, 0.62 mmol) and ethyldiisopropylamine (4.4 g, 34 mmol) in THF (5.0 ml) at room temperature under an argon atmosphere. The reaction mixture was heated at reflux for 3 h. After cooling, triethylamine (2.0 ml) and MeOH (3.0 ml) was added successively to the mixture cooled in an ice bath and stirring was continued for 15 min. The mixture was diluted with AcOEt, washed successively with 3M HCl, saturated aqueous $NaHCO_3$, and brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by purification by column chromatography (SiO_2 AcOEt-hexane), afforded pure **13** as a colorless solid (0.34 g, 91%). Recrystallization from ether-hexane gave an analytical sample of **13** as colorless crys-

tals, mp 115-116 °C and $[\alpha]_D^{20}$ -16.2° (c 1.10, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.82 (3H, s, C_2-Me), 2.96 and 3.00 (3H, two s, NMe), 3.23, 3.28, and 3.40 (9H, three s, $CH_2O\underline{Me}$ x 3), 3.5-4.3 (18H, m, C_3-H, C_4-H, C_5-H, ArOMe x 4, CO_2Me), 4.3-5.3 (7H, m, C_6-H, $C\underline{H}_2OMe$ x 3), 6.82 (2H, s, $C_{6'}$-H, $C_{7'}$-H), 7.74 (1H, s, $C_{3'}$-H); IR (KBr) 1700, 1600, 1450, 1390, 1350, 1270, 1020, 990, 920, 810, 750 cm^{-1}; MS m/z 613 (M^+). *Anal.* Calcd. for $C_{29}H_{43}NO_{13}$: C, 56.76; H, 7.06; N, 2.28%. Found: C, 56.63; H, 7.17; N, 2.21%.

b) Preparation of a Mixture of 13 and 14. The treatments of a mixture of **11** and **12** (0.60 g, 1.1 mmol) in the same manner as that described in a) gave a crude mixture of **13** and **14** after concentration of the ethyl acetate solution *in vacuo*. Separation by column chromatography (SiO_2, AcOEt-hexane) afforded pure **13** as a pale yellow solid (0.49 g, 76%) and pure **14** as a pale yellow caramel (0.11 g, 17%), $[\alpha]_D^{20}$ -14.8° (c 1.00, $CHCl_3$). The spectral data of **14** are as follows. ^1H NMR (90 MHz, $CDCl_3$) δ 1.94 (3H, s, C_2-Me), 3.03 and 3.06 (6H, two s, NMe, $CH_2O\underline{Me}$), 3.32 and 3.36 (9H, two s, $CH_2O\underline{Me}$ x 3), 3.71, 3.75, 3.89, and 3.96 (15H, four s, ArOMe x 4, CO_2Me), 4.4-5.0 (6H, m, $C\underline{H}_2OMe$ x 3), 5.24 (1H, d, J = 3 Hz, C_6-H), 6.75 (2H, s, $C_{6'}$-H, $C_{7'}$-H), 7.72 (1H, s, $C_{3'}$-H); IR (neat) 1700, 1600, 1450, 1385, 1355, 1270, 1150, 1070, 1030, 990, 920, 810, 750 cm^{-1}; MS m/z 613 (M^+).

(2R,3R,4R,5S,6R)-(-)-4-Dimethylamino-3,5,6-tris(methoxymethyloxy)-2-methyl-2-(1,4,5,8-tetramethoxy-2-naphthalenyl)tetrahydropyran (15). $LiAlH_4$ (0.18 g, 4.8 mmol) was added to a solution of **13** (0.73 g, 1.2 mmol) in ether (40 ml) at room temperature under an argon atmosphere. The reaction mixture was heated at reflux for 1 h and then cooled to ambient temperature. The excess hydride was decomposed by the addition of MeOH (1.0 ml) and the mixture was diluted with AcOEt. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO_2, AcOEt-hexane) to afford pure **15** as colorless crystals (0.64 g, 95%), mp 109-110 °C and $[\alpha]_D^{20}$ 0.00° (c 1.08, $CHCl_3$), $[\alpha]_{435}^{20}$ -10.3° (c 1.08, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.85 (3H, s, C_2-Me), 2.54 (6H, s, NMe_2), 3.05 (1H, t, J = 9 Hz, C_4-H), 3.37 (6H, s, $CH_2O\underline{Me}$ x 2), 3.40 (3H, s, $CH_2O\underline{Me}$), 3.70 (1H, dd, J = 8 and 9 Hz, C_5-H), 3.74, 3.87, 3.93, and 3.95 (12H, four s, ArOMe x 4), 4.6-5.3 (7H, m, C_6-H, $C\underline{H}_2OMe$ x 3), 6.83 (2H, s, $C_{6'}$-H, $C_{7'}$-H), 7.73 (1H, s, $C_{3'}$-H); IR (KBr) 1600, 1390, 1355, 1270, 1070, 1040, 1020 cm^{-1}; MS m/z 569 (M^+), 464. *Anal.* Calcd. for $C_{28}H_{43}NO_{11}$: C, 59.04; H, 7.61; N, 2.46%. Found: C, 58.86; H, 7.57; N, 2.40%.

(2R,3R,4R,5S,6S)-(-)-4-Dimethylamino-3,5,6-tris(methoxymethyloxy)-2-methyl-2-(1,4,5,8-tetramethoxy-2-naphthalenyl)tetrahydropyran (16). The same reduction of **14** (0.16 g, 0.26 mmol) as that described for **13** gave crude **16** after concentration of the ethyl acetate solution *in vacuo*. This was separated by column chromatography (SiO_2, AcOEt-hexane) to give pure **16** as a colorless caramel (0.13 g, 86%), $[\alpha]_D^{20}$ -24.1° (c 1.70, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.91 (3H, s, C_2-Me), 2.53 (6H, s, NMe_2), 3.11 (1H, t, J = 9 Hz, C_4-H), 3.23, 3.34, and 3.45 (9H, three s, $CH_2O\underline{Me}$ x 3), 3.74 (3H, s, ArOMe), 3.90 (6H, s, ArOMe x 2), 3.96 (3H, s, ArOMe), 4.2-5.2 (6H, m, $C\underline{H}_2OMe$ x 3) 5.42 (1H, d, J = 3 Hz, C_6-H), 6.78 (2H, s, $C_{6'}$-H, $C_{7'}$-H), 7.61 (1H, s, $C_{3'}$-H); IR (neat) 1600, 1450, 1380, 1350, 1250, 1050, 1020 cm^{-1}; MS m/z 569 (M^+), 464, 348. *Anal.* Calcd. for $C_{28}H_{43}NO_{11}$: C, 59.04; H, 7.61; H, 2.46%. Found: C, 58.79; H, 7.86; N, 2.33%.

5,8-Dimethoxy-1,4-naphthoquinone (17). An aqueous solution (0.50 ml) of CAN (0.20 g, 0.45 mmol) was added to a solution of **6** (82 mg, 0.33 mmol) in acetonitrile (1.0 ml) in an ice bath. After stirring for 40 min in an ice bath, the mixture was extracted with $CHCl_3$. The combined extracts were washed with brine and dried ($MgSO_4$). Filtration and concentration *in vacuo* gave **17** as an orange solid (70 mg, 97%). Recrystallization from ether-hexane gave pure **17** as orange

crystals, mp 153-155 °C [lit. 157 °C[6b]]. ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.00 (6H, s, ArOMe x 2), 6.83 and 7.38 (4H, two s, ArH_4).

2-(1-Methoxy-1-methylethyl)-1,4,5,8-tetramethoxynaphthalene (18). Butyllithium (1.3 ml, 1.5M hexane solution, 2.0 mmol) was added to a solution of **6** (0.50 g, 2.0 mmol) in THF (50 ml) cooled in an ice bath. After stirring for 30 min in an ice bath, acetone (2.0 ml) was added to the reaction mixture and stirring was further continued for 1 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with AcOEt. The extracts were combined, washed with brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo* gave a residue, which was separated by column chromatography (SiO_2, AcOEt-$CHCl_3$) to afford a crude 2-(1-hydroxy-1-methylethyl)-1,4,5,8-tetramethoxynaphthalene as a colorless solid. Recrystallization from ether-hexane gave a pure sample as colorless crystals (0.38 g, 62%), mp 100-101 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.69 (6H, s, CMe_2), 3.82, 3.90, 3.92, and 3.93 (12H, four s, OMe x 4), 5.01 (1H, s, OH), 6.83 (2H, s, C_6-H, C_7-H), 6.90 (1H, s, C_3-H); IR (KBr) 3360, 1600, 1470, 1380, 1355, 1255, 1220, 1130, 1070, 1045 cm^{-1}; MS m/z 306 (M^+), 291, 276, 261, 248, 234. *Anal.* Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24%. Found: C, 66.85; H, 7.31%.

NaH (96 mg, 50% dispersion in oil, 2.0 mmol) and methyl iodide (4.6 g, 32 mmol) were successively added to a solution of the alcohol (0.37 g, 1.2 mmol) in DMF (3.0 ml) in an ice bath under an argon atmosphere. The mixture was heated at 40 °C for 1 h, cooled to room temperature, and diluted with ether. The ethereal solution was washed with water, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed (SiO_2, AcOEt-$CHCl_3$) to give pure **18** as a colorless solid (0.37 g, 96%). Recrystallization from ether-hexane gave an analytical sample of **18** as colorless crystals, mp 99-100 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.72 (6H, s, CMe_2), 3.21 (3H, s, OMe), 3.71 and 3.93 (6H, two s, ArOMe x 2), 3.96 (6H, s, ArOMe x 2), 6.86 (2H, s, C_6-H, C_7-H), 7.16 (1H, s, C_3-H); IR (KBr) 1605, 1390, 1260, 1070, 1060 cm^{-1}; MS m/z 320 (M^+), 305, 274, 273. *Anal.* Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55%. Found: C, 67.46; H, 7.72%.

5,8-Dimethoxy-2-(1-methoxy-1-methylethyl)-1,4-naphthoquinone (19) and 5,8-Dimethoxy-7-(1-methoxy-1-methylethyl)-1,4-naphtoquinone (20). An aqueous solution of CAN (0.43 g, 0.78 mmol) was added to a solution of **18** (96 mg, 0.30 mmol) in acetonitrile (10 ml) in an ice bath. After stirring was continued for 15 min in an ice bath, the reaction mixture was diluted with AcOEt. The ethyl acetate solution was washed successively with water and brine, dried ($MgSO_4$), and filtered. Concentration *in vacuo*, followed by purification of the residue by column chromatography (SiO_2, AcOEt-hexane), gave pure **19** as an orange solid (75 mg, 86%) and pure **20** as an orange solid (10 mg, 11%).

19: Recrystallization from ether-hexane gave an analytical sample of **19** as orange crystals, mp 166-167 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.58 (6H, s, CMe_2), 3.28 (3H, s, OMe), 3.98 (6H, two s, C_5-OMe, C_8-OMe), 6.96 (1H, s, C_3-H), 7.33 (2H, s, C_6-H, C_7-H); IR (KBr) 1650, 1270, 1205, 1145, 1050, 1035, 950 cm^{-1}; MS m/z 290 (M^+), 275, 245. *Anal.* Calcd. for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25%. Found: C, 65.97; H, 6.38%.

20: Recrystallization from ether-hexane gave an analytical sample of **20** as orange crystals, mp 116-117 °C. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.65 (6H, s, CMe_2), 3.28 (3H, s, OMe), 3.82 and 4.02 (6H, two s, C_5-OMe, C_8-OMe), 6.82 (2H, s, C_2-H, C_3-H), 7.65 (1H, s, C_6-H); IR (KBr) 1655, 1330, 1230, 1060, 1040 cm^{-1}; MS m/z 290 (M^+), 275, 245. *Anal.* Calcd. for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25%. Found: C, 66.07; H, 6.36%.

(2R,3R,4R,5S,6R)-(+)-2-(5,8-Dimethoxy-1,4-dioxo-2-naphthalenyl)-4-dimethylamino-3,5,6-tris(methoxymethyloxy)-2-methyltetrahydropyran (21) and (2R,3R,4R,5S,6R)-(+)-2-(1,4-Dimethoxy-5,8-dioxo-2-naphthalenyl)-4-dimethylamino-3,5,6-tris(methoxymethyloxy)-2-methyltetrahydropyran (22). An aqueous solution (30 ml) of CAN (19 g, 35 mmol) was added to a solution of 15 (5.7 g, 10 mmol) in EtOH (80 ml) cooled at -78 °C. After stirring for 2 h at the same temperature, the reaction mixture was allowed to warm up to -10 °C over 30 min. After addition of AcOEt and water, the mixture was neutralized to pH 8 with saturated aqueous $NaHCO_3$. The upper organic layer was separated and the lower aqueous phase was further extracted with AcOEt. The ethyl acetate layers were combined, washed with brine, and extracted with 1M HCl. The aqueous extracts were combined and neutralized to pH 8 with saturated aqueous $NaHCO_3$. The neutralized aqueous layer was again extracted with AcOEt. The ethyl acetate extracts were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was separated by column chromatography (SiO_2, AcOEt) to give pure **21** as an orange solid (4.0 g, 74%) and pure **22** as an orange solid (0.85 g, 16%).

21: Recrystallization from ether-hexane gave an analytical sample of **21** as orange crystals, mp 147-148 °C and $[\alpha]_D^{20}$ +14.3° (c 0.280, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.82 (3H, s, C_2-Me), 2.46 (6H, s, NMe_2), 2.83 (1H, t, J = 6 Hz, C_4-H), 3.32 (3H, s, $CH_2O\underline{Me}$), 3.40 (6H, s, $CH_2O\underline{Me}$ x 2), 3.83 (1H, dd, J = 6 and 7 Hz, C_5-H), 3.92 and 3.96 (6H, two s, $C_{5'}$-OMe, $C_{8'}$-OMe), 4.17 (1H, d, J = 6 Hz, C_3-H), 4.5-5.1 (7H, m, C_6-H, $C\underline{H}_2OMe$ x 3), 7.27 (3H, s, $C_{3'}$-H, $C_{6'}$-H, $C_{7'}$-H); ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (3H, s, C_2-Me), 2.46 (6H, s, NMe_2), 2.82 (1H, t, J = 5.7 Hz, C_4-H), 3.32, 3.39, and 3.40 (9H, three s, $CH_2O\underline{Me}$ x 3), 3.82 (1H, dd, J = 5.7 and 6.9 Hz, C_5-H), 3.91 and 3.95 (6H, two s, $C_{5'}$-OMe, $C_{8'}$-OMe), 4.16 (1H, d, J = 5.7 Hz, C_3-H), 4.59 and 4.66 (2H two d, each J = 6.8 Hz, $C\underline{H}_2OMe$), 4.68 and 4.69 (2H, two d, each J = 6.5 Hz, $C\underline{H}_2OMe$), 4.81 (1H, d, J = 6.9 Hz, C_6-H), 4.88 and 4.97 (2H, two d, each J = 6.5 Hz, $C\underline{H}_2OMe$), 7.25 (2H, s, $C_{6'}$-H, $C_{7'}$-H), 7.26 (1H, s, $C_{3'}$-H); IR (KBr) 1665, 1045, 1020 cm^{-1}; MS m/z 539 (M^+), 508, 479, 478. *Anal.* Calcd. for $C_{26}H_{37}NO_{11}$: C, 57.86; H, 6.91; N, 2.60%. Found: C, 57.46; H, 7.09; N, 2.50%.

22: Recrystallization from ether-hexane gave an analytical sample of **22** as orange crystals, mp 115-116 °C and $[\alpha]_D^{20}$ +44.9° (c 0.530, $CHCl_3$). ^1H NMR (90 MHz, $CDCl_3$) δ 1.82 (3H, s, C_2-Me), 2.50 (6H, s, NMe_2), 2.85 (1H, t, J = 6 Hz, C_4-H), 3.25, 3.41, and 3.42 (9H, three s, $CH_2O\underline{Me}$ x 3), 3.83 (1H, t, J = 6 Hz, C_5-H), 3.85 and 4.01 (6H, two s, $C_{1'}$-OMe, $C_{4'}$-OMe), 4.28 (1H, d, J = 6 Hz, C_3-H), 4.6-5.2 (7H, m, C_6-H, $C\underline{H}_2OMe$ x 3), 6.80 (2H, s, $C_{6'}$-H, $C_{7'}$-H), 8.08 (1H, s, $C_{3'}$-H); IR (KBr) 1740, 1660, 1620, 1470, 1240, 1150, 1090, 1040, 1010 cm^{-1}; MS m/z 539 (M^+), 508, 479, 478. *Anal.* Calcd. for $C_{26}H_{37}NO_{11}$: C, 57.86; H, 6.91; N, 2.60%. Found: C, 57.78; H, 6.80; N, 2.56%.

(2R,3S,4R,5R,6R)-(+)-3,5-Diacetoxy-9,12-dimethoxy-4-dimethylamino-8-hydroxy-6-methyl-2,6-epoxy-3,4,5,6-tetrahydro-2H-naphthaleno[1,2-b]oxocine (25). An aqueous solution (20 ml) of $Na_2S_2O_4$ (0.25 g, 1.4 mmol) was added to a solution of **21** (0.10 g, 0.19 mmol) in $CHCl_3$ (10 ml). The mixture was stirred vigorously until the yellow color disappeared. The lower chloroform layer was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5.0 ml) under an argon atmosphere. TMSBr (1.2 g, 7.8 mmol) was added to the dichloromethane solution under reflux and heating at reflux was further continued for 10 min. After being cooled to ambient temperature, the mixture was concentrated *in vacuo*. After MeOH (1.0 ml) was added to the residue cooled at -78 °C, the methanolic solution was warmed up to room temperature and concentrated *in vacuo*. The residue was dissolved again in MeOH (1.0 ml) at room temperature and

the methanolic solution was concentrated *in vacuo*. Potassium acetate (0.30 g, 3.1 mmol) and Ac_2O (2.2 g, 22 mmol) was added to a solution of the residual oil in MeOH (3.0 ml) at ambient temperature. After stirring for 1 h at room temperature, the reaction mixture was concentrated *in vacuo*. Column chromatography (SiO_2, AcOEt) of the residue gave pure **25** as colorless crystals (69 mg, 78%), mp 182-183 °C and $[\alpha]_D^{20}$ +79.7° (c 0.310, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 (3H, s, C_6-Me), 2.07 and 2.13 (6H, two s, COMe x 2), 2.26 (6H, s, NMe_2), 2.76 (1H, t, J = 10.3 Hz, C_4-H), 3.86 and 4.02 (6H, two s, OMe x 2), 5.12 (1H, d, J = 10.3 Hz, C_5-H), 5.15 (1H, dd, J = 4.4 and 10.3 Hz, C_3-H), 5.85 (1H, d, J = 4.4 Hz, C_2-H), 6.61 (1H, s, C_7-H), 6.77 (2H, s, C_{10}-H, C_{11}-H), 9.35 (1H, s, OH); IR (KBr) 3440, 1745, 1250, 1235, 1220, 1040 cm^{-1}; MS m/z 475 (M^+), 318. *Anal.* Calcd. for $C_{24}H_{29}NO_9$: C, 60.62; H, 6.15; N, 2.95%. Found: C, 60.41; H, 6.13; N, 2.88%.

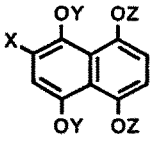
(2R,3S,4R,5R,6R)-(+)-3,5-Diacetoxy-4-dimethylamino-8-hydroxy-6-methyl-2,6-epoxy-3,4,5,6-tetrahydro-2H-naphthaleno[1,2-b]oxocine-9,12-dione (4). BBr_3 (0.90 ml, 1.0M CH_2Cl_2 solution, 0.90 mmol) was added to a solution of **25** (45 mg, 95 μmol) in CH_2Cl_2 (4.5 ml) in an ice bath under an argon atmosphere. After stirring for 30 min in an ice bath, the reaction mixture was concentrated *in vacuo* at 0 °C. Triethylamine (0.50 ml) and MeOH (3.0 ml) was added to the residue cooled to -78 °C. The mixture was allowed to warm up to room temperature, and then concentrated *in vacuo*. A solution of CAN in a mixture of water (0.30 ml) and EtOH (1.5 ml) was added to a solution of the residue in EtOH (12 ml) cooled at -78 °C. After stirring was continued for 10 min at the same temperature, the reaction was quenched by the addition of triethylamine (0.27 ml). The mixture was diluted with water and extracted with $CHCl_3$. The combined chloroform extracts were washed with successively with brine, 1M HCl, saturated $NaHCO_3$, and brine, and dried ($MgSO_4$). Filtration and concentration *in vacuo*, followed by separation by column chromatography (SiO_2, AcOEt-hexane), afforded pure **4** as red crystals (30 mg, 71%), mp 153-155 °C and $[\alpha]_D^{20}$ +420° (c 0.050, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.58 (3H, s, C_6-Me), 2.12 and 2.15 (6H, two s, COMe x 2), 2.28 (6H, s, NMe_2), 2.65 (1H, t, J = 10.8 Hz, C_4-H), 5.11 (1H, d, J = 10.8 Hz, C_5-H), 5.19 (1H, dd, J = 4.0 and 10.8 Hz, C_3-H), 5.85 (1H, d, J = 4.0 Hz, C_2-H), 6.98 (2H, s, C_{10}-H, C_{11}-H), 7.04 (1H, s, C_7-H), 12.40 (1H, s, OH); IR (KBr) 3460, 1745, 1640, 1220, 1040 cm^{-1}; MS m/z 445 (M^+). *Anal.* Calcd. for $C_{22}H_{23}NO_9 \cdot 0.5H_2O$: C, 58.15; H, 5.32; N, 3.08%. Found: C, 58.36; H, 5.26; N, 3.01%.

References and Notes

1) Parts of this series of reports have been the subjects of four preliminary communications: a) M. Kawasaki, F. Matsuda, and S. Terashima, *Tetrahedron Lett.*, **26**, 2693 (1985); b) *Idem*, *ibid.*, **27**, 2145 (1986); c) *Idem*, *ibid.*, **29**, 791 (1988); d) F. Matsuda, M. Kawasaki, M. Ohsaki, K. Yamada, and S. Terashima, *Chem. Lett.*, 653 (1988).

2) Part 1: M. Kawasaki, F. Matsuda, and S. Terashima, *Tetrahedron*, the preceding paper.

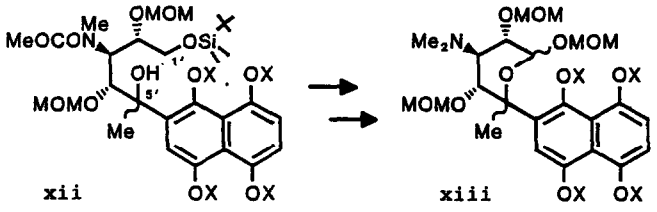
3) At first, the addition reaction to acetone was studied as a model experiment



X = Br, Y = Bn, Z = Me	i	X = H, Y = Bn, Z = Me	vi
X = Br, Y = CH_2OBn, Z = Me	ii	X = H, Y = CH_2OBn, Z = Me	vii
X = Br, Y = SEM, Z = Me	iii	X = H, Y = SEM, Z = Me	viii
X = Br, Y = Z = Bn	iv	X = H, Y = Z = Bn	ix
X = Br, Y = Z = CH_2OBn	v	X = H, Y = Z = CH_2OBn	x
		X = H, Y = Z = MOM	xi
		X = H, Y = Z = Me	6

by employing various 2-lithio-1,4,5,8-tetraalkoxynaphthalenes which were generated from the bromides (**i-v**), tetrakis(methoxymethyloxy)naphthalene (**xi**), or **6** with butyllithium. While the 2-lithionaphthalene derivatives generated from **xi** and **6** were found to afford the addition products, recovery of the 1,4,5,8-tetraalkoxynaphthalenes (**vi-x**) was only observed for the reactions with the 2-lithionaphthalenes produced from **i-v**.

4) The addition reaction of 2-lithio-1,4,5,8-tetrakis(methoxymethyloxy)naphthalene generated from **xi** with **5** also underwent smoothly with formation of the addition product (**xii**) (a mixture of the $C_{5'}$-epimers). According to the similar procedure to that described for **7**, **xii** could be further elaborated to the dimethylamine (**xiii**) (a mixture of the diastereomers due to the $C_{1'}$- and $C_{5'}$-positions). Attempted intramolecular acetalization by treating **xiii** with trimethylsilyl bromide met with failure due to preferential oxidation of the naphthalene ring. This results suggested that the C_1- and C_4-alkoxy groups of the 2-alkyl-1,4,5,8-tetraalkoxynaphthalene moiety should be selectively deprotected prior to the stage of acetalization.



X = MOM

5) R. Huot, and P. Brssard, *Can. J. Chem.*, **52**, 838 (1974).

6) a) D.B. Bruce and R.H. Thomson, *J. Chem. Soc.*, 2759 (1952); b) *Idem*, *ibid.*, 1089 (1955).

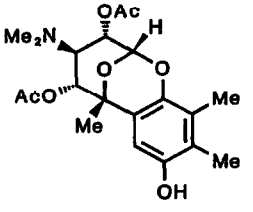
7) In contrast to the model study on the synthesis of **3**,[2] Parikh-Doering oxidation of **9** gave a mixture of **11**, **12**, and **10**.

8) Coupling constants exhibited by the protons involved in the C-glycoside moieties of **15** and **16** are as follows. **15**: ^{1}H NMR (90 MHz, $CDCl_3$) $J_{1'2'}$ = 8 Hz, $J_{2'3'} = J_{3'4'}$ = 9 Hz. **16**: ^{1}H NMR (90 MHz, $CDCl_3$) $J_{1'2'}$ = 3 Hz, $J_{2'3'} = J_{3'4'}$ = 9 Hz.

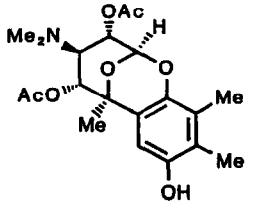
9) P. Jacob, III, P.S. Callery, A.T. Shulgin, and N. Castagnoli, Jr., *J. Org. Chem.*, **41**, 3627 (1976); L. Syper, K. Kloc, J. Mlochowski, and Z. Szule, *Synthesis*, 521 (1979).

10) Oxidation of **15** with CAN under the same conditions as those described for **18** (H_2O-MeCN, 0 °C) yielded equal amounts of **21** and **22**. This is probably due to the fact that the aminosugar moiety of **15** is sterically bulkier than the 1-methoxy-1-methylethyl group of **18**.

11) Representative ^{1}H NMR spectral data of **25** and the model compounds (**xiv** and **xv**)



xiv



xv

are as follows. The 2',4'-diacetates (**xiv** and **xv**) were derived from **3** and its isomeric bicyclic acetal, respectively, as mentioned in the preceding paper.[2] **25**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (1H, t, J = 10.3 Hz, $C_{3'}$-H), 5.12 (1H, d, J = 10.3 Hz, $C_{4'}$-H), 5.15 (1H, dd, J = 4.4 and 10.3 Hz, $C_{2'}$-H), 5.85 (1H, d, J = 4.4 Hz, $C_{1'}$-H). **xiv**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (1H, t, J = 10.5 Hz, $C_{3'}$-H), 5.05 (1H, d, J = 10.5 Hz, $C_{4'}$-H), 5.11 (1H, dd, J = 4.2 and 10.5 Hz, $C_{2'}$-H), 5.67 (1H, d, J = 4.2 Hz, $C_{1'}$-H). **xv**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (1H, dd, J = 7.7 and 11.7 Hz, $C_{3'}$-H), 5.05 (1H, dd, J = 3.1 and 11.7 Hz, $C_{2'}$-H), 5.24 (1H, d, J = 7.7 Hz, $C_{4'}$-H), 5.43 (1H, d, J = 3.1 Hz, $C_{1'}$-H).

12) Direct oxidation of **25** with CAN resulted in ring opening of the bicyclic acetal.

13) M. Kawasaki, F. Matsuda, and S. Terashima, *Tetrahedron*, the accompanying paper.