

A Novel and Highly Efficient Asymmetric Synthesis of Optically Active Anthracyclines¹⁾

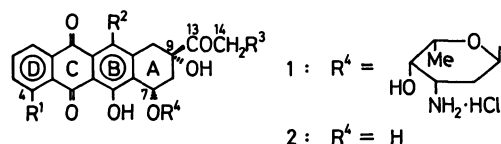
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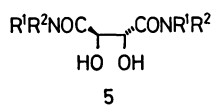
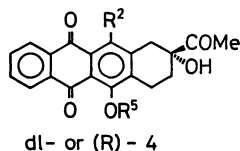
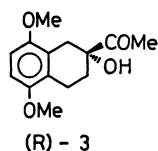
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The bromolactonization of the optically active acetals derived from 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene and (*R,R*)-*N,N':N',N'*-tetraalkyltartaramide was found to proceed highly diastereoselectively, giving mixtures of the seven-membered bromo lactones and the bromohydrins. The predominantly produced bromo lactones could be effectively converted to (*R*)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol, the AB ring synthon of optically active 11-hydroxyanthracyclines, >95% ee, in one pot reaction. Application of the explored synthetic scheme to 2-acetyl-5,12-dimethoxy- and 2-acetyl-5-methoxy-3,4-dihydro-6,11-naphthacenedione similarly gave (*R*)-2-acetyl-2,5,12-trihydroxy- and (*R*)-2-acetyl-2,5-dihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione, the advanced key synthetic intermediates of optically active 4-demethoxy- and 11-deoxy-4-demethoxyanthracyclines, 94% ee and >99% ee, respectively, by way of mixtures of the seven- and six-membered bromo lactones.

The anthracycline antibiotics, adriamycin (**1a**) and daunorubicin (**1b**), hold leading positions of anti-cancer agents because of their prominent activity against various types of human cancers.²⁾ While various undesirable side effects, the most notable and serious of which is dose-related cardiotoxicity,^{2,3)} restrict their wide utilization for cancer chemotherapy, more improved therapeutic indices can be expected for recently discovered natural 11-deoxyanthracyclines (**1e,f**)⁴⁾ and synthetically explored unnatural 4-demethoxy-⁵⁾ and 11-deoxy-4-demethoxyanthracyclines⁶⁾ (**1c,d** and **1g,h**).



	R ¹	R ²	R ³		R ¹	R ²	R ³
a:	OMe	OH	OH	e:	OMe	H	OH
b:	OMe	OH	H	f:	OMe	H	H
c:	H	OH	OH	g:	H	H	OH
d:	H	OH	H	h:	H	H	H



	R ¹	R ²
a:	Me	Me
b:	-(CH ₂) ₄ -	

	R ²	R ⁵
d:	OH	H
h:	H	H
i:	OMe	Me
j:	H	Me

Syntheses of optically active natural and unnatural 11-hydroxyanthracyclines (**2a—d**),⁷⁾ the aglycones of **1a—d**, have been achieved by employing asymmetric syntheses^{8—13)} or optical resolutions^{5a—e, 14—23)} as key processes for producing optically active compounds. However, a synthetic scheme which is generally applicable not only to optically active **2a—d** but also to their 11-deoxy congeners (**2e—h**), seems to be still lacking.²⁴⁾

By selecting (*R*)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*R*)-**3**) as a model target compound, an efficient synthetic method being generally applicable to the whole family of optically active anthracyclines (**2a—h**) was sought. As for (*R*)-**3** which is anticipated to be one of the most versatile AB ring synthons for the chiral synthesis of **2a—d**,⁷⁾ numerous synthetic methods have so far been explored by employing asymmetric synthesis^{8—11,13)} or optical resolution.^{5a—e, 14, 22)}

Previously, the authors reported the asymmetric synthesis of (*R*)-**3** in which the bromolactonization of (*S*)-*N*-(α,β -unsaturated acyl)proline derivatives constitutes the key diastereoselective reaction.⁸⁾ We succeeded in obtaining (*R*)-**3** of 97% ee by sequential manipulation of the formed bromo lactone by way of (*R*)-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic acid. However, this asymmetric synthesis was found to be less practical and to lack generality because of long synthetic steps for obtaining the reaction substrates, requirement of a stoichiometric amount of expensive (*S*)-proline as a chiral source, and failure of construction of the α -hydroxy ketone functionality from the optically active α -hydroxy acid moiety involved in the 1,2,3,4-tetrahydro-6,11-naphthacenedione system.²⁵⁾

We have now explored another efficient asymmetric synthesis of (*R*)-**3** by featuring the bromolactonization of the optically active acetal (**8**) prepared from readily available 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**6**) and (*R,R*)-*N,N':N',N'*-tetraalkyltartaramide (**5**).²⁶⁾ Moreover, it appears that this asymmetric

synthesis can be similarly employed for producing highly optically active (*R*)-2-acetyl-2,5,12-trihydroxy- and (*R*)-2-acetyl-2,5-dihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((*R*)-7-deoxy- and (*R*)-7,11-dideoxy-4-demethoxydaunomycinone) ((*R*)-**4d,h**) from the tetracyclic 2-acetyl-3,4-dihydro-6,11-naphthacenedione derivatives (**21**). These optically active tetracyclic α -hydroxy ketones (*R*)-**4d,h** are usable as the advanced key synthetic intermediates of unnatural 4-demethoxy and 11-deoxy-4-demethoxyanthracyclines (**2c,d** and **2g,h**).^{6,7,9,15,23}

This report details the exploration of this novel asymmetric synthesis which is considered to be more practical and general than the previously reported methods.⁸⁻¹³

Asymmetric Synthesis of Optically Active (*R*)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*R*)-3**).** The starting material (**6**) of the asymmetric synthesis could be prepared from 5,8-dimethoxy-2-tetralone²⁷ by addition of ethynylmagnesium bromide and Rupe rearrangement of the formed propargylic alcohol.⁹ However, modification of the method reported by Russell et al.²⁸ was found to be more promising for obtaining a large quantity of **6**. Thus, treatment of 4a,5,8a-tetrahydro-1,4-naphthoquinone²⁹ with acetic anhydride and potassium hydroxide, followed by isomerization of the C_{6,7}-double bond of 1,4-diacetoxy-5,8-dihydronaphthalene catalyzed with

pentacarbonyliron(0), Friedel-Crafts acetylation of 1,4-diacetoxy-5,6-dihydronaphthalene, alkaline hydrolysis of the diacetates, and methylation of the two phenolic hydroxyl groups, readily produced **6**.

While the direct acetalization of **6** with **5** was found to be sluggish, preparation of the optically active acetals **8** could be effectively accomplished by successive acetalization and transacetalization as shown in Chart 1. Thus, acetalization of **6** with trimethoxymethane in the presence of *dl*-10-camphorsulfonic acid (CSA) followed by transacetalization of the formed dimethylacetal (**7**) with (*R,R*)-*N,N'*-tetramethyltartaramide (**5a**)³⁰ gave **8a** in 92% overall yield.

After numerous unsuccessful attempts,^{31,32} it was finally found that when **8a** was treated with *N*-bromoacetamide in a mixture of *N,N*-dimethylformamide (DMF) and water (100:1)³³ at 0 °C for 15.5 h, a mixture of the bromo lactone (**9a**) and the bromohydrin (**10a**) could be obtained in 83 and 7% yields, respectively. Separation of **9a** and **10a** was readily accomplished by column chromatography. The bromo lactone obtained as a mixture of the two diastereomers (**9aA** and **9aB**) (vide infra) showed mp 140 °C (decomp) and $[\alpha]_D^{20} -110^\circ$ (chloroform). The formation ratio of **9aA** to **9aB** was estimated to be more than 97.5:2.5 based on the optical purity of (*R*)-**3** derived from this sample. Recrystallization of the mixture of **9aA** and **9aB** from a mixture of dichloromethane and ether gave the predominantly formed bromo lactone **9aA** in a pure form, mp 140–140.5 °C and $[\alpha]_D^{20} -114^\circ$ (chloroform). The structures of **9aA** and **9aB** could be assigned as (2*S*,11*S*)- and (2*R*,11*R*)-configurations, by assuming that the bromolactonization and epoxide formation (vide infra)

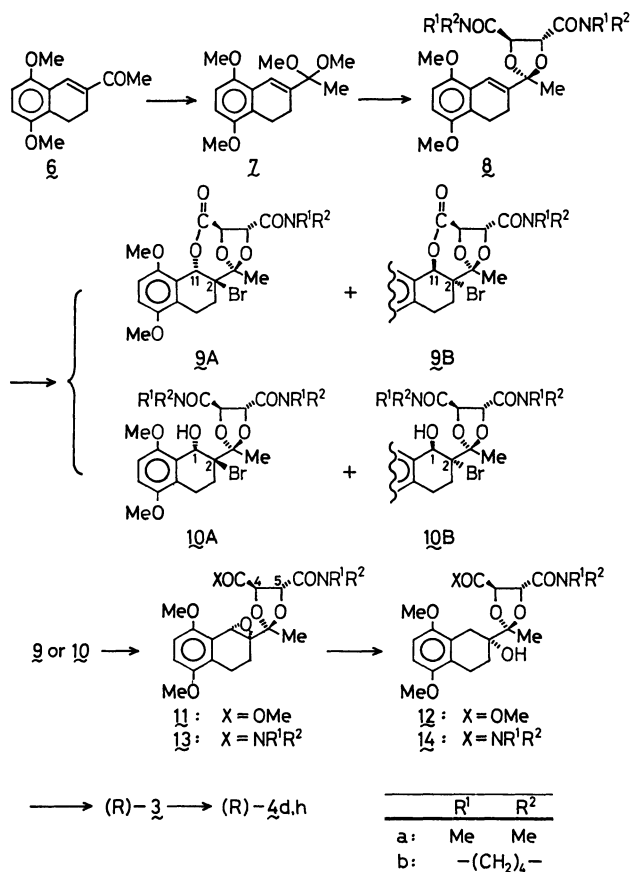


Chart 1.

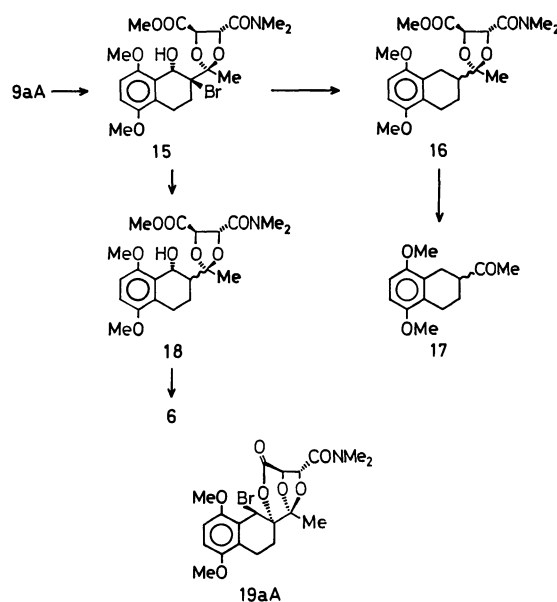


Chart 2.

proceed in a trans fashion and an S_N2 manner, respectively. The bromohydrin (**10a**) isolated as a caramel, also consisted of the two diastereomers (**10aA** and **10aB**). The formation ratio could be similarly estimated to be 85.5:14.5 by converting this mixture to (**R**)-**3**. By assuming that the epoxide formation proceeds in an S_N2 manner, **10aA** and **10aB** were anticipated to belong (1*S*,2*S*)- and (1*R*,2*R*)-configurations, respectively.

In order to establish rigorously the seven-membered bromo lactone structure of **9a**, some chemical transformations were next examined using predominantly formed **9aA**. As shown in Chart 2, **9aA** was treated with methanol in the presence of triethylamine to give the methyl ester (**15**) as a colorless caramel, $[\alpha]_D^{20} +35.8^\circ$ (chloroform), in a quantitative yield. The C_{11} -proton of **9aA**, which appeared as a doublet at δ 5.87, moved to δ 5.47 in the NMR spectrum of **15**. This spectral feature may strongly support the seven-membered structure of **9aA**. Catalytic reduction of **15** over palladium on carbon under a hydrogen atmosphere produced the acetal (**16**) as a diastereomeric mixture. Without separation of the two diastereomers, hydrolysis of **16** with concd hydrochloric acid gave 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-naphthalene (**17**)³⁴ in 94% overall yield from **15**. On the other hand, debromination of **15** with tributyltin hydride followed by acidic removal of the chiral acetal group regenerated **6** with concomitant dehydration of the primarily formed β -hydroxy ketone. Since these chemical transformations should afford (**R**)-**3** if **9aA** has the six-membered bromo lactone structure (**19aA**), the successful preparation of **17** and **6** clearly discloses the seven-membered bromo lactone structure of **9aA**. The similarity of the NMR spectrum of the mixture of **10aA** and **10aB** to that of **15** unambiguously supports the bromohydrin structure of **10a**.

The bromo lactone **9aA** was elaborated to (**R**)-**3** by the following three successive operations. As shown in Chart 1, treatment of **9aA** with anhyd potassium carbonate in methanol gave an 80% yield of the epoxide (**11a**). Catalytic hydrogenation of **11a** over palladium on carbon quantitatively produced the alcohol (**12a**), which on acidic hydrolysis yields (**R**)-**3**, mp 127.5–129 °C and $[\alpha]_D^{20} -48.4^\circ$ (chloroform), 100% ee,³⁵ in 89% yield. Recrystallization of this sample from ether gave analytically pure (**R**)-**3**, mp 129.5–130.5 °C, $[\alpha]_D^{20} -48.7^\circ$ (chloroform). On the other hand, when the mixture of **9aA** and **9aB** directly obtained from the bromolactonization, was successively treated in methanol under the conditions for epoxide formation, catalytic hydrogenation, and acidic hydrolysis without isolation of the intermediates **11a** and **12a** (one pot reaction), (**R**)-**3**, mp 129.5–130.5 °C and $[\alpha]_D^{20} -49.0^\circ$ (chloroform), >95% ee,³⁵ could be obtained in 75% overall yield. The same

successive treatments of the mixture of **10aA** and **10aB** as described (for above mixture of **9aA** and **9aB**), gave (**R**)-**3**, mp 111–126.5 °C and $[\alpha]_D^{20} -32.4^\circ$ (chloroform), 71% ee,³⁵ in 38% overall yield by way of the epoxide **13a** and the alcohol **14a**. Based on these results, the formation ratio of **9aA** to **9aB** and that of **10aA** to **10aB** could be firmly established as described above.

Taking into account the chemical yields and formation ratios, separation of **9a** and **10a** seems to be unnecessary for a large scale preparation of (**R**)-**3**. Namely, it is desirable to immediately subject the crude reaction products of the bromolactonization reaction to the three sequential operations in a single flask to yield highly optically active (**R**)-**3**.

In place of **5a**, (*R,R*)-*N,N':N',N'*-bis(tetramethylene)tartramide (**5b**) was similarly usable as a chiral source of the asymmetric synthesis. The enone **6** was converted to **8b** in 85% overall yield by the similar manner to that described for **8a**. The bromolactonization of **8b** under the same conditions as described for **8a** gave **9b** and **10b** in 78 and 8% yields, respectively. The bromo lactone produced as a mixture of **9bA** and **9bB** showed mp 150.5 °C (decomp) and $[\alpha]_D^{20} -114^\circ$ (chloroform). The mixture of the bromohydrins **10bA** and **10bB** was obtained as a caramel. The formation ratio of **9bA** and **9bB** could be estimated as more than 97.5:2.5 by the optical purity of (**R**)-**3** derived from this mixture. However, since the mixture of **10bA** and **10bB** was not subjected to further chemical elaborations, their formation ratio could not be determined. Recrystallization of the mixture of **9bA** and **9bB** readily gave the major bromo lactone **9bA** in a pure state, mp 149.5–150.5 °C (decomp) and $[\alpha]_D^{20} -116^\circ$ (chloroform). Similarly to the case for **9a**, three successive treatments of the mixture **9bA** and **9bB** afforded (**R**)-**3**, mp 129.5–130 °C and $[\alpha]_D^{20} -47.6^\circ$ (chloroform), >95% ee,³⁵ in 81% overall yield.

The highly diastereoselective bromolactonization may be explained in terms of the kinetically controlled mechanism. As shown in Chart 3, the two diastereomeric bromonium ions (**20A** and **20B**) are anticipated as intermediates for the formation of the

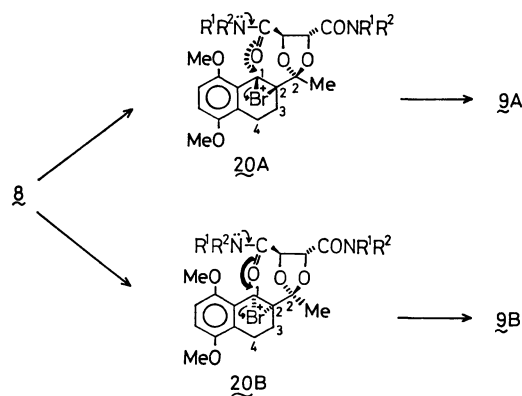


Chart 3.

major and the minor bromo lactones (**9A** and **9B**). Examinations using molecular models disclose that the bond angle between the C₂—C₃ bond and the C₂—CH₃ bond is clearly smaller in **20A** than in **20B**. That is, the C₂-methyl group should be involved in the plane of the 3,4-dihydronaphthalene ring in the conformer of **8** leading to **20A**. On the other hand, the conformer of **8** giving rise to **20B** should have the C₂-methyl group below the plane of the 3,4-dihydronaphthalene ring. Accordingly, less steric interaction between the incoming bromonium ion (Br⁺) and the C₂-methyl group may be expected for **20A**, resulting in the formation of **9A** as a kinetically more favored product.

The formation of **10** may be reasonably explained by assuming that the intermediate bromonium ions **20A** and **20B** are opened by the intermolecular nucleophilic attack of water instead of the intramolecular oxygen atom of the amide group. Similar steric interaction between the bromonium ion (Br⁺) and the C₂-methyl group may well account for the observed preferential production of **10A** being derived to (**R**)-**3**.

As mentioned above, the highly efficient asymmetric synthesis of (**R**)-**3** was explored by featuring the bromolactonization as a key diastereoselective reaction. While partial racemization is accompanied, Friedel-Crafts reaction of (**R**)-**3** with phthalic anhydride in the presence of aluminium chloride can give rise to the optically active tetracyclic α -hydroxy ketone ((**R**)-**4d**),^{9,14} the advanced key intermediate of **2c,d**. Aiming to overcome the inefficient partial racemization and to explore practicality and generality of the developed synthetic scheme, application of the asymmetric synthesis to the preparation of (**R**)-**4d,h** was attempted. This is the subject of the next section.

Asymmetric Synthesis of Optically Active (R**)-2-Acetyl-2,5,12-trihydroxy- and (**R**)-2-Acetyl-2,5-dihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((**R**)-**7-Deoxy**- and (**R**)-**7,11-Dideoxy**-4-demethoxydaunomycinone) ((**R**)-**4d,h**).** In the field of the asymmetric synthesis of optically active anthracyclines,⁸⁻¹³ no general methods which are applicable to both the bicyclic AB and the tetracyclic ABCD ring systems have been explored. Accordingly, application of the developed asymmetric synthesis of (**R**)-**3** to optically active (**R**)-2-acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((**R**)-**7-deoxy**-4-demethoxydaunomycinone) ((**R**)-**4d**) was first attempted. Since the methods for stereoselectively introducing the C_{7 α} -hydroxyl group into (**R**)-**4d** and for converting the C₁₄-position into a hydroxymethyl group have been explored,¹⁵ the ready access to (**R**)-**4d** holds a pivotal position in the synthesis of optically active **2c,d**.

The starting tetracyclic enone (**21i**) required for the asymmetric synthesis of (**R**)-**4d** could be readily produced from **dl**-**4d**.^{14,23} Namely, dehydration of **dl**-

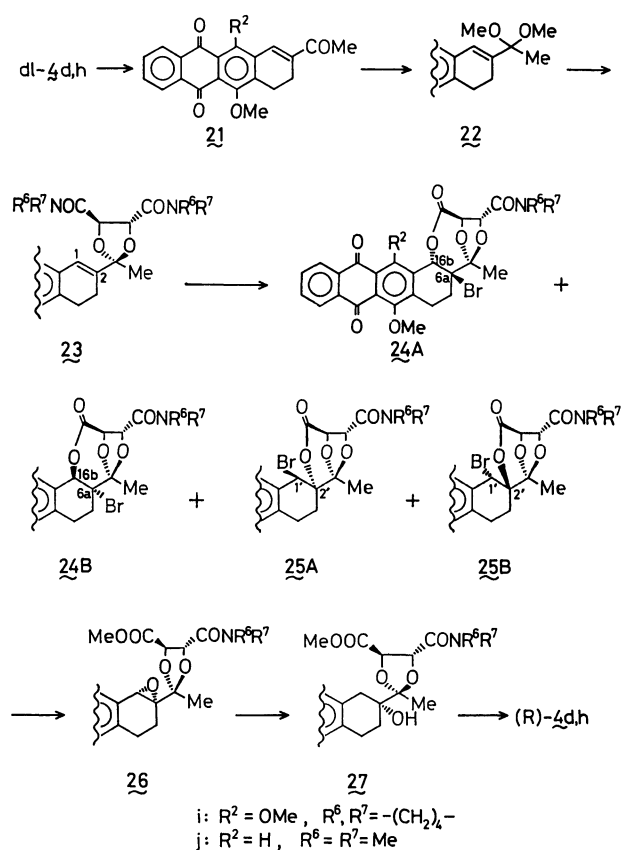


Chart 4.

4d with trifluoroacetic anhydride and collidine³⁶) gave 2-acetyl-5,12-dihydroxy-3,4-dihydro-6,11-naphthacenedione (77%), which on methylation with dimethyl sulfate under phase-transfer conditions afforded **21i** in 82% yield.³⁷ The dehydrated product of **dl**-**4d** can be also synthesized according to the reported method.¹⁸

Acetalization of **21i** with trimethoxymethane followed by transacetalization of the crude dimethyl acetal (**22i**) with **5b** gave the optically active acetal (**23i**) in 89% overall yield. Treatment of **23i** under the same bromolactonization conditions as that employed for **8** produced a mixture of the bromo lactones (**24i** and **25i**) in 78% combined yield. Recrystallization of the mixture with a mixture of chloroform and ether gave the predominantly formed diastereomer of the seven-membered bromo lactone (**24iA**) as a yellow powder, mp 217–219 °C and $[\alpha]_{\text{D}}^{20} -263^\circ$ (chloroform). The minor six-membered bromo lactone (**25iA**) could be also isolated in a pure state as an unstable yellow solid by concentration of the mother liquor of recrystallization in vacuo followed by column chromatography. Structures of **24iA** and **25iA** were tentatively assigned based on their spectral data and successful preparation of highly optically active (**R**)-**4d** from this bromo lactone mixture (vide infra). The NMR spectrum of the bromo lactone mixture (**24i** and **25i**) clearly disclosed that no detectable amounts of the undesired bromo lactones **24iB** and **25iB** were involved in the bromo lactone mixture **24i** and **25i** (<5%). The

formation ratio of **24iA** to **25iA** could be roughly estimated as 6:1 by integral intensity of the C_{16b} and C₁₇-methine signals observed in the NMR spectrum: **24iA**, δ 6.04 ($J=2.0$ Hz); **25iA**, δ 5.60 ($J=2.1$ Hz).

Being different from the case for **8**, no bromohydrins corresponding to **10** could not be detected in the crude reaction products. This may be explained by stability of the cationic species at the benzylic position (the C₁-position), which transiently develops during the bromolactonization reaction. The cationic species at the C₁-position produced from **8** can be effectively stabilized by the two methoxyl groups present in the adjacent aromatic ring. Accordingly, the mixture of **9** and **10** can be produced by the intra- and intermolecular nucleophilic attacks at the C₁-position, respectively, in the bromolactonization of **8**. On the other hand, the generation of the cationic species at the benzylic C₁-position should be less favored for **23i** than for **8** by the presence of two carbonyl groups at the C_{6,11}-positions. Therefore, the six-membered bromo lactone **25i** resulting from the intramolecular nucleophilic attack at the C₂-tertiary carbon atom, could be obtained in addition to the common seven-membered bromo lactone **24i**. The bromohydrins similar to **10**, which could be produced by the intermolecular trap of the cationic species at the benzylic C₁-position with water, was not detected in the bromolactonization of **23i**.

Similarly to the preparation of (*R*)-**3** from **9a**, direct treatment of the mixture of **24i** and **25i** with anhydrous potassium carbonate in methanol yields the epoxide **25i**, which without isolation was hydrogenated over palladium on carbon to give the alcohol **27i**. Removal of the chiral acetal group with concd hydrochloric acid in ethanol followed by demethylation of the phenolic dimethyl ethers with aluminum chloride in benzene, produced (*R*)-**4d**, mp 215–218.5 °C and $[\alpha]_D^{20} -90.4^\circ$ (chloroform), 94% ee,³⁵ in 68% overall yield. Recrystallization of this sample readily gave optically pure (*R*)-**4d**, mp 219–220.5 °C and $[\alpha]_D^{20} -90.9^\circ$ (chloroform), $[\alpha]_D^{20} -20.0^\circ$ (chloroform-methanol 1:1).

The same reaction scheme was further applied to the asymmetric synthesis of (*R*)-2-acetyl-2,5-dihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((*R*)-**7**), 11-dideoxy-4-demethoxydaunomycinone ((*R*)-**4h**). While 11-deoxy-4-demethoxyanthracyclines (**1g,h**) have been reported to show notable anticancer activity,⁶ no methods have been developed for preparing optically active (*R*)-**4h** which is usable as a versatile synthetic intermediate of their aglycones (**2g,h**).

The substrate **21j** was prepared from *dl*-**4h** synthesized according to the reported method.³⁸ Sequential methylation of the *dl*-**4h** with dimethyl sulfate in the presence of anhydrous potassium carbonate and dehydration of the formed methyl ether *dl*-**4j** with thionyl chloride in pyridine gave **21j**.³⁹ The yields of

the two steps were 87 and 50%, respectively. The enone **21j** was treated by the similar manner to that described for **21i** except for the use of **5a** in place of **5b**, giving **23j** in 77% overall yield. Subjection of **23j** to the bromolactonization conditions gave rise to a mixture of the bromo lactones **24j** and **25j** in 85% combined yield. The predominantly formed diastereomer of the seven-membered bromo lactone **24jA** could be separated in a pure form by recrystallization from a mixture of chloroform and ether, mp 238–239.5 °C and $[\alpha]_D^{20} -103^\circ$ (chloroform). The structures of **24j** and **25j** were assigned by comparing their spectral data with those of **24i** and **25i**, respectively, and by the successful conversion to highly optically active (*R*)-**4h** (vide infra). The formation ratio of **24j** to **25j** was similarly estimated as 6:1 based on the NMR spectrum. The undesired bromo lactones **24jB** and **25jB** being diastereomeric to **24jA** and **25jA**, were not detected by means of the NMR of the crude reaction products (<5%).

The same successive treatments of the bromolactone mixture mainly consisting of **24jA** and **25jA**, as those described for the 11-hydroxy series produced (*R*)-**4h**, mp 202.5–204.5 °C and $[\alpha]_D^{20} -32.7^\circ$ (chloroform), >99% ee,³⁵ by way of **26j** and **27j** in 49% overall yield.

The bromolactonization reactions of **23i,j**, which preferentially produce **24A** and **25A**, can be best explained by the mechanism similar to that proposed for the asymmetric synthesis of (*R*)-**3**.

Following various notable merits are recognizable for the explored asymmetric synthesis: 1) the reaction substrates **6** and **21** are readily available, 2) inexpensive **5**, readily available from natural (*R,R*)-(+)-tartaric acid by way of its diester, can be used as a chiral source, 3) conversion of **6** and **21** to the corresponding optically active α -hydroxy ketones ((*R*)-**3** and (*R*)-**4d,h**) can be accomplished using readily available cheap reagents in one-pot reaction and in good overall yields, 4) (*R*)-**3** and (*R*)-**4d,h** whose optical purity is equal to or more than 95% ee can be regularly produced, 5) all reactions can be performed above 0 °C and strictly anhydrous conditions are not required. Due to these reasons, the asymmetric synthesis developed herein is anticipated to be one of the most practical and general synthetic methods of various structural types of optically active anthracyclines.

Experimental

General. All melting points were determined with a Yamato MP-21 melting point apparatus and were uncorrected. IR spectral measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer. NMR spectra were recorded with a Varian EM-390 spectrometer (90 MHz), a Hitachi R-90H spectrometer (90 MHz), and a Bruker AM-400 spectrometer (400 MHz). All signals were expressed as ppm downfield from TMS

used as an internal standard (δ value). Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Measurements of optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 was used as an adsorbent for column chromatography. All reactions were carried out using anhydrous solvents. Especially, tetrahydrofuran and ether freshly distilled from sodium benzophenone ketyl, and dichloromethane, acetone, pyridine, and *N,N*-dimethylformamide freshly distilled from calcium hydride were used. Following abbreviations are used for solvents and reagents; acetone (Me_2CO), α,α' -azobis(isobutyronitrile) (AIBN), benzene (C_6H_6), *N*-bromoacetamide (NBA), *dl*-10-camphorsulfonic acid (CSA), chloroform (CHCl_3), dichloromethane (CH_2Cl_2), *N,N*-dimethylformamide (DMF), dimethyl sulfate (Me_2SO_4), ethanol (EtOH), ether (Et_2O), ethyl acetate (EtOAc), hexane (C_6H_{14}), methanol (MeOH), pyridine ($\text{C}_5\text{H}_5\text{N}$), tetrahydrofuran (THF), triethylamine (Et_3N), trimethoxymethane ($\text{CH}(\text{OMe})_3$).

2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (6). a) **Preparation from 5,8-Dimethoxy-2-tetralone:** Similarly to the reported methods,⁹ successive addition of ethynylmagnesium bromide to 5,8-dimethoxy-2-tetralone²⁷ and Rupe rearrangement of formed *dl*-2-ethynyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol gave **6** after purification on column chromatography (CH_2Cl_2 then CH_2Cl_2 - Et_2O 9:1). NMR spectrum of this sample were identical with that previous reported.⁹

b) **Preparation from 4a,5,8,8a-Tetrahydro-1,4-naphthoquinone:** According to the reported method,²⁸ potassium hydroxide (35 g, 0.62 mol) and acetic anhydride (70 mL, 0.74 mol) were successively added to an acetone solution (300 mL) of crude unstable 4a,5,8,8a-tetrahydro-1,4-naphthoquinone²⁹ (30 g, 0.18 mol) cooled in an ice bath. The mixture was stirred in an ice bath for 3 h, then at room temperature for 1.5 h. After filtration, the filtrate was concentrated in vacuo to give a residue, which was purified by column chromatography (C_6H_6 - EtOAc 10:1) to afford 1,4-diacetoxy-5,8-dihydronaphthalene as a solid. Recrystallization from MeOH gave a pure sample as colorless crystals (20.9 g, 46%), mp 131.5–133.5 °C. IR (KBr) 2900, 1760, 1475, 1370, 1235, 1220, 1195, 1185, 1040, 895, 680, 615, 600 cm^{-1} . ^1H NMR (CDCl_3) δ =2.29 (6H, s, $\text{CH}_3\text{CO}\times 2$), 3.19 (4H, br s, C_5 -H₂ and C_8 -H₂), 5.83 (2H, m, C_6 -H and C_7 -H), 6.92 (2H, s, aromatic protons). Found: C, 67.91; H, 5.67%. Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_4$: C, 68.28; H, 5.73%.

A mixture of 1,4-diacetoxy-5,8-dihydronaphthalene (20.9 g, 85 mmol) and pentacarbonyliron(0) (0.5 mL, 3.8 mmol, 0.04 equiv) was heated in a sealed tube at 135–140 °C for 6.75 h. After further amount of pentacarbonyliron(0) (1.0 mL, 7.6 mmol, total 1.5 mL, 11.4 mmol, 0.13 equiv) was added, the heating in a sealed tube was continued at the same temperature for 12 h. After cooling, the mixture was directly subjected to column chromatography (CH_2Cl_2 then EtOAc) to give 1,4-diacetoxy-5,6-dihydronaphthalene as a pale yellow solid (16.5 g, 79%). Recrystallization from MeOH gave a pure sample as colorless crystals, mp 140–141 °C (lit.,²⁸ mp 137–138 °C).

Sequential Friedel–Crafts acetylation of 1,4-diacetoxy-5,6-dihydronaphthalene (13.9 g, 56 mmol), hydrolysis of formed 2-acetyl-5,8-diacetoxy-3,4-dihydronaphthalene, and in situ methylation according to the same method as that

reported²⁸ gave **6** (7.6 g, 58%) after purification by column chromatography (C_6H_6 - EtOAc 10:1). Recrystallization from Et_2O afforded a pure sample as pale brown crystals, mp 106–106.5 °C (lit.,⁹ mp 106–107 °C). NMR spectrum of this sample was identical with that of the authentic sample obtained in a).

c) **Preparation from 15:** A mixture of **15** (49.1 mg, 0.10 mmol), tributyltin hydride (123 mg, 0.42 mmol), and AIBN (0.2 mg, 0.001 mmol) in C_6H_6 (1.5 mL) was stirred at 65 °C for 3 h under an argon atmosphere. After further amount of AIBN (0.2 mg, 0.001 mmol) was added, the stirring was continued for 3 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography (C_6H_6 - Et_2O then EtOAc) to give **18** as a caramel (23.8 mg, 57%). IR (KBr) 3525, 1755, 1660, 1490, 1260, 1095 cm^{-1} . ^1H NMR (CDCl_3) δ =1.57 (3H, s, C_2 -CH₃), 1.7–3.2 (6H, m, C_2 -H, C_3 -H₂, C_4 -H₂, and OH), 3.00, 3.14 (6H, two s, $\text{N}(\text{CH}_3)_2$), 3.78, 3.83 (9H, three s, $\text{OCH}_3\times 3$, integration ratio of the two signals was 2:1), 4.84 (1H, d, J =6.6 Hz, C_4 -H), 5.37 (1H, d, J =6.6 Hz, C_5 -H), 5.0–5.5 (1H, m, C_1 -H), 6.69 (2H, s, aromatic protons). The NMR spectrum clearly shows that this sample solely consists of the (2*R*)- or (2*S*)-isomer and not of a mixture of these two isomers. MS m/z : 424, 423 (M^+), 216.

A mixture of **18** (23.8 mg, 0.056 mmol) and concd HCl (0.5 mL) in EtOH (2.0 mL) was heated at reflux for 2 h. After cooling, the whole was diluted with EtOAc (50 mL), and the organic mixture was washed successively with H_2O and satd NaCl. After drying over anhyd MgSO_4 , filtration and concentration in vacuo followed by separation on column chromatography (C_6H_6 - EtOAc 10:1), gave **6** as colorless crystals (9.3 mg, 71%), mp 103.5–105 °C. IR and NMR spectra of this sample were identical with those of the authentic sample obtained in a).

(*R,R*)-(+)-*N,N'*-*N',N'*-Tetramethyltartaramide (5a).

This was prepared from commercially available (*R,R*)-(+)-diethyl tartrate according to the reported method.³⁰ A sample recrystallized from a mixture of CH_2Cl_2 and Et_2O showed mp 184.5–188.5 °C and $[\alpha]_D^{20} +44.3^\circ$ (c 1.06, EtOH) (lit.,³⁰ mp 189–190 °C and $[\alpha]_D^{20} +43^\circ$ (c 3.0, EtOH)).

(*R,R*)-(+)-*N,N'*-*N',N'*-Bistetramethylenetartaramide (5b). A mixture of commercially available (*R,R*)-(+)-diethyl tartrate (10.0 g, 49 mmol) and pyrrolidine (10.0 g, 0.14 mol) was stirred at room temperature for 18 h. After concentration in vacuo, the residue was purified by filtration through a short column (EtOAc then EtOAc - MeOH 9:1), to give **5b** as a pale yellow solid (11.6 g, 93%). Recrystallization of this solid from CH_2Cl_2 - Et_2O gave an analytical sample of **5b** as colorless crystals, mp 132.5–135 °C and $[\alpha]_D^{20} +34.2^\circ$ (c 1.02, EtOH). IR (KBr) 3450, 3400, 1645, 1630, 1460, 1385, 1110, 1090 cm^{-1} . ^1H NMR (CDCl_3) δ =1.6–2.2 (8H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}\times 2$), 3.3–3.8 (8H, m, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{N}\times 2$), 4.20 (2H, d, J =7 Hz, $\text{OH}\times 2$), 4.50 (2H, d, J =7 Hz, $\text{CHOH}\times 2$). Found: C, 56.00; H, 7.88; N, 10.85%. Calcd for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_4$: C, 56.24; H, 7.87; N, 10.93%.

(–)-5,8-Dimethoxy-2-[(4*R*,5*R*)-2-methyl-4,5-bis(dimethylcarbamoyl)-1,3-dioxolan-2-yl]-3,4-dihydronaphthalene (8a). A mixture of **6** (698 mg, 3.0 mol), CSA (15.9 mg, 0.07 mmol), and $\text{CH}(\text{OMe})_3$ (1.0 mL, 9.1 mmol) in MeOH (15 mL) was stirred at 0 °C for 12 h, then poured onto satd NaHCO_3 (40 mL) cooled in an ice bath. The aqueous

mixture was extracted with EtOAc. The combined organic extracts were washed successively with H₂O and satd NaCl, then dried over anhyd MgSO₄. Filtration and concentration in vacuo gave crude **7** as an oil, which was immediately subjected to the next transacetalization.

The diamide **5a** (1.23 g, 6.0 mmol) dissolved in C₆H₆ (25 mL) was added to crude **7** prepared above, and the mixture was heated at reflux for 1.25 h using a Dean-Stark apparatus packed with molecular sieves 3A to remove a small amount of H₂O. After cooling, CSA (20 mg, 0.09 mmol) was added to the reaction mixture, the reflux was further continued for 1.25 h. The whole mixture was poured onto satd NaHCO₃ (50 mL) after being cooled, and was extracted with EtOAc. The combined extracts were washed successively with satd NaHCO₃, H₂O, and satd NaCl, then dried over anhyd MgSO₄. Filtration and concentration in vacuo followed by purification on column chromatography (EtOAc then EtOAc-MeOH 19:1) gave pure **8a** as a colorless caramel (1.16 g, 92%), [α]_D²⁰ -4.0° (c 0.99, CHCl₃). IR (KBr) 1650, 1490, 1260, 1105, 1045, 870, 800, 720, 675 cm⁻¹. ¹H NMR (CDCl₃) δ =1.60 (3H, s, CH₃), 2.1–2.4 (2H, m, C₃-H₂), 2.6–3.0 (2H, m, C₄-H₂), 2.90, 2.97, 3.20, 3.24 (12H, four s, NCH₃×4), 3.77 (6H, two s, OCH₃×2), 5.19, 5.30 (2H, two d, *J*=each 6.6 Hz, CHCON×2), 6.59, 6.69 (2H, two d, *J*=each 9.3 Hz, aromatic protons), 6.90 (1H, m, C₁-H). MS *m/z*: 419, 418 (M⁺), 187, 116, 72. Found: C, 62.40; H, 7.22; N, 6.52%. Calcd for C₂₂H₃₀N₂O₆·0.25H₂O: C, 62.47; H, 7.27; N, 6.62%.

(-)-5,8-Dimethoxy-2-[(4*R*,5*R*)-2-methyl-4,5-bis(1-pyrrolidinylcarbonyl)-1,3-dioxolan-2-yl]-3,4-dihydronaphthalene (**8b**). The diamide **5b** (1.15 g, 4.5 mmol) in C₆H₆ (30 mL) was added to crude **7** similarly prepared from **6** (518 mg, 2.2 mmol), and the resulting benzene solution was heated at reflux for 1.25 h using a Dean-Stark apparatus packed with molecular sieves 3A to remove a small amount of H₂O. After cooling, CSA (17 mg, 0.07 mmol) was added to the reaction mixture, and the reflux was further continued for 2 h. After being cooled, the reaction mixture was worked up in the same manner as that described for the preparation of **8a**, giving **8b** as a colorless solid (892 mg, 85%) after purification on column chromatography (EtOAc then EtOAc-MeOH 19:1). Recrystallization from EtOAc-Et₂O-C₆H₁₄ gave an analytical sample of **8b** as colorless crystals, mp 163.5–164.5 °C and [α]_D²⁰ -21.1° (c 1.03, CHCl₃). IR (KBr) 1665, 1635, 1490, 1440, 1260, 1105, 1045, 800, 705 cm⁻¹. ¹H NMR (CDCl₃) δ =1.61 (3H, s, CH₃), 1.7–2.1 (8H, m, NCH₂CH₂-CH₂CH₂N×2), 2.1–2.4 (2H, m, C₃-H₂), 2.6–2.9 (2H, m, C₄-H₂), 3.3–4.0 (8H, m, NCH₂CH₂CH₂CH₂N×2), 3.76 (6H, two s, OCH₃×2), 5.04, 5.17 (2H, two d, *J*=each 6.9 Hz, CHCON×2), 6.59, 6.70 (2H, two d, *J*=each 9.0 Hz, aromatic protons), 6.92 (1H, m, C₁-H). MS *m/z*: 470 (M⁺). Found: C, 66.22; H, 7.46; N, 5.88%. Calcd for C₂₆H₃₄O₆N₂: C, 66.36; H, 7.28; N, 5.95%.

(1*R*,2*S*,11*S*,14*R*,15*R*)-(-)-2-Bromo-15-dimethylcarbamoyl-6,9-dimethoxy-1-methyl-12,16,17-trioxatetracyclo[12.2.1.0^{2,11}.0^{5,10}]-heptadeca-5,7,9-trien-13-one (**9aA**), (1*S*,2*S*)-2-Bromo-5,8-dimethoxy-2-[(4*R*,5*R*)-2-methyl-4,5-bis(dimethylcarbamoyl)-1,3-dioxolan-2-yl]-1,2,3,4-tetrahydro-1-naphthol (**10aA**), and Their (2*R*,11*R*)- and (1*R*,2*R*)-Isomers (**9aB** and **10aB**).

Bromolactonization of 8a: *N*-Bromoacetamide (718 mg, 5.2 mmol) was added to a solution of **8a** (724 mg, 1.7 mmol) in a mixture of DMF-H₂O (100:1) (15 mL), and the mixture

was stirred at 0 °C for 15.5 h. After further amount of NBA (239 mg, 1.7 mmol, total 6.9 mmol, 4.0 equiv) was added, the stirring was continued at the same temperature for 6 h. The reaction mixture was diluted with 10% Na₂S₂O₃ (30 mL), and extracted with EtOAc (×3) and CH₂Cl₂ (×2). The organic extracts were combined, washed successively with 10% Na₂S₂O₃, H₂O, and satd NaCl, then dried over anhyd MgSO₄. Filtration and concentration in vacuo gave a residue (876 mg), a part of which (799 mg) was separated by column chromatography (EtOAc) to give a mixture of **9aA** and **9aB** as a colorless solid (615 mg, 83%), mp 140 °C (decomp) and [α]_D²⁰ -110° (c 1.02, CHCl₃), and a mixture of **10aA** and **10aB** as a colorless caramel (55.8 mg, 7%). IR and NMR spectra of the mixture of **9aA** and **9aB** were identical with those of pure **9aA** (vide infra). Recrystallization of the mixture of **9aA** and **9aB** from CH₂Cl₂-Et₂O gave pure **9aA** as colorless crystals, mp 140–140.5 °C and [α]_D²⁰ -114° (c 1.00, CHCl₃). IR (KBr) 1750, 1645, 1495, 1265, 1240, 1220, 1100, 1090, 1080, 960, 800, 650 cm⁻¹. ¹H NMR (CDCl₃) δ =1.95 (3H, s, C₁-CH₃), 2.0–3.3 (4H, m, C₃-H₂ and C₄-H₂), 3.00, 3.17 (6H, two s, NCH₃×2), 3.78, 3.81 (6H, two s, OCH₃×2), 5.23, 5.38 (2H, two d, *J*=each 2.0 Hz, C₁₄-H and C₁₅-H), 5.87 (1H, d, *J*=1.9 Hz, C₁₁-H), 6.70, 6.80 (2H, two d, *J*=each 9.6 Hz, aromatic protons). MS *m/z*: 473, 471, 470, 469 (M⁺), 467. Found: C, 51.01; H, 5.10; N, 2.94; Br, 17.05%. Calcd for C₂₀H₂₄NO₇Br: C, 51.08; H, 5.14; N, 2.98; Br, 16.99%. The mixture of **10aA** and **10aB** exhibited the following spectra. IR (KBr): 3450, 1650, 1490, 1260, 1100, 1050 cm⁻¹. ¹H NMR (CDCl₃) δ =1.87 (3H, s, C₂-CH₃), 2.1–3.3 (5H, m, C₃-H₂, C₄-H₂, and OH), 3.00, 3.02, 3.18, 3.26 (12H, four s, NCH₃×4), 3.80, 3.86 (6H, two s, OCH₃×2), 5.16, 5.24 (1H, two d, *J*=7.2 Hz and 6.6 Hz, C₄-H or C₅-H), 5.52, 5.67 (1H, two d, *J*=7.2 and 6.6 Hz, C₅-H or C₄-H), 5.53 (1H, br s, C₁-H), 6.76 (2H, s, aromatic protons). The integration ratio of the two doublets at 5.16 and 5.24 ppm, or at 5.52 and 5.67 ppm was found to be 5.4:1. This value appeared to be consistent with the formation ratio of **10aA** to **10aB** determined by the optical purity of (*R*)-**3** derived from this sample (vide infra). MS *m/z*: 516, 514 (M⁺), 496, 418, 229, 189, 187. The formation ratio of **9aA** to **9aB** and that of **10aA** to **10aB** could be determined as more than 97.5:2.5 and 85.5:14.5, respectively, based on the optical purity of (*R*)-**3** derived from these samples (vide infra).

(1*R*,2*S*,11*S*,14*R*,15*R*)-(-)-2-Bromo-15-(1-pyrrolidinylcarbonyl)-6,9-dimethoxy-1-methyl-12,16,17-trioxatetracyclo[12.2.1.0^{2,11}.0^{5,10}]-heptadeca-5,7,9-trien-13-one (**9bA**), (1*S*,2*S*)-2-Bromo-5,8-dimethoxy-2-[(4*R*,5*R*)-2-methyl-4,5-bis(1-pyrrolidinylcarbonyl)-1,3-dioxolan-2-yl]-1,2,3,4-tetrahydro-1-naphthol (**10bA**), and Their (2*R*,11*R*)- and (1*R*,2*R*)-Isomers (**9bB** and **10bB**). **Bromolactonization of 8b:** *N*-Bromoacetamide (372 mg, 2.7 mmol, 3.0 equiv) was added to a solution of **8b** (419 mg, 0.89 mmol) in a mixture of DMF-H₂O (100:1) (7.5 mL) cooled at 0 °C, and the mixture was stirred at the same temperature for 18 h. After 10% Na₂S₂O₃ (20 mL) was added, the mixture was worked up in the same manner as that for the bromolactonization of **8a**, giving a mixture of **9bA** and **9bB** as colorless crystals (347 mg, 78%), mp 150.5 °C (decomp) and [α]_D²⁰ -114° (c 1.04, CHCl₃), and a mixture of **10bA** and **10bB** as a caramel (41.3 mg, 8%), after separation by column chromatography (EtOAc then EtOAc-MeOH 95:5). IR and NMR spectra of the mixture of **9bA** and **9bB** were identical with those of pure **9bA** (vide infra). Recrystallization of the

mixture of **9bA** and **9bB** from EtOAc–Et₂O gave pure **9bA** as colorless crystals, mp 149.5–150.5 °C (decomp) and $[\alpha]_D^{20}$ –116° (*c* 1.04, CHCl₃). IR (KBr) 1750, 1650, 1495, 1450, 1265, 1225, 1105, 1095, 965, 955 cm⁻¹. ¹H NMR (CDCl₃) δ =2.00 (3H, s, C₁–CH₃), 1.7–2.1 (4H, m, NCH₂CH₂CH₂CH₂N), 2.1–3.1 (4H, m, C₃–H₂ and C₄–H₂), 3.4–3.8 (4H, m, NCH₂CH₂CH₂CH₂N), 3.80, 3.83 (6H, two s, OCH₃×2), 5.10, 5.29 (2H, two d, *J*=each 2.0 Hz, C₁₄–H and C₁₅–H), 5.88 (1H, d, *J*=1.7 Hz, C₁₁–H), 6.74, 6.77 (2H, two d, *J*=each 8.7 Hz, aromatic protons). Found: C, 53.30; H, 5.21; N, 2.74; Br, 16.18%. Calcd for C₂₂H₂₆O₇NBr: C, 53.24; H, 5.28; N, 2.82; Br, 16.10%. The mixture of **10bA** and **10bB** showed the following spectra. IR (KBr): 3450, 1645, 1490, 1450, 1260, 1100 cm⁻¹. ¹H NMR (CDCl₃) δ =1.83 (3H, s, C₂–CH₃), 1.5–2.2 (8H, m, NCH₂CH₂CH₂CH₂N×2), 2.2–3.1 (5H, C₃–H₂, C₄–H₂, and OH), 3.2–4.0 (8H, m, NCH₂CH₂CH₂CH₂N×2), 3.77, 3.82 (6H, two s, OCH₃×2), 4.96, 5.34 (2H, two d, *J*=each 7.1 Hz, C₄–H and C₅–H), 5.51 (1H, br s, C₁–H), 6.69 (2H, s, aromatic protons). MS *m/z*: 551, 550, 549, 548. The formation ratio of **9bA** to **9bB** could be determined as more than 97.5:2.5 based on the optical rotation of (**R**)-**3** derived from the mixture of **9bA** and **9bB**. However, the formation ratio of **10bA** to **10bB** could not be determined since the mixture of **10bA** and **10bB** was not derived to optically active **3**.

(1*S*,2*S*)-(+)-2-bromo-5,8-dimethoxy-2-[(2*R*,4*R*,5*R*)-4-methoxycarbonyl-2-methyl-5-dimethylcarbamoyl-1,3-dioxolan-2-yl]-1,2,3,4-tetrahydro-1-naphthol (**15**). A mixture of **9aA** (98.0 mg, 0.21 mmol) and Et₃N (0.05 mL, 0.68 mmol) in MeOH (2.0 mL) was stirred at 0 °C for 0.25 h under an argon atmosphere. Concentration of the mixture in vacuo followed by purification on column chromatography (EtOAc), gave pure **15** as a colorless caramel (106 mg, 100%), $[\alpha]_D^{20}$ +35.8° (*c* 1.02, CHCl₃). IR (KBr) 3500, 1745, 1655, 1490, 1260, 1100 cm⁻¹. ¹H NMR (CDCl₃) δ =1.83 (3H, s, C₂–CH₃), 2.1–3.1 (4H, m, C₃–H₂ and C₄–H₂), 3.01, 3.15 (6H, two s, N(CH₃)₂), 3.21 (1H, d, *J*=3.6 Hz, OH), 3.79, 3.81, 3.83 (9H, three s, OCH₃×3), 4.97, 5.39 (2H, two d, *J*=each 7.3 Hz, C₄–H and C₅–H), 5.47 (1H, d, *J*=3.6 Hz, C₁–H), 6.72 (2H, s, aromatic protons). The doublet at δ 3.21 disappeared on treatment with D₂O. Irradiation of the doublets at δ 3.21 and 4.97 changed the doublets at δ 5.47 and 5.39 into singlets, respectively. Accordingly, the doublet at δ 5.47 was rigorously assigned to the C₁-proton. MS *m/z*: 504, 503, 502, 501 (M⁺), 270, 268. Found: C, 50.05; H, 5.62; N, 2.70; Br, 15.61%. Calcd for C₂₁H₂₈NO₈Br: C, 50.21; H, 5.62; N, 2.79; Br, 15.91%.

2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (**17**). A mixture of **15** (49.3 mg, 0.098 mmol) and 5% Pd/C (20 mg) in MeOH (20 mL) was stirred under a hydrogen atmosphere at room temperature for 16.5 h. After further amount of 5% Pd/C (20 mg) was added, the mixture was stirred under the same conditions for 48 h. Insoluble materials were removed by filtration and washed with EtOAc. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography (C₆H₆–EtOAc 4:1) to give **16** as a colorless oil. IR (neat) 1760, 1740, 1660, 1485, 1255, 1100, 755 cm⁻¹. ¹H NMR (CDCl₃) δ =1.44 (3H, s, C₂–CH₃), 1.8–3.2 (7H, C₁–H₂, C₂–H, C₃–H₂, and C₄–H₂), 3.00, 3.14 (6H, two s, N(CH₃)₂), 3.77 (9H, three s, OCH₃×3), 4.79, 4.83 (1H, two d, *J*=each 6.6 and 6.2 Hz, integration ratio ca. 2:1, C₄–H), 5.33, 5.34 (1H, two d, *J*=each 6.2 and

6.6 Hz, integration ratio ca. 1:2, C₅–H), 6.60 (2H, s, aromatic protons). Based on the NMR spectrum, this sample was found to consist of the two isomers concerning the C₂-position in a ratio of ca. 2:1. MS *m/z*: 409, 408, 407 (M⁺). The total amount of **16** was immediately subjected to the next hydrolysis. Conc'd hydrochloric acid (0.25 mL) was added to a solution of **16** in EtOH (1.0 mL), and the mixture was heated at reflux for 1 h. After dilution with EtOAc, the organic solution was washed successively with H₂O and sat'd NaCl. After drying over anhyd MgSO₄, filtration and concentration in vacuo followed by separation on column chromatography (C₆H₆–EtOAc 30:1), gave **17** as colorless crystals (21.6 mg, 94% overall yield from **15**), mp 79–83.5 °C (lit.³⁴ mp 81–82 °C for *dl*-**17**) and $[\alpha]_D^{20}$ +5.0° (*c* 0.12, CHCl₃).⁴⁰ IR and NMR spectra of this sample were identical with those reported for *dl*-**17**.³⁴

(1*S*,2*S*)-(-)-1,2-Epoxy-5,8-dimethoxy-2-[(2*R*,4*R*,5*R*)-4-methoxycarbonyl-2-methyl-5-dimethylcarbamoyl-1,3-dioxolan-2-yl]-1,2,3,4-tetrahydronaphthalene (**11a**). Anhyd potassium carbonate (16 mg, 0.12 mmol) was added to a suspension of **9aA** (50.6 mg, 0.11 mmol) in MeOH (1.5 mL) under an argon atmosphere, and the mixture was stirred in an ice bath for 0.5 h, then at room temperature for 4 h.⁴¹ After cooling in an ice bath, H₂O (10 mL) was added to the mixture, and the aqueous mixture was extracted with EtOAc. The combined extracts were washed successively with H₂O and sat'd NaCl, then dried over anhyd MgSO₄. Filtration and concentration in vacuo followed by purification on column chromatography (EtOAc), gave **11a** as a colorless caramel (36.2 mg, 80%), $[\alpha]_D^{20}$ –132° (*c* 1.02, CHCl₃). IR (KBr) 1760, 1735, 1660, 1495, 1260, 1095, 875, 715 cm⁻¹. ¹H NMR (CDCl₃) δ =1.57 (3H, s, C₂–CH₃), 1.6–3.3 (4H, m, C₃–H₂ and C₄–H₂), 3.00, 3.20 (6H, two s, N(CH₃)₂), 3.75, 3.77, 3.79 (9H, three s, OCH₃×3), 4.41 (1H, s, C₁–H), 5.21 (2H, s, C₄–H and C₅–H), 6.70 (2H, m, aromatic protons). MS *m/z*: 422, 421 (M⁺), 217, 216. Found: C, 59.62; H, 6.45; N, 3.28%. Calcd for C₂₁H₂₇NO₈: C, 59.85; H, 6.46; N, 3.32%.

(2*R*)-(-)-5,8-Dimethoxy-2-[(2*R*,4*R*,5*R*)-4-methoxycarbonyl-2-methyl-5-dimethylcarbamoyl-1,3-dioxolan-2-yl]-1,2,3,4-tetrahydro-2-naphthol (**12a**). A mixture of **11a** (129 mg, 0.31 mmol) and 5% Pd/C (33 mg) in THF (5.0 mL) was stirred at room temperature for 21.5 h under a hydrogen atmosphere. The mixture was filtered through a pad of Celite and the Celite layer was washed with CH₂Cl₂. The combined filtrates were concentrated in vacuo. The residue was purified by column chromatography (EtOAc) to give **12a** as a colorless caramel (129 mg, 99%) $[\alpha]_D^{20}$ –58.1° (*c* 1.01, CHCl₃). IR (KBr) 3500, 1745, 1660, 1655, 1485, 1260, 1100 cm⁻¹. ¹H NMR (CDCl₃) δ =1.46 (3H, s, C₂–CH₃), 1.5–2.2 (2H, m, C₃–H₂), 2.4–3.2 (5H, m, C₁–H₂, C₄–H₂, and OH), 2.99, 3.14 (6H, two s, N(CH₃)₂), 3.73, 3.77 (9H, three s, OCH₃×3), 5.00, 5.35 (2H, two d, *J*=each 6.3 Hz, C₄–H and C₅–H), 6.59 (2H, s, aromatic protons). MS *m/z*: 423 (M⁺), 217, 216, 207, 206. Found: C, 59.43; H, 6.83; N, 3.19%. Calcd for C₂₁H₂₉NO₈: C, 59.56; H, 6.90; N, 3.31%.

(**R**)-(-)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((**R**)-**3**). a) Preparation from **12a**: Conc'd hydrochloric acid (0.5 mL) was added to a solution of **12a** (94.5 mg, 0.22 mmol) in EtOH (2.0 mL), and the mixture was stirred under reflux for 2 h. After cooling, the mixture was diluted with H₂O (10 mL) and extracted with EtOAc. The combined organic extracts were washed successively

with H₂O and satd NaCl, then dried over anhyd MgSO₄. Filtration and concentration in vacuo followed by purification on column chromatography (C₆H₆-EtOAc 4:1), gave (**R**)-**3** as a colorless solid (49.7 mg, 89%), mp 127.5–129 °C and $[\alpha]_D^{20}$ –48.4° (*c* 0.977, CHCl₃). This sample showed identical IR and NMR spectra with those of the authentic sample.^{8,9} Optical purity of this sample was determined to be 100% ee by measuring the NMR spectrum in the presence of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium[III] (Eu(hfc)₃) in a similar manner to that previously reported.⁹ Recrystallization of this sample from Et₂O gave pure (**R**)-**3** as colorless needles, mp 129.5–130.5 °C and $[\alpha]_D^{20}$ –48.7° (*c* 0.368, CHCl₃) (lit.⁸) mp 128–129 °C and $[\alpha]_D^{20}$ –48.2° (*c* 0.982, CHCl₃); lit.⁹ mp 128–128.5 °C and $[\alpha]_D^{20}$ –47.1° (*c* 1.11, CHCl₃); lit.¹⁰ mp 128–128.5 °C and $[\alpha]_D^{20}$ –46.3° (*c* 0.54, CHCl₃).

b) Preparation from the Mixture of 9aA and 9aB: Anhyd Potassium carbonate (55 mg, 0.40 mmol) was added to a suspension of the mixture of **9aA** and **9aB** (179 mg, 0.38 mmol) in MeOH (4.0 mL), and the mixture was stirred at room temperature under an argon atmosphere for 10.5 h. After further amount of anhyd K₂CO₃ (10 mg, 0.07 mmol, total 0.47 mmol) was added, the stirring was continued for 13 h to completely produce the epoxide. 5% palladium on carbon (50 mg) was directly added to the reaction mixture, and the whole mixture was stirred at room temperature under a hydrogen atmosphere for 8.5 h to cleave the epoxide. After concd HCl (1.0 mL) was added, the mixture was heated at reflux for 2 h to effect hydrolysis of the chiral acetal. Concd hydrochloric acid (1.0 mL) was added after 2 h reaction, and the reflux was further continued for 2 h. The reaction mixture was cooled, and the insoluble materials were removed by filtration and washed with EtOAc. The combined filtrates and washings were diluted with H₂O (10 mL), and extracted with EtOAc. The organic extracts were combined, washed successively with H₂O and satd NaCl, then dried over anhyd MgSO₄. Filtration and concentration in vacuo followed by purification on column chromatography (C₆H₆-EtOAc 4:1), gave (**R**)-**3** as a colorless solid (71.0 mg, 75%), mp 129.5–130.5 °C and $[\alpha]_D^{20}$ –49.0° (*c* 0.988, CHCl₃). This sample showed the IR and NMR spectra identical with those of the authentic sample.^{8,9} The optical purity of this sample was similarly calculated to be more than 95% ee by measuring the NMR spectrum in the presence of Eu(hfc)₃.⁹ Accordingly, the formation ratio of **9aA** and **9aB** could be firmly determined as more than 97.5:2.5. Recrystallization from Et₂O gave pure (**R**)-**3** as colorless needles, mp 130–131 °C and $[\alpha]_D^{20}$ –48.6° (*c* 0.987, CHCl₃) (for the reported values, see a)).

c) Preparation from the Mixture of 10aA and 10aB: Treatment of the crude mixture of **10aA** and **10aB** (55.8 mg, 0.11 mmol) with anhyd K₂CO₃ (23 mg, 0.17 mmol) in MeOH (2.0 mL), followed by hydrogenation over 5% Pd/C (23 mg) in MeOH (2.0 mL) and hydrolysis with concd HCl (2.0 mL) in EtOH (2.0 mL) in a similar manner to that described for the preparation of (**R**)-**3** from a mixture of **9aA** and **9aB**, gave (**R**)-**3** as a colorless solid (10.4 mg, 38% overall yield), mp 111–126.5 °C and $[\alpha]_D^{20}$ –32.4° (*c* 1.04, CHCl₃) (for the reported values, see a)). This was identified by comparing its IR and NMR spectra with those of the authentic sample.^{8,9} Measurement of the NMR spectrum in the presence of Eu(hfc)₃ clearly disclosed that the optical purity

of this sample was 71% ee. Based on this value, the formation ratio of **10aA** to **10aB** could be calculated as 85.5:14.5.

d) Preparation from the Mixture of 9bA and 9bB: The same successive treatments of the mixture of **9bA** and **9bB** (201 mg, 0.40 mmol) as those described for the preparation of (**R**)-**3** from the mixture of **9aA** and **9aB** gave (**R**)-**3** as a colorless solid (82.4 mg, 81%), mp 129.5–130 °C and $[\alpha]_D^{20}$ –47.6° (*c* 1.02, CHCl₃) (for the reported value, see a)). IR and NMR spectra of this sample were identical with those of the authentic sample.^{8,9} Measurement of the NMR spectrum in the presence of Eu(hfc)₃ disclosed that the optical purity of this sample and the formation ratio of **9bA** to **9bB** were more than 95% ee and 97.5:2.5, respectively.⁹

2-Acetyl-5,12-dimethoxy-3,4-dihydro-6,11-naphthacenedione (21i). **a) Preparation of 2-Acetyl-5,12-dihydroxy-3,4-dihydro-6,11-naphthacenedione:** Trifluoroacetic anhydride (2.0 mL, 14 mmol) was added to a mixture of **dl-4d**^{14,23} (137 mg, 0.39 mmol) and collidine (4.0 mL) cooled in an ice bath under an argon atmosphere. After being stirred in an ice bath for 0.5 h and at room temperature for 1 h, the reaction mixture was diluted with H₂O (1.0 mL). The reaction mixture was stirred for 5 min, then poured onto ice-water (50 mL). A solid separated was collected by filtration, and washed successively with H₂O, MeOH, and Et₂O. After drying in vacuo, the crude product obtained as a red solid weighed 99.4 mg (77%), mp 225–236.5 °C. Recrystallization from CHCl₃-EtOH gave an analytical sample as red crystals, mp 245–246 °C (lit.¹⁸) mp 235–237 °C). IR (KBr) 1665, 1620, 1590, 1400, 1370, 1335, 1290, 1270, 1260, 1220, 1010, 800, 770, 735 cm⁻¹. ¹H NMR (CDCl₃) δ =2.52 (3H, s, CH₃), 2.5–2.85 (2H, m, C₃-H₂), 2.85–3.2 (2H, m, C₄-H₂), 7.7–8.0 (2H, m, aromatic protons), 7.89 (1H, s, C₁-H), 8.3–8.5 (2H, m, aromatic protons), 13.23, 13.56 (2H, two s, phenolic OH×2). Found: C, 71.80; H, 4.33%. Calcd for C₂₀H₁₄O₅: C, 71.85; H, 4.22%.³⁷

b) Preparation of 21i: Tetrahydrofuran (20 mL) was added to a mixture of 2-acetyl-5,12-dihydroxy-3,4-dihydro-6,11-naphthacenedione (102 mg, 0.31 mmol) and sodium hydride (50% oil dispersion) (36 mg, 0.75 mmol) cooled at –78 °C, and the mixture was degassed in vacuo. Then, the mixture was stirred at room temperature for 0.5 h and at 50 °C for 1 h under an argon atmosphere. After tetrabutylammonium bromide (242 mg, 0.75 mmol) was added, the mixture was stirred at 50 °C for 0.25 h. Dimethyl sulfate (0.25 mL, 2.6 mmol) was added to the resulting mixture, and the whole was stirred at 50 °C for 5 h. After cooling, the mixture was diluted with 1.5 M[†] HCl and extracted with CH₂Cl₂. The combined extracts were washed with H₂O, and dried over anhyd MgSO₄. Filtration and concentration in vacuo followed by purification on column chromatography (CH₂Cl₂-EtOAc 20:1), gave **21i** as a yellow solid (90.8 mg, 82%). Recrystallization from CHCl₃-MeOH gave an analytical sample of **21i** as yellow crystals, mp 202.5–204 °C. IR (KBr) 1670, 1325, 1275, 1255, 1035 cm⁻¹. ¹H NMR (CDCl₃) δ =2.53 (3H, s, CH₃), 2.4–2.7 (2H, m, C₃-H₂), 2.8–3.2 (2H, m, C₄-H₂), 3.92, 3.99 (6H, two s, OCH₃×2), 7.6–7.9 (2H, m, aromatic protons), 7.80 (1H, s, C₁-H), 8.1–8.3 (2H, m, aromatic protons). Found: C, 72.95;

[†] 1 M=1 mol dm⁻³.

H, 4.96%. Calcd for $C_{22}H_{18}O_5$: C, 72.92; H, 5.01%.

2-Acetyl-5-methoxy-3,4-dihydro-6,11-naphthacenedione (21j). a) **Preparation of *dl*-4j:** A mixture of *dl*-4h³⁸⁾ (506 mg, 1.5 mmol), Me_2SO_4 (596 mg, 4.7 mmol), and anhyd K_2CO_3 (624 mg, 4.5 mmol) in Me_2CO (20 mL) was heated at reflux for 8.5 h. After cooling, insoluble materials were separated and washed with CH_2Cl_2 . The combined organic layer was washed with satd $NaHCO_3$ and dried over anhyd $MgSO_4$. Filtration and concentration followed by column chromatography (C_6H_6 -EtOAc 4:1) gave *dl*-4j as a yellow solid (458 mg, 87%). An analytical sample was prepared as yellow crystals by recrystallization from $CHCl_3$ -MeOH, mp 209–209.5 °C. IR (KBr) 3500, 1710, 1675, 1585, 1335 cm^{-1} . 1H NMR ($CDCl_3$) δ =1.9–2.1 (2H, m, C_3 -H₂), 2.37 (3H, s, COCH₃), 2.7–3.5 (4H, m, C_1 -H₂ and C_4 -H₂), 3.77, 3.93 (6H, two s, OCH₃×2), 7.6–7.9 (2H, m, aromatic protons), 7.83 (1H, C_{12} -H), 8.1–8.4 (2H, m, aromatic protons). Found: C, 71.41; H, 5.23%. Calcd for $C_{21}H_{18}O_5 \cdot 1/6H_2O$: C, 71.38; H, 5.23%.

b) **Preparation of 21j:** Thionyl chloride (0.15 mL, 2.1 mmol) was added dropwise to a suspension of *dl*-4j (481 mg, 1.4 mmol) in C_6H_5N (10 mL) at room temperature under an argon atmosphere, and the mixture was stirred at the same temperature for 0.5 h. After being cooled in an ice bath, the mixture was diluted with H_2O (30 mL), and extracted with CH_2Cl_2 . The combined extracts were washed with H_2O , dried over anhyd $MgSO_4$, then concentrated in vacuo. The residue was purified by column chromatography (CH_2Cl_2 then C_6H_6 -EtOAc 10:1), giving 21j as a yellow solid (230 mg, 50%). Recrystallization from $CHCl_3$ -MeOH gave an analytical sample of 21j as yellow crystals, mp 241.5–243 °C. IR (KBr) 1670, 1580, 1330, 1310, 1280 cm^{-1} . 1H NMR ($CDCl_3$) δ =2.49 (3H, s, COCH₃), 2.3–2.8 (2H, m, C_3 -H₂), 2.9–3.2 (2H, m, C_4 -H₂), 3.93 (3H, s, OCH₃), 7.43 (1H, m, C_1 -H), 7.6–7.9 (2H, m, aromatic protons), 8.00 (1H, s, C_{12} -H), 8.1–8.4 (2H, m, aromatic protons). Found: C, 75.43; H, 4.73%. Calcd for $C_{21}H_{16}O_4 \cdot 1/8H_2O$: C, 75.38; H, 4.89%.

(–)-**5,12-Dimethoxy-2-[(4*R*,5*R*)-2-methyl-4,5-bis(1-pyrrolidinylcarbonyl)-1,3-dioxolan-2-yl]-3,4-dihydro-6,11-naphthacenedione (23i).** A mixture of 21i (254 mg, 0.70 mmol), $CH(OMe)_3$ (1.0 mL, 9.1 mmol), and CSA (21.5 mg, 0.093 mmol) in MeOH (25 mL) was stirred at room temperature for 5.5 h under an argon atmosphere. After cooling in an ice bath, the mixture was diluted with satd $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 . The organic extracts were combined, washed with dil $NaHCO_3$, then dried over anhyd $MgSO_4$. Filtration and concentration in vacuo gave crude 22i as a red solid. 1H NMR ($CDCl_3$) δ =1.43 (3H, s, C_2 -CH₃), 2.2–2.5 (2H, m, C_3 -H₂), 2.8–3.1 (2H, m, C_4 -H₂), 3.26 (6H, two s, $C(OCH_3)_2$), 3.90, 3.93 (6H, two s, OCH₃×2), 7.15 (1H, t, J =1.5 Hz, C_1 -H), 7.6–7.8 (2H, m, aromatic protons), 8.1–8.3 (2H, m, aromatic protons). The total amount of 22i was immediately subjected to the next transacetalization.

A mixture of crude 22i and 5b (358 mg, 1.4 mmol) in C_6H_6 (30 mL) was heated at reflux for 0.5 h using a Dean-Stark apparatus packed with molecular sieves 3A to remove a small amount of H_2O . After CSA (22 mg, 0.095 mmol) was added, the reflux was further continued for 1 h. After being cooled, the mixture was poured onto satd $NaHCO_3$ (50 mL) cooled in an ice bath, and extracted with CH_2Cl_2 . The organic extracts were combined, washed with dil $NaHCO_3$,

then dried over anhyd $MgSO_4$. Filtration and concentration in vacuo followed by purification on column chromatography (EtOAc-MeOH 19:1), gave almost pure 23i as a yellow caramel (375 mg, 89% overall yield from 21i). This was recrystallized from $CHCl_3$ -Et₂O to give pure 23i as a yellow powder, mp 148.5–150.5 °C and $[\alpha]_D^{20}$ –20.4° (*c* 1.02, $CHCl_3$).⁴²⁾ IR (KBr) 1675, 1645, 1450, 1330, 1275, 1255, 1155, 1045, 995 cm^{-1} . 1H NMR ($CDCl_3$) δ =1.67 (3H, s, C_2 -CH₃), 1.7–2.2 (8H, m, $NCH_2CH_2CH_2CH_2N$ ×2), 2.2–2.5 (2H, m, C_3 -H₂), 2.8–3.1 (2H, m, C_4 -H₂), 3.3–4.0 (8H, m, $NCH_2CH_2CH_2CH_2N$ ×2), 3.89, 3.90 (6H, two s, OCH₃×2), 5.11, 5.18 (2H, two d, J = each 7.2 Hz, C_4 -H and C_5 -H), 7.05 (1H, m, C_1 -H), 7.6–7.8 (2H, m, aromatic protons), 8.1–8.3 (2H, m, aromatic protons). Found: C, 67.75; H, 6.00; N, 4.60%. Calcd for $C_{34}H_{36}N_2O_8$: C, 67.99; H, 6.04; N, 4.66%.

(–)-**5-Methoxy-2-[(4*R*,5*R*)-2-methyl-4,5-bis(dimethylcarbamoyl)-1,3-dioxolan-2-yl]-3,4-dihydro-6,11-naphthacenedione (23j).** A mixture of 21j (244 mg, 0.73 mmol), $CH(OMe)_3$ (1.0 mL, 9.1 mmol), and pyridinium *p*-toluenesulfonate (PPTS) (39 mg, 0.16 mmol) in a mixture of MeOH (5.0 mL) and CH_2Cl_2 (20 mL) was stirred at 45 °C for 17.5 h under an argon atmosphere. Similar treatments of the reaction mixture to that described for the preparation of 22i gave crude 22j after concentration of the combined organic extracts (256 mg, 100%). 1H NMR ($CDCl_3$) δ =1.40 (3H, s, C_2 -CH₃), 2.2–2.5 (2H, m, C_3 -H₂), 2.8–3.1 (2H, m, C_4 -H₂), 3.23 (6H, two s, $C(OCH_3)_2$), 3.85 (3H, s, C_5 -OCH₃), 6.77 (1H, m, C_1 -H), 7.5–7.8 (2H, m, aromatic protons), 7.73 (1H, s, C_{12} -H), 8.0–8.3 (2H, m, aromatic protons). This was directly used for the next transacetalization.

A mixture of crude 22j (256 mg, 0.73 mmol) and 5a (308 mg, 1.5 mmol) in C_6H_6 (20 mL) was heated at reflux for 0.5 h using a Dean-Stark apparatus packed with molecular sieves 3A to remove a small amount of H_2O . After PPTS (16.2 mg, 0.06 mmol) was added, the mixture was further heated at reflux for 0.5 h. Work-up of the reaction mixture in the same manner as that described for the preparation of 23i gave as a yellow caramel (294 mg, 77%) after purification on column chromatography (Florisil, EtOAc). This was dissolved in Et₂O (10 mL), and the ethereal solution was stirred in an ice bath to afford an analytical sample of 23j as a yellow powder, mp 132.5–135.5 °C and $[\alpha]_D^{20}$ –14.6° (*c* 1.03, $CHCl_3$). IR (KBr) 1665, 1630, 1580, 1330, 1280 cm^{-1} . 1H NMR ($CDCl_3$) δ =1.64 (3H, s, C_2 -CH₃), 2.2–2.5 (2H, m, C_3 -H₂), 2.8–3.1 (2H, m, C_4 -H₂), 2.97, 3.02, 3.24, 3.27 (12H, four s, $N(CH_3)_2$ ×2), 3.90 (3H, s, OCH₃), 5.29, 5.31 (2H, two d, J = each 7.0 Hz, C_4 -H and C_5 -H), 6.68 (1H, m, C_1 -H), 7.6–7.9 (2H, m, aromatic protons), 7.79 (1H, s, C_{12} -H), 8.1–8.4 (2H, m, aromatic protons). Found: C, 67.24; H, 5.94; N, 5.35%. Calcd for $C_{29}H_{30}N_2O_7$: C, 67.17; H, 5.83; N, 5.40%.

(3*R*,4*R*,6*R*,6*aS*,16*bS*)-6*a*-Bromo-3,6-epoxy-9,16-dimethoxy-6-methyl-4-(1-pyrrolidinylcarbonyl)-3,4,6*a*,7,8,16*b*-hexahydro-2*H*,6*H*-naphthaceno[1,2-*b*][1,5]dioxocin-2,10,15-trione (24iA), (1*R*,1'*R*,2*S*,5*R*,6*R*)-1'-Bromo-5',12'-dimethoxy-1-methyl-6-(1-pyrrolidinylcarbonyl)-3',4'-dihydro-3,7,8-trioxaspiro[bicyclo-[3.2.1]octane-2,2'(1'*H*)-naphthacene]-4,6',11'-trione (25iA), and Their (6*aR*,16*bR*)- and (1'*S*,2*R*)-Isomers (24iB and 25iB). **Bromolactonization of 23i:** *N*-Bromoacetamide (100 mg, 0.73 mmol) was added to a solution of 23i (213 mg, 0.35 mmol) in a mixture of DMF- H_2O (100:1) (5.0 mL), and the mixture was stirred at room temperature for 8 h under an

argon atmosphere. After further amount of NBA (49 mg, 0.36 mmol, total 1.1 mmol, 3.0 equiv) was added, the stirring was continued for 3 h. The mixture was cooled in an ice bath, diluted with 10% NaHSO₃ (10 mL), and extracted with CH₂Cl₂. The organic extracts were combined, washed successively with 10% NaHSO₃ and H₂O, then dried over anhyd MgSO₄. Filtration and concentration in vacuo followed by purification on column chromatography (EtOAc), afforded a pale yellow solid which mainly consisted of **24iA** and **25iA** (174 mg, 78%). The formation ratio of **24i** to **25i** was roughly estimated as 6:1 based on the NMR spectrum showing the C_{16b} and C₁₇-protons as two sets of doublets at δ 6.04 and 5.60. Recrystallization of the mixture of **24i** and **25i** from CHCl₃-Et₂O gave pure **24iA** as a yellow powder, mp 217–219 °C and $[\alpha]_D^{20}$ -263° (*c* 0.104, CHCl₃). IR (KBr) 1755, 1675, 1645, 1450, 1340, 1250, 1225, 1045, 955 cm⁻¹. ¹H NMR (CDCl₃) δ =1.99 (3H, s, C₆-CH₃), 1.7–2.3 (4H, m, NCH₂CH₂CH₂CH₂N), 2.3–2.9 (2H, m, C₇-H₂), 3.0–3.3 (2H, m, C₈-H₂), 3.3–3.9 (4H, m, NCH₂CH₂CH₂CH₂N), 3.96, 4.03 (6H, two s, OCH₃×2), 5.13, 5.44 (2H, two d, *J*= each 2.0 Hz, C₃-H and C₄-H), 6.04 (1H, d, *J*=2.0 Hz, C_{16b}-H), 7.6–7.9 (2H, m, aromatic protons), 8.1–8.4 (2H, m, aromatic protons). MS *m/z*: 628, 627, 626, 625 (M⁺). Found: C, 56.87; H, 4.51; N, 2.14%. Calcd for C₃₀H₂₀NO₉Br·0.5H₂O: C, 56.70; H, 4.60; N, 2.20%.

Concentration of the mother liquor from the recrystallization in vacuo gave a solid (27 mg) in which **25iA** was enriched. This was further separated by column chromatography (C₆H₆-EtOAc 2:1) to give pure **25iA** as a pale yellow solid (7.8 mg), mp 143–184.5° (decomp) and $[\alpha]_D^{20}$ +295° (*c* 0.124, CHCl₃). IR (KBr) 1770, 1675, 1455, 1340, 1265, 1040 cm⁻¹. ¹H NMR (CDCl₃) δ =1.95–2.14 (4H, m, NCH₂CH₂CH₂CH₂N), 2.11 (3H, s, C₁-CH₃), 2.40 (1H, dddd, *J*=14.0, 7.6, 2.1, and 1.1 Hz, C_{3'}-eq-H), 2.60 (1H, ddd, *J*=14.0, 11.2, and 7.4 Hz, C_{3'}-ax-H), 3.06 (1H, ddd, *J*=18.9, 11.2, and 7.6 Hz, C_{4'}-ax-H), 3.34 (1H, ddd, *J*=18.9, 7.4, and 1.1 Hz, C_{4'}-eq-H), 3.50–3.63 (4H, m, NCH₂CH₂CH₂CH₂N), 3.94, 4.06 (6H, s, OCH₃×2), 4.81, 5.15 (2H, two s, C₅-H and C₆-H), 5.60 (1H, d, *J*=2.1 Hz, C₁-H), 7.72–7.80 (2H, m, aromatic protons), 8.17–8.25 (2H, m, aromatic protons). MS *m/z*: 627, 625 (M⁺). High resolution MS: Found: 627.0902 and 625.0881. Calcd for C₃₀H₂₈NO₉Br: 627.0925 and 625.0946.

Although the pale yellow solid obtained by the bromolactonization was expected to involve small amounts of **24iB** and **25iB**, these undesired isomers could not be detected by the NMR spectrum. Based on the optical purity of (**R**)-**4d** derived from the mixture of **24i** and **25i**, the total amount of **24iB** and **25iB** should be less than 5%. Since **25i** being a sort of benzyl bromide, seemed to be fairly unstable, the mixture of **24i** and **25i** was immediately subjected to the next reaction.

(3R,4R,6R,6aS,16bS)-6a-Bromo-3,6-epoxy-9-methoxy-6-methyl-4-(dimethylcarbamoyl)-3,4,6a,7,8,16b-hexahydro-2H,6H-naphthaceno[1,2-b][1,5]dioxocin-2,10,15-trione (24jA), (1R,1'R,2S,5R,6R)-1'-Bromo-5'-methoxy-1-methyl-6-(dimethylcarbamoyl)-3',4'-dihydro-3,7,8-trioxaspiro[bicyclo[3.2.1]octane-2,2'-(1'H)-naphthacene]-4,6',11'-trione (25jA), and Their (6aR,16bR)- and (1'S,2R)-Isomers (24jB and 25jB).
Bromolactonization of 23j: N-Bromoacetamide (205 mg, 1.5 mmol) was added to a solution of **23j** (254 mg, 0.49 mmol) in a mixture of DMF-H₂O (100:1) (7.0 mL), and the mixture

was stirred at room temperature under an argon atmosphere for 7 h. After further amount of NBA (67 mg, 0.49 mmol, total 2.0 mmol, 4.0 equiv) was added, the stirring was continued for 3 h. Work-up of the reaction mixture in the same manner as that described for the bromolactonization of **23i** gave a pale yellow solid which mainly consisted of **24jA** and **25jA** (239 mg, 85%). The formation ratio of **24j** to **25j** was estimated as 6:1, based on the NMR spectrum showing the C₆ and C₁-methyl groups as two singlets at δ 1.98 and 2.05. This solid was recrystallized from CHCl₃-Et₂O to give **24jA** as a yellow powder, mp 238–239.5 °C (decomp) and $[\alpha]_D^{20}$ -103° (*c* 0.105, CHCl₃). IR (KBr) 1750, 1680, 1640, 1590, 1275, 1255, 1245, 1220 cm⁻¹. ¹H NMR (CDCl₃) δ =1.98 (3H, s, C₆-CH₃), 2.36 (1H, dddd, *J*=14.8, 7.5, 1.8, and 1.4 Hz, C₇-eq-H), 2.65 (1H, ddd, *J*=14.8, 10.6, and 6.9 Hz, C₇-ax-H), 3.06, 3.23 (6H, two s, N(CH₃)₂), 3.08 (1H, ddd, *J*=19.1, 10.6, and 7.5 Hz, C₈-ax-H), 3.30 (1H, ddd, *J*=19.1, 6.9, and 1.4 Hz, C₈-eq-H), 3.98 (3H, s, OCH₃), 5.32, 5.47 (2H, two d, *J*= each 1.9 Hz, C₃-H and C₄-H), 7.74–7.83 (2H, m, aromatic protons), 8.13 (1H, s, C₁₆-H), 8.23–8.30 (2H, m, aromatic protons). Found: C, 56.70; H, 4.29; N, 2.38; Br, 14.11%. Calcd for C₂₇H₂₄NO₈Br: C, 56.86; H, 4.24; N, 2.46; Br, 14.01%.

Concentration of the mother liquor from the recrystallization in vacuo gave a solid in which the amount of **25jA** was increased. The NMR spectrum of this sample showed the followed signals assignable to **25jA** in addition to those of **24j**. ¹H NMR (CDCl₃) δ =2.05 (3H, s, C₁-CH₃), 2.42 (1H, dddd, *J*=14.1, 7.6, and 1.9 Hz, another coupling constant could not be determined due to overlapping, C_{3'}-eq-H), 2.54 (1H, ddd, *J*=14.1, 11.3, and 7.0 Hz, C_{3'}-ax-H), 3.03, 3.20 (6H, two s, N(CH₃)₂), 3.98 (3H, s, OCH₃), 4.98 (1H, s, C₁-H, C₅-H, or C₆-H), 5.28 (2H, s, two protons of C₁-H, C₅-H, and C₆-H), 7.70–7.84 (2H, m, aromatic protons), 8.08 (1H, s, C₁₂-H), 8.23–8.30 (2H, m, aromatic protons).

While the pale yellow solid obtained by the bromolactonization was anticipated to contain small amounts of **24jB** and **25jB**, these undesired isomers could not be detected by the NMR spectrum. Based on the optical purity of (**R**)-**4h** derived from this sample, the total amount of these isomers should be less than 5%. The mixture of **24j** and **25j** was immediately subjected to the next reaction.

(R)-(-)-2-Acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((R)-(-)-7-deoxy-4-demethoxydaunomycinone) ((R)-4d). A methanolic suspension (7.5 mL) containing the mixture of **24i** and **25i** (**24i**:**25i** 6:1) (177 mg, 0.28 mmol) and anhyd K₂CO₃ (80 mg, 0.58 mmol) was stirred at room temperature under an argon atmosphere for 3.5 h to produce the epoxide. After 5% Pd/C (30 mg) was added to the resulting suspension, the mixture was stirred under a hydrogen atmosphere for 23 h to cleave the epoxide. Insoluble materials were removed by filtration, and the filtrate was concentrated in vacuo. Ethanol (2.0 mL) and concd HCl (1.0 mL) were added to the concentration residue, and the mixture was heated at reflux for 1 h to hydrolyse the chiral acetal group. After concd HCl (1.0 mL) was added, the reflux was further continued for 1 h. The mixture was cooled, diluted with H₂O (20 mL), and extracted with CH₂Cl₂. The organic extracts were combined, washed with H₂O, then dried over anhyd MgSO₄. Filtration and concentration in vacuo gave crude (**R**)-**4i** as a yellow solid. A benzene solution (15 mL) of crude (**R**)-**4i** and anhyd AlCl₃

(408 mg, 3.1 mmol) was stirred at 50 °C for 2 h under an argon atmosphere to cleave the two phenolic methyl ethers. After cooling, the mixture was diluted with satd oxalic acid solution (40 mL), and extracted with CH₂Cl₂. The organic extracts were combined, washed with H₂O, then dried over anhyd MgSO₄. Filtration and concentration in vacuo followed by purification on column chromatography (C₆H₆-EtOAc 10:1), gave (**R**)-**4d** as orange crystals (67.9 mg, 68% overall yield from the mixture of **24i** and **25i**), mp 215–218.5 °C and $[\alpha]_D^{20}$ –90.4° (*c* 0.104, CHCl₃), $[\alpha]_D^{20}$ –20.1° (*c* 0.189, CHCl₃-MeOH 1:1) (lit.⁹ mp 218–219 °C and $[\alpha]_D^{20}$ –87.0° (*c* 0.115, CHCl₃); lit.¹⁴ mp 218–219.5 °C and $[\alpha]_D^{20}$ –90.0° (*c* 0.106, CHCl₃); lit.¹⁵ mp 217–219 °C and $[\alpha]_D^{20}$ –90.3° (*c* 0.106, CHCl₃); lit.⁴³ $[\alpha]_D^{20}$ –95.2° (*c* 0.13, CHCl₃) and $[\alpha]_D^{20}$ –20.0° (*c* 0.18, CHCl₃-MeOH 1:1)). IR and NMR spectra of this sample were superimposable on those of the authentic sample.⁹ Methylation of this sample with Me₂SO₄ and anhyd K₂CO₃ in Me₂CO according to the reported procedure⁹ reproduced (**R**)-**4i** as a yellow solid in 98% yield after purification on column chromatography (C₆H₆-EtOAc 3:1). The optical purity of (**R**)-**4i** was rigorously determined as 94% ee by measuring the NMR spectrum in the presence of Eu(hfc)₃ following the same manner as that reported.⁹ Accordingly, the optical yield of (**R**)-**4d** produced from the mixture of **24i** and **25i** was estimated as 94% ee.

(**R**)-2-Acetyl-2,5-dihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione ((**R**)-**7,11-dideoxy-4-demethoxydaunomycinone**) ((**R**)-**4h**). The same four successive treatments of the mixture of **24j** and **25j** (**24j**:**25j** 6:1) (188 mg, 0.33 mmol) as those described for the preparation of (**R**)-**4d** gave (**R**)-**4h** as yellow crystal (53.8 mg, 49% overall yield from the mixture of **24j** and **25j**), after purification on column chromatography (CH₂Cl₂-EtOAc 7:1), mp 202.5–204.5 °C and $[\alpha]_D^{20}$ –32.7° (*c* 0.104, CHCl₃), $[\alpha]_D^{20}$ +17.3° (*c* 0.104, CHCl₃-MeOH 1:1). A part of (**R**)-**4h** was recrystallized from C₆H₆ to give an analytical sample as yellow crystals, mp 204.5–206.5 °C and $[\alpha]_D^{20}$ –35.3° (*c* 0.102, CHCl₃), $[\alpha]_D^{20}$ +16.0° (*c* 0.100, CHCl₃-MeOH 1:1). IR (KBr) 3475, 1705, 1670, 1630, 1590, 1360, 1290 cm^{–1}. ¹H NMR (CDCl₃) δ =1.8–2.1 (2H, m, C₃-H₂), 2.37 (3H, s, COCH₃), 2.75, 3.30 (2H, two d, *J*= each 18.0 Hz, C₁-H₂), 2.6–3.1 (2H, m, C₄-H₂), 3.70 (1H, s, OH), 7.47 (1H, s, C₁₂-H), 7.7–7.9 (2H, m, aromatic protons), 8.1–8.4 (2H, m, aromatic protons), 12.95 (1H, s, phenolic OH). Found: C, 70.90; H, 4.74%. Calcd for C₂₀H₁₆O₅·1/6H₂O: C, 70.79; H, 4.85%.

In order to determine the optical purity of (**R**)-**4h**, the sample (20.2 mg, 0.06 mmol) obtained from the column chromatography was methylated according to the same procedure as that described for (**R**)-**4i**. Purification of the crude product by column chromatography (C₆H₆-EtOAc 4:1) gave (**R**)-**4j** as a yellow solid (18.5 mg, 88%), mp 140–141 °C and $[\alpha]_D^{20}$ +64.7° (*c* 0.102, CHCl₃), $[\alpha]_D^{20}$ +43.0° (*c* 0.107, CHCl₃-MeOH 1:1). This sample showed the identical NMR spectrum with that of **dl-4j**. The NMR spectrum of **dl-4j** measured in the presence of Eu(hfc)₃ exhibited two sets of two singlets at δ 4.01, 4.24 and 9.18, 9.47. The former two singlets could be assigned to the acetyl group and the latter to the C₁₂-proton. Two singlets at δ 4.24 and 9.47 were only observed in the NMR spectrum of (**R**)-**4j** measured under the same conditions as that for the racemic compound. Accordingly, the optical yield of (**R**)-**4h** produced from the mixture of **24j** and **25j** was determined as more than 99% ee.

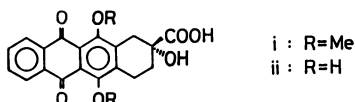
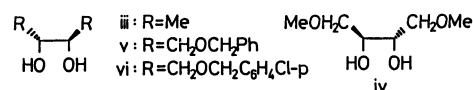
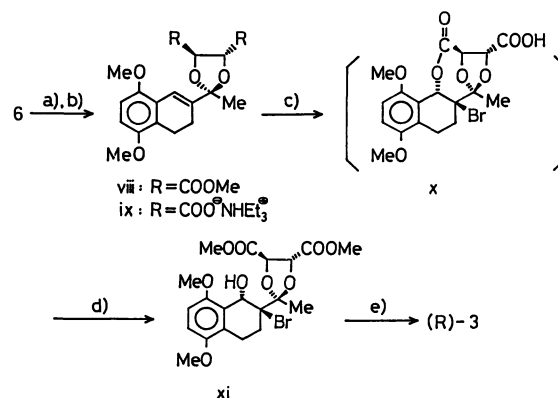
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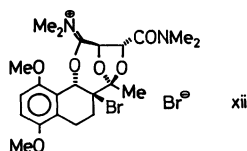
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Soc.*, **104**, 7372 (1982).25) (*R*)-(+)-2-Hydroxy-5,12-dimethoxy-1,2,3,4-tetrahydro-6,11-dioxo-2-naphthacene-1-carboxylic acid (**i**) produced from 5,12-dimethoxy-3,4-dihydro-6,11-dioxo-2-naphthacene-1-carboxylic acid by the asymmetric bromolactonization, could not be derived to (*R*)-**4i** by treating with methylolithium.⁹ However, we have recently explored that sequential treatments of (*R*)-2,5,12-trihydroxy-1,2,3,4-tetrahydro-6,11-dioxo-2-naphthacene-1-carboxylic acid (**ii**) with *N,N'*-carbonyldiimidazole, trimethylsilyl trifluoromethanesulfonate, and methylmagnesium bromide efficiently afford (*R*)-**4d**. The acid (**ii**) could be readily obtained from **i** or independently prepared from 5,12-dihydroxy-1,2,3,4-tetrahydro-2,6,11-naphthacene-1-trione. See ref. 23 and references cited therein.26) The C_2 -symmetric nature of optically active tartaric acid derivatives has been introduced as efficient chiral templates in asymmetric synthesis. For example, P. A. Bartlett, W. 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Synth.*, **61**, 24 (1983).31) At the outset of this work, (2*R*,3*R*)-2,3-butanediol (**iii**), (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol (**iv**), (2*R*,3*R*)-1,4-bis(benzyloxy)-2,3-butanediol (**v**), and (2*R*,3*R*)-1,4-bis(4-chlorobenzyloxy)-2,3-butanediol (**vi**) were employed as chiral sources. When the acetals (**vii**) prepared from **6** and the chiral diols (**iii**–**vi**) were treated with *N*-bromoacetamide and barium hydroxide in a mixture of tetrahydrofuran and water, diastereomeric mixtures of the bromohydrins similar to **10** could be obtained as sole reaction products in almost quantitative yields. Thesebromohydrins were converted to optically active **3**, 10% ee [(*R*)-**3**, **iii** as a chiral source], 17% ee [(*S*)-**3**, **iv** as a chiral source], 19% ee [(*R*)-**3**, **v** as a chiral source], and 17% ee [(*R*)-**3**, **vi** as a chiral source], by the same sequential treatments as those employed for the preparation of (*R*)-**3** from the mixture of **10aA** and **10aB**. On the other hand, the diastereoselective epoxidation of **vii** with *m*-chloroperbenzoic acid, *t*-butyl hydroperoxide-oxobis(acetylacetonato)vanadium(IV), hydrogen peroxide-sodium tungstate, etc., were all found to be fruitless and simply recovered the starting material (**vii**). By accumulating these numerous unsuccessful results, the novel bromolactonization reaction reported herein was finally explored.32) When (*R,R*)-(+)-dimethyl tartrate was used in place of **5**, the same successive acetalization and transacetalization gave the chiral acetal (**viii**) in 80% overall yield. Treatment of the bis(triethylamine) salt (**ix**) derived from **viii**, under the conditions for bromolactonization produced the bromolactone which was presumed to mainly consist of **x**. Since **x** was found to be unstable, it was immediately derived to the bromohydrin (**xi**) in 79% yield from **viii** by methanolysis and esterification. Successive epoxide formation, catalytic hydrogenation, and acidic hydrolysis in the same manner as that described for **9** and **10**, afforded (*R*)-**3**, mp 126.5–127.5 °C and $[\alpha]_D^{20} -45.8^\circ$ (c 0.94, CHCl₃), 96% ee,³⁵ in 47% overall yield from **xi** (M. Suzuki, Y. Kimura, and S. Terashima, unpublished results). This asymmetric synthesis of (*R*)-**3** is considered to be less practical than that reported herein because of the complex multi-step operations and the lower overall yield.a) (i) CH(OMe)₃-CSA in MeOH, (ii) (+)-Dimethyl (2*R*,3*R*)-tartrate-CSA-MS3A in C₆H₆. b) Et₄N-H₂O. c) CH₃CONHBr (4.0 equiv) in DMF, 0 °C, 45.5 h. d) (i) Et₃N-MeOH, (ii) CH₂N₂. e) (i) K₂CO₃ in MeOH, (ii) H₂-5%Pd/C, (iii) concd HCl.33) Presence of a small amount of water in the reaction medium was found to be necessary for effecting the successful formation of **9a** and **10a** from **8a**. Considering the fact that the bromolactonization of the bis(triethylamine) salt (**ix**) proceeds in anhyd DMF (see, Ref. 32), the role of

water is considered to promote hydrolysis of the intermediary immonium salt (**xii**) during the bromolactonization.



34) C. M. Wong, D. Popien, R. Schwenk, and J. Teraa, *Can. J. Chem.*, **49**, 2712 (1971).

35) The optical yield of this sample was determined by measuring the NMR spectrum, directly or after converting to the methyl ether, in the presence of the chiral shift reagent. See the experimental section.

36) G. Cassinelli and F. Arcamone, *Ger. Offen*, 2757101 (1978).

37) By the same method as that described herein, 2-acetyl-5,12-dimethoxy-3,4-dihydro-6,11-naphthacenedione could be also prepared from partially optically active (*S*)-**4d** which was available in a large quantity by the optical resolution of *dl*-**4d**.^{14,15)}

38) A. V. R. Rao, A. R. Mehendale, and K. B. Reddy, *Tetrahedron Lett.*, **24**, 1093 (1983); N. Tanno, M. Muramatsu, H. Sato, and K. Ishizumi, Japan Patent, JP-58-198435.

39) Attempted dehydration of *dl*-**4h** with trifluoroacetic anhydride and collidine simply recovered the starting materials. The methyl ether (*dl*-**4j**) was found to be dehydrated more effectively than *dl*-**4h** under the reaction conditions.

40) Considering the ratio of the two isomers of **16**, the optical purity of this sample could be estimated as ca. 30%.

41) When **9aA** (200 mg, 0.43 mmol) was treated with sodium methylate (1.3 mmol) in MeOH for 32 h, a mixture of **11a** and its (4*S*)-epimer (the formation ratio 20:1) separable by column chromatography, could be obtained in 84% yield.

42) The TLC and NMR spectral analyses showed that this sample was contaminated with a small amount of the C_{3,4}-dehydro isomer of **23i** (M. Suzuki, Y. Kimura, and S. Terashima, unpublished results).

43) R. A. Russell, R. W. Irvine, and A. S. Krauss, *Tetrahedron Lett.*, **25**, 5817 (1984).