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Asymmetric Synthesis of optically Active Anthracyclinone Intermediate and 4-Demethoxyanthracyclinones by the Use of a Novel Chiral Reducing Agent[1]

NORIHIKO TANNO and SHIRO TERASHIMA*

Faculty of Pharmaceutical Sciences, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan

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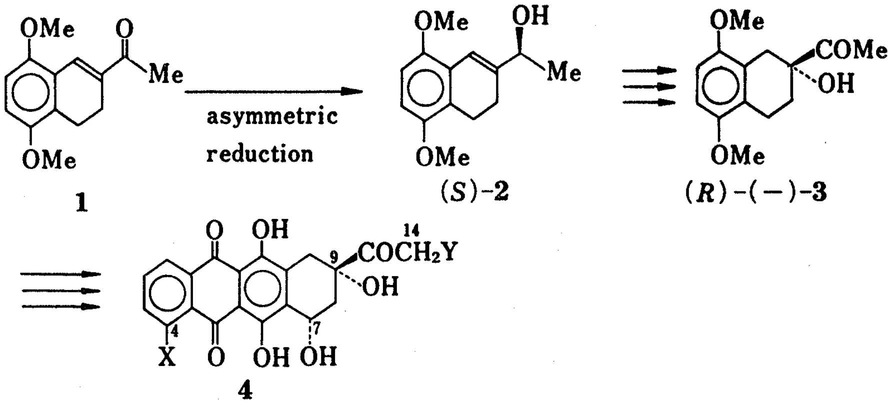
Asymmetric reduction of 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**1**) with a novel modified hydride, originally prepared by partial decomposition of lithium aluminum hydride with (1*R*,2*S*)-(−)-*N*-methylephedrine (1.0 eq) and *N*-ethylaniline (2.0 eq), was found to proceed highly stereoselectively, giving (*S*)-(−)-2-1′-hydroxyethyl-5,8-dimethoxy-3,4-dihydronaphthalene ((*S*)-(−)-**2**) in 100% chemical and 92% optical yields. Direct recrystallization of (*S*)-(−)-**2**, 92% e.e., afforded optically pure (*S*)-(−)-**2** in 87% yield based on **1**.

Optically pure (*S*)-(−)-**2** was converted to (*R*)-(−)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*R*)-(−)-**3**), 100% e.e., a versatile key intermediate for optically active anthracyclinone synthesis, in a good overall yield according to the reaction scheme established in the preceding paper.

Synthesis of optically pure (+)-4-demethoxydaunomycinone ((+)-**4d**) and (+)-4-demethoxyadriamycinone ((+)-**4c**) was accomplished by using optically pure (*R*)-(−)-**3** as a starting material and by following the reported synthetic scheme with slight modifications.

Keywords——anthracycline; anthracyclinone; 4-demethoxydaunomycinone; 4-demethoxyadriamycinone; asymmetric synthesis; asymmetric reduction; modified lithium aluminum hydride; (1*R*,2*S*)-(−)-*N*-methylephedrine; *N*-ethylaniline; Friedel–Crafts reaction

In the preceding paper,[2] it was reported that, when asymmetric reduction of the α,β-unsaturated ketone (**1**) proceeds in a highly stereoselective manner to afford the (*S*)-allylic alcohol ((*S*)-**2**) in high chemical and optical yields, the optically pure (*R*)-(−)-α-hydroxy ketone ((*R*)-(−)-**3**), a versatile key intermediate for optically active anthracyclinones (**4**),[3,4] can be readily elaborated from (*S*)-**2**.



1 (*S*)-**2** (*R*)-(−)-**3**

4

	X	Y
a :	OMe	OH
b :	OMe	H
c :	H	OH
d :	H	H

Asymmetric reductions which have hitherto been reported to produce optically active secondary alcohols from ketones consist of the following four types of reactions: a) asymmetric reduction with a chiral Grignard or aluminum alkoxide reagent (Meerwein–Ponndorf–Verley reagent); b) asymmetric hydrogenation or hydrosilylation with a chiral transition metal catalyst; c) asymmetric reduction with a chiral metal hydride; d) asymmetric reduction by the use of microorganisms or enzymes.$^{5,6)}$ However, it is expected that method c) would be one of the most operationally simple and economical methods if readily available optically active compounds could be utilized as chiral sources. In method a), recovery of the chiral source is mechanistically impossible.$^{5)}$ Specific hydrogenation of the ketonic function of an α,β-unsaturated ketone such as **1** seems to be quite difficult, and moreover, preparation of a chiral ligand required for producing a chiral metal catalyst is sometimes tedious in method b).$^{5)}$ Asymmetric reduction of α,β,-unsaturated ketones according to method d) has been reported to usually give low chemical yields.$^{6,7)}$

For the reasons delineated above, the authors planned to examine the asymmetric reduction of **1** to (*S*)-**2** by the use of a chiral metal hydride prepared by partial decomposition of lithium aluminum hydride (LAH) with a chiral compound. While there have been reports of various types of partially decomposed LAH which can reduce alkyl aryl ketones and alkyl alkynyl ketones in high optical yields,$^{5,8-12)}$ the number of modified LAH applicable to asymmetric reduction of α,β-unsaturated ketones is quite limited,$^{8c,13)}$ and rather low optical yields (25—30% e.e.) of optically active allylic alcohols are usually obtained$^{8c,13)}$ except for the recent successful result achieved by using LAH decomposed with optically active 2,2′-dihydroxy-1,1′-binaphthyl.$^{12)}$ Taking into account these points, we first looked at the possibility of exploiting a novel modified LAH which could efficiently reduce **1** to (S)-**2** in high chemical and optical yields.

This report deals with the development of a novel chiral reducing agent effective for the asymmetric reduction of **1**, successful transformation of optically pure (*S*)-(−)-**2** to (*R*)-(−)-**3** according to the established reaction scheme,$^{2)}$ and further elaboration of (*R*)-(−)-**3** to optically pure (+)-4-demethoxydaunomycinone((+)-**4d**) and (+)-4-demethoxyadriamycinone((+)-**4c**) according to the reported synthetic route with slight modifications.$^{14-18)}$

Results and Discussion

A. Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (1) by the Use of Modified Lithium Aluminum Hydride (LAH)

In order to investigate the effectiveness of the hitherto reported modified LAH, and moreover, to develop an effective chiral reducing agent for the preparation of (*S*)-**2** from **1**, some reported hydrides were employed for the asymmetric reduction of **1**. Thus, as shown in Table I, when **1** was treated with the chiral reagent produced by decomposing LAH with (*S*)-(+)-2-(anilinomethyl)pyrrolidine$^{11)}$ (Table I, run 1), (−)-**2** was obtained in 60% yield. Based on detailed stereochemical studies on the epoxidation of (±)-**2**$^{2)}$ and the successful synthesis of (*R*)-(−)-**3** from (−)-**2** (*vide infra*), the absolute configuration of (−)-**2** was assigned as (*S*). The optical yield of this sample could be also determined as 54% e.e., since optically pure (*S*)-(−)-**2** gave $[\alpha]_D^{20}$ −20.5° (EtOH) (*vide infra*). When the amount of the reducing agent was increased (Table I, run 2), the chemical yield of (*S*)-(−)-**2** reached 100% with a slight increase of the optical yield.

Treatment of **1** with LAH partially decomposed with (1*R*, 2*S*)-(−)-*N*-methylephedrine [(−)-*N*-methylephedrine] and 3,5-dimethylphenol$^{10)}$ gave lower chemical and optical yields of (*S*)-(−)-**2** (Table I, run 3). A chiral hydride which had been successfully applied to the asymmetric reduction of 2-alkylcyclopentane-1,3,4-trione derivatives,$^{19)}$ gave a similar disappointing result (Table I, run 4). A decrease in the amount of (−)-*N*-methylephedrine only resulted in an improvement of the chemical yield (Table I, runs 5,6).

TABLE I. Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**1**) with Various Types of Modified LAH[a]

Run	Chiral reducing agent (molar ratio to **1**)			Reaction conditions		(*S*)-(−)-2-1′-Hydroxyethyl-5,8-dimethoxy-3,4-dihydronaphthalene ((*S*)-(−)-**2**)		
	LAH	chiral source[b]	additive[c]	Temp. (°C)	Time (h)	Chemical yield (%)[d]	$[\alpha]_D^{20}$ (°) (*c*, EtOH)	Optical yield(%e.e.)[e]
1	2.36	2.73(A)[f]	—	−78	5	60	−11.0(1.93)	54
2	6.6	6.6(A)	—	−78	5	100	−12.8(2.01)	62
3	3.3	3.3(E)	6.6(D)[g]	−20	3	11	−2.7(0.52)	13
4	3.3	9.9(E)[h]	—	25	23	34	—[i]	17[i]
5	3.3	6.6(E)	—	0	8	32	0(0.61)	0
6	3.3	3.3(E)	—	−78	1	92	−0.82(1.71)	4
7	3.3	3.3(E)	6.6(P)	−78	3	0	—	—
8	3.3	3.3(E)	6.6(T)	−78	3	0	—	—
9	3.3	3.3(E)	6.6(M)	−78	3	97	−17.6(1.81)	86

[a] All chiral reducing agents were prepared by partially decomposing LAH with a chiral source or with a combination of chiral source and additive.

[b] A, (*S*)-(+)-2-(anilinomethyl)pyrrolidine; E, (−)-*N*-methylephedrine.

[c] D, 3,5-dimethylphenol; P, phenol; T, thiophenol; M, *N*-methylaniline.

[d] Based on **1** after purification by preparative TLC (C_6H_6–EtOAc 8: 1).

[e] Optically pure (*S*)(−)-**2** gives $[\alpha]_D^{20}$ −20.5° (*c*=1.07, EtOH) (see text).

[f] See ref. 11. [g] See ref. 10. [h] See ref. 19.

[i] Determined by measuring the NMR spectrum in the presence of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium (III) ($Eu(hfc)_3$).

At this stage, it became evident that the asymmetric reduction of **1** could not be achieved in high chemical and optical yields by employing the hitherto reported modified LAH,[10,11,19] and that a novel reducing agent would have to be developed.

In the reduction of a ketone with LAH, it is well established that four hydrogen atoms successively participate in the reaction, giving lithium tetraalkoxyaluminate, $Li^+Al^-(OCHRR')_4$, as a final product, and that the rate of each reduction step is slower than that of the preceding step.[20] This means that the nucleophilicity of hydride gradually decreases with an increase of the number of alkoxy groups binding with the central aluminum atom. Therefore, in order to effectively reduce the resonance-stabilized carbonyl group of **1** with partially decomposed LAH, introduction of a less electronegative atom onto the aluminum atom should be required in order to avoid a decrease of the nucleophilicity of hydride.

Thus, the asymmetric reduction of **1** was attempted using LAH partially decomposed with (−)-*N*-methylephedrine and *N*-methylaniline (Table I, run 9). As expected, (*S*)-(−)-**2** could be obtained in 97% yield. Measurement of the optical rotation disclosed that the asymmetric reduction of **1** proceeded highly stereoselectively to give (*S*)-(−)-**2** in 86% optical yield.[21] Replacements of the nitrogen atom presumably bound with the aluminum atom in the chiral hydride[23] with a more electronegative atom such as oxygen or sulfur resulted in complete recovery of the starting material (Table I, runs 7,8).

A similar explanation might also be valid for the results shown in Table I, runs 1—3. Thus, the chiral reducing agent in which two nitrogen atoms take part in decomposing LAH (Table I, runs 1,2), gives a superior result to that obtained by replacing hydrogen atoms of LAH with three oxygen atoms (Table I, run 3).

Since *N*-methylaniline was found to be an excellent achiral additive which could enhance the nucleophilicity of hydride, the asymmetric reduction of **1** was further examined with various amines as achiral additives. These results are summarized in Table II. It is clear that *N*-alkylanilines having no steric hindrance in the vicinity of the nitrogen, especially *N*-ethylaniline (Table II, run 2), are the best achiral amine additives (Table II, runs 1—4,7,9), and that aliphatic secondary amines (Table II, runs 10—16) and heterocyclic amines (Table II, runs 17—20) afford lower chemical and optical yields of (*S*)-(−)-**2**. The results obtained by employing aliphatic secondary and heterocyclic amines as achiral additives might be rationalized by the lowered acidity of the N–H group which could interfere with the formation of a chiral reducing agent containing one molecule of (−)-*N*-methylephedrine and two molecules

TABLE II. Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**1**) with LAH partially decomposed with (−)-*N*-Methylephedrine and Various Achiral Amine Additives[a]

Run	Achiral amine additive	(*S*)(−)-2-1′-Hydroxyethyl-5,8-dimethoxy-3,4-dihydronaphthalene ((*S*)-(−)-**2**) Chemical yield (%)[b]	[α]$_D^{20}$ (°) (*c*, EtOH)	Optical yield (% e.e.)[c]	Recovery of **1** (%)
1	PhNHMe	97	−17.6 (1.81)	86	—[d]
2	PhNHEt	100	−18.8 (2.48)	92	—[d]
3	PhNHn-Pr	91	−17.3 (1.11)	85	—[d]
4	PhNHn-Bu	96	−17.7 (1.79)	86	—[d]
5	PhNHiso-Pr	99	−3.9 (1.86)	19	—[d]
6	PhNH*tert*-Bu	36	−2.7 (0.67)	13	61
7	3,5-Me_2PhNHEt	95	−16.4 (1.79)	80	—[d]
8	2,6-Me_2PhNHMe	62	−0.3 (1.16)	2	40
9	PhNHPh	94	−17.2 (1.76)	84	—[d]
10	PhNH$(CH_2)_2$NHPh	5	—[e]	—[e]	—[f]
11	*n*-BuNHMe	7	—[e]	—[e]	91
12	PhCH_2NHMe	19	—[e]	—[e]	67
13	c-C_6H_{13}NHMe	46	−4.6 (0.43)	24	46
14	Pyrrolidine	0	—	—	97
15	Piperidine	16	−5.4 (0.30)	27	86
16	Morpholine	23	−1.3 (0.43)	7	81
17	Pyrrole	0	—	—	97
18	Pyrazole	0	—	—	97
19	Carbazole	18	−15.0 (0.34)	74	79
20	Benzotriazole	0	—	—	100

a) All reactions were carried out using LAH (3.3 eq to **1**) partially decomposed with (−)-*N*-methylephedrine (3.4 eq to **1**) and an achiral amine additive (6.8 eq to **1**) in ether at −78 °C for 3 h. (*S*)-(−)-**2** was obtained as a sole reduction product.

b) Based on **1** after purification by preparative TLC (C_6H_6–EtOAc 8:1).

c) Optically pure (*S*)-(−)-**2** gives [α]$_D^{20}$ −20.5° (*c*=1.07, EtOH) (see text).

d) The starting material (**1**) was not detected by TLC analysis.

e) Measurement of the optical rotation was not attempted.

f) Recovery of the starting material was not performed.

TABLE III. Effects of the Amount of *N*-Ethylaniline on the Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**1**)[a]

Run	Chiral reducing agents (molar ratio to **1**) LAH : (−)-*N*-methylephedrine : PhNHEt (*vs.* LAH)	(*S*)(−)-2-1′-Hydroxyethyl-5,8-dimethoxy-3,4-dihydronaphthalene ((*S*)-(−)-**2**) Chemical yield (%)[b]	[α]$_D^{20}$ (°) (*c*, EtOH)	Optical yield (% e.e.)[c]
1	3.3 : 3.4 : 3.4(×1.0)	81	−13.2(1.51)	65
2	3.3 : 3.4 : 5.1(×1.5)	100	−17.8(1.93)	87
3	3.3 : 3.4 : 6.0(×1.75)	96	−18.2(1.80)	89
4	3.3 : 3.4 : 6.8(×2.0)	100	−18.8(2.48)	92
5	3.3 : 3.4 : 8.5(×2.5)	47[d]	−12.2(0.89)	59
6	3.3 : 3.4 : 10.2(×3.0)	62[d]	−12.4(1.16)	60

a) All reactions were arried out using LAH partially decomposed with (−)-*N*-methylephedrine and *N*-ethylaniline in ether at −78°C for 3 h. (*S*)-(−)-**2** was obtained as a sole reduction product.

b) Based on **1** after purification by preparative TLC (C_6H_6: EtOAc 8: 1).

c) Optically pure (*S*)-(−)-**2** gives [α]$_D^{20}$ −20.5° (*c*=1.07, EtOH).

d) Recovery of the starting material (**1**) was not attempted, though the presence of **1** in the crude reaction product was observed by TLC analysis.

of achiral amine additive.[23]

Next, the effect of the amount of *N*-ethylaniline on the asymmetric reduction of **1** was studied. As shown in Table III, even if 1.0 eq of *N*-ethylaniline was used, a 65% optical yield of (*S*)-(—)-**2** could be obtained (Table III, run 1). This figure is very close to that achieved with the chiral reagent prepared using (*S*)-(+)-2-(anilinomethyl)pyrrolidine as a chiral source (Table I, runs 1,2). This result also indicates that decomposition of LAH with 1.0 eq of (—)-*N*-methylephedrine and 1.0 eq of *N*-ethylaniline has already induced an asymmetry into one of the two remaining hydrogens. While the use of 2.0 eq of *N*-ethylaniline gave the best asymmetric induction (Table III, run 3), the chiral reducing agent produced by using 3.0 eq of *N*-ethylaniline still possessed reducing ability (Table III, run 6). This means that, due to steric hindrance, the third molecule of *N*-ethylaniline cannot react with the aluminum which already carries three nitrogen atoms.

To investigate other possible factors which may modify the nature of the chiral reagent, examination of *N*-alkyl substituents of (—)-*N*-alkylephedrines, reaction solvents, reaction temperatures, and temperatures for preparing the chiral reducing agent (aging temperatures)

TABLE IV. Effects of *N*-Alkyl Substituent of (—)-*N*-Alkylephedrine (A) and Reaction Solvent (B) on the Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**1**)[a]

A

N-Alkyl substituent of (—)-*N*-alkylephedrine	(*S*)-(—)-**2** Chemical yield(%)[b]	$[\alpha]_D^{20}$ (°) (*c*, EtOH)	Optical yield(% e.e.)[c]
Me	94	−18.9(1.77)	92
Et	73	−15.5(1.37)	76
iso-Pr	58[d]	−15.4(1.09)	75
$PhCH_2$	82	−16.8(1.71)	82

B

Solvent	(*S*)-(—)-**2** Chemical yield(%)[b]	$[\alpha]_D^{20}$ (°) (*c*, EtOH)	Optical yield(% e.e.)[c]
Et_2O	94	−18.9(1.77)	92
THF	59[d]	−1.1(1.10)	5
Toluene	62[d]	−5.7(1.16)	28
DME	16[d]	—[e]	—[e]
Methylal	0[d]	—	—

a) All reactions were performed using LAH (3.3 eq to **1**) partially decomposed with (—)-*N*-alkylephedrine (3.4 eq to **1**) (for A) or with (—)-*N*-methylephedrine (3.4 eq to **1**) (for B) and *N*-ethylaniline (6.8 eq to **1**) in ether (for A) or in the indicated solvent (for B) at −78°C for 3 h. (*S*)-(—)-**2** was obtained as a sole reaction product.

b—*d*) See, Table III footnotes *b*—*d*).

e) Measurement of the optical rotation was not attempted.

TABLE V. Effects of Reaction (A) and Aging (B) Temperatures on the Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**1**)[a]

A

Reaction temp. (°C)	(*S*)-(—)-**2** Chemical yield(%)[b]	$[\alpha]_D^{20}$ (°) (*c*, EtOH)	Optical yield(% e.e.)[c]
35	95	−14.4(1.77)	69
0	98	−16.2(1.84)	79
−20	93	−16.8(1.74)	82
−78	94	−18.9(1.77)	92
−100	53[d]	−18.8(0.99)	92

B

Aging temp. (°C)	(*S*)-(—)-**2** Chemical Yield(%)[b]	$[\alpha]_D^{20}$ (°) (*c*, EtOH)	Optical yield(%)e.e.)[c]
35	100	−18.8(2.48)	92
20	100	−6.6(2.06)	33
0	45[d]	−4.1(2.13)	20

a) All reactions were carried out using LAH (3.3 eq to **1**) partially decomposed with (—)-*N*-methylephedrine (3.4 eq to **1**) and *N*-ethylaniline (6.8 eq to **1**) at the indicated temperature (for A) or at −78°C (for B) for 3 h. The chiral reducing agent was prepared at 35°C (for A) or at the indicated temperature (for B). (*S*)-(—)-**2** was obtained as a sole reaction product.

b—*d*) See, Table III footnotes *b*—*d*).

were also carried out, and the results are shown in Tables IV and V.

The results in Table IVA show that (—)-*N*-methylephedrine is the best chiral source. Change of the coordination ability resulting from the steric bulkiness of the *N*-substituent might explain the observed results. In accord with the reported results,$^{10,11)}$ the best chemical and optical yields were obtained by utilizing ether as a solvent. The results given in Table IVB might reflect subtle differences of coordination and solvation ability of the utilized solvents. In tetrahydrofuran (THF), the reducing agent may be present as a separated ion pair in the same way as LAH itself,$^{24)}$ and in toluene, the solvent will not coordinate with aluminum of the reducing agent present as a contact ion pair. Dimethoxyethane (DME) and methylal may remove a lithium cation from the reducing agent.$^{11b)}$ These solvent effects would deform the rigid structure of partially decomposed LAH which can be achieved in ether.

Studies on the reaction temperature (Table VA) clearly showed that the best chemical and optical yields of (*S*)-(—)-**2** could be obtained when the asymmetric reduction was carried out at —78°C. The fact that *ca.* 80% optical yield of (*S*)-(—)-**2** could be realized at 0— —20°C, may show one of the practical aspects for the developed chiral reducing agent. As to partially decomposed LAH, it is well recognized that the temperature at which a reducing agent is produced sometimes alters the stereoselectivity of the produced chiral hydride.$^{25)}$ The results in Table VB show that the chiral reducing agent prepared in refluxing ether (35°C) gives the best chemical and optical yields. At lower temperatures, the reactions of (—)-*N*-methylephedrine and/or *N*-ethylaniline with LAH might be incomplete.

While the reduction mechanism will be discussed in detail in the accompanying paper,$^{22)}$ these studies definitely established the optimized reaction conditions for producing a chiral reducing agent able to effect the asymmetric reduction of **1** to (*S*)-(—)-**2** in 100% chemical and 92% optical yields.

In a large-scale preparation, (*S*)-(—)-**2** obtained after concentration of the ethereal extracts was directly subjected to recrystallization, affording optically pure (*S*)-(—)-**2**, $[\alpha]_D^{20}$ —20.5° (EtOH), in 87% chemical yield based on **1**. The optical purity of this sample was ascertained by measuring its ^{1}H-nuclear magnetic resonance (NMR) spectrum in the presence of the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium (III) (Eu(hfc)$_3$). Concentration of the mother liquor from the recrystallization yielded (*S*)-(—)-**2** of low optical purity, 18% e.e., in 17% yield based on **1**, and oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in recovery of **1** in 94% yield. From the acidic aqueous layer obtained by the aqueous work-up, a mixture of (—)-*N*-methylephedrine and *N*-ethylaniline was recovered in 98% yield by successive acidification and extractive isolation. Fractional distillation of the mixture gave (—)-*N*-methylephedrine without racemization and *N*-ethylaniline in 83 and 100% recovery yields, respectively.

It is noteworthy that this procedure offers high chemical and optical yields, operational simplicity (no chromatographic separation), use of a readily available chiral source and additive, and efficient recovery of the chiral source and additive for reuse (simple fractional distillation), so that the asymmetric synthesis of (*S*)-(—)-**2** with the exploited reducing agent might fulfill the criteria required for a practical asymmetric synthesis.$^{26)}$ Since the asymmetric reduction of **1** was successfully achieved as detailed above, the preparation of (*R*)-(—)-**3** from (*S*)-(—)-**2** was next examined.

B. Preparation of (*R*)-(—)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*R*)-(—)-3) from (*S*)-(—)-2-1′-Hydroxyethyl-5,8-dimethoxy-3,4-dihydronaphthalene ((*S*)-(—)-2)

Preparation of (*R*)-(—)-**3** from optically pure (*S*)-(—)-**2** was attempted according to the reaction scheme established in the preceding paper.$^{2)}$ As shown in Chart 1, epoxidation of (*S*)-(—)-**2**$^{27)}$ gave a diastereomeric mixture of the α,β-epoxyalcohols (**5a** and **5b**) as an unstable oil, which without separation was subjected to reduction with LAH$^{27)}$ to give a diastereomeric mixture of the *vicinal*-diols ((—)-**6a** and **6b**) as colorless crystals in 85% yield based on (*S*)-(—)-

2. The predominantly formed diastereomer ((—)-**6a**) could be isolated in a pure state in 70% yield by recrystallization from ether. Oxidation of pure (—)-**6a** with Fetizon reagent[27] or with a combination of sulfur trioxide·pyridine complex–dimethyl sulfoxide–triethylamine[27] afforded optically pure (*R*)-(—)-**3** in 69 or 87% yield. Measurement of the ^{1}H-NMR spectrum in the presence of Eu(hfc)$_3$ confirmed the optical purity of (*R*)-(—)-**3** as 100% e.e. When Fetizon oxidation was performed using a mixture of (—)-**6a** and **6b**, (*R*)-(—)-**3**, 90% e.e. was obtained in 84% yield. Accordingly, the formation ratio of (—)-**6a** and **6b** in the epoxidation of (*S*)-(—)-**2** was disclosed to be 95: 5. This value is in good agreement with the formation ratio for the racemic modification determined from the ^{1}H-NMR spectrum.[2]

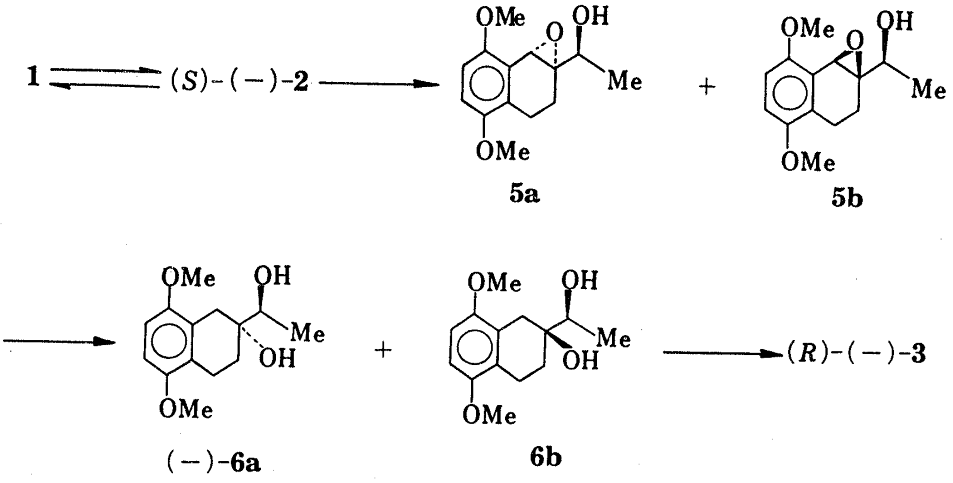


Chart 1

As mentioned above, the transformation of (*S*)-(—)-**2** to the optically pure key synthetic intermediate ((*R*)-(—)-**3**) for optically active anthracyclinones was accomplished in a good overall yield.

C. Synthesis of optically Pure (+)-4-Demethoxydaunomycinone ((+)-4d) and (+)-4-Demethoxyadriamycinone ((+)-4c)

With optically pure (*R*)-(—)-**3** in hand, preparation of (+)-**4d** and (+)-**4c** was next examined according to the reported synthetic scheme with slight modifications.[4,14–18]

According to the methods reported for the racemic modification,[2] treatment of (*R*)-(—)-**3** with *o*-methoxycarbonylbenzoyl chloride in the presence of anhyd. aluminum chloride, followed by alkaline hydrolysis of the methyl ester and ring closure of the acid with hydrogen fluoride[27] gave the (—)-dimethyl ether ((—)-**7**) in 67% yield from (*R*)-(—)-**3**. In contrast to the reported data,[15] (—)-**7** thus obtained was found to have *ca.* 75% e.e. probably due to partial racemization during the synthetic steps.[28] Fractional recrystallization from ether readily separated almost racemic and optically pure (—)-**7** in 18 and 32% yields, respectively. While the observed optical rotation of (—)-**7**, $[\alpha]_D^{20}$ —23.1° (CHCl$_3$), was rather lower than the reported value,[15] the optical purity of our sample was definitely determined as 100% e.e. by measuring its ^{1}H-NMR spectrum in the presence of Eu(hfc)$_3$.

When a mixture of (*R*)-(—)-**3**, phthalic anhydride, anhyd. aluminum chloride, and sodium chloride was heated at 180°C for 4 min in a similar manner to that reported for (±)-**3**,[27] partially racemized (—)-7-deoxy-4-demethoxydaunomycinone ((—)-**8**), 71% e.e. was obtained in 91% yield. This result also differs from the reported observation that the simultaneous inter- and intramolecular Friedel–Crafts reaction proceeds without racemization.[16,28] Repeated recrystallizations of this sample gave optically pure (—)-**8** in 38% yield. Partially optically active and optically pure (—)-**8** were subjected to methylation with dimethyl sulfate,[27] giving samples of (—)-**7** with 75 and 100% e.e. respectively. The former partially optically active (—)-**7** yielded optically pure (—)-**7** on recrystallization from ether.

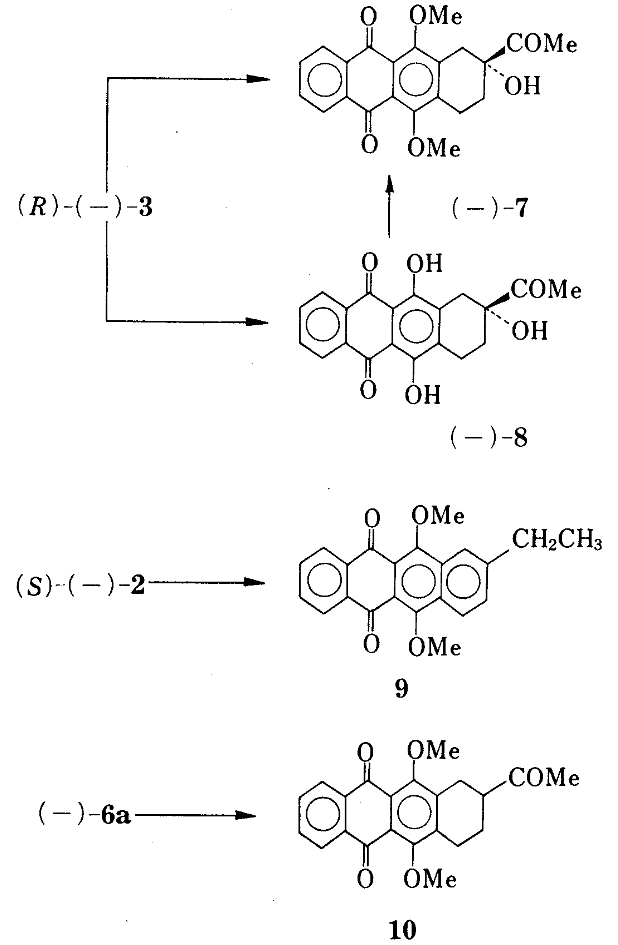
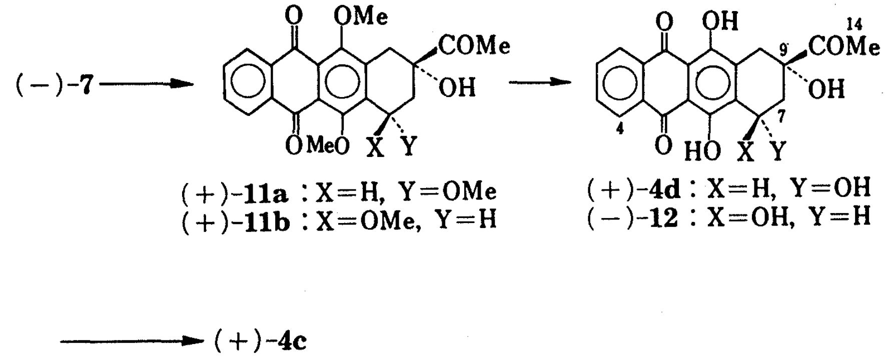


Chart 2

In order to prevent the racemization observed in the preparations of (—)-**7** and (—)-**8** from (*R*)(—)-**3**, successive Friedel–Crafts reaction with phthalic anhydride and methylation with dimethyl sulfate were attempted using (*S*)-(—)-**2** or (—)-**6a**, which lacked the α-hydroxy ketone moiety, as a reaction substrate. However, as shown in Chart 2, the aromatized product (**9**) was obtained from (*S*)-(—)-**2** in 46% yield due to successive dehydration–isomerization during the Friedel–Crafts reaction. When (—)-**6a** was utilized as a reaction substrate, pinacolic rearrangement of the *vicinal*-diol system concomitantly occurred to afford a 25% yield of the ketone (**10**).[30] Accordingly, synthesis of (+)-**4d** and (+)-**4c** was carried out using optically pure (—)-**7** prepared from (*R*)-(—)-**3**.

Acetalization of (—)-**7** (97% yield), followed by photo-sensitized bromination, acid-catalyzed methanolysis, and deacetalization (3 steps, 70%), according to the reported procedure[14,15] afforded an epimeric mixture of 4-demethoxydaunomycinone trimethyl ether ((+)-**11a** and (+)-**11b**). Separation by column chromatography gave (+)-**11a** and (+)-**11b** in 44 and 26% yields, respectively. Spectral properties of these products were identical with those of the racemic compounds reported by Wong.[14] 7-Epianthracyclinone is known to epimerize to anthracyclinone on treatment with trifluoroacetic acid followed by aqueous work-up.[31] Therefore, the crude mixture of (+)-**11a** and (+)-**11b** obtained from (—)-**7** was treated successively with aluminum chloride to cleave the two phenolic methoxy groups, trifluoroacetic acid to effect substitution of the C_7-methoxy group with a trifluoroacetoxy group[14,15] and epimerization of the formed C_7-trifluoroacetate, then aqueous ammonia to hydrolyze the C_7-trifluoroacetate. Chromatographic separation of the crude reaction product gave (+)-**4d**, $[\alpha]^{20}_{D}$ +153° (dioxane), and its 7β-epimer ((—)-**12**), $[\alpha]^{20}_{D}$ −62.0° (dioxane), in 37 and 9.4% yields, respectively. These aglycones ((+)-**4d** and (—)-**12**) showed the same spectral properties and optical rotations as those reported.[15,16,32,33]

Since asymmetric synthesis of (+)-**4d** was accomplished as cited above, further derivation of (+)-**4d** to (+)-**4c** was next examined. As the reported procedure for introducing a hydroxy group into the C_{14}-position of daunomycinone (**4b**)[17] or racemic **4d**[18] had not been reproduced, preparation of (+)-**4c** was attempted by employing various reaction conditions. After several unsuccessful experiments, it was found that bromination of (+)-**4d** with pyridinium hydrobromide–perbromide followed by treatment with aqueous alkaline solution gave (+)-**4c**, $[\alpha]^{20}_{D}$



(+)-**11a** : X=H, Y=OMe
(+)-**11b** : X=OMe, Y=H

(+)-**4d** : X=H, Y=OH
(−)-**12** : X=OH, Y=H

(+)-**4c**

Chart 3

+147° (dioxane), in 74% yield. This sample was characterized by spectroscopy and elemental analysis.

As described above, asymmetric synthesis of the optically pure anthracyclinone intermediate ((*R*)-(−)-**3**) and 4-demethoxyanthracyclinones ((+)-**4c** and (+)-**4d**) was completed. By applying the accumulated results, it should be possible to produce various structural types of optically pure anthracyclinones by asymmetric synthesis. In the course of these studies, we developed a novel chiral reducing agent able to effect the asymmetric reduction of **1** to (*S*)-(−)-**2**. Detailed studies on the general applicability and reduction mechanism of the exploited chiral hydride are the subject of the accompanying paper.[22)]

Experimental[34)]

(1*R*,2*S*)-(−)-*N*-Methylephedrine——Prepared according to the reported procedure.[35)] Colorless needles (recrystallized from MeOH), mp 86.5—87.5°C, [α]$^{20}_{D}$ −29.5° (*c*=4.54, MeOH) (lit.,[35)] mp 87—88°C, [α]$^{20}_{D}$ −29.5 (*c*=4.5, MeOH)).

(1*R*,2*S*)-(−)-*N*-Ethyl-, (1*R*,2*S*)-(−)-*N*-Isopropyl-, and (1*R*,2*S*)-(−)-*N*-Benzylephedrine——Samples previously prepared in this laboratory[36)] were used.

(*S*)-(+)-2-(Anilinomethyl)pyrrolidine——Preparation of this compound was carried out according to the reported method.[37)] Colorless oil, bp 116—118°C (0.09 mmHg), [α]$^{24}_{D}$ +20.1° (*c*=2.06, EtOH) (lit.,[37)] bp 117—120°C (0.4 mmHg), [α]$^{24}_{D}$ +19.1° (*c*=1.1, EtOH); lit.,[11b)] bp 111—112°C (0.55 mmHg), [α]$^{20}_{D}$ +19.7° (*c*=1.09, EtOH)). Spectral (IR and ^{1}H-NMR) properties of this sample were identical with those reported.[37)]

Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (1) under Various Conditions——a) Table I, Runs 1 and 2: An ethereal solution (5 ml) of (*S*)-(+)-2-(anilinomethyl)pyrrolidine (bp 116—118°C (0.09 mmHg), [α]$^{24}_{D}$ +20.1° (*c*=2.06, EtOH)) (481 mg, 2.73 mmol) was added to a stirred suspension of LAH (90 mg, 2.36 mmol) in Et$_2$O (5 ml) at room temperature, and the whole mixture was stirred at the same temperature for 1 h to give a solution of the reducing agent.[11)]

An ethereal solution (10 ml) of **1**[2)] (232 mg, 1.0 mmol) was added to the cooled (−78°C), stirred solution of the reducing agent prepared above, and the mixture was stirred at the same temperature for 5 h. After 10% HCl (10 ml) has been added to the mixture to quench the reduction, the whole was extracted with EtOAc (15 ml×3). The combined organic extracts were washed with satd. NaCl (15 ml×3). Filtration and concentration *in vacuo* gave crude (*S*)-(−)-**2**, which was purified by preparative TLC (C$_6$H$_6$–EtOAc 8: 1) to give (*S*)-(−)-**2** as colorless crystals (140 mg, 60%), mp 83—85°C, [α]$^{20}_{D}$ −11.0° (*c*=1.93, EtOH), 54% e.e., based on [α]$^{20}_{D}$ −20.5° (*c*=1.07, EtOH) (*vide infra*). The IR and ^{1}H-NMR spectra of this sample were identical with those of optically pure (*S*)(−)-**2** obtained in e).

The reduction of **1**[2)] (93 mg, 0.40 mmol) was similarly carried out using the reducing agent prepared from LAH (100 mg, 2.64 mmol) and (*S*)-(+)-2-(anilinomethyl)pyrrolidine (467 mg, 2.65 mmol), to provide (*S*)-(−)-**2** (94 mg, quantitative yield), mp 83—85.5°C, [α]$^{20}_{D}$ −12.1° (*c*=2.01, EtOH), 64% e.e. based on [α]$^{20}_{D}$ −20.5° (*c*=1.07, EtOH) (*vide infra*), after extractive isolation and purification by preparative TLC.

b) Table I, Run 3: An ethereal solution (5 ml) of (−)-*N*-methylephedrine (mp 86.5—87.5°C, [α]$^{20}_{D}$ −29.5° (*c*=4.54, MeOH)) (237 mg, 1.32 mmol) was added to a stirred suspension of LAH (50 mg, 1.32 mmol) in Et$_2$O (2.5 ml), and the mixture was heated at reflux for 1 h with stirring. An ethereal solution (3 ml) of 3,5-dimethylphenol (323 mg, 2.64 mmol) was further added to the ethereal solution prepared above, and the mixture was refluxed for 1 h with stirring to afford a solution of the reducing agent.[10)]

An ethereal solution (11 ml) of **1**[2] (93 mg, 0.40 mmol) was gradually added to the solution of the reducing agent cooled at −20°C, and the whole mixture was stirred at the same temperature for 3 h. After addition of 1 N HCl (2.8 ml), the mixture was extracted with EtOAc (10 ml × 3). The organic extracts were combined, and washed successively with 10% NaOH (10 ml × 3), H_2O (10 ml × 3), and satd. NaCl (10 ml × 2). Filtration and concentration *in vacuo*, followed by purification with preparative TLC (C_6H_6–EtOAc 8: 1), gave (*S*)-(−)-**2** as colorless crystals (10.4 mg, 11%), mp 81—82.5°C, $[\alpha]_D^{20}$ −2.7° (*c*=0.52, EtOH), 13% e.e. based on $[\alpha]^D_{20}$ −20.5° (*c*=1.07, EtOH) (*vide infra*). This sample was found to be identical with the sample obtained in e) by spectral (IR and ^{1}H-NMR) comparisons.

c) Table I, Run 6: An ethereal solution (6 ml) of (−)-*N*-methylephedrine (mp 86.5—87.5°C, $[\alpha]_D^{20}$ −29.5° (*c*=4.54, MeOH)) (237 mg, 1.32 mmol) was added to a suspension of LAH (50 mg, 1.32 mmol) in Et_2O (2 ml), and the mixture was heated at reflux for 1 h with stirring, giving a solution of the reducing agent.

An ethereal solution (4 ml) of **1**[2] (93 mg, 0.40 mmol) was gradually added to the solution of the reducing agent cooled at −78°C, and the mixture was stirred at the same temperature for 1 h. After 10% HCl (5 ml) had been added to the reaction mixture, the whole was extracted with EtOAc (10 ml × 3). The organic extracts were combined, and washed successively with 5% NaOH (5 ml × 1), H_2O (10 ml × 1), and satd. NaCl (10 ml × 1). Filtration and concentration *in vacuo*, followed by purification by preparative TLC (C_6H_6–EtOAc 8: 1), gave (*S*)-(−)-**2** as colorless crystals (86 mg, 92%), mp 78—80°C, $[\alpha]_D^{20}$ −0.84° (*c*=1.71, EtOH), 4% e.e. based on $[\alpha]_D^{20}$ −20.5° (*c*=1.07, EtOH) (*vide infra*). This sample was found to be identical with the sample obtained in e) by spectral (IR and ^{1}H-NMR) comparisons.

d) Table I, Run 9 and Table II, Run 2 (Small-scale Experiment under the Optimum Reaction Conditions): An ethereal solution (5 ml) of (−)-*N*-methylephedrine (mp 86.5—87.5°C, $[\alpha]_D^{20}$ −29.5° (*c*=4.54, MeOH)) (243 mg, 1.36 mmol) was added to a suspension of LAH (50 mg, 1.32 mmol) in Et_2O (2.5 ml), and the mixture was heated at reflux for 1 h with stirring. An ethereal solution (3 ml) of *N*-methylaniline (291 mg, 2.72 mmol) was added to the ethereal solution prepared above, and the mixture was further heated at reflux for 1 h with stirring to give a solution of the reducing agent.

A solution of **1**[2] (93 mg, 0.40 mmol) in Et_2O (12 ml) was gradually added to the ethereal solution of the reducing agent cooled at −78°C, and the mixture was stirred at the same temperature for 3 h. After 1 N HCl (5.5 ml, 5.5 mmol) had been added to the reaction mixture to quench the reduction, the whole was extracted with EtOAc (10 ml × 3). The organic extracts were combined and washed successively with 1% HCl (10 ml × 2), H_2O (10 ml × 2), and satd. NaCl (10 ml × 1). Filtration and concentration *in vacuo* gave crude (*S*)-(−)-**2** as colorless crystals (105 mg). This sample was purified by preparative TLC (C_6H_6–EtOAc 8: 1), giving (*S*)-(−)-**2** as colorless crystals (91 mg, 97%), mp 86—88°C, $[\alpha]_D^{20}$ −17.6° (*c*=1.81, EtOH), 86% e.e. based on $[\alpha]_D^{20}$ −20.5° (*c*=1.07, EtOH) (*vide infra*). Spectral (IR and ^{1}H-NMR) properties of this sample were identical with those of (*S*)-(−)-**2** obtained in e).

The same asymmetric reduction of **1**[2] was attempted using *N*-ethylaniline in place of *N*-methylaniline, to provide (*S*)-(−)-**2** (86 mg, 94%), mp 85—87°C, $[\alpha]_D^{20}$ −18.9° (*c*=1.71, EtOH), 92% e.e. based on $[\alpha]_D^{20}$ −20.5° (*c*=1.07, EtOH) (*vide infra*), after purification by preparative TLC. This sample was similarly identified by spectral (IR and ^{1}H-NMR) comparisons.

The other asymmetric reductions shown in Tables II—V were all carried out according to the same reaction procedure as that described above. The reduction product ((*S*)-(−)-**2**) and the recovered starting material (**1**) were identified by spectral (IR and ^{1}H-NMR) and chromatographic (TLC) comparisons with corresponding authentic samples.

e) Table II, Run 2 (Large-scale Experiment under the Optimum Reaction Conditions): An ethereal solution (45 ml) of (−)-*N*-methylephedrine (mp 86.5—87.5°C, $[\alpha]_D^{20}$ −29.5° (*c*=4.54, MeOH)) (2.43 g, 13.6 mmol) was added to a suspension of LAH (500 mg, 13.2 mmol) in Et_2O (25 ml) with stirring, and the mixture was heated at reflux for 1 h with stirring. A solution of *N*-ethylaniline (3.30 g, 27.2 mmol) in Et_2O (25 ml) was gradually added to the reaction mixture, and the whole was further heated at reflux for 1 h with stirring, giving a solution of the reducing agent.

A solution of **1**[2] (930 mg, 4.0 mmol) in Et_2O (10 ml) was gradually added to the solution of the reducing agent cooled at −78°C, and the whole mixture was stirred at the same temperature for 3 h. After addition of 1 N HCl (55 ml, 55 mmol), the mixture was extracted with EtOAc (100 ml × 3). The organic extracts were combined and washed successively with 1% HCl (100 ml × 2), 5% $NaHCO_3$ (100 ml × 1), H_2O (100 ml × 2), and satd. NaCl (100 ml × 2). Filtration and concentration *in vacuo* gave (*S*)-(−)-**2** as colorless crystals (980 mg, 100%), mp 87—87.5°C, $[\alpha]_D^{20}$ −18.8° (*c*=2.48, EtOH), 92% e.e. based on $[\alpha]_D^{20}$ −20.5° (*c*=1.07, EtOH) (*vide infra*). Direct recrystallization from C_6H_{14} gave optically pure (*S*)-(−)-**2** as colorless needles (817 mg, 87%), mp 88—89°C, $[\alpha]_D^{20}$ −20.4° (*c*=1.55, EtOH). Further repeated recrystallizations from C_6H_{14} afforded an analytical sample of optically pure (*S*)-(−)-**2** as colorless needles, mp 88—89°C, $[\alpha]_D^{20}$ −20.5° (*c*=1.07, EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}: 3340, 1260, 1090 (OH), 1600 (aromatic ring). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1}: 3600, 1200, 1100 (OH). ^{1}H-NMR (in $CDCl_3$): 1.32 (3H, d, *J*=6 Hz, $CH(OH)C\underline{H}_3$), 2.00—2.36 (2H, m, $C\underline{H}_2CH_2C=$), 2.12 (1H, s, $O\underline{H}$), 2.64—2.88 (2H, m, $CH_2C\underline{H}_2C=$), 3.74 (6H, two s, $OC\underline{H}_3 \times 2$), 4.40 (1H, q, $C\underline{H}(OH)$), 6.60 (2H, s, aromatic protons), 6.72 (1H, br s, $C\underline{H}=$). The IR (in $CHCl_3$) and ^{1}H-NMR spectra of this sample were superimposable on those of (±)-**2**[2] measured under the same conditions. *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.57; H, 7.76. Since this sample showed a doublet methyl group signal at

10.4 ppm in the ^{1}H-NMR spectrum measured in the presence of Eu(hfc)$_3$((*S*)-(−)-**2**: Eu(hfc)$_3$ 1: 1 in CCl_4), the optical purity of this sample was definitely determined as 100% e.e. The spectrum of (±)-**2**[2] recorded in the same state exhibited the methyl group signal as two sets of doublets at 10.15 and 10.4 ppm.

Concentration of the mother liquor obtained from the first recrystallization *in vacuo*, gave crude (*S*)-(−)-**2** (161 mg, 17%), $[\alpha]_D^{20}$ −3.6° (c=2.79, EtOH), 18% e.e. based on $[\alpha]_D^{20}$ −20.5° (c=1.07, EtOH) (*vide supra*). A part of this sample (103 mg, 0.44 mmol) was dissolved in C_6H_6 (10 ml), and DDQ (134 mg, 0.59 mmol) was added to the solution. The whole mixture was stirred at room temperature for 1 h, then a crystalline precipitate was filtered off and washed with C_6H_6 (30 ml). The filtrate and washings were combined and concentrated *in vacuo* to give crude **1** as pale yellow crystals (97 mg, 94%), mp 105—106°C (lit.,[2] mp 106—107°C). This sample was found to be identical with authentic **1**[2] by spectral (IR and ^{1}H-NMR) comparisons.

On the other hand, the acidic aqueous phases (1 N HCl, 1% HCl, and H_2O washings) obtained during the isolation of (*S*)-(−)-**2** were combined, made alkaline (pH>11) with 10% NaOH (50 ml), then extracted with EtOAc (100 ml × 3). The organic extracts were combined, and washed with satd. NaCl (100 ml × 4). Filtration and concentration *in vacuo* gave a mixture of (−)-*N*-methylephedrine and *N*-ethylaniline as a mixture of a pale yellow oil and crystals (5.62 g, 98%). Direct fractional distillation *in vacuo* gave *N*-ethylaniline (3.3 g, quantitative recovery), bp 87—90°C (15 mmHg), and (−)-*N*-methylephedrine (2.0 g, 83% recovery), bp 120°C (0.01 mmHg), mp 85—87.5°C, $[\alpha]_D^{20}$ −29.1° (c=4.59, MeOH), 99% e.e. based on $[\alpha]_D^{20}$ −29.5° (c=4.54, MeOH) (*vide supra*). These samples were confirmed to be identical with corresponding authentic samples by spectral (IR and ^{1}H-NMR) comparisons.

(1′*S*,2*R*)-(−)-2-1′-Hydroxyethyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((−)-**6a**) **and Its (2*S*)-Isomer (6b)**——Successive epoxidation of optically pure (*S*)-(−)-**2** (mp 88—89°C, $[\alpha]_D^{20}$ −20.5° (c=1.07, EtOH)) (703 mg, 3.0 mmol) with *tert*-butyl hydroperoxide in C_6H_6 in the presence of vanadium oxyacetylacetonate and reduction of the diastereomeric mixture of the α,β-epoxyalcohols (**5a** and **5b**) with LAH in THF in a similar manner to that described for (±)-**2**,[27] gave a crude mixture of (−)-**6a** and **6b** as colorless crystals (730 mg, 97%) after extractive isolation with EtOAc and concentration *in vacuo*.

A part of this sample (380 mg) was subjected to column chromatography (C_6H_6–EtOAc 1: 1), giving a diastereomeric mixture of (−)-**6a** and **6b** as colorless needles (335 mg, 85%), mp 140—150°C, $[\alpha]_D^{20}$ −39.3° (c=1.04, EtOH). Spectral (IR and ^{1}H-NMR) properties of this sample were identical with those of pure (−)-**6a** (*vide infra*). Since this sample was transformed to (*R*)-(−)-**3**, 90% e.e. (*vide infra*), the formation ratio of (−)-**6a** to **6b**, and that of **5a** to **5b**, could be calculated as 95: 5.

The remaining portion of the crystals (350 mg) was directly recrystallized from Et_2O to give pure (−)-**6a** as colorless needles (252 mg, 70%), mp 154—155°C, $[\alpha]_D^{20}$ −49.7° (c=0.50, EtOH). IR ν_{max}^{KBr} cm^{-1}: 3360, 1260, 1085 (OH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 1260, 1105, 1090 (OH). ^{1}H-NMR (in $CDCl_3$–CD_3OD): 1.23 (3H, d, J=6 Hz, $CH(OH)C\underline{H}_3$), 1.40—2.05 (2H, m, $CH_2C\underline{H}_2C(OH)$), 2.50—2.88 (4H, m, $C\underline{H}_2CH_2C(OH)C\underline{H}_2$), 3.20 (2H, two s, $O\underline{H}$ × 2), 3.62 (1H, q, J=6 Hz, $C\underline{H}(OH)CH_3$), 3.72 (3H, s, $OC\underline{H}_3$), 3.74 (3H, s, $OC\underline{H}_3$), 6.60 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.78; H, 8.06. The IR (in $CHCl_3$) and ^{1}H-NMR spectra of this sample were superimposable on those of (±)-**6a**[2] measured under the same conditions.

(*R*)-(−)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((***R***)(−)-**3**)——a) Oxidation with Fetizon Reagent:[27] A diastereomeric mixture of (−)-**6a** and **6b** (mp 140—150°C, $[\alpha]_D^{20}$ −39.3° (c=1.04, EtOH)) (135 mg, 0.54 mmol) was treated with Fetizon reagent in C_6H_6 in the same manner as described for (±)-**6a**,[27] to give (*R*)-(−)-**3** as colorless needles (105 mg, 84%), mp 123—127°C, $[\alpha]_D^{20}$ −42.5° (c=0.89, $CHCl_3$), 90% e.e. based on $[\alpha]_D^{20}$ −47.1° (c=1.11, $CHCl_3$) (*vide infra*), after purification by preparative TLC. This sample exhibited the same spectral (IR and ^{1}H-NMR) properties as those of optically pure (*R*)-(−)-**3** (*vide infra*).

When pure (−)-**6a** (mp 154—155°C, $[\alpha]_D^{20}$ −49.6° (c=1.08, EtOH)) (134 mg, 0.53 mmol) was similarly oxidized, (*R*)-(−)-**3** was obtained as colorless crystals (91 mg, 69%), mp 127—128.5°C, $[\alpha]_D^{20}$ −44.0° (c=1.92, $CHCl_3$), after purification by preparative TLC. Repeated recrystallizations of this sample from $CHCl_3$–Et_2O gave an analytical sample of optically pure (*R*)-(−)-**3** as colorless needles, mp 128—129°C, $[\alpha]_D^{20}$ −47.1° (c=1.11, $CHCl_3$) (lit.,[15b,c] mp 130—132°C, $[\alpha]_D^{20}$ −50° (c=1, $CHCl_3$); lit.,[38] mp 128—129°C, $[\alpha]_D^{20}$ −48.6° (c=0.982, $CHCl_3$); lit.,[39] mp 128—130°C, $[\alpha]_D$ −49° (concentration and solvent were not specified)). IR ν_{max}^{KBr} cm^{-1}: 1700 (ketone). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (ketone). ^{1}H-NMR (in $CDCl_3$): 1.86—2.10 (2H, m, $CH_2C\underline{H}_2C(OH)CH_2$), 2.29 (3H, s, $COC\underline{H}_3$), 2.70—3.10 (4H, m, $C\underline{H}_2CH_2C(OH)C\underline{H}_2$), 3.58 (1H, s, $O\underline{H}$), 3.72 (3H, s, $OC\underline{H}_3$), 3.76 (3H, s, $OC\underline{H}_3$), 6.62 (2H, s, aromatic protons). These spectral properties were identical with those of (*R*)-(−)-**3** previously reported.[38] The optical purity of this sample was determined as 100% e.e. by measuring the ^{1}H-NMR spectrum in the presence of Eu(hfc)$_3$((*R*)-(−)-**3**: Eu(hfc)$_3$1.0: 0.6 in $CDCl_3$). The ^{1}H-NMR spectrum showed the acetyl group signal as a singlet at 4.6 ppm, in contrast to that of (±)-**3**[2] which exhibited two singlets at 4.4 and 4.6 ppm.

b) Oxidation of (−)-**6a** with a Combination of Sulfur Trioxide·Pyridine Complex–Dimethyl Sulfoxide–Triethylamine:[27] Similar treatments of (−)-**6a** (mp 153.5—154°C, $[\alpha]_D^{20}$ −47.9° (c=1.02, EtOH)) (2.52 g, 10.0 mmol) to those of (±)-**6a**,[27] gave crude (*R*)(−)-**3** as colorless crystals (2.47 g, 99%) after extractive isolation with $CHCl_3$ and concentration *in vacuo*. This sample was purified by column chromatography (C_6H_6–EtOAc 7: 1) to give (*R*)-(−)-**3** as colorless crystals (2.41 g, 96%), mp 127—128°C, $[\alpha]_D^{20}$ −42.6° (c=

1.22, $\mathrm{CHCl_3}$). Recrystallization from $\mathrm{CHCl_3}$–$\mathrm{Et_2O}$ gave a pure sample of optically pure (*R*)-(−)-**3** as colorless needles (2.17 g, 87%), mp 128—129°C, $[\alpha]_\mathrm{D}^{20}$ −46.0° (*c*=1.10, $\mathrm{CHCl_3}$). Spectral (IR and ^{1}H-NMR) properties of this sample were identical with those given in a).

(−)-7-Deoxy-4-demethoxydaunomycinone Dimethyl Ether ((***R***)-(−)-**2-Acetyl-2-hydroxy-5,12-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione**) ((−)-**7**)——a) (−)-**7** from (*R*)-(−)-**3**:[15,27] Similarly to the preparation of (±)-**7**,[27] successive Friedel–Crafts acylation of optically pure (*R*)-(−)-**3** (mp 127.5—129°C, $[\alpha]_\mathrm{D}^{20}$ −46.6° (*c*=1.02, $\mathrm{CHCl_3}$)) (500 mg, 2.0 mmol) with *o*-methoxycarbonylbenzoyl chloride in the presence of anhyd. $\mathrm{AlCl_3}$ in $\mathrm{CH_2Cl_2}$, hydrolysis of the crude methyl ester with aq. NaOH, and cyclization of the acid with HF, gave crude (−)-**7** as pale yellow crystals (512 mg, 67%), after purification by column chromatography ($\mathrm{C_6H_6}$–EtOAc 6: 1). The optical purity of this sample was roughly estimated as *ca.* 75% e.e. since two lots of (−)-**7** with 20 and 100% e.e., could be obtained from this sample in 18 and 32% yields, respectively.

Recrystallization of crude (−)-**7** from MeOH (15 ml) gave (−)-**7** having low optical purity as pale yellow crystals (137 mg, 18%), mp 185—187.5°C. IR and ^{1}H-NMR spectra of the recrystallized sample were identical with those of (±)-**7**.[2] Since the ^{1}H-NMR spectrum of this sample measured in the presence of $\mathrm{Eu(hfc)_3}$((−)-**7**: $\mathrm{Eu(hfc)_3}$ 1: 1 in $\mathrm{CDCl_3}$) showed the two methoxy groups as two sets of two singlets (7.5, 8.8 and 8.0, 8.3 ppm; integration ratio 3: 2) and the acetyl group as two singlets (2.8 and 2.6 ppm; integration ratio 3: 2), it became evident that this sample consisted of (−)- and (+)-**7** in a ratio of 3: 2. The ^{1}H-NMR spectrum of (±)-**7**[2] recorded under the same conditions exhibited two sets of two singlets (7.5, 8.8 and 8.0, 8.3 ppm; integration ratio 1: 1) and two singlets (2.8 and 2.6 ppm; integration ratio 1: 1). Therefore, the optical purity of this sample was estimated as 20% e.e.

The mother liquor from the recrystallization was concentrated *in vacuo*, and the yellow residue was recrystallized from $\mathrm{Et_2O}$ to give optically pure (−)-**7** as pale yellow crystals (246 mg, 32%), mp 138—140°C, $[\alpha]_\mathrm{D}^{20}$ −23.1° (*c*=1.04, $\mathrm{CHCl_3}$). Further recrystallization from toluene–$\mathrm{C_6H_{14}}$ gave an analytical sample of optically pure (−)-**7** as pale yellow crystals (190 mg, 25%), mp 139—140°C, $[\alpha]_\mathrm{D}^{20}$ −23.0° (*c*=1.06, $\mathrm{CHCl_3}$) (lit.,[15a] mp 142—144°C, $[\alpha]_\mathrm{D}^{20}$ −32° (*c*=1, $\mathrm{CHCl_3}$); lit.,[15b] mp 142—144°C, $[\alpha]_\mathrm{D}^{20}$ −33° ($\mathrm{CHCl_3}$)). IR $\nu_\mathrm{max}^\mathrm{KBr}$ $\mathrm{cm^{-1}}$: 3440 (OH), 1700 (ketone), 1670 (quinone), 1595, 1555 (aromatic rings). ^{1}H-NMR (in $\mathrm{CDCl_3}$): 1.84—2.02 (2H, m, $\mathrm{CH_2C\underline{H}_2C(OH)CH_2}$), 2.36 (3H, s, $\mathrm{COC\underline{H}_3}$), 2.76—3.28 (4H, m, $\mathrm{C\underline{H}_2CH_2C(OH)C\underline{H}_2}$), 3.84 (3H, s, $\mathrm{OC\underline{H}_3}$), 3.86 (1H, s, $\mathrm{O\underline{H}}$), 3.88 (3H, s, $\mathrm{OC\underline{H}_3}$), 7.60—7.78 (2H, m, aromatic protons), 8.02—8.20 (2H, m, aromatic protons). This ^{1}H-NMR spectrum was superimposable on that of (±)-**7**.[2] *Anal.* Calcd for $\mathrm{C_{22}H_{20}O_6}$: C, 69.46; H, 5.30. Found: C, 69.21; H, 5.23. The ^{1}H-NMR spectrum of this sample measured in the presence of $\mathrm{Eu(hfc)_3}$((−)-**7**: $\mathrm{Eu(hfc)_3}$ 1: 1 in $\mathrm{CDCl_3}$) showed two singlets at 7.5 and 8.8 ppm and one singlet at 2.8 ppm. Therefore, the optical purity of this sample was determined as 100% e.e.

b) (−)-**7** from (−)-**8**:[27] Methylation of optically pure (−)-**8** (mp 218—220°C, $[\alpha]_\mathrm{D}^{20}$ −87.0° (*c*=0.115, $\mathrm{CHCl_3}$)) (*vide infra*) (25.0 mg, 0.070 mmol) in the same manner as described for (±)-**8**[27] gave (−)-**7** as pale yellow crystals (27.0 mg, quantitative yield), mp 139—141°C, $[\alpha]_\mathrm{D}^{20}$ −23.7° (*c*=1.35, $\mathrm{CHCl_3}$), after purification by preparative TLC ($\mathrm{C_6H_6}$–EtOAc 6: 1). Recrystallization from $\mathrm{Et_2O}$ gave a pure sample of optically pure (−)-**7** as pale yellow crystals, mp 140.5—141°C, $[\alpha]_\mathrm{D}^{20}$ −23.3° (*c*=1.16, $\mathrm{CHCl_3}$). The IR and ^{1}H-NMR spectra of this sample were identical with those recorded in a).

When crude (−)-**8** (336 mg, 0.95 mmol), prepared from (*R*)-(−)-**3** (mp 128—129°C, $[\alpha]_\mathrm{D}^{20}$ −46.0° (*c*=1.10, $\mathrm{CHCl_3}$)) (250 mg, 1.0 mmol) (*vide infra*), was immediately subjected to methylation, (−)-**7** showing $[\alpha]_\mathrm{D}^{20}$ −17.3° (*c*=1.32, $\mathrm{CHCl_3}$) was obtained as pale yellow crystals (318 mg, 88%) after chromatographic purification. The optical purity of this sample could be calculated as 75% e.e. by assuming that (−)-**7**, $[\alpha]_\mathrm{D}^{20}$ −23.0° (*c*=1.06, $\mathrm{CHCl_3}$), was optically pure. This sample was dissolved in $\mathrm{Et_2O}$ (100 ml); almost racemic **7** crystallized out and was separated by filtration (64 mg, 18%), mp 179—185°C. The mother ethereal layer was concentrated *in vacuo* to one-tenth of the original volume, giving optically pure (−)-**7** as pale yellow crystals (184 mg, 51% based on (*R*)-(−)-**3**), mp 140—141°C, $[\alpha]_\mathrm{D}^{20}$ −22.5° (*c*=1.01, $\mathrm{CHCl_3}$). This sample was found to be identical with (−)-**7** obtained in a) by spectral (IR and ^{1}H-NMR) comparisons.

(−)-7-Deoxy-4-demethoxydaunomycinone ((***R***)-(−)-**2-Acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione**) ((−)-**8**)——Treatments of a mixture of optically pure (*R*)-(−)-**3** (mp 128—129°C, $[\alpha]_\mathrm{D}^{20}$ −46.0° (*c*=1.10, $\mathrm{CHCl_3}$)) (501 mg, 4.0 mmol), phthalic anhydride (593 mg, 4.0 mmol), anhyd. $\mathrm{AlCl_3}$ (5.0 g, 37.5 mmol), and NaCl (1 g) in the same manner as described for (±)-**3**[27] gave crude (−)-**8** as a red solid (640 mg, 91%), mp 214—218°C, $[\alpha]_\mathrm{D}^{20}$ −61.8° (*c*=0.11, $\mathrm{CHCl_3}$), 71% e.e. based on $[\alpha]_\mathrm{D}^{20}$ −87.0° (*c*=0.115, $\mathrm{CHCl_3}$) (*vide infra*), after extractive isolation with $\mathrm{CHCl_3}$ and concentration *in vacuo*. Repeated recrystallizations of a part of this sample (120 mg) from $\mathrm{C_6H_6}$–$\mathrm{Et_2O}$ afforded optically pure (−)-**8**[40] as red crystals (50 mg, 38%), mp 218—220°C, $[\alpha]_\mathrm{D}^{20}$ −87.0° (*c*=0.115, $\mathrm{CHCl_3}$) (lit.,[16a] mp 228—230°C, $[\alpha]_\mathrm{D}^{20}$ −87° (*c*=0.1, $\mathrm{CHCl_3}$); lit.,[16b] mp 210—216°C, $[\alpha]_\mathrm{D}^{20}$ −84.4° (*c*=0.1, $\mathrm{CHCl_3}$)). IR $\nu_\mathrm{max}^\mathrm{Nujol}$ $\mathrm{cm^{-1}}$: 3450 (OH), 1700 (ketone), 1620, 1580 (quinone). ^{1}H-NMR (in $\mathrm{CDCl_3}$): 1.85—2.15 (2H, m, $\mathrm{CH_2C\underline{H}_2C(OH)CH_2}$), 2.38 (3H, s, $\mathrm{COC\underline{H}_3}$), 2.95—3.10 (4H, m, $\mathrm{C\underline{H}_2CH_2C(OH)C\underline{H}_2}$), 3.60 (1H, s, $\mathrm{O\underline{H}}$), 7.75—8.00 (2H, m, aromatic protons), 8.30—8.46 (2H, m, aromatic protons), 13.36 (2H, s, two phenolic OH). *Anal.* Calcd for $\mathrm{C_{20}H_{16}O_6 \cdot 1/3H_2O}$: C, 67.63; H, 4.69. Found: C, 67.31; H, 4.41.

2-Ethyl-5,12-dimethoxynaphthacene-6,11-dione (**9**)——The same treatments of optically pure (*S*)-(−)-**2** (mp 88—89°C, $[\alpha]_\mathrm{D}^{20}$ −20.5° (*c*=1.05, EtOH)) (469 mg, 2.0 mmol) as described for the preparation of (−)-**7**, 75% e.e., from (*R*)(−)-**3** by way of (−)-**8** (*vide supra*), afforded crude **9** as yellow crystals (332 mg) after extractive isolation. Purification of this sample by column chromatography (C_6H_6–EtOAc 20: 1) gave **9** as yellow crystals (181 mg, 46%), mp 100—104°C. Recrystallization from MeOH gave an analytical sample of **9** as yellow plates, mp 102—104°C. IR ν_{max}^{Nujol} cm^{-1}: 1680 (quinone), 1600 (aromatic rings). ^{1}H-NMR (in $CDCl_3$): 1.29 (3H, br t, *J*=8 Hz, $CH_2C\underline{H}_3$), 2.75 (2H, br, q, *J*=8 Hz, $C\underline{H}_2CH_3$), 4.10 (6H, two s, $OC\underline{H}_3 \times 2$), 7.40—7.80 (3H, m, aromatic protons), 7.95—8.45 (4H, m, aromatic protons). *Anal.* Calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 76.01; H, 5.17.

2-Acetyl-5,12-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione (10)——The *vicinal*-diol((−)-**6a**) (mp 152—154°C, $[\alpha]_D^{20}$ −47.1° (*c*=1.10, EtOH)) (68.1 mg, 0.27 mmol) was treated in the same manner as described for the preparation of (−)-**7**, 75% e.e, from (*R*)-(−)-**3** by way of (−)-**8** (*vide supra*), giving crude **10** as yellow crystals (66 mg) after extractive isolation. Purification by preparative TLC (C_6H_6–EtOAc 4: 1) gave **10**[30] as yellow crystals (24.8 mg, 25%). An analytical sample of **10**[30] (10.8 mg) was prepared by recrystallization from MeOH, mp 142—144°C. IR ν_{max}^{KBr} cm^{-1}: 1700 (ketone), 1680 (quinone), 1580, 1550 (aromatic rings). ^{1}H-NMR (in $CDCl_3$): 1.80—2.25 (2H, m, $CH_2C\underline{H}_2CHCOCH_3$), 2.26 (3H, s, $COC\underline{H}_3$), 2.60—3.30 (5H, m, $C\underline{H}_2C\underline{H}$-$(COCH_3)CH_2C\underline{H}_2$), 3.88 (3H, s, $OC\underline{H}_3$), 3.90 (3H, s, $OC\underline{H}_3$), 7.60—7.72 (2H, m, aromatic protons), 8.00—8.18 (2H, m, aromatic protons). *Anal.* Calcd for $C_{22}H_{20}O_5 \cdot 1/3H_2O$: C, 71.34; H, 5.53. Found: C, 71.49; H, 5.44.

(+)-4-Demethoxydaunomycinone Trimethyl Ether (**(2*S*,4*S*)-(+)-2-Acetyl-2-hydroxy-4,5,12-trimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione** ((+)-**11a**) **and Its (+)-7-Epimer** (**(4*R*)-(+)-Epimer** ((+)-**11b**)——a) (−)-7-Deoxy-4-demethoxydaunomycinone Dimethyl Ether Ethylene Acetal ((*S*)-(−)-2-(2-Methyl-1,3-dioxolan-2-yl)-2-hydroxy-5,12-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione): A mixture of (−)-**7** (mp 139—140°C, $[\alpha]_D^{20}$ −23.0° (*c*=1.06, $CHCl_3$)) (91 mg, 0.24 mmol), ethylene glycol (2 ml, 35.9 mmol), and *p*-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol) in C_6H_6 (20 ml) was heated at reflux for 5 h, using a Dean–Stark apparatus to remove the separated water. The reaction mixture was cooled, pyridine (0.1 ml) was added, and the whole was washed successively with H_2O (10 ml × 3) and satd. NaCl (10 ml × 1). Filtration and concentration *in vacuo* gave the acetal as yellow crystals (99 mg, 97%). Recrystallization of this sample from $CHCl_3$–Et_2O afforded the pure acetal as pale yellow needles (61 mg, 60%), mp 176—178°C, $[\alpha]_D^{20}$ −24.0° (*c*=1.00, $CHCl_3$) (lit.,[15b,c] mp 175—177°C, $[\alpha]_D^{20}$ −29° (*c*=1, $CHCl_3$)). IR ν_{max}^{Nujol} cm^{-1}: 3420 (OH), 1670 (quinone), 1590, 1550 (aromatic rings). ^{1}H-NMR (in $CDCl_3$): 1.48 (3H, s, $C\underline{H}_3$), 1.65—2.10 (2H, m, $CH_2C\underline{H}_2C(OH)CH_2$), 2.00 (1H, s, $O\underline{H}$), 2.80—3.20 (4H, m, $C\underline{H}_2CH_2C(OH)C\underline{H}_2$), 3.90 (7H, two s, $OC\underline{H}_3$ and $OC\underline{H}_2C\underline{H}_2O$), 4.05 (3H, s, $OC\underline{H}_3$), 7.50—7.85 (2H, m, aromatic protons), 8.00—8.35 (2H, m, aromatic protons).

b) (+)-**11a** and (+)-**11b**:[14,15] A mixture of (−)-acetal (mp 178—179°C, $[\alpha]_D^{20}$ −24.0° (*c*=1.01, $CHCl_3$)) (348 mg, 0.82 mmol) and *N*-bromosuccinimide (175 mg, 0.98 mmol) in CCl_4 (35 ml) was heated at reflux for 10 min with stirring under irradiation with a 500W halogen lamp. After being cooled, the mixture was concentrated *in vacuo*, and the residue was dissolved in MeOH (15 ml). The methanolic solution was refluxed for 5 min with stirring, then concentrated *in vacuo*. The residue was dissolved in a mixture of H_2O (6 ml), conc. HCl (2 ml), and dioxane (15 ml), and the acidic solution was stirred at room temperature for 20 h to hydrolyze the acetal group. The residue obtained by concentration of the reaction mixture *in vacuo* was dissolved in $CHCl_3$ (20 ml). The $CHCl_3$ solution was washed successively with H_2O (20 ml × 2), 5% $NaHCO_3$ (20 ml × 1), H_2O (20 ml × 2), and satd. NaCl (20 ml × 2). Filtration and concentration *in vacuo* afforded a crude mixture of (+)-**11a** and (+)-**11b** as pale yellow crystals (472 mg), and this mixture was subjected to column chromatography (C_6H_6–EtOAc 4: 1) to give (+)-**11a** as pale yellow needles (148 mg, 44%), mp 120—130°C, $[\alpha]_D^{20}$ +140° (*c*=0.30, $CHCl_3$) and (+)-**11b** as a pale yellow caramel (88 mg, 26%).

Recrystallization of (+)-**11a** from MeOH (2 ml) gave pure (+)-**11a** as pale yellow needles (48 mg), mp 138—139°C, $[\alpha]_D^{20}$ +228° (*c*=0.45, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3410 (OH), 1710 (ketone), 1670 (quinone), 1590, 1555 (aromatic rings). ^{1}H-NMR (in $CDCl_3$): 1.86 (1H, dd, *J*=15 and 4 Hz, C_8–$\underline{H}_e$), 2.43 (3H, s, $COC\underline{H}_3$), 2.40 (1H, ddd, *J*=15, 2, and 2 Hz, C_8–$\underline{H}_a$), 3.05 (1H, d, *J*=18 Hz, C_{10}–$\underline{H}_a$), 3.38 (1H, dd, *J*=18 and 2 Hz, C_{10}–$\underline{H}_e$), 3.60 (3H, s, C_7–$OC\underline{H}_3$), 3.90 (3H, s, $OC\underline{H}_3$), 4.00 (3H, s, $OC\underline{H}_3$), 4.90 (1H, m, C_7–$\underline{H}_e$), 5.02 (1H, s, $O\underline{H}$), 7.60 (2H, m, aromatic protons), 8.04—8.20 (2H, m, aromatic protons). These spectral properties were identical with those reported for (±)-**11a**.[14a] *Anal.* Calcd for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40. Found: C, 67.19; H, 5.30.

(+)-7-Epimer ((+)-**11b**) obtained as a pale yellow caramel was crystallized by triturating it with $CHCl_3$–C_6H_{14}. Pale yellow crystals, mp 55—65°C, $[\alpha]_D^{20}$ +31.7° (*c*=0.53, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1710 (ketone), 1670 (quinone), 1590, 1555 (aromatic rings). ^{1}H-NMR (in $CDCl_3$): 2.00—2.75 (2H, m, $CH_2C\underline{H}_2C$-$(OH)C\underline{H}_2$), 2.42 (3H, s, $COC\underline{H}_3$), 3.05 (1H, d, *J*=17 Hz, C_{10}–$\underline{H}_a$), 3.30 (1H, d, *J*=17 Hz, C_{10}–$\underline{H}_e$), 3.30 (3H, s, C_7–$OC\underline{H}_3$), 3.80 (1H, s, $O\underline{H}$), 3.90 (3H, s, $OC\underline{H}_3$), 3.93 (3H, s, $OC\underline{H}_3$), 5.05 (1H, m, C_7–$\underline{H}$), 7.60—7.85 (2H, m, aromatic protons), 8.02—8.35 (2H, m, aromatic protons). These spectral properties were almost identical with those reported for (±)-**11b**.[14a] *Anal.* Calcd for $C_{23}H_{22}O_7 \cdot 1/2H_2O$: C, 65.92; H, 5.53. Found: C, 65.91; H, 5.78.

(+)-4-Demethoxydaunomycinone ((+)-4d) and (−)-7-Epi-4-demethoxydaunomycinone ((−)-12)——Powdered $AlCl_3$ (320 mg, 2.4 mmol) was added to a C_6H_6 solution (20 ml) of a crude mixture of (+)-**11a** and (+)-**11b** (214 mg) prepared from (−)-acetal (175 mg, 0.41 mmol) in the same manner as described above, and the mixture was stirred at 40°C for 2 h. After being cooled, the reaction mixture was added to a mixture of 3% aq. oxalic acid (100 ml) and $CHCl_3$ (50 ml), and the whole was stirred at room temperature for 2 h.

The organic layer was separated and washed successively with H_2O (100 ml × 1), 5% $NaHCO_3$ (100 ml × 1), H_2O (100 ml × 2), and satd. NaCl (100 ml × 1). Filtration and concentration *in vacuo*, followed by purification by column chromatography ($CHCl_3$), gave a mixture of the 7-*O*-methyl ethers of (+)-**4d** and (−)-**12** as reddish-brown crystals (105 mg, 67%). The epimeric mixture was dissolved in trifluoroacetic acid (15 ml). The red solution was stirred for 17 h at room temperature, then concentrated *in vacuo*. A mixture of 4% NH_4OH (8 ml) and Me_2CO (8 ml) was added to the residue, and the alkaline solution was kept standing at room temperature for 30 min. Concentration *in vacuo* followed by purification by column chromatography ($CHCl_3$) afforded (+)-**4d** as reddish-brown crystals (55 mg, 54%), $[\alpha]_D^{20}$ +98.2° (c=0.112, dioxane), and (−)-**12** as reddish-brown crystals (14 mg, 14%).

Two recrystallizations of (+)-**4d** from $CHCl_3$–Et_2O gave pure (+)-**4d** as reddish-brown crystals, mp 183.5—184.5°C, $[\alpha]_D^{20}$ +153° (c=0.09, dioxane) (lit.,15a) mp 184—186°C, $[\alpha]_D^{20}$ +140° (c=1, dioxane); lit.,15b,c) mp 185—187°C, $[\alpha]_D^{20}$ +165° (c=0.1, dioxane); lit.,16) mp 184—186°C, $[\alpha]_D^{20}$ +170° (c=0.1, dioxane); lit.,33) mp 182.5—183°C, $[\alpha]_D^{20}$ +165° (dioxane)).41) IR ν_{max}^{KBr} cm^{-1}: 3330 (OH), 1720 (ketone), 1618, 1584 (quinone and aromatic rings). ^{1}H-NMR (in $CDCl_3$): 2.12 (1H, dd, J=16 and 4 Hz, C_8–$\underline{H}_a$), 2.32 (1H, br d, J=16 Hz, C_8–$\underline{H}_e$), 2.44 (3H, s, $COC\underline{H}_3$), 2.88 (1H, d, J=18 Hz, C_{10}–$\underline{H}_a$), 3.12 (1H, dd, J=18 and 1 Hz, C_{10}–$\underline{H}_e$), 3.90 (1H, d, J=6 Hz, C_7–$O\underline{H}$), 4.61 (1H, s, C_9–$O\underline{H}$), 5.22 (1H, m, C_7–H, $\nu_{1/2}$=12 Hz), 7.68—7.85 (2H, m, aromatic protons), 8.12—8.25 (2H, m, aromatic protons), 12.96 (1H, s, phenolic $O\underline{H}$), 13.24 (1H, s, phenolic $O\underline{H}$). These spectral data were identical with those reported for (+)- and (±)-**4d**.32,33) *Anal.* Calcd for $C_{20}H_{16}O_7 \cdot 1/3H_2O$: C, 64.17; H, 4.49. Found: C, 64.32; H, 4.23.

Recrystallization of (−)-**12** from $CHCl_3$–Et_2O gave pure (−)-**12** as red crystals, mp 198—202°C, $[\alpha]_D^{20}$ −62.0° (c=0.1, dioxane) (lit.,15b,c) $[\alpha]_D^{20}$ −86° (c=0.1, dioxane)).41) IR ν_{max}^{KBr} cm^{-1}: 3320 (OH), 1720 (ketone), 1615, 1580 (quinone and aromatic rings). ^{1}H-NMR (in $CDCl_3$): 2.15 (1H, d, J=16 Hz, C_8–$\underline{H}_a$), 2.37 (1H, dd, J=16 and 2 Hz, C_8–$\underline{H}_e$), 2.41 (3H, s, $COC\underline{H}_3$), 2.95 (1H, d, J=20 Hz, C_{10}–$\underline{H}_a$), 3.16 (1H, d, J=20 Hz, C_{10}–$\underline{H}_e$), 3.89 (1H, s, C_9–$O\underline{H}$), 4.26 (1H, d, J=2 Hz, C_7–$O\underline{H}$), 5.40 (1H, m, C_7–$\underline{H}$, $\nu_{1/2}$=20 Hz), 7.75—7.96 (2H, m, aromatic protons), 8.24—8.46 (2H, m, aromatic protons), 12.85 (1H, s, phenolic $O\underline{H}$), 13.10 (1H, s, phenolic $O\underline{H}$).

(+)-4-Demethoxyadriamycinone ((+)-4c)——Pyridinium hydrobromide perbromide (32 mg, 0.10 mmol) was added to a THF solution (2 ml) of (+)-**4d** (mp 172—178°C, $[\alpha]_D^{20}$ +136° (c=0.11, dioxane)) (18.4 mg, 0.050 mmol), and the mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo*, to give a red residue which was dissolved in Me_2CO (8 ml). After the acetone solution had been made alkaline (pH≒8) by the addition of 1% NaOH (8 ml), it was refluxed for 5 min and concentrated *in vacuo*. Water (10 ml) was added to the residue, and the aqueous mixture was extracted with MeOH–$CHCl_3$ (1:1) (20 ml × 3). The organic extracts were combined, and washed with satd. NaCl (20 ml × 1). Filtration and concentration *in vacuo* gave reddish-brown crystals (32 mg). This product was purified by column chromatography ($CHCl_3$: MeOH 97:3) to afford pure (+)-**4c** as reddish-brown crystals (14.2 mg, 74%). Repeated recrystallizations from a mixture of $CHCl_3$–MeOH–C_6H_{14} gave an analytical sample of (+)-**4c** as reddish-brown crystals, mp 174—176°C (dec.), $[\alpha]_D^{20}$ +147° (c=0.10, dioxane). IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1720 (ketone), 1620 (quinone), 1585 (aromatic rings). ^{1}H-NMR (in $CDCl_3$): 2.16 (1H, dd, J=16 and 4 Hz, C_8–$\underline{H}_a$), 2.42 (1H, br d, J=16 Hz, C_8–$\underline{H}_e$), 3.00 (1H, br t, J=3 Hz, $CH_2O\underline{H}$), 3.02 (1H, d, J=20 Hz, C_{10}–$\underline{H}_a$), 3.28 (1H, dd, J=20 and 2 Hz, C_{10}–$\underline{H}_e$), 3.40 (1H, br s, C_7–$O\underline{H}$), 4.60 (1H, s, C_9–$O\underline{H}$), 4.80 (2H, d, J=3 Hz, $COC\underline{H}_2OH$), 5.38 (1H, br s, C_7–$O\underline{H}$, $\nu_{1/2}$=10 Hz), 7.75—8.00 (2H, m, aromatic protons), 8.23—8.50 (2H, m, aromatic protons), 13.23 (1H, s, phenolic $O\underline{H}$), 13.55 (1H, s, phenolic $O\underline{H}$). Ms *m/e*: 384 (M^+), 348 ($M^+ - 2H_2O$), 306 ($M^+ - H_2O - COCH_2OH$–H), 317 ($M^+ - 2H_2O - CH_2OH$), 289 ($M^+ - 2H_2O - CH_2OH - CO$), 261 ($M^+ - 2H_2O - CH_2OH - 2CO$), 233 ($M^+ - 2H_2O - CH_2OH - 3CO$). High resolution mass spectrum: Calcd for $C_{20}H_{16}O_8$: 384.0845. Found: 384.0889. *Anal.* Calcd for $C_{20}H_{16}O_8 \cdot 1/3H_2O$: C, 58.82; H, 4.28. Found: C, 58.78; H, 3.96.

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(100 MHz), a JEOL JNM-PS-100 spectrometer (100 MHz), and a Hitachi R-24 high resolution spectrometer (60 MHz). All signals are expressed as ppm downfield from tetramethylsilane, used as an internal standard (δ-value). The following abbreviations were used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Measurements of optical rotations were carried out using a Yanaco OR-50 automatic polarimeter and a JASCO DIR-181 digital polarimeter. Mass spectra were taken with a JMS-01 SG-2 mass spectrometer and a Hitachi M-80 mass spectrometer (for high resolution mass spectra). All reactions were performed using anhyd. solvents, and the combined organic extracts obtained in each experiment were dried over anhyd. Na_2SO_4 or anhyd. $MgSO_4$, then filtered and concentrated *in vacuo* with a rotary evaporator. Column chromatography and preparative TLC were all performed using silica gel as an adsorbent. The following abbreviations are used for solvents and reagents: acetone (Me_2CO), benzene (C_6H_6), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), dimethyl sulfoxide (DMSO), ether (Et_2O), ethyl acetate (EtOAc), hexane (C_6H_{14}), isopropyl ether (iso-Pr_2O), dimethoxyethane (DME), tetrahydrofuran (THF).

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