Asymmetric Synthesis of optically Active Anthracyclinone Intermediate and 4-De- 
methoxyanthracyclinones by the Use of a Novel Chiral Reducing Agent\textsuperscript{1)}

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Asymmetric reduction of 2-acetyl-5,8-dimethoxy-3,4-dihyronaphthalene (1) with a 
ro? novel modified hydride, originally prepared by partial decomposition of lithium aluminum 
hydride with (1R,2S)-(−)-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.

\textbf{Keywords}—anthracycline; anthracyclinone; 4-demethoxydaunomycinone; 4-de- 
methoxyadriamycinone; asymmetric synthesis; asymmetric reduction; modified lithium 
alanum hydride; (1R,2S)-(−)-N-methylephedrine; N-ethylaniline; Friedel–Crafts 
reaction

In the preceding paper,\textsuperscript{2)} it was reported that, when asymmetric reduction of the \(\alpha,\beta\)- 
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)-(−)-\(\alpha\)-hydroxy ketone 
((R)-(−)-3), a versatile key intermediate for optically active anthracyclinones (4),\textsuperscript{3,4)} can 
be readily elaborated from (S)-2.
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. 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. Specific hydrogenation of the ketonic function of an \(\alpha,\beta\)-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). Asymmetric reduction of \(\alpha,\beta\)-unsaturated ketones according to method d) has been reported to usually give low chemical yields.

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, the number of modified LAH applicable to asymmetric reduction of \(\alpha,\beta\)-unsaturated ketones is quite limited, and rather low optical yields (25–30\% e.e.) of optically active allylic alcohols are usually obtained except for the recent successful result achieved by using LAH decomposed with optically active 2,2',dihydroxy-1,1'-binaphthyl. 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, 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.

Results and Discussion

A. Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihyronaphthalene (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 (Table I, run 1), (−)-2 was obtained in 60\% yield. Based on detailed stereochemical studies on the epoxidation of (±)-23 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 \([\alpha]_D^{20} = -20.5^\circ\) (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 (1R, 2S)-(−)-N-methylephedrine [(−)-N-methylephedrine] and 3,5-dimethylphenol 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 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 (I) with Various Types of Modified LAH^\text{a)}

<table>
<thead>
<tr>
<th>Run</th>
<th>Chiral reducing agent (molar ratio to 1)</th>
<th>Reaction conditions</th>
<th>(S)-(−)-2-1′-Hydroxyethyl-5,8-dimethoxy-3,4-dihydronaphthalene [(S)-(−)-2]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAH: chiral source^\text{b)}: additive^\text{c)}</td>
<td>Temp. (°C)</td>
<td>Time (h)</td>
</tr>
<tr>
<td>1</td>
<td>2.36 : 2.73(A)^\text{e)}</td>
<td>−78</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>6.6 : 6.6(A)</td>
<td>−78</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>3.3 : 3.3(E) : 6.6(D)^\text{g)}</td>
<td>−20</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>3.3 : 9.9(E)^\text{h)}</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>3.3 : 6.6(E)</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>3.3 : 3.3(E)</td>
<td>−78</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>3.3 : 3.3(E) : 6.6(P)</td>
<td>−78</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>3.3 : 3.3(E) : 6.6(T)</td>
<td>−78</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>3.3 : 3.3(E) : 6.6(M)</td>
<td>−78</td>
<td>3</td>
</tr>
</tbody>
</table>

^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)pyridine; 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\text{H}_2\text{O}_{18} 8:1).

^e) Optically pure (S)-(−)-2 gives [\alpha]_D^\text{c) 20.0}(c=1.07, EOH) (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-(heptafluoropropylhydroxy)methylene)-d-camphoratoeuropium (III) (Eu(bften)3).

At this stage, it became evident that the asymmetric reduction of I could not be achieved in high chemical and optical yields by employing the hitherto reported modified LAH,^\text{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 tetraalkoxylaluminate, LiAl(OCHRR')_4, as a final product, and that the rate of each reduction step is slower than that of the preceding step.\textsuperscript{20)} This means that the nucleophilicity of hydride gradually decreases with an increase of the number of alkoy groups binding with the central aluminum atom. Therefore, in order to effectively reduce the resonance-stabilized carbonyl group of I 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 nucleophilelicity of hydride.

Thus, the asymmetric reduction of I 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 I proceeded highly stereoselectively to give (S)-(−)-2 in 86% optical yield.\textsuperscript{21)} Replacements of the nitrogen atom presumably bound with the aluminum atom in the chiral hydride\textsuperscript{20)} 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 I 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-dihydroporphaphthene (1) with LAH partially decomposed with (−)-N-Methylephedrine and Various Achiral Amine Additives a) |
|----------------|----------------|----------------|----------------|----------------|
| **Run** | **Achiral amine additive** | **Chemical yield (%) b)** | **[α] D20 (°) (c, EtOH)** | **Optical yield (% e.e.) c)** | **Recovery of 1 (%)** |
| 1 | PhNHMe | 97 | −17.6 (1.81) | 86 | — d) |
| 2 | PhNHex | 100 | −18.8 (2.48) | 92 | — d) |
| 3 | PhNHPr | 91 | −17.3 (1.11) | 85 | — d) |
| 4 | PhNHPr-Bu | 96 | −17.7 (1.79) | 86 | — d) |
| 5 | PhNHSO-Pr | 99 | −3.9 (1.86) | 19 | — d) |
| 6 | PhNHt-Bu | 36 | −2.7 (0.67) | 13 | 61 |
| 7 | 3,5-Me2PhNHEt | 82 | −16.4 (1.79) | 80 | — d) |
| 8 | 3,5-Me2PhNHMe | 82 | −0.3 (1.16) | 7 | 40 |
| 9 | PhNHPh | 94 | −17.2 (1.76) | 84 | — d) |
| 10 | PhNH(CH3)2NHPh | 5 | — e) | — e) | — e) |
| 11 | n-BuNHMe | 7 | — e) | — e) | 91 |
| 12 | PhCH2NHMe | 19 | — e) | — e) | 67 |
| 13 | c-C6H5NHMe | 46 | −4.6 (0.43) | 24 | 46 |
| 14 | Pyrrolidine | 0 | — | — | 97 |
| 15 | Piperidine | 16 | −5.4 (0.30) | 27 | 86 |
| 16 | Thiomorpholine | 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 | Benzotriazolol | 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 (0.8 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 (C6H6-EtOAc 8:1).
c) Optically pure (S)-(-)-2 gives [α] D20 = 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-Ethylamine on the Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydroporphaphthene (1) a) |
|----------------|----------------|----------------|----------------|----------------|
| **Run** | **Chiral reducing agents (molar ratio to 1)** | **PhNHET (vs. LAH)** | **(S)(−)-2-1'-Hydroxyethyl-5,8-dimethoxy-3,4-dihydroporphaphthene ((S)-(−)-2)** |
| 1 | LAH : (−)-N-methylephedrine | 3.3 : 3.4 | 3.4 (×1.0) | 81 | −13.2 (1.51) | 65 |
| 2 | 3.3 : 3.4 | 3.4 (×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 | −18.2 (2.48) | 92 |
| 5 | 3.3 : 3.4 | 8.5 (×2.5) | 47 e) | −12.2 (0.89) | 59 |
| 6 | 3.3 : 3.4 | 10.2 (×3.0) | 62 e) | −12.4 (1.16) | 60 |

a) All reactions were carried out using LAH partially decomposed with (−)-N-methylephedrine and N-ethylamine in ether at −78°C for 5 h. (S)-(−)-2 was obtained as a sole reduction product.
b) Based on 1 after purification by preparative TLC (C6H6-EtOAc 8:1).
c) Optically pure (S)-(−)-2 gives [α] D20 = 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.\textsuperscript{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 \((S)-(\rightarrow)\)-2 could be obtained (Table III, run 1). This figure is very close to that achieved with the chiral reagent prepared using \((S)-(\rightarrow)\)-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 \((\rightarrow)\)-\(N\)-methylpyrrolidine 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 \((\rightarrow)\)-\(N\)-alkylpyrrolidines, reaction solvents, reaction temperatures, and temperatures for preparing the chiral reducing agent (aging temperatures)

### Table IV. Effects of \(N\)-Alkyl Substituent of \((\rightarrow)\)-\(N\)-Alkylpyrrolidine (A) and Reaction Solvent (B) on the Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (1)\textsuperscript{a)}

<table>
<thead>
<tr>
<th>(N)-Alkyl substituent of ((\rightarrow))-(N)-alkylpyrrolidine</th>
<th>((S)-(\rightarrow))-2</th>
<th>((S)-(\rightarrow))-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>94</td>
<td>-18.9 (1.77)</td>
</tr>
<tr>
<td>Et</td>
<td>73</td>
<td>-15.5 (1.37)</td>
</tr>
<tr>
<td>iso-Pr</td>
<td>58\textsuperscript{a)}</td>
<td>-15.4 (1.09)</td>
</tr>
<tr>
<td>PhCH(_2)</td>
<td>82</td>
<td>-16.8 (1.71)</td>
</tr>
<tr>
<td>Solvent</td>
<td>Chemical yield(%)\textsuperscript{b)}</td>
<td>Optical yield(% e.e.)\textsuperscript{c)}</td>
</tr>
<tr>
<td>Et(_2)O</td>
<td>94</td>
<td>-18.9 (1.77)</td>
</tr>
<tr>
<td>THF</td>
<td>59\textsuperscript{e)}</td>
<td>-1.1 (1.10)</td>
</tr>
<tr>
<td>Toluene</td>
<td>62\textsuperscript{d)}</td>
<td>-5.7 (1.16)</td>
</tr>
<tr>
<td>DME</td>
<td>16\textsuperscript{e)}</td>
<td>-\textsuperscript{e)}</td>
</tr>
<tr>
<td>Methyln</td>
<td>0\textsuperscript{e)}</td>
<td>-\textsuperscript{e)}</td>
</tr>
</tbody>
</table>

\(a)\) All reactions were performed using LAH (3.3 eq to 1) partially decomposed with \((\rightarrow)\)-\(N\)-alkylpyrrolidine (3.4 eq to 1) (for A) or with \((\rightarrow)\)-\(N\)-methylpyrrolidine (3.4 eq to 1) (for B) and \(N\)-ethylaniline (6.8 eq to 1) in either (for A) or in the indicated solvent (for B) at \(-78^\circ\text{C}\) for 3 h. \((S)-(\rightarrow)\)-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)\textsuperscript{a)}

<table>
<thead>
<tr>
<th>Reaction temp. (\degreeCelsius)</th>
<th>((S)-(\rightarrow))-2</th>
<th>((S)-(\rightarrow))-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical yield(%)\textsuperscript{b)}</td>
<td>([\alpha]_p^{\text{D}} (\degree))</td>
<td>Optical yield(% e.e.)\textsuperscript{c)}</td>
</tr>
<tr>
<td>((S)-(\rightarrow))-2</td>
<td>Chemical yield(%)\textsuperscript{b)}</td>
<td>([\alpha]_p^{\text{D}} (\degree))</td>
</tr>
<tr>
<td>35</td>
<td>95</td>
<td>-14.4 (1.77)</td>
</tr>
<tr>
<td>0</td>
<td>98</td>
<td>-16.2 (1.84)</td>
</tr>
<tr>
<td>-20</td>
<td>93</td>
<td>-16.8 (1.74)</td>
</tr>
<tr>
<td>-78</td>
<td>94</td>
<td>-18.9 (1.77)</td>
</tr>
<tr>
<td>-100</td>
<td>53\textsuperscript{d)}</td>
<td>-18.8 (0.99)</td>
</tr>
<tr>
<td>Aging temp. (\degreeCelsius)</td>
<td>Chemical yield(%)\textsuperscript{b)}</td>
<td>([\alpha]_p^{\text{D}} (\degree))</td>
</tr>
<tr>
<td>((S)-(\rightarrow))-2</td>
<td>Chemical yield(%)\textsuperscript{b)}</td>
<td>([\alpha]_p^{\text{D}} (\degree))</td>
</tr>
<tr>
<td>35</td>
<td>100</td>
<td>-18.8 (2.48)</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
<td>-6.6 (2.06)</td>
</tr>
<tr>
<td>0</td>
<td>45\textsuperscript{e)}</td>
<td>-4.1 (2.13)</td>
</tr>
</tbody>
</table>

\(a)\) All reactions were carried out using LAH (3.3 eq to 1) partially decomposed with \((\rightarrow)\)-\(N\)-methylpyrrolidine (3.4 eq to 1) and \(N\)-ethylaniline (6.8 eq to 1) at the indicated temperature (for A) or at \(-78^\circ\text{C}\) (for B) for 3 h. The chiral reducing agent was prepared at \(35^\circ\text{C}\) (for A) or at the indicated temperature (for B). \((S)-(\rightarrow)\)-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 V A) 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-ethylamline 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, [α]D 20 −20.5° (EtOH), in 87% chemical yield based on 1. The optical purity of this sample was ascertained by measuring its 1H-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-ethylamline was recovered in 98% yield by successive acidification and extractive isolation. Fractional distillation of the mixture gave (−)-N-methylephedrine without racemization and N-ethylamline 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′-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. 23 As shown in Chart 1, epoxidation of (S)-(−)-2 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 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 68 or 87% yield. Measurement of the \(^1\)H-NMR spectrum in the presence of \(\text{Eu(hfc)}_3\) 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.\(^{29}\)

![Chart 1](image)

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,\(^{21}\) treatment of (R)-(--)–3 with \(\text{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, [\(\alpha\)]\(_{D}^{25}\) = 23.1\(^{\circ}\) (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 \(\text{Eu(hfc)}_3\).

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 \((-\rangle-8\) were subjected to methylation with dimethyl sulfate,\textsuperscript{271} giving samples of \((-\rangle-7\) with 75 and 100\% e.e. respectively. The former partially optically active \((-\rangle-7\) yielded optically pure \((-\rangle-7\) on recrystallization from ether.

In order to prevent the racemization observed in the preparations of \((-\rangle-7\) and \((-\rangle-8\) from \((R)(-\rangle-3\), successive Friedel–Crafts reaction with phthalic anhydride and methylation with dimethyl sulfate were attempted using \((S)(-\rangle-2\) or \((-\rangle-6a\), which lacked the \(\alpha\)-hydroxy ketone moiety, as a reaction substrate. However, as shown in Chart 2, the aromatized product \((9)\) was obtained from \((S)(-\rangle-2\) in 46\% yield due to successive dehydration–isomerization during the Friedel–Crafts reaction. When \((-\rangle-6a\) was utilized as a reaction substrate, pinacol rearrangement of the vicinal-diol system concomitantly occurred to afford a 25\% yield of the ketone \((10)\).\textsuperscript{280} Accordingly, synthesis of \((+\rangle-4d\) and \((+\rangle-4c\) was carried out using optically pure \((-\rangle-7\) prepared from \((R)(-\rangle-3\).

Acetalization of \((-\rangle-7\) (97\% yield), followed by photo-sensitized bromination, acid-catalyzed methanolysis, and deacetalization (3 steps, 70\%), according to the reported procedure\textsuperscript{14,150} afforded an epimeric mixture of 4-demethoxydaunomycinone trimethyl ether ((+\rangle-11a and (+\rangle-11b). Separation by column chromatography gave (+\rangle-11a and (+\rangle-11b in 44 and 26\% yields, respectively. Spectral properties of these products were identical with those of the racemic compounds reported by Wong.\textsuperscript{140} 7-Epianthracyclinone is known to epimerize to anthracyclinone on treatment with trifluoroacetic acid followed by aqueous work-up.\textsuperscript{311} Therefore, the crude mixture of (+\rangle-11a and (+\rangle-11b obtained from \((-\rangle-7\) 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\textsuperscript{14,150} 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 (+\rangle-4d, [\(\alpha\)]\textsubscript{D} +153° (dioxane), and its \(7\beta\)-epimer ((-\rangle-12), [\(\alpha\)]\textsubscript{D} -62.0° (dioxane), in 37 and 9.4\% yields, respectively. These aglycones ((+\rangle-4d and \((-\rangle-12\) showed the same spectral properties and optical rotations as those reported.\textsuperscript{15,16,25,33}

Since asymmetric synthesis of (+\rangle-4d was accomplished as cited above, further derivation of (+\rangle-4d to (+\rangle-4c was next examined. As the reported procedure for introducing a hydroxy group into the \(C_{14}\)-position of daunomycinone \((4b)\textsuperscript{177} or racemic \(4d\textsuperscript{181})\) had not been reproduced, preparation of (+\rangle-4c was attempted by employing various reaction conditions. After several unsuccessful experiments, it was found that bromination of (+\rangle-4d with pyridinium hydrobromide–perbromide followed by treatment with aqueous alkaline solution gave (+\rangle-4c, [\(\alpha\)]\textsubscript{D}...
$+147^\circ$ (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.23)

**Experimental**

(1R,2S)-(−)-N-Methylephedrine—Prepared according to the reported procedure.24) Colorless needles (recrystallized from MeOH), mp 86.5−87.5°C, $[\alpha]_D^20 - 29.5^\circ$ ($c=4.54$, MeOH) (lit.,25) mp 87−88°C, $[\alpha]_D^20 - 29.5$ ($c=4.5$, MeOH).

(1R,2S)-(−)-N-Ethyl-, (1R,2S)-(−)-N-Isopropyl-, and (1R,2S)-(−)-N-Benzylephedrine—Samples previously prepared in this laboratory26) were used.

(5S)-(−)-2-(Anilinomethyl)pyrrolidine—Preparation of this compound was carried out according to the reported method.27) Colorless oil, bp 116−118°C (0.09 mmHg), $[\alpha]_D^20 + 20.1^\circ$ ($c=2.06$, EtOH) (lit.,28) bp 117−120°C (0.4 mmHg), $[\alpha]_D^20 + 19.1^\circ$ ($c=1.1$, EtOH); lit.28) bp 111−112°C (0.55 mmHg), $[\alpha]_D^20 + 19.7^\circ$ ($c=1.09$, EtOH). Spectral (IR and $^1$H-NMR) properties of this sample were identical with those reported.29)

**Asymmetric Reduction of 2-Acetyl-5,8-dimethoxy-3,4-dihydropyridaphtalene (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), $[\alpha]_D^20 + 20.1^\circ$ ($c=2.06$, EtOH)) (481 mg, 2.73 mmol) was added to a stirred suspension of LAH (50 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.31)

An ethereal solution (10 ml) of 1 (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 x 3). The combined organic extracts were washed with satd. NaCl (15 ml x 3). Filtration and concentration _in vacuo_ gave crude (S)-(−)-2, which was purified by preparative TLC (C$_9$H$_4$-EtOAc 8:1) to give (S)-(−)-2 as colorless crystals (140 mg, 60%), mp 83−85°C, $[\alpha]_D^20 − 11.0^\circ$ ($c=1.93$, EtOH), 54% e.e., based on $[\alpha]_D^20 − 20.5^\circ$ ($c=1.07$, 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 (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, $[\alpha]_D^20 − 12.1^\circ$ ($c=2.01$, EtOH), 64% e.e. based on $[\alpha]_D^20 − 20.5^\circ$ ($c=1.07$, 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, $[\alpha]_D^20 − 29.5^\circ$ ($c=4.54$, 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 with 1 h with stirring to afford a solution of the reducing agent.19)
An ethereal solution (11 ml) of 1H (93 mg, 0.40 mmol) was gradually added to the solution of the reducing agent cooled at \(-20^\circ C\), 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 x 3). The organic extracts were combined, and washed successively with 10% NaOH (10 ml x 3), H₂O (10 ml x 3), and satd. NaCl (10 ml x 2). Filtration and concentration in vacuo, followed by purification with preparative TLC (C₂H₅–EtoAc 8: 1), gave (S)-(-)-2 as colorless crystals (10.4 mg, 11%), mp 81–82.5°C, [x]₂⁰ = -2.7° (c=0.52, EtoH), 13% e.e. based on [x]₂⁰ = -20.5° (c=1.07, EtoH) \textit{vide infra}. This sample was found to be identical with the sample obtained in e) by spectral (IR and ¹H-NMR) comparisons.

c) Table I, Run 6: An ethereal solution (6 ml) of (--)N-methylpentahydrindine (mp 86.5–87.5°C, [x]₂⁰ = -29.5° (c=4.54, MeOH)) (257 mg, 1.32 mmol) was added to a suspension of LAH (50 mg, 1.32 mmol) in E₂O (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 1H (93 mg, 0.40 mmol) was gradually added to the solution of the reducing agent cooled at \(-78^\circ C\), 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 x 3). The organic extracts were combined, and washed successively with 5% NaOH (5 ml x 1), H₂O (10 ml x 1), and satd. NaCl (10 ml x 1). Filtration and concentration in vacuo, followed by purification by preparative TLC (C₂H₅–EtoAc 8: 1), gave (S)-(-)-2 as colorless crystals (86 mg, 92%), mp 78–80°C, [x]₂⁰ = -0.84° (c=1.71, EtoH), 4% e.e. based on [x]₂⁰ = -20.5° (c=1.07, EtoH) \textit{vide infra}. This sample was found to be identical with the sample obtained in e) by spectral (IR and ¹H-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-methylpentahydrindine (mp 86.5–87.5°C, [x]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 E₂O (2.5 ml), and the mixture was heated at reflux for 1 h with stirring. An ethereal solution (3 ml) of N-methylinlaniline (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 1H (93 mg, 0.40 mmol) in E₂O (12 ml) was gradually added to the ethereal solution of the reducing agent cooled at \(-78^\circ C\), 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 x 3). The organic extracts were combined and washed successively with 1% HCl (10 ml x 2), H₂O (10 ml x 2), and satd. NaCl (10 ml x 1). Filtration and concentration in vacuo gave crude (S)-(-)-2 as colorless crystals (165 mg). This sample was purified by preparative TLC (C₂H₅–EtoAc 8: 1), giving (S)-(-)-2 as colorless crystals (91 mg, 97%), mp 86–88°C, [x]₂⁰ = -17.6° (c=1.81, EtoH), 86% e.e. based on [x]₂⁰ = -20.5° (c=1.07, EtoH) \textit{vide infra}. Spectral (IR and ¹H-NMR) properties of this sample were identical with those of (S)-(-)-2 obtained in e).

The same asymmetric reduction of 1H was attempted using N-ethylalaniline in place of N-methylinlaniline, to provide (S)-(-)-2 (86 mg, 94%), mp 85–87°C, [x]₂⁰ = -18.9° (c=1.71, EtoH), 92% e.e. based on [x]₂⁰ = -20.5° (c=1.07, EtoH) \textit{vide infra}, after purification by preparative TLC. This sample was similarly identified by spectral (IR and ¹H-NMR) comparisons.

The other asymmetric reductions shown in Tables IV–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 (I) were identified by spectral (IR and ¹H-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-methylpentahydrindine (mp 86.5–87.5°C, [x]₂⁰ = -20.5° (c=4.54, MeOH)) (2.43 g, 13.6 mmol) was added to a suspension of LAH (500 mg, 13.2 mmol) in E₂O (25 ml) with stirring, and the mixture was heated at reflux for 1 h with stirring. A solution of N-ethylalaniline (3.30 g, 27.2 mmol) in E₂O (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 1H (930 mg, 4.00 mmol) in E₂O (10 ml) was gradually added to the solution of the reducing agent cooled at \(-78^\circ C\), 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 x 3). The organic extracts were combined and washed successively with 1% HCl (100 ml x 2), 5% NaHCO₃ (100 ml x 1), H₂O (100 ml x 2), and satd. NaCl (100 ml x 2). Filtration and concentration in vacuo gave (S)-(-)-2 as colorless crystals (980 mg, 100%), mp 87–87.5°C, [x]₂⁰ = -18.8° (c=2.48, EtoH), 92% e.e. based on [x]₂⁰ = -20.5° (c=1.07, EtoH) \textit{vide infra}. Direct recrystallization from C₆H₄₃ afforded an optical sample of optically pure (S)-(-)-2 as colorless needles (817 mg, 87%), mp 88–89°C, [x]₂⁰ = -20.4° (c=1.55, EtoH). Further repeated recrystallizations from C₆H₄₃ afforded colorless needles, mp 88–89°C, [x]₂⁰ = -20.5° (c=1.07, EtoH). IR νmax cm⁻¹: 3340, 1260, 1690 (OH), 1600 (aromatic ring). IR νmax cm⁻¹: 3600, 1200, 1100 (OH). ¹H-NMR (in CDCl₃): 1.32 (3H, d, J=6 Hz, CH(CH₃)CH₂). 2.00–2.36 (2H, m, CH₂(CH₃)₃C). 2.12 (1H, s, OH). 2.64–2.88 (2H, m, CH₂CH₃). 2.74 (5H, s, OCH₃x2), 3.74 (6H, t, CH₂O), 4.40 (1H, q, CH(OH)), 6.60 (2H, s, aromatic protons), 6.72 (1H, br s, CH₃). The IR (in CHCl₃) and ¹H-NMR spectra of this sample were superimposable on those of (±)-2) measured under the same conditions. Anal. Calcd for C₁₄H₂₀O₅: C, 71.77; H, 7.74. Found: C, 71.37; H, 7.76. Since this sample showed a doublet methyl group signal at
10.4 ppm in the 1H-NMR spectrum measured in the presence of Eu(hfc)₃(Cl)·(S)-(−)-2: Eu(hfc)₃·1:1 in CCl₄, the optical purity of this sample was definitely determined as 100% e.e. The spectrum of (+)-2 and 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, 17.5%), [α]ᵢ₀ = −3.6° (c = 2.79, EtOH), 18% e.e. based on [α]ᵢ₀ = −20.5° (c = 1.07, EtOH) (vide supra). A part of this sample (103 mg, 0.44 mmol) was dissolved in C₄H₄ (10 ml), and DDAO (143 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 C₄H₄ (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. 94°, mp 106–107°C). This sample was found to be identical with authentic (+)−1 by spectral (IR and 1H-NMR) comparisons.

On the other hand, the acidic aqueous phases (1 N HCl, 1% HCl, and H₂O 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 x 3). The organic extracts were combined, and washed with satd. NaCl (100 ml x 4). Filtration and concentration in vacuo gave a mixture of (−)-N-methylpyrrolidine and N-ethanolamine as a mixture of a pale yellow oil and crystals (5.62 g, 98%). Direct fractional distillation in vacuo gave N-ethanolamine (3.3 g, quantitative recovery), bp 87–90°C (15 mmHg), and (−)-N-methylpyrrolidine (2.0 g, 83% recovery), bp 120°C (0.01 mmHg), mp 85–87.5°C, [α]ᵢ₀ = −29.1° (c = 4.59, MeOH), 99% e.e. based on [α]ᵢ₀ = −29.5° (c = 4.54, MeOH) (vide supra). These samples were confirmed to be identical with corresponding authentic samples by spectral (IR and 1H-NMR) comparisons.

(1'S,2'R)-(−)-2'−Hydroxyethyl−5,8−dimethoxy−1,2,3,4−tetrahydro−2−naphthol ((−)-6a) and Its (2S)-Isomer (6b)—Successive epoxidation of optically pure (S)-(−)-2 (mp 88−89°C, [α]ᵢ₀ = −20.5° (c = 1.07, EtOH)) (703 mg, 3.0 mmol) with tert-butyldihydroperoxide in C₄H₄ in the presence of vanadium oxyacetate 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 and gave a crude mixture of (−)-6a and 6b as colorless crystals (730 mg, 97% yield) after extraction isolation with EtOAc and concentration in vacuo.

A part of this sample (380 mg) was subjected to column chromatography (C₄H₄-EtOAc 1:1, giving a diastereomeric mixture of (−)-6a and 6b as colorless needles (355 mg, 85%), mp 140–150°C, [α]ᵢ₀ = −39.3° (c = 1.04, EtOH). Spectral (IR and 1H-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 Et₂O to give pure (−)-6a as colorless needles (252 mg, 70%), mp 154–155°C, [α]ᵢ₀ = −49.7° (c = 0.50, EtOH). IR νmax cm⁻¹: 3360, 1260, 1085 (OH). IR υmax cm⁻¹: 3580, 1260, 1105, 1090 (OH). 1H-NMR (in CDCl₃-CDOD): 1.23 (3H, d, J = 6 Hz, CH(OH)CH₂), 1.40–2.05 (2H, m, CH₂CH(C(OH))H), 2.50–2.88 (4H, m, CH₂CH₂CH(OH)CH₃), 3.20 (2H, two s, CH₂O x 2), 3.62 (1H, q, J = 6 Hz, CH₂(OH)CH₃), 3.72 (3H, s, OCH₃), 3.74 (3H, s, OCH₃), 6.60 (2H, s, aromatic protons). Anal. Calculd for C₂₅H₂₀O₄: C, 66.64; H, 7.99. Found: C, 66.78; H, 8.06. The IR (in CDCl₃) and 1H-NMR spectra of this sample were superimposable on those of (±)-6a measured under the same conditions.

(R)-(−)-2′−Acetyl−5,8−dimethoxy−1,2,3,4−tetrahydro−2−naphthol ((R)-(−)-3) a) Oxidation with Fetzion Reagent: (55) A diastereomeric mixture of (−)-6a and 6b (mp 140–150°C, [α]ᵢ₀ = −39.3° (c = 1.04, EtOH)) (153 mg, 0.54 mmol) was treated with Fetzion reagent in C₄H₄ in the same manner as described for (±)-6a and gave (R)-(−)-3 as colorless needles (105 mg, 84%), mp 123–127°C, [α]ᵢ₀ = −42.5° (c = 0.89, CHCl₃), 90% e.e. based on [α]ᵢ₀ = −47.1° (c = 1.11, CHCl₃) (vide infra), with purification by preparative TLC. This sample exhibited the same spectral (IR and 1H-NMR) properties as those of optically pure (R)-(−)-3 (vide infra).

When pure (−)-6a (mp 154–155°C, [α]ᵢ₀ = −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, [α]ᵢ₀ = −44.0° (c = 1.92, CHCl₃), after purification by preparative TLC. Repeated recrystallizations of this sample from CHCl₃-Et₂O gave an analytical sample of optically pure (R)-(−)-3 as colorless needles, mp 128–129°C, [α]ᵢ₀ = −47.1° (c = 1.11, CHCl₃) (lit., 65° mp 130–132°C, [α]ᵢ₀ = −50° (c = 1.01, CHCl₃)); lit., 65° mp 128–129°C, [α]ᵢ₀ = −48.6° (c = 0.982, CHCl₃); lit., 65° mp 128–130°C, [α]ᵢ₀ = −49° (concentration and solvent were not specified). IR νmax cm⁻¹: 1700 (ketone). IR υmax cm⁻¹: 1710 (ketone). 1H-NMR (in CDCl₃): 0.86–2.10 (2H, m, CH₂CH₂O(CH₂)H₂), 2.29 (3H, s, COCl₂), 2.70–3.10 (4H, m, CH₂CH₂O(CH₂)H₂), 3.58 (1H, s, OH), 3.72 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 6.62 (2H, s, aromatic protons). These spectral properties were identical with those of (R)-(−)-3 previously reported. The optical purity of this sample was determined as 100% e.e. by measuring the 1H-NMR spectrum in the presence of Eu(hfc)₃((R)-(−)-3: Eu(hfc)₃·1.0: 0.6 in CDCl₃). The 1H-NMR spectrum showed the acetyl group signal as a singlet at 4.6 ppm, in contrast to that of (±)-3, 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: (55) Similar treatments of (−)-6a (mp 153.5–154°C, [α]ᵢ₀ = −47.9° (c = 1.02, EtOH)) (2.52 g, 10.0 mmol) to those of (±)-6a and gave crude (R)-(−)-3 as colorless crystals (2.47 g, 99%) after extractive isolation with CHCl₃ and concentration in vacuo. This sample was purified by column chromatography (C₄H₄-EtOAc 7:1) to give (R)-(−)-3 as colorless crystals (2.41 g, 96%), mp 127–128°C, [α]ᵢ₀ = −42.8° (c =
1.22, CHCl₃). Recrystallization from CHCl₃-Et₂O gave a pure sample of optically pure (R)-(−)-3 as colorless needles (2.17g, 87%), mp 128–129°C, [α]D° = −46.0° (c=1.10, CHCl₃). Spectral (IR and ¹H-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)-(−)-3.¹⁴,²¹ Similarly to the preparation of (±)-7,²¹ successively Friedel–Crafts acylation of optically pure (R)-(−)-3 (mp 127.5–129°C, [α]D° = −46.6° (c=1.02, CHCl₃)) (500 mg, 2.0 mmol) with o-methoxybenzylbenzoyl chloride in the presence of anhyd. AlCl₃ in CH₂Cl₂, hydrolysis of the crude methyl ester with aq. NaOH, and cyclization of the acid with H₂SO₄ gave crude (−)-7 as pale yellow crystals (512 mg, 67%), after purification by column chromatography (C₂H₅–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 ¹H-NMR spectra of the recrystallized sample were identical with those of (−)-7. Since the ¹H-NMR spectrum of this sample measured in the presence of Eu(hfc)₃(−)-7: Eu(hfc)₃ 1: 1 in CDCl₃ 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 (−)-7 and (+)-7 in a ratio of 3:2. The ¹H-NMR spectrum of (±)-7 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 Et₂O to give optically pure (−)-7 as pale yellow crystals (246 mg, 32%), mp 138–140°C, [α]D° = −23.1° (c=1.04, CHCl₃). Further recrystallization from toluene–CH₂Cl₂ gave an analytical sample of optically pure (−)-7 as pale yellow crystals (190 mg, 25%), mp 139–140°C, [α]D° = −23.0° (c=1.06, CHCl₃) (lit.,¹⁴,²¹ mp 142–144°C, [α]D° = −32° (c=1, CHCl₃); lit.,¹⁴,²¹ mp 142–144°C, [α]D° = −33° (CHCl₃)). IR νmax cm⁻¹: 3440 (OH), 1700 (ketone), 1670 (quione), 1505, 1555 (aromatic rings). ¹H-NMR (in CDCl₃): 1.84–2.02 (2H, m, CH₂CH₂CH(OH)CH₃), 2.76–3.28 (4H, m, CH₂CH₂(COH)CH₃), 3.44 (3H, s, COCH₃), 3.88 (3H, s, OCH₃), 5.02–5.20 (2H, m, aromatic protons), 7.60–7.70 (2H, m, aromatic protons). This ¹H-NMR spectrum was superimposable on that of (±)-7.¹⁴,²¹ Anal. Calcd. for C₁₇H₁₅O₃: C, 69.46; H, 5.30. Found: C, 69.21; H, 5.23. The ¹H-NMR spectrum of this sample measured in the presence of Eu(hfc)₃(−)-7: Eu(hfc)₃ 1: 1 in CDCl₃ 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 (−)-8.²¹ Methylation of optically pure (−)-8 (mp 218–220°C, [α]D° = −87.0° (c=0.115, CHCl₃)) (25.0 mg, 0.070 mmol) in the same manner as described for (±)-8 was obtained as an optically pure sodium salt from Et₂O (150 mg, 1.0 mmol) (νmax cm⁻¹: 1640 (OH), 1720 (ketone), 3450 (OH), 1620, 1580 (quione)). ¹H-NMR (in CDCl₃): 1.85–2.15 (2H, m, CH₂CH₂CH(OH)CH₃), 2.38 (3H, s, COCH₃), 2.95–3.10 (4H, m, CH₂CH₂(COH)CH₃), 3.60 (1H, s, OH), 7.75–8.00 (2H, m, aromatic protons), 8.02–8.20 (2H, aromatic protons). The ¹H-NMR spectrum of this sample was identical with those recorded in a).

When crude (−)-8 (336 mg, 0.95 mmol), prepared from (R)-(−)-3 (mp 128–129°C, [α]D° = −46.0° (c=1.10, CHCl₃)) (250 mg, 1.0 mmol) (νmax cm⁻¹: 1640 (OH), 1720 (ketone), 3450 (OH), 1620, 1580 (quione)), was immediately subjected to methylation, (−)-7 showing [α]D° = −17.3° (c=1.32, CHCl₃) 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, [α]D° = −23.0° (c=1.06, CHCl₃), was optically pure. This sample was dissolved in Et₂O (100 ml), almost racemic 7 crystallized out and was separated by filtration (84 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, [α]D° = −22.5° (c=1.01, CHCl₃). This sample was found to be identical with (−)-7 obtained in a) by spectral (IR and ¹H-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 (S)-(−)-3 (mp 128–129°C, [α]D° = −46.0° (c=1.10, CHCl₃)) (501 mg, 4.0 mmol), phthalic anhydride (593 mg, 4.0 mmol), anhyd. AlCl₃ (5.0 g, 37.5 mmol), and NaCl (1 g) in the same manner as described for (±)-8 was a red solid (640 mg, 91%), mp 214–218°C, [α]D° = −61.8° (c=0.11, CHCl₃), 71% e.e. based on [α]D° = −87.0° (c=0.115, CHCl₃) (νmax cm⁻¹: 1640 (OH), 1720 (ketone), 1620, 1580 (quione)). ¹H-NMR (in CDCl₃): 1.85–2.15 (2H, m, CH₂CH₂CH(OH)CH₃), 2.38 (3H, s, COCH₃), 2.95–3.10 (4H, m, CH₂CH₂(COH)CH₃), 3.60 (1H, s, OH), 7.75–8.00 (2H, m, aromatic protons), 8.02–8.46 (2H, aromatic protons), 13.36 (2H, s, two phenolic OH). Anal. Calcd. for C₁₇H₁₅O₃·1/3H₂O: C, 67.63; H, 4.69. Found: C, 67.31; H, 4.41.

2-Ethyl-5,12-dimethoxydihydronaphthacene-6,11-dione (9) —The same treatments of optically pure (S)-(−)-2 (mp 88–89°C, [α]D° = −20.5° (c=1.05, EtOH)) (460 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_{8}H_{14}−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} cm⁻¹: 1680 (quinoine), 1600 (aromatic rings). 1H-NMR (in CDCl₃): 1.29 (3H, br t, J = 5 Hz, CH₂CH₃), 2.75 (2H, br q, J = 8 Hz, CH₂CH₃), 4.10 (6H, two s, OCH₂₂), 7.40−7.80 (3H, m, aromatic protons), 7.95−8.45 (4H, m, aromatic protons). Anal. Caled for C_{22}H_{26}O₄: C, 76.28; H, 5.24. Found: C, 76.01; H, 5.17.

2-Acetyl-5,5-dimethoxy-1,2,3,4-tetrahydronaphthalene-6,11-dione (10)—The vicinal-diol[(−)-6a] (mp 152−154°C, [α]D⁻³⁰ = 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_{8}H₄−EtOAc 4:1) gave 10 as yellow crystals (24.8 mg, 25%). An analytical sample of 100 (10.80 mg) was prepared by recrystallization from MeOH, mp 142−144°C. IR ν_{max} cm⁻¹: 1700 (ketone), 1680 (quinone), 1580, 1550 (aromatic rings). 1H-NMR (in CDCl₃): 1.80−2.25 (2H, m, CH₂CH₂CH₂COCH₂), 2.26 (3H, s, OCH₃), 2.60−3.05 (5H, m, CH₂CH₂COCH₂), 3.88 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 7.60−7.72 (2H, m, aromatic protons), 8.00−8.18 (2H, m, aromatic protons). Anal. Caled for C_{22}H_{22}O₄: C, 73.14; H, 5.53. Found: C, 71.49; H, 5.44.

(+)-4-Demethoxydaunomycinone 15 trimethyl ether (25,4S;R)(−)-2-Acetyl-2-hydroxy-4,5,12-trimethoxy-1,2,3,4-tetrahydronaphthalene-6,11-dione [(+)−11a] and its (+)−7-Epimer (4R;R)(−)-Epimer [(+)−11b]—(−)-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-tetrahydronaphthalene-6,11-dione: A mixture of (−)−7 (mp 139−140°C, [α]D⁻³⁰ = −23.0° (c = 1.00, CHCl₃)) [91 mg, 0.24 mmol], ethylene glycol (2 ml, 35.9 mmol), and 3-toluenesulfonyl acid monohydride (10 mg, 0.05 mmol) in C₆H₆ (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 H₂O (10 ml × 3) and satd. NaCl (10 ml × 1). Filtration and concentration in vacuo gave the acetyl as yellow crystals (99 mg, 97%). Recrystallization of this sample from CHCl₃−Et₂O afforded the pure acetal as pale yellow needles (61 mg, 60%), mp 176−178°C, [α]D⁻³⁰ = −29° (c = 1.00, CHCl₃). IR ν_{max} cm⁻¹: 3420 (OH), 1670 (quinine), 1590, 1560 (aromatic rings). 1H-NMR (in CDCl₃): 1.48 (6H, s, OCH₃), 1.65−2.10 (2H, m, CH₂CH₂CO(OH)CH₂), 2.00 (1H, s, O), 2.80−3.20 (4H, m, CH₂CH₂CO(OH)CH₂), 3.90 (7H, two s, OCH₃ and OCH₂CH₃), 4.05 (3H, s, OCH₃), 7.50−7.85 (3H, m, aromatic protons), 8.00−8.35 (2H, m, aromatic protons).

b) (−)-11a and (−)-11b—A mixture of (−)-acetal (mp 178−179°C, [α]D⁻³⁰ = −24.0° (c = 1.01, CHCl₃)) (348 mg, 0.82 mmol) and N-bromosuccinimide (175 mg, 0.98 mmol) in CCl₄ (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 H₂O (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 CHCl₃ (20 ml). The CHCl₃ solution was washed successively with H₂O (20 ml × 2), 5% NaHCO₃ (20 ml × 1), H₂O (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 (C₆H₄−EtOAc 4:1) to give (−)-11a as pale yellow needles (148 mg, 44%), mp 120−130°C, [α]D⁻³⁰ = +140° (c = 0.30, CHCl₃) 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, [α]D⁻³⁰ = +228° (c = 0.45, CHCl₃). IR ν_{max} cm⁻¹: 3410 (OH), 1710 (ketone), 1670 (quinoine), 1590, 1555 (aromatic rings). 1H-NMR (in CDCl₃): 1.86 (1H, dd, J = 15 and 4 Hz, C₆H₅), 2.43 (3H, s, COCH₃), 2.40 (1H, dd, J = 15, 2, and 2 Hz, C₆H₅), 3.05 (1H, d, J = 18 Hz, C₆H₅), 3.38 (1H, d, J = 18 and 2 Hz, C₆H₅), 3.60 (3H, s, C₆H₅), 3.90 (3H, s, OCH₃), 4.00 (3H, s, OCH₃), 4.90 (1H, m, C₆H₅), 5.02 (1H, s, O), 7.60 (2H, m, aromatic protons), 8.04−8.20 (2H, m, aromatic protons). These spectral properties were identical with those reported for (−)-11a. Anal. Caled for C₂₀H₁₆O₂: C, 73.61; H, 5.40. Found: C, 71.69; H, 5.30.

(+)-7-Epimer ((+)−4d) and (−)-7-Epi-4-demethoxydaunomycinone ((−)−12)—Powdered AlCl₃ (320 mg, 2.4 mmol) was added to a CHCl₃ 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 CHCl₃ (50 ml), and the whole was stirred at room temperature for 2 h.
The organic layer was separated and washed successively with H₂O (100 ml x 1), 5% NaHCO₃ (100 ml x 1), H₂O (100 ml x 2), and satd. NaCl (100 ml x 1). Filtration and concentration in vacuo, followed by purification by column chromatography (CHCl₃), 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% NH₄OH (8 ml) and Me₂CO (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 (CHCl₃) afforded (+)-4d as reddish-brown crystals (55 mg, 54%), \[\text{x}^\circ_{D} = 98.2^\circ (c = 0.112, \text{dioxane})\], and (−)-12 as reddish-brown crystals (14 mg, 14%).

Two recrystallizations of (+)-4d from CHCl₃-Et₂O gave pure (+)-4d as reddish-brown crystals, mp 183.5–184.5°C, \[\text{x}^\circ_{D} = 153^\circ (c = 0.09, \text{dioxane})\] (lit., 4d, mp 184–186°C, \[\text{x}^\circ_{D} = 140^\circ (c = 1, \text{dioxane})\] lit., 4d, mp 185–187°C, \[\text{x}^\circ_{D} = 165^\circ (c = 0.1, \text{dioxane})\] lit., 4d, mp 184–186°C, \[\text{x}^\circ_{D} = 170^\circ (c = 0.1, \text{dioxane})\] lit., 4d, mp 185–187°C, \[\text{x}^\circ_{D} = 165^\circ (\text{dioxane})\] IR νmax cm⁻¹; 3330 (OH), 1720 (ketone), 1618, 1584 (quinine and aromatic rings). ¹H-NMR (in CDCl₃): 2.12 (1H, dd, J = 16 Hz, C₂-H₂), 2.32 (1H, br d, J = 16 Hz, C₄-H₄), 2.44 (3H, s, COCH₃), 2.88 (1H, d, J = 18 Hz, C₆-H₆), 3.12 (1H, dd, J = 18 and 1 Hz, C₂-H₂), 3.50 (1H, d, J = 6 Hz, C₂-OH), 4.61 (1H, s, C₂-OH), 5.22 (1H, m, C₂-H₂, r_{12} = 12 Hz), 7.68–7.85 (2H, m, aromatic protons), 8.12–8.25 (2H, m, aromatic protons), 12.96 (1H, s, phenolic OH), 13.24 (1H, s, phenolic OH). These spectral data were identical with those reported for (+)-4d and (±)-4d. Anal. Calcd for C₇₀H₇₀O₂·1.5H₂O: C, 64.17; H, 4.49. Found: C, 64.32; H, 4.23.

Recrystallization of (−)-12 from CHCl₃-Et₂O gave pure (−)-12 as red crystals, mp 198–202°C, \[\text{x}^\circ_{D} = -62.0^\circ (c = 0.1, \text{dioxane})\] (lit., 12, mp 178–178°C, \[\text{x}^\circ_{D} = -86^\circ (c = 0.1, \text{dioxane})\] IR νmax cm⁻¹; 3320 (OH), 1720 (ketone), 1615, 1580 (quinine and aromatic rings). ¹H-NMR (in CDCl₃): 2.15 (1H, d, J = 16 Hz, C₂-H₂), 2.37 (1H, dd, J = 16 and 2 Hz, C₂-H₂), 2.41 (3H, s, COCH₃), 2.95 (1H, d, J = 20 Hz, C₂-H₂), 3.16 (1H, d, J = 20 Hz, C₄-H₄), 3.98 (1H, s, C₂-OH), 4.26 (1H, d, J = 2 Hz, C₂-OH), 5.40 (1H, m, C₂-H₂, r_{12} = 20 Hz), 7.75–7.96 (2H, m, aromatic protons), 8.24–8.46 (2H, m, aromatic protons), 12.85 (1H, s, phenolic OH), 13.10 (1H, s, phenolic OH).

(+)–4-Demethoxyatramycinone (±)-4c—Pyridinium hydrobromide perbromide (32 mg, 0.10 mmol) was added to a THF solution (2 ml) of (+)-4d (mp 172–178°C, \[\text{x}^\circ_{D} = 136^\circ (c = 0.11, \text{dioxane})\] 18.4 mg, 0.60 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 Me₂CO (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–CHCl₃ (1:1) (20 ml x 3). The organic extracts were combined, and washed with satd. NaCl (20 ml x 1). Filtration and concentration in vacuo gave reddish-brown crystals (32 mg). This product was purified by column chromatography (CHCl₃-MeOH 97:3) to afford pure (+)-4c as reddish-brown crystals (14.2 mg, 74%). Repeated recrystallizations from a mixture of CHCl₃-MeOH–C₄H₁₄ gave an analytical sample of (+)-4c as reddish-brown crystals, mp 174–176°C (dec.), \[\text{x}^\circ_{D} = 147^\circ (c = 0.10, \text{dioxane})\] IR νmax cm⁻¹; 3420 (OH), 1720 (ketone), 1620 (quinine aromatic rings). ¹H-NMR (in CDCl₃): 2.16 (1H, dd, J = 16 and 4 Hz, C₂-H₂), 2.42 (1H, br d, J = 16 Hz, C₂-H₂), 3.00 (1H, br t, J = 3 Hz, CH₂O), 3.02 (1H, dd, J = 20 Hz, C₂-H₂), 3.28 (1H, dd, J = 20 and 2 Hz, C₂-H₂), 3.40 (1H, br s, C₂-OH), 4.60 (1H, s, C₂-OH), 4.80 (2H, d, J = 3 Hz, COCH₂), 5.38 (1H, br s, C₂-OH, r_{12} = 10 Hz), 7.75–8.00 (2H, m, aromatic protons), 8.23–8.50 (2H, m, aromatic protons), 13.23 (1H, s, phenolic OH), 13.55 (1H, s, phenolic OH). MS m/z: 384 (M⁺), 348 (M⁺–2H₂O), 306 (M⁺–H₂O–CH₂O–OH), 217 (M⁺–CH₂O–CO), 261 (M⁺–2H₂O–CH₂O–CO), 233 (M⁺–2H₂O–CH₂O–CO). High resolution mass spectrum: Calcd for C₇₀H₇₀O₁·1.5H₂O: C, 58.82; H, 4.28. Found: C, 58.78; H, 3.96.

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References and Notes
1) Part of this work has been the subject of a preliminary communication: S. Terashima, N. Tanno, and K. Koga, Tetrahedron Lett., 21, 2753 (1980).
3) Synthetic studies on optically active anthracyclinones (4), the aglycones of anthracycline antibiotics, are desirable for developing anticancer agents with improved therapeutic activities. See the introduction in ref. 2 and references cited therein.
21. Highly enantioselective formation of (S)-(-)-2, which could not have been foreseen at this stage, was later rationalized in terms of the transition state of the asymmetric reduction. See the accompanying paper.22
23. Detailed discussions on the structure of the exploited reducing agent and on the transition state for the asymmetric reduction are presented in the accompanying paper.23
25. Reduction of acetophenone with the chiral hydride prepared by partial decomposition of LAH with (25,3R)-(+)-dimethylamino-3-methyl-1,2-diphenyl-2-butanol was reported to give either (R)-(-)- or (S)-(-)-1-phenylethanol in 6–70% optical yields depending upon whether the reagent was used immediately after its preparation or after being aged overnight or refluxed for a few minutes.24 a,b
27. For experimental details, see ref. 2.
28. The examined reaction conditions of Friedel–Crafts acylation had been reported to give (−)-7 (or (−)-8) without racemization.24 a,b While the mechanism by which the asymmetric center originally involved in (R)-(−)-3 racemizes under the conditions of the Friedel–Crafts reaction is quite obscure, the optical lability of the α-hydroxy ketone moiety has been successfully utilized for other efficient syntheses of optically pure anthracenone intermediates recently developed in this laboratory.25
30. Measurement of the optical rotation was not performed on this compound.
34. All melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. All boiling points are uncorrected. A Büchi GKR-50 apparatus was used for a bulb-to-bulb distillation. IR spectra were measured with a JASCO DS-402G infrared spectrometer and a JASCO IRA-1 grating infrared spectrometer. NMR spectra were measured with a JEOL FX-100 spectrometer.
(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. Na₂SO₄ or anhyd. MgSO₄, 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 (Me₂CO), benzene (C₆H₆), chloroform (CHCl₃), dichloromethane (CH₂Cl₂), dimethyl sulfoxide (DMSO), ether (Et₂O), ethyl acetate (EtOAc), hexane (C₆H₁₄), isopropyl ether (iso-Pr₂O), dimethoxyethane (DME), tetrahydrofuran (THF).

40) This sample gave optically pure (−)-7 showing [α]D₂⁺ 23.3° (c=1.16, CHCl₃).
41) The fairly large difference between the observed and reported optical rotations might be partially due to low solubility of the sample in dioxane, which might have resulted in the calculation of large [α]D values based on small αD values.