[Chem. Pharm. Bull. 31(3) 811—820 (1983)]

Development of a Novel Synthetic Route to optically Active Anthracyclinones: Preliminary Synthesis of the Racemic Key Intermediate[1)]

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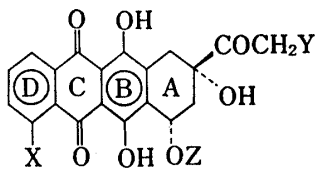
(Received July 9, 1982)

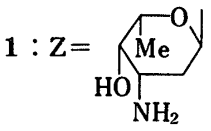
In order to develop a novel synthetic route to a key synthetic intermediate ((*R*)-(−)-**3**) for optically active anthracyclinones (**2a**—**d**), preparation of the racemic intermediate ((±)-**3**) from the α,β-unsaturated ketone (**6**), obtainable from the α,β-unsaturated acid (**5**) or the 2-tetralone (**11**), was attempted according to the designed synthetic scheme. Since epoxidation of the racemic allylic alcohol ((±)-**7**) produced by reduction of **6**, followed by reductive cleavage of the epoxides ((±)-**8a, b**) and oxidation of the *vicinal*-diol ((±)-**9a**), was found to readily give the desired (±)-**3** in good overall yield, optically pure (*R*)-(−)-**3** should be obtainable from **6** if **6** can be asymmetrically reduced to afford (*S*)-**7** in a high optical yield.

The racemic ketone ((±)-**3**) was further transformed to (±)-7-deoxy-4-demethoxydaunomycinone dimethyl ether ((±)-**13**), from which racemic 4-demethoxyanthracyclinone ((±)-**2c, d**) could be elaborated.

Keywords——adriamycin; daunorubicin; 4-demethoxyanthracycline; 4-demethoxyadriamycinone; 4-demethoxydaunomycinone; anticancer agent; asymmetric synthesis; asymmetric reduction; epoxidation; oxidation of *vicinal*-diol

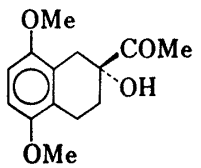
The anthracycline antibiotics, adriamycin (**1a**) and daunorubicin (**1b**), have attracted much attention in recent years because of their promising antineoplastic activity against various experimental tumors and certain types of human cancer.[2–4)] While chemotherapy employing **1a, b** is hampered due to a number of undesirable side effects, most notably dose-related cardiotoxicity,[3)] studies on the structure–activity relationships[2)] have disclosed that improved therapeutic properties can be expected for the unnatural 4-demethoxy analogs of **1a, b**, 4-demethoxyadriamycin (**1c**) and 4-demethoxydaunorubicin (**1d**), whose antineoplastic activities are *ca.* 10 times higher than those of natural **1a, b**.[2b,c,e,5)]





2 : Z=H

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



(±)- or (*R*)-(−)-**3**

Although various syntheses of anthracyclinones (**2**), the aglycones of **1**, have been reported along with increased clinical utility of **1**,[4)] the synthetic route originally explored by Wong[6)] and successively developed by Arcamone,[2b,c,5,7,8)] in which the tetracyclic system of **1** can be elaborated by successive inter- and intramolecular Friedel–Crafts reactions, appears to be the most versatile. According to this synthetic scheme, various structural types of unnatural anthracyclinones[4–11)] including 4-demethoxyadriamycinone (**2c**) and 4-demethoxydaunomycinone (**2d**) can be synthesized in racemic or optically active forms from the common synthetic intermediate, (±)- or (*R*)-(−)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((±) or (*R*)-(−)-**3**), in addition to the natural aglycones (**2a, b**).[6,7,9,11)]

Several improved syntheses have been reported for the racemic key intermediate ((±)-**3**)[11,12] originally produced from 2,5-dimethoxybenzaldehyde.[6] While preparation of optically active (*R*)-(−)-**3** had been accomplished by the optical resolution of (±)-**3**,[2b,c,5,7] we more recently explored the asymmetric synthesis of (*R*)-(−)-**3** by utilizing halolactonization as a key diastereoselective reaction.[13] Although the asymmetric halolactonization reaction proceeds with 98.5% diastereomeric excess to afford the bromolactone from which optically pure (*R*)-(−)-**3** can be elaborated,[14] the requirement for precious chiral source and reagents seems to reduce its practical value.[15]

With the aim of preparing optically pure (*R*)-(−)-**3** by a synthetic process more practical than that previously reported,[13] we examined another novel synthetic route to (*R*)-(−)-**3**. This report concerns with 1) the design of a new synthetic route to (*R*)-(−)-**3** in which asymmetric reduction of the α,β-unsaturated ketone (**6**) is employed as a key step, 2) evaluation of the designed scheme by obtaining the racemic key intermediate ((±)-**3**) from the racemic allylic alcohol ((±)-**7**) expectedly produced as (*S*)-**7** in high chemical and optical yields by asymmetric reduction of **6**, and 3) further elaboration of (±)-**3** to the racemic tetracyclic ketone ((±)-**13**), from which (±)-**2c, d** have been synthesized.[4–11]

Results and Discussion

A. Design of the Asymmetric Synthesis of (*R*)-(−)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((*R*)-(−)-3)

While various types of asymmetric syntheses have been reported,[16] asymmetric reduction of achiral ketones is one of the most extensively studied reactions,[16] and highly optically active secondary alcohols can be produced employing lithium aluminum hydride (LAH) partially decomposed with a bifunctional chiral source (and an additive) as a reducing agent.[17–21] In particular, when achiral ketones in which steric and/or electronic effects of the two substituents of the ketonic function are significantly different are utilized as reduction substrates, high optical yields of more than 90% e.e. have been realized.[20,21]

Taking into account these considerations, we designed a novel synthetic route to (*R*)-(−)-**3** as shown in Chart 1. Thus, if the α,β-unsaturated ketone (**6**), which is readily obtainable from the previously utilized acid (**5**),[13e,f] is subjected to asymmetric reduction using a chiral reducing agent prepared by partial decomposition of LAH, it might be possible to produce the optically active (*S*)-allylic alcohol ((*S*)-**7**) in high chemical and optical yields by a suitable choice of modified LAH due to the clear difference of steric and electronic effects of the two substituents of the ketonic group.[22] Since (*S*)-**7** involves a functionality corresponding to an α,β-disubstituted allylic alcohol, epoxidation of (*S*)-**7** under the Sharpless conditions[23] should afford a mixture of the α,β-epoxyalcohols ((1*S*, 2*R*)-**8a** and (1*R*, 2*S*)-**8b**) in which one diastereomer ((1*S*, 2*R*)-**8a**) is highly predominant. This might be explained based on the conformational reasons recently discussed by Sharpless *et al.* (*vide infra*).[24,25] Reductive cleavage of optically active **8** at the benzylic position readily affords the *vicinal*-diols ((2*R*)-**9a** and (2*S*)-**9b**). Therefore, even if separation of (1*S*, 2*R*)-**8a** and (1*R*, 2*S*)-**8b** is impossible, the diols ((2*R*)-**9a** and (2*S*)-**9b**) which involve two alcoholic functions at the *vicinal*-position, should be more easily separable than the optically active epoxides. Oxidative removal of the secondary alcoholic function of optically active **9a** originally introduced by the asymmetric reduction should give optically pure (*R*)-(−)-**3**.

In order to study whether the designed synthetic route to (*R*)-(−)-**3** from (*S*)-**7** can proceed in the expected manner when the preparation of highly optically active (*S*)-**7** from achiral **6** is accomplished, stereoselective synthesis of the racemic key intermediate ((±)-**3**) from the racemic allylic alcohol ((±)-**7**) was first attempted.

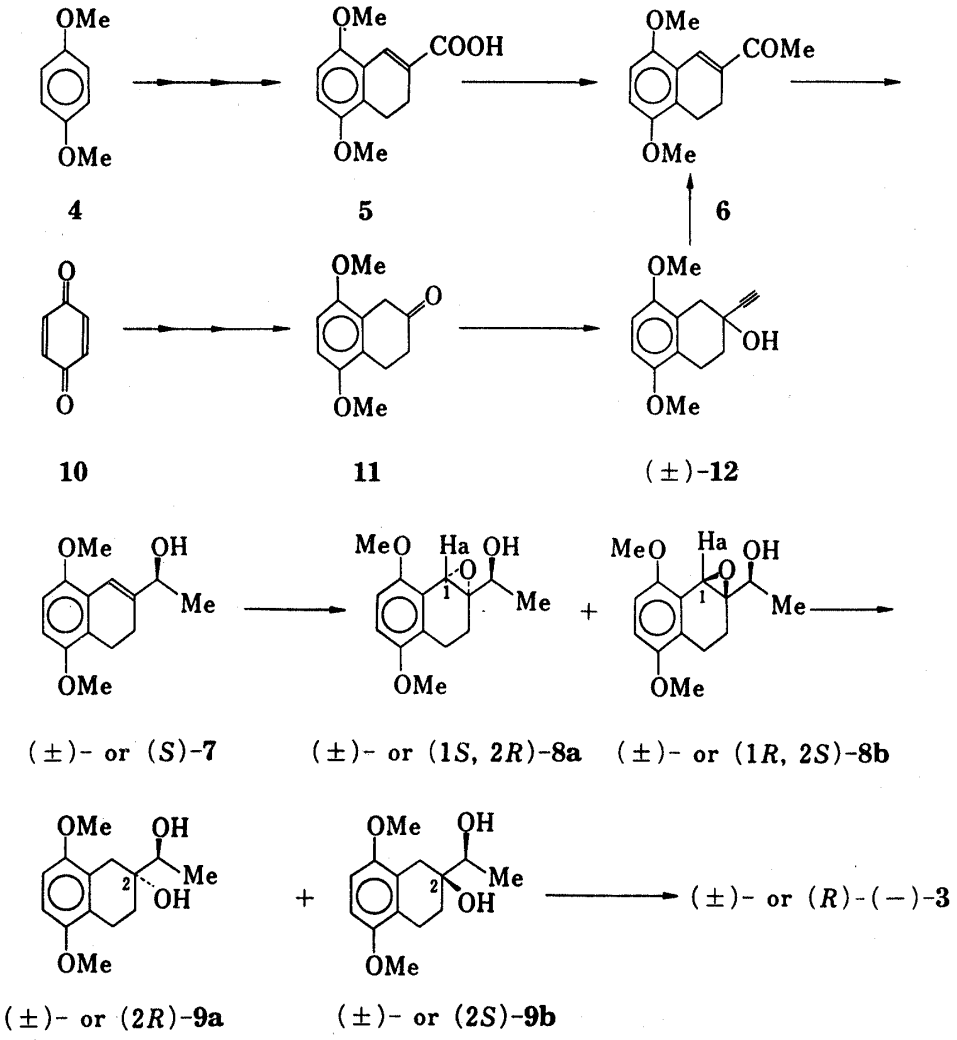


Chart 1

B. Preparation of (±)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((±)-3)

Preparation of **6** was examined by employing two different synthetic schemes. Thus, treatment of the α,β-unsaturated acid (**5**), which had been prepared from 1,4-dimethoxybenzene (**4**) and utilized as a starting material for the asymmetric halolactonization,[13e-g] with an excess of methyllithium[26] gave **6** as a sole reaction product in 87% yield. On the other hand, reaction of ethynylmagnesium bromide with 2-tetralone (**11**)[10,12b] which is readily obtainable from *p*-quinone (**10**) according to the reported procedure,[12,27] was found to give the tertiary alcohol ((±)-**12**)[12b] in 79% yield, and on treatment under the conditions of the Rupe rearrangement,[28] (±)-**12** successfully gave **6** in 61% yield.[29,30] Since the preparation of **11** from **10** can be performed more simply than that of **5** from **4** on a large scale, the latter method might be more practical if the yield of **6** from **11** can be improved.

Reduction of **6** with sodium borohydride gave crystalline (±)-**7** in quantitative yield without formation of the 1,4-reduction product.[29,31] Epoxidation of (±)-**7** was effected by using a combination of *tert*-butyl hydroperoxide and a catalytic amount of vanadium oxyacetylacetonate,[23] giving crude (±)-**8** as an unstable oil. The oily sample showed two spots on thin layer chromatography (TLC), the less polar one of which constituted the major product. The ^{1}H-nuclear magnetic resonance (NMR) spectrum of this sample exhibited the epoxide proton (Ha) as two singlets at 4.50 and 4.41 ppm with an integration ratio of 96 : 4. These chromatographic and spectral properties of (±)-**8** revealed that the epoxidation of (±)-**7**

proceeded highly stereoselectively, as expected (*vide supra*). Considering the proposed reaction mechanism of catalytic epoxidation,[24] the two conformers (I and II) shown in Fig. 1 might afford (±)-**8a** and (±)-**8b**, respectively. Since steric interaction between the C_3-methylene and the (1′-hydroxy)ethyl group is clearly smaller in I than in II, the conformer (I) will predominate in the epoxidation, resulting in the preferential formation of (±)-**8a**. Successful preparation of optically active (*R*)-(−)-**3**, 90% e.e. from optically pure (*S*)-(−)-**7** as detailed in the accompanying paper,[32] provides further support for the above explanation.

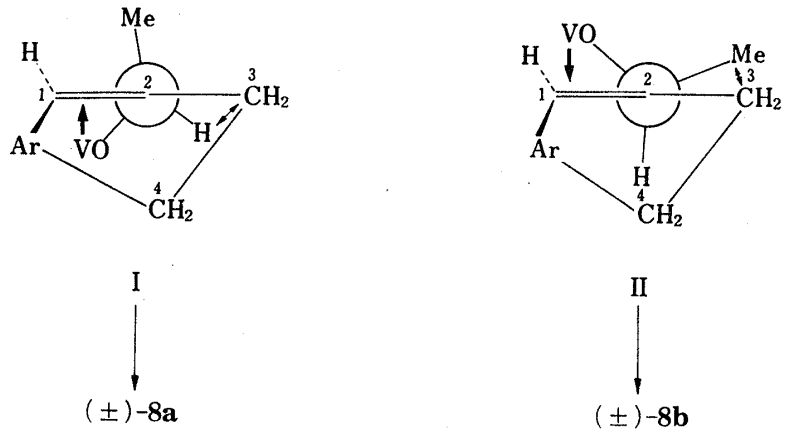


Fig. 1

Since oily (±)-**8** was quite unstable, it was immediately subjected to reduction with LAH,[33] to give crude (±)-**9** in 86% yield based on (±)-**7**. Direct recrystallization of this sample afforded the major diastereomer ((±)-**9a**) in a pure state. Crude (±)-**9** showed the two benzylic carbons as two strong signals at 29.4 and 30.5 ppm and two weak signals at 27.5 and 32.6 ppm in the ^{13}C-NMR spectrum. The integration ratio for the two sets of signals was found to be very close to the formation ratio of (±)-**8a** and (±)-**8b**. As the ^{13}C-NMR spectrum of a recrystallized sample only showed two signals at 29.4 and 30.5 ppm, it was concluded that the major diastereomer ((±)-**9a**) could be successfully isolated in a pure state by such recrystallization.

Next, we considered the oxidation of the secondary alcohol to complete the designed scheme. At the outset, it was expected that (±)-**9a** could be readily oxidized to give (±)-**3** by using ordinary oxidizing reagents. However, this synthetic step turned out to be quite refractory. Thus, when (±)-**9a** was treated with Jones reagent,[34] a complex mixture of products showing many spots on TLC analysis was obtained. Oxidation of (±)-**9a** with Collins reagent,[35] pyridinium chlorochromate,[36] or pyridinium dichromate[37] afforded **11** as a main reaction product due to oxidative cleavage of the *vicinal*-diol system with *ca.* 10% yield of the desired (±)-**3**. Treatments of (±)-**9a** under various oxidation conditions employing dimethyl sulfoxide–acetic anhydride,[38] dimethyl sulfoxide–trifluoroacetic anhydride,[39] or dimethyl sulfide–*N*-chlorosuccinimide–triethylamine,[40] simply resulted in the recovery of the starting material. Moffatt oxidation[41] of (±)-**9a** gave a 61% yield of (±)-**3** with many side-reaction products. It was finally found that oxidation of (±)-**9a** with a combination of dimethyl sulfoxide–sulfur trioxide·pyridine complex–triethylamine[42] or with Fetizon reagent (silver carbonate–celite)[43] could successfully produce the desired (±)-**3** in 92 or 90% yield. From the viewpoints of economy and operational simplicity, the former reagent was anticipated to be more practical. The α-hydroxy ketone ((±)-**3**) showed spectral properties identical with the reported data.[6a,9b]

Based on the results exemplified above, it appeared evident that optically pure (*R*)-(−)-**3** should be produced from **6** if **6** can be asymmetrically reduced with high stereoselectivity to

give a high optical yield of (*S*)-**7**. This was found to be the case, as described in the accompanying paper.[32]

C. Preparation of (±)-7-Deoxy-4-demethoxydaunomycinone Dimethyl Ether ((±)-13)

The synthetic scheme exploited in section B was regarded as one of the most practical methods available for preparing (±)-**3**[6,9b,12,44] due to its operational simplicity and directness. While (±)-**3** had already been utilized for preparing natural and unnatural anthracyclinones (**2a—d**),[5–11] synthesis of (±)-**13**, another key intermediate for the preparation of (±)-**2c, d** from (±)-**3**,[6,10,11] was further examined as shown in Chart 2.

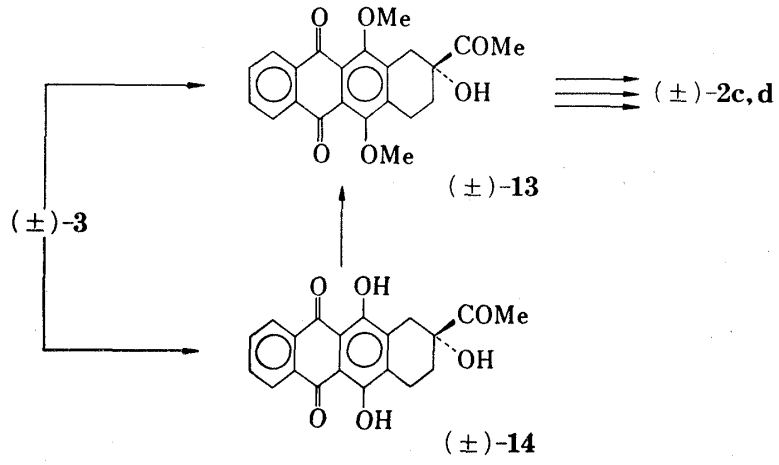


Chart 2

Treatment of (±)-**3** with *o*-methoxycarbonylbenzoyl chloride[45] in the presence of aluminum chloride, followed by alkaline hydrolysis and ring closure with hydrogen fluoride, according to the reported procedure,[5–7] afforded (±)-**13** in 48% overall yield from (±)-**3**. On the other hand, when(±)-**3** was treated with phthalic anhydride in the presence of a mixture of aluminum chloride and sodium chloride,[8,12a] (±)-7-deoxy-4-demethoxydaunomycinone ((±)-**14**, was obtained in 65% yield. Methylation of (±)-**14** gave rise to (±)-**13** in a quantitative yield. Two lots of (±)-**13** obtained from (±)-**3** by the different schemes exhibited the same spectral properties as those reported.[6a]

Since our original objectives had been accomplished, as mentioned above, our attention was next focused on the asymmetric reduction of **6** This is the subject of the accompanying paper.[32]

Experimental[46]

5,8-Dimethoxy-3,4-dihydro-2-naphthoic Acid (**5**)——This was prepared from **4** according to the reported procedure[13f,g] with slight modifications.[47] Colorless needles, mp 234—237°C (lit.,[13f,g] mp >220°C). Spectral (infrared (IR) and ^{1}H-NMR) properties of this sample were identical with those reported.[13g]

5,8-Dimethoxy-2-tetralone (**11**)——Prepared from **10** by following the reported procedure.[27] mp 98—99°C (lit.,[27a] mp 98—99.5°C; lit.,[27b] mp 98.6—99.4°C; lit.,[27c] mp 97—99°C).

2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**6**)——a) Preparation of **6** from **5**:[26] An ethereal solution (82 ml) of freshly distilled methyl iodide (82.0 g, 0.58 mol) was gradually added to a stirred ethereal suspension (174 ml) of metal lithium (8.70 g, 1.25 mol) over 1 h under an argon atmosphere, to keep the reaction mixture gently refluxing. When the addition was over, the whole was refluxed for another 1 h to give a solution of methyllithium in Et_2O.

The solution of methyllithium thus prepared was added to a suspension of **5** (11.7 g, 0.050 mol) in Et_2O (23 ml) at 0°C with vigorous stirring, and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was gradually poured into a vigorously stirred mixture of conc. HCl (650 ml) and ice-water (1 l).

The ethereal layer was separated and the aqueous phase was extracted with EtOAc (500 ml×1, then 250 ml×2). The organic extracts were combined and washed successively with satd. $NaHCO_3$ (200 ml×1), 10% $Na_2S_2O_3$ (500 ml×1), and satd. NaCl (500 ml×3). Filtration and concentration *in vacuo* gave crude **6** as pale yellow crystals (12.5 g), which were subjected to column chromatography (C_6H_6–EtOAc 20: 1), giving **6** as pale yellow crystals (10.1 g, 87%), mp 105—106.5°C. Recrystallization from iso-Pr_2O afforded an analytical sample of **6** as pale yellow plates, mp 106—107°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655 (ketone). ^{1}H-NMR (in $CDCl_3$): 2.43 (3H, s, $COC\underline{H}_3$), 2.40—3.10 (4H, m, $C\underline{H}_2C\underline{H}_2CCOCH_3$), 3.77 (3H, s, $OC\underline{H}_3$), 3.81 (3H, s, $OC\underline{H}_3$), 6.68 (1H, d, J=9 Hz, one of the aromatic protons), 6.83 (1H, d, J=9 Hz, one of the aromatic protons), 7.75 (1H, br s, C$\underline{H}$=). *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.43; H, 6.89.

b) Preparation of **6** from **11**: (±)-2-Ethynyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((±)-**12**):[12b] A solution of ethylmagnesium bromide in THF was prepared by adding freshly distilled ethyl bromide (1.20 g, 11 mmol) to a stirred suspension of magnesium turnings (243 mg, 10 mmol) in tetrahydrofuran (THF) (6 ml) under an argon atmosphere, and by stirring the mixture at room temperature for 3 h. The THF solution of ethylmagnesium bromide prepared above was added to THF (4 ml) through which dried acetylene gas was being passed, to give a THF solution of ethynylmagnesium bromide.

A THF solution (3 ml) of **11** (206 mg, 1.0 mmol) was added to the solution of ethynylmagnesium bromide, and the whole was stirred at room temperature for 18 h. The reaction was quenched by the addition of 10% NH_4Cl (30 ml), and the resulting mixture was extracted with Et_2O (30 ml×3). The combined ethereal extracts were washed with satd. NaCl, then concentrated *in vacuo* to give crude (±)-**12** as an oil (244 mg). This was purified by column chromatography (C_6H_6–EtOAc 20: 1) to afford (±)-**12** as a solid (184 mg, 79%). Further successive purifications by bulb-to-bulb distillation, bp 260°C (3 mmHg), and by recrystallization from iso-Pr_2O gave an analytical sample of (±)-**12** as colorless needles, mp 105—106°C.[12b] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3300 (acetylene), 1600 (aromatic ring). ^{1}H-NMR (in $CDCl_3$): 1.90—2.15 (2H, m, $CH_2C\underline{H}_2C(OH)$), 2.25 (1H, s, O$\underline{H}$), 2.40 (1H, s, C≡C$\underline{H}$), 2.70—3.10 (4H, m, $C\underline{H}_2CH_2C(OH)C\underline{H}_2$), 3.76 (6H, two s, $OC\underline{H}_3$×2), 6.65 (2H, s, aromatic protons). *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.18; H, 7.06.

6:[28] A solution of (±)-**12** (46.5 mg, 0.20 mmol) in 85% formic acid (2 ml) was heated at 100—110°C for 2 h with stirring.[28] After cooling, the reaction mixture was diluted with H_2O (10 ml), and extracted with EtOAc (20 ml×1, 10 ml×1). The combined organic extracts were washed successively with H_2O (10 ml×2), satd. $NaHCO_3$ (10 ml×2), H_2O (10 ml×3), and satd. NaCl (10 ml×1). Filtration and concentration *in vacuo* gave crude **6** (52 mg), which was purified by column chromatography (C_6H_6–EtOAc 10: 1) to afford **6** as pale yellow crystals (28.5 mg, 61%), mp 96—100°C. Recrystallization from iso-Pr_2O gave pure **6** as pale yellow plates, mp 103—104°C. IR and ^{1}H-NMR spectra of this sample were identical with those of **6** obtained in a).

(±)-2-1′-Hydroxyethyl-5,8-dimethoxy-3,4-dihydronaphthalene ((±)-**7**)——Sodium borohydride (284 mg, 7.5 mmol) was added to an ethanolic solution (55 ml) of **6** (1.16 g, 5.0 mmol), and the mixture was stirred at room temperature for 4 h. H_2O (2 ml) was added to the reaction mixture, and the whole was concentrated *in vacuo*. The residual solution was diluted with EtOAc (30 ml) and satd. NaCl (20 ml), and the upper organic phase was separated. The aqueous layer was further extracted with EtOAc (15 ml×3). The organic extracts were combined and washed with satd. NaCl. Filtration and concentration *in vacuo* gave (±)-**7** as a pale yellow oil (1.21 g, quantitative yield), which solidified on trituration with C_6H_{14}. Recrystallization from C_6H_{14} afforded pure (±)-**7** as colorless needles (1.09 g, 93%), mp 78—79°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1260, 1100 (OH). ^{1}H-NMR (in $CDCl_3$): 1.31 (3H, d, J=6 Hz, CH(OH)C$\underline{H}_3$), 2.06—2.44 (2H, m, $CH_2C\underline{H}_2C$=), 2.44 (1H, s, O$\underline{H}$), 2.68—2.94 (2H, m, $C\underline{H}_2CH_2C$=), 3.71 (6H, two s, $OC\underline{H}_3$×2), 4.42 (1H, q, J=6 Hz, C$\underline{H}$(OH)), 6.60 (2H, s, aromatic protons), 6.78 (1H, br s, C$\underline{H}$=). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.90; H, 7.73.

(1′*S,2*R**)-2-1′-Hydroxyethyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol** ((±)-**9a**) **and Its (2*S**)-Isomer** ((±)-**9b**)——A C_6H_6 solution (2.5 ml) of *tert*-butyl hydroperoxide (22 mg/ml, 0.60 mmol) was added to a mixture of (±)-**7** (117 mg, 0.50 mmol) and vanadium oxyacetylacetonate (1.9 mg, 0.07 mmol) in C_6H_6 (10 ml), and the whole was stirred at room temperature for 45 min.[23] Concentration *in vacuo* gave a crude mixture of the (±)-α,β-epoxyalcohols ((±)-**8a, b**) as a yellow oil. TLC (Et_2O–C_6H_{14} 1: 1, 3 developments): *Rf* 0.74 (major component), 0.68 (minor component). ^{1}H-NMR (in $CDCl_3$): 1.30 (3H, d, J=7 Hz, CH(OH)-C$\underline{H}_3$), 1.2—3.3 (5H, m, $C\underline{H}_2C\underline{H}_2CCH(O\underline{H})$), 3.75 (3H, s, $OC\underline{H}_3$), 3.78 (3H, s, $OC\underline{H}_3$), 4.07 (1H, q, J=7 Hz, C$\underline{H}$-(OH)CH_3), 4.50, 4.41 (total 1H, two s, C$\underline{H}$a–C, the ratio of the two singlets determined from their integration areas was 96: 4), 6.71 (2H, s, aromatic protons). Based on the mechanism of the epoxidation reaction,[24] the major and minor diastereomers were assigned as (1*S**,1′*S**,2*R**)-1,2-epoxy-2-1′-hydroxyethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene ((±)-**8a**) and its (1*R**,2*S**)-isomer ((±)-**8b**), respectively. Since oily (±)-**8a, b** were quite unstable, they were immediately subjected to the next reduction.

A THF solution (5 ml) of crude (±)-**8a, b** was added to a suspension of LAH (38.0 mg, 1.0 mmol) in THF (5 ml), and the whole was stirred at room temperature for 4 h. When the reduction was over, 2 N NaOH (10 ml) was added to the reaction mixture, and the upper organic phase was separated. The aqueous phase was further extracted with EtOAc (15 ml×3). The organic extracts were combined and washed successively with H_2O (15 ml×1) and satd. NaCl (15 ml×1). Filtration and concentration *in vacuo* gave a crude mixture of the two diastereomers ((±)-**9a, b**) as colorless crystals (131 mg). Purification of this sample by preparative

TLC (C_6H_6–EtOAc 1: 1) gave pure (±)-**9a**, **b** as colorless crystals (108 mg, 86%), mp 138—141°C. Since separation of the two diastereomers ((±)-**9a**, **b**) was not carried out throughout the purification steps, this sample should consist of the two diastereomers ((±)-**9a**, **b**) in a ratio of 96: 4. The ^{13}C-NMR spectrum of this sample supported this assumption. ^{13}C-NMR (in $CDCl_3$): 29.4 (C_1 or C_4), 30.5 (C_4 or C_1) for (±)-**9a** and 27.5 (C_1 or C_4), 32.6 (C_4 or C_1) for (±)-**9b** (the ratio of two sets of signals was 94: 6).[48] Recrystallization from Et_2O gave the major diastereomer ((±)-**9a**) in a pure state, mp 145—146°C. IR ν_{max}^{KBr} cm^{-1}: 3340, 1260, 1100, 1070 (OH). ^{1}H-NMR (in $CDCl_3$–CD_3OD): 1.26 (3H, d, J=6 Hz, CH(OH)C$\underline{H}_3$), 1.30—2.05 (2H, m, $CH_2C\underline{H}_2C$(OH)), 2.70—3.00 (4H, m, $C\underline{H}_2CH_2C$(OH)$C\underline{H}_2$), 3.20—3.80 (2H, m, C$\underline{H}$(O$\underline{H}$)CH_3), 3.76 (3H, s, OC$\underline{H}_3$), 3.78 (3H, s, OC$\underline{H}_3$), 6.68 (2H, s, aromatic protons). ^{13}C-NMR (in $CDCl_3$): 17.0 (CH(OH)$\underline{C}H_3$), 19.9 ($\underline{C}_3$), 29.4 (C_1 or C_4), 30.5 (C_4 or C_1), 55.6 (C_5–O$\underline{C}H_3$ or C_8–O$\underline{C}H_3$), 55.7 (C_8–O$\underline{C}H_3$ or C_5–O$\underline{C}H_3$), 72.3 ($\underline{C}_2$), 73.4 ($\underline{C}$H(OH)), 107.1 ($\underline{C}_6$ and $\underline{C}_7$), 124.4 ($\underline{C}_{4a}$ or $\underline{C}_{8a}$), 126.4 ($\underline{C}_{8a}$ or $\underline{C}_{4a}$), 151.2 ($\underline{C}_5$ or $\underline{C}_8$), 151.9 ($\underline{C}_8$ or $\underline{C}_5$). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.34; H, 7.94.

(±)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol ((±)-**3**)——a) Oxidation of (±)-**9a** with Fetizon Reagent:[43] Fetizon reagent (Ag_2CO_3 on celite) (1.0 mmol of Ag_2CO_3 on 1.0 g of the reagent)[43] (2.0 g, 2.0 mmol) was added to a C_6H_6 solution (10 ml) of pure (±)-**9a** (101 mg, 0.40 mmol), and the mixture was heated at reflux for 30 min, then cooled. An insoluble material, mainly consisting of silver on celite, was filtered off and washed with C_6H_6 (50 ml). The combined filtrate and washings were concentrated *in vacuo*, giving a reddish-brown solid (100 mg). The residue was purified by preparative TLC (C_6H_6–EtOAc 5: 1) to give (±)-**3** as colorless crystals (90 mg, 90%), mp 98—100°C. Recrystallization from $CHCl_3$–Et_2O gave pure (±)-**3** as colorless needles, mp 100—101°C (lit.,[6a] mp 100—102°C; lit.,[9b] mp 97°C; lit.,[12a] mp 99°C). IR ν_{max}^{mujol} cm^{-1}: 3480 (OH), 1700 (ketone). ^{1}H-NMR (in $CDCl_3$) δ: 1.85—2.10 (2H, m, $CH_2C\underline{H}_2C$(OH)), 2.30 (3H, s, COC$\underline{H}_3$), 2.70—3.00 (4H, m, $C\underline{H}_2CH_2C$(OH)$C\underline{H}_2$), 3.67 (1H, s, O$\underline{H}$), 3.72 (3H, s, OC$\underline{H}_3$), 3.76 (3H, s, OC$\underline{H}_3$), 6.58 (2H, s, aromatic protons). These spectral properties were identical with those reported.[6a,9b]

b) Oxidation of (±)-**9a** with a Combination of Dimethyl Sulfoxide–Sulfur Trioxide·Pyridine Complex–Triethylamine:[42] A DMSO solution (2.0 ml) of triethylamine (1.21 g, 12 mmol) and sulfur trioxide·pyridine complex (621 mg, 3.9 mmol) was added to a solution of (±)-**9a** (101 mg, 0.40 mmol) in DMSO (1.0 ml) at room temperature with stirring. Stirring was continued at room temperature for 1 h, then the reaction mixture was diluted with 10% HCl (20 ml) under ice-cooling, and extracted with EtOAc (20 ml×2). The combined organic extracts were washed successively with H_2O (20 ml×3) and satd. NaCl (20 ml×1). Filtration and concentration *in vacuo* gave a colorless crystalline solid (110 mg), which was purified by preparative TLC in a manner similar to that described in a) to give (±)-**3** as colorless crystals (91.2 mg, 92%), mp 100—102°C. Recrystallization from $CHCl_3$–Et_2O gave pure (±)-**3** as colorless needles, mp 103—104°C. Spectral (IR and ^{1}H-NMR) properties of this sample were identical with those of the product obtained in a).

c) Oxidation of (±)-**9a** by Pfitzner–Moffatt Oxidation:[41] A C_6H_6 solution (1.0 ml) of pyridine (15.8 mg, 0.20 mmol), a C_6H_6 solution (1.0 ml) of trifluoroacetic acid (11.4 mg, 0.10 mmol), and dicyclohexylcarbodiimide (124 mg, 0.60 mmol) were successively added to a DMSO solution (1.0 ml) of (±)-**9a** (50.5 mg, 0.20 mmol) at room temperature with stirring. Stirring was continued for 39 h at the same temperature, then the white precipitate was filtered off and washed with C_6H_6. The filtrate and washings were combined and washed successively with H_2O (10 ml×3) and satd. NaCl (10 ml×1). Filtration and concentration *in vacuo* gave an oily residue, which was purified as described in a) to give (±)-**3** as a semisolid (30.4 mg, 61%). Recrystallization from $CHCl_3$–Et_2O afforded pure (±)-**3** as colorless needles, mp 100—101°C. IR and ^{1}H-NMR spectra of this sample were superimposable on those of the product obtained in a).

d) Oxidation of (±)-**9a** with Collins Reagent:[35] Collins reagent[35] (619 mg, 2.4 mmol) and celite (620 mg) were added to a solution of (±)-**9a** (101 mg, 0.40 mmol) in CH_2Cl_2 (5.0 ml), and the heterogeneous mixture was stirred at room temperature for 45 min. Then the reaction mixture was diluted with Et_2O (60 ml), and the precipitates were filtered and washed with Et_2O (20 ml). The ethereal filtrates were combined and concentrated *in vacuo* to give an oily residue (50 mg). This was subjected to preparative TLC in a manner similar to that described in a), giving (±)-**3** as colorless crystals (10 mg, 10%) and **11** as colorless needles (28 mg, 40%), mp 96—98°C. These samples were identical with the authentic samples prepared in a) (for (±)-**3**) and from **10** (for **11**), respectively, on the basis of spectral (IR and ^{1}H-NMR) comparisons.

(±)-7-Deoxy-4-demethoxydaunomycinone Dimethyl Ether ((±)-**2-Acetyl-2-hydroxy-5,12-dimethoxy-1,2,3,4-tetrahydronaphthacene-6,11-dione**) ((±)-**13**)——a) (±)-**13** from (±)-**3**:[5-7] Powdered anhyd. aluminum chloride (1.40 g, 10.5 mmol) was added portionwise to a stirred CH_2Cl_2 solution (7.0 ml) of (±)-**3** (500 mg, 2.0 mmol) and *o*-methoxycarbonyl benzoyl chloride[45] (2.0 g, 10 mmol) at room temperature over 1.5 h. Stirring was continued at room temperature for 3 h, then the mixture was poured into ice-water (50 ml) and extracted with $CHCl_3$ (30 ml×3). The organic extracts were combined, and washed successively with 5% $NaHCO_3$ (50 ml), H_2O (50 ml×2), and satd. NaCl (50 ml×1). Filtration and concentration *in vacuo*, followed by column chromatography (Et_2O), gave (±)-2-acetyl-6- and/or -7-(2-methoxycarbonylbenzoyl)-5,8-dimethyl-1,2,3,4-tetrahydro-2-naphthol[6,13f,g] as a yellow caramel (950 mg, quantitative yield). IR ν_{max}^{film} cm^{-1}: 1710 (ketone and ester).

A part of this caramel (915 mg) was dissolved in aq. EtOH (EtOH: H_2O 3: 2), and NaOH (95% pure) (800 mg, 20 mmol) was added to the ethanolic solution. After being stirred at 60°C for 1 h, the mixture was diluted with H_2O (30 ml), acidified (pH≒2) with 10% HCl, then extracted with $CHCl_3$ (30 ml×2). The organic extracts were combined and washed with satd. NaCl (50 ml×2). Filtration and concentration *in vacuo* gave crude (±)-2-acetyl-6- and/or -7-(2-carboxybenzoyl)-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol[6,13f,g] as a yellow caramel (760 mg, 96%). IR ν_{max}^{film} cm^{-1}: 1700 (ketone and COOH).

The crude acidic product (760 mg) was dissolved in HF (8 ml), and the solution was stirred at 0—10°C for 20 h. After concentration *in vacuo*, the residue was dissolved in $CHCl_3$ (50 ml). The $CHCl_3$ solution was washed successively with H_2O (50 ml×2), satd. NaCl (50 ml×2), H_2O (50 ml×2), and satd. NaCl (50 ml×1). Filtration and concentration *in vacuo* gave crude (±)-**13** as yellow crystals (713 mg), which were subjected to column chromatography (C_6H_6–Me_2CO 6: 1) to afford (±)-**13** as pale yellow crystals (368 mg, 48% based on (±)-3), mp 183—187°C. Recrystallization from MeOH gave pure (±)-**13** as pale yellow minute plates, mp 186—188°C (lit.,[6a] mp 186—188°C). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1690 (ketone), 1675 (quinone), 1595, 1555 (aromatic rings). ^{1}H-NMR (in $CDCl_3$): 1.82—2.02 (2H, m, $CH_2C\underline{H}_2C(OH)$), 2.35 (3H, s, $COC\underline{H}_3$), 2.80—3.28 (4H, m, $C\underline{H}_2CH_2C(OH)C\underline{H}_2$), 3.82 (3H, s, $OC\underline{H}_3$), 3.85 (3H, s, $OC\underline{H}_3$), 3.87 (1H, s, O<u>H</u>), 7.58—7.76 (2H, m, aromatic protons), 8.02—8.20 (2H, m, aromatic protons). These spectral properties were identical with those reported.[6a]

b) (±)-**13** from (±)-**14**: A mixture of (±)-**14** (2.5 g, 7.1 mmol), dimethyl sulfate (4.04 g, 32 mmol), and powdered anhyd. K_2CO_3 (4.9 g, 35 mmol) in Me_2CO (500 ml) was heated at reflux for 8 h with stirring, then cooled. Filtration and concentration *in vacuo* gave a yellow residue which was dissolved in $CHCl_3$ (500 ml). The $CHCl_3$ solution was washed successively with H_2O (200 ml×2) and satd. NaCl (200 ml×1). Filtration and concentration *in vacuo* afforded crude (±)-**13** as a yellow solid (2.80 g, quantitative yield). Recrystallization from MeOH (50 ml) gave (±)-**13** as yellow crystals (2.48 g, 92%), mp 186—187°C. IR and ^{1}H-NMR spectra of this sample were identical with those of the product obtained in a).

(±)-7-Deoxy-4-demethoxydaunomycinone ((±)-2-Acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((±)-14)[8,12a]——The racemic ketone ((±)-3) (5.0 g, 20 mmol), phthalic anhydride (5.9 g, 40 mmol), anhyd. $AlCl_3$ (50 g, 0.375 mol), and NaCl (10 g) were well mixed in a mortar, and the mixture was placed in a reaction flask preheated at 180—185°C. The whole was stirred with a glass rod until the mixture had clearly melted, and was kept at the same temperature for 3 min. After cooling, the solidified reaction mixture was gradually added to aq. satd. oxalic acid solution (300 ml), and the whole was extracted with $CHCl_3$ (500 ml, then 300 ml). The organic extracts were combined and washed successively with H_2O (150 ml), aq. Na_2CO_3 (150 ml), and H_2O (200 ml). Filtration and concentration *in vacuo* gave crude (±)-**14** as a red solid (5.6 g, 79%). Recrystallization from C_6H_6 (500 ml) gave pure (±)-**14** as minute red crystals (4.6 g, 65%), mp 214—216°C (lit.,[12a] mp 212—215°C; lit.,[49] mp 210—212°C). IR ν_{max}^{KBr} cm^{-1}: 3360, 1265 (OH), 1700 (ketone), 1620 (quinone), 1585 (aromatic rings). ^{1}H-NMR (in DMSO-d_6): 1.60—2.00 (2H, m, $CH_2C\underline{H}_2C$-(OH)), 2.31 (3H, s, $COC\underline{H}_3$), 2.64—2.90 (4H, m, $C\underline{H}_2CH_2C(OH)C\underline{H}_2$), 5.57 (1H, s, O<u>H</u>), 7.60—8.20 (4H, m, aromatic protons).

Acknowledgements The authors are grateful to Prof. Kenji Koga, Faculty of Pharmaceutical Sciences, University of Tokyo, for his encouragement and advice throughout this work.

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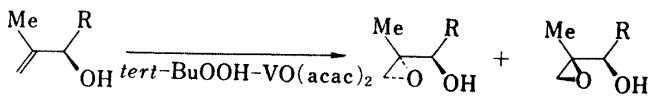

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44) Arcamone *et al.* recently reported the synthesis of (±)-**3** from 5,8-dimethoxy-1-tetralone (see refs. 29 and 30) *via* (±)-**7**. They employed the same synthetic route as that developed by us for transforming (±)-**7** into (±)-**3**. S.D. Nero, C. Gandolfi, P. Lombardi, and F. Arcamone, *Chem. Ind.* (London), **1981**, 810.
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46) All melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. All boiling points are uncorrected. IR spectral measurements were performed 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 are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). 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. $MgSO_4$ before filtration and concentration *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), tetrahydrofuran (THF).
47) In contrast to the original method[13f,g] which featured Clemmensen reduction, 4-(2,5-dimethoxyphenyl)-4-oxo-butyric acid synthesized by Friedel–Crafts reaction of **4** with succinic anhydride (88%) was subjected to Huang–Minlon reduction. Since partial demethylation occurred due to the strongly basic reaction conditions, the crude product was methylated with dimethyl sulfate and anhyd. K_2CO_3 in Me_2CO, giving 4-(2,5-dimethoxyphenyl)butyric acid in 98% yield (2 steps). This sample was elaborated to **5** by successive esterification (83%), formylation (85%), cyclization (57%), and hydrolysis (98%), in the same manner as reported elsewhere.[13f,g]
48) An authentic mixture containing (±)-**9a** and (±)-**9b** in *ca.* 1: 1 ratio was prepared by successive epoxidation of (±)-**7** with *m*-chloroperbenzoic acid and reduction of the mixture of (±)-**8a** and (±)-**8b** with LAH. N. Tanno and S. Terashima, unpublished results.
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