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A Simple and Efficient Synthesis of Optically Active (+)-4-Demethoxydaunomycinone[1)]

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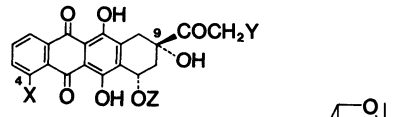
Diels-Alder reaction of 2-chloro-1,3-butadiene with anthracene-1,4,9,10-tetrone was found to occur exclusively at the external ($C_{2,3}$) double bond, giving the adduct in an excellent yield. The adduct was elaborated to 5,12-dihydroxy-1,2,3,4-tetrahydro-2,6,11-naphthacenetrione. The conventional cyanohydrin formation of this sample followed by acid hydrolysis gave (±)-2,5,12-trihydroxy-6,11-dioxo-1,2,3,4-tetrahydro-2-naphthacenecarboxylic acid. The racemic acid was found to be cleanly resolved by forming a salt with (−)-*N*-methylephedrine, furnishing optically pure (*R*)-carboxylic acid. Successive treatments of the (*R*)-carboxylic acid with *N*,*N*′-carbonyldiimidazole and methylmagnesium bromide in the presence of trimethylsilyl triflate readily produced optically pure (*R*)-(−)-7-deoxy-4-demethoxydaunomycinone, the key synthetic intermediate of (+)-4-demethoxydaunomycinone.

The anthracycline antibiotics, adriamycin (**1a**) and daunorubicin (**1b**), are important antitumor agents with clinical effectiveness against various types of human solid tumors and leukemias.[2,3)] However, their utilization for cancer chemotheraphy is hampered by various undesired side effects, the most notable and serious one of which is dose-related cardiotoxicity. Based on extensive studies on analogues of **1a**, **b**,[2)] 4-demethoxyanthracyclines, 4-demethoxyadriamycin (**1c**) and 4-demethoxydaunorubicin (**1d**) have been developed as unnatural anthracyclines which could show more improved therapeutic properties than natural **1a**, **b**. Since unnatural **1c**, **d** are obtainable only by chemical synthesis, numerous synthetic efforts have been devoted to 4-demethoxyanthracyclinones (**2c**, **d**), the aglycones of 4-demethoxyanthracyclines.[4)]

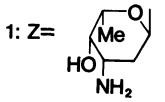
In connection with our continuing synthetic studies on optically active **2c**,**d**,[1,5–10)] we have hitherto developed various preparation methods of optically active (*R*)-(−)-7-deoxy-4-demethoxydaunomycinone ((*R*)-(−)-**14**) by featuring asymmetric synthesis[5,6,10,11)] or optical resolution.[1,7,8,9,12)] The optically active α-hydroxy ketone ((*R*)-(−)-**14**) is anticipated to place a central position in the synthesis of optically active **2c**, **d**,[4a,b)] since introduction of the C_7-hydroxyl group (anthracycline numbering) into (*R*)-(−)-**14** can be achieved in a highly stereoselective manner[8)] and optically active **2d** can be readily converted to optically active **2c** by sequential bromination and substitution.[6,8)] However, considering various impracticalities including uses of expensive reagents and/or chiral sources,[5,6,8)] reactions at low or high temperatures,[6)] and also substantial loss of optical integrities observed in the synthesis of (*R*)-(−)-**14**,[6,7)] the previously explored synthetic methods[1,4–10)] seem not to be adequate for a large scale preparation of (*R*)-(−)-**14**.

We have now developed another synthetic scheme for optically pure (*R*)-(−)-**14**, starting from cheap and readily available 1,4-dihydroxyanthracene-9,10-dione (quinizalin) (**3**).

This report deals with the exploration of this novel synthetic route which is considered to be more practical and efficient than the previously reported methods[1,5–10)]



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



2: Z= H

Commercially available **3** was oxidized with lead tetraacetate to give anthracene-1,4,9,10-tetrone (**4**) in 58% yield according to the reported method.[13)] The Diels-Alder reaction of **4** with 2-chloro-1,3-butadiene (chloroprene) as an enophile regiospecifically occurred at the external $C_{2,3}$-double bond, giving a 79% of 2-chloro-1,4,4a,12a-tetrahydronaphthacene-5,6,11,12-tetrone (**5a**). TLC and NMR analyses of the crude product clearly disclosed complete absence of the undesired Diels-Alder adduct which might result from the attack of chloroprene on the internal $C_{4a,9a}$-double bond of **4**. While 2-acetoxy-1,3-butadiene which had been employed as an excellent enophile in the synthesis of natural anthracyclinones (**2a**, **b**)[14)] afforded a 58% yield of the desired adduct in the Diels-Alder reaction with **4**, this diene could only be prepared in less than 10% yield according to the reported method by our hands.[15)] 2-Acetoxy-1,3-butadiene could be also prepared from methyl vinyl ketone in 38% yield by simultaneous metallation with lithium diisopropylamide and acylation with acetic anhydride. However, it is obvious that this synthetic method is not applicable to a large scale preparation of 2-acetoxy-1,3-butadiene. Therefore, chloroprene seems to be one of the best enophile for the construction of desired tetracyclic ring system such as **5a** because of its superior regioselectivity and ready availability.[16)] Since **5a** was found to be fairly unstable, it was immediately aromatized with anhyd sodium acetate in acetic acid to afford the

dihydroxyanthraquinone **6a** in 91% yield. Hydrolysis of the vinylic chloride functionality was readily accomplished with concd sulfuric acid, giving rise to 5,12-dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione (**7**)[16b,17] in 98% yield.

According to the conventional method, **7** was smoothly converted to (±)-2,5,12-trihydroxy-6,11-dioxo-1,2,3,4-tetrahydro-2-naphthacenecarboxylic acid ((±)-**9**). Thus, treatment of **7** with potassium cyanide and hydrochloric acid in acetic acid yielded the unstable cyanohydrin **8**, which without isolation was subjected to acid hydrolysis to afford (±)-**9** in 83% yield.

With a large quantity of (±)-**9** in hand, the optical resolution of (±)-**9** was first attempted. After several unsuccessful attempts, (−)-*N*-methylephedrine was found to be the best optically active amine, being neccessary for the salt formation with (±)-**9**. Treatment of (±)-**9** with (−)-*N*-methylephedrine (1.2 equiv) in ethanol gave the crude salt of (*R*)-**9** in 51% (102%)[19] yield. Two recrystallizations of the crude salt from ethanol containing a small amount of (−)-*N*-methylephedrine (0.2 equiv to the amount of the salt)[20] afforded the pure salt of (*R*)-**9** in 31% (62%)[19] yield which showed the constant melting point and optical rotation, mp 217.5—220°C, $[\alpha]_D^{20}$ −12.0° ($CHCl_3$). The optically pure acid ((*R*)-**9**) was readily regenerated in a quantitative yield by stirring a suspension of the pure salt in aqueous hydrochloric acid. Unfortunately, the optical rotation of (*R*)-**9** could not be measured because of its extremely low solubility to almost all solvents.

While the absolute configuration and optical purity of optically active **9** could be determined by the successful synthesis of (*R*)-(−)-**14** (vide infra), the independent determination of these physical indices was examined at this stage by transforming optically active **9** into its derivatives. Thus, esterification of optically active **9** in a mixture of methanol and dimethyl sulfoxide[21] using a catalytic amount of concd sulfuric acid gave the corresponding (−)-methyl ester ((−)-**10**) in 91% yield, $[\alpha]_D^{20}$ −55.0° ($CHCl_3$), after purification by column chromatography. Further methylation of the phenolic hydroxyl groups of (−)-**10** with potassium carbonate and dimethyl sulfate in acetone, followed by purification by column chromatography, produced the (+)-dimethoxy ester ((+)-**11**) in 90% yield, $[\alpha]_D^{20}$ +11.7° ($CHCl_3$).[22] Measurement of the NMR spectrum of (+)-**11** in the presence of chiral shift reagent clearly disclosed that optically active **9** produced by the resolution was optically pure (100% ee). In order to determine the absolute configuration, (+)-**11** was further hydrolyzed under alkaline conditions to give the (+)-dimethoxy acid ((+)-**12**)[5,23] in 82% yield, $[\alpha]_D^{20}$ +16.9° ($CHCl_3$). Since (+)-**12** showing $[\alpha]_D^{20}$ +14.0° ($CHCl_3$) had been reported to belong to (*R*)-series,[5] optically active **9** was definitely established to belong to (*R*)-configuration.

Since determination of the absolute configuration and optical purity of optically active **9** was completed as mentioned above, our next attention was focused on the elaboration of (*R*)-**9** to (*R*)-(−)-**14**. At the outset, the synthesis of (*R*)-(−)-**14** from (*R*)-**9** seemed to be simply accomplished by employing one of the reported methods which could afford a methyl ketone from the corresponding acid. However, this was found to be quite refractory. After several unsuccessful attempts employing (±)-**9** as a substrate,[24] the reaction of the (±)-*N*-acylimidazole ((±)-**13**) in situ produced from (±)-**9**[25] with methylmagnesium bromide was turned out to be promising. Thus, the reaction of (±)-**9** with *N*,*N*′-carbonyldiimidazole (2.0 equiv) in tetrahydrofuran containing hexamethylphosphoric triamide furnished (±)-**13**. Without isolation, (±)-**13** was immediately treated with trimethylsilyl trifluoromethanesulfonate (trimethylsilyl triflate) (1 equiv) at −20°C, then with methylmagnesium bromide at −40°C, giving (±)-**14** in 65% yield. By applying the developed sequential reactions to (*R*)-**9**, optically pure (*R*)-(−)-**14**, $[\alpha]_D^{20}$ −90.3° ($CHCl_3$) was obtained in 58% overall yield from (*R*)-**9** by way of (*R*)-**13**.

In order to clearly elucidate several notable aspects of the explored one pot synthesis of (*R*)-(−)-**14** from (*R*)-**9**, some preliminary results obtained by using (*R*)- and (±)-**9** are summarized in Table 1. Absence of hexamethylphosphoric triamide and/or trimethylsilyl

Table 1. Preparation of (*R*)-(−)- or (±)-**14** from (*R*)- or (±)-**9** by Way of (*R*)- or (±)-**13**

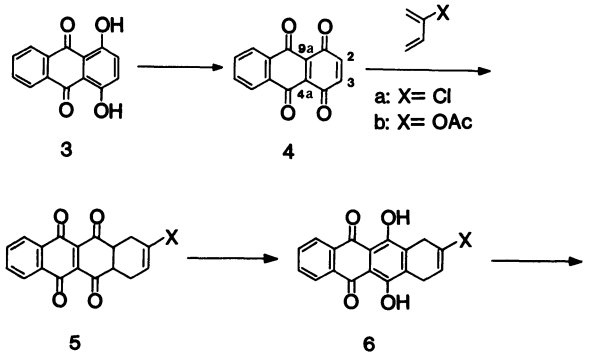
Run	**9**	Solvent[a]	Additive[b]	Reaction[c] Temp/°C	Yield of (*R*)-(−)-[d] or (±)-**14**/%
1	(*R*)-	THF-HMPA[e]	TMSOTf	−40	58
2	(*R*)-	THF	TMSOTf	−40	44
3	(*R*)-	THF	—	−20	23[f]
4	(±)-	THF-HMPA[e]	TMSOTf	−40	65
5	(±)-	THF-HMPA[e]	BF_3·OEt_2	−20	51
6	(±)-	THF-HMPA[e]	—	−20	40[f]
7	(±)-	THF	—	−20	25[f]

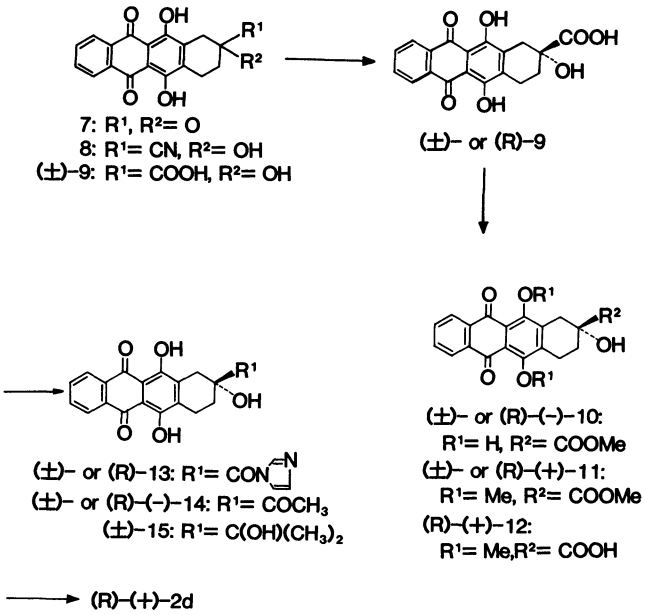
a) Tetrahydrofuran (THF), hexamethylphosphoric triamide (HMPA). b) Trimethylsilyl triflate (TMSOTf), boron trifluoride etherate (BF_3·OEt_2). c) Reaction temperature in the reaction with methylmagnesium bromide. The *N*-acylimidazole ((*R*)- or (±)-**13**) was prepared at room temperature. d) Based on (*R*)- or (±)-**9**. e) The volume ratio of THF to HMPA was 50:1. f) NMR analysis showed that this sample was contaminated with the (*R*)-(−)- or (±)-methyl ester of (*R*)-(−)- or (±)-**9** ((*R*)-(−)- or (±)-**10**) ((*R*)-(−)- or (±)-**9**/(*R*)-(−)- or (±)-**10**=9/1—4/1) (see text).

triflate in the reaction medium significantly decreased the yield of (*R*)-(−)- or (±)-**14** (see runs 1—3). Addition of the Grignard reagent to (*R*)- or (±)-**13** began to occur at −20 °C in the absence of trimethylsilyl triflate, affording a low yield of (*R*)-(−)- or (±)-**14** (see runs 1, 3 and 4, 6). In this case, the reaction product ((*R*)-(−)- or (±)-**14**) was accompanied by a significant amount of the methyl ester ((*R*)-(−)- or (±)-**10**) ((*R*)-(−)- or (±)-**14**/(*R*)-(−)- or (±)-**10**=9/1—4/1). While the formation mechanism of (*R*)-(−)- or (±)-**10** from (*R*)- or (±)-**9** is quite obscure, the amount of (*R*)-(−)- or (±)-**10** seems to be proportional to the temperature at which the Grignard reagent was added to a solution of (*R*)- or (±)-**13**. In the reaction carried out at −40 °C, no formation of undesired (*R*)-(−)- or (±)-**10** was definitely ascertained by NMR analysis of the crude reaction product. When methylmagnesium iodide was employed as a Grignard reagent in place of methylmagnesium bromide, the tertiary alcohol ((±)-**15**) was formed in 74% yield. It is noteworthy that a negligible amount of (*R*)- or (±)-**15**, usually less than 3% yield, was produced even though a large excess of methylmagnesium bromide was employed as a Grignard reagent. This may be explained by the assumption that the magnesium salt produced by the reaction of methylmagnesium iodide is more unstable than that formed by employing methylmagnesium bromide and liberates (*R*)-(−)- or (±)-**14** in the reaction medium.

By accumulating these results described above, we have finally succeeded in preparing (*R*)-(−)- or (±)-**14** directly from (*R*)- or (±)-**9** in ca. 60% yield. Numerous synthetic approaches to anthracyclinones hitherto reported, terminate at or proceed through 1,2,3,4-tetrahydro-2,6,11-naphthacenetrione derivatives.[4,14,16b,17,26] Therefore, the explored process is anticipated to hold promise for adding the racemic or optically active C_9-α-hydroxy ketone moiety to those tetracyclic systems.

As mentioned in the introduction part, the methods for converting (*R*)-(−)-**14** to optically pure **2d**, then to optically pure **2c**, have been firmly established by us.[6,8] Accordingly, the developed overall scheme to (*R*)-(−)-**14** which can be characterized by its operational simplicity and directness is expected to facilitate a large scale preparation of optically pure **2c**, **d** more readily than the previously reported method.[4-10]





Scheme 1.

Experimental

General. All melting points were determined with a Yamato MP-21 melting point apparatus and were uncorrected. IR spectral measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer. NMR spectra were recorded with a Varian EM-390 spectrometer (90 MHz) and a Varian XL-100A spectrometer (100 MHz). All signals were expressed as ppm downfield from TMS, used as an internal standard (δ-value). Mass spectra were taken with a Hitachi RMU-6MG mass spectrometer. Measurements of optical rotation were performed with a Union PM-201 automatic digital polarimeter and Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 and Kieselgel 60 (Merck) were used as an adsorbent for column chromatography. All reactions were carried out using anhydrous solvents. Especially tetrahydrofuran, ether, and dioxane freshly distilled from sodium benzophenone ketyl, and dichloromethane, acetone, and pyridine freshly distilled from calcium hydride were used. Lead tetraacetate purchased from Wako Pure Chemical Industries, Ltd., was used for a reaction without further purification. Following abbreviations are used for solvents and reagents: acetic acid (AcOH), benzene (C_6H_6), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), dimethyl sulfoxide (DMSO), ether (Et_2O), ethyl acetate (EtOAc), ethanol (EtOH), hexamethylphosphoric triamide (HMPA), hexane (C_6H_{14}), methanol (MeOH), tetrahydrofuran (THF).

Anthracene-1,4,9,10-tetrone (Quinizalin Quinone) (4). A mixture of **3** (31.9 g, 0.133 mol) and lead tetraacetate (purity 90%) (98.4 g, 0.200 mol) in AcOH (80 mL) are stirred in a mortal for 30 min. The brown precipitate was collected by filtration, washed with AcOH and H_2O, and dried over P_2O_5 in vacuo to give crude **4** (26.6 g, 84%). This was added to nitrobenzene (400 mL), and the mixture was stirred for 2 h at 70 °C, then filtered through a pad of celite. The filtrate was concentrated in vacuo below 70 °C until crystals appeared. After cooling to room temperature, the crystals were collected by filtration, washed with Et_2O, then dried in

vacuo to afford pure **4** (18.2 g, 58%), mp 210—212°C (decomp) (lit,[13] mp 208—210°C (decomp)). IR (KBr): 1700, 1685, 1645, 1595 cm^{-1}. ^1H NMR ($CDCl_3$) δ=6.87 (s, 2H, C<u>H</u>=C<u>H</u>), 7.70—8.15 (m, 4H, Ar).

2-Chloro-1,4,4a,12a-tetrahydronaphthacene-5,6,11,12-tetrone (5). Chloroprene (9.80 g, 0.111 mol) was added to a suspension of **4** (mp 210—212°C) (16.2 g, 0.068 mol) in a mixture of C_6H_6 and xylene (5 : 1) (170 mL). After reflux for 3 h, additional amount of chloroprene (3.53 g, 0.040 mol) was added to the mixture, then the whole suspension was heated at reflux for 1 h. After cooling, the crystals were collected by filtration, washed with Et_2O, then dried over P_2O_5 in vacuo, to give pure **5** (17.6 g, 79%), mp 232—234°C (decomp). A part of this sample was recrystallized from xylene to give an analytical sample of **5**, mp 232—234°C (decomp). IR (KBr): 1710, 1665, 1595 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.34—2.83 (m, 4H, 1-H_2+4-H_2), 3.39—3.81 (m, 2H, 4a-H+12a-H), 5.88 (m, 1H, C<u>H</u>=CCl), 7.76—8.22 (m, 4H, Ar). Found: C, 66,23; H, 3.34; Cl, 10.61%. Calcd for $C_{18}H_{11}O_4Cl$: C, 66.17; H, 3.39; Cl, 10.85%.

2-Chloro-5,12-dihydroxy-1,4-dihydro-6,11-naphthacenedione (6). The powdered tetrone (**5**) (mp 232—234°C (decomp)) (19.6 g, 60.0 mmol) was added to a mixture of anhyd sodium acetate (100 mg, 1.22 mmol) in AcOH (200 mL) over 15 min. After reflux for 30 min, the red crystals were collected by filtration, washed successively with H_2O, MeOH, and Et_2O, then dried over P_2O_5 in vacuo, to afford pure **6** (17.9 g, 91%), mp 285.5—286.5°C. A part of this sample was recrystallized from toluene to give an analytical sample of **6**, mp 285.5—286.5°C. IR (KBr): 1625, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ=3.44—3.82 (m, 4H, 1-H_2+4-H_2), 6.00—6.13 (m, 1H, C<u>H</u>=CCl), 7.77—8.50 (m, 4H, Ar), 13.41 (s, 1H, ArO<u>H</u>), 13.42 (s, 1H, ArO<u>H</u>). Found: C, 65.95; H, 3.38; Cl 10.86%. Calcd for $C_{18}H_{11}O_4Cl$: C, 66.17; H, 3.39; Cl, 10.85%.

5,12-Dihydroxy-1,2,3,4-tetrahydro-2,6,11-naphthacenetrione (7). The vinylic chloride (**6**) (mp 285.5—286.5°C) (17.4 g, 53.3 mmol) was gradually added to a stirred concd H_2SO_4 (170 mL). The reaction mixture was stirred for 1 h under an exclusion of moisture ($CaCl_2$ tube), then poured onto ice-H_2O (3 L). The aqueous mixture was kept standing at room temperature for 3 d. Red powderlike crystals were collected by centrifugation and suspended in AcOH (250 mL). The acidic suspension was heated at reflux for 2 h with stirring. After cooling, the red powderlike crystals were collected by filtration, washed with MeOH, and dried over P_2O_5 in vacuo, to give **7** (16.1 g, 98%), mp > 250°C (decomp). A part of this sample was recrystallized from AcOH to give an analytical sample of **7**, mp > 250°C (decomp) (lit,[16b] mp 313—315°C, lit,[17a] mp>310°C (decomp), lit,[17b] mp> 300°C, lit,[17c] mp 296—298°C (decomp)). IR (KBr): 1730, 1620, 1585 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.68 (t, J=7 Hz, 2H, 3-H_2), 3.30 (t, J=7 Hz, 2H, 4-H_2), 3.70 (s, 2H, 1-H_2), 7.78—8.02 (m, 2H, Ar), 8.30—8.52 (m, 2H, Ar), 13.40 (s, 1H, ArO<u>H</u>), 13.50 (s, 1H, ArO<u>H</u>). Found: C, 69.92; H, 4.01%. Calcd for $C_{18}H_{12}O_5$: C, 70.13; H, 3.92%.

(±)-2-Cyano-2,5,12-trihydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione (8). Potassium cyanide (15.8 g, 24.3 mmol) was added to a suspension of **7** (mp > 250°C) (5.00 g, 16.2 mmol) in a mixture of EtOH (130 mL) and THF (170 mL) at 0°C with stirring. After stirring for 20 min, AcOH (20 mL) was added dropwise to the reaction mixture at 0°C. The whole mixture was stirred for 30 min at 0°C, then overnight at room temperature. The mixture was poured onto 3% HCl (1 L). The red powder was collected by filtration, washed with H_2O, and dried over P_2O_5 in vacuo, to afford crude **8** (4.50 g, 83%). IR (KBr): 3400, 2240, 1630, 1595, 1417, 1377, 1253, 1105, 1077, 1008, 797, 739 cm^{-1}. ^1H NMR ($(CD_3)_2CO$) δ=2.34 (t, J=6.5 Hz, 2H, 3-H_2), 3.06 (m, 2H, 4-H_2), 3.18 (d, J=18.4 Hz, 1H, one of 1-H), 3.45 (d, J=18.4 Hz, 1H, one of 1-H), 5.93 (brs, 1H, OH), 8.05 (m, 2H, Ar), 8.38 (m, 2H, Ar), 13.42 (s, 1H, ArO<u>H</u>), 13.47 (s, 1H, ArO<u>H</u>).

(±)-2,5,12-Trihydroxy-6,11-dioxo-1,2,3,4-tetrahydro-2-naphthacenecarboxylic Acid ((±)-9). A mixture of **8** (3.66 g, 10.9 mmol) AcOH (37 mL), and concd HCl (9 mL) was refluxed for 4.5 h. Additional amount of concd HCl (9 mL) was added to the mixture, and the whole mixture was heated at reflux for 5.5 h. After cooling, the red powder was collected by filtration, washed with H_2O, then dried over P_2O_5 in vacuo, to afford crude (±)-**9** (3.63 g, 94%). This was recrystallized from nitrobenzene to give pure (±)-**9**, mp 251—252°C (lit,[25] 253—258°C). IR (KBr): 3400, 3250, 1730, 1625, 1590 cm^{-1}. ^1H NMR ($(CD_3)_2SO$) δ=1.80—2.20 (m, 2H, 3-H_2), 2.57—3.00 (m, 4H, 1-H_2+4-H_2), 7.80—8.35 (m, 4H, Ar), 13.29 (s, 1H, ArO<u>H</u>), 13.31 (s, 1H, ArO<u>H</u>). Found: C, 64.03; H, 3.98%. Calcd for $C_{19}H_{14}O_7$: C, 64.41; H, 3.98%.

(*R*)-2,5,12-Trihydroxy-6,11-dioxo-1,2,3,4-tetrahydro-2-naphthacenecarboxylic Acid ((*R*)-9). Optical Resolution of (±)-9: A mixture of (±)-**9** (mp 251—252°C) (10.0 g, 28.2 mmol) and (−)-*N*-methylephedrine[17] (mp 85—86°C, $[\alpha]_D^{20}$ −30.2° (*c* 4.48, MeOH)) (6.07 g, 33.9 mmol) in EtOH (2 L) was heated at reflux for 2 h. After the hot solution was filtered, the filtrate was concentrated to a half volume and kept standing overnight at room temperature. The red crystals were collected by filtration to afford the crude salt of (*R*)-**9** (7.72 g, 51% (102%)[19]), mp 200—204°C, $[\alpha]_D^{20}$ −64.0° (*c* 0.10, $CHCl_3$). The salt was twice recrystallized from EtOH containing (−)-*N*-methylephedrine of 0.2 equiv to the total amount of the salt,[20] affording the pure *N*-methylephedrine salt of (*R*)-**9** as a red powder (4.71 g, 31% (62%)[19]), mp 217.5—220°C, $[\alpha]_D^{20}$ −12.0° (*c* 0.05, $CHCl_3$). IR (KBr): 3420, 1625, 1595 cm^{-1}. Found: C, 67.50; H, 5.60; N, 2.35%. Calcd for $C_{30}H_{31}NO_8$: C, 67.53; H, 5.86; N, 2.63%. The pure *N*-methylephedrine salt of (*R*)-**9** (1.17 g, 2.19 mmol) was added to stirred 3.6% HCl (350 mL), and the mixture was stirred at room temperature for 17 h. The red powder was collected by filtration, washed with dil HCl and H_2O, and dried over KOH at 100°C in vacuo, to give optically pure (*R*)-**9** (0.776 g, 100%), mp > 280°C. IR (KBr): 3450, 1730, 1625, 1590 cm^{-1}. MS *m/z*: 354 (M^+), 336, 291.

(±)-Methyl 2,5,12-Trihydroxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene-2-carboxylate ((±)-10). A mixture of (±)-**9** (mp 251—252°C) (506 mg, 1.43 mmol) and concd H_2SO_4 (7 drops) in MeOH (50 mL) and DMSO (10 mL) was heated at reflux for 4 h with stirring. After cooling, the reaction mixture was poured onto satd $NaHCO_3$ and extracted with EtOAc. The combined ethyl acetate extracts were washed with H_2O and satd NaCl, then dried over $MgSO_4$. Filtration and concentration in vacuo gave crude (±)-**10** as a red solid (524 mg, 100%), mp 198.5—199.5°C. This was recrystallized from toluene to afford pure (±)-**10**, mp 211.5—213.5°C. IR (KBr): 3470, 1743, 1620, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.95—2.20 (m, 2H, 3-H_2), 2.80—3.20 (m, 4H, 1-H_2+4-H_2), 3.09 (brs, 1H, OH), 3.84 (s, 3H, CH_3), 7.70—7.90 (m, 2H, Ar), 8.20—8.40 (m, 2H, Ar), 13.43 (s, 2H, ArO<u>H</u> ×2). MS *m/z*: 368 (M^+). Found: C, 65.23; H, 4.39%. Calcd for $C_{20}H_{16}O_7$: C, 65.22; H, 4.38%.

(*R*)-(−)-Methyl 2,5,12-Trihydroxy-6,11-dioxo-1,2,3,4-tetra-

hydronaphthacene-2-carboxylate ((*R*)-(−)-10). Treatments of (*R*)-**9** (mp > 280°C) (350 mg, 0.99 mmol) in the same manner as described for (±)-**10** gave crude (*R*)-(−)-**10** (345 mg, 95%) after concentration of the ethyl acetate extracts. This was purified by silica-gel column chromatography (C_6H_6/EtOAc=5/1—3/1) to afford pure (*R*)-(−)-**10** (293 mg, 81%) as red crystals, mp 206.5—210°C, $[\alpha]_D^{20}$ −55.0° (*c* 0.10, $CHCl_3$). A part of this sample was recrystallized from toluene to give an analytical sample of (*R*)-(−)-**10**, mp 210.5—211.5°C, $[\alpha]_D^{20}$ −60.0° (*c* 0.10, $CHCl_3$). IR (KBr): 3470, 1734, 1620, 1590 cm^{-1}. NMR spectrum of this sample was identical with that of (±)-**10**. Found: C, 65.21; H, 4.20%. Calcd for $C_{20}H_{16}O_7$ C, 65.22; H, 4.38%.

(±)-Methyl 2-Hydroxy-5,12-dimethoxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene-2-carboxylate ((±)-11). Anhyd potassium carbonate (150 mg, 1.09 mmol) and dimethyl sulfate (137 mg, 1.09 mmol) were added to a suspension of (±)-**10** (mp 198.5—199.5°C) (100 mg, 0.27 mmol) in Me_2CO (12 mL). After reflux for 5.5 h, the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc, and the ethyl acetate solution was washed successively with satd $NaHCO_3$, H_2O, and satd NaCl, then dried over $MgSO_4$. Filtration and concentration in vacuo gave crude (±)-**11** (97.6 mg, 91%), which was purified by silica-gel column chromatography (Et_2O) to afford pure (±)-**11** as a yellow solid (78.6 mg, 73%), mp 152 and 186°C. A part of this sample was triturated with Et_2O to give an analytical sample of (±)-**11**, mp 152 and 186°C. IR (KBr): 3540, 1728, 1675 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.90—2.20 (m, 2H, 3-H_2), 2.90—3.20 (m, 4H, 1-H_2+4-H_2), 3.16 (brs, 1H, OH), 3.84 (s, 3H, CO_2Me), 3.86 (s, 3H, OMe), 3.91 (s, 3H, OMe), 7.63—7.82 (m, 2H, Ar), 8.05—8.30 (m, 2H, Ar). MS *m/z*: 396 (M^+). Found: C, 66.56; H, 5.07%. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09%.

(*R*)-(−)-Methyl 2-Hydroxy-5,12-dimethoxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene-2-carboxylate ((*R*)-(+)-11). Treatments of (*R*)-(−)-**10** (mp 206.5—210°C, $[\alpha]_D^{20}$ −55.0° (*c* 0.10, $CHCl_3$)) (50.0 mg, 0.14 mmol) in the same manner as described for (±)-**11** gave (*R*)-(+)-**11** as a yellow solid (48.5 mg, 90%) after purification by silica-gel chromatography, mp 152—154°C, $[\alpha]_D^{20}$ +11.7° (*c* 0.22, $CHCl_3$)[22] (lit,[5] mp 154—155°C). IR (KBr): 3540, 1728, 1675 cm^{-1}. ^1H NMR spectrum of this sample was identical with that of (±)-**11**. NMR spectrum of (*R*)-(+)-**11** measured in the presence of chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (Eu(hfc)$_3$) exhibited the methyl ester as a singlet at δ=6.07. Since NMR spectrum of (±)-**11** measured under the same conditions as described for (*R*)-(+)-**11** showed two singlets at δ=5.82 and 6.07, the optical purity of optically active **9** produced by the optical resolution was established to be 100% ee.

(*R*)-(+)-2-Hydroxy-5,12-dimethoxy-6,11-dioxo-1,2,3,4-tetrahydro-2-naphthacenecarboxylic Acid ((*R*)-(+)-12). Three percent potassium hydroxide (0.50 mL, 0.27 mmol) was added to a mixture of (*R*)-(+)-**11** (mp 152—154°C, $[\alpha]_D^{20}$ +11.7° (*c* 0.22, $CHCl_3$)) (70 mg, 0.18 mmol) in THF (1.4 mL) and MeOH (2.0 mL), and the mixture was stirred at room temperature for 3 h. After concentration in vacuo, the residue was diluted with satd NaCl, and the aqueous solution was washed with EtOAc. The aqueous layer was acidified (pH=2) with concd HCl, saturated with NaCl, then extracted with EtOAc. The combined organic extracts were washed with satd NaCl, dried over $MgSO_4$, and concentrated in vacuo, affording crude (*R*)-(+)-**12** (55.2 mg, 82%) as a yellow solid. Recrystallization of this sample from C_6H_{14}–EtOAc gave pure (*R*)-(+)-**12**, mp 202—207°C, $[\alpha]_D^{20}$+16.9° (*c* 0.20, $CHCl_3$) (lit,[5] mp 200—201°C, $[\alpha]_D^{20}$+13.6° (*c* 0.430, $CHCl_3$); lit,[23] mp 200—205°C, $[\alpha]_D^{20}$+14.0° (*c* 0.20, $CHCl_3$)). IR (KBr): 3440, 1715, 1675 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.92—2.29 (m, 2H, 3-H_2), 2.93—3.37 (m, 4H, 1-H_2+4-H_2), 3.91 (s, 3H, OMe), 3.94 (s, 3H, OMe), 5.76 (brs, 2H, OH+COOH), 7.60—7.84 (m, 2H, Ar), 8.00—8.30 (m, 2H, Ar). MS *m/z*: 382 (M^+), 319. Found: C, 65.32; H, 4.74%. Calcd for $C_{21}H_{18}O_7$–0.25H_2O: C, 65.20; H, 4.82%.

(±)-7-Deoxy-4-demethoxydaunomycinone ((±)-14). A mixture of (±)-**9** (mp 251—252°C) (52.7 mg, 0.15 mmol) and *N,N'*-carbonyldiimidazole (48.6 mg, 0.30 mmol) in THF (10 mL) containing HMPA (0.2 mL) was stirred at room temperature for 18 h to give a solution of (±)-**13**. Trimethylsilyl triflate (0.03 mL, 0.16 mmol) was added to the solution of (±)-**13** cooled at −20°C, and stirring was continued at −20°C for 15 min. After cooling at −40°C, an ethereal solution of methylmagnesium bromide (3 M[1] solution, 0.50 mL, 1.5 mmol) was added to the stirred reaction mixture. After stirring was continued at the same temperature for 2 h, additional amount of the ethereal solution of methylmagnesium bromide (3 M solution, 0.2 mL, total 0.7 mL, 2.1 mmol) was added to the reaction mixture. After being stirred at −40°C for 1 h, the reaction mixture was poured onto a vigorously stirred mixture of 1 M HCl (50 mL) and EtOAc (50 mL) to quench the reaction. The upper organic phase was separated, washed with satd NaCl, then dried over $MgSO_4$. Filtration and concentration in vacuo gave a red residue, which was purified by filtration through a short silica-gel column (C_6H_6/EtOAc=9/1) to give (±)-**14** as a red solid (34.0 mg, 65%), mp 194—198°C. Recrystallization of this sample from C_6H_6 gave a pure sample of (±)-**14** as a red minute crystals (29.3 mg, 56%), mp 213—215°C (lit,[6] mp 214—216°C). IR and NMR spectra of this sample were identical with those reported.[6]

(*R*)-(−)-7-Deoxy-4-demethoxydaunomycinone ((*R*)-(−)-14). Treatments of (*R*)-**9** (mp > 280°C) (50.5 mg, 0.14 mmol) in the same manner as described for (±)-**14** gave (*R*)-(−)-**14** as a red solid (29.1 mg, 58%), after extractive isolation with EtOAc and purification by filtration through a short silica-gel column, mp 195—203°C, $[\alpha]_D^{20}$ −85.7° (*c* 0.105, $CHCl_3$). This sample was recrystallized from C_6H_6 to afford pure (*R*)-(−)-**14** as a red minute crystals (23.3 mg, 46%), mp 214—216°C, $[\alpha]_D^{20}$ −90.6° (*c* 0.106, $CHCl_3$) (lit,[8] mp 218—219°C, $[\alpha]_D^{20}$−90.3° (*c* 0.106, $CHCl_3$)). IR and NMR spectra of this sample were superimposable on those of the authentic sample.[8]

(±)-2-Hydroxy-2-(1-hydroxy-1-methylethyl)-1,2,3,4-tetrahydro-6,11-naphthacenedione ((±)-15). A mixture of (±)-**9** (mp 251—252°C) (201 mg, 0.568 mmol) and *N,N'*-carbonyldiimidazole (185 mg, 1.14 mmol) in THF (40 mL) containing HMPA (0.8 mL) was stirred at room temperature for 18.5 h, to give a solution of (±)-**13**. Trimethylsilyl triflate (0.12 mL, 0.621 mmol) was added to the solution of (±)-**13** cooled at −40°C, and stirring was continued at −40°C for 20 min. An ethereal solution of methylmagnesium iodide (3 M solution, 1.9 mL, 5.70 mmol) was added to the reaction mixture at the same temperature. After stirring for 2 h, additional amount of the ethereal solution of methylmagnesium iodide (3M solution, 1.9 mL, 5.70 mmol) was added to the reaction mixture at −40°C. A reaction temper-

[1] 1 M=1 mol dm^{-3}.

ature was gradually raised up to −20°C, then the whole mixture was stirred at −20°C for 5 h. Extractive isolation followed by purification by silica-gel column chromatography (C_6H_6/EtOAc=5/1) in the same manner as described for (±)-**14** afforded pure (±)-**15** (155 mg, 74%), mp 234.5—237.5°C. IR (KBr): 3525, 1620, 1588 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.36 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.5—3.1 (m, 8H), 7.55—7.85 (m, 2H, Ar), 8.05—8.33 (m, 2H, Ar), 13.32 (s, 1H, ArOH), 13.36 (s, 1H, ArOH). MS *m/z*: 368 (M^+), 310.

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19) This yield was calculated based on (*R*)-**9** originally contained in (±)-**9**.

20) Existence of a small amount of (−)-*N*-methylephedrine (ca. 0.2 equiv to the total amount of the salt of (*R*)-**9**) was indispensable for improving purity of the salt of (*R*)-**9** by repeated recrystallizations.

21) When the esterification was carried out in the absence of dimethyl sulfoxide, only 64% yield of (−)-**10** was obtained under the similar reaction conditions. This might be due to extremely low solubility of optically active **9** in methanol.

22) This sample showed the following optical rotations in solvents other than chloroform: $[\alpha]_D^{20}$ 0.0° (*c* 0.22, Me_2CO), $[\alpha]_D^{20}$ −5.2° (*c* 0.23, MeOH), $[\alpha]_D^{20}$ −13.1° (*c* 0.25, EtOH), and $[\alpha]_D^{20}$ −23.5° (*c* 0.22, C_6H_6). Although $[\alpha]_D^{20}$ −7.8° (*c* 0.613, Me_2CO) was previously reported for this compound,[5] this rotation value should be corrected.

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24) Before developing the efficient one-pot preparation method of (*R*)-(−)-**14** reported here, the following multi-step syntheses were found to produce (±)-**14** from (±)-**9** in rather low overall yields. Thus, esterification of (±)-**9** (concd H_2SO_4 in methanol and dimethyl sulfoxide) followed by protection of the C_9-hydroxyl group (dihydropyran-pyridinium *p*-toluenesulfonate in tetrahydrofuran or trimethylsilyl triflate-triethylamine in tetrahydrofuran) and reaction with sodium methylsulfinyl methanide in tetrahydrofuran, gave the corresponding C_9-*O*-protected methylsulfinyl ketone in ca. 60% overall yields. Successive reductive cleavage of the methylsulfinyl ketones (aluminum-amalgam in tetrahydrofuran or Raney-Ni in ethanol) and deprotection of the C_9-*O*-protective groups (pyridinium *p*-toluenesulfonate in ethanol, 50% acetic acid in ethyl acetate or 10% hydrochloric acid in tetrahydrofuran, etc.) gave (±)-**14** in 18—25% yields. On the other hand, (±)-**9** was converted to the corresponding thiol ester in 67% yield by treating with ethanethiol, magnesium ethoxide, and *N,N'*-carbonyldiimidazole in tetrahydrofuran. Reaction of thiol ester with lithium dimethylcuprate(I) in tetrahydrofuran at −40°C gave (±)-**14** in 23% yield.

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