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Short-Step Asymmetric Syntheses of Anthracycline Antibiotics via Enantioselective Dihydroxylation by Osmium Tetroxide with a Chiral Diamine

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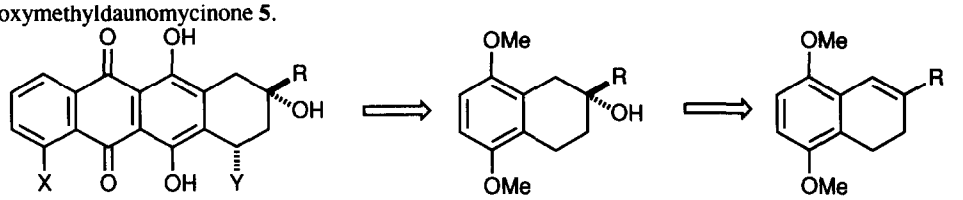
Abstract. Short-step asymmetric syntheses of (+)-7-dehydroxy-4-demethoxydaunomycinone **4** and (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyldaunomycinone **5** were accomplished via enantioselective dihydroxylation by osmium tetroxide with chiral diamine **13**.

The clinical utility of the anthracycline antitumor antibiotics such as adriamycin (doxorubicin) **1** and daunomycin (daunorubicin) **2** is well established.[1] The 4-demethoxy series of compounds **4** and **5** have been developed as artificial anthracyclines of improved pharmacological profile. Since the biological activity of the anthracyclines is critically dependent on the chirality at C-9, extensive efforts have been devoted to asymmetric construction of this chiral center in the desired absolute configuration.[2, 3]

We have reported the highly enantioselective dihydroxylation of olefins by osmium tetroxide with a chiral diamine **13**.[4] Employing our system, diols of exceptionally high ee can be obtained from mono-, *trans*-di-, and trisubstituted olefins. The enantioface selection is shown by the general presentation in Fig. 2. Since both (+)- and (-)-**13** are readily accessible in optically pure form, this method provide a powerful tool for the synthesis of optically active alcohols in high ee with desired absolute configuration from achiral olefins. In order to demonstrate the synthetic utility of our method, asymmetric syntheses of the anthracyclinones were examined. We describe herein the details of successful short-step asymmetric syntheses of (+)-7-dehydroxy-4-demethoxydaunomycinone **4** and its hydroxymethyl analog (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyldaunomycinone **5**.



	R	X	Y
1	$COCH_2OH$	OMe	O-Daunosaminyl
2	COMe	OMe	O-Daunosaminyl
3	CH_2OH	OMe	O-Daunosaminyl
4	COMe	H	H
5	CH_2OH	H	H
6	COOMe	H	H

	R
7	COOMe
8	COMe
9	C(ethylenedioxy)Me

	R
10	COOMe
11	COMe
12	C(ethylenedioxy)Me

Fig 1 Asymmetric Syntheses of Anthracyclines

Synthetic Plan

Optically active **7** and **8** are the most common key intermediates for the synthesis of anthracyclines because it can be easily transformed into tetracycline skeleton by Friedel-Crafts condensation to afford **6** and **4**, respectively. Our original plan for the asymmetric synthesis of **7** and **8** is to construct the stereocenter by enantioselective dihydroxylation of **10** and **11** followed by reductive removal of benzylic hydroxyl group. Applying the general presentation of the asymmetric dihydroxylation in Fig. 2, (-)-**13** should be employed as a chiral diamine in order to obtain **7** and **8** with desired absolute configuration.

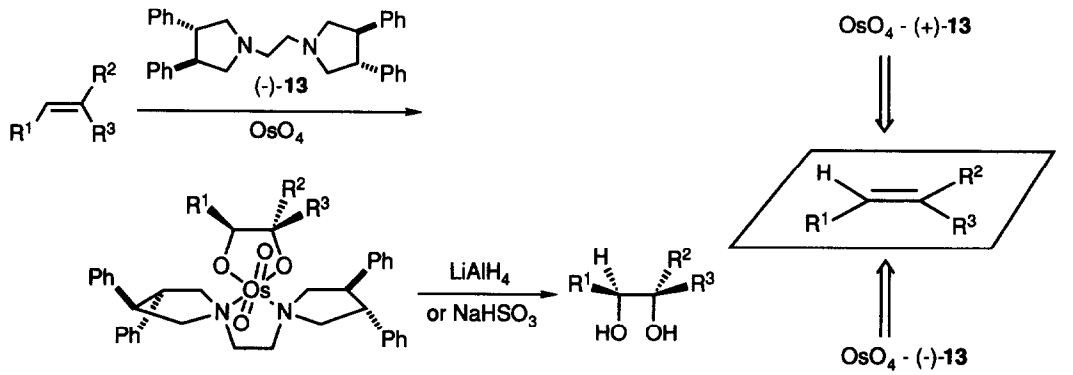


Fig. 2. Enantioselective Dihydroxylation of Olefins with OsO_4 with Chiral Diamine **13**

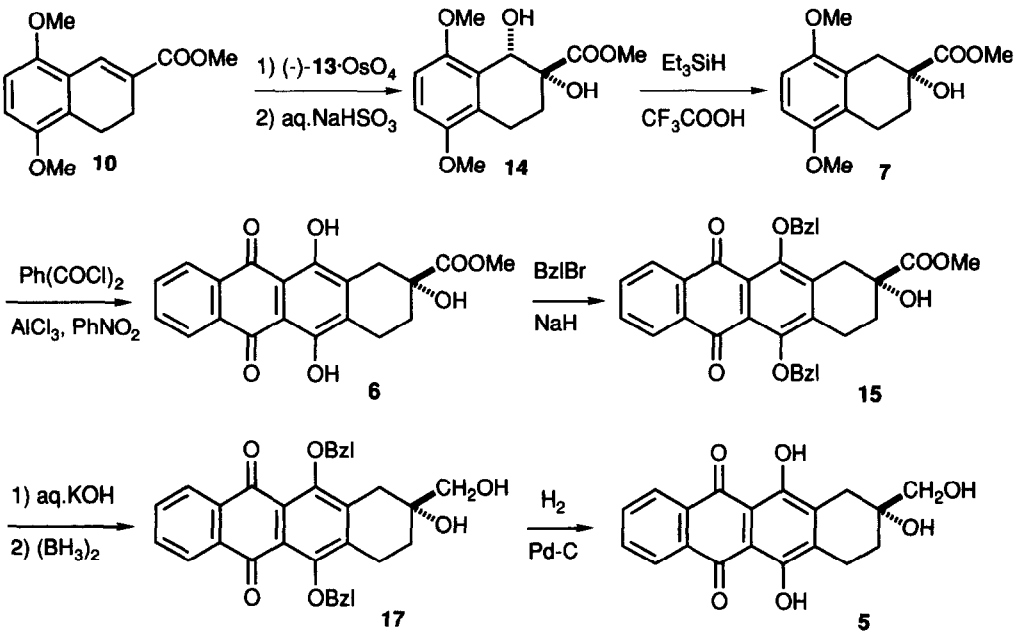
Enantioselective dihydroxylation of dihydronaphthalenes was studied with regard to the effect of vinylic substituents on efficiency in asymmetric induction. Treatment of dihydronaphthalene with osmium tetroxide (1.1 eq) in the presence of (-)-**13** (1.2 eq) in THF (0.01 M) at -110°C for 6 h and the following reductive hydrolysis of the resultant osmate with sodium bisulfite in refluxing aqueous THF, provided the corresponding diol. The optical purity and absolute configuration were determined by their conversion to **7** and **8**. As shown in Table 1, both **10** and **11** were oxidized in satisfactory ee with predicted absolute configuration (Run 1, 2). However, the dihydroxynaphthalene with an ethylene acetal group provided the diol in only 36 % ee (Run 3). The steric size of the substituents apparently affected the enantioselectivity. Since **7** and **8** are the important key intermediates for the synthesis of anthracyclines, this enantioselective dihydroxylation was proved to be effective in constructing the requisite chiral centers of anthracyclines. The successful results in the enantioselective dihydroxylation of **10** and **11** prompted us to accomplish the asymmetric syntheses of (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyldaunomycinone **5** from **10** and (+)-7-dehydroxy-4-demethoxydaunomycinone **4** from **11**.

Table 1. Enantioselective Dihydroxylation of Dihydronaphthalenes by OsO_4 with (-)-**13**

Run	Olefin	$[\alpha]_D^{25}(CHCl_3)$ (°)	ee (%)	yield (%)
1	**10**	-35.3	85	96
2	**11**	-17.6	82	96
3	**12**	-24.5	36	77

Synthesis of 9-Deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyldaunomycinone 5

Total synthesis of (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyldaunomycinone **5** was performed as shown in Scheme 1. The diol **14** obtained by enantioselective dihydroxylation was treated with triethylsilane in trifluoroacetic acid to provide **7** {85 % ee, $[\alpha]_D^{20}$-29.5° ($CHCl_3$); lit.[5] $[\alpha]_D^{20}$-34.5° ($CHCl_3$)} in 94 % yield. Friedel-Crafts condensation was carried out with phthaloyl dichloride-aluminum chloride in nitrobenzene[6] to provide tetracyclic core skeleton **6**. Recrystallization from toluene gave practically optically pure **6** {$[\alpha]_D^{20}$-57.2° ($CHCl_3$); lit.[7] $[\alpha]_D^{25}$-60.0° ($CHCl_3$)} in 68 %. This three-step procedure is the shortest route via asymmetric synthesis to obtain **6**, which is a versatile key intermediate for the synthesis of anthracyclines with correct absolute configuration. We transformed **6** into 9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyldaunomycinone **5**. To overcome the solubility problem, **6** was benzylated with benzyl bromide to obtain **15**. Reduction of ester was performed by successive hydrolysis and diborane reduction. Debenzylation by catalytic hydrogenation afforded optically pure **5** {$[\alpha]_D^{25}$-31° (dioxane), lit.[3k] ($[\alpha]_D^{25}$-32° (dioxane)} in overall 22 % yield from **6**.

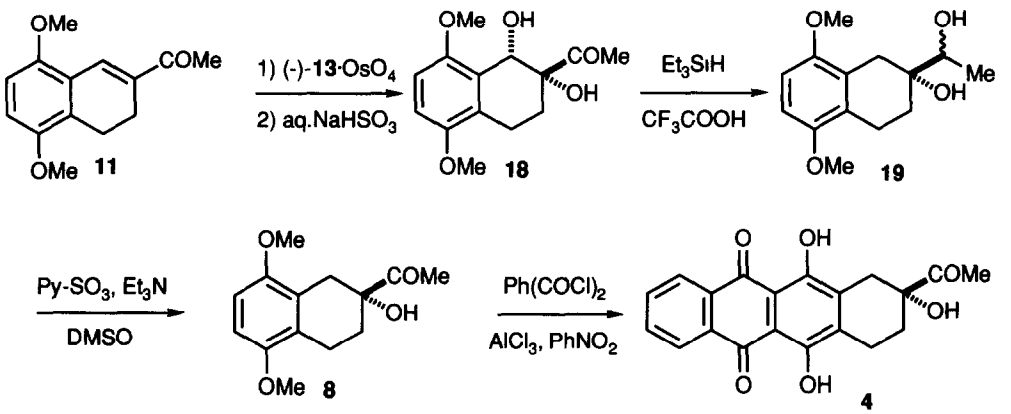


Scheme 1 Asymmetric Synthesis of **5**

Synthesis of 7-Dehydroxy-4-demethoxydaunomycinone 4

Total synthesis of (+)-7-dehydroxy-4-demethoxydaunomycinone **4** was performed as shown in Scheme 2. The diol **18** obtained by enantioselective dihydroxylation was treated with triethylsilane in trifluoroacetic acid to provide **19** as a 3:4 diastereomeric mixture which was then oxidized with sulfur trioxide-pyridine complex and triethylamine in dimethylsulfoxide to afford **8** {82 % ee, $[\alpha]_D^{25}$-39.3° ($CHCl_3$); lit.[5] $[\alpha]_D^{25}$-48.2° ($CHCl_3$)} in 68 % overall yield. Friedel-Crafts condensation with phthaloyl dichloride-aluminum chloride in nitrobenzene[6] to provide the tetracyclic core skeleton **4**. Recrystallization from benzene afforded **4** {$[\alpha]_D^{20}$+150° (dioxane); lit.[9]

$[\alpha]_D^{20}$+157° (dioxane)} in optically pure form. The present four-step asymmetric synthesis in optically pure form constitutes the shortest route to **4**. Elaboration of **4** to 4-demethoxydaunomycin is established technology.[9]



Scheme 2. Asymmetric Synthesis of **4**

Summary

The shortest asymmetric syntheses of (+)-7-dehydroxy-4-demethoxydaunomycinone **4** and (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyldaunomycinone **5** were accomplished via enantioselective dihydroxylation by osmium tetroxide with chiral diamine **13**. These syntheses proved that enantioselective dihydroxylation mediated by the chiral diamine **13** is effective in constructing the requisite chiral centers of the target molecules.

Experimental Section

Melting points were measured using a Büchi 510 melting point apparatus and are not corrected. Optical rotations were taken with a JASCO DIP-370 digital polarimeter. IR spectra were taken with a JASCO IRA-1 infrared spectrometer and expressed in cm^{-1}. ^1H-NMR spectra were taken with a JEOL FX-100 spectrometer at 100MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. MS spetra were taken with a JEOL DX-300 mass spectrometer.

(1*S*,2*R*)-Methyl 1,2,3,4-Tetrahydro-1,2-dihydroxy-5,8-dimethoxynaphthalene-2-carboxylate (14)

To a cooled (-78°C) solution of the chiral diamine (-)-**13** (80 mg, 0.17 mmol) in THF (6 ml) was added a solution of osmium tetroxide (40 mg, 0.16 mmol) in THF (3 ml). A solution of **10** (37 mg, 0.14 mmol)) in THF (5 ml) was added to the bright wine-red solution above at -110°C and the whole was stirred for 6 h at the same temperature. Sodium bisulfite (1.0 g) and water (2 ml) was added to the reaction mixture and the whole was stirred for 10 h under reflux. The reaction mixture was basified with $NaHCO_3$ and concentrated. The residue

was suspended in ethyl acetate (50 ml) and filtered through Celite pad. The water layer of the filtrate was extracted with ethyl acetate (20 ml x2) and combined organic layer was washed with brine and dried over Na_2SO_4. Concentration and following purification by silica gel column chromatography (benzene-ethyl acetate, 10/1 to 1/1) gave chiral diamine **13** (77 mg, 96 %) and diol **14** (40 mg, 95 %) as a caramel of $[\alpha]_D^{25}$-35.3° (c=0.80, $CHCl_3$). IR ($CHCl_3$): 3550, 1740. ^{1}H-NMR ($CDCl_3$) δ: 2.0-2.3 (2H, m, CH_2), 2.8-3.0 (2H, m, CH_2), 3.7-3.9 (11H, m, OCH_3, OH), 5.29 (1H, s, CH), 6.73 (2H, s, Ar). MS m/z: 282 (M^+). HRMS Calcd for $C_{14}H_{18}O_6$: 282.1100. Found: 282.1068.

(2*R*)-Methyl 1,2,3,4-Tetrahydro-2-hydroxy-5,8-dimethoxy-naphthalene-2-carboxylate (7)

A mixture of diol **14** (23 mg, 0.078 mmol), triethylsilane (0.016 ml, 0.093 mmol), and trifluoroacitic acid (0.4 ml) was stirred at 0°C for 20 min. Satd.$NaHCO_3$ (10 ml) and ethyl acetate (30 ml) was added to the mixture and the organic layer was washed with satd.$NaHCO_3$ and brine. After drying over Na_2SO_4 and concentration, the residue was purified by silica gel column chromatography (hexane-ethyl acetate, 20/1) to afford **7** (20.3 mg, 94 %) as a caramel of $[\alpha]_D^{20}$-29.5° (c=2.03, $CHCl_3$), {85 %ee, lit.[5] $[\alpha]_D^{20}$-34.5° (c=1.24, $CHCl_3$)}. IR ($CHCl_3$): 3550, 1730. ^{1}H-NMR ($CDCl_3$) δ: 1.9-2.1 (2H, m, CH_2), 2.7-3.0 (5H, m, CH_2,OH), 3.76 (3H, s, CH_3O), 3.78 (3H, s, CH_3O), 3.82 (3H, s, CH_3O), 6.64 (2H, s, Ar). MS m/z: 267 (MH^+), 266 (M^+), 248 (M^+-H_2O).

(2*R*)-Methyl 1,2,3,4,6,11-Hexahydro-2,5,12-trihydroxy-6,11-dioxonaphthacene-2-carboxylate (6)

To a solution of **7** ($[\alpha]_D^{20}$-29.5° (c=2.03, $CHCl_3$), 85 %ee,10 mg, 0.038 mmol) in nitrobenzene (1 ml) was added a solution of aluminum chloride (10 mg, 0.075 mmol) in nitrobenzene (1 ml) and the mixture was stirred for 30 min at room temperature. Phthaloyl dichloride (7.6 mg, 0.037 mmol) was added to the resulting green solution and the whole was stirred at 100°C for 30 min. 0.2N oxalic acid (10 ml) and ethyl acetate (20 ml) were added to the resulting purple solution and the whole was filtered through Celite pad. The water layer was extracted with ethyl acetate (20 ml x3) and the combined organic layer was washed with satd.$NaHCO_3$ (20 ml x2), brine (20 ml). After drying over $MgSO_4$, concentration followed by silica gel column chromatography (benzene-dichloromethane, 1/4) afforded **6** (11.0 mg, 80 %) as red prisms of mp 198-205°C. $[\alpha]_D^{20}$-51.0° (c=0.10, $CHCl_3$), (85 %ee). Recrystallization from toluene (0.1 ml) at -78°C gave red prisms (9.4 mg, 68 %) of mp 209-210°C. $[\alpha]_D^{20}$-57.2° (c=0.10, $CHCl_3$). {lit.[7] mp 210.5-211.5°C, $[\alpha]_D^{25}$-60.0° (c=0.10, $CHCl_3$)}. IR (KBr): 1730, 1620, 1590. ^{1}H-NMR ($CDCl_3$) δ: 2.0-2.2 (2H, m, CH_2), 2.9-3.1 (5H, m, CH_2,OH), 3.88 (3H, s, CH_3O), 7.8-7.9 (2H, m, Ar), 8.3-8.4 (2H, m, Ar), 13.49 (2H, s, ArOH). MS m/z: 368 (M^+).

(2*R*)-Methyl 5,12-Bis(phenylmethoxy)-1,2,3,4,6,11-hexahydro-2-hydroxy-6,11-dioxonaphthacene-2-carboxylate (15)

A suspension of NaH (60 % dispersion in oil, 25 mg, 0.62 mmol) in THF (1 ml) was added to a solution of **6** (100 mg, 0.27 mmol) in THF (100 ml) at -78°C under Ar atmosphere and allowed to stand at room temperature. Tetra-n-butylammonium iodide (220 mg, 0.60 mmol) and benzyl bromide (0.5 ml, 4.2 mmol) were added to the reaction mixture and the whole was stirred under reflux for 5 h. After adding 10 % HCl (20 ml), the whole was extracted with ethyl acetate (20 ml x3). The combined organic layer was washed with 10 % HCl (20 ml), satd. $NaHCO_3$ (20 ml), brine (20 ml) and dried over $MgSO_4$. Purification by silica gel column

chromatography (benzene-dichloromethane, 1/0 to 1/4) followed by recrystallization from benzene afforded **15** (137 mg, 92 %) as yellow prisms of mp 191°C. $[\alpha]_{546}^{25}$+25° (c=0.12, $CHCl_3$). IR ($CHCl_3$): 1730, 1670. ^{1}H-NMR ($CDCl_3$) δ: 1.8-2.0 (2H, m, CH_2), 2.9-3.0 (5H, m, CH_2,OH), 3.80 (3H, s, CH_3O), 5.03 (4H, s, CH_2), 7.3-7.8 (12H, m, Ar), 8.2-8.3 (2H, m, Ar). MS m/z: 548 (M^+), 530 (M^+-H_2O). *Anal.* calcd for $C_{34}H_{28}O_7$: C, 74.44; H, 5.14. Found: C, 74.28; H, 5.10.

(2*R*)-5,12-Bis(phenylmethoxy)-1,2,3,4,6,11-hexahydro-2-hydroxy-6,11-dioxonaphthacene-2-carboxylic acid (16)

3 % KOH (0.45 ml, 0.24 mmol) was added to a solution of **15** (93 mg, 0.17 mmol) in THF-MeOH (1:1, 4 ml) and the whole was stirred for 1 h. After adding 10 % HCl (5 ml), and the whole was extracted with ethyl acetate (20 ml x3) and washed with water (10 ml x3), brine (10 ml) and dried over $MgSO_4$. Purification by silica gel column chromatography (dichloromethane-methanol, 8/1) afforded **16** (70 mg, 77 %) as a caramel. $[\alpha]_D^{25}$-27° (c=0.55, $CHCl_3$). IR ($CHCl_3$): 1670, 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.8-2.1 (2H, m, CH_2), 2.7-3.1 (4H, m, CH_2), 5.00 (4H, s, CH_2), 6.1 (2H, brs, COOH, OH), 7.0-7.8 (12H, m, Ar), 8.0-8.2 (2H, m, Ar). MS m/z: 534 (M^+). HRMS Calcd for $C_{33}H_{26}O_7$: 534.1679. Found: 534.1631.

(8*R*)-6,11-Bis(phenylmethoxy)-7,8,9,10-tetrahydro-8-hydroxy-8-hydroxymethyl-5,12-naphthacenedione (17)

Diborane (1M in THF, 0.37 ml, 0.37 mmol) was added to a solution of **16** (20 mg, 0.037 mmol) in THF (2 ml) at 0°C and the reaction mixture was stirred for 4 h at room temperature. 10 % HCl (20 ml) was added to the mixture and the whole was stirred for 1 h at room temperature. After extraction with ethyl acetate (20 ml x3), the organic layer was washed with 10 % HCl (20 ml), satd. $NaHCO_3$ (20 ml), brine (20 ml) and dried over Na_2SO_4. Purification by silica gel column chromatography (benzene-ethyl acetate, 3/1) afforded **17** (10 mg, 51 %) as yellow prisms of mp 170°C. $[\alpha]_D^{25}$-37° (c=0.32, $CHCl_3$). IR ($CHCl_3$): 1670, 1400. ^{1}H-NMR ($CDCl_3$) δ: 1.5-2.0 (2H, m, CH_2), 2.7-3.0 (5H, m, CH_2, OH), 3.44 (1H, s, OH), 5.04 (4H, s, CH_2), 7.3-7.6 (10H, m, Ar), 7.7-7.8 (2H, m, Ar), 8.2-8.3 (2H, m, Ar). MS m/z: 521 (MH^+), 520 (M^+), 502 (M^+-H_2O). HRMS Calcd for $C_{33}H_{28}O_6$: 520.1886. Found: 520.1906.

(8*R*)-7,8,9,10-Tetrahydro-6,8,11-trihydroxy-8-hydroxymethyl-5,12-naphthacenedione (9-Deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyldaunomycinone **5**)

A mixture of **17** (5 mg) and palladium on carbon (10 %, 2 mg) in dioxane-ethanol (1:1, 2 ml) was stirred for 12 h at room temperature under hydrogen atmosphere. Filtration followed by purification with silica gel column chromatography (dichloromethane-acetone, 4:1) afforded **5** (2 mg, 61 %) as red prisms of mp 233-236°C. $[\alpha]_D^{25}$-31° (c=0.20, dioxane).{lit.[3k] mp 235-238°C, $[\alpha]_D^{25}$-32° (c=0.06, dioxane).} IR (dioxane): 1630, 1590. ^{1}H-NMR (pyridine-d_5) δ: 2.0-2.5 (2H, m, CH_2), 3.0-4.0 (8H, m, CH_2, OH, singlet at 4.02), 7.6-7.7 (2H, m, Ar), 8.3-8.4 (2H, m, Ar). MS m/z: 340 (M^+), 309 (M^+-CH_2OH), 291 (M^+-CH_2OH-H_2O). HRMS Calcd for $C_{19}H_{16}O_6$: 340.0947. Found: 340.0959.

(1*R*,2*R*)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene-1,2-diol (18)

To a cooled (-78°C) solution of the chiral diamine (-)-**13** (98 mg, 0.21 mmol) in THF (10 ml) was added a solution of osmium tetroxide (48 mg, 0.19 mmol) in THF (1 ml). A solution of **11** (40 mg, 0.17 mmol)) in THF

(1 ml) was added to the bright wine-red solution above at -110°C and the whole was stirred for 6 h at the same temperature. Sodium bisulfite (0.20 g) and water (4 ml) was added to the reaction mixture and the whole was stirred for 14 h under reflux. The reaction mixture was basified with $NaHCO_3$ and concentrated. The residue was suspended in ethyl acetate (50 ml) and filtered through Celite pad. The water layer of the filtrate was extracted with ethyl acetate (20 ml x2) and combined organic layer was washed with brine and dried over Na_2SO_4. Concentration and the following purification by silica gel column chromatography (benzene-ethyl acetate, 10/1 to 1/1) gave chiral diamine **13** (94 mg, 96 %) and diol **18** (44 mg, 96 %) as a caramel of $[\alpha]_D^{25}$-17.6° (c=1.10, $CHCl_3$). IR ($CHCl_3$): 1710, 1600. ^{1}H-NMR ($CDCl_3$) δ: 1.7-2.1 (2H, m, CH_2), 2.39 (3H, s, CH_3CO), 3.7-3.9 (2H, m, CH_2), 3.8-4.0 (8H, m, CH_3O, and OH), 5.31 (1H, s, CH), 6.72 (2H, s, Ar). MS m/z: 267 (MH^+), 266 (M^+). HRMS Calcd for $C_{14}H_{18}O_5$: 266.1154. Found: 266.1174.

(2*R*,1'*R*) and (2*R*,1'*S*)-1,2,3,4-Tetrahydro-2-(1-hydroxyethyl)-5,8-dimethoxynaphthalen-2-ol (19)

A mixture of diol **18** (17 mg, 0.064 mmol), triethylsilane (0.14 ml, 0.088 mmol), and trifluoroacetic acid (0.7 ml) was stirred at -20°C for 12 h. Satd.$NaHCO_3$ (10 ml) and ethyl acetate was added to the mixture and the organic layer was washed with satd. $NaHCO_3$ and brine. After drying over Na_2SO_4 and concentration, the residue was purified by silica gel column chromatography (hexane-ethyl acetate, 3/1) to afford **19** (12.5 mg, 78 %) as a caramel. IR ($CHCl_3$): 3400-3450, 1600, 1480. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (isomer: 1.27) (3H, d, *J*=7Hz, CH_3), 1.5-2.0 (5H, m, CH, CH_2, OH), 2.5-2.9 (4H, m, CH_2), 3.77 (3H, s, CH_3O), 3.78 (3H, s, CH_3O), 6.63 (2H, s, Ar). MS m/z: 253 (MH^+), 252 (M^+). ^{1}H-NMR showed the ratio of isomers was 3:4.

(2*R*)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalen-2-ol (8)

Triethylamine (0.32 ml, 2.3 mmol) and sulfur trioxide-pyridine complex (130 mg, 0.82 mmol) were added to a solution of diol **19** (20 mg, 0.080 mmol) in DMSO (0.2 ml). After adding 10 % HCl (10 ml) and ethyl acetate (50 ml), the organic layer was washed with 10 % HCl (10 ml), satd. $NaHCO_3$ (10 ml x2), brine and dried over Na_2SO_4. Concentration followed by purification by silica gel column chromatography (benzene-ethyl acetate, 7/1) afforded **8** as colorless prisms (8.8 mg, 87 %) of mp 122-125°C. $[\alpha]_D^{25}$-39.3° (c=0.88, $CHCl_3$){82 %ee, lit.[5] mp 128-129°C, $[\alpha]_D^{25}$-48.2° (c=0.982, $CHCl_3$)}. IR ($CHCl_3$): 1710, 1490. ^{1}H-NMR ($CDCl_3$) δ: 1.8-2.1 (2H, m, CH_2), 2.30 (3H, s, CH_3CO), 3.61 (1H, s OH), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.71 (2H, s, Ar). MS m/z: 251 (MH^+), 250 (M^+), 232 (M^+-H_2O).

3,4-Dihydro-5,8-dimethoxy-2-(1-methyl-2,5-dioxan-1-yl)naphthalene (12)

A mixture of ketone **8** (36 mg, 0.16 mmol) , ethylene glycol (96 mg, 1.5 mmol) and p-toluenesulfonic acid (3 mg, 0.016 mmol) in benzene (15 ml) was stirred under reflux azeotropically for 12 h. The reaction mixture was diluted with ethyl acetate (40 ml) and washed with satd.$NaHCO_3$ (10 ml), water (20 ml x2), brine (20 ml) and dried over $MgSO_4$. Concentration followed by purification by silica gel column chromatography (benzene) afforded **12** as a caramel (47 mg, 99 %). IR ($CHCl_3$): 1660, 1600. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, s CH_3), 2.1-2.3 (2H, m, CH_2), 3.78 (6H, s, OCH_3), 3.8-4.0 (4H, m, CH_2), 6.68 (2H, s, Ar), 6.98 (1H, s, CH). MS m/z: 276 (M^+). Calcd for $C_{16}H_{20}O_4$: 276.1361. Found: 276.1384.

(1*S*,2*R*)-3,4-Dihydro-5,8-dimethoxy-2-(1-methyl-2,5-dioxan-1-yl)naphthalene-1,2-diol (20)

To a cooled (-78°C) solution of the chiral diamine (-)-**13** (60 mg, 0.13 mmol) in THF (8 ml) was added a solution of osmium tetroxide (29 mg, 0.12 mmol) in THF (1 ml). A solution of **12** (29 mg, 0.11 mmol)) in THF (2 ml) was added to the bright wine-red solution above at -110°C and the whole was stirred for 2 h at the same temperature and then 4 h at -78°C. Sodium bisulfite (1.0 g) and water (5 ml) was added to the reaction mixture and the whole was stirred for 12 h under reflux. The reaction mixture was basified with $NaHCO_3$ and concentrated. The residue was suspended in ethyl acetate (30 ml) and filtered through Celite pad. The water layer of the filtrate was extracted with ethyl acetate (10 ml x2) and combined organic layer was washed with brine and dried over Na_2SO_4. Concentrated and purification by silica gel column chromatography (dichloromethane-ethyl acetate, 6/1) afforded diol **20** (25 mg, 77 %) as a caramel of $[\alpha]_D^{25}$-24.5° (c=1.24, $CHCl_3$). IR ($CHCl_3$): 3500, 1600. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, s, CH_3), 2.1-2.3 (2H, m, CH_2), 2.7-2.9 (2H, m, CH_2, OH), 3.56 (1H, s, OH), 3.77 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.02 (4H, s, CH_2CH_2), 5.14 (1H, s, CH), 6.70 (2H, s, Ar). MS m/z: 311 (MH^+), 310 (M^+). HRMS Calcd for $C_{16}H_{22}O_6$: 310.1415. Found: 310.1410.

(2*R*)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalen-2-ol (18) from ketal 20

A solution of ketal **20** (19 mg) and 10 % HCl (0.4 ml) in THF (4 ml) was stirred for 2 d at room temperature. The mixture was diluted with ethyl acetate (90 ml) and washed with satd.$NaHCO_3$ (10 ml), brine (20 ml) and dried over Na_2SO_4. Concentration followed by silica gel column chromatography (benzene-ethyl acetate, 10/1) gave **18** (14.3 mg, 88 %) as a caramel of $[\alpha]_D^{25}$-7.7° (c=1.43, $CHCl_3$), (36 %ee based on the optical rotation of Table 1 Run 2).

(8*R*)-8-Acetyl-7,8,9,10-tetrahydro-6,11,8-trihydroxy-5,12-naphthacenedione (4-Demethoxy-7-dehydroxydaunomycinone **4**)

To a solution of **8** ($[\alpha]_D^{25}$-39.3° (c=0.880, $CHCl_3$), 82 % ee, 15 mg, 0.060 mmol) in nitrobenzene (2 ml) was added a solution of aluminum chloride (16 mg, 0.12 mmol) in nitrobenzene (0.5 ml) and the mixture was stirred for 30 min at room temperature. Phthaloyl dichloride (12 mg, 0.060 mmol) was added to the resulting orange solution and the whole was stirred at 100°C for 1 h. 0.2N oxalic acid (10 ml) and chloroform (30 ml) were added to the resulting purple solution and the whole was filtered through celite pad. The water layer was extracted with chloroform (10 ml x3) and the combined organic layer was washed with satd.$NaHCO_3$ (20 ml x2), brine (20 ml). After drying over $MgSO_4$, concentration followed by silica gel column chromatography (benzene-dichloromethane, 1/3) afforded **4** (16 mg, 76 %) as red prisms of mp 209-215°C. $[\alpha]_D^{20}$-73.0° (c=0.14, $CHCl_3$), (81 %ee). Recrystallization from benzene (0.5 ml) gave red prisms (9.0 mg, 53 %) of mp 217-218°C. $[\alpha]_D^{20}$ -86.2° (c=0.10, $CHCl_3$), {(96 %ee, lit.[9] mp 218-219.5°C, $[\alpha]_D^{25}$-90.6° (c=0.106, $CHCl_3$)}. IR (KBr): 3400, 1700, 1620. ^{1}H-NMR ($CDCl_3$) δ: 1.7-2.2 (2H, m, CH_2), 2.39 (3H, s, OCH_3), 2.8-3.5 (4H, m, CH_2), 3.80 (1H, s, OH), 7.7-7.9 (2H, m, Ar), 8.2-8.5 (2H, m, Ar), 13.49 (2H, s, ArOH). MS m/z: 352 (M^+), 309 (M^+-$COCH_3$).

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