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Syntheses of Optically Active 9-Hydroxymethyl- and 9-Carbamoyloxymethyl-9-deacetyl-4-demethoxydaunomycinone[1)]

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Reduction of (*R*)-methyl 2,5,12-trihydroxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene-2-carboxylate ((*R*)-**5**) with lithium tri-*tert*-butoxyaluminum hydride in dimethyl sulfoxide was found to proceed chemoselectively, giving the corresponding alcohol ((*R*)-**11**) in 50—55% yield. The produced (*R*)-alcohol ((*R*)-**11**) could be readily isolated as its acetonide ((*R*)-**12**) or *tert*-butyldimethylsilyl ether ((*R*)-**13**). Stereoselective $C_{7\alpha}$-hydroxylation (the anthracycline numbering) of (*R*)-**13** and urethane formation produced the optically active title compounds, which are the aglycones of unnatural anthracyclines showing excellent anticancer activity.

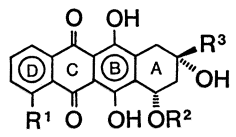
Keywords——anthracyclinone; 9-deacetyl-anthracyclinone; 9-hydroxymethyl-9-deacetyl-4-demethoxydaunomycinone; 9-carbamoyloxymethyl-9-deacetyl-4-demethoxydaunomycinone; chemoselective reduction; dimethyl sulfoxide; lithium tri-*tert*-butoxyaluminum hydride; $C_{7\alpha}$-hydroxylation; isocyanate; urethane formation

The anthracycline antibiotics, represented by adriamycin (**1a**) and daunorubicin (**1b**), are clinically useful antitumor agents which have recently been the subjects of much synthetic endeavor.[2,3)] Attempts have been made to prepare various structural types of congeners by chemical synthesis or by modification of natural anthracyclines with the aim of finding unnatural anthracyclines which show superior therapeutic properties to natural **1a**, **b**.[2,4,5)]

Among synthetically elaborated analogues of **1a**, **b**, 4-demethoxyadriamycin (**1c**) and 4-demethoxydaunorubicin (**1d**) are well known to exhibit better therapeutic indices than **1a**, **b**[6)] and are currently under clinical trials.[7)] We are interested in 9-hydroxymethyl-9-deacetyl-4-demethoxydaunorubicin (**1e**) and 9-carbamoyloxymethyl-9-deacetyl-4-demethoxydaunorubicin (**1f**), originally developed by a research group at Roche,[8)] because of their prominent anticancer activity, comparable with that of **1c**, **d**.

Numerous synthetic routes to the aglycones (**2c**, **d**) of **1c**, **d** have been explored.[3)] However, the number of methods applicable to the preparation of the aglycones (**2e**, **f**) of **1e**, **f**,[8,9)] seems to be quite limited in spite of their promising anticancer activity.[8a)] While **2e**, **f** were first synthesized by employing the Diels–Alder reaction as a key synthetic strategy,[8)] another synthesis of **2e** starting from D-lactose[9)] has recently been reported. The latter synthetic scheme[9)] seems to be superior to the original one[8)] except for the non-stereoselective construction of the C_7-hydroxy group (the anthracycline numbering).

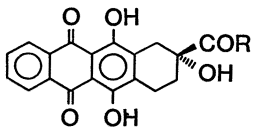
It was previously reported from these laboratories that (*R*)-2,5,12-trihydroxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene-2-carboxylic acid ((*R*)-**3**) could be directly converted to (*R*)-7-deoxy-4-demethoxydaunomycinone ((*R*)-**4**), the key intermediate to **2c**, **d**, through Grignard addition to the acyl imidazole derivative.[10)] Since a large amount of optically pure (*R*)-**3** is available by conventional optical resolution of the readily obtainable racemic acid ((±)-**3**),[10)] we attempted to develop a novel synthetic route to **2e**, **f**, more practical than those so far reported,[8,9)] by converting (*R*)-**3** to the corresponding primary alcohol ((*R*)-**11**).



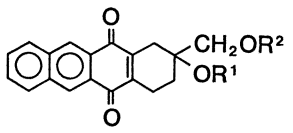
1 : R^2 =

2 : R^2 = H

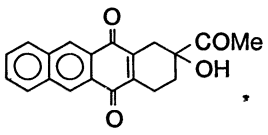
	R^1	R^3
a	OMe	$COCH_2OH$
b	OMe	COMe
c	H	$COCH_2OH$
d	H	COMe
e	H	CH_2OH
f	H	$CH_2OCONHPh$



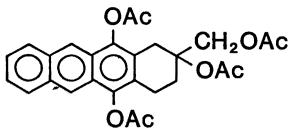
	R
(±)- or (*R*)-**3** :	OH
(±)- or (*R*)-**4** :	Me
(±)- or (*R*)-**5** :	OMe



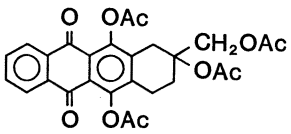
	R^1	R^2
(±)-**6** :	H	H
(±)-**8** :	Ac	Ac



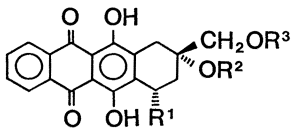
(±)-**7**



(±)-**9**



(±)-**10**



	R^1	R^2	R^3
(±)- or (*R*)-**11** :	H	H	H
(±)- or (*R*)-**12** :	H	CMe_2	
(±)- or (*R*)-**13** :	H	H	$SiMe_2tert$-Bu
(+)-**14** :	OH	H	$SiMe_2tert$-Bu

Chart 1

This report deals with chemoselective reduction of the methyl ester ((*R*)-**5**) derived from (*R*)-**3** and elaboration of ((*R*)-**11**) to **2e**, **f** in a straightforward manner by sequential stereoselective $C_{7\alpha}$-hydroxylation (the anthracycline numbering) and urethane formation.[1)]

Results and Discussion

At the outset, it was expected that chemoselective conversion of (*R*)-**3** to (*R*)-**11** could be simply accomplished by usual reduction of (*R*)-**5** with lithium aluminum hydride because the anthraquinone functionality present in the BCD ring system should be protected from hydride attack by intramolecular chelation with the adjacent aluminum phenoxide. However, this was not the case.

In order to save optically pure (*R*)-**5**, examinations to find the optimum reaction conditions were performed with the racemic ester ((±)-**5**). Thus, when (±)-**5** was treated with lithium aluminum hydride in tetrahydrofuran, both the ester and anthraquinone systems were simultaneously reduced, giving (±)-2-hydroxy-2-hydroxymethyl-5,12-dioxo-1,2,3,4-tetrahydronaphthacene ((±)-**6**) in 68% yield. The structure of (±)-**6** was rigorously determined by comparing its spectral data with those reported for (±)-2-acetyl-2-hydroxy-5,12-dioxo-1,2,3,4-tetrahydronaphthacene ((±)-**7**)[11)] and by successful transformation to (±)-**11** (*vide infra*). Formation of (±)-**6** can be rationalized in terms of the reduction of two carbonyl groups of the anthraquinone moiety to the corresponding aluminum alkoxides followed by

concomitant dehydration and quinone formation during acidic work-up.

Aiming to confirm the structure of (±)-**6** and to explore the synthetic route to (±)-**11**, we examined the conversion of (±)-**6** to (±)-**11** through a reaction sequence similar to that employed for the synthesis of (±)-**4** from (±)-**7**.[11] Usual acetylation of (±)-**6** followed by reductive acetylation of the diacetate ((±)-**8**) with zinc produced the tetraacetate ((±)-**9**). This was derived to (±)-**11** by way of the anthraquinone tetraacetate ((±)-**10**) by successive oxidation and alkaline hydrolysis. Since (±)-**11** showed extremely low solubility in usual organic solvents, it was directly subjected to acetonide formation with 2,2-dimethoxypropane in the presence of *dl*-camphorsulfonic acid. The acetonide ((±)-**12**) having improved solubility could be readily purified by column chromatography. The overall yield of (±)-**12** from (±)-**6** was 34%.

Chemoselective reduction of (±)-**5** was further attempted by the use of diisobutylaluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride in toluene. However, these reactions simply produced complex mixtures of products in which (±)-**11** could not be detected by thin layer chromatography (TLC) analysis. Prior to the reductions of (±)-**5** described above, (±)-**3** was directly subjected to reduction with diborane or with sodium borohydride by way of the corresponding mixed anhydride.[12] However, these attempts were all fruitless.

Finally, reduction with lithium tri-*tert*-butoxyaluminum hydride[13] in dimethyl sulfoxide was found to be quite promising. Treatment of (±)-**5** with lithium tri-*tert*-butoxyaluminum hydride in dimethyl sulfoxide at room temperature for 5 h, followed by acetonide formation of crude (±)-**11**, afforded (±)-**12** in 55% overall yield. When crude (±)-**11** was silylated with 4-*tert*-butyldimethylsilyloxy-3-pentene-2-one in the presence of *p*-toluenesulfonic acid,[14] a 51% yield of the silyl ether ((±)-**13**) could be obtained after purification by column chromatography. As both acetonide formation and silylation, employed to increase the solubility of (±)-**11**, proceeded quantitatively on the pure sample of (±)-**11**, the chemical yields of (±)-**12** and (±)-**13** should reflect those of the reduction step. In this reduction, the starting ester ((±)-**5**) was always recovered in 19—34% yield and formation of a small amount of (±)-**6** was usually observed.[15]

Next, the established reaction conditions were applied to the reduction of optically pure (*R*)-**5**[16] derived from (*R*)-**3**.[10] Treatment of optically pure (*R*)-**5**, $[\alpha]_D^{20}$ −60.0° (chloroform), by the same procedure as described for (±)-**5** produced (*R*)-**12**,[9b] $[\alpha]_D^{20}$ −52.0° (chloroform), and (*R*)-**13**, $[\alpha]_D^{20}$ −40.7° (chloroform), in 53% and 55% overall yields, respectively, by way of crude (*R*)-**11**. Recovery of (*R*)-**5** and formation of (*R*)-**6** were also observed by TLC analysis of the crude reduction product. The racemic and optically active alcohols ((±)- and (*R*)-**11**), $[\alpha]_D^{20}$ −52.0° (chloroform), were regenerated from (±)-**12** and (*R*)-**13**, respectively, by treatment with concentrated hydrochloric acid. Taking into account the increased solubility, the $C_{7\alpha}$-hydroxylation (the anthracycline numbering) was directly attempted using (*R*)-**13** without deprotection.

According to the reported procedure,[17] bromination of (*R*)-**13** was attempted with bromine in carbon tetrachloride, and the bromide formed was treated with aqueous alkaline solution, giving the $C_{7\alpha}$-hydroxylated silyl ether ((+)-**14**) in 43% overall yield. While a small amount of the starting material ((*R*)-**13**) was recovered, formation of the undesired $C_{7\beta}$-epimer could not be detected in the nuclear magnetic resonance (NMR) spectrum of the crude reaction product. Similarly to the case of preparation of **2d** from (*R*)-**4**, highly stereoselective formation of (+)-**14** can be rationalized in terms of attack of the hydroxide anion hydrogen-bonded with the $C_{9\alpha}$-hydroxyl group.[16] Deprotection of (+)-**14** with aqueous hydrofluoric acid in acetonitrile afforded **2e**, $[\alpha]_D^{20}$ +167° (dioxane), in a quantitative yield. The spectral data of this sample were almost identical with those reported.[9b]

Reaction of **2e** with phenyl isocyanate in pyridine at room temperature effected

chemoselective urethane formation to give **2f**, $[\alpha]_D^{20}$ +121° (dioxane), in 52% yield. Various urethanes useful as the aglycones of 9-carbamoyloxymethyl-9-deacetyl-4-demethoxydaunorubicins should be obtainable by the use of isocyanates other than phenyl isocyanates.

As described above, we have succeeded in developing a novel synthetic route to **2e, f**. Due to its brevity and directness, this approach is expected to be applicable to the practical synthesis of these unnatural anthracyclinones.

Experimental[18]

(±)- and (*R*)-Methyl 2,5,12-Trihydroxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene-2-carboxylate ((±)- and (*R*)-5)——The racemic and the optically pure esters ((±)- and (*R*)-**5**) showing mp 207.5—209.5 °C and mp 213—214 °C, $[\alpha]_D^{20}$ −60.0° (*c*=0.110, $CHCl_3$),[16] respectively (lit.,[10] mp 211.5—213.5 °C (for (±)-**5**) and mp 210.5—211.5 °C, $[\alpha]_D^{20}$ −60.0° (*c*=0.10, $CHCl_3$) (for (*R*)-**5**)), were prepared according to the reported method.[1] The NMR spectra of these samples were identical with those reported.[10]

(±)-2-Hydroxy-2-hydroxymethyl-1,2,3,4-tetrahydro-5,12-naphthacenedione ((±)-6)——A suspension of lithium aluminum hydride (264 mg, 7.0 mmol) in THF (20 ml) was added to a solution of (±)-**5** (508 mg, 1.4 mmol) in THF (50 ml) with stirring at room temperature. The mixture was stirred at the same temperature for 16 h, then heated at reflux for 1 h. Further lithium aluminum hydride (110 mg, 2.9 mmol) was added to the reaction mixture, and stirring under reflux was continued for 2 h. After being cooled in an ice bath, the mixture was diluted with saturated aqueous oxalic acid solution (50 ml), stirred for 0.5 h, then extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, EtOAc) to afford (±)-**6** as a dark orange solid (288 mg, 68%). A sample recrystallized from EtOAc showed mp 234—237.5 °C. IR (KBr): 3450, 1655, 1615, 1590, 1400, 1295 cm^{-1}. NMR ($CDCl_3$) δ: 1.4—2.3 (4H, C_3-H_2 and OH×2), 2.6—3.1 (4H, m, C_1-H_2 and C_4-H_2), 3.63, 3.71 (2H, two d, *J*=each 12 Hz, CH_2O), 7.6—7.89 (2H, m, aromatic protons), 7.9—8.2 (2H, m, aromatic protons), 8.60 (2H, two s, C_6-H and C_{11}-H). MS *m/z*: 309 ($[M+1]^+$), 308 (M^+), 277 ($[M-CH_2OH]^+$).

(±)- and (*R*)-3,4-Dihydro-5,12-dihydroxy-2′,2′-dimethyl-spiro[1*H*-naphthaceno-2,4′-dioxolan]-6,11-dione ((±)- and (*R*)-12)——a) Preparation of (±)-**12** from (±)-**6**: A mixture of (±)-**6** (65.4 mg, 0.21 mmol), acetic anhydride (0.5 ml, 5.3 mmol), and DMAP (6.3 mg, 0.052 mmol) in pyridine (0.5 ml) was stirred at room temperature for 2 h, then concentrated *in vacuo*. The residue was dissolved in EtOAc, and this solution was washed successively with 3 M HCl, H_2O, and saturated NaCl. Drying over anhydrous $MgSO_4$, filtration and concentration *in vacuo* gave crude (±)-2-acetoxy-2-acetoxymethyl-1,2,3,4-tetrahydronaphthacene-5,12-dione ((±)-**8**) as a yellow solid (82.5 mg, 99%). NMR ($CDCl_3$) δ: 2.00, 2.14 (6H, two s, CH_3CO×2), 1.7—3.5 (6H, m, C_1-H_2, C_3-H_2, and C_{11}-H_2), 4.50, 4.66 (2H, two d, *J*= each 12 Hz, CH_2O), 7.5—7.8 (2H, m, aromatic protons), 7.9—8.1 (2H, m, aromatic protons), 8.57 (2H, two s, C_6-H and C_{11}-H). This was immediately subjected to the next reduction.

Zinc powder (58.5 mg, 0.89 mmol) was added to a mixture of crude (±)-**8** (82.5 mg, 0.21 mmol) and triethylamine (0.5 ml, 3.6 mmol) in acetic anhydride (2 ml), and the mixture was stirred at room temperature for 1 h. After filtration, the filtrate was concentrated *in vacuo*, and the residue was dissolved in EtOAc. The ethyl acetate solution was washed successively with 3 M HCl, H_2O, and saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*, giving crude (±)-2,5,12-triacetoxy-2-acetoxymethyl-1,2,3,4-tetrahydronaphthacene ((±)-**9**) as a pale yellow solid (109 mg, 100%). NMR ($CDCl_3$) δ: 1.7—3.0 (6H, m, C_1-H_2, C_3-H_2, and C_4-H_2), 2.07, 2.44, 2.45, 2.48 (12H, four s, CH_3CO×4), 4.06 (2H, s, CH_2O), 7.3—7.5 (2H, m, aromatic protons), 7.8—8.1 (2H, m, aromatic protons), 8.23 (2H, s, C_6-H and C_{11}-H).

Chromium trioxide (88 mg, 0.88 mmol) was added to a mixture of (±)-**9** (109 mg, 0.23 mmol) in 80% aqueous AcOH with stirring at 50 °C. The stirring was continued for 3 h while two further lots of chromium trioxide (87 and 41 mg, total 216 mg, 2.2 mmol) were added at intervals of 1 h. The mixture was diluted with EtOAc, and washed successively with H_2O and saturated NaCl. Drying over anhydrous $MgSO_4$, filtration and concentration *in vacuo* gave crude (±)-2,5,12-triacetoxy-2-acetoxymethyl-1,2,3,4-tetrahydronaphthacene-6,11-dione ((±)-**10**) as a solid (93.9 mg, 81%). NMR ($CDCl_3$) δ: 1.7—3.6 (6H, m, C_1-H_2, C_3-H_2, and C_4-H_2), 1.93, 2.11, 2.51, 2.53 (12H, four s, CH_3CO×4), 4.56 (2H, s, CH_2O), 7.6—7.8 (2H, m, aromatic protons), 8.0—8.3 (2H, m, aromatic protons). This was directly subjected to hydrolysis and acetalizaion.

A 2 M aqueous NaOH solution (2 ml) was added to a solution of crude (±)-**10** (93.9 mg, 0.18 mmol) in THF (2 ml), and the mixture was stirred at room temperature for 15 min. After being acidified with 3 M HCl, the mixture was concentrated *in vacuo* to remove THF. Crude (±)-**11** separated as a red solid was collected by filtration (52.4 mg, 83%). This was subjected to acetonide formation by the same procedure as described in b), giving (±)-**12** as a reddish orange solid (27.5 mg, 34% overall from (±)-**6**) after purification by column chromatography. The NMR spectrum of this sample was identical with that of (*R*)-**6** obtained in d).

b) Preparation of (±)-**12** from (±)-**11**: 2,2-Dimethoxypropane (0.1 ml, 0.81 mmol) and CSA (3.8 mg,

0.016 mmol) were added to a solution of (±)-**11** (22.3 mg, 0.066 mmol) in THF (5 ml), and the mixture was stirred at room temperature for 2 h under an argon atmosphere. Further amounts of 2,2-dimethoxypropane (0.1 ml, 0.81 mmol) and CSA (8.0 mg, 0.034 mmol) were added to the reaction mixture, and stirring was continued for 3 h. The mixture was diluted with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, $CHCl_3$) to give (±)-**12** as reddish orange crystals (24.6 mg, 99%). Recrystallization from C_6H_6 gave a pure sample of (±)-**12** as reddish orange crystals, mp 263—265.5 °C. IR (KBr): 3475, 1625, 1590, 1410, 1370, 1265, 1245, 800 cm^{-1}. The NMR spectrum and MS of this sample were identical with those of (*R*)-**12** obtained in d).

c) Preparation of (±)-**12** from (±)-**5** by Way of (±)-**11**: Lithium tri-*tert*-butoxyaluminum hydride[13] (708 mg, 2.9 mmol) was added to a solution of (±)-**5** (68.2 mg, 0.19 mmol) in DMSO (5 ml), and the mixture was stirred at room temperature for 5 h. After being cooled in an ice bath, the mixture was diluted with saturated aqueous oxalic acid solution (10 ml), and extracted with a mixture of THF and EtOAc. The extracts were combined, washed with H_2O, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. The TLC analysis (SiO_2, C_6H_6–AcOEt 1 : 1) revealed that the residue contained (±)-**5** and (±)-**6** (a trace amount) in addition to the desired (±)-**11**. Without separation, this mixture was subjected to acetonide formation by a procedure similar to that described in b). Separation of the crude product by column chromatography gave (±)-**5** as a red solid (22.9 mg, 34%), and (±)-**12** as a red solid (38.6 mg, 55% from (±)-**5**). Spectral comparisons showed that (±)-**5** was identical with an authentic sample.[10] The NMR spectrum of (±)-**12** was identical with that of (*R*)-**12** described in d).

d) Preparation of (*R*)-**12** from (*R*)-**5** by Way of (*R*)-**11**: Lithium tri-*tert*-butoxyaluminum hydride (563 mg, 2.2 mmol) was added to a solution of (*R*)-**5** (54.5 mg, 0.15 mmol) in DMSO (5 ml), and the mixture was stirred at room temperature for 10 h. Treatment of the reaction mixture as described in c) gave crude (*R*)-**11** contaminated with (*R*)-**5** and (*R*)-**6** (a trace amount), after concentration of the combined organic extracts *in vacuo*. Acetonide formation of crude (*R*)-**11** as described for (±)-**11**, followed by separation by column chromatography (SiO_2, $CHCl_3$–EtOAc 20 : 1), gave (*R*)-**12** as reddish orange crystals (29.9 mg, 53%). In this case, separation of (*R*)-**5** was not attempted. Recrystallization from C_6H_6 gave pure (*R*)-**12** as reddish orange crystals, mp 221.5—222.5 °C and $[\alpha]_D^{20}$ −52.0° (c = 0.050, $CHCl_3$) (lit.,[9b] mp 232—234 °C and $[\alpha]_D^{20}$ −52° (c = 0.03, $CHCl_3$)). IR (KBr): 1625, 1590, 1410, 1260, 1240 cm^{-1}. NMR ($CDCl_3$) δ: 1.44 (6H, two s, Me_2C), 1.5—2.3 (2H, m, C_3-H_2), 2.9—3.2 (4H, m, C_1-H_2 and C_4-H_2), 3.95 (2H, s, CH_2O), 7.8—8.0 (2H, m, aromatic protons), 8.3—8.5 (2H, m, aromatic protons), 13.49, 13.50 (2H, two s, OH × 2). MS *m/z*: 381 ($[M+1]^+$), 380 (M^+), 322 ($[M-Me_2CO]^+$), 305 ($[M-Me_2CO_2]^+$). These spectral data were almost identical with those reported.[9b] *Anal.* Calcd for $C_{22}H_{20}O_6$: C, 69.49; H, 5.30. Found: C, 69.43; H, 5.50.

(±)- and (*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((±)- and (*R*)-13)——a) Preparation of (±)-**13** from (±)-**11**: 4-(*tert*-Butyldimethylsilyloxy)-3-pentene-2-one[14] (85.3 mg, 0.40 mmol) and a THF solution of TSA (0.052 M solution, 0.25 ml, 0.013 mmol) were added to a solution of (±)-**11** (30.6 mg, 0.090 mmol) in DMF (3 ml), and the mixture was stirred at room temperature for 10 min under an argon atmosphere. After being diluted with H_2O, the mixture was extracted with CH_2Cl_2 and AcOEt. The organic extracts were combined, washed with H_2O, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, $CHCl_3$–EtOAc 20 : 1) to give (±)-**13** as a reddish orange solid (41.3 mg, 100%). Recrystallization from a mixture of C_6H_6 and C_6H_{14} gave pure (±)-**13** as reddish orange crystals, mp 146—148 °C. IR (KBr): 3600, 3475, 1620, 1590, 1410, 1250, 840 cm^{-1}. The NMR spectrum of this sample was identical with that of (*R*)-**13** described in c).

b) Preparation of (±)-**13** from (±)-**5** by Way of (±)-**11**: Reduction of (±)-**5** (301 mg, 0.82 mmol) with lithium tri-*tert*-butoxyaluminum hydride[13] (5.22 g, 20.5 mmol) in DMSO (30 ml) for 5 h by the same procedure as described for the preparation of (±)-**12** gave a mixture of crude (±)-**11** contaminated with (±)-**5** and (±)-**6** (a trace amount) after evaporation of the organic extracts. This mixture was silylated by the same method as described in a) to afford (±)-**13** as a red solid (190 mg, 51%) after separation by column chromatography. The NMR spectrum of this sample was identical with that of (*R*)-**13** obtained in c). Separation by column chromatography gave (±)-**5** (57 mg, 19%) which was identical with an authentic sample[10] on the basis of spectral comparisons.

c) Preparation of (*R*)-**13** from (*R*)-**5** by Way of (*R*)-**11**: A solution of (*R*)-**5** (253 mg, 0.69 mmol) in DMSO (20 ml) was added to a solution of lithium tri-*tert*-butoxyaluminum hydride[13] (4.31 g, 17.0 mmol) in DMSO (15 ml), and the mixture was stirred at room temperature for 5 h. After being cooled in an ice bath, the mixture was diluted with saturated aqueous oxalic acid solution (50 ml), and extracted with $CHCl_3$. The chloroform extracts were combined, washed with 1 M HCl and H_2O, and dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave crude (*R*)-**11** as a red solid. The TLC analysis (SiO_2, C_6H_6–AcOEt 1 : 1) revealed that this was contaminated with (*R*)-**5** and (*R*)-**6** (a trace amount). Crude (*R*)-**11** was subjected to silylation as described in a). Separation of the crude silylation product by column chromatography gave (*R*)-**5** as an orange solid (67 mg, 26%) and (*R*)-**13** as a red solid (171 mg, 55% from (*R*)-**5**). The NMR spectrum of (*R*)-**5** was identical with that of an authentic sample.[10] Recrystallization from CCl_4 gave an analytical sample of (*R*)-**13** as reddish orange crystals, mp 158.5—159.5 °C and $[\alpha]_D^{20}$ −40.7° (c = 0.059, $CHCl_3$). IR (KBr): 3600, 3450, 1620, 1590, 1410, 1250, 840 cm^{-1}. NMR ($CDCl_3$) δ: 0.13 (6H, two s, Me_2Si), 0.96 (9H, three s, Me_3CSi), 1.5—2.2 (2H, m, C_3-H_2), 2.57 (1H, s, C_2-OH), 2.7—3.1 (4H, m, C_1-H_2 and C_4-

H_2), 3.64 (2H, s, CH_2O), 7.7—7.9 (2H, m, aromatic protons), 8.2—8.4 (2H, m, aromatic protons), 13.27 (2H, two s, OH×2). MS *m/z*: 455 ($[M+1]^+$), 454 (M^+), 397 ($[M-CMe_3]^+$), 349 ($[M-SiMe_2CMe_3]^+$). *Anal.* Calcd for $C_{25}H_{30}O_6Si$: C, 66.05; H, 6.65. Found: C, 66.09; H, 6.94.

(±)- and (*R*)-2,5,12-Trihydroxy-2-hydroxymethyl-1,2,3,4-tetrahydronaphthacene-6,11-dione ((±)- and (*R*)-11)——a) Preparation of (±)-**11** from (±)-**12**: Concentrated hydrochloric acid (1 ml) was added to a suspension of (±)-**12** (107 mg, 0.28 mmol) in THF (3 ml), and the mixture was stirred at 60 °C for 1 h. After being diluted with H_2O, the aqueous mixture was extracted with a mixture of THF and EtOAc. The organic extracts were combined, washed with H_2O, then dried over anhydrous $MgSO_4$. Filtration and concentration *in vacuo* gave (±)-**11** as a red solid (94 mg, 98%). Recrystallization of this sample from a mixture of THF and C_6H_6 gave pure (±)-**11** as red crystals, mp 267—269 °C. IR (KBr): 3450, 1620, 1585, 1410, 1250 cm^{-1}. The NMR spectrum of this sample was identical with that of (*R*)-**11** described in b).

b) Preparation of (*R*)-**11** from (*R*)-**13**: Concentrated hydrochloric acid (0.5 ml) was added to a solution of (*R*)-**13** (71.0 mg, 0.16 mmol) in THF (2 ml), and the mixture was stirred at room temperature for 0.5 h. After being diluted with H_2O, the mixture was worked up by a procedure similar to that described in a), giving (*R*)-**11** as an orange solid (55.3 mg, 100%) after concentration of the organic extracts *in vacuo*. Recrystallization from a mixture of THF and C_6H_6 gave pure (*R*)-**11** as orange crystals, mp 264.5—266.5 °C and $[\alpha]_D^{20}$ −52.0° (*c*=0.050, dioxane) (lit.,[9b] mp 235—238 °C and $[\alpha]_D^{20}$ −32° (*c*=0.062, dioxane)). IR (KBr): 3425, 1620, 1590, 1420, 1405, 1280, 1250 cm^{-1}. NMR (DMSO-d_6) δ: 1.64—1.80 (2H, m, C_3-H_2), 2.68 (2H, s, C_1-H_2), 2.70—2.85 (2H, m, C_4-H_2), 3.36—3.45 (2H, m, CH_2O), 4.24 (1H, s, C_2-OH), 4.60 (1H, t, *J*=5 Hz, CH_2OH), 7.88—7.94 (2H, m, aromatic protons), 8.17—8.23 (2H, m, aromatic protons), 13.29 (2H, two s, OH×2). MS *m/z*: 341 ($[M+1]^+$), 340 (M^+), 309 ($[M-CH_2OH]^+$), 291 ($[M-CH_2OH-H_2O]^+$). These spectral data were very similar to those reported.[9b] *Anal.* Calcd for $C_{19}H_{16}O_6 \cdot 1/10H_2O$: C, 66.70; H, 4.77. Found: C, 66.70; H, 4.88.

(2*S*,4*S*)-(+)-2-(*tert*-Butyldimethylsilyloxy)methyl-2,4,5,12-tetrahydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione ((+)-14)——A solution of bromine in CCl_4 (0.089 M solution, 4.0 ml, 0.36 mmol) was added to a solution of (+)-**13** (163 mg, 0.36 mmol) in CCl_4 (35 ml) over 15 min with stirring in an ice bath under an argon atmosphere and irradiation with a tungsten lamp. After 1 h and 1.5 h, further amounts of a solution of bromine in CCl_4 (each 0.5 ml; total 5.0 ml, 0.45 mmol) were added, and the reaction was continued for 2 h. The mixture was diluted with 0.3 M NaOH (15 ml) in an ice bath, and stirred at the same temperature for 15 min. The alkaline mixture was cooled in an ice bath, diluted with H_2O, neutralized with 3 M HCl, then extracted with $CHCl_3$. The chloroform extracts were combined, washed with H_2O, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, $CHCl_3$, then $CHCl_3$–EtOAc 30:1), giving pure (+)-**14** as a reddish orange solid (72.5 mg, 43%), mp 138—147 °C $[\alpha]_D^{20}$ +135° (*c*=0.055, $CHCl_3$). A small amount of (+)-**13** (12.3 mg, 8%) was also recovered. IR (KBr): 3480, 1625, 1590, 1430, 1415, 1375, 1255, 1070, 840, 780 cm^{-1}. NMR ($CDCl_3$) δ: 0.13 (6H, two s, Me_2Si), 0.95 (9H, three s, Me_3CSi), 1.92 (1H, dd, *J*=15.0, 5.4 Hz, C_{3ax}-H), 2.29 (1H, ddd, *J*=15.0, 1.8, 1.7 Hz, C_{3eq}-H), 2.68 (1H, d, *J*=18.9 Hz, C_{1ax}-H), 3.13 (1H, dd, *J*=18.9, 1.7 Hz, C_{1eq}-H), 3.32 (1H, s, C_2-OH), 3.62, 3.64 (2H, two d, *J*=each 9.6 Hz, CH_2O), 3.90 (1H, d, *J*=7.0 Hz, C_4-OH), 5.28 (1H, ddd, *J*=7.0, 5.4, 1.8 Hz, C_4-H), 7.7—7.9 (2H, m, aromatic protons), 8.2—8.4 (2H, m, aromatic protons), 13.35 and 13.61 (2H, two s, C_5-OH and C_{12}-OH or *vice versa*). MS *m/z*: 471 ($[M+1]^+$), 470 (M^+), 434 ($[M-2H_2O]^+$), 395 ($[M-2H_2O-Me_3C]^+$), 377 ($[M-SiMe_2CMe_3]^+$).

(2*S*,4*S*)-(+)-2,4,5,12-Tetrahydroxy-2-hydroxymethyl-1,2,3,4-tetrahydronaphthacene-6,11-dione ((+)-2e)——An MeCN solution of hydrogen fluoride (0.68 M solution, 1 ml, 0.68 mmol) was added to a solution of (+)-**14** (66.1 mg, 0.14 mmol) in MeCN (5 ml), and the mixture was stirred at room temperature for 0.5 h. After being diluted with H_2O, the mixture was extracted with a mixture of THF and EtOAc. The organic extracts were combined, washed with H_2O, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*, giving (+)-**2e** as a reddish orange solid (52.2 mg, 100%). Recrystallization from C_6H_6 gave pure (+)-**2e** as reddish orange crystals, mp 201.5—204.5 °C, $[\alpha]_D^{20}$ +167° (*c*=0.024, dioxane) and $[\alpha]_D^{30}$ +111° (*c*=0.052, THF) (lit.,[8a] $[\alpha]_D^{20}$ +131.3° (*c*=0.1, dioxane): lit.,[9b] mp 230 °C, $[\alpha]_D$ +95° (*c*=0.05, THF)).[19] IR (KBr): 3460, 1625, 1590, 1415, 1405, 1375, 1265, 1240, 1050, 985 cm^{-1}. NMR (pyridine-d_5) δ: 2.31 (1H, dd, *J*=14.2, 4.4 Hz, C_{3ax}-H), 2.72 (1H, ddd, *J*=14.2, 2.1, 1.8 Hz, C_{3eq}-H), 3.24 (1H, d, *J*=18.9 Hz, C_{1ax}-H), 3.68 (1H, dd, *J*=18.9, 1.8 Hz, C_{1eq}-H), 4.08, 4.10 (2H, d, *J*=each 10.8 Hz, CH_2O), 5.69 (1H, dd, *J*=4.4, 2.1 Hz, C_4-H), 6.49 (3H, br s, C_2-OH, C_4-OH, and CH_2OH), 7.70—7.77 (2H, m, aromatic protons), 8.33—8.40 (2H, m, aromatic protons), 13.79, 14.08 (2H, two s, C_5-OH and C_{12}-OH or *vice versa*). MS *m/z*: 357 ($[M+1]^+$), 356 (M^+), 338 ($[M-H_2O]^+$), 320 ($[M-2H_2O]^+$), 308 ($[M-H_2O-CH_2OH+1]^+$), 307 ($[M-H_2O-CH_2OH]^+$). These spectral data were almost identical with those reported.[9b] *Anal.* Calcd for $C_{19}H_{16}O_7 \cdot 1/4H_2O$: C, 63.24; H, 4.61. Found: C, 63.43; H, 4.55.

(2*S*,4*S*)-(+)-2,4,5,12-Tetrahydroxy-2-phenylcarbamoyloxymethyl-1,2,3,4-tetrahydronaphthacene-6,11-dione ((+)-2f)——A pyridine solution of phenyl isocyanate (0.19 M solution, 0.44 ml, 0.082 mmol) was added to a solution of (+)-**2e** (29.0 mg, 0.081 mmol) in pyridine (1.5 ml), and the mixture was stirred at room temperature for 3 h. After further amounts of a pyridine solution of phenyl isocyanate (0.19 M solution) were added three times to the reaction mixture every 2 h (0.22 ml×2, then 0.11 ml×1, total 0.99 ml, 0.19 mmol), the stirring was continued at room temperature for 5 h. After concentration *in vacuo*, the residue was dissolved in EtOAc, and the insoluble materials

were removed by filtration. The filtrate was washed successively with 3 M HCl and H_2O, dried over anhydrous $MgSO_4$, filtered, then concentrated *in vacuo*. The residue was twice purified by column chromatography (SiO_2, C_6H_6–EtOAc 1 : 1) to afford (+)-**2f** as an orange solid (20.3 mg, 52%). An analytical sample was obtained as orange crystals by recrystallization from Et_2O–C_6H_{14}, mp 222—223 °C and $[\alpha]_D^{20}$ +121° (c=0.053, dioxane), (lit.,[8b] mp 225—226 °C and $[\alpha]_D^{20}$ +136.0° (c=0.05, dioxane)).[19] IR (KBr): 3450, 1735, 1715, 1625, 1590, 1440, 1235 cm^{-1}. NMR ($CDCl_3$) δ: 1.97 (1H, dd, J=15.0, 5.4 Hz, C_{3ax}-H), 2.46 (1H, ddd, J=15.0, 2.0, 1.7 Hz, C_{3eq}-H), 2.73 (1H, d, J=18.9 Hz, C_{1ax}-H), 3.30 (1H, dd, J=18.9, 1.7 Hz, C_{1eq}-H), 3.69 (1H, d, J=4.6 Hz, C_4-OH), 3.96 (1H, s, C_2-OH), 4.33 (2H, s, CH_2O), 5.36 (1H, ddd, J=5.4, 4.6, 2.0 Hz, C_1-H), 6.88 (1H, br s, NH), 7.0—7.5 (2H, m, aromatic protons), 7.75—8.0 (2H, m, aromatic protons), 13.32, 13.58 (2H, two s, C_5-OH and C_{12}-OH, or *vice versa*). MS m/z: 476 ($[M+1]^+$), 475 (M^+), 356 ($[M-H_2O-1]^+$), 338 ($[M-2H_2O+1]^+$), 320 ($[M-H_2O-C_6H_5NHCOO-1]^+$). *Anal.* Calcd for $C_{26}H_{21}NO_8 \cdot 1/3H_2O$: C, 64.86; H, 4.54; N, 2.91. Found: C, 64.91; H, 4.43; N, 2.84.

References and Notes

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16) The optical purity of (*R*)-**5** could be readily estimated by measuring the NMR spectrum of the dimethyl ether of (*R*)-**5** in the presence of a chiral shift reagent. See ref. 10.
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18) All melting points were determined with a Yamato MP-21 melting point apparatus and are uncorrected. Infrared (IR) spectral measurements were performed on a JASCO A-202 diffraction grating infrared spectrometer. NMR spectra were measured with a Varian EM-390 spectrometer (90 MHz), a Hitachi R-90H spectrometer (90 MHz), and a Bruker AM-400 spectrometer (400 MHz). All signals were expressed as ppm downfield from tetramethylsilane (TMS) used as an internal standard (δ-value). Mass spectra (MS) were taken with a Hitachi RMU-6MG mass spectrometer. Measurements of optical rotations were carried out with a

Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 was used as an adsorbent for column chromatography. All reactions and measurements were carried out in anhydrous solvents. In particular, tetrahydrofuran, ether, and dioxane were freshly distilled from sodium benzophenone ketyl, and dichloromethane was freshly distilled from calcium hydride. The following abbreviations are used for reagents and solvents: acetic acid (AcOH), acetone (Me_2CO), acetonitrile (MeCN), benzene (C_6H_6), *dl*-camphorsulfonic acid (CSA), carbon tetrachloride (CCl_4), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), 4-dimethylaminopyridine (DMAP), dimethyl sulfoxide (DMSO), dimethylformamide (DMF), ether (Et_2O), ethyl acetate (EtOAc), hexane (C_6H_{14}), tetrahydrofuran (THF), *p*-toluenesulfonic acid (TSA).

19) Because of the extremely low solubility and characteristic reddish orange color of the sample, measurement of optical rotation was carried out at a low concentration. This might be the reason why the observed rotation value is fairly different from the reported value.