Asymmetric Synthesis of Anthracyclinones: Regio- and Stereoselective Synthesis of (−)-7-Deoxydaunomycinone through Direct Asymmetric Introduction of an Alkynyl Unit into C9 Ketone

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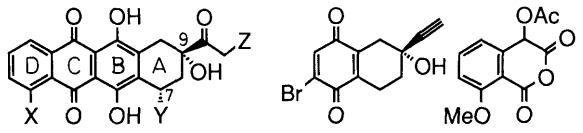
A new chiral AB-building block (5) for preparing optically active anthracyclinones was synthesized *via* compound 13a, which was obtained by the stereoselective nucleophilic addition of (trimethylsilyl)ethynylmagnesium chloride to the chiral 6-bromo-1-oxo-β-tetralone 1-acetal (12) derived from (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol. Synthesis of (−)-7-deoxydaunomycinone [(−)-4] was achieved through a regiospecific condensation of 5 and 4-acetoxy-8-methoxyhomophthalic anhydride (18). The optical purity (100% ee) of (−)-4 was unambiguously confirmed by high performance liquid chromatographic analysis of (±)-4 and (−)-4 on a chiral column and also by proton nuclear magnetic resonance examination of the methylated compounds, (±)- and (−)-21, using the chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) [Eu(tfc)$_3$].

Keywords asymmetric synthesis; chiral acetal; (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol; stereoselective nucleophilic addition; regiospecific cycloaddition; anthracyclinone; (−)-7-deoxydaunomycinone

The anthracycline antibiotics are of interest as potential antitumor agents against a broad spectrum of human cancers.[1] The daunomycin family (daunomycin, adriamycin, and carminomycin) is one of the most clinically useful groups of drugs, possessing a chiral A ring with a 9-substituted 7,9-*cis*-dihydroxy functionality as a characteristic structural feature. A large number of studies have been directed toward syntheses of their aglycones, daunomycinone (**1**), adriamycinone (**2**), and carminomycinone (**3**), during the past decade.[2] Recently, much effort has been focused on the syntheses of the optically active aglycones to avoid the complex and wasteful separation of diastereomeric products in the final glycosidation step and also to economize on the use of the valuable sugar moiety. Asymmetric synthesis is one of the choices and many methodologies such as asymmetric reduction,[3a] asymmetric epoxidation,[3b] asymmetric bromolactonization,[3c] and asymmetric osmium tetroxide oxidation[3d] have been developed so far, mainly addressed to constructing the chiral tertiary alcohol moiety at the C9 position.[4] Recently we have briefly reported the synthesis of (−)-7-deoxydaunomycinone (**4**),[5] a late-stage precursor for (+)-daunomycinone (**1**). Our synthesis includes an effective preparation of a new chiral AB-building block (**5**), *via* a novel construction of the C9 (anthracycline numbering) chiral tertiary alcohol moiety through a diastereoselective nucleophilic addition to C9 ketone and a regioselective coupling reaction of **5** with the CD-synthon (**18**). Here we present a full account of this work.



1 : X=OMe, Y=OH, Z=H
2 : X=OMe, Y=Z=OH
3 : X=Y=OH, Z=H
4 : X=OMe, Y=Z=H

5 18

Chart 1

Synthesis of the Chiral AB Synthon, (6*R*)-2-Bromo-6-ethynyl-6-hydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (5) The chiral AB synthon (**5**) was synthesized from **13a** obtained by nucleophilic addition of (trimethylsilyl)ethynylmagnesium chloride to the chiral 6-bromo-1-oxo-β-tetralone 1-acetal (**12**).

The acetal (**12**) was synthesized as shown in Chart 2. The known bromo acid (**6**)[6] was cyclized under acidic conditions to give the 6-bromo-1-tetralone derivative (**7**). Demethylation of **7** with aluminum chloride in dichloromethane gave **8**, which was subjected to protection reaction of the phenolic hydroxy functions to afford **9**. Treatment of **9** under Moriarty's conditions {phenyl iodine(III) diacetate [PhI(OAc)$_2$/KOH/MeOH}[7] gave the labile α-hydroxydimethylacetal (**10**), which is easily hydrolyzed on a silica gel column and was used in the subsequent reaction without purification. Transacetalization of **10** with 1.1 eq of (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol[8] in the presence of a catalytic amount of camphorsulfonic acid (CSA) gave the α-hydroxy acetal (**11**), which was converted to the chiral acetal (**12**) by modified pyridinium dichromate (PDC)

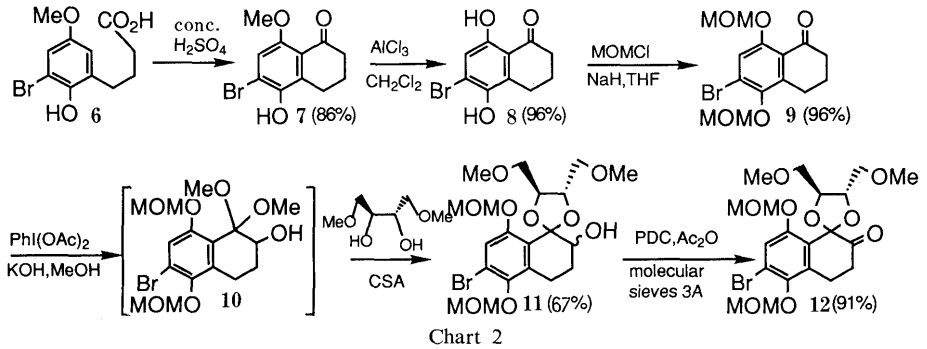
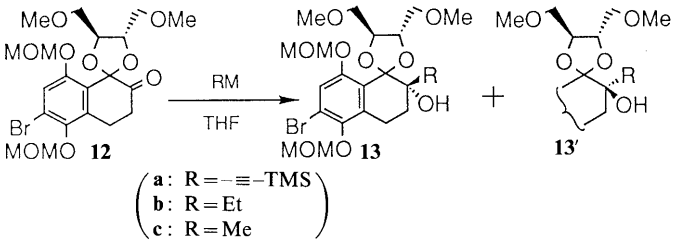


Chart 2

oxidation.[9]

The results of nucleophilic addition of organometallics to the chiral 6-bromo-1-oxo-β-tetralone 1-acetal (**12**) are summarized in Table I.[10] The reaction of **12** with some Grignard reagents (5 eq), which have alkynyl or alkyl units (R=–≡–TMS, Et, Me) being convertible to the side chains (–$COCH_3$, –$COCH_2OH$, Et, Me) observed in natural anthracyclines[11] such as daunomycin, adriamycin, rhodomycins, and feudomycins, was carried out in tetrahydrofuran (THF) (runs 1—3). Extremely high diastereoselectivity (100% ee) was observed in every run. An authentic diastereomeric mixture (**13a**:**13'a**=3:1) for comparison with the product in run 1 was obtained by the reaction of **12** with (trimethylsilyl)ethynyllithium (run 4). The purity of **13b** and **13c** was determined by proton nuclear magnetic resonance (^{1}H-NMR) (500 MHz). The stereochemistry of the products was tentatively assigned from our preliminary results[10] and that of **13a** and **13b** was unambiguously determined by the conversion of **13a** to (–)-7-deoxydaunomycinone and by correlation between **13a** and **13b**.

TABLE I. Nucleophilic Addition of RM to **12**



Run	RM	Temp. (°C)	Yield (%)	Ratio (13:13')	Product
1	TMS–≡–MgCl	–23—r.t.	96	100:0	**13a** only
2	EtMgCl	–78—–23	99	100:0	**13b** only
3	MeMgBr	–78—–23	96	100:0	**13c** only
4	TMS–≡–Li	–78	81	75:25	**13a**+**13'a**

Conversion of **13a** to the bromoquinone (**5**) was achieved as shown in Chart 3. Detrimethylsilylation of **13a** under alkaline conditions afforded **14**, which was converted to **15** by acid hydrolysis. Acetylation of **15** was carried out in the presence of a catalytic amount of 4-dimethylaminopyridine (4-DMAP) to give the triacetate (**16**). Sodium borohydride ($NaBH_4$) reduction of **16** in aqueous THF[12] followed by alkaline treatment afforded the triol (**17**). Without prior acetylation of the C2 alcohol, the reduction of the C1 ketone resulted in the formation of the C1 secondary hydroxy functionality. The triol (**17**) was relatively unstable and immediately oxidized with ceric ammonium nitrate (CAN) without further purification to give the chiral bromoquinone (**5**). The complete chiral integrity of the tertiary alcohol moiety during the conversion of **13a** to **5** was deduced from the successful synthesis of optically pure (–)-7-deoxydaunomycinone (*vide infra*).

Synthesis of (–)-7-Deoxydaunomycinone (4) The coupling reaction of 4-acetoxy-8-methoxyhomophthalic anhydride (**18**)[13] with **5** was carried out in the presence of sodium hydride (NaH) in THF. The coupled product **19** was obtained regioselective by [4+2]cycloaddition of **18** followed by extrusion of carbon dioxide and hydrogen bromide.[14] Treatment of **19** with mercuric oxide under acidic conditions afforded **20**, which was deacetylated with aqueous trifluoroacetic acid to give (–)-7-deoxydaunomycinone [(–)-(**4**)] (Chart 4). The melting point (mp) and spectral data (infrared (IR), ^{1}H-NMR) of (–)-**4** were identical with those of authentic (±)-**4** prepared earlier by us[13] and the specific rotation of ours was in good agreement with the reported value [mp 232—233.5 °C, $[\alpha]_D$ –87.4° (c=0.093, $CHCl_3$); lit.[15] mp 229—233.5 °C,[12] $[\alpha]_D$ –87.5° (c=0.094, $CHCl_3$)].

The optical purity (100% ee) of (–)-**4** was unambiguously confirmed[16] by high-performance liquid chromatographic (HPLC) analysis of (–)- and (±)-**4** using a chiral column (Daicel Chiral Cel OA) (Fig. 1) and by ^{1}H-

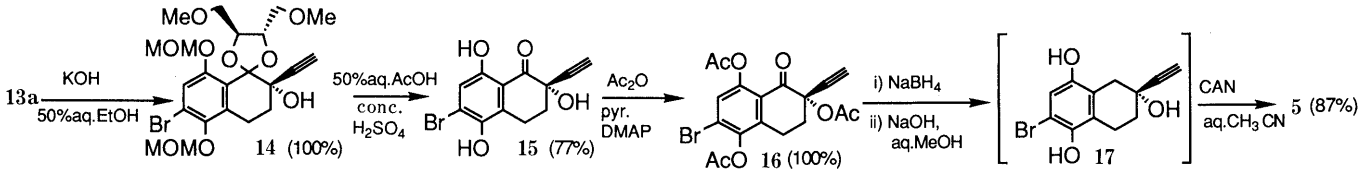
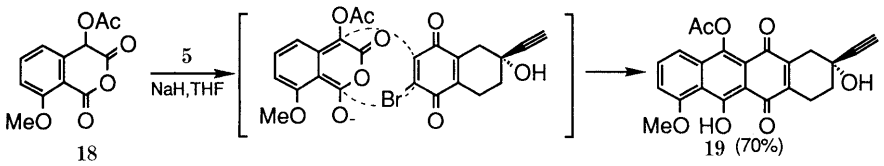


Chart 3



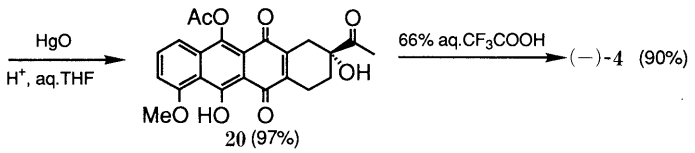


Chart 4

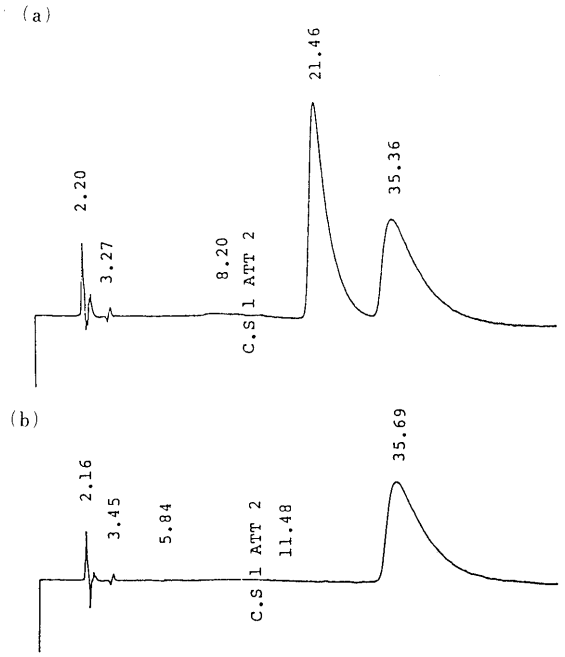


Fig. 1. HPLC Analyses of (±)- and (−)-7-Deoxydaunomycinone
(a) (±)-7-Deoxydaunomycinone. (b) (−)-7-Deoxydaunomycinone.

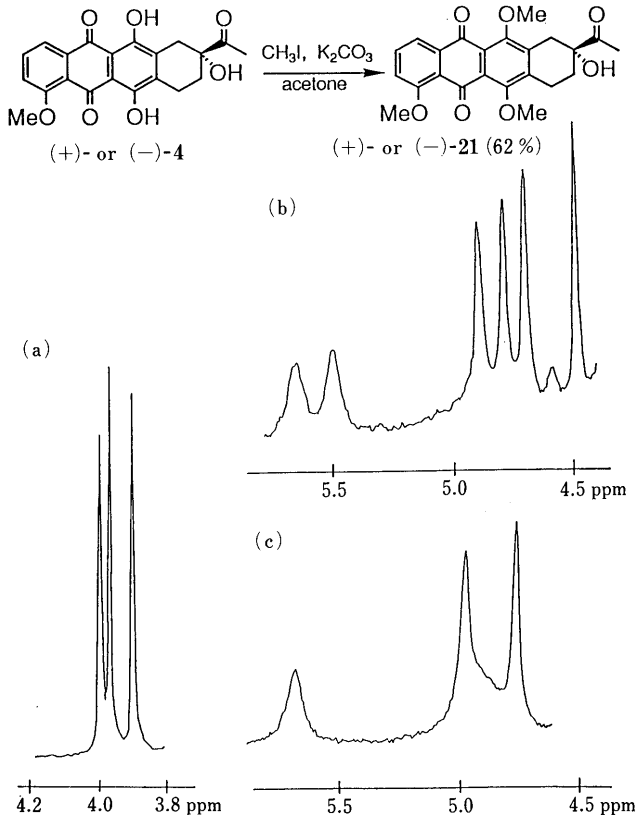


Fig. 2. Partial ^{1}H-NMR Spectra (90 MHz, $CDCl_3$)
(a) **21** only. (b) (±)-**21** + Eu(tfc)$_3$. (c) (−)-**21** + Eu(tfc)$_3$.

NMR experiments on (−)-**21** and (±)-**21**, obtained by methylation of **4** according to Terashima's procedure,[17] using the chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) [Eu(tfc)$_3$]; (±)-**21** showed six methoxy resonances, whereas (−)-**21** showed three singlet signals in place of these resonances (Fig. 2).

Our asymmetric synthesis is, to our knowledge, the only method so far available for the synthesis of optically active anthracyclinone *via* asymmetric addition to the C9 (anthracycline numbering) ketone and has the following advantages: i) direct asymmetric introduction of the required alkynyl or alkyl units to the C9 position; ii) the use of acetal as a chiral auxiliary, which promises further transformation as a synthetic equivalent of the versatile carbonyl function. Therefore, this methodology should open an effective route to various types of anthracyclinones, and studies along this line are in progress.[18]

Experimental

The following instruments were used to obtain physical data: specific rotation, Perkin-Elmer 241 polarimeter; IR spectra, JASCO IRA-1 spectrometer; ^{1}H-NMR spectra, Hitachi R-22 (90 MHz), JEOL JNM-FX 90Q FT-NMR (90 MHz) or JEOL LNM-GX 500 FT-NMR (500 MHz) spectrometer (with tetramethylsilane as an internal standard); low- and high-resolution mass spectra (MS), JEOL JMS D-300 mass spectrometer (with a direct inlet system). A JASCO TRIROTAR-II high-pressure liquid chromatography (UV detector) was used for HPLC analysis. E. Merck silica gel (0.063—0.200 mm, 70—230 mesh ASTM) for column chromatography and E. Merck TLC plates pre-coated with Silica gel 60F_{254} for preparative thin layer chromatography (TLC) (0.5 mm) and TLC detection (0.2 mm) were used. Specific rotation was measured at 20 °C in $CHCl_3$, unless otherwise mentioned. All melting points are uncorrected.

6-Bromo-5-hydroxy-8-methoxy-1-oxotetralin (7) A mixture of **6** (19.4 g, 67.1 mmol) and concentrated H_2SO_4 (80 ml) was stirred for 1 h at 80—90 °C under a nitrogen atmosphere. The mixture was cooled to room temperature, diluted with water, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using CH_2Cl_2 as an eluent to give **7** (15.5 g, 86%). Yellow plates (hexane–CH_2Cl_2), mp 133—134 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3545, 1678, 1463, 1085. ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.22 (m, 2H, –C$\underline{H}_2$–), 2.54 (t, 2H, J=6.4 Hz, –C$\underline{H}_2$–), 2.94 (t, 2H, J=6.4 Hz, –C$\underline{H}_2$–), 3.84 (s, 3H, –OC$\underline{H}_3$), 5.52 (s, 1H, –O$\underline{H}$), 6.97 (s, 1H, aromatic proton). Exact MS Calcd for $C_{11}H_{11}Br^{79}O_3$+H: 270.9926. Found: 270.9946.

6-Bromo-5,8-dihydroxy-1-oxotetralin (8) $AlCl_3$ (7.3 g, 55.2 mmol) was added to a stirred solution of **7** (5.0 g, 18.4 mmol) in dry CH_2Cl_2 (200 ml) at 0 °C and the mixture was stirred overnight at room temperature under a nitrogen atmosphere. The reaction was quenched with saturated aqueous oxalic acid at 0 °C and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using hexane–ether (2 : 1) as an eluent to give **8** (4.5 g, 96%). Yellow plates ($CHCl_3$), mp 153—154 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3547, 1640, 1609, 1445. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.22 (m, 2H, –C$\underline{H}_2$–), 2.67 (t, 2H, J=5.9 Hz, –C$\underline{H}_2$–), 2.94 (t, 2H, J=5.9 Hz, –C$\underline{H}_2$–), 5.29 (s, 2H, –O$\underline{H}$ ×2), 7.01 (s, 1H, aromatic proton). Exact MS Calcd for $C_{10}H_9Br^{79}O_3$: 255.9736. Found: 255.9753. Calcd for $C_{10}H_9Br^{81}O_3$: 257.9716. Found: 257.9727.

6-Bromo-5,8-dimethoxymethyloxy-1-oxotetralin (9) A solution of **8** (4.5 g, 17.5 mmol) in dry THF (55 ml) was added dropwise to a stirred suspension of NaH (2.3 g, 60% in oil, 57 mmol) in dry THF (5 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 20 min at room temperature, then chloromethyl methyl ether (5.3 ml, 70 mmol) was added slowly at 0 °C and the resulting solution was stirred for 1 h at room temperature. The reaction was quenched with water and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using hexane–ether (1 : 2) as an eluent to give **9** (5.8 g, 96%). White plates (CH_2Cl_2), mp 52—54 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2960, 1680, 1563, 1156, 970. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.25 (m, 2H, –C$\underline{H}_2$–), 2.64 (t, 2H, J=6.8 Hz, –C$\underline{H}_2$–), 3.06 (t, 2H, J=6.8 Hz, –C$\underline{H}_2$–), 3.57 (s, 3H, –OC$\underline{H}_3$), 3.68 (s, 3H, –OC$\underline{H}_3$), 5.11 (s, 2H, –OC$\underline{H}_2$O–), 5.23 (s, 2H, –OC$\underline{H}_2$O–), 7.42 (s, 1H, aromatic proton). Exact MS Calcd for $C_{14}H_{17}Br^{79}O_5$: 344.0257. Found: 344.0246. Calcd for $C_{14}H_{17}Br^{81}O_5$: 346.0239. Found: 346.0214.

6-Bromo-5,8-dimethoxymethyloxy-2-hydroxy-1-oxotetralin (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (11) PhI(OAc)$_2$ (300 mg, 0.71 mmol) was added portionwise to a stirred solution of **9** (245 mg, 0.71 mmol) and KOH

(140 mg, 2.49 mmol) in absolute MeOH (4 ml) at 0 °C. The mixture was stirred for 3 h at the same temperature under a nitrogen atmosphere. MeOH was evaporated off under reduced pressure. The residue was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure in the presence of a small amount of K_2CO_3 to give a crude product (**10**), which was used in the next reaction without purification. A mixture of the crude **10**, (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol (130 mg, 0.85 mmol), and a catalytic amount of CSA was stirred for 10 min under reduced pressure (0.5 mmHg). Dry CH_2Cl_2 (2.5 ml) was added to the resulting mixture and the whole was stirred for an additional 10 min at room temperature. The reaction was quenched by the addition of K_2CO_3 (one microspatula-full) and the inorganic salt was filtered off. The filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (5 ml) and treated with a suitable amount of $NaBH_4$ for 20 min at 0 °C.[19] Usual work-up afforded a crude product, which was purified by silica gel column chromatography using hexane–ether (1 : 4) as an eluent to give **11** (225 mg, 67%) as a diastereomeric mixture. White prisms (hexane), mp 85 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 2949, 1574, 1461, 1155. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.25 (m, 2H, $-CH_2-$), 2.65—3.14 (m, 2H, $-CH_2-$), 3.37, 3.39, 3.44, 3.46, 3.49, 3.60, 3.61 (each s, total 12H, $-OCH_3$ ×4), 3.20—4.00 (m, 4H, $-CH_2OCH_3$ ×2), 4.00—4.75 (m, 3H, $-OCH-$ ×2 and $-CHOH$), 4.99 (s, 2H, $-OCH_2O-$), 5.16 (s, 2H, $-OCH_2O-$), 7.25 (s, 1H, aromatic proton). Exact MS Calcd for $C_{20}H_{29}Br^{79}O_9$: 492.0996. Found: 492.1006.

6-Bromo-5,8-dimethoxymethyloxy-1,2-dioxotetralin 1-[(2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene] Acetal (12) Activated molecular sieves 3A (7.0 g), PDC (5.6 g, 14.82 mmol), and Ac_2O (1.0 ml, 10 mmol) were added to a stirred solution of **11** (4.3 g, 8.72 mmol) in dry CH_2Cl_2 (43 ml) at 0 °C and the resulting mixture was stirred for 2 h at the same temperature under a nitrogen atmosphere. Ether (200 ml) was added to the mixture and the insoluble salt was removed by passage through a short celite column. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ether (1 : 4) as an eluent to afford **12** (3.90 g, 91%). Colorless oil, $[\alpha]_D$ +8.85° (c=1.2). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1573, 1464. ^{1}H-NMR ($CDCl_3$) δ: 2.68—3.00 (m, 2H, $-CH_2-$), 3.04—3.30 (m, 2H, $-CH_2-$), 3.39, 3.41, 3.50, 3.57 (all s, 3H each, $-OCH_3$ ×4), 3.4—3.8 (m, 4H, $-CH_2OCH_3$ ×2), 4.22 (m, 2H, $-OCH-$ ×2), 4.98, 5.19 (both s, total 4H, $-OCH_2O-$ ×2), 7.32 (s, 1H, aromatic proton). Exact MS Calcd for $C_{20}H_{27}Br^{79}O_9-CO$: 462.0890. Found: 462.0893. Calcd for $C_{20}H_{27}Br^{81}O_9-CO$: 464.0868. Found: 464.0868.

Nucleophilic Addition of Organometallics to the Chiral Acetal (12) General Procedure: An organometallic reagent (5 mmol) in dry THF was added dropwise to a stirred solution of **12** (1 mmol) in dry THF (10 ml), and the resulting mixture was stirred for 3 h at the temperature shown in Table I under a nitrogen atmosphere. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane–ether as an eluent to give the adduct.

Run 1: (2*S*)-6-Bromo-2-hydroxy-5,8-dimethoxymethyloxy-2-trimethylsilylethynyl-1-oxotetralin (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**13a**, 1.96 g) was prepared from **12** (1.6 g) and TMS–≡–MgCl in 96% yield (eluent, hexane : ether = 1 : 2). White needles (hexane), mp 99—101 °C, $[\alpha]_D^{18}$ +37.6° (c=0.123). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 2160, 1575, 1462, 1155, 1105. ^{1}H-NMR (C_6D_6) δ: 0.03 (s, 9H, $-Si(CH_3)_3$), 2.30 (m, 1H, $-CH_2-$), 2.58 (m, 1H, $-CH_2-$), 3.0—3.15 (m, 2H, $-CH_2-$), 3.00, 3.06, 3.12, 3.33 (all s, 3H each, $-OCH_3$ ×4), 3.42 (d, 1H, J=9 Hz, $-CH_2OCH_3$), 3.47 (dd, 1H, J=9, 6.5 Hz, $-CH_2OCH_3$), 3.61 (dd, 1H, J=9, 5.5 Hz, $-CH_2OCH_3$), 3.73 (dd, J=9, 3 Hz, $-CH_2OCH_3$), 4.36 (br d, 1H, J=8.5 Hz, $-OCH-$), 4.7 (s, 2H, $-OCH_2O-$), 4.92, 5.00 (both d, 1H each, J=6 Hz, $-OCH_2O-$), 5.04 (m, 1H, $-OCH-$), 7.35 (s, 1H, aromatic proton). Exact MS Calcd for $C_{25}H_{37}Br^{79}O_9Si$: 588.1391. Found: 588.1403. Calcd for $C_{25}H_{37}Br^{81}O_9Si$: 590.1368. Found: 590.1367.

Run 2: (2*R*)-6-Bromo-2-ethyl-2-hydroxy-5,8-dimethoxymethyloxy-1-oxotetralin (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**13b**, 151 mg) was prepared from **12** (143.6 mg) and EtMgCl in 99% yield. Colorless oil, $[\alpha]_D$ +10.8° (c=0.46). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3457, 1570, 1460, 1150. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (t, 3H, J=7 Hz, $-CH_2CH_3$), 1.2—2.3 (m, 4H, $-CH_2-$ ×2), 2.6—3.2 (m, 2H, $-CH_2-$), 3.35, 3.41, 3.50, 3.59 (all s, 3H each, $-OCH_3$ ×4), 3.68—3.93 (m, 4H, $-CH_2OCH_3$ ×2), 4.26 (dt, 1H, J=8, 2 Hz, $-OCH-$), 4.63 (dt, 1H, J=8, 6 Hz, $-OCH-$), 4.94 (A part in ABq, 1H, J=5 Hz, $-OCH_2O-$), 5.00 (B part in ABq, 1H, J=5 Hz, $-OCH_2O-$), 5.09 (s, 2H, $-OCH_2O-$), 7.19 (s, 1H, aromatic proton). Exact MS Calcd for $C_{22}H_{33}Br^{79}O_9$: 520.1305. Found: 520.1293. Calcd for $C_{22}H_{33}Br^{81}O_9$: 522.1288. Found: 522.1293.

Run 3: (2*R*)-6-Bromo-2-hydroxy-2-methyl-5,8-dimethoxymethyloxy-1-oxotetralin (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**13c**, 48.6 mg) was prepared from **12** (49 mg) and MeMgBr in 96% yield. Colorless needles, mp 81 °C, $[\alpha]_D$ +26.5° (c=0.19). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1575, 1463, 1155. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (s, 3H, $-CH_3$), 1.65—2.4 (m, 2H, $-CH_2-$), 2.5—3.1 (m, 2H, $-CH_2-$), 3.36, 3.48, 3.52, 3.61 (all s, 3H each, $-OCH_3$ ×4), 3.5—3.7 (m, 3H, $-CH_2OCH_3$), 3.91 (dd, 1H, J=10, 2.5 Hz, $-CH_2OCH_3$), 4.25 (dt, 1H, J=8, 2.5 Hz, $-OCH-$), 4.65 (dt, 1H, J=8, 5 Hz, $-OCH-$), 4.98 (s, 2H, $-OCH_2O-$), 5.12 (s, 2H, $-OCH_2O-$), 7.20 (s, 1H, aromatic proton). *Anal.* Calcd for $C_{21}H_{31}O_9$: C, 49.70; H, 6.17; Br, 15.75. Found: C, 49.97; H, 6.20; Br, 15.73.

Run 4: The product (**13a** : **13'a** = 3 : 1, 136 mg) was prepared from **12** (140 mg) and TMS–≡–Li in 81% yield. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 2160, 1575, 1462. ^{1}H-NMR (C_6D_6) δ: 0.03 (s, 9H, $-Si(CH_3)_3$), 2.3—2.45 (m, 1H, $-CH_2-$), 2.5—2.75 (m, 1H, $-CH_2-$), 3.0—3.15 (m, 2H, $-CH_2-$), 3.00, 3.06, 3.12, 3.13, 3.16, 3.19, 3.33 (all s, total 12H, ratio 3 : 3 : 3 : 2 : 1 : 1 : 3, $-OCH_3$ ×4), 3.42 (d, 1H, J=9 Hz, $-CH_2OCH_3$), 3.47 (dd, 1H, J=9, 6.5 Hz, $-CH_2OCH_3$), 3.61 (dd, 1H, J=9, 5.5 Hz, $-CH_2OCH_3$), 3.73 (dd, 1H, J=9, 3 Hz, $-CH_2OCH_3$), 4.36 (br d, 1H, J=8.5 Hz, $-OCH-$), 4.7 (br s, 2H, $-OCH_2-$), 4.92, 5.00 (both d, 1H each, J=6 Hz, $-OCH_2O-$), 5.04 (m, 1H, $-OCH-$), 7.35 (s, 1H, aromatic proton). Exact MS Calcd for $C_{25}H_{37}Br^{79}O_9Si$: 588.1388. Found: 588.1378. Calcd for $C_{25}H_{37}Br^{81}O_9Si$: 590.1369. Found: 590.1364.

(2*S*)-6-Bromo-2-ethynyl-2-hydroxy-5,8-dimethoxymethyloxy-1-oxotetralin (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (14) KOH (4.26 g, 76 mmol) was added to a solution of **13a** (3.76 g, 6.56 mmol) in 50% aqueous EtOH (250 ml). The mixture was refluxed for 15 min. After the removal of EtOH *in vacuo*, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using hexane–ether (1 : 4) as an eluent to afford **14** (3.39 g) in a quantitative yield. Yellow oil, $[\alpha]_D$ +55.6° (c=0.653). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370, 3310, 1578, 1461, 1155, 1105. ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.36 (m, 4H, $-CH_2-$ ×2), 2.35 (s, 1H, $-\equiv-H$), 3.11—3.75 (m, 3H, $-CH_2OCH_3$ ×2), 3.35 (s, 3H, $-OCH_3$), 3.50 (s, 6H, $-OCH_3$ ×2), 3.60 (s, 3H, $-OCH_3$), 3.95 (dd, 1H, J=10, 2 Hz, $-CH_2OCH_3$), 4.3 (br d, 1H, J=10 Hz, $-OCH-$), 4.7 (dt, 1H, J=8, 6 Hz, $-OCH-$), 5.01, 5.15 (both s, 1H each, $-CH_2O-$), 5.29, 5.40 (both s, 1H each, $-OCH_2O-$), 7.26 (s, 1H, aromatic proton). Exact MS Calcd for $C_{22}H_{29}Br^{79}O_9$: 516.0994. Found: 516.0974. Calcd for $C_{22}H_{29}Br^{81}O_9$: 518.0974. Found: 518.0944.

Hydrogenation of 14 Compound (**14**) (51.6 mg) was dissolved in AcOEt (1 ml) and hydrogenated in the presence of a catalytic amount of 5% Pd–C under atmospheric pressure at room temperature. After the completion of the reaction (checked by TLC), the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–AcOEt (1 : 1) as an eluent to give **13b** (46.5 mg, 90%), which was identical with **13b** obtained in run 2 by ^{1}H-NMR comparison.

(2*S*)-6-Bromo-2-ethynyl-2,5,8-trihydroxy-1-oxotetralin (15) A solution of **14** (3.59 g, 6.95 mmol) and concentrated H_2SO_4 (1 ml) in 50% aqueous AcOH (500 ml) was refluxed overnight. The resulting mixture was cooled to room temperature, neutralized with NaOH and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane–ether (1 : 4) as an eluent to give **15** (1.59 g, 77%). Yellow needles (hexane–ether), mp 160—161 °C. $[\alpha]_D$ +49.4° (c=1.11). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3548, 3300, 1650, 1610, 1447, 1180, 1013. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.7 (m, 2H, $-CH_2-$), 2.53 (s, 1H, $-\equiv-H$), 3.0—3.15 (m, 2H, $-CH_2-$), 4.11 (s, 1H, $-OH$), 7.02 (s, 1H, aromatic proton), 10.9 (s, 1H, $-OH$). Exact MS Calcd for $C_{12}H_9Br^{79}O_4$: 295.9685. Found: 295.9703. Calcd for $C_{12}H_9Br^{81}O_4$: 297.9666. Found: 297.9686.

(2*S*)-6-Bromo-2-ethynyl-2,5,8-triacetoxy-1-oxotetralin (16) A mixture of **15** (330 mg, 1.1 mmol), Ac_2O (0.6 ml) and 4-DMAP (10 mg) in pyridine (10 ml) was stirred for 2 h at 50 °C under a nitrogen atmosphere. Pyridine was evaporated off under reduced pressure. Then 10% aqueous HCl was added to the residue and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using hexane–ether (1 : 2) to give **16** in a quantitative yield. Colorless plates (benzene), mp 170 °C. $[\alpha]_D^{22}$ +10.0° (c=0.655). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3310, 1778, 1716, 1590, 1455, 1370, 1180. ^{1}H-NMR ($CDCl_3$) δ: 2.12, 2.36, 2.39 (all s, 3H each, $-COCH_3$ ×3), 2.4—2.72 (m, 2H, $-CH_2-$), 2.72 (s, 1H, $-\equiv-H$), 2.8—3.1 (m, 2H, $-CH_2-$),

7.31 (s, 1H, aromatic proton). Exact MS Calcd for $C_{18}H_{15}Br^{79}O_7$: 422.0000. Found: 422.0000. Calcd for $C_{18}H_{15}Br^{81}O_7$: 423.9982. Found: 424.0007.

(6*R*)-2-Bromo-6-ethynyl-6-hydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (5) A solution of **16** (116 mg, 0.27 mmol) in dry THF (5 ml) was added to a stirred solution of $NaBH_4$ (150 mg, 4 mmol) in water (5 ml) at 0 °C. The mixture was stirred for 48 h at 0 °C. After the addition of NaOH (30 mg), the resulting solution was stirred for an additional 6 h at the same temperature. The reaction was quenched with concentrated HCl. The product was extracted with ether. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure to give crude **17**, which was used in the next reaction without further purification. A solution of **17** obtained above in CH_3CN (4 ml) was added dropwise to a stirred solution of CAN (296 mg, 0.54 mmol) in water (4 ml) at 0 °C. The mixture was stirred for 30 min at the same temperature. After the addition of water (10 ml), the product was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ether (1 : 4) as an eluent to give **5** (66 mg, 87%). Yellow needles ($CHCl_3$), mp 156 °C. $[\alpha]_D$ −23.3° (c=0.9). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3300, 1670, 1654, 1595, 1276. ^{1}H-NMR ($CDCl_3$) δ: 2.01 (t, 2H, J=6 Hz, $-CH_2-$), 2.51 (s, 1H, $-\equiv-H$), 2.6—2.9 (m, 4H, $-CH_2-$ ×2), 7.25 (s, 1H, aromatic proton). *Anal.* Calcd for $C_{12}H_9BrO_3$: C, 51.27; H, 3.23; Br, 28.42. Found: C, 50.95; H, 3.15; Br, 28.15.

(2*R*)-11-Acetoxy-2-ethynyl-2,6-dihydroxy-7-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (19) A solution of **18** (32 mg, 0.12 mmol) in dry THF (2 ml) was added dropwise to a stirred suspension of NaH (60% in oil, 6.4 mg, 0.16 mmol) in dry THF at 0 °C under a nitrogen atmosphere. Stirring was continued for 10 min, then a solution of **5** (30 mg, 0.106 mmol) in dry THF (2 ml) was added to the reaction mixture. The resulting solution was stirred for 30 min at 0 °C and for 2 h at room temperature. The reaction was quenched with 10% aqueous HCl, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (benzene : AcOEt = 4 : 1) to afford **19** (30.1 mg, 70%). Orange powder (hexane–$CHCl_3$), mp 130—132 °C. $[\alpha]_D$ +9.41° (c=0.085). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3300, 1761, 1663, 1621, 1583, 1185. ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.4 (m, 4H, $-CH_2-$ ×2), 2.49 (s, 4H, $-COCH_3$ and $-\equiv-H$), 3.05 (t, 2H, J=8 Hz $-CH_2-$), 4.05 (s, 3H, $-OCH_3$), 7.30 (d, 1H, J=8 Hz, aromatic proton), 7.60—7.90 (m, 2H, aromatic protons), 13.75 (s, 1H, $-OH$). Exact MS Calcd for $C_{23}H_{18}O_7$: 406.1053. Found: 406.1061.

(2*R*)-11-Acetoxy-2-acetyl-2,6-dihydroxy-7-methoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione (20) A solution of **19** (28 mg, 0.07 mmol), 20% aqueous H_2SO_4 (1 ml), and HgO (60 mg, 0.28 mmol) in THF (3.3 ml) was stirred for 40 min at 50 °C. The reaction mixture was treated with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (hexane : ether = 1 : 4) to give **20** (28.4 mg, 97%). Orange powder (hexane–$CHCl_3$), mp 125 °C. $[\alpha]_D^{22}$ +6.8° (c=0.074). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1755, 1702, 1620, 1580, 1180. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.0 (m, 2H, $-CH_2-$), 2.28 (s, 3H, $-COCH_3$), 2.38 (s, 3H, $-COCH_3$), 2.4—3.0 (m, 4H, $-CH_2-$), 3.98 (s, 3H, $-OCH_3$), 7.23 (d, 1H, J=7.5 Hz, aromatic proton), 7.71—7.54 (m, 2H, aromatic protons), 13.70 (s, 1H, $-OH$). Exact MS Calcd for $C_{23}H_{20}O_8$: 424.1155. Found: 424.1144.

(−)-7-Deoxydaunomycinone (4) A solution of **20** (30 mg, 0.078 mmol) in 66% aqueous CF_3COOH (5 ml) was stirred for 7.5 h at 50—55 °C. The resulting mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC ($CHCl_3$: acetone = 5 : 1) to afford **4** (26.8 mg, 90%). Red powder (hexane–$CHCl_3$), mp 232—233.5 °C. $[\alpha]_D^{15}$ −87.4° (c=0.094). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1705, 1605, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.92—2.05 (m, 2H, $-CH_2-$), 2.38 (s, 3H, $-COCH_3$), 2.92 (d, 1H, J=17 Hz, $-CH_2-$), 2.90—3.0 (m, 1H, $-CH_2-$), 3.05 (d, 1H, J=17 Hz, $-CH_2-$), 3.16 (dd, 1H, J=19, 4 Hz, $-CH_2-$), 4.08 (s, 3H, $-OCH_3$), 7.38 (d, 1H, J=8 Hz, aromatic proton), 7.76 (t, 1H, J=8 Hz, aromatic proton), 8.02 (d, 1H, J=8 Hz, aromatic proton), 13.44 (s, 1H, $-OH$), 13.84 (s, 1H, $-OH$). Exact MS Calcd for $C_{21}H_{18}O_7$: 382.1052. Found: 382.1057. HPLC analysis was carried out at 15 °C: Daicel ChiralCel OA; eluent, hexane : EtOH : MeOH : AcOH = 170 : 20 : 10 : 1; flow rate, 1.5 ml/min; retention time (t_R), 35.69 min for (−)-**4**, 21.46 and 35.36 min for (±)-**4**.

Syntheses of 2-Acetyl-2-hydroxy-5,7,12-trimethoxy-1,2,3,4-tetrahydronaphthacene-5,12-dione [(−)-21 and (±)-21] and the ^{1}H-NMR Experiment A solution of **4** (15 mg, 0.04 mmol), CH_3I (0.5 ml), and K_2CO_3 (50 mg) in dry acetone (3 ml) was stirred at 60 °C for 10 h under a nitrogen atmosphere. The insoluble salt was removed by filtration, and the acetone was evaporated off. The residue was purified by preparative TLC ($CHCl_3$: acetone = 6 : 1) to give **21** (9.8 mg, 60%). ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.00 (m, 2H, $-CH_2-$), 2.36 (s, 3H, $-COCH_3$), 2.80—3.20 (m, total 4H, $-CH_2-$ ×2), 3.90, 3.97, 4.00 (all s, total 9H, $-OCH_3$ ×3), 7.25 (d, 1H, J=8 Hz, aromatic proton), 7.61 (t, 1H, J=8 Hz, aromatic proton), 7.80 (d, 1H, J=8 Hz, aromatic proton). A solution of **21** (1.7 mg) and $Eu(tfc)_3$ (1 mg) in $CDCl_3$ (0.15 ml) was used for the ^{1}H-NMR experiment [JEOL JNM-FX90Q FT-NMR (90 MHz)]; see text and Fig. 2.

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