Asymmetric Synthesis Using Chiral Acetals: Highly Diastereoselective Nucleophilic Addition of Grignard Reagents to Chiral 1-Oxo-β-tetralone 1-Acetals

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Nucleophilic addition of organometallic reagents (Grignard reagents and organolithium reagents) to two chiral 1-oxo-β-tetralone 1-acetals (1a, b) was studied. Extremely high stereoselectivity was achieved in the reactions of 1a and 1b with Grignard reagents leading to the α-hydroxy acetals (6) bearing a chiral tertiary alcohol moiety at the homobenzylic position. The stereochemistry of the products derived from 1a was determined by correlation with compound 9 and that of the products derived from 1b was determined by consideration of the circular dichroism spectrum of the benzoate (11) prepared from 6bC.

Keywords asymmetric synthesis; chiral 1-oxo-β-tetralone 1-acetal; diastereoselective nucleophilic addition; Grignard reagent; (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol; chiral tertiary alcohol

The development of methodologies for constructing chiral tertiary alcohol moieties at the homobenzylic position of the tetralin system has drawn much attention in relation to the asymmetric synthesis of antitumor antibiotics, particularly the anthracycline family.[1] Many studies have been made and, for example, methods using asymmetric reduction,[2a] asymmetric epoxidation,[2b] asymmetric bromolactonization,[2c] asymmetric hydroxylation,[2d] and asymmetric osmium tetroxide oxidation[2e] have been reported so far. We recently reported that the nucleophilic addition of Grignard reagents to chiral α-keto acetals derived from (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol proceeds in a highly diastereoselective manner.[3] We have now found that the α-keto acetal method can also be applied to the 1-oxo-β-tetralone 1-acetal system (**1**).[4] The present paper describes a highly asymmetric induction in the reactions of **1** with Grignard reagents, leading to the α-hydroxy acetals (**6**) bearing a tertiary alcohol moiety at the homobenzylic position and the determination of the stereochemistries of the products.

Results and Discussion

Syntheses of the Chiral α-Keto Acetals (1a, b) The chiral α-keto acetals (**1a, b**) were readily prepared as depicted in Chart 2. α-Tetralone (**2a**) was treated with 1.2 eq of phenyl iodine (III) diacetate [PhI(OAc)$_2$] and 3 eq of potassium hydroxide (KOH) in absolute methanol (MeOH)[5] to give the α-hydroxydimethyl acetal (**3a**). Compound **3a** was unstable and was easily hydrolyzed to give the α-hydroxy ketone (**4a**), so it was used in the subsequent reaction without purification. Transacetalization of **3a** with 1.2 eq of (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol[6] in the pres-

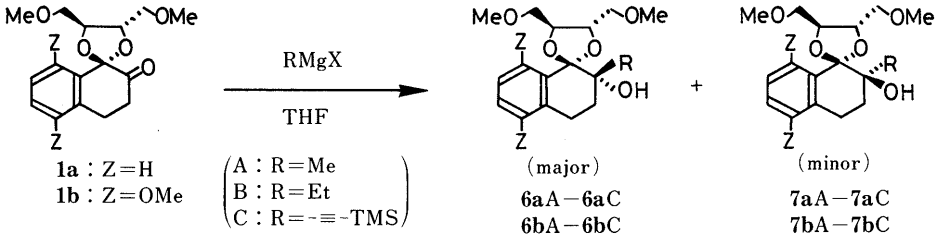


Chart 1

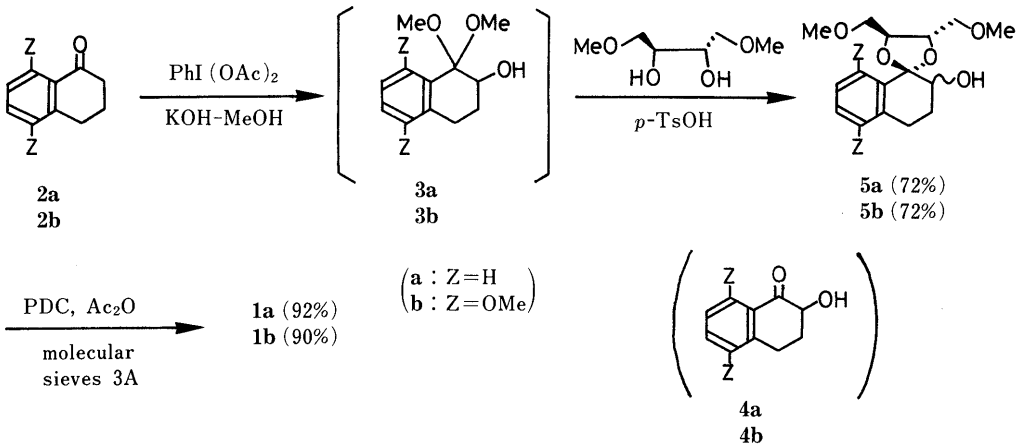


Chart 2

ence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in dichloromethane (CH_2Cl_2) afforded **5a** as a diastereomeric mixture at the secondary alcohol moiety. Oxidation of **5a** by modified pyridinium dichromate (PDC) oxidation[7] gave the 1-oxo-β-tetralone 1-acetal (**1a**). The 5,8-dimethoxy-1-oxo-β-tetralone 1-acetal (**1b**) was also prepared from 5,8-dimethoxy-1-tetralone (**2b**)[8] in the same manner as in the case of **1a**.

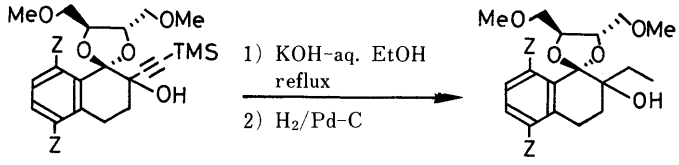
Nucleophilic Addition of Organometallics to the α-Keto Acetals (1a, b) The nucleophilic addition of 10 eq of organometallic reagents to **1a** and **1b** was carried out in tetrahydrofuran (THF). The results are summarized in Table I. Very high diastereoselectivity was realized in the reactions of **1a** and Grignard reagents (runs 1—3), and a single diastereomer was obtained in the reaction of **1b** with Grignard reagents (runs 4—6). Authentic diastereomeric mixtures at the tertiary alcohol moiety for comparison with the products of runs 1, 3, 4 and 6 were obtained by the reactions of **1a** or **1b** with organolithium reagents, which showed poor selectivity (runs 7—10). The authentic mixtures for the products in runs 2 and 5 were synthesized from the products in runs 8 and 10 by desilylation followed by hydrogenation (Chart 3).

The stereochemistries of the products were determined as

TABLE I. Nucleophilic Addition of RMgX to **1**

Run	Substrate	RMgX	Temperature	Yield (%)	Product	Ratio (6:7)
1		MeMgBr	−78 °C	92	**6aA**+**7aA**	98: 2[a]
2	**1a**	EtMgCl	−78 °C	91	**6aB** only	100: 0[a]
3		TMS−≡−MgCl	r.t.	90	**6aC**+**7aC**	92: 8[a]
4		MeMgBr	−78 °C	95	**6bA** only	100: 0[b]
5	**1b**	EtMgCl	−78 °C	93	**6bB** only	100: 0[a]
6		TMS−≡−MgCl	r.t.	93	**6bC** only	100: 0[a]
7	**1a**	MeLi	−78 °C	83	**6aA**+**7aA**	41: 59[a]
8		TMS−≡−Li	−78 °C	80	**6aC**+**7aC**	34: 66[a]
9	**1b**	MeLi	−78 °C	80	**6bA**+**7bA**	50: 50[b]
10		TMS−≡−Li	−78 °C	78	**6bC**+**7bC**	78: 22[a]

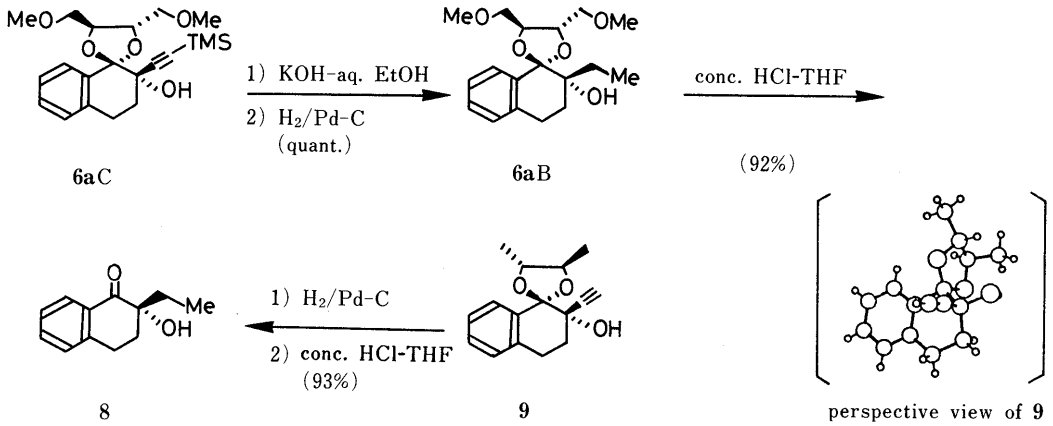
a) Determined by HPLC analysis. *b*) Determined by ^{1}H-NMR. r.t. = room temperature.



Z=H
(**6aC** : **7aC**=34 : 66) (run 8)
Z=OMe
(**6bC** : **7bC**=78 : 22) (run 10)

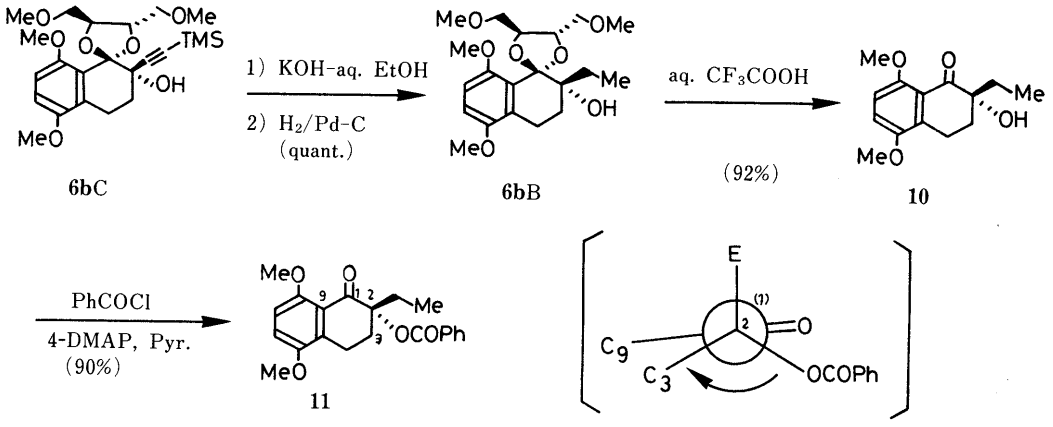
Z=H
(**6aB** : **7aB**=34 : 66)
Z=OMe
(**6bB** : **7bB**=78 : 22)

Chart 3



6aC **6aB** **8** **9**

Chart 4



6bC **6bB** **10** **11**

Newman projection at C2 of **11**

Fig. A

Chart 5

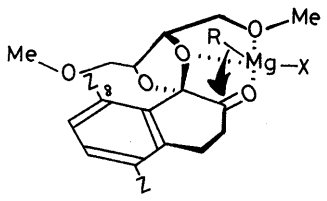


Fig. 1

follows. The products derived from **1a** were assigned by correlation to **9**, whose stereochemistry was unambiguously determined by X-ray analysis[9] (Chart 4). That is, alkaline treatment of **6a**C followed by hydrogenation gave the ethyl compound (**6a**B), which was converted to **8**. The specific rotation ($[\alpha]_D$ +17.5°) of this **8** showed good agreement with the specific rotation ($[\alpha]_D$ +18.1°) of **8** derived from **9** by hydrogenation followed by acid hydrolysis. The stereochemistry of **6a**A was assigned on the basis of mechanistic analogy. The stereochemistries of the products derived from **1b** were determined as shown in Chart 5. Compound **6b**C was converted to the α-hydroxy ketone (**10**) *via* the ethyl compound (**6b**B) in the same manner as described above. Treatment of **10** with benzoyl chloride (PhCOCl) in the presence of 4-dimethylaminopyridine (DMAP) gave **11**. Since **11** showed a positive Cotton effect ($[\theta]_{237}$ +20000, $[\theta]_{217}$ −19000), the absolute configurations of C2 of **6b**B and **6b**C were determined as *R* (see Fig. A in Chart 5).[10] The stereochemistry of **6b**A was tentatively assigned by assuming the same sense of diastereoselection.

The predominant formation of **6a**A—**6a**C (or **6b**A—**6b**C) in the reactions of **1a** (or **1b**) with Grignard reagents might be rationalized by considering the chelation model previously proposed by us.[3] Thus, in the transition state of the reaction the chelating intermediate is formed and the alkyl group of the reagent attacks the *si*-face of the ketone (Fig. 1). The fact that a single diastereomer was obtained in the reactions of **1b** would suggest a strong influence of the substituent at C8.

In conclusion, our α-keto acetal method was successfully applied to tetralin systems and the formation of a chiral tertiary alcohol moiety at the homobenzylic position was attained. This methodology was successfully applied for asymmetric synthesis of anthracycline compounds and their derivatives,[4] and the details of these results will be published soon.

Experimental

The following instruments were used to obtain physical data: specific rotation, Perkin–Elmer 241 polarimeter; infrared (IR) spectra, JASCO IRA-1 spectrometer; proton nuclear magnetic resonance (^{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 chromatograph ultraviolet (UV) detector was used for high-performance liquid chromatographic (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.

α-Hydroxy Acetals (5a, b) General Procedure: α-Tetralone (**2a**) [or 5,8-dimethoxy-1-tetralone (**2b**)] (1 mmol) and $PhI(OAc)_2$ (1.2 mmol) were added to a stirred solution of KOH (3 mmol) in absolute MeOH (3 ml) at 0 °C. The reaction mixture was stirred for 3 h at the same temperature under a nitrogen atmosphere, then diluted with ice-cold water (10 ml), and MeOH was evaporated off under reduced pressure. 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 to afford the crude α-hydroxydimethylacetal (**3a**) (or **3b**). (These acetals were used in a subsequent transacetalization reaction without further purification.) The acetal **3a** (or **3b**) was dissolved in dry CH_2Cl_2 (4 ml) and stirred with (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol (1.2 mmol) in the presence of one microspatula-full of *p*-TsOH for 10 min at room temperature under a nitrogen atmosphere. One microspatula-full of K_2CO_3 was added to the reaction mixture, which was stirred for a further 10 min. The insoluble salt was removed by passage through a short celite column. The filtrate was concentrated under reduced pressure to give a crude product (**5a** or **5b**). In the case of **5a**, the crude product was purified by column chromatography on silica gel to give **5a** as a diastereomeric mixture at the secondary alcohol moiety. In the case of **5b**, the crude product was treated with $NaBH_4$ in MeOH before purification by column chromatography on silica gel, because of the difficulty of the separation of **4b** and **5b**.

Compound **5a** (1.45 g) was prepared from **2a** (1 g, 6.8 mmol) in 72% yield (eluent, hexane : ether = 1 : 1). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1605. ^{1}H-NMR (C_6D_6) δ: 2.0—2.4 (2H, m, $-CH_2-$), 2.4—2.8 (2H, m, $-CH_2-$), 2.98, 2.99, 3.05, 3.10 (total 6H, all s, ratio 1 : 1 : 1 : 1, $-OCH_3/2\times4$), 3.2–3.7 (4H, m, $-CH_2OCH_3\times2$), 4.1—4.4 (2H, m, $-OCH-\times2$), 4.70 (1H, m, $-OCH-$), 6.8—7.3 (3H, m, aromatic protons), 7.6—8.0 (1H, m, aromatic proton). Exact MS Calcd for $C_{16}H_{22}O_5$: 294.1464. Found: 294.1462.

Compound **5b** (1.24 g) was prepared from **2b** (1 g, 6.8 mmol) in 72% yield (eluent, hexane : ether = 1 : 2). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 1600, 1480. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.1 (2H, m, $-CH_2-$), 2.4—3.1 (2H, m, $-CH_2-$), 3.38, 3.40, 3.43, 3.46 (total 6H, all s, ratio 1 : 1 : 1 : 1, $-OCH_3\times2$), 3.73, 3.80 (3H each, both s, $-OCH_3\times2$), 3.5—4.0 (5H, m, $-OCH_2OCH_3\times2$ and $-OCH-$), 4.1—4.8 (2H, m, $-OCH-$), 6.71 (2H, s, aromatic protons). Exact MS Calcd for $C_{18}H_{26}O_7$: 354.1678. Found: 354.1696.

α-Keto Acetals (1a, b) General Procedure: Activated molecular sieves 3A (600 mg), PDC (1.6 mmol), and Ac_2O (0.1 ml) were added to a stirred solution of **5a** (or **5b**) (1 mmol) in dry CH_2Cl_2 (5 ml) at 0 °C and the resulting mixture was stirred for 2 h at room temperature under a nitrogen atmosphere. Ether was added to the mixture and the insoluble salt was removed by passage through a short celite column (ether then AcOEt). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the α-keto acetal **1a** (or **1b**).

1,2,3,4-Tetrahydronaphthalene-1,2-dione 1-(2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**1a**, 457 mg) was prepared from **5a** (500 mg, 1.7 mmol) in 92% yield (eluent, hexane : ether = 2 : 1). Colorless oil, $[\alpha]_D$ −4.8° (*c* = 1.0). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1605, 1075. ^{1}H-NMR (C_6D_6) δ: 2.2—2.5 (2H, m, $-CH_2-$), 2.6—2.8 (2H, m, $-CH_2-$), 3.08, 3.13 (3H each, both s, $-OCH_3\times2$), 3.3—3.8 (4H, m, $-CH_2OCH_3\times2$), 4.1—4.6 (2H, m, $-OCH-\times2$), 6.7—7.3 (3H, m, aromatic protons), 7.86 (1H, m, aromatic proton). *Anal.* Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.84; H, 6.97.

5,8-Dimethoxy-1,2,3,4-tetrahydronaphthalene-1,2-dione 1-(2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**1b**, 537 mg) was prepared from **5b** (600 mg, 1.7 mmol) in 90% yield (eluent, hexane : ether = 1 : 3). Colorless oil, $[\alpha]_D$ +29.7° (*c* = 1.7). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1600, 1070. ^{1}H-NMR ($CDCl_3$) δ: 2.6—2.9 (2H, m, $-CH_2-$), 2.9—3.1 (2H, m, $-CH_2-$), 3.37, 3.38 (3H each, both s, $-OCH_3\times2$), 3.5—3.8 (4H, m, $-CH_2OCH_3\times2$), 3.72, 3.78 (3H each, both s, $-OCH_3\times2$), 4.0—4.4 (2H, m, $-OCH-\times2$), 6.72 (2H, s, aromatic protons). *Anal.* Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.16; H, 6.76.

Nucleophilic Addition of Organometallic Reagents to the α-Keto Acetals (1a, b) General Procedure: Organometallic reagent (10 mmol) was added dropwise to a stirred solution of **1a** (or **1b**) (1 mmol) in dry THF (10 ml), and the resulting mixture was stirred for 5 h at the temperature given in Table I under a nitrogen atmosphere. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether. 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 adducts (**6** and **7**).

Run 1: The product (**6a**A : **7a**A = 98 : 2, 31 mg) was prepared from **1a** (32 mg, 0.11 mmol) and MeMgBr in 92% yield (eluent, hexane : ether = 2 : 1). The ratio of the product was determined by HPLC analysis: see run 7. (2*R*)-2-Hydroxy-2-methyl-1,2,3,4-tetrahydronaphthalen-1-one (2*S*,3*S*)-

1,4-dimethoxy-2,3-butylene acetal (**6aA**) (96% de): Colorless needles, mp 83–85 °C (pet. ether), $[\alpha]_D$ +34.1 ° (c=0.66). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3420, 1605, 1085. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, s, –CH$_3$), 1.6—2.5 (2H, m, –CH$_2$–), 2.7—3.0 (2H, m, –CH$_2$–), 3.36, 3.46 (3H each, both s, –OCH$_3$ × 2), 3.5—3.7 (3H, m, –CH$_2$OCH$_3$ and –CHOCH$_3$), 3.88 (1H, dd, J=2.9, 10.5 Hz, –CHOCH$_3$), 4.2—4.6 (2H, m, –OCH– × 2), 6.9—7.3 (3H, m, aromatic protons), 7.42 (1H, m, aromatic proton). *Anal.* Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.19; H, 8.00.

Run 2: (2*R*)-2-Ethyl-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6aB**) (45 mg) was prepared from **1a** (45 mg, 0.15 mmol) and EtMgCl in 91% yield (eluent, hexane : ether = 1 : 1). The ratio of the product was determined by HPLC analysis (Nucleosil 50-5 column; eluent, $CHCl_3$; flow rate, 1 ml/min; t_R; **6a**B, 13.4 min, **7a**B, 8.5 min). **6a**B: Colorless needles, mp 84—85 °C (pet. ether), $[\alpha]_D$ +47.3 ° (c=1.1), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1600, 1080. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.5 Hz, –CH$_2$CH$_3$), 1.2—2.4 (4H, m, –CH$_2$– × 2), 2.7—2.9 (2H, m, –CH$_2$–), 3.34, 3.45 (3H each, both s, –OCH$_3$ × 2), 3.4—3.7 (3H, m, –CH$_2$OCH$_3$ and –HCHOCH$_3$), 3.88 (1H, dd, J=2.9, 10.5 Hz, –HCHOCH$_3$), 4.2—4.7 (2H, m, –OCH– × 2), 6.9—7.3 (3H, m, aromatic protons), 7.42 (1H, m, aromatic proton). *Anal.* Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.95; H, 8.35.

Run 3: Trimethylsilylethynylmagnesium chloride was prepared from trimethylsilylacetylene (1.5 mmol) and EtMgCl (1 mmol) in dry THF (12 ml) at room temperature within 2 h under a nitrogen atmosphere. (2*R*)-2-Hydroxy-2-trimethylsilylethynyl-1,2,3,4-tetrahydronaphthalen-1-one (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6a**C) (84% de, 36 mg) was prepared from **1a** (30 mg, 0.1 mmol) and trimethylsilylethynylmagnesium chloride in 90% yield (eluent, hexane : ether = 2 : 1). The ratio of the product was determined by HPLC analysis: see run 8. **6a**C (84% de): Colorless oil, $[\alpha]_D$ +44.4° (c=0.52, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560, 3375, 2170, 1605, 1090. ^{1}H-NMR ($CDCl_3$) δ: 0.1 (9H, s, –Si(CH$_3$)$_3$), 2.1—2.4 (2H, m, –CH$_2$–), 2.96 (2H, t, J=6.3 Hz, –CH$_2$–), 3.40, 3.46 (3H each, both s, –OCH$_3$ × 2), 3.65 (2H, d, J=4.4 Hz, –CH$_2$OCH$_3$), 3.76 (2H, dd, J=3.6, 5.5 Hz, –CH$_2$OCH$_3$), 4.37 (1H, dt, J=3.6, 8.7 Hz, –OCH–), 4.64 (1H, dt, J=4.4, 8.7 Hz, –OCH–), 6.9—7.3 (3H, m, aromatic protons), 7.50 (1H, m, aromatic proton). *Anal.* Calcd for $C_{21}H_{30}O_5Si$: C, 64.58; H, 7.74. Found: C, 64.51; H, 7.94.

Run 4: (2*R*)-2-Hydroxy-2-methyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-one (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6bA**) (15 mg) was prepared from **1b** (15 mg, 0.044 mmol) and MeMgBr in 95% yield (eluent, hexane : ether = 1 : 2). The ratio of the product was determined by ^{1}H-NMR spectroscopy; see run 9. Colorless needles, mp 124—126 °C (hexane), $[\alpha]_D$ +61.7 ° (c=0.23). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410, 1595, 1260. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s, –CH$_3$), 1.6—3.0 (4H, m, –CH$_2$– × 2), 3.37, 3.47 (3H each, both s, –OCH$_3$ × 2), 3.5—4.0 (4H, m, –CH$_2$OCH$_3$ × 2), 3.75, 3.81 (3H each, both s, –OCH$_3$ × 2), 4.2—4.8 (2H, m, –OCH– × 2), 6.71 (2H, s, aromatic protons). *Anal.* Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.83; H, 7.78.

Run 5: (2*R*)-2-Ethyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-one (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6bB**) (20 mg) was prepared from **1b** (20 mg, 0.057 mmol) and EtMgCl in 93% yield (eluent, hexane : ether = 1 : 2). The ratio of the product was determined by HPLC analysis (Finepack sil C_{18} column; eluent, hexane : ether = 1 : 1; flow rate, 1 ml/min; t_R; **6b**B, 8.4 min, **7b**B, 10 min). Colorless needles, mp 128—129 °C (hexane), $[\alpha]_D$ +63.5 ° (c=0.45). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1600, 1265. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.2 Hz, –CH$_2$CH$_3$), 1.2—2.8 (6H, m, –CH$_2$– × 3), 3.36, 3.46 (3H each, both s, –OCH$_3$ × 2), 3.5—4.0 (4H, m, –CH$_2$O– × 2), 3.75, 3.80 (3H each, both s, –OCH$_3$ × 2), 4.2—4.8 (2H, m, –OCH– × 2), 6.70 (2H, s, aromatic protons). *Anal.* Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91. Found: C, 62.93; H, 8.09.

Run 6: (2*R*)-2-Hydroxy-5,8-dimethoxy-2-trimethylsilylethynyl-1,2,3,4-tetrahydronaphthalen-1-one (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene acetal (**6b**C) (25 mg) was prepared from **1b** (22 mg, 0.062 mmol) and trimethylsilylethynylmagnesium chloride (prepared in the same manner as in run 3) in 93% yield (eluent, hexane : ether = 1 : 2). The ratio of the product was determined by HPLC analysis: see run 10. Colorless needles, mp 120—121 °C (hexane), $[\alpha]_D$ +92.4 ° (c=0.39). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3375, 2350, 1600, 1265. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (9H, s, –Si(CH$_3$)$_3$), 2.0—2.3 (2H, m, –CH$_2$–), 2.7—2.9 (2H, m, –CH$_2$–), 3.37, 3.50 (3H each, both s, –OCH$_3$ × 2), 3.5—4.0 (4H, m, –CH$_2$OCH$_3$ × 2), 3.75, 3.79 (3H each, both s, –OCH$_3$ × 2), 4.2—4.4 (1H, m, –OCH–), 4.5—4.8 (1H, m, –OCH–), 6.71 (2H, s, aromatic protons). *Anal.* Calcd for $C_{23}H_{34}O_7Si$: C, 61.31; H, 7.61. Found: C, 61.33; H, 7.66.

Run 7: The product (**6a**A : **7a**A = 41 : 59, 28 mg) was prepared from **1a** (32 mg, 0.11 mmol) and MeLi in 83% yield. The ratio of the product was determined by HPLC analysis (Finepack sil C_{18} column; eluent, hexane : ether = 3 : 1; flow rate, 2 ml/min; t_R, **6a**A, 8.5 min, **7a**A, 7.5 min). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3345, 1605, 1082. ^{1}H-NMR (C_6D_6) δ: 1.36, 1.44 (total 3H, both s, ratio 2 : 3, –CH$_3$), 1.7—2.1 (1H, m, –CH$_2$–), 2.2—2.8 (3H, m, –CH$_2$–), 2.96, 3.00, 3.03, 3.10 (total 6H, all s, ratio 3 : 2 : 2 : 3, –OCH$_3$ × 2), 3.15—3.6 (4H, m, –OCH$_2$OCH$_3$ × 2), 3.98—4.38 (1H, m, –OCH–), 4.5—4.9 (1H, m, –OCH–), 6.8—7.3 (3H, m, aromatic protons), 7.72, 8.05 (total 1H, both m, ratio 2 : 3, aromatic proton). Exact MS Calcd for $C_{17}H_{24}O_5$: 308.1622. Found: 308.1622.

Run 8: Trimethylsilylethynyllithium was prepared from trimethylsilylacetylene (1.5 mmol) and *n*-BuLi (1 mmol) in dry THF (12 ml) at −40 °C within 1 h under a nitrogen atmosphere. The product (**6a**C : **7a**C = 34 : 66, 20 mg) was prepared from **1a** (23 mg, 0.079 mmol) in trimethylsilylethynyllithium in 80% yield. The ratio of the product was determined by HPLC analysis (Finepack sil C_{18} column; eluent, hexane : ether = 5 : 1; flow rate, 1 ml/min; t_R, **6a**C, 7.4 min, **7a**C, 9.2 min). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570, 3400, 2165, 1605, 1247, 1090. ^{1}H-NMR (C_6D_6) δ: 0.04, 0.06 (total 9H, both s, ratio 1 : 1, Si(CH$_3$)$_3$), 2.3—2.6 (2H, m, –CH$_2$–), 2.7—3.0 (2H, m, –CH$_2$–), 3.03, 3.04, 3.05 (total 6H, all s, ratio 1 : 1 : 2, –OCH$_3$ × 2), 3.3—3.8 (4H, m, –OCH$_2$OCH$_3$ × 2), 4.18—4.44 (1H, m, –OCH–), 4.7—4.96 (1H, m, –OCH–), 6.7—7.2 (3H, m, aromatic protons), 7.6—7.9 (1H, m, aromatic proton). Exact MS Calcd for $C_{21}H_{30}O_5Si$: 390.1862. Found: 390.1862.

Run 9: The product (**6b**A : **7b**A = 50 : 50, 10 mg) was prepared from **1b** (12 mg, 0.034 mmol) and MeLi in 80% yield. The ratio of the product was determined by ^{1}H-NMR spectroscopy from the ratios of the singlet signals due to the methoxy protons. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 1600, 1260, 1095, 1075. ^{1}H-NMR (C_6D_6) δ: 1.47, 1.51 (total 3H, both s, ratio 1 : 1, –CH$_3$), 1.8—2.3 (2H, m, –CH$_2$–), 2.35—3.0 (2H, m, –CH$_2$–), 3.01, 3.03, 3.12, 3.18 (total 6H, ratio 1 : 1 : 1 : 1, –OCH$_3$ × 2), 3.35, 3.39, 3.46 (total 6H, ratio 2 : 1 : 1, –OCH$_3$ × 2), 3.4—3.8 (4H, m, –OCH$_2$OCH$_3$ × 2), 4.3—4.5 (1H, m, –OCH–), 4.78—5.08 (1H, m, –OCH–), 6.47 (1H, s, aromatic proton), 6.45, 6.53 (total 1H, ABq, J=9 Hz, aromatic proton). Exact MS Calcd for $C_{19}H_{28}O_7$: 368.1836. Found: 368.1837.

Run 10: The product (**6b**C : **7b**C = 78 : 22, 16 mg) was prepared from **1b** (16 mg, 0.047 mmol) and trimethylsilylethynyllithium (prepared in the same way as in run 8). The ratio of the product was determined by HPLC analysis (Finepack sil C_{18} column; eluent, hexane : ether = 1 : 1; flow rate, 1 ml/min; t_R, **6b**C, 8.5 min, **7b**C, 7.5 min). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370, 2355, 1600, 1262, 1100. ^{1}H-NMR (C_6D_6) δ: 0.02, 0.18 (total 9H, both s, ratio 4 : 1, –Si(CH$_3$)$_3$), 2.3—3.0 (4H, m, –CH$_2$– × 2), 3.06, 3.10, 3.18, 3.22 (total 6H, all s, ratio 4 : 4 : 1 : 1, –OCH$_3$ × 2), 3.31, 3.34, 3.39, 3.40 (total 6H, all s, ratio 1 : 4 : 1 : 4, –OCH$_3$ × 2), 3.4—4.0 (4H, m, –OCH$_2$OCH$_3$ × 2), 4.3—5.2 (2H, m, –OCH– × 2), 6.45 (2H, s, aromatic protons). Exact MS Calcd for $C_{23}H_{34}O_7Si$: 450.2071. Found: 450.2048.

Conversion of Trimethylsilylethynyl Compounds (6aC, 6bC, 7aC, and 7bC) to the Ethyl Compounds (6aB, 6bB, 7aB, and 7bB) General Procedure: A solution of the trimethylsilylethynyl compound (1 mmol) in aqueous KOH (170 mg of KOH in 10 ml of water) and EtOH (10 ml) was refluxed for 20 min. EtOH was evaporated off and the resulting mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude product. This crude product was dissolved in AcOEt (5 ml) and hydrogenated in the presence of 5% Pd–C (30 mg) at atmospheric pressure. The insoluble precipitate 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 as an eluent to give the ethyl compounds.

A diasteromeric mixture of **6a**B and **7a**B (34 : 66, 8.2 mg) was prepared in a quantitative yield from the product (10 mg, 0.026 mmol) of run 8. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 1600, 1138, 1080. ^{1}H-NMR ($CDCl_3$) δ: 0.95, 0.99 (total 3H, each t, J=7 Hz, ratio 2 : 3, –CH$_2$CH$_3$), 1.3—2.2 (4H, m, –CH$_2$– × 2), 2.65—2.9 (2H, m, –CH$_2$–), 3.34, 3.41, 3.46, 3.47 (total 6H, all s, ratio 2 : 3 : 2 : 3, –OCH$_3$ × 2), 3.3—4.0 (4H, m, –OCH$_2$OCH$_3$ × 2), 4.0—4.7 (2H, m, –CHO– × 2), 7.0—7.3 (3H, m, aromatic protons), 7.35—7.55 (2/5H, m, aromatic proton), 7.7—7.82 (3/5H, m, aromatic proton). Exact MS Calcd for $C_{18}H_{26}O_5$: 322.1781. Found: 322.1793.

A diastereomeric mixture of **6b**B and **7b**B (78 : 22, 12.7 mg) was prepared in a quantitative yield from the product (15 mg, 0.033 mmol) of run 10. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1600, 1265, 1075. ^{1}H-NMR ($CDCl_3$) δ: 0.96, 0.995 (total 3H, each t, J=7.2 Hz, ratio 4 : 1, –CH$_2$CH$_3$), 1.3—2.8 (6H, m, –CH$_2$– × 3), 3.36, 3.41, 3.42, 3.46 (total 6H, all s, ratio 4 : 1 : 1 : 4, –OCH$_3$ × 2), 3.75, 3.77, 3.80, (total 6H, all s, ratio 5 : 1 : 4, –OCH$_3$ × 2), 3.4—4.0 (4H, m, –OCH$_2$OCH$_3$ × 2), 4.1—4.4 (1H, m, –CHO–), 4.5—4.8 (1H, m, –CHO–), 6.70 (2H, s, aromatic protons). Exact MS Calcd for $C_{20}H_{31}O_7$: 382.1989. Found: 382.1989.

Compound **6a**B (25 mg) was prepared in a quantitative yield from **6a**C (31 mg, 0.079 mmol). This **6a**B was identical with **6a**B obtained in run 2 as judged from the ^{1}H-NMR spectra ($CDCl_3$).

Compound **6b**B (12 mg) was prepared in a quantitative yield from **6b**C (15 mg, 0.033 mmol). This **6b**B was identical with **6b**B obtained in run 5 as judged from the ^{1}H-NMR spectra ($CDCl_3$).

Conversion of 6aB to 8 A solution of **6a**B (22 mg, 0.068 mmol) in concentrated HCl–THF (1 : 3) (2 ml) was stirred for 1 h at 50 °C. The mixture was poured into ice-water and extracted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ether (3 : 1) as an eluent to give (2*R*)-2-ethyl-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (**8**) (12 mg, 92%). **8**: Colorless oil, $[\alpha]_D$ +17.5° (c=0.6). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1680, 1600. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.3 Hz, $-CH_2CH_3$), 1.6—1.9 (2H, m, $-CH_2-$), 1.95—2.5 (2H, m, $-CH_2-$), 2.9—3.2 (2H, m, $-CH_2-$), 7.1—7.6 (3H, m, aromatic protons), 8.01 (1H, dd, J=2.0, 7.4 Hz, aromatic proton). Exact MS Calcd for $C_{12}H_{14}O_2$: 190.0991. Found: 190.0975.

Conversion of 9 to 8 Compound **9** (30 mg, 0.12 mmol) was hydrogenated in the presence of a catalytic amount of 5% Pd–C in AcOEt (5 ml) at atmospheric pressure. The usual work-up afforded the crude product (30 mg), which was used in a subsequent reaction without further purification. The crude product (30 mg) was treated with concentrated HCl–THF (1 : 3) (1 ml) solution at 50 °C for 1 h. The resulting mixture was poured into ice-water and extracted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using CH_2Cl_2 as an eluent to afford **8** (20 mg, 93%), which was identical with the **8** derived from **6a**B as judged from the ^{1}H-NMR spectra ($CDCl_3$) and $[\alpha]_D$ +18.1° (c=0.6).

Conversion of 6bB to 10 Compound **6b**B (111 mg, 0.29 mmol) was treated with 80% CF_3COOH (6 ml) overnight at room temperature. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ at 0 °C. The mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$, 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 (2*R*)-2-ethyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-one (**10**) (69 mg, 95%). Colorless oil, $[\alpha]_D$ −26.0° (c=0.63). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475, 1680, 1585, 1265. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz, $-CH_2CH_3$), 1.68 (2H, q, J=7.3 Hz, $-CH_2CH_3$), 1.8—2.3 (2H, m, $-CH_2-$), 2.6—3.1 (2H, m, $-CH_2-$), 3.82, 3.86 (3H each, both s, $-OCH_3\times2$), 6.79 (1H, d, J=10 Hz, aromatic proton), 7.00 (1H, d, J=10 Hz, aromatic proton). Exact MS Calcd for $C_{14}H_{18}O_4$: 250.1205. Found: 250.1215.

Conversion of 10 to 11 A solution of **10** (4 mg, 0.016 mmol), PhCOCl (0.08 mmol), and a catalytic amount of 4-dimethylaminopyridine in dry pyridine (0.1 ml) was stirred overnight at 60 °C. The reaction was quenched with saturated aqueous NH_4Cl 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 (SiO_2, hexane : ether = 2 : 3, developed twice) to give (2*R*)-2-benzoyloxy-2-ethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-one (**11**) (5 mg, 90%). Colorless oil, $[\alpha]_D$ −10.8° (c=0.21). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1685, 1580, 1260. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7.3 Hz, $-CH_2CH_3$), 1.9—2.4 (4H, m, $-CH_2-\times2$), 2.8—3.2 (2H, m, $-CH_2-$), 3.80, 3.85 (3H each, both s, $-OCH_3\times2$), 6.75 (1H, d, J=9 Hz, aromatic proton), 6.93 (1H, d, J=9 Hz, aromatic proton), 7.3—7.6 (5H, m, aromatic protons). Exact MS Calcd for $C_{21}H_{22}O_5$: 354.1465. Found: 354.1458. CD (EtOH) $[\theta]_{237}$ (nm): +20000 (positive maximum); $[\theta]_{217}$ nm: −19000 (negative maximum).

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9) Compound **9** was prepared by desilylation of **13**, which was obtained in the reaction of the chiral acetal **12**, [having the acetal moiety derived from (−)-(2*R*,3*R*)-2,3-butanediol] and trimethylsilylethynylmagnesium chloride. **9**: Crystal data: $C_{16}H_{18}O_3$, M_r=258.32, monoclinic, $P2_1$; a=10.380 (1), b=7.915 (1), c=17.134 (1) Å; β=95.76 (1)°, U=1400.4 (2) Å^3, Z=4, D_c=1.225 g cm^{-1}, μ=6.849 cm^{-1}, Crystal size 0.20 mm × 0.25 mm × 0.35 mm. X-Ray analysis: Transparent needle-like crystals were obtained from the solution in iso-PrOH. Intensity data were measured on an automated diffractometer (Rigaku AFC-5) with graphitemonochromated CuK_α radiation (λ=1.5418 Å). In total, 2574 reflections were measured, of which 2242 were judged significant ($|F_O| \geq 2.67\sigma(|F_O|)$). The structure was solved by the direct method using MULTAN-80 and the difference-Fourier method, and was refined by the block-diagonal matrix least-squares method with anisotropic temperature factors for all non-hydrogen atoms. The hydrogen atoms were positioned geometrically. The final R value was 0.068 (R_w=0.076). The atomic scattering factors were taken from "International Tables for X-ray Crystallography." Further detail of the crystal structure investigation are available on request. We thank Dr. Tadamasa Date (Tanabe Seiyaku Pharmaceutical Co., Ltd) for his generous contribution to this X-ray analysis.
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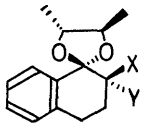

12 : X, Y=O
13 : X=-≡-TMS, Y=OH

Fig. 2