Asymmetric Synthesis Using Chiral Acetals: Highly Stereoselective Reduction of Chiral α-Keto-β,γ-unsaturated Acetals and Its Application for the Syntheses of (*R*)-(−)- and (*S*)-(+)-3′-Methoxy-4′-*O*-methyljoubertiamine

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Reduction of the chiral α-keto-β,γ-unsaturated acetals (1) derived from (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol was studied. Extremely high stereoselectivity was attained with $LiAlH_4$ and two epimeric allyl alcohols (2aA—2cA and 2aB—2cB) were prepared selectively by a proper choice of additive. As an application of this methodology, total syntheses of (*R*)-(−)-3′-methoxy-4′-*O*-methyljoubertiamine [(*R*)-(−)-4] and its enantiomer [(*S*)-(+)-4] were achieved from the single chiral enone acetal (3) through a highly stereocontrolled reduction followed by the Claisen–Eschenmoser rearrangement.

Keywords asymmetric synthesis; diastereoselective reduction; chiral α-keto-β,γ-unsaturated acetal; (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol; (*R*)-(−)-, (*S*)-(+)-3′-methoxy-4′-*O*-methyljoubertiamine

Optically active allyl alcohols are very versatile intermediates for the synthesis of optically active compounds through various stereoselective transformations.[1] Therefore, the stereoselective synthesis of them and their use for the asymmetric synthesis of natural products are very attractive areas of research in organic synthesis. We have previously reported that a highly stereoselective reduction of the chiral α-keto-β,γ-unsaturated acetals (**1a**—**1c**) derived from (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol to each of two epimeric allyl alcohols (**2a**A—**2c**A and **2a**B—**2c**B) can be attained by $LiAlH_4$ reduction using a proper additive (Chart 1).[2] That is, reduction of **1a**—**1c** with $LiAlH_4$ or $LiAlH_4$–LiBr afforded *R*-allyl alcohols (**2a**A—**2c**A), whereas $LiAlH_4$–$MgBr_2$ reduction afforded *S*-allyl alcohols (**2a**B—**2c**B). Since these allyl alcohols (**2**) have the acetal moiety, a synthetic equivalent of the ketone function, they promise to be versatile chiral building blocks for natural product synthesis. We have now applied our asymmetric reduction method to the synthesis of the Sceletium alkaloids,[3,4] possessing a mesembrane carbon skeleton (bold skelton (**a**)) and succeeded in the first total synthesis of 3′-methoxy-4′-*O*-methyljoubertiamine (**4**) in both enantiomerically pure forms from a single starting material (**3**) (Chart 2). The synthesis includes the complementary construction of the chiral quaternary carbon center (*) *via* highly stereoselective reduction of the enone acetal followed by Claisen–Eschenmoser rearrangement. Here we present a full account of the asymmetric reduction of the chiral enone acetals and its application to the asymmetric synthesis of the Sceletium alkaloid (**4**).

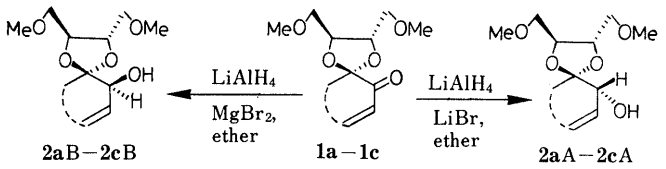

Chart 1

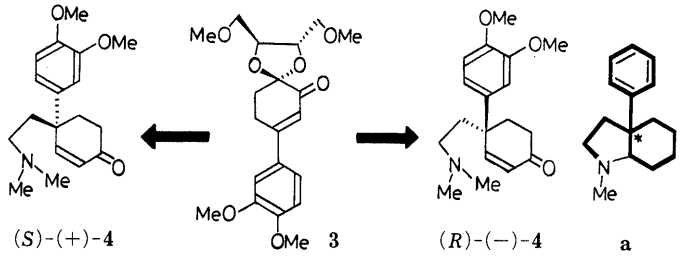

Chart 2

Results and Discussion

Syntheses of the Chiral Enone Acetals (1a—c) The chiral enone acetals were synthesized as depicted in Chart 3. The known 4-hydroxy-1-methoxy-1-cyclohexene (**5**)[5] was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) in methanol (MeOH) to give **6** (90%), which was transacetalized with (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol[6] to afford **7** (80%) as a mixture of four diastereomers. Pyridinium chlorochromate (PCC) oxidation[7] of **7** afforded **8** (90%). Alkylation of **8** with phenylmagnesium bromide (PhMgBr) afforded **9a** (90%), which was oxidized by the modified pyridinium dichromate (PDC) method[8] followed by passage through an alumina column for dehydration to give the desired enone acetal (**1a**) (65%). The enone acetal (**1b**) was similarly prepared from **8** by alkylation with methylmagnesium bromide (MeMgBr) and the subsequent procedures. The enone acetal (**1c**) was prepared from the α-hydroxy acetal (**11**)[9] derived from α-tetralone (**10**). Bromination of the benzylic position of **11** with *N*-bromosuccinimide (NBS) in the presence of azabisisobutyronitrile (AIBN) followed by PDC oxidation[8] afforded **1c** (70%).

Reduction of the Enone Acetals (1a—1c) A detailed study on the reduction of **1a** was performed. Thus, various reducing agents were allowed to react with **1a** at −78 °C and the ratio of the two diastereomers (**2a**A and **2a**B) obtained in each run was determined by HPLC analysis (runs 1—6, Table I). It was found that $LiAlH_4$ reacted with **1a** highly regio- and stereo-selectively to give predominantly the (*R*)-allyl alcohol (**2a**A) (run 1). As a reaction solvent, ether was the most effective (run 1) and a lower

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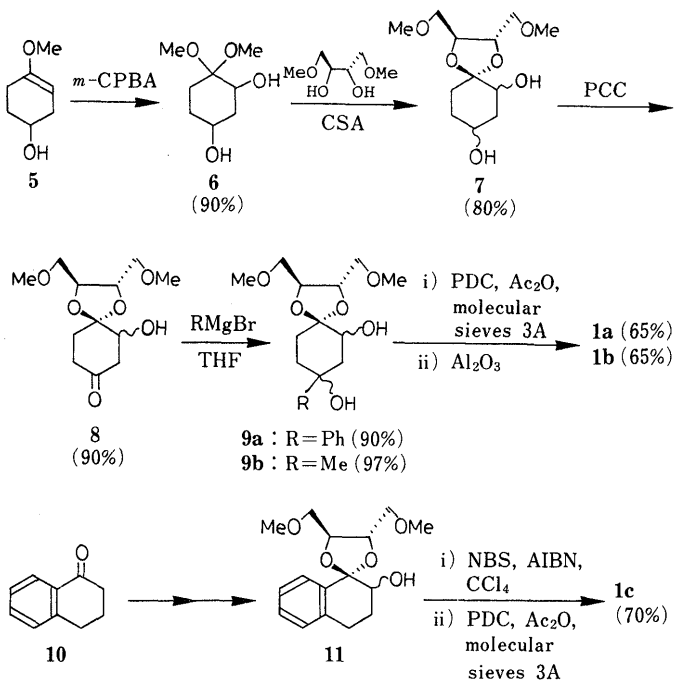

Chart 3

reaction temperature gave a better outcome (run 8; *cf.* run 1). The effect of additives on the stereoselectivity of this reaction was next examined (runs 10—15). Addition of LiBr increased the formation of **2a**A (runs 10, 11), while $ZnBr_2$ or $SnCl_2$ were less effective (runs 12, 13). However, the use of $MgBr_2$ as an additive reversed the stereoselectivity and yielded predominantly the (*S*)-allyl alcohol (**2a**B) (runs 14, 15). In the cases of other substrates (**1b** and **1c**), similar reactivity was observed (runs 16—19) and the generality of the enone-acetal reduction method was confirmed.

The stereochemistries of the products were determined as follows. The product (**2c**A, 70% de) of run 18 was converted to the known (*R*)-(+)-β-tetralol (**12**) [$[\alpha]_D$ +50. 4° (*c*=0.5, EtOH); lit.[10] +68.0° as (93% ee)] by catalytic hydrogenation followed by reductive removal of the acetal by sodium in liquid ammonia. Thus, the absolute configration of the secondary alcohol moiety was determined as *R*. The stereochemistries of the products derived from **1a** and **1b** were tentatively assigned by assuming the same sense of diasteroselection as obserbed for **1c**.

The formation of the (*R*)-allyl alcohols (**2a**A—**2c**A) in the case of $LiAlH_4$ or $LiAlH_4$–LiBr may be rationalized as follows. That is the Li cation chelates with the carbonyl oxygen atom, the methoxy oxygen atom, and one of the

TABLE I. Reduction of **1a**—**1c**

1a—**1c** $\xrightarrow[\text{additive}]{\text{reducing agent (M}-\text{H)}}$ **2a**A—**2c**A + **2a**B—**2c**B
$-78\,^{\circ}C$ (>95%)

Run	Substrate	M−H	Solvent	Additive	Product	Ratio (A : B)[c]
1	**1a**	$LiAlH_4$	Ether	None		92 : 8
2	**1a**	$LiAlH(OBu^t)_3$	Ether	None		77 : 23
3	**1a**	$Zn(BH_4)_2$[a]	Ether	None		85 : 15
4	**1a**	Red-Al	Toluene	None		58 : 42
5	**1a**	$NaBH_4/CeCl_3$	MeOH	None		44 : 56
6	**1a**	DIBAH	Toluene	None		42 : 58
7	**1a**	$LiAlH_4$	Toluene–ether (1 : 1)	None		89 : 11
8	**1a**	$LiAlH_4$[b]	Ether	None		95 : 5
9	**1a**	$LiAlH_4$	THF	None		81 : 19
10	**1a**	$LiAlH_4$	Ether	LiBr		95 : 5
11	**1a**	$LiAlH_4$[b]	Ether	LiBr	**2a**A: X=H, Y=OH **2a**B: X=OH, Y=H	96 : 4
12	**1a**	$LiAlH_4$	Ether	$ZnBr_2$		88 : 12
13	**1a**	$LiAlH_4$	Ether	$SnCl_2$		87 : 13
14	**1a**	$LiAlH_4$	Ether	$MgBr_2$		15 : 85
15	**1a**	$LiAlH_4$[b]	Ether	$MgBr_2$		10 : 90
16	**1b**	$LiAlH_4$[b]	Ether	LiBr		96 : 4[d]
17	**1b**	$LiAlH_4$[b]	Ether	$MgBr_2$	**2b**A: X=H, Y=OH **2b**B: X=OH, Y=H	10 : 90[d]
18	**1c**	$LiAlH_4$[b]	Ether	LiBr		85 : 15
19	**1c**	$LiAlH_4$[b]	Ether	$MgBr_2$	**2c**A: X=H, Y=OH **2c**B: X=OH, Y=H	15 : 85

a) The reaction was carried out at $-78\,^{\circ}C$—$0\,^{\circ}C$. *b*) The reaction was carried out at $-100\,^{\circ}C$. *c*) Determined by HPLC analysis. *d*) Determined by ^{1}H-NMR spectroscopy from the ratio of the singlet signals due to the methoxymethyl protons.

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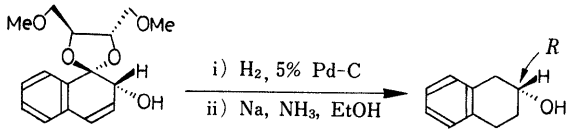
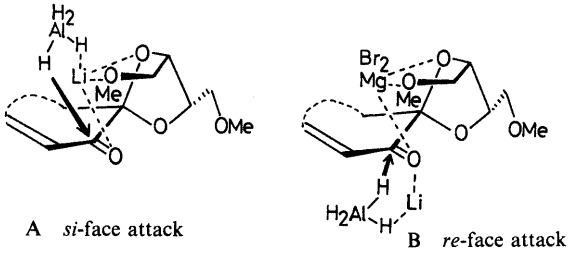


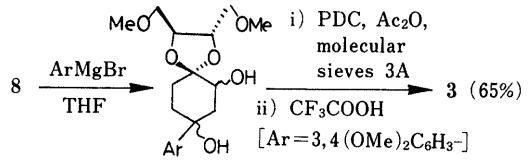
2cA (70% de) 12 (90%)

Chart 4



A *si*-face attack B *re*-face attack

Fig. 1



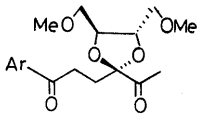


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Chart 5

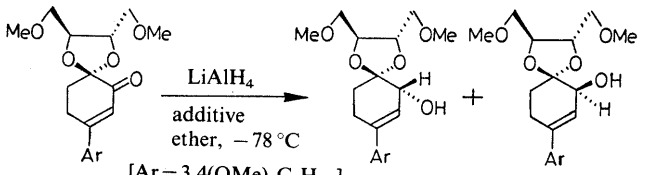
acetal oxygen atoms and then the hydride attacks on the *si*-face of the ketone *via* internal hydride transfer[11] (Fig. 1A). On the other hand, in the case of $LiAlH_4$–$MgBr_2$, Mg chelates in the same manner as above and $LiAlH_4$ approaches to the *re*-face of the ketone owing to repulsion between Mg and Li and/or steric hindrance (Fig. 1B).[12]

Syntheses of (*R*)-(−)- and (*S*)-(+)-3′-Methoxy-4′-*O*-methyljoubertiamine The chiral enone acetal (**3**) was synthesized as follows (Chart 5). Reaction of **8** with 3,4-dimethoxyphenylmagnesium bromide afforded **13** (95%) as a mixture of four diastereomers. Although PDC oxidation of **13** followed by passage through an alumina column as applied for the syntheses of **1a** and **1b** resulted in a poor yield of **3** and the formation of the retro-aldol product (**14**), PDC oxidation of **13** followed by treatment with CF_3CO_2H gave **3** in good yield (65%).

Reduction of **3** with a 5-fold molar excess of $LiAlH_4$ in dry ether at −78 °C proceeded in a highly diastereoselective manner to give a 95% yield of the allyl alcohols (**15A** and **15B**, a 95:5 ratio from the HPLC analysis), which were readily separated by flash column chromatography on silica gel using hexane/ether as an eluent. Addition of a 6-fold molar excess of $MgBr_2$ resulted in the formation of **15B** as a predominant isomer, whereas addition of a 6-fold molar excess of LiBr gave almost the same stereoselectivity.

The stereochemistries of the products (**15A** and **15B**) were determined by their conversion into (*R*)-(−)-3′-methoxy-4′-*O*-methyljoubertiamine [(*R*)-(−)-**4**] and its enantiomer [(*S*)-(+)-**4**], respectively (*vide infra*). Thus, the Claisen–Eschenmoser [3,3]-sigmatropic rearrangement[13] of both separated isomers (**15A** and **15B**) with *N*,*N*-dimethylacetamide dimethylacetal proceeded at 110 °C in a stereospecific manner to give **16** and **17** in 89 and 90% yields, respectively; the completeness of chirality transfer during both reactions was verified since **16** and **17** were each homogeneous as judged from the 500 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectra.[13] Reduction of **16** and **17** with a 3-fold molar excess of $LiAlH_4$ in anhydrous ether at 0 °C followed by acid hydrolysis of the acetal group furnished naturally occurring (*R*)-(−)-3′-methoxy-4′-*O*-methyljoubertiamine [(*R*)-(−)-**4**] [85%, $[\alpha]_D$ −49.5° (c=0.1, $CHCl_3$), circular dichroism (CD)θ_{340} −6400 (abs. MeOH) (lit. −6420)] and its enantiomer [(*S*)-(+)-**4**] [82%, $[\alpha]_D$ +49.5° (c=0.08, $CHCl_3$), CD θ_{340} +6400 (abs. MeOH)], respectively, whose ^{1}H-NMR, infrared (IR), and mass spectra (MS) were identical with those reported.[14] Both products were estimated to be essentially optically pure (>99% ee), from their CD values.

TABLE II. Reduction of **3**



Additive	A : B[a]	Yield (%)
None	95 : 5	95
LiBr	96 : 4	95
$MgBr_2$	10 : 90	85

a) Determined by HPLC analysis.

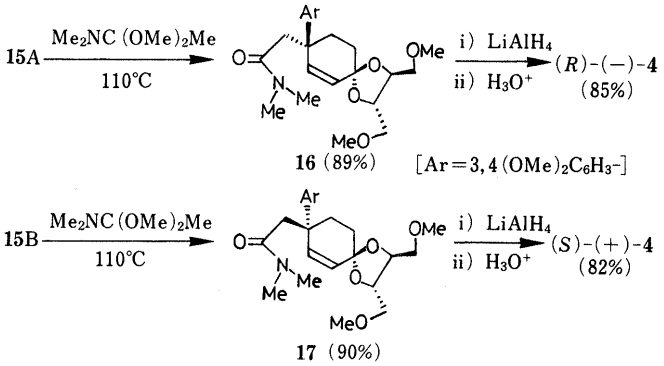


Chart 6

It is noteworthy that the chiral acetal group in this asymmetric synthesis acts not only as a chiral auxiliary but also as a protecting group for the ketone function. The method for the syntheses of both enantiomers [(*R*)-(−)-**4** and (*S*)-(+)-**4**] from the single chiral enone acetal (**3**) simply by changing the metal salt (LiBr or $MgBr_2$) is very useful especially from a practical point of view and will be utilized for the synthesis of other Sceletium alkaloids and related compounds bearing the chiral quaternary carbon center.

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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 JNM-GX 500 FT-NMR (500 MHz) spectrometer (with tetramethylsilane as an internal standard); low- and high-resolution MS, JEOL JMS D-300 mass spectrometer (with a direct inlet system). A JASCO TRIROTAR-II high-pressure liquid chromatograph (UV detector) was used for high-performance liquid chromatographic (HPLC) analysis. E. Merck silica gel (0.063—0.200 mm, 70—230 mesh ASTM) was used 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). Specific rotation was measured at 20°C in $CHCl_3$, unless otherwise mentioned. All boiling points are uncorrected.

4-Hydroxy-1-methoxy-1-cyclohexene (5) This compound was prepared from 4-methoxyphenol (10 g, 80.6 mmol) according to the reported method[5] in 90% (9.28 g) yield. Colorless oil, bp 93—95 °C/0.85 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620, 3450, 2950, 1665, 1175. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.5 (m, 6H, $-CH_2-\times 3$), 3.50 (s, 3H, $-OCH_3$), 4.0 (m, 1H, $-CH-OH$), 4.48 (m, 1H, $>C=CH-$). *Anal.* Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.41; H, 9.70.

2,4-Dihydroxycyclohexanone Dimethylacetal (6) A solution of *m*-CPBA (80% purity; 3.7 g, 17 mmol) in anhydrous MeOH (15 ml) was added dropwise to a stirred solution of **5** (2 g, 15.6 mmol) in anhydrous MeOH (10 ml) at 0 °C under a nitrogen atmosphere. After being stirred for 30 min at room temperature, the mixture was quenched with $NaHCO_3$ (2.62 g) and $NaNO_2$ (645 mg), and then MeOH was evaporated off. The residue was diluted with $CHCl_3$ and the insoluble salt was removed by the use of a Celite column. Evaporation of the solvent afforded a residue, which was purified by column chromatography on silica gel with hexane–AcOEt (1 : 2) as an eluting solvent to give **6** in 90% (2.48 g) yield, as a mixture of diastereoisomers. Viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570, 3540, 2950, 1100, 1060. ^{1}H-NMR ($CDCl_3$) δ: 1.2—2.2 (m, 6H, $-CH_2-\times 3$), 3.18, 3.23, 3.25 (each s, total 6H, $-OCH_3\times 2$), 3.46 (br s, 2H, $-OH\times 2$), 3.95 (m, 2H, $-CHOH\times 2$). Exact MS Calcd for $C_8H_{16}O_4$: 176.1048. Found: 176.1070.

2,4-Dihydroxycyclohexanone (2*S*,3*S*)-1,4-dimethoxy-2,3-butylene Acetal (7) One microspatula-full of camphorsulfonic acid (CSA) was added to a mixture of **6** (1 g, 5.68 mmol) and (−)-(2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol (852 mg, 5.68 mmol), and the resulting mixture was stirred for 6 h at room temperature under reduced pressure (0.5 mmHg). Then, CH_2Cl_2 (5 ml) and K_2CO_3 (one microspatula-full) were added. The reaction mixture was stirred for 10 min, and the precipitate was filtered off. Concentration of the filtrate gave a residue, which was purified by column chromatography on silica gel using ether–AcOEt (1 : 3) as an eluent to afford **7** in 80% (1.19 g) yield as a mixture of diastereoisomers. Viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 2950, 1100. ^{1}H-NMR ($CDCl_3$) δ: 1.4—2.1 (m, 6H, $-CH_2\times 3$), 3.4 (s, 6H, $-OCH_3\times 2$), 3.45—3.6 (m, 4H, $-CH_2OCH_3\times 2$), 3.7—4.38 (m, 4H, $-CHO-\times 2$ and $-CHOH\times 2$). Exact MS Calcd for $C_{12}H_{22}O_6$: 262.1416. Found: 262.1433.

2-Hydroxy-1,4-cyclohexanedione 1-[(2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene]Acetal (8) PCC (1.25 g, 5.83 mmol) and Celite (2 g) were added to a solution of **7** (1.02 g, 3.89 mmol) in anhydrous CH_2Cl_2 (2 ml) at 0 °C, and the resulting mixture was stirred for 12 h at room temperature. Ether (30 ml) was added and the insoluble material was filtered off. After evaporation of the solvent, the residue was chromatographed on silica gel with ether–AcOEt (1 : 1) as an eluent to give **8** in 93% (941 mg) yield as a mixture of diastereoisomers. Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 2950, 1720, 1100. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.8 (6H, m, $-CH_2-\times 3$), 3.41, 3.43 (each s, total 6H, $-OCH_3\times 2$), 3.4—3.65 (m, 4H, $-CH_2OCH_3\times 2$), 3.7—4.5 (m, 3H, $-CHO-\times 2$ and $-CHOH$). Exact MS Calcd for $C_{12}H_{20}O_6$: 260.1260. Found: 260.1267.

4-Alkyl-2,4-dihydroxy Acetals (9a,9b) General Procedure: Grignard reagent (10 mmol; 1—1.5 M solution) was added dropwise to a stirred solution of **8** in anhydrous tetrahydrofuran (THF) (10 ml) at −78 °C under a nitrogen atmosphere. After being stirred for 2 h at the same themperature, the mixture was stirred for an additional 1 h at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl, allowed to warm to room temperature, and then extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel to afford **9a** or **9b** as a mixture of diastereoisomers.

2,4-Dihydroxy-4-phenylcyclohexanone (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (9a) Compound **9a** was prepared from **8** (620 mg, 2.38 mmol) and PhMgBr in 90% (725 mg) yield (eluent; ether:AcOEt = 1 : 4). Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3450, 2950, 1100, 910. ^{1}H-NMR ($CDCl_3$) δ: 1.45—2.4 (m, 6H, $-CH_2-\times 3$), 3.39, 3.41 (each s, total 6H, $-OCH_3\times 2$), 3.45—3.65 (m, 4H, $-CH_2OCH_3\times 2$), 3.65—4.7 (m, 3H, $-CHO-\times 2$ and $-CHOH$), 7.15—7.7 (m, 5H, aromatic protons). Exact MS Calcd for $C_{18}H_{26}O_6$: 338.1729. Found: 338.1741.

2,4-Dihydroxy-4-methylcyclohexanone (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (9b) Compound **9b** was prepared from **8** (229 mg, 0.88 mmol) and MeMgBr in 97% (236 mg) yield (eluent; ether : AcOEt = 1 : 5). Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 3450, 2950, 1090. ^{1}H-NMR ($CDCl_3$) δ: 1.1, 1.18, 1.24 (each s, total 3H, $-CH_3$), 1.3—2.35 (m, 6H, $-CH_2-\times 3$), 3.31, 3.33, 3.39, 3.4 (each s, total 6H, $-OCH_3\times 2$), 3.4—3.65 (m, 4H, $-CH_2OCH_3\times 2$), 3.65—4.5 (m, 3H, $-CHO-\times 2$ and $-CHOH$). Exact MS Calcd for $C_{13}H_{24}O_6$: 276.1570. Found: 276.1568.

α-Keto-β,γ-unsaturated Acetals (1a,b) General Procedure: PDC (564 mg, 1.5 mmol), activated molecular sieves 3A (810 mg), and Ac_2O (0.1 ml) were added to a stirred solution of **9** (1 mmol) in anhydrous CH_2Cl_2 (1.5 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 2 h at room temperature, then the insoluble material was removed by the use of a short alumina column with ether–AcOEt as an eluent. The filtrate was evaporated *in vacuo* to give a residue, which was chromatographed on silica gel to afford **1**.

4-Phenyl-3-cyclohexene-1,2-dione 1-[(2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene] Acetal (1a) Compound **1a** was prepared from **9a** (676 mg, 2 mmol) in 65% (208 mg) yield (eluent; hexane : ether = 1 : 1). Pale yellow oil. $[\alpha]_D$ −10.9° (c = 0.3). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 1680, 1605, 1095. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (t, 2H, J = 7.2 Hz, $-CH_2-$), 2.99 (t, 2H, J = 7.2 Hz, $-CH_2-C=CH-$), 3.39, 3.41 (both s, 3H each, $-OCH_3\times 2$), 3.41—3.75 (m, 4H, $-CH_2OCH_3\times 2$), 4.0—4.4 (m, 2H, $-CHO-\times 2$), 6.38 (br s, 1H, $-C=CH-C=O$), 7.3—7.8 (m, 5H, aromatic protons). Exact MS Calcd for $C_{18}H_{22}O_5$: 318.1466. Found: 318.1461.

4-Methyl-3-cyclohexene-1,2-dione 1-[(2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene]Acetal (1b) Compound **1b** was prepared from **9b** (276 mg, 1 mmol) in 65% (168 mg) yield (eluent; ether : AcOEt = 2 : 1). Pale yellow oil. $[\alpha]_D$ −30.1° (c = 1.2). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2940, 1680, 1080. ^{1}H-NMR ($CDCl_3$) δ: 1.96 (br s, 3H, $H_3C-C=CH-$), 2.17 (t, 2H, J = 5.2 Hz, $-CH_2-$), 2.50 (t, 2H, J = 5.2 Hz, $-CH_2-$), 3.38, 3.40 (both s, 3H each, $-OCH_3\times 2$), 3.45—3.75 (m, 4H, $-CH_2OCH_3\times 2$), 3.9—4.38 (m, 2H, $-CHO-\times 2$), 5.86 (br s, 1H, $-C=CH-C=O$). Exact MS Calcd for $C_{13}H_{20}O_5$: 256.1311. Found: 256.1323.

1,2-Naphthaquinone 1-[(2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene]Acetal (1c) NBS (194 mg, 1.09 mmol) and a catalytic amount of AIBN were added to a solution of **11** (320 mg, 1.09 mmol) in anhydrous CCl_4 (25 ml), and the mixture was heated under reflux for 10 min under a nitrogen atmosphere. The succinimide formed was filtered off and the solvent was removed *in vacuo*. PDC (615 mg, 1.635 mmol), molecular sieves 3A (800 mg) and Ac_2O (0.1 ml) were added to a solution of the residue in anhydrous CH_2Cl_2 (5 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred for 4 h, then the insoluble material was removed by the use of a celite column with ether as an eluent. The solvent was evaporated off *in vacuo* to give a residue, which was purified by column chromatography on silica gel using hexane–benzene (1 : 3) to afford **1c** in 70% (221 mg) yield. Yellow oil. $[\alpha]_D$ −60.3° (c = 0.31). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 1680, 1135, 1095, 1070. ^{1}H-NMR ($CDCl_3$) δ: 3.41, 3.42 (both s, 3H each, $-OCH_3\times 2$), 3.6—3.95 (m, 4H, $-CH_2OCH_3\times 2$), 4.3—4.6 (m, 2H, $-CHO\times 2$), 6.07 (d, 1H, J = 10.1 Hz, $-CH=CH-C=O$), 7.12—7.8 (m, 5H, $-CH=CH-C=O$ and aromatic protons). Exact MS Calcd for $C_{16}H_{18}O_5$: 290.1153. Found: 290.1148.

Reduction of α-Keto-β,γ-unsaturated Acetals (1a—c) i) In the Absence of Additive: Reducing agent (0.5 mmol) was added to a solution of **1** (0.1 mmol) in an anhydrous solvent (10 ml) at −78°C under a nitrogen atmosphere, and the mixture was stirred for 4 h at the same temperature. After decomposition of excess reducing agent with saturated aqueous NH_4Cl, the product was extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give a residue, which was subjected to column chromatography on silica gel using hexane–ether (1 : 1) to afford **2** in >95% yield. The reaction conditions are listed in Table I.

ii) In the Presence of Additive: A metal salt (0.6 mmol) was dried at 140 °C for 2.5 h under reduced pressure, then allowed to cool to room temperature. A solution of **1** (0.1 mmol) in anhydrous solvent (10 ml) was added and the resulting mixture was stirred for 1 h at the same temperature. Reduction and work-up were carried out in the same manner as descrived above in i) to give **2** in >95% yield. The reaction conditions are listed in Table I.

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Runs 1—15: The ratio of diastereoisomers was determined by HPLC analysis [Nucleosil 50—5 column; eluent, hexane : AcOEt = 3 : 2; flow rate, 0.9 ml/min; t_R, **2aA**, 33.0 min, **2aB**, 29.8 min]. The diastereomers (**2aA** and **2aB**) were separated by preparative TLC using hexane–ether (1 : 3, development three times).

2*R*-2-Hydroxy-4-phenyl-3-cyclohexen-1-one (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (2aA) Colorless oil, $[\alpha]_D$ −12.2° (c = 0.27). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 2950, 1090. ^{1}H-NMR (C_6D_6) δ: 1.45—2.25 (m, 2H, –C$\underline{H}_2$–), 2.4—2.8 (m, 2H, –C$\underline{H}_2$–), 3.01, 3.07 (both s, 3H each, –OC$\underline{H}_3$ × 2), 3.4—3.75 (m, 4H, –C$\underline{H}_2$OCH$_3$ × 2), 3.9—4.2 (m, 1H, –C$\underline{H}$O–), 4.3—4.6 (m, 2H, –C$\underline{H}$O– and –C=CH–C$\underline{H}$OH), 6.17 (m, 1H, –C=C$\underline{H}$–CHOH), 6.95—7.45 (m, 5H, aromatic protons). Exact MS Calcd for $C_{18}H_{24}O_5$: 320.1621. Found: 320.1614.

2*S*-2-Hydroxy-4-phenyl-3-cyclohexen-1-one (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (2aB) Colorless oil, $[\alpha]_D$ +18.5° (c = 1.1). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 2950, 1090. ^{1}H-NMR (C_6D_6) δ: 1.6—2.35 (m, 2H, –C$\underline{H}_2$–), 2.4—2.8 (m, 2H, –C$\underline{H}_2$–), 2.95, 3.08 (both s, 3H, each, –OC$\underline{H}_3$ × 2), 3.2—3.55 (m, 4H, –C$\underline{H}_2$OCH$_3$ × 2), 3.9—4.1 (m, 1H, –C$\underline{H}$O–), 4.3—4.65 (m, 2H, –C$\underline{H}$O– and –C=CH–C$\underline{H}$OH), 6.19 (m, 1H, –C=C$\underline{H}$–CHOH), 6.95—7.4 (m, 5H, aromatic protons). Exact MS Calcd for $C_{18}H_{24}O_5$: 320.1621. Found: 320.1605.

2*R*-2-Hydroxy-4-methyl-3-cyclohexen-1-one (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (2bA) and 2*S*-2-Hydroxy-4-methyl-3-cyclohexen-1-one (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (2bB) Run 16: Two diastereoisomers (**2bA** and **2bB**) were obtained in a ratio of 96 : 4. The ratio of the products was determined by ^{1}H-NMR spectroscopy from the ratio of the singlet signals due to the methoxymethyl protons. Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 2935, 1125, 1095, 910. ^{1}H-NMR (C_6D_6) δ: 1.51 (br s, 3H, H$_3$C–C=CH–), 1.6—2.18 (m, 4H, –C$\underline{H}_2$– × 2), 2.95, 3.03, 3.08 (each s, total 6H, ratio 1 : 24 : 25, –OC$\underline{H}_3$ × 2), 3.2—3.55 (m, 4H, –C$\underline{H}_2$OCH$_3$ × 2), 3.95—4.15 (m, 1H, –C$\underline{H}$O–), 4.2—4.45 (m, 2H, –C$\underline{H}$O– and –C=CH–C$\underline{H}$OH), 5.53 (m, 1H, –C=C$\underline{H}$–CHOH). Exact MS Calcd for $C_{13}H_{22}O_5$: 258.1467. Found: 258.1475.

Run 17: Two diastereoisomers (**2bA** and **2bB**) were obtained in the ratio of 10 : 90. Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 2935, 1125, 1095, 910. ^{1}H-NMR (C_6D_6) δ: 1.5 (br s, 3H, H$_3$C–C=CH–), 1.6—2.32 (m, 4H, –C$\underline{H}_2$– × 2), 2.95, 3.03, 3.08 (each s, tatal 6H, ratio 9 : 1 : 10, –OC$\underline{H}_3$ × 2), 3.13—3.5 (m, 4H, –C$\underline{H}_2$OCH$_3$ × 2), 3.89—4.05 (m, 1H, –C$\underline{H}$O–), 4.2—4.6 (m, 2H, –C$\underline{H}$O– and –C=CH–C$\underline{H}$OH), 5.54 (m, 1H, –C=C$\underline{H}$–CHOH). Exact MS Calcd for $C_{13}H_{22}O_5$: 258.1467. Found: 258.1452.

Runs 18, 19: The ratio of diastereoisomers was determined by HPLC analysis [Nucleosil 50—5 column; eluent, hexane : AcOEt = 3 : 2; flow rate, 0.9 ml/min; t_R, **2cA**, 17.2 min, **2cB**, 15.2 min]. The diastereoisomers (**2cA** and **2cB**) were separated by preparative TLC using hexane–ether (1 : 2, development three times).

2*R*-2-Hydroxyl (2*H*)-Naphthalenone (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (2cA) Colorless oil, $[\alpha]_D$ −101.6° (c = 0.26). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 2950, 1130. ^{1}H-NMR (C_6D_6) δ: 2.91, 2.93 (both s, 3H each, –OC$\underline{H}_3$ × 2), 3.1—3.4 (m, 3H, –C$\underline{H}_2$OCH$_3$ × 3/4), 3.6 (dd, 1H, J = 10.5, 2.8 Hz, –C$\underline{H}_2$OCH$_3$), 4.0—4.4 (m, 1H, –C$\underline{H}$O–), 4.6—4.9 (m, 1H, –C$\underline{H}$O–), 4.95 (s, 1H, –HC=CH–C$\underline{H}$OH), 6.21 (s, 2H, –C$\underline{H}$=C$\underline{H}$–CHOH), 6.7—7.3, 7.55—7.83 (both m, total 5H, aromatic protons). Exact MS Calcd for $C_{16}H_{20}O_5$: 292.1308. Found: 292.1308.

2*S*-2-Hydroxy (2*H*)-Naphthalenone (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (2cB) Colorless oil, $[\alpha]_D$ +97.3° (c = 0.42). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 2950, 1140, 1110. ^{1}H-NMR (C_6D_6) δ: 2.89, 3.07 (both s, 3H each, –OC$\underline{H}_3$ × 2), 3.1—3.6 (m, 4H, –C$\underline{H}_2$OCH$_3$ × 2), 3.75—4.1 (m, 1H, –C$\underline{H}$O–), 4.6—5.1 (m, 2H, –C$\underline{H}$O– and –CH=CH–C$\underline{H}$OH), 6.01 (dd, 1H, J = 11.2, 1.3 Hz, –CH=C$\underline{H}$–CHOH), 6.1 (dd, 1H, J = 11.2, 2.0 Hz, –C$\underline{H}$=CH–CHOH), 6.7—7.3, 7.85—8.1 (both m, total 5H, aromatic protons). Exact MS Calcd for $C_{16}H_{20}O_5$: 292.1308. Found: 292.1301.

Conversion of 2cA Obtained in Run 18 into (*R*)-(+)-β-Tetralol (12) Compound **2cA** (70% de; 146 mg, 0.5 mmol) was dissolved in AcOEt (4 ml) and hydrogenated in the presence of a catalytic amount of 5% Pd–C under atmospheric pressure at room temperature. After completion of the reaction (checked by TLC), the catalyst was removed by the use of a celite column, and the filtrate was concentrated *in vacuo* to give a residue, which was subjected to reductive deacetalization without purification. Thus, a solution of the residue and absolute EtOH (0.15 ml) in anhydrous THF (4 ml) was added to a solution of Na metal (70 mg) in liquid NH_3 (10 ml) at −78 °C under a nitrogen atmosphere. After being stirred for 3 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and allowed to warm to room temperature to remove NH_3. The product was extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel using pentane–AcOEt (2 : 1) as an eluent to give a 90% (66.5 mg) yield of (*R*)-(−)-β-tetralol (**12**), whose spectroscopic data (^{1}H-NMR and IR) were identical with those of an authentic sample.[10] Colorless oil. $[\alpha]_D$ +50.4° (c = 0.5, EtOH) [lit. +68.0° (EtOH) (93% ee)].

2,4-Dihydroxy-4-(3,4-dimethoxyphenyl)cyclohexanone (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (13) This compound was prepared from **8** (500 mg, 1.92 mmol) and 3,4-(MeO)$_2$C$_6$H$_3$MgBr in 90% (689 mg) yield. Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 2940, 1260, 1145, 1080. ^{1}H-NMR ($CDCl_3$) δ: 1.4—2.8 (m, 6H, –C$\underline{H}_2$– × 3), 3.4, 3.41, 3.42 (each s, total 6H, –CH$_2$OC$\underline{H}_3$ × 2), 3.4—3.6 (m, 4H, –C$\underline{H}_2$OCH$_3$ × 2), 3.86, 3.88 (both s, 3H each, Ar-OC$\underline{H}_3$ × 2), 3.65—4.4 (m, 3H, –C$\underline{H}$O– × 2 and –C$\underline{H}$OH), 6.6—7.3 (m, total 5H, aromatic protons). Exact MS Calcd for $C_{20}H_{30}O_8$: 398.1940. Found: 398.1953.

4-(3,4-Dimethoxyphenyl)-3-cyclohexene-1,2-dione 1-[(2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene]Acetal (3) Compound **13** (570 mg, 1.43 mmol) was subjected to the PDC–Ac_2O-molecular sieves 3A oxidation by the same procedure as described for the synthesis of **1a**,**b**. Then, the product was treated with anhydrous CF_3COOH (0.8 ml) at 0 °C, and stirring was continued for 10 min at the same temperature. After neutralization of the reaction mixture with saturated aqueous $NaHCO_3$, the product was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–ether (1 : 3) as an eluent to afford **3** in 65% (349 mg) yield. Colorless oil, $[\alpha]_D$ −9.9° (c = 1.6). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 1670, 1600, 1260, 1150, 1090. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (t, 2H, J = 5.7 Hz, –C$\underline{H}_2$–), 2.99 (t, 2H, J = 5.7 Hz, –C$\underline{H}_2$–C=CH–), 3.4, 3.42 (both s, 3H each, –CH$_2$OC$\underline{H}_3$ × 2), 3.5—3.8 (m, 4H, –C$\underline{H}_2$OCH$_3$ × 2), 3.91, 3.92 (both s, 3H each, Ar-OC$\underline{H}_3$ × 2), 3.95—4.4 (m, 2H, –C$\underline{H}$O– × 2), 6.37 (s, 1H, –C=C$\underline{H}$–C=O), 6.87 (d, 1H, J = 8.4 Hz, aromatic proton), 7.06 (d, 1H, J = 1.9 Hz, aromatic proton), 7.16 (dd, 1H, J = 8.4, 1.9 Hz, aromatic proton). Exact MS Calcd for $C_{20}H_{26}O_7$: 378.1679. Found: 378.1702.

Reduction of 3 with $LiAlH_4$ i) In the Absence of Additive: A suspension of $LiAlH_4$ (15 mg, 0.4 mmol) in anhydrous ether (0.8 ml) was added to a solution of **3** (30 mg, 0.08 mmol) in anhydrous ether (8 ml) at −78 °C under a nitrogen atmosphere. After being stirred for 4 h at the same temperature, the mixture was worked up in the same manner as described in the reduction of **1a**—**c** to give **15A** and **15B** in 95% (29 mg) yield. The ratio was determined by HPLC analysis [Nucleosil 50—5 column; **15A**: **15B** = 95 : 5; eluent, hexane : AcOEt = 1 : 1; flow rate, 0.9 ml/min; t_R, **15A**, 47.8 min, **15B**, 40.4 min]. Two diastereoisomers were readily separated by flash column chromatography on silica gel (Merk Kieselgel 60, 230—400 mesh) using hexane–ether (1 : 10) as an eluent.

ii) In the Presence of LiBr or $MgBr_2$: By the same procedure as used for the reduction of **1a**—**c** using an additive, a suspension of $LiAlH_4$ (9 mg, 0.25 mmol) in anhydrous ether (0.5 ml) was added to a mixture of **3** (18 mg, 0.05 mmol) and LiBr or $MgBr_2$ (0.3 mmol) in anhydrous ether (4.8 ml) at −78 °C under a nitrogen atmosphere. After being stirred for 4 h at the same temperature, the mixture was worked up in the same manner as described above in i) to give a 95% (17.5 mg) yield of **15A** and **15B** (**15A** : **15B** = 96 : 4), or an 85% (15.6 mg) yield of **15A** and **15B** (**15A** : **15B** = 10 : 90). Flash column chromatography on silica gel of each product afforded **15A** (15.3 mg), or **15B** (13.1 mg) in a pure state.

2*R*-4-(3,4-Dimethoxyphenyl)-2-hydroxy-3-cyclohexen-1-one (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (15A) Colorless oil, $[\alpha]_D$ +6.92° (c = 0.26). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 2950, 1518, 1260, 1142, 1090. ^{1}H-NMR (C_6D_6) δ: 1.93 (m, 1H, –C$\underline{H}_2$–), 2.12 (m, 1H, –C$\underline{H}_2$–), 2.51 (m, 1H, –C$\underline{H}_2$–), 2.82 (m, –C$\underline{H}_2$–), 3.02, 3.08 (both s, 3H each, –OC$\underline{H}_3$ × 2), 3.34 (dd, 1H, J = 10.1, 3.7 Hz, –C$\underline{H}_2$OCH$_3$), 3.35 (t, 2H, J = 4.3 Hz, –C$\underline{H}_2$OCH$_3$), 3.37, 3.4 (both s, 3H each, Ar-OC$\underline{H}_3$ × 2), 3.49 (dd, 1H, J = 10.1, 3.7 Hz, –C$\underline{H}_2$OCH$_3$), 4.14 (dt, 1H, J = 7.9, 3.7 Hz, –C$\underline{H}$O–), 4.53 (dt, 1H, J = 7.9, 4.3 Hz, –C$\underline{H}$O–), 4.62 (m, 1H, –C=CH–C$\underline{H}$OH), 6.24 (m, 1H, –C=C$\underline{H}$–CHOH), 6.56 (d, 1H, J = 9.2 Hz, aromatic proton), 6.94 (dd, 1H, J = 9.2, 1.8 Hz, aromatic proton), 6.95 (d, 1H, J = 1.8 Hz, aromatic proton). Exact MS Calcd for $C_{20}H_{28}O_7$: 380.1832. Found: 380.1831.

2*S*-4-(3,4-Dimethoxyphenyl)-2-hydroxy-3-cyclohexen-1-one (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (15B) Colorless oil, $[\alpha]_D$ +6.67° (c = 0.22). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 2950, 1518, 1260, 1250, 1140, 1095. ^{1}H-NMR (C_6D_6) δ: 1.95 (m, 1H, –C$\underline{H}_2$–), 2.19 (m, 1H, –C$\underline{H}_2$–), 2.51 (m, 1H, –C$\underline{H}_2$–), 2.76 (m, 1H, –C$\underline{H}_2$–), 2.93, 3.08 (both s, 3H each, –CH$_2$OC$\underline{H}_3$ × 2), 3.18 (dd, 1H, J = 10.7, 3.1 Hz, –C$\underline{H}_2$OCH$_3$), 3.35 (dd, 1H, J = 10.7, 4.9 Hz, –C$\underline{H}_2$OCH$_3$), 3.37 (dd, 1H, J = 10.7, 4.9 Hz, –C$\underline{H}_2$OCH$_3$), 3.38, 3.39 (both s, 3H each, Ar-OC$\underline{H}_3$ × 2), 3.44 (dd, 1H, J = 10.7, 3.1 Hz, –C$\underline{H}_2$OCH$_3$), 4.03 (dt, 1H, J = 11.6, 3.1 Hz, –C$\underline{H}$O–), 4.61

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(dt, 2H, J=11.6, 4.9 Hz, –CHO–), 4.6 (m, 1H, –C=CH–CHOH), 6.24 (m, 1H, –C=CH–CHOH), 6.55 (d, 1H, J=8.5 Hz, aromatic proton), 6.94 (dd, 1H, J=8.5, 1.8 Hz, aromatic proton), 6.95 (d, 1H, J=1.8 Hz, aromatic proton). Exact MS Calcd for $C_{20}H_{28}O_7$: 380.1832. Found: 380.1851.

The Claisen–Eschenmoser [3,3]-Sigmatropic Rearrangement of the Allyl Alcohol (15A or 15B) General Procedure: A solution of **15A** or **15B** (38 mg, 0.1 mmol) in *N*,*N*-dimethyl acetamide dimethyl acetal (0.2 ml) was gradually heated to 110 °C under a nitrogen stream. Stirring was continued for 1 h at the same temperature. The resulting mixture was diluted with benzene and the solvent was evaporated off under reduced pressure to remove excess *N*,*N*-dimethyl acetamide dimethyl acetal. The residue was purified by column chromatography on silica gel using ether–AcOEt (1 : 5) as an eluent to give **16** in 89% (40 mg) yield or **17** in 90% (41 mg) yield.

4*R*-4-(3,4-Dimethoxyphenyl)-4-(2-*N*,*N*-dimethylamino-2-oxoethyl)-2-cyclohexen-1-one (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (16) Pale yellow oil. $[\alpha]_D$ −6.15° (c=0.73). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 1630, 1130, 1090. ^{1}H-NMR (C_6D_6) δ: 2.1 (s, 3H, –N(CH_3)$_2$), 2.05—2.22 (m, 2H, –CH_2–), 2.25—2.49 (m, 2H, –CH_2–), 2.51 (d, 1H, J=15.3 Hz, –CH_2–C(=O)N–), 2.55 (s, 3H, –N(CH_3)$_2$), 2.66 (d, 1H, J=15.3 Hz, –CH_2–C(=O)N–), 3.12, 3.16 (both s, 3H each, –CH_2OCH_3 × 2), 3.45, 3.5 (both s, 3H each, Ar-OCH_3 × 2), 3.46 (d, 2H, J=4.9 Hz, –CH_2OCH_3), 3.47 (d, 2H, J=4.9 Hz, –CH_2OCH_3), 4.15 (dt, 1H, J=7.9, 4.9 Hz, –CHO–), 4.26 (dt, 1H, J=7.9, 4.9 Hz, –CHO–), 6.16 (d, 1H, J=10.4 Hz, –CH=CHC(O–)$_2$), 6.6 (d, 1H, J=8.6 Hz, aromatic proton), 6.91 (d, 1H, J=10.4 Hz, –CH=CHC(O–)$_2$), 6.94 (dd, 1H, J=8.6, 1.8 Hz, aromatic proton), 7.05 (d, 1H, J=1.8 Hz, aromatic proton). Exact MS Calcd for $C_{24}H_{35}NO_7$: 449.2413. Found: 449.2449.

4*S*-4-(3,4-Dimethoxyphenyl)-4-(2-*N*,*N*-dimethylamino-2-oxoethyl)-2-cyclohexen-1-one (2*S*,3*S*)-1,4-Dimethoxy-2,3-butylene Acetal (17) Pale yellow oil. $[\alpha]_D$ −16.45° (c=1.1). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2950, 1625, 1090. ^{1}H-NMR (C_6D_6) δ: 2.1 (s, 3H, –N(CH_3)$_2$), 2.0—2.16 (m, 2H, –CH_2–), 2.25—2.49 (m, 2H, –CH_2–), 2.45 (d, 1H, J=15.8 Hz, –CH_2–C(=O)N–), 2.54 (s, 3H, –N(CH_3)$_2$), 2.65 (d, 1H, J=15.8 Hz, –CH_2–C(=O)N–), 3.1, 3.17 (both s, 3H each, –CH_2OCH_3 × 2), 3.41 (d, 2H, J=4.9 Hz, –CH_2OCH_3), 3.45, 3.54 (both s, 3H, each, Ar-OCH_3 × 2), 3.49 (d, 2H, J=4.3 Hz, –CH_2OCH_3), 4.17 (dt, 1H, J=12.0, 4.9 Hz, –CHO–), 4.26 (dt, 1H, J=12.0, 4.3 Hz, –CHO–), 6.11 (d, 1H, J=10.4 Hz, –CH=CHC(O–)$_2$), 6.61 (d, 1H, J=7.9 Hz, aromatic proton), 6.93 (d, 1H, J=10.4 Hz, –CH=CHC(O–)$_2$), 6.95 (dd, 1H, J=7.9, 2.4 Hz, aromatic proton), 7.05 (d, 1H, J=2.4 Hz, aromatic proton). Exact MS Calcd for $C_{24}H_{35}NO_7$: 449.2413. Found: 449.2427.

(*R*)-(−)- and (*S*)-(+)-4′-Methoxy-3′-*O*-methyljoubertiamine [(*R*)-(−)- and (*S*)-(+)-4] $LiAlH_4$ (7 mg, 0.17 mmol) was added to a stirred solution of **16** or **17** (25 mg, 0.06 mmol) in anhydrous ether (1 ml) at 0 °C under a nitrogen atmosphere. After being stirred for 2 h at the same temperature, the mixture was quenched by successive addition of AcOEt, MeOH, and 10% aqueous NaOH. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure to afford a residue, which was subjected to acid hydrolysis without further purification. Thus, the residue was dissolved in 80% aqueous AcOH (1 ml) containing a catalytic amount of concentrated H_2SO_4 and refluxed for 1 h. The mixture was made basic with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to give the residue, which was chromatogtaphed on silica gel using $CHCl_3$–MeOH (10 : 1) as an eluent to afford (*R*)-(−)-**4** in 85% (14.5 mg) yield, or (*S*)-(+)-**4** in 82% (14 mg) yield. These compounds were identical with authentic samples in terms of ^{1}H-NMR, IR and mass spectral data.

(*R*)-(−)-3′-Methoxy-4′-*O*-methyljoubertiamine [(*R*)-(−)-4] Colorless oil. $[\alpha]_D$ −49.5° (c=0.1). CD θ_{340} −6400 (absolute MeOH) [lit.[14] CD θ_{340} −6420 (absolute MeOH)].

(*S*)-(+)-3′-Methoxy-4′-*O*-methyljoubertiamine [(*S*)-(+)-4] Colorless oil. $[\alpha]_D$ +49.5° (c=0.09). CD θ_{340} −6400 (absolute MeOH).

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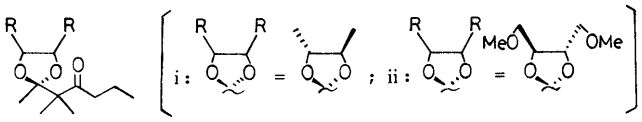

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