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A STEREOCONTROLLED CONSTRUCTION OF *rel*-(7*S*,8*S*,7'*R*,8'*S*)-7,7'-EPOXYLIGNAN SKELETON

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Abstract – We have developed a highly diastereoselective route to construct *rel*-(7*S*,8*S*,7'*R*,8'*S*)-7,7'-epoxylignan skeleton, wherein stereocontrolled Michael addition to γ-oxyenone intermediate and subsequent α-alkylation to the resulting ketone are keys to the synthesis.

INTRODUCTION

Many kinds of 7,7'-epoxylignan having structural and enantiomeric diversity were isolated from various plant sources. They contain fully substituted THF ring and four contiguous stereogenic centers. Some of them have interesting biological activities, such as antioxidant,[1] neuroprotective activity,[2] trypanocidal activity,[3] inhibition of nitric acid production,[4] and platelet-activating factor (PAF) antagonist activity.[5]

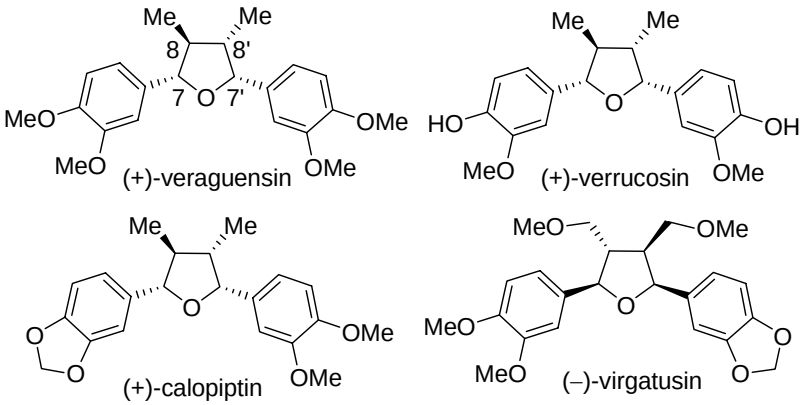
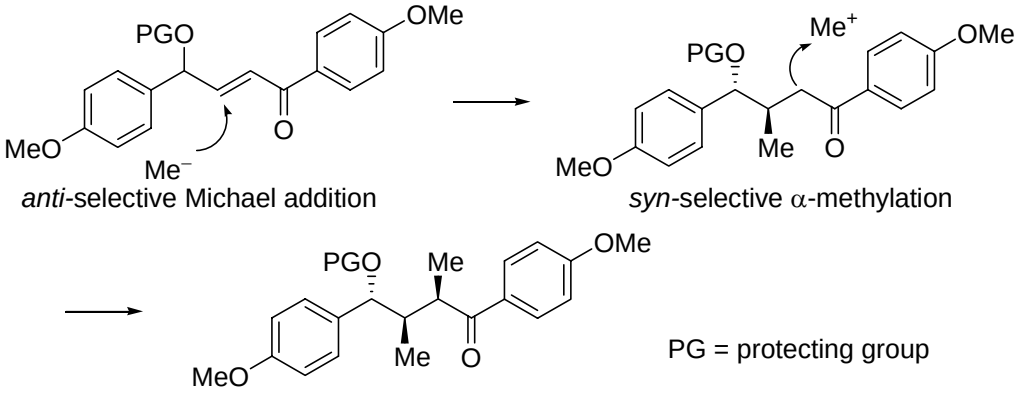


Figure 1 *rel*-(7*S*,8*S*,7'*R*,8'*S*)-7,7'-Epoxylignans

Therefore, considerable efforts have been devoted to synthesize the natural products,[6] but there are few approach based on diastereoselective Michael addition.[7]

We have developed a new method to construct a skeleton of *rel*-(7*S*,8*S*,7'*R*,8'*S*)-7,7'-epoxylignans, which involves many congeners represented by Figure 1. Scheme 1 shows our key reaction to construct the three contiguous stereogenic centers using *anti*-selective Michael addition to γ-oxyenone followed by *syn*-selective α-methylation of the resulting ketone. Since there are comparatively few applications of diastereoselective Michael reaction to γ-oxyenones[8] in contrast to that to γ-oxyenoate,[9] stereocontrol in this system and stereoselective construction of the epoxylignan framework are of our interests.

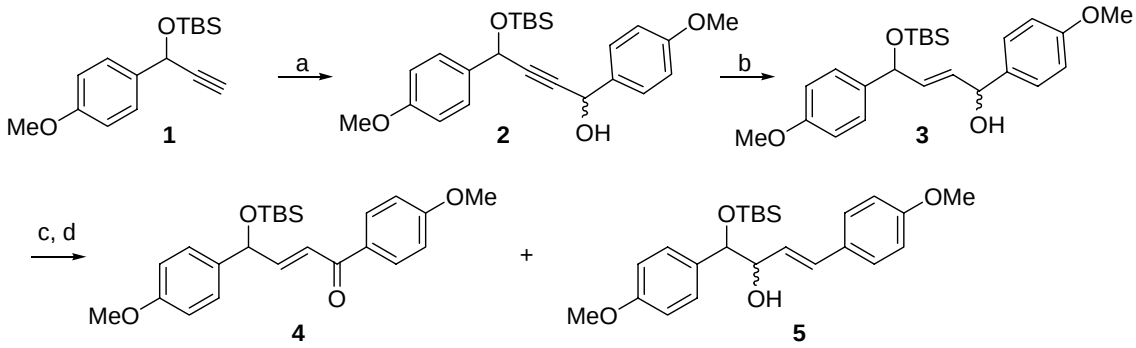
Herein, we will describe a full detail of our research regarding a synthesis of 7,7'-epoxylignan skeleton with *rel*-(7*S*,8*S*,7'*R*,8'*S*) stereochemistry.



Scheme 1 Stereocontrolled construction of three contiguous stereocenters

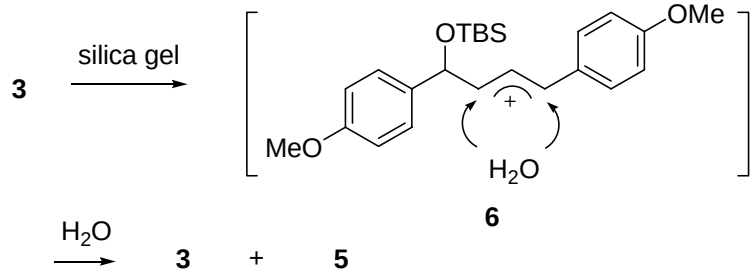
RESULTS AND DISCUSSION

Propargylic alcohol intermediate (**2**) was synthesized from known alkyne (**1**),[10] which was prepared in 64% in three steps from commercially available *p*-anisaldehyde in a subsequent reaction: 1) alkynylation with lithium trimethylsilylacetylide, 2) protection of the resulting alcohol with TBS ether, and 3) K_2CO_3-promoted desilylation on the alkyne. Coupling of the alkyne (**1**) with *p*-anisaldehyde was carried out in the presence of HMPA to give **2** in 90% yield. The propargylic alcohol (**2**) was stereoselectively reduced to (*E*)-allylic alcohol (**3**) with Red-Al®. After purification of the crude **3** with silica gel column chromatography, oxidation to enone (**4**) was carried out using MnO_2 under ultrasound irradiation. Unexpectedly, the reaction provided a considerable amount of migration product (**5**) (11% from **3**) along with desired **4** (34% from **3**) (Scheme 2).



Scheme 2 *Reagents and Conditions:* (a) *n*-BuLi, HMPA, *p*-anisaldehyde, THF, −78 °C, 90%; (b) Red-Al®, THF, 0 °C to rt, 66%; (c) column chromatography on silica gel; (d) MnO_2, CH_2Cl_2, ultrasound, rt, 38% of **4** and 11% of **5** each from **3**.

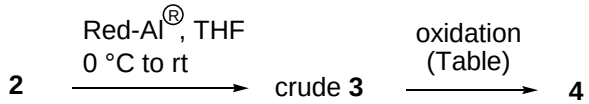
The results were rationalized as shown in Scheme 3. The *p*-methoxybezylic alcohol moiety in **3** was acid-sensitive to form readily an allylic cation intermediate (**6**) due to stabilization by +R effect of the *p*-methoxyphenyl group. Thus, treatment with acidic silica gel resulted in allylic rearrangement to give isomeric allylic alcohol (**5**), which was not be oxidized by MnO_2 due to steric demand.



Scheme 3

Therefore, the crude allylic alcohol (**3**) was used in the next step without purification. The results are shown in Table 1.

Table 1 Conversion of propargylic alcohol (**2**) into enone (**4**) without purification of allylic alcohol intermediate (**3**).[a]



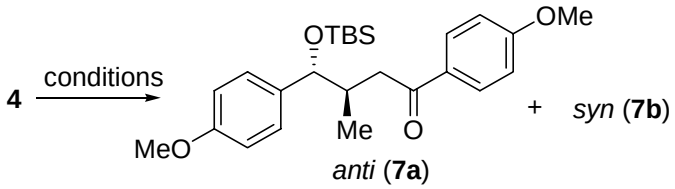
Entry	Conditions (equiv)	Time (h)	Yield (%)
1	MnO_2 (10), ultrasound, CH_2Cl_2, rt	48	54
2	TPAP (0.1), NMO (1.5), CH_2Cl_2, 4A molecular sieves, rt	23	49
3	TPAP (0.16), NMO (2), CH_2Cl_2/MeCN, 4A molecular sieves, rt	2	55

[a] Reduction of **2** was carried out with 2 equiv of Red-Al® in THF. The resulting crude (*E*)-allylic alcohol (**3**) was used for oxidation without column chromatograpy.

As a result, the yield of **4** was improved to 54% by oxidation with MnO_2, but it takes long reaction time even under ultrasound irradiation (entry 1). The oxidation reaction could be replaced by tetra-*n*-propylammonium perruthenate (TPAP) oxidation in CH_2Cl_2 using *N*-methylmorpholine oxide (NMO) as co-oxidant in the presence of 4A molecular sieves (entry 2). The reaction time was remarkably retarded when a 9:1 mixture of MeCN and CH_2Cl_2 was employed as a solvent[11] in 55% yield (entry 3).

Michael addition of organocopper reagents to the enone (**4**) was examined as shown in Table 2. Gilman reagent afforded an adduct (**7a**) predominately in good yield and with high diastereoselectivity (entry 1). BF_3 promoted Michael addition exhibited comparative yield and selectivity (entry 3). However, TMSCl stimulated Michael addition followed by methanolysis of the resulting TMS enolate and hetero cuplate reduced both the yield and selectivity (entries 2 and 4). Higher ordered organocopper reagent showed high diastereoselectivity but with moderate yield (entry 5). The CuI catalyzed Michael addition using Grignard reagent furnished only a trace amount of product (entry 6).

Table 2 Diastereoselective Michael addition to **4**.

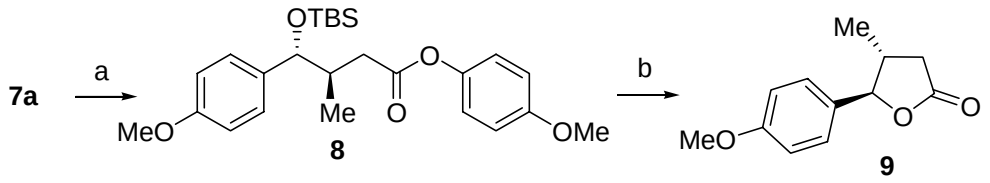


Entry	Conditions (equiv)	Yield (%)	**7a**/**7b** ratio[a]
1	Me_2CuLi (1.5), THF, −40 °C, rt	74	30:1
2	1) Me_2CuLi (1.5), HMPA (2), TMSCl (2), Et_3N (2), THF, −78 °C 2) K_2CO_3, MeOH, rt	52	5:1
3	Me_2CuLi (1.5), BF_3•Et_2O (1), THF, −78 °C	72	33:1
4	MeCu(CN)Li (4), THF, −30 °C	37	9:1
5	$Me_2Cu(CN)Li_2$ (1.5), THF, −45 °C	41	28:1
6	CuI (0.25), MeMgBr (1.2), −78 °C	trace	–

[a] Determined by ^{1}H NMR spectroscopic data.

The stereochemistry of the *anti*-adduct (**7a**) was determined by comparison with structurally related compounds, wherein *anti*-adducts have larger coupling constant than those of the corresponding *syn*-adducts.[12] The methine proton neighboring the TBSO group in *anti*-adduct appeared higher field than the corresponding *syn*-adduct. In the major adduct (**7a**), the methine proton appeared δ = 4.49 ppm with 6.1 Hz of vicinal coupling. On the other hand, that of the minor adduct exhibited doublet with J = 4.6 Hz at δ = 4.62 ppm. The assignment was confirmed by conversion of **7a** into known γ-lactone (**9**) by Dakin oxidation of **7a** with *m*-CPBA and subsequent lactonization with TBAF (Scheme 4). The spectral

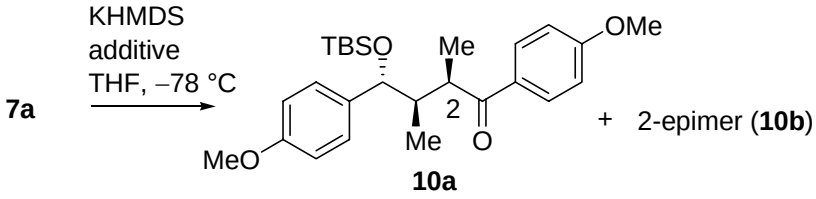
data was identified with those of the reported values.[13] The stereochemical outcome was identical with that is predicted from reaction mechanism of diastereoselective Michael addition to γ-oxy-α,β-unsaturated esters, which is reported in literature.[9]



Scheme 4 *Reagents and Conditions*: (a) *m*-CPBA, $CHCl_3$, rt; (b) TBAF, THF, 37% in two steps (dr 20:1).

Diastereoselectivity of α-methylation of the ketone (**7a**) was affected by additive (Table 3). Optimal results were obtained by the addition of HMPA, giving dimethyl adduct (**10a**) in 99% yield and with 14:1 dr (entry 2).[14]

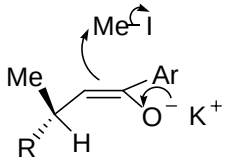
Table 3 Diastereoselective methylation of **7a**.[a]



Entry	Additive (equiv)	Yield (%)	**10a**/**10b** ratio[b]
1	none	94	5:1
2	HMPA (5)	99	14:1
3	18-crown-6 (2)	88	3:1

[a] 2 equiv of KHMDS and 5 equiv of MeI were used.
[b] Determined by ^{1}H NMR spectroscopic data.

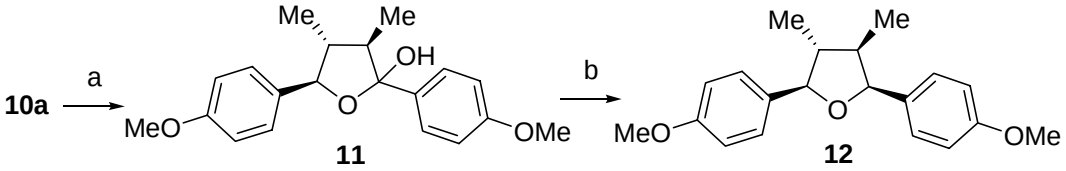
Stereochemistry of the product was tentatively assumed as *syn*-dimethyl that is expected from the reaction mechanism, that is, methylation from less hindered face of the enolate, which would take preferred conformation minimizing $A^{(1,3)}$-strain as shown in Scheme 5. The speculation was confirmed later by NOE experiments of final product.



R = *p*-$MeOC_6H_4CH(OTBS)$
Ar = *p*-$MeOC_6H_4$

Scheme 5 Plausible reaction mechanism of α-methylation.

Upon treatment with TBAF, the resulting ketol was immediately cyclized to give hemiacetal (**11**) as a single isomer, which was hydrogenated on $Pd(OH)_2$ in EtOAc to give **12** in 81% yield in two steps.[6d] In this reaction amount of Pd-catalyst was important. When 0.44 g of catalyst was employed for 1 mmol of substrate, hydrogenolysis of the THF ring occurred and product (**12**) was not obtained. The problem was solved by reducing the catalyst to 0.25 g/mmol. Thus, tetrasubstituted THF skeleton was constructed with high diastereoselectivity (Scheme 6).[15]



Scheme 6 *Reagents and Conditions*: (a) TBAF, THF, rt; (b) H_2, $Pd(OH)_2$ (20% on carbon, 0.25 g/mmol), EtOAc, rt, 81% in two steps.

In conclusion, we have developed a novel method to construct the framework of *rel*-(7*S*,8*S*,7'*R*,8'*S*)-7,7'-epoxylignans involved in many THF lignan congeners. In addition, the route would be applicable to a synthesis of THF lignan analogues, which are expected to have interesting biological activity. Furthermore, since optically active 1-(4-methoxyphenyl)-2-propyn-1-ol is available,[16] the synthetic route would be extended to an asymmetric synthesis.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 400 and 100 MHz, respectively, with a JEOL JNM-AL-400 spectrometer. Chemical shifts of ^1H NMR are expressed in ppm downfield from tetramethylsilane as an internal standard ($\delta = 0$). Chemical shifts of ^{13}C NMR are expressed as ppm in $CDCl_3$ as an internal standard ($\delta = 77$). IR absorption spectra (FT: diffuse reflectance spectroscopy) were recorded with KBr powder with a JASCO FT-6300 IR spectrophotometer, and only noteworthy absorptions (cm^{-1}) are listed. MS spectra were measured by a JEOL GC-Mate II mass spectrometer. Purification of the crude products was carried out by flash column chromatography. Fuji Silysia Silica Gel BW-300 was used as an adsorbent for column chromatography. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under Ar atmosphere. All organic extracts were dried over anhydrous Na_2SO_4, filtrated, and concentrated with a rotary evaporator under reduced pressure.

4-(*tert*-Butyldimethylsilyloxy)-1,4-bis(4-methoxyphenyl)-2-butyn-1-ol (2) HMPA (0.19 mL, 1.09 mmol) was added to a stirred solution of **1**[10] (300 mg, 1.09 mmol) in THF (6 mL) at −78 °C under Ar and

then *n*-BuLi (1.60 M in *n*-hexane, 0.74 mL, 1.19 mmol) was added to the mixture, and the stirring was continued at this temperature. After 15 min, a solution of *p*-anisaldehyde (162 mg, 1.19 mmol) in THF (1 mL) was added to the mixture and the stirring was continued at −78 °C for 10 min and then at 0 °C for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, and the resulting mixture was extracted with EtOAc. The combined extracts were washed with saturated aqueous NH_4Cl and brine prior to drying and solvent evaporation. The crude residue was chromatographed on silica gel eluting with *n*-hexane–EtOAc (5:1) to give **2** (402 mg, 90%, 1:1 dr) as a yellow oil. ^{1}H NMR δ: 0.12 (s, 3H, $SiCH_3$), 0.14 (s, 1.5H, $SiCH_3$), 0.14 (s, 1.5H, $SiCH_3$), 0.917 (s, 4.5H, $C(CH_3)_3$), 0.920 (s, 4.5H, $C(CH_3)_3$), 2.16 (br s, 1H, OH), 3.80 (s, 3H, OCH_3), 3.80 (s, 1.5H, OCH_3), 3.81 (s, 1.5H, OCH_3), 5.46 (d, J = 1.5 Hz, 1H, C*H*OH), 5.53 (s, 1H, C*H*OTBS), 6.86–6.89 (m, 4H, Ar), 7.40 (d, J = 8.8 Hz, 2H, Ar), 7.44 (d, J = 8.5 Hz, 1H, Ar), 7.44 (d, J = 8.8 Hz, 1H, Ar); ^{13}C NMR δ: −4.88, −4.50, 18.27, 25.77 (3C), 55.24, 55.28, 64.26, 64.47, 85.11 (1/2C), 85.13 (1/2C), 87.64, 113.65 (2C), 113.84 (2C), 127.37 (2C), 128.09 (2C), 132.79, 133.75, 159.14, 159.60; IR (KBr) cm^{-1} 3422 (OH), 2954, 2931, 2896, 2856, 1611, 1511; MS (FAB) *m/z* 413 (MH^+); HRMS (FAB) calcd for $C_{24}H_{33}O_4Si$ (MH^+): 413.2148, found: 413.2142.

(*E*)-4-(*tert*-Butyldimethylsilyloxy)-1,4-bis(4-methoxyphenyl)-2-buten-1-one (4): Red-Al reduction followed by MnO_2 (II) oxidation (Table 1, entry 1) Red-Al® (1.52 mL, 5.00 mmol) was added to a solution of **2** (1.03 g, 2.50 mmol) in THF (20 mL) with stirring at 0 °C under Ar and the stirring was continued at the temperature for 40 min. The reaction was quenched with saturated aqueous Rochelle salt (8 mL) and the whole was stirred at rt for 30 min. The organic layer was separated and the aqueous phase was extracted with EtOAc. The combined extracts were washed with water and brine prior to drying and solvent evaporation. MnO_2 (*ca* 85%) (2.56 g, 25.0 mmol) was added to a stirred solution of the crude allylic alcohol **3** (1.23 g) in CH_2Cl_2 (12 mL) at rt under Ar. The reaction mixture was allowed to stand under ultrasound irradiation for 48 h. After diluted with CH_2Cl_2, the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude was chromatographed on silica gel eluting with *n*-hexane–EtOAc (5:1) to give **4** (559 mg, 54% in two steps) as a yellow oil. ^{1}H NMR δ: −0.03 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.94 (s, 9H, $C(CH_3)_3$), 3.80 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.38 (dd, J = 4.1, 1.6 Hz, 1H, C*H*OTBS), 6.87 (d, J = 8.8 Hz, 2H, Ar), 6.95 (d, J = 9.0 Hz, 2H, Ar), 7.03 (dd, J = 15.1, 4.1 Hz, 1H, C*H*=CHCO), 7.18 (dd, J = 15.1, 1.6 Hz, 1H, CH=C*H*CO), 7.26 (d, J = 8.5 Hz, 2H, Ar), 7.94 (d, J = 8.8 Hz, 2H, Ar); ^{13}C NMR δ: −4.87, −4.78, 18.32, 25.83 (3C), 55.24, 55.45, 74.18, 113.78 (2C), 113.89 (2C), 122.16, 127.57 (2C), 130.82 (2C), 130.92, 133.91, 149.72, 159.12, 163.36, 189.19; IR (KBr) cm^{-1} 2954, 2931, 2897, 2856, 1667, 1621, 1600, 1574, 1511, 1463, 1256, 1170, 1032; MS (FAB) *m/z* 413 (MH^+); HRMS (FAB) calcd for $C_{24}H_{33}O_4Si$ (MH^+): 413.2148, found: 413.2137.

Red-Al reduction followed by Ley oxidation without MeCN (Table 1, entry 2) Compound **2** (1.00 g, 2.43 mmol) was converted into the crude allylic alcohol **3** (1.34 g) in the same manner that described for the procedure of compound **4**. TPAP (42 mg, 5 mol%) was added to a mixture of the crude (1.34 g), 4A molecular sieves (1.20 g), and NMO (428 mg, 3.70 mmol) in CH_2Cl_2 (8 mL) with stirring at rt under Ar. After 3 h, an additional TPAP (42 mg, 5 mol%) was added to the mixture and the mixture had been stirred at rt for 6 h. Then, NMO (428 mg, 3.70 mmol) was added to the mixture and the whole was stirred at the temperature for 14 h. After diluted with CH_2Cl_2, the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude was chromatographed on silica gel eluting with *n*-hexane–EtOAc (7:1) to give **4** (494 mg, 49% in two steps) as a yellow oil.

Red-Al reduction followed by Ley oxidation with MeCN (Table 1, entry 3): Compound **2** (0.97 g, 2.35 mmol) was converted into the allylic alcohol **3** (935 mg) in the same manner that described for the procedure of compound **4**. TPAP (64 mg, 8 mol%) was added to a mixture of the crude (935 mg), 4A molecular sieves (1.10 g), and NMO (560 mg, 4.80 mmol) in CH_2Cl_2/MeCN (9:1, 8 mL) with stirring at rt under Ar. After 5 min, TPAP (64 mg, 8 mol%) was added to the mixture with stirring at the temperature for 2 h. After diluted with CH_2Cl_2, the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude residue was chromatographed on silica gel eluting with *n*-hexane–EtOAc (7:1) to give **4** (530 mg, 55% in two steps) as a yellow oil**.**

(*E*)-1-(*tert*-Butyldimethylsilyloxy)-1,4-bis(4-methoxyphenyl)-3-buten-2-ol (5) ^{1}H NMR δ: −0.13 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $C(CH_3)_3$), 2.11 (d, J = 4.1 Hz, 1H, OH), 3.80 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.25–4.29 (m, C*H*OH), 4.61 (d, J = 5.4 Hz, 1H, C*H*OTBS), 5.98 (dd, J = 16.0, 6.8 Hz, 1H, C*H*=CHAr), 6.50 (d, J = 16.0 Hz, 1H, CH=C*H*Ar), 6.83 (d, J = 8.8 Hz, 2H, Ar), 6.86 (d, J = 8.8 Hz, 2H, Ar), 7.25 (d, J = 8.7 Hz, 2H, Ar), 7.26 (d, J = 8.7 Hz, 2H, Ar); ^{13}C NMR δ: −4.99, −4.60, 18.18, 25.78 (3C), 55.18, 55.24, 77.32, 78.05, 113.45 (2C), 113.92 (2C), 126.20, 127.61 (2C), 128.29 (2C), 129.80, 131.39, 133.02, 159.12, 159.15; IR (KBr) cm^{-1} 3520, 2954, 2931, 2896, 2856, 1671, 1608, 1511, 1464, 1302, 1250, 1175, 1089, 1036; MS (FAB) *m/z* 437 (MNa^+); HRMS (FAB) calcd for $C_{24}H_{34}O_4SiNa$ (MNa^+): 437.2124, found: 437.2115.

***rac*-(3*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-1,4-bis(4-methoxyphenyl)-3-methyl-1-butanone (7a): Michael addition with Me_2CuLi (Table 2, entry 1)** Methyllithium (1.5 M in Et_2O, 1.24 mL, 1.86 mmol) was added dropwise to a suspension of copper(I) iodide (177 mg, 0.93 mmol) in dry THF (2.0 mL) with stirring at −30 °C under Ar and the stirring was continued for 15 min at the temperature. Then, the reaction mixture was cooled to –40 °C and a solution of **4** (240 mg, 0.58 mmol) in dry THF (1.3 mL)

was added dropwise. The whole was stirred at the temperature for 1 h. The reaction mixture was quenched with a 9:1 mixture of saturated aqueous NH_4Cl and 28% NH_4OH, and extracted with EtOAc. The combined extracts were washed with saturated aqueous NH_4Cl, water, and brine prior to drying and solvent evaporation. The crude residue was chromatographed on silica gel eluting with *n*-hexane–EtOAc (10:1) to give **7a** (184 mg, 74%, 30:1 dr) as a colorless oil. ^{1}H NMR δ: −0.21 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.83 (d, J = 6.8 Hz, 3H, 2-CH_3), 0.90 (s, 9H, $C(CH_3)_3$), 2.31–2.41 (m, 1H, C*H*CH_3), 2.59 (dd, J = 15.4, 9.8 Hz, 1H, 2-H), 3.24 (dd, J = 15.4, 3.4 Hz, 1H, 2-H), 3.80 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.49 (d, J = 6.1 Hz, 1H, C*H*OTBS), 6.84 (d, J = 8.8 Hz, 2H, Ar), 6.89 (d, J = 8.8 Hz, 2H, Ar), 7.20 (d, J = 8.8 Hz, 2H, Ar), 7.86 (d, J = 8.8 Hz, 2H, Ar); ^{13}C NMR δ: –5.09, −4.56, 16.57, 18.15, 25.87 (3C), 38.92, 40.87, 55.13, 55.37, 78.54, 113.21 (2C), 113.55 (2C), 127.79 (2C), 130.32, 130.39 (2C), 135.71, 158.64, 163.18, 199.13; IR (KBr) cm^{-1} 2955, 2931, 2898, 2856, 1674, 1601, 1576, 1511, 1463, 1254, 1172, 1068, 1035; MS (FAB) *m/z* 429 (MH^+); HRMS (FAB) calcd for $C_{25}H_{37}O_4Si$ (MH^+): 429.2461, found: 429.2455.

Michael addition with Me_2CuLi in the presence of BF_3·Et_2O (Table 2, entry 3) Methyllithium (1.5 M in Et_2O, 0.50 mL, 0.75 mmol) was added dropwise to a suspension of copper(I) iodide (72 mg, 0.38 mmol) in dry THF (1.0 mL) with stirring at −30 °C under Ar and the stirring was continued for 15 min. Then, the reaction mixture was cooled to −78 °C and BF_3·Et_2O (0.032 mL, 0.25 mmol) was added to the mixture. After 5 min, a solution of **4** (104 mg, 0.25 mmol) in dry THF (0.8 mL) was added dropwise and the whole was stirred at −78 °C for 1.5 h. The reaction was quenched with a 9:1 mixture of saturated aqueous NH_4Cl and 28% NH_4OH, and extracted with EtOAc. The combined extracts were washed with saturated aqueous NH_4Cl, water, and brine prior to drying and solvent evaporation. The crude residue was chromatographed on silica gel eluting with *n*-hexane–EtOAc (10:1) to give **7a** (78 mg, 72%, 33:1 dr) as a colorless oil.

***rac*-(3*R*,4*R*)-4-(4-Methoxyphenyl)-3-methyl-4-butanolide (9):** *m*-CPBA (205 mg, 1.19 mmol) was added to a solution of **7a** (102 mg, 0.24 mmol) in $CHCl_3$ (0.6 mL) with stirring at rt for 2 days under Ar. The reaction mixture was dissolved in CH_2Cl_2 and quenched with saturated aqueous $Na_2S_2O_3$. The organic layers were extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, water, and brine prior to drying and solvent evaporation. TBAF (1 M in THF, 0.72 mL, 0.72 mmol) was added to a solution of the crude **8** (95 mg, 0.24 mmol) in THF (1.0 mL) with stirring at rt for 20 h under Ar. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with water and brine prior to drying and solvent evaporation. The

residue was chromatographed on silica gel eluting with *n*-hexane–EtOAc (3:1) to give **9** (18 mg, 37% in two steps) as a colorless solid. The spectral data was identified with the reported data.[13]

***rac*-(2*R*,3*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-1,4-bis(4-methoxyphenyl)-2,3-dimethyl-1-butanone (10a) (Table 3, entry 2)** KHMDS (3.14 mL, 1.57 mmol) was added to a solution of **7a** (336 mg, 0.78 mmol) in THF (5.0 mL) with stirring at −78 °C under Ar and then HMPA (0.682 mL, 3.92 mmol) was added. After 5 min, MeI (0.244 mL, 3.92 mmol) was added to the mixture and the stirring was continued at −78 °C for 40 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with EtOAc. The combined extracts were washed with water and brine prior to drying and solvent evaporation. The crude residue was chromatographed on silica gel eluting with *n*-hexane–EtOAc (6:1) to give **10a** (342 mg, 99%, 14:1 dr) as a colorless oil. ^{1}H NMR δ: –0.28 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.46 (d, J = 6.8 Hz, 3H, 3-CH_3), 0.93 (s, 9H, $C(CH_3)_3$), 1.12 (d, J = 6.8 Hz, 3H, 2-CH_3), 2.22–2.30 (m, 1H, 3-H), 3.78 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.11–4.14 (m, 1H, 2-H), 4.37 (d, J = 8.8 Hz, 1H, C*H*OTBS), 6.81 (d, J = 8.8 Hz, 2H, Ar), 6.93 (d, J = 8.8 Hz, 2H, Ar), 7.14 (d, J = 8.8 Hz, 2H, Ar), 8.05 (d, J = 8.8 Hz, 2H, Ar). ^{13}C NMR δ: −5.12, −4.46, 8.96, 10.62, 18.13, 25.88 (3C), 39.99, 43.38, 55.16, 55.41, 77.60, 113.34 (2C), 113.60 (2C), 128.10 (2C), 129.25, 130.96 (2C), 135.81, 158.88, 163.08, 202.15; IR (KBr) cm^{-1} 2955, 2932, 2898, 2856, 1674, 1602, 1575, 1510, 1462, 1251, 1174, 1070, 1053, 1036; MS (FAB) *m/z* 441 $(M-H)^+$; HRMS (FAB) calcd for $C_{26}H_{37}O_4Si$ $(M-H)^+$: 441.2461, found: 441.2471.

***rac*-(2*R*,3*R*,4*R*,5*S*)-2,5-Bis(4-methoxyphenyl)-3,4-dimethyltetrahydrofuran (12):** TBAF (1 M in THF, 0.62 mL, 0.62 mmol) was added to a solution of **10a** (91 mg, 0.21 mmol) in THF (1.5 mL) with stirring at rt for 15 h under Ar. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with EtOAc. The combined extracts were washed with water and brine prior to drying and solvent evaporation. A solution of the crude hemiacetal **11** (70 mg, 0.21 mmol) in THF (1.5 mL) was hydrogenated on $Pd(OH)_2$ (20% on carbon, 0.20 g/mmol) with stirring at rt for 40 min. Additional $Pd(OH)_2$ (20% on carbon, 0.05 g/mmol) was added to the mixture and the whole was stirred for 30 min. The catalyst was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel eluting with *n*-hexane–EtOAc (5:1) to give **12** (52 mg, 81%) as colorless crystals. Mp 88.0 °C. ^{1}H NMR δ: 0.64 (d, J = 7.1 Hz, 3H, CH_3), 1.04 (d, J = 6.1 Hz, 3H, CH_3), 1.71–1.81 (m, 1H, C*H*CH_3), 2.18–2.28 (m, 1H, C*H*CH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.39 (d, J = 9.3 Hz, 1H, C*H*Ar), 5.14 (d, J = 8.8 Hz, 1H, C*H*Ar), 6.89 (d, J = 8.8 Hz, 2H, Ar), 6.93 (d, J = 8.8 Hz, 2H, Ar), 7.28 (d, J = 8.8 Hz, 2H, Ar), 7.43 (d, J = 8.8 Hz, 2H, Ar); ^{13}C NMR δ:14.88, 15.23, 45.95, 48.48, 55.19, 55.24, 82.75, 87.19, 113.31(2C), 113.78 (2C), 127.79 (2C), 128.09 (2C), 132.94, 133.30, 158.66, 159.16;

IR (KBr) cm^{-1} 2953, 2870, 1613, 1586, 1516, 1455, 1250, 1032; MS (FAB) *m/z* 313 (MH^+); HRMS (FAB) calcd for $C_{20}H_{25}O_3$ (MH^+): 313.1804, found: 313.1798.

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14. We examined one-pot methylation of the resulting enolate in the Michael addition, but the results were fruitless. The reaction did not completed even by the addition of large excess of MeI, and separation of **7a** and **10a** was difficult.
15. The stereochemistry was confirmed by nuclear Overhauser effect (NOE) experiments. The NOE was observed between two methine protons beside the THF oxygen and one of two methine protons bearing methyl group. It was also observed between another methine proton bearing the methyl group and the aryl proton.
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