HETEROCYCLES, Vol.53, No.7, 2000, p.1505 - 1513, Received, 30th March, 2000

SYNTHESIS OF (-)-SUGIRESINOL DIMETHYL ETHER UTILIZING (-)-QUINIC ACID

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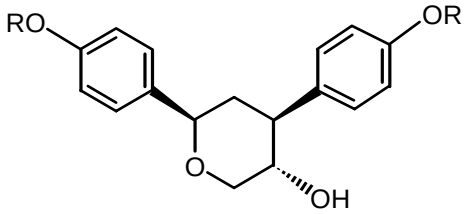
Abstract- (-)-Sugiresinol dimethyl ether, a derivative of (-)-sugiresinol isolated from *Cryptomeria japonica*, was synthesized through 1,4-conjugate addition of arylmetal reagent to a substituted chiral 2-cyclohexen-1-one derived from (-)-quinic acid.

(-)-Sugiresinol (**1a**) is a norlignan isolated from heartwood of *Cryptomeria japonica* by Funaoka *et al.*[1] in 1963, and its chemical structure including absolute stereochemistry was determined by Enzell *et al.*[2] in 1967. (-)-Sugiresinol (**1a**) has been reported to show biological activities such as antifungal activity,[3] inhibitory effect on cyclic AMP phosphodiesterase,[4] inhibitory activity against *C. shiitake* hyphae growth and fruiting body formation,[5] and vinyl polymerization-inhibitory activity.[6]



1a: R=H (Sugiresinol)

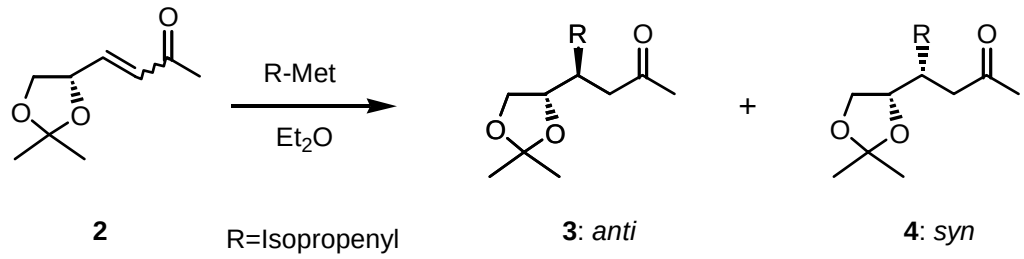
1b: R=Me (Sugiresinol dimethyl ether)

In the course of our synthetic studies on biologically active natural products utilizing (-)-quinic acid as a chiral source,[7] we planned to synthesize (-)-sugiresinol dimethyl ether (**1b**).

Synthesis of sugiresinol dimethyl ether (**1b**) has been reported by Horii *et al.*[8] as racemic form and by Muraoka *et al.*[9] and Dujardin *et al.*[10] as optically active form, respectively.

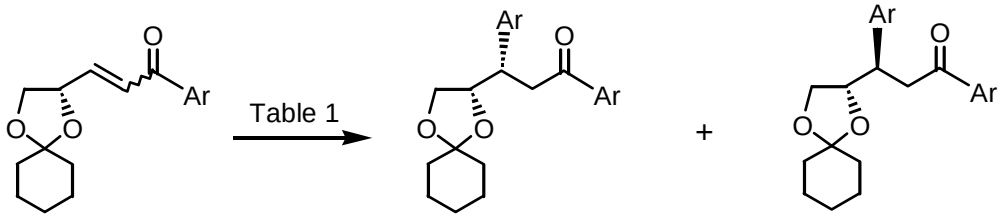
Leonard and Ryan[11] have reported that isopropenylcopper was reacted with α,β-unsaturated ketone (**2**) (*E:Z*=6:1) which has an oxygen function at γ-position to give a mixture of *anti*- and *syn*-adducts (**3:4**=7:1) in 79% yield, on the other hand, in the reaction of isopropenyllithium with **2** (*E:Z*=7:2), a mixture of *anti*- and *syn*-adducts (**3:4**=1:36) in 60% yield. These results indicated that the copper reagent added to **2** from the less hindered side of the molecule to afford the *anti*-isomer (**3**) predominantly (kinetic control), but in the latter case, the lithium reagent chelated first to the oxygen atom at γ-position and then the alkyl group

attacked the β-position of the α,β-unsaturated ketone from the same face to give the *syn*-isomer (**4**) predominantly (chelation control).



2 **3**: *anti* **4**: *syn*

Therefore, we had examined the conjugate addition reaction of 4-methoxyphenylmetal reagents to the chiral α,β-unsaturated ketone (**5**) (*E*:*Z*=3:1),[12] which had the oxygen function in the γ-position of the molecule, expecting to obtain the *syn*-adduct **6** predominantly where the reaction proceeded under the chelation control. Two stereogenic centers of **6** suit for the stereochemistry of 4 and 5 positions of **1b**. But, when a mixture of 4-methoxyphenylmagnesium bromide (3.3 eq.) and CuBr-Me_2S complex (1.6 eq.)[13] was reacted with **5** (*E*:*Z*=3:1) in THF at –15 °C, a mixture of **6** and **7** in a ratio of 1:3 was obtained in 46% yield. The reaction of 4-methoxyphenyllithium (prepared from 4-iodoanisole and *n*-butyllithium)[14] with **5** in THF at –78 °C resulted in formation of a mixture of **6** and **7** in 1:4 in 45 % yield. In both case, the *anti*-isomer (**7**) was obtained predominantly. These results suggested that the reaction of the arylmetal reagents used above proceeded mostly under the kinetically controlled conditions to give **6** from (*Z*)-**5** and **7** from (*E*)-**5**. This evident was provably attributable to the steric hindrance of the aryl group.



5: *E*:*Z*=3:1 **6** **7**

Ar=4-Methoxyphenyl

Table 1. Conjugate Addition of Arylmetal Reagents to **5**

Entry	Reagents	Temp. (°C)	Yield (%)	**6** : **7**
1	ArMgBr (3.3 eq.) CuBr-Me_2S (1.6 eq.), THF	-15	46	1 : 3
2	ArLi (1.2 eq.), THF	-78	45	1 : 4

Therefore, we tried to react arylmetal reagents with a chiral and fixed (*Z*)-α,β-unsaturated ketone which also possessed the oxygen function at the γ-position. As such a compound, the enone (**8**) was selected. It was expected that the enone (**8**) would react with arylmetal reagents to give an *anti*- adduct predominantly under kinetically controlled conditions. The enone (**8**) was known[15] and derived easily

from (-)-quinic acid. We obtained **8** by a little modified method of the reported procedures.[15]

The conjugate addition reaction of 4-methoxyphenylmetal reagents to the chiral α,β-unsaturated cyclic enone (**8**) was examined. The results are summarized in Table 2. Thus, the use of 4-methoxyphenyllithium reagent gave poor results (Entries 1, 2). But, when 4-methoxyphenylmagnesium bromide (10 eq.) was treated with **8** in the presence of CuCN (5 eq.) in ether at –20 °C for 30 min, the desired ketone (**9**) and its dehydration product (**10**) were obtained in 36 and 6% yields, respectively (Entry 4). The reaction of **8** with 4-methoxyphenylmagnesium bromide (3.4 eq.) and CuBr-Me_2S (1.7 eq.) in THF at –15 °C for 30 min gave **9** in 50% yield (Entry 5). It was hard to determine the stereochemistry of **9** and it was postponed.

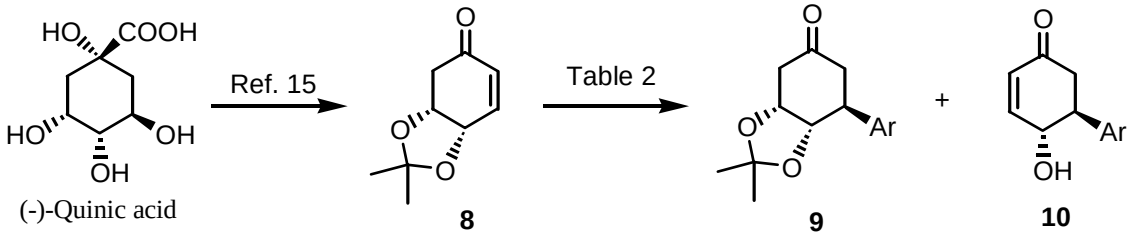
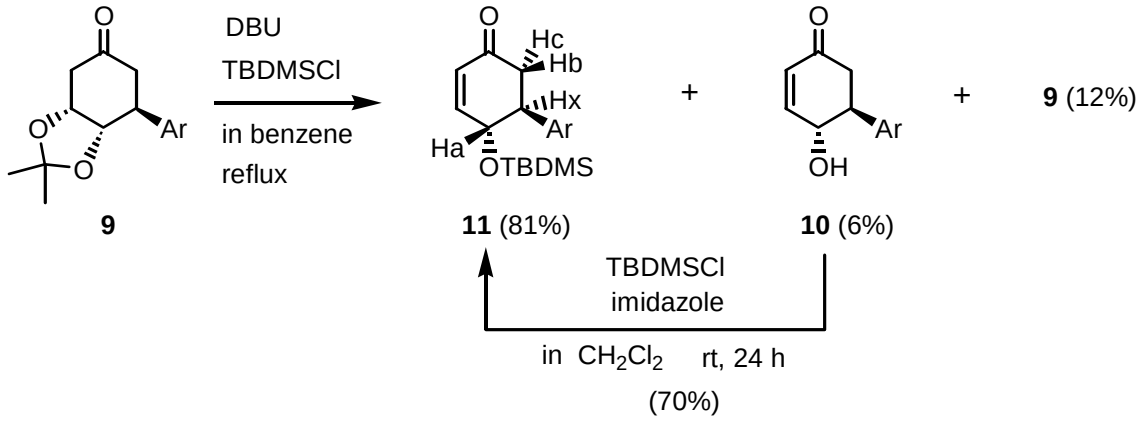


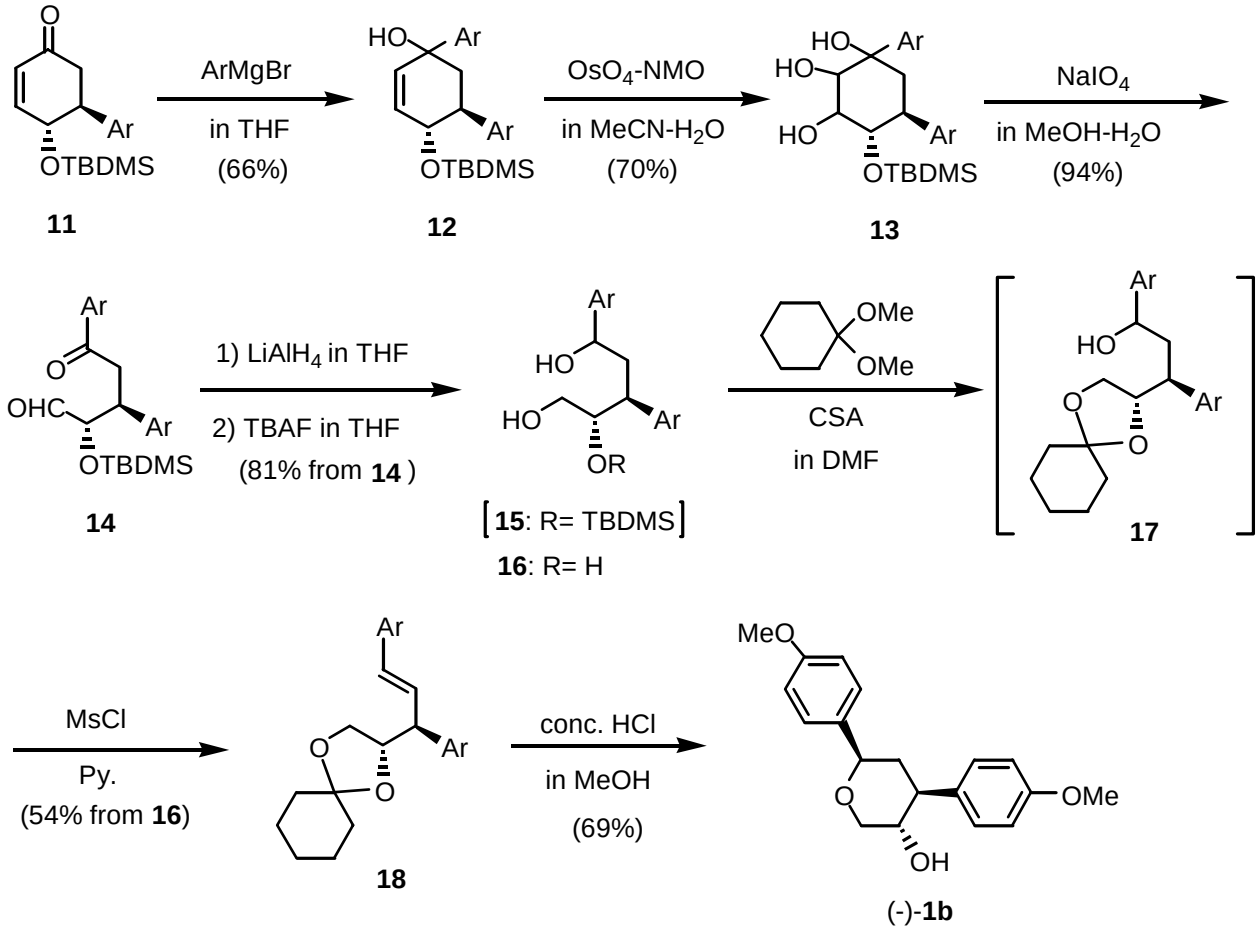
Table 2. Conjugate Addition of Arylmetal Reagents to **8**

Entry	Reagents (eq.)	Solvent	Temp. (°C)	Time	Yield (%)	
					9	**10**
1	Ar-I, *n*-BuLi (1.5), CuI (3.0)	THF	-78	1.5 h	many spots	
2	Ar-I, *n*-BuLi (4.0), CuCN (2.0)	THF	-30	45 min	16	–
3	ArMgBr (10), CuI (5.0)	THF	-20	30 min	9	–
4	ArMgBr (10), CuCN (5.0)	Ether	-20	30 min	36	6
5	ArMgBr (3.4), CuBr-Me_2S (1.7)	THF	-15	30 min	50	–

The ketone (**9**) was treated with DBU (1.3 eq) in the presence of TBDMSCl (3.0 eq.) in refluxing benzene for 5 h to form the enone (**11**) and the hydroxy ketone (**10**) in 81 and 6% yields, respectively, along with 12% of the starting material.[16] The hydroxy ketone (**10**) was converted to **11** by treatment with TBDMSCl and imidazole in 70% yield.



The stereochemistry of **11** was determined by examination of its ^{1}H-NMR spectrum. Thus, Hx appeared at δ 3.20 ppm as ddd with coupling constants 13.0, 9.0 and 5.0 Hz, Ha at 4.46 ppm as dt with coupling constants 9.0 and 2.0 Hz, and Hb at 2.74 ppm as dd with coupling constants 15.0 and 13.0 Hz. These observations indicated that the OTBDMS and Ar groups oriented as *trans* diequatorial and the compound (**11**) had suitable stereochemistry for the synthesis of **1b**. Therefore, the conjugate addition of 4-methoxyphenylmetal reagent to **5** occurred stereoselectively under kinetic control mode as expectedly.
Introduction of the second aryl group was performed by Grignard reaction of **11** and 4-methoxyphenylmagnesium bromide to furnish the alcohol (**12**) in 66% yield. Dihydroxylation of the carbon-carbon double bond in **12** with OsO_4 and NMO proceeded to give the triol **13** in 70% yield, which was successively treated with $NaIO_4$ to furnish the keto aldehyde (**14**) in 94% yield. The keto aldehyde (**14**) was reduced with $LiAlH_4$ to form the diol (**15**), which was successively converted to the triol (**16**) in 81% yield from **14**. The triol (**16**) was treated with 1,1-dimethoxycyclohexane and CSA to protect the glycol portion to furnish **17** which was dehydrated to give **18** by reaction with MsCl and pyridine in 54% yield from **16**. Finally, **18** was treated with conc. HCl in MeOH to produce (-)-sugiresinol dimethyl ether ((-)-**1b**) in 69% yield. IR and ^{1}H-NMR spectral data were identical with those of the authentic sample.[3, 17, 18] Specific rotation of the synthesized (-)-**1b** was –4.05^o (*c*=1.000, $CHCl_3$). The reported rotation was –4.0^o (*c*=1.0, $CHCl_3$).[2, 18] Thus, (-)-sugiresinol dimethyl ether ((-)-**1b**) was synthesized through1,4-conjugate addition of arylmetal reagent to a substituted chiral 2-cyclohexen-1-one derived from (-)-quinic acid.



EXPERIMENTAL

Melting points were determined using a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. IR spectra were measured with a Hitachi 260-30 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX270 (270 MHz) spectrometer using tetramethylsilane as the internal standard. High-resolution MS spectra (HRMS) were measured with a JEOL JMS-HX100 instrument at 70 eV.

(*3R,4S,5S*)-3,4-Isopropylidenedioxy-5-(4-methoxyphenyl)cyclohexan-1-one (9)

A mixture of Mg (836 mg, 34.37 mg atom) and 4-bromoanisole (4.4 mL, 35.38 mmol) in dry THF (17.1 mL) was stirred at rt for 2 h. A cold solution (-10 ^{o}C) of CuBr-Me_2S (3.53 g, 17.18 mmol) and Me_2S (16 mL) in dry THF (36.3 mL) was added dropwise to the above solution at –28 ^{o}C under stirring and the whole was stirred at the same temperature for 30 min. A solution of **8** (1.70 g, 10.11 mmol) in dry THF (17.7 mL) was added dropwise to the above mixture at –15 ^{o}C and the whole was stirred at the same temperature for 30 min. Saturated NH_4Cl aqueous solution was added to the mixture and the inorganic salts formed were filtered off. The organic layer was separated from the filtrate and concentrated under reduced pressure. The residue was dissolved in H_2O and the solution was extracted with AcOEt. The organic layer was washed with 10% NH_4OH aqueous solution, H_2O, and brine, successively. After drying over anhydrous Na_2SO_4, the organic layer was concentrated under reduced pressure to give the residue which was purified by SiO_2 column chromatography (*n*-hexane:AcOEt=5:1) to furnish **9** (1.405 g, 50%) as a colorless crystalline powder. The analytical sample was obtained by recrystallization from *n*-hexane-*i*-PrOH. mp 123-125 ^{o}C. IR(Nujol): 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 1.365 (3H, s, CH_3), 1.525 (3H, s, CH_3), 2.56 (2H, dd, *J*=18.0, 8.5 Hz, COC*H*$_2$CH), 2.72 (2H, dd, *J*=18.0, 4.5 Hz, COC*H*$_2$CH), 3.31-3.40 (1H, m, CCHAr), 3.80 (3H, s, OCH_3), 4.52-4.63 (2H, m, OC*H*C*H*O), 6.88 (2H, dt, *J*=8.5, 2.0 Hz, ArH), 7.15 (2H, dt, *J*=8.5, 2.0 Hz, ArH). HRMS (*m/z*): Calcd for $C_{16}H_{20}O_4$: 276.1350. Found: 276.1362. *Anal*. Calcd for $C_{16}H_{20}O_4$: C; 69.55, H; 7.29. Found: C; 69.61, H; 7.25. $[\alpha]_D^{20}$: -44.29^o (*c*=2.00, $CHCl_3$).

(*4R,5S*)-4-Hydroxy-5-(4-methoxyphenyl)cyclohex-2-en-1-one (10) an (*4R,5S*)-4-*tert*-Butyldimethyl-silyloxy-5-(4-methoxyphenyl)cyclohex-2-en-1-one (11)

A mixture of **9** (750 mg, 2.71 mmol), TBDMSCl (1.230 g, 8.16 mmol) and DBU (0.53 mL, 3.54 mmol) in dry benzene (23 mL) was refluxed for 5 h. After cooling to rt, the mixture was diluted with ether and then washed with H_2O, 0.1N HCl, saturated $NaHCO_3$ aqueous solution, and brine, successively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give an oil. The crude oil was purified by SiO_2 column chromatography (*n*-hexane:AcOEt=5:1) to afford **11** (728 mg, 81%), **10** (37 mg, 6%), and **9** (92 mg, 12%) as colorless crystalline powder. **10**: mp 96-97 ^{o}C. IR (Nujol): 3400, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 2.65 (1H, dd, *J*=18.0, 8.5 Hz, COC*H*$_2$CH), 2.685 (1H, dd, *J*=18.0, 4.5 Hz, COC*H*$_2$CH), 3.20 (1H, dd, *J*=18.0, 10.0 Hz, CHAr), 3.80 (3H, s, OCH_3), 4.59-4.66 (1H, m, C*H*OH), 6.07 (1H, dd, *J*=10.0, 2.5 Hz, C*H*=CH), 6.88 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.01 (1H, dd, *J*=10.0, 2.0 Hz, CH=C*H*), 7.23 (2H, dt, *J*=9.0, 2.5 Hz, ArH). HRMS (*m/z*): Calcd for $C_{13}H_{14}O_3$: 218.0943. Found: 218.0977. *Anal*. Calcd for $C_{13}H_{14}O_3$: C; 71.54, H; 6.47. Found: C; 71.21, H; 6.44. $[\alpha]_D^{22}$: -119.01^o (*c*=1.805, $CHCl_3$). **11**: mp 59-60 ^{o}C. IR (Nujol): 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : -0.46 (3H, s,$SiCH_3$), -0.13 (3H, s, $SiCH_3$), 0.77 (9H, s, *t*-Bu), 2.62 (1H, ddd, *J*=15.0, 5.0, 1.0 Hz, COC*H*$_2$CH), 2.74 (1H, dd, *J*=15.0, 13.0 Hz, COC*H*$_2$CH), 3.20 (1H, ddd, *J*=13.0, 9.0, 5.0 Hz, CHAr), 3.80 (3H, s, OCH_3), 4.46 (1H,

dt, *J*=9.0, 2.0 Hz, CHC*H*OTBDMS), 6.01 (1H, ddd, *J*=10.0, 2.0, 1.0 Hz, C*H*=CH), 6.84 (1H, dd, *J*=10.0, 2.0 Hz, CH=C*H*), 6.87 (2H, dt, *J*=9.0, 2.0 Hz, ArH), 7.16 (2H, dt, *J*=9.0, 2.0 Hz, ArH). HRMS (*m/z*): Calcd for $C_{18}H_{25}O_3Si$ (M^+-CH_3): 317.1573. Found: 317.1565. *Anal*. Calcd. For $C_{19}H_{28}O_3Si$: C; 68.63, H; 8.49. Found: C; 68.33, H; 8.27. $[\alpha]_D^{22}$: -123.48° (*c*=1.04, $CHCl_3$).

(*4R,5S*)-4-*tert*-Butyldimethylsilyloxy-5-(4-methoxyphenyl)cyclohex-2-en-1-one (11) from 10

To a solution of **10** (33 mg, 0.15 mmol) and imidazole (0.33 mg, 0.46 mmol) in dry CH_2Cl_2 (1.5 mL) was added TBDMSCl (45 mg, 0.30 mmol) under ice-cooling and the mixture was stirred at rt for 24 h. After addition of saturated $NaHCO_3$ aqueous solution, the mixture was extracted with $CHCl_3$ (x 4).Theorganic layer was washed with H_2O and brine, respectively, and dried over anhydrous Na_2SO_4. Concentration of the organic layer under reduced pressure gave 85.4 mg of an yellow oil which was purified by preparative SiO_2 plates (*n*-hexane-AcOEt= 5:1) to afford **11** (35 mg, 70%) and **10** (9 mg, 27%). Physical data of **11** were shown above.

(*4R,5S*)-4-*tert*-Butyldimethylsilyloxy-1,5-bis(4-methoxyphenyl)cyclohex-2-en-1-ol (12)

A mixture of Mg (187 mg, 7.69 mg atom) and 4-bromoanisole (0.97 mL, 7.75 mmol) in dry THF was stirred at rt for 1 h. A solution of **11** (1.022 g, 3.07 mmol) in dry THF (6 mL) was added dropwise to the above mixture at –20 °C. The reaction mixture was stirred at rt for 3.5 h. After addition of saturated NH_4Cl aqueous solution, the organic layer was separated and concentrated under reduced pressure. The residue was dissolved in H_2O and the mixture was extracted with AcOEt. The organic layer was separated and washed with H_2O and brine, respectively and dried over anhydrous Na_2SO_4. Concentration of the organic layer under reduced pressure gave an yellow oil (2.252 g) which was purified by SiO_2 column chromatography (*n*-hexane: AcOEt= 5:1~0:1) to afford **12** (1.069 g, 66%) as an yellow oil. IR (neat): 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.00 (3H, s, CH_3), 0.26 (3H, s, CH_3), 0.46 (9H, s, *t*-Bu), 2.69 (1H, dt, *J*=13.0, 2.5 Hz, CCH_2CHAr), 2.83 (1H, t, *J*=13.0 Hz, CCH_2CHAr), 3.00-3.11 (1H, m, CHC*H*Ar), 4.24 (3H, s, OCH_3), 4.28 (3H, s, OCH_3), 4.68 (1H, dt, *J*=9.0, 2.0 Hz, CHC*H*OTBDMS), 6.25 (1H, dt, *J*=10.0, 2.0 Hz, C*H*=CH), 6.38 (1H, dd, *J*=10.0, 2.0 Hz, CH=C*H*), 7.25 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.36 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.51 (2H, dt, *J*=9.0, 2.0 Hz, ArH), 7.96 (2H, dt, *J*=9.0, 2.0 Hz, ArH).

(*4S,5S*)-4-*tert*-Butyldimethylsilyloxy-1,2,3-trihydroxy-1,5-bis(4-methoxyphenyl)-cyclohexane (13)

NMO (325 mg, 2.77 mmol) and OsO_4 (2.8 mL, 1 g/50 mL H_2O soln, 0.22 mmol) were added toasolution of **13** (489 mg, 1.11 mmol) in MeCN (9.6 mL) and the whole was stirred at rt for 43 h. After addition of saturated $NaHCO_3$ aqueous solution (10 mL), the mixture was extracted with AcOEt (x 3) and the organic layer was washed with brine. After drying over anhydrous Na_2SO_4, the organic layer was concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography (*n*-hexane:AcOEt=2:1) to give **14** (368 mg, 70%) as colorless crystalline powder. mp 148-150 °C. IR (Nujol): 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: -0.66 (3H, s, CH_3), -0.07 (3H, s, CH_3), 0.65 (9H, br s, *t*-Bu), 1.25 (1H, s, OH), 2.32 (1H, dt, *J*=10.0, 2.0 Hz, CCH_2CHAr), 2.46 (1H, t, *J*=13.0 Hz, C*H*Ar), 2.53 (1H,dd, *J*=10.0, 3.0 Hz, CCH_2CHAr), 2.68 (1H, s, OH), 3.13 (1H, s, OH), 3.42 (1H, br d *J*=9.0 Hz, C*H*OH),3.80 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.97 (1H, t, *J*=9.0 Hz, C*H*OH), 4.54 (1H, t, *J*=2.0 Hz, CHC*H*OTBDMS), 6.86 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 6.95 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.15 (1H, dt, *J*=9.0, 2.5 Hz, ArH), 7.51 (2H, dt, *J*=9.0, 2.5 Hz, ArH). *Anal*. Calcd for $C_{26}H_{38}O_6Si$: C; 65.79, H; 8.07. Found: C; 65.67, H; 8.01. $[\alpha]_D^{20}$: +25.87° (*c*=2.08, $CHCl_3$).

(*2S,3S*)-2-*tert*-Butyldimethylsilyloxy-3,5-bis(4-methoxyphenyl)-5-oxopentanal (14)

A solution of $NaIO_4$ (53 mg, 0.25 mmol) in H_2O (1 mL) was added to a solution of **13** (40 mg, 0.08 mmol) in MeOH (2 mL) and the mixture was stirred at rt for 2.5 h. After addition of saturated $NaHCO_3$ aqueous solution, the mixture was extracted with AcOEt (x 3), and the organic layer was washed with brine and then concentrated under reduced pressure. The residue was purified by SiO_2 preparative TLC (*n*-hexane:AcOEt=4:1, developed 3 times) to give **14** (35 mg, 94%) as a colorless oil. The keto aldehyde (**14**) was unsatable and used for the next reaction immediately. IR (neat): 1725, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: -0.12 (3H, s, CH_3), -0.01 (3H, s, CH_3), 0.90 (9H, s, *t*-Bu), 3.23 (1H, dd, *J*=18.0, 5.5 Hz, CC*H*$_2$CHAr), 3.53 (1H, dd, *J*=18.0, 8.5 Hz, CC*H*$_2$CHAr), 3.79-3.89 (1H, m, CHAr), 3.77 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.37 (1H, dd, *J*=4.5, 2.0 Hz, C*H*OTBDMS), 6.80 (2H, dt, *J*=8.5, 2.5 Hz, ArH), 6.92 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.24 (2H, dt, *J*=8.5 , 2.5 Hz, ArH), 7.91 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 9.42 (1H, d, *J*=2.0 Hz, CHO).

(*2S*,*3S*)-3,5-Bis(4-methoxyphenyl)pentane-1,2,5-triol (16)

$LiAlH_4$ (64 mg, 1.69 mmol) was added to a solution of **14** (250 mg, 0.56 mmol) in dry THF (3mL) under ice-cooling and the mixture was stirred at rt for 5 h. After addition of H_2O, the mixture was extracted with ether (x 4) and then $CHCl_3$ (x 3). The organic extracts were combined and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a colorless oil which was treated again with $LiAlH_4$ (32 mg, 0.84 mmol) in dry THF (3 mL) (rt, 16.5 h). After addition of H_2O, the mixture was extracted with AcOEt (x 4) and $CHCl_3$ (x 3). The organic layers were combined and treated similarly as above to give **15** (182 mg, colorless oil) as a mixture of diastereomers which were submitted to the next reaction without purification.

TBAF (0.61 mL, 1.0 M THF soln, 0.61 mmol) was added to a solution of **15** (182 mg) in dry THF(2mL) under ice-cooling and the reaction mixture was stirred at that temperature for 1.5 h. After addition of saturated NH_4Cl aqueous solution, the mixture was extracted with AcOEt (x 4) and $CHCl_3$ (x 4), successively, and the organic layers were combined and dried over anhydrous Na_2SO_4. Concentration of the organic layers under reduced pressure gave an oil which was purified by SiO_2 column chromatography ($CHCl_3$:MeOH=30:1~20:1) to afford **16** (152 mg, oil, 81% from **14**) as a mixture of diastereomers. Major isomer: IR (neat): 3350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.68-1.80 (3H, br s, OH), 2.13 (1H, ddd, *J*=14.0, 8.0, 5.5 Hz, ArCHC*H*$_2$CHAr), 2.28 (1H, ddd, *J*=14.0, 11.0, 6.0 Hz, ArCHC*H*$_2$CHAr), 2.50 (1H, dt, *J*=9.5, 5.5 Hz, CHAr), 3.37 (1H, dd, *J*=11.0, 7.5 Hz, CHC*H*$_2$OH), 3.63 (1H, dd, *J*=11.0, 3.5 Hz, CHC*H*$_2$OH), 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.78-3.86 (1H, m, CH_2C*H*(Ar)OH), 4.44 (1H, dd, *J*=8.0, 6.0 Hz, CH_2C*H*OH), 6.87 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 6.88 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.11 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.16 (2H, dt, *J*=9.0, 2.5 Hz, ArH).

(*2S*,*3S*)-(*4E*)-1,2-Cyclohexylidenedioxy-3,5-bis(4-methoxyphenyl)pent-4-ene (18)

CSA (0.5 mg, 2.2 μmol) and cyclohexanone dimethyl acetal (33 μL, 0.22 mmol) were added successively to a solution of **16** (mixture of diastereomers; 52 mg, 0.16 mmol) in dry DMF (1 mL). After the mixture was stirred at 50 ^{o}C for 5.5 h, cyclohexanone dimethyl acetal (33 μL, 0.22mmol)was added and the whole was stirred at 50 ^{o}C for 2 h and at rt for 14 h. After addition of saturated $NaHCO_3$ aqueous solution, the mixture was extracted with AcOEt (x 4) and then with $CHCl_3$ (x 4). The organic layers were combined and dried over anhydrous Na_2SO_4 and cencentrated under reduced pressure to give an oil (64 mg) which was purified by SiO_2 column chromatography (*n*-hexane:AcOEt=2:1) to afford **17** (53 mg) as a colorless oil. MsCl (41 μL, 0.53 mmol) was added to a solution of **17** (53 mg, 0.13 mmol) in dry

pyridine (3.0 mL) and the whole was stirred at rt for 1 h and then refluxed for 3 h. After cooling, H_2O was added and the mixture was extracted with $CHCl_3$ (x 4). The organic layer was washed with 1% HCl solution and brine, respectively and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to give a brown oil (43.8 mg) which was purified by SiO_2 column chromatography (*n*-hexane:AcOEt=2:1) to furnish **18** (33 mg, 54% from **16**) as an yellow oil. IR (neat): 965 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.56-1.70 (10H, m, cyclohexylidene), 3.55 (1H, t, *J*=7.0 Hz, CHAr), 3.76-3.82 (1H, m, CH_2CHO-), 3.80 (6H, s, 2 x OCH_3), 4.03 (1H, dd, *J*=8.0, 6.0 Hz, OCH_2), 4.41 (1H,q-like, *J*=8.0 Hz, OCH_2), 6.17 (1H, dd, *J*=16.0, 8.5 Hz, CH=C*H*Ar), 6.41 (1H, d, *J*=16.0 Hz, CHC*H*=CH), 6.83 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 6.87 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.23 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.27 (2H, dt, *J*=9.0, 2.5 Hz, ArH). HRMS (*m/z*): Calcd for $C_{25}H_{30}O_4$: 394.2144. Found: 394.2149.[α]$_D^{22}$: -2.35^o (*c*=1.08, $CHCl_3$).

(-)-Sugiresinol dimethyl ether (1b)

To a solution of **18** (75 mg, 0.19 mmol) in dry MeOH (4.0 mL) was added concentrated HCl (1.9mL) and the mixture was refluxed for 2.5 h. After cooling, the mixture was basified with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Concentration of the organic layer under reduced pressure gave pale yellow crystals (58 mg) which was purified by SiO_2 preparative TLC (*n*-hexane:AcOEt=2:1) to afford (-)-**1b** (41 mg, 69%) as colorless crystalline powder. Analytical sample was obtained by recrystallization from *n*-hexane. mp 104-105 ^{o}C (lit.,[2] 104-105 ^{o}C). IR (Nujol): 3400, 1610, 1585, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (1H, br s, OH), 1.91 (1H, ddd, *J*=14.0, 12.5, 11.0 Hz, ArCHCH_2CHAr), 2.06 (1H, ddd, *J*=14.0, 4.0, 2.0 Hz, ArCHCH_2CHAr), 2.77 (1H, ddd, *J*=12.5, 10.0, 4.0 Hz, CH_2CH(Ar)CH), 3.48 (1H, dd, *J*=11.0, 10.0 Hz, OCH_2CH), 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.80-3.91 (1H, m, C*H*OH), 4.29 (1H, dd, *J*=11.0, 4.5 Hz, OCH_2CH), 4.47 (1H, dd, *J*=11.0, 2.0 Hz, OC*H*(Ar)CH_2), 6.87 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 6.90 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.22 (2H, dt, *J*=9.0, 2.5 Hz, ArH), 7.30 (2H, dt, *J*=9.0, 2.5 Hz,ArH).HRMS (*m/z*): Calcd for $C_{19}H_{22}O_4$: 314.1518. Found: 314.1532. [α]$_D^{21}$: -4.05^o (*c*=1.00, $CHCl_3$)(lit.,[2,17] [α]$_D$:– 4.0^o).

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