Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 2168

Received 4th January 2021,
Accepted 16th February 2021

DOI: 10.1039/d1ob00008j

rsc.li/obc

Stereocontrolled syntheses of (−)- and (+)-γ-diisoeugenol along with optically active eight stereoisomers of 7,8′-epoxy-8,7′-neolignan†

Tatsuaki Takubo, Nao Kikuchi, Hisashi Nishiwaki and Satoshi Yamauchi *

It was shown that reduction of the tertiary benzylic hydroxy group of (2*R*,3*S*,4*R*,5*S*)-3,5-bis(4-benzyloxy-3-methoxyphenyl)-2,4-dimethyltetrahydro-3-furanol 17 followed by the intramolecular Friedel–Crafts reaction gave exclusively indane with (7*S*,7′*S*,8*R*,8′*R*)-2,7′-cyclo-7,8′-neolignan structure 18 along with (7*S*,7′*R*,8*S*,8′*R*)-7,8′-epoxy-8,7′-neolignan structure 19. Indane 18 was converted to (−)-γ-diisoeugenol ((−)-4). On the other hand, (2*S*,3*R*,4*R*,5*S*)-3,5-bis(4-benzyloxy-3-methoxyphenyl)-2,4-dimethyltetrahydro-3-furanol 22 did not afford indane, but the tetrahydrofuran structure with (7*S*,7′*S*,8*S*,8′*S*)-7,8′-epoxy-8,7′-neolignan structure 23 and 7′-*epi*-23.

Introduction

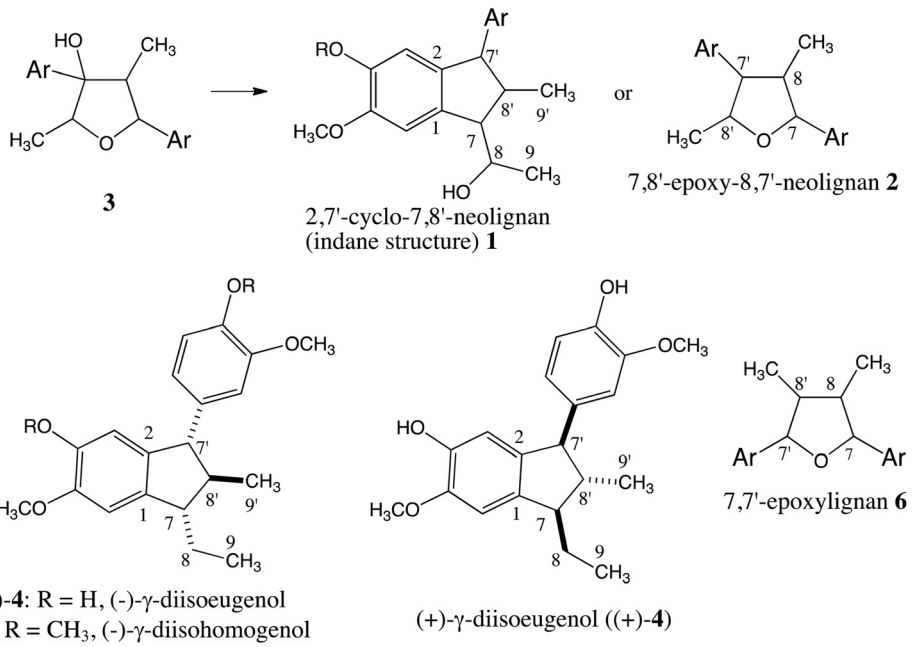
The cytotoxicity, apoptosis, and inhibition of cyclooxygenase-2 gene expression of 2,7′-cyclo-7,8′-neolignan (diisoeugenol) (Scheme 1) have been reported.[1] To clarify the effect of stereochemistry on the biological activity, the synthesis of an optically pure compound is required. However, only the racemic syntheses of 2,7′-cyclo-7,8′-neolignan have been reported to date.[2] On the other hand, 7,7′-epoxy-8,8′-lignan (2,5-bisaryl-3,4-dimethyltetrahydrofuran) **6** possesses antimicrobial activity,[3] plant growth regulatory activity,[4] and cytotoxicity.[5] The synthetic research of the stereoisomers of 7,8′-epoxy-8,7′-neolignan **2**, which is the positional isomer of **6**, would contribute to the structure–activity relationship research of the neolignan.[6] Although the isolation,[7] biological activity,[8] and synthetic study[9] of 7,8′-epoxy-8,7′-neolignan **2** have been reported, there are no reports on the syntheses of optically pure compounds. We expected that the exposure of 3-furanol **3** bearing tertiary benzyl alcohol to a Lewis acid and Et_3SiH would give the indane structure bearing 2,7′-cyclo-7,8′-neolignan structure **1**, which is a synthetic intermediate to diisoeugenol **4**, *via* reduction and the intramolecular Friedel–Crafts reaction. It would also be possible to obtain 7,8′-epoxy-8,7′-neolignan **2** by controlling the reaction conditions. This article describes the first syntheses of (−)- and (+)-γ-diisoeugenol **4** and (−)-γ-diisohomogenol **5**,[10] which are 2,7′-cyclo-7,8′-neolignan bearing indane structures, along with some stereoisomers of 7,8′-epoxy-8,7′-neolignan **2**.

Results and discussion

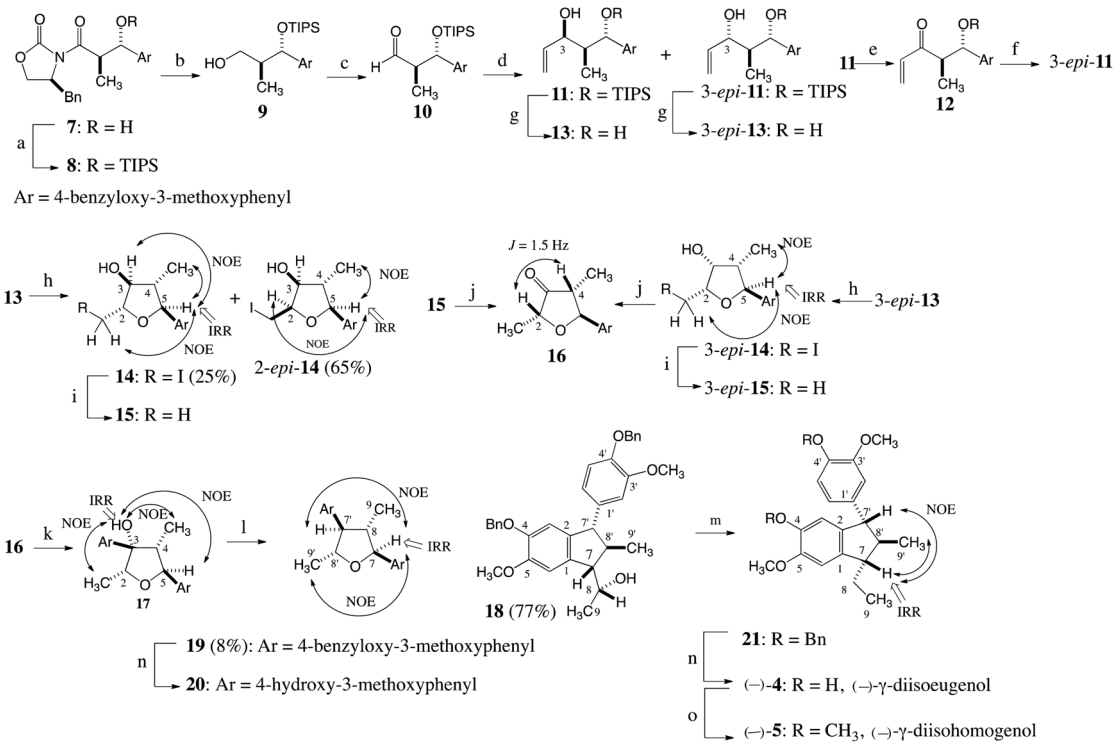
To construct the optically active 2,7′-cyclo-7,8′-neolignan or 7,8′-epoxy-8,7′-neolignan, 3-furanol with tertiary benzyl alcohols **17** and **22** were selected as substrates for reductions and intramolecular Friedel–Crafts reactions (Schemes 2 and 3). Evans' *anti*-aldol[11] product **7** was converted to aldehyde **10**. Treatment of aldehyde **10** with vinylmagnesium bromide gave allyl alcohol **11** (49%) and 3-*epi*-**11** (14%). After the desilylation of **11**, the resulting diol **13** was subjected to iodoetherification[12] to give iodomethyltetrahydrofuran **14** (25%) and 2-*epi*-**14** (65%). Irradiation at 5-H of **14** revealed the differential NOEs of 2-CH_2I (3%), 4-CH_3 (7%), and 3-H (7%). In 2-*epi*-**14**, the NOEs of 2-H/5-H (7%) and 5-H/4-CH_3 (7%) were observed. The reduction of iodide **14** followed by PCC oxidation gave furanone **16**, in which the coupling constant between 2-H and 4-H (1.5 Hz) was observed to confirm the stereochemistry of 2,4-*cis*. The minor Grignard product 3-*epi*-**11** was desilylated to give diol 3-*epi*-**13** (91% yield). Iodoetherification of 3-*epi*-**13** gave stereoselectively iodomethyltetrahydrofuran 3-*epi*-**14** (88% yield), whose configuration between 2- and 4-positions was confirmed by differential NOE experiments (2-CH_2I/5-H: 3%, 5-H/4-CH_3: 7%). Furanol 3-*epi*-**14** was transformed to furanone **16** (94% yield) by $LiAlH_4$ reduction followed by PCC oxidation. Furanol with tertiary benzyl alcohol **17** was stereoselectively obtained (74%) by the treatment of ketone **16** with 4-benzyloxy-3-methoxyphenyllithium. The NOEs of OH/2-CH_3 (4%), OH/4-CH_3 (4%), and OH/5-H (3%) were observed to confirm the stereochemistry. Reduction of **17** using Et_3SiH[13] in the

Graduate School of Agriculture, Ehime University, 3-5-7 Tarumi, Matsuyama, Ehime 790-8566, Japan. E-mail: syamauch@agr.ehime-u.ac.jp

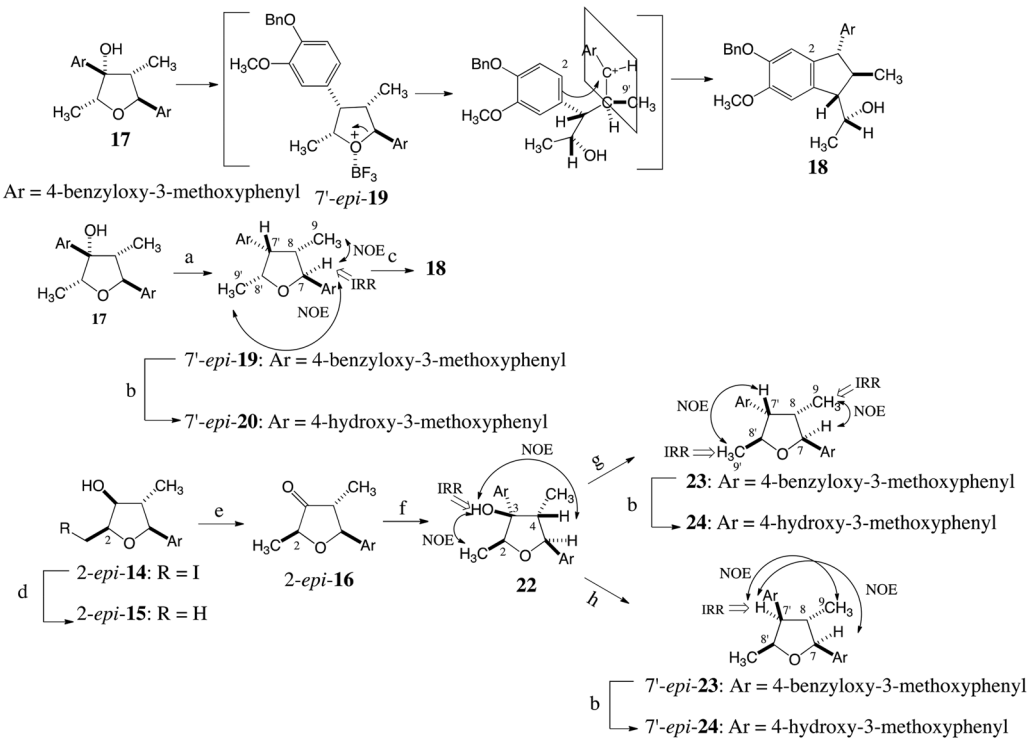
†Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ob00008j



Scheme 1 Conversion of 3-furanol **3** to 2,7′-cyclo-7,8′-neolignan **1** (indane structure) and/or 7,8′-epoxy-8,7′-neolignan **2**.



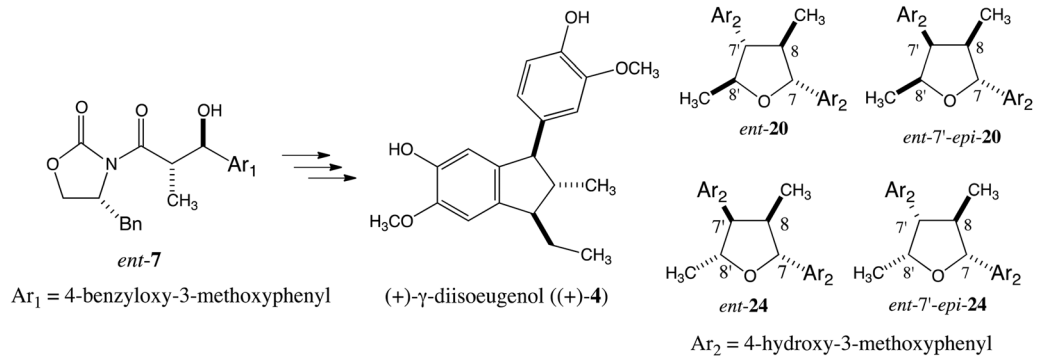
Scheme 2 Syntheses of (–)-γ-diisoeugenol ((–)-**4**) and (–)-γ-diisohomogenol ((–)-**5**) along with (7*S*,7′*R*,8*S*,8′*R*)-7,8′-epoxy-8,7′-neolignan (**20**). (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 1 h, 93% yield. (b) $LiBH_4$, MeOH, THF, r.t., 1 h, 95% yield. (c) PCC, MS 4A, CH_2Cl_2, 0 °C, 16 h, 70% yield. (d) Vinylmagnesium bromide, THF, r.t., 1 h, **11** (49%), 3-*epi*-**11** (14%). (e) PDC, MS 4A, CH_2Cl_2, r.t., 16 h, 66% yield. (f) Method A, $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, THF, −60 °C, 3-*epi*-**11** (37% yield), **11** (47% yield). Method B, DIBAL-H, toluene, −75 °C, 2 h, 3-*epi*-**11** (54% yield), **11** (8% yield). (g) *n*-Bu_4NF, THF (from **11** to **13**: 95% yield; from 3-*epi*-**11** to 3-*epi*-**13**: 91% yield). (h) I_2, $NaHCO_3$, MeCN, 0 °C, 1 h (from **13** to **14**: 25% yield, 2-*epi*-**14**: 65% yield; from 3-*epi*-**13** to 3-*epi*-**14**: 88% yield). (i) $LiAlH_4$, THF, r.t., 30 min (from **14** to **15**: 79% yield; from 3-*epi*-**14** to 3-*epi*-**15**: 71% yield). (j) PCC, MS 4A, CH_2Cl_2, 0 °C, 16 h (from **15** to **16**: 82% yield; from 3-*epi*-**15** to **16**: 94% yield). (k) 4-Benzyloxy-3-methoxyphenyllithium, THF, −70 °C, 1.5 h, 74% yield. (l) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0–5 °C, 2 h, **18** (77% yield), **19** (8% yield). (m) (1) MsCl, Et_3N, CH_2Cl_2, r.t., 1 h; (2) $NaBH_4$, HMPA, 80 °C, 12 h, 48% yield (2 steps). (n) H_2, 5% Pd/C, EtOAc, r.t., 2 h (from **21** to (–)-**4**: 92% yield; from **19** to **20**: 53% yield). (o) MeI, K_2CO_3, dibenzo-18-crown-6, MeCN, reflux, 16 h (91% yield).



Scheme 3 Reaction mechanism to prepare indane bearing 2,7′-cyclo-7,8′-neolignan structure **18** and preparation of stereoisomers of 7,8′-epoxy-8,7′-neolignan (7′-*epi*-**20**, **24**, 7′-*epi*-**24**). (a) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −40 °C, 2 h, 22% yield, recovered **17** (74%). (b) H_2, 5% Pd/C, EtOAc, r.t., 2 h (7′-*epi*-**20**: 53% yield, **24**: 100% yield, 7′-*epi*-**24**: 96% yield). (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0–3 °C, 1 h, 76% yield. (d) $LiAlH_4$, THF, r.t., 30 min, 74% yield. (e) PCC, MS 4A, CH_2Cl_2, 0 °C, 16 h, 94% yield. (f) 4-Benzyloxy-3-methoxyphenyllithium, THF, −70 °C, 1.5 h, 94% yield. (g) ZnI_2, $NaBH_3CN$, 1,2-dichloroethane, reflux, 4 h, 27% yield, recovered **22** (71%). (h) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0–3 °C, 30 min, 7′-*epi*-**23** (57% yield), **23** (3% yield).

presence of $BF_3{\cdot}OEt_2$ at 0 °C led to 2,7′-cyclo-7,8′-neolignan with indane skeleton **18** (77%) along with (7*S*,7′*R*,8*S*,8′*R*)-7,8′-epoxy-8,7′-neolignan **19** (8%). The reaction did not proceed by employing $NaBH_3CN$ in the presence of ZnI_2. (−)-γ-Diisoeugenol **4** was obtained from **18** by the reduction of the hydroxy group (48%, 2 steps) followed by hydrogenolysis (91%). The irradiation of 7-H appeared the NOEs of 7-H/7′-H (7%) and 7-H/9′-H (4%). The ^{1}H-NMR datum was similar to that of the literature.[2b] The ^{1}H-NMR datum of (−)-γ-diisohomogenol **5** obtained by methylation of (−)-γ-diisoeugenol **4** was also similar to that of the literature.[10] On the other hand, hydrogenolysis of **19** afforded phenolic (7*S*,7′*R*,8*S*,8′*R*)-7,8′-epoxy-8,7′-neolignan **20** (53%). The NOEs of 7-H/9′-H (3%), 7-H/9H (7%), and 7-H/7′-H (7%) confirmed this stereochemistry. To obtain furanone **16** efficiently, allyl alcohol **11** was isomerized to 3-*epi*-**11** *via* ketone **12**.

The proposed mechanism of the production of indane bearing 2,7′-cyclo-7,8′-neolignan structure **18** is shown in Scheme 3. An explanation for the selective production of the indane structure involves the initial formation of 7′-*epi*-**19**, which was not obtained under this reaction condition (0–5 °C); however, a lower reaction temperature (−40 °C) allows the production of 7′-*epi*-**19** in 22% yield along with the recovery of **17** (74%). The NOEs of 7-H/9′-H (3%) and 7-H/9-H (7%) in 7′-*epi*-**19** were observed. The tetrahydrofuran ring of 7′-*epi*-**19** was opened by treatment with $BF_3{\cdot}OEt_2$ to induce the benzylic cation, which stimulated the intramolecular Friedel–Crafts reaction. The aryl group bonded to the carbocation would be placed at a farther position from the 9′-methyl group on the SP_2 plane. The π electron pair attacked the benzylic carbocation to form the *trans* configuration. It could be assumed that the intramolecular Friedel–Crafts reaction did not occur in the case of stereoisomer **19** in Scheme 2 due to its stable 7,8-*trans*, 7′,8-*trans*, and 7′,8′-*trans* stereochemistry. The reaction of **19** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ at 25 °C resulted in the recovery of **19** (81%). 3-Franol with tertiary benzyl alcohol **22** was obtained from 2-*epi*-**14**, which was a major product of the iodoetherification of diol **13**, by the same method described for the preparation of **17**. The NOEs of HO/2-CH_3 (3%) and HO/4-H (3%) were observed in **22**. Treatment of **22** with ZnI_2 and $NaBH_3CN$[14] afforded (7*S*,7′*S*,8*S*,8′*S*)-7,8′-epoxy-8,7′-neolignan **23** in 23% yield along with the recovery of **22** (71%). The approach of the hydride reagent to the resulting 3-C carbocation would occur from the same side of the 7-aryl group, giving the 7,7′-*trans* form. On the other hand, application of **22** to Et_3SiH and $BF_3{\cdot}OEt_2$ at 0 °C gave 7′-*epi*-**23** in 57% yield. At this lower temperature, the attack of the hydride reagent would occur from the opposite side of the 7-aryl group to give the 7,7′-*cis* form. Hydrogenolyses of **23** and 7′-*epi*-**23** gave **24** (100%) and 7′-*epi*-**24** (96%), respectively. The NOEs of



Scheme 4 Synthesis of (+)-γ-diisoeugenol ((+)-**4**) along with 7,8′-epoxy-8,7′-neolignans (*ent*-**20**, *ent*-7′-*epi*-**20**, *ent*-**24**, *ent*-7′-*epi*-**24**).

7′-H/9′-H (7%) and 7-H/9-H (7%) in **24** and 7′-H/9-H (7%) and 7′-H/7-H (7%) in 7′-*epi*-**24** confirmed their stereochemistries. The indane structure was not obtained from tertiary benzyl alcohol **22** by our entries.

(+)-γ-Diisoeugenol ((+)-**4**), *ent*-**20**, *ent*-7′-*epi*-**20**, *ent*-**24**, and *ent*-7′-*epi*-**24** were synthesized from the enantiomer of Evnas' *anti*-aldol product *ent*-**7** (Scheme 4). The enantiomeric excess of the synthesized compounds was determined as >99%ee ((−)- and (+)-diisoeugenol (**4**), **20**, 7′-*epi*-**20**, *ent*-7′-*epi*-**20**, **24**, *ent*-**24**, 7′-*epi*-**24**) and 97%ee (*ent*-7′-*epi*-**24**, *ent*-**20**) by chiral column chromatography.

Conclusion

The stereoselective synthetic methods of optically pure (−)-γ-diisoeugenol and (+)-γ-diisoeugenol bearing the 2,7′-cyclo-7,8′-neolignan structure were explored by employing reduction and the Friedel–Crafts reaction of tetra-substituted 3-furanol with tertiary benzylic alcohol. (7*S*,7′*R*,8*S*,8′*R*)-, (7*S*,7′*S*,8*S*,8′*R*)-, (7*S*,7′*S*,8*S*,8′*S*)-, (7*S*,7′*R*,8*S*,8′*S*)-7,8′-Epoxy-8,7′-neolignan and their enantiomers were also obtained by controlling the reaction conditions. The enantiomeric excess of these compounds was determined as 97–100%ee.

Experimental

General experimental procedures

The melting point (mp) data are uncorrected. Optical rotations were measured on a JASCO P-2100 instrument. NMR data were obtained using a JNM-EX400 spectrometer. EI and FABMS data were measured with a JMS-MS700V spectrometer. The silica gel used was Silica Gel 60N (spherical, neutral, Kanto Chemical, 40–50 μm). HPLC analysis was performed with Shimadzu LC-6AD and SPD-6AV instruments. The chiral column used for the HPLC analysis of enantiomeric excess was CHIRALCEL AD-H (250 mm × 4.6 mm, i.d., 5 μm, DAICEL Chemical Industries, Ltd, Tokyo, Japan, 20% iso-PrOH/hexane, 1 mL min^{-1}, detected at 283 nm). The numbering of compounds follows the IUPAC rule. The nomenclature of the lignan structure follows the literature.[6]

The synthetic methods and data of **7–13** and 3-*epi*-**13** are shown in the ESI.†

(2*S*,3*R*,4*S*,5*S*)-5-(4-Benzyloxy-3-methoxyphenyl)-2-iodomethyl-4-methyltetrahydro-3-furanol 3-*epi*-14. To a suspension of diol 3-*epi*-**13** (1.18 g, 3.59 mmol) and $NaHCO_3$ (2.80 g, 33.3 mmol) in MeCN (40 mL) was added iodine (8.10 g, 31.9 mmol) in MeCN (170 mL) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 h, and then sat. aq. $Na_2S_2O_3$ and EtOAc were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave iodomethyltetrahydrofuranol 3-*epi*-**14** (1.44 g, 3.16 mmol, 88%) as colorless crystals, mp 139–141 °C, $[\alpha]_D^{25}$ −31 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, d, *J* = 6.8 Hz, CH_3), 1.95 (1H, br s, OH), 2.21 (1H, m, 4-H), 3.31 (1H, dd, *J* = 9.0, 4.9 Hz, 2-C*H*H-I), 3.38 (1H, dd, *J* = 10.5, 9.0 Hz, 2-CH*H*-I), 3.90 (3H, s, OCH_3), 4.45 (1H, m, 3-H), 4.53 (1H, ddd, *J* = 10.5, 4.9, 3.1 Hz, 2-H), 4.69 (1H, d, *J* = 10.5 Hz, 5-H), 5.14 (2H, s, OCH_2Ph), 6.77 (1H, dd, *J* = 8.3, 1.8 Hz), 6.84 (1H, d, *J* = 8.3 Hz), 6.87 (1H, d, *J* = 1.8 Hz), 7.29 (1H, m), 7.35 (2H, br dd, *J* = 7.6, 7.6 Hz), 7.42 (2H, br d, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.59 (CH_3), 9.59 (4-C), 48.0 (2-CH_2-I), 56.0 (OCH_3), 71.0 (OCH_2Ph), 75.0 (2-C), 82.9 (5-C), 86.6 (3-C), 109.6, 113.7, 118.7, 127.2, 127.8, 128.5, 134.0, 137.1, 147.8, 149.7. FABMS: 455 $(M + H)^+$. HRMS (FAB): calculated $C_{20}H_{25}O_4I$: 455.0721, found: 455.0716.

ent-3-*epi*-**14**. Colorless crystals, mp 140–142 °C, $[\alpha]_D^{25}$ +31 (*c* 0.3, $CHCl_3$).

(2*S*,3*S*,4*S*,5*S*)-5-(4-Benzyloxy-3-methoxyphenyl)-2-iodomethyl-4-methyltetrahydro-3-furanol 14 and (2*R*,3*S*,4*S*,5*S*)-5-(4-benzyloxy-3-methoxyphenyl)-2-iodomethyl-4-methyltetrahydro-3-furanol 2-*epi*-14. 3-Franol **14** was obtained from **13** in 25% yield by iodoetherification along with 2-*epi*-**14** in 65% yield. **14**: colorless oil, $[\alpha]_D^{25}$ −28 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, d, *J* = 6.7 Hz, CH_3), 2.19 (1H, m, 4-H), 2.25 (1H, br s, OH), 3.38–3.40 (2H, m, 2-CH_2-I), 3.82 (1H, m, 3-H), 3.90 (3H, s, OCH_3), 3.96 (1H, ddd, *J* = 6.3, 6.3, 5.0 Hz, 2-H), 4.49 (1H, d, *J* = 10.3 Hz, 5-H), 5.15 (2H, s, OCH_2Ph), 6.78 (1H, dd, *J* = 8.2, 1.8 Hz), 6.84 (1H, d, *J* = 8.2 Hz), 6.92 (1H, d, *J* = 1.8 Hz), 7.29 (1H,

m), 7.35 (2H, m), 7.42 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.96 (CH_3), 13.2 (4-C), 50.0 (2-CH_2-I), 56.0 (OCH_3), 71.0 (OCH_2Ph), 81.7 (2-C), 83.1 (5-C), 85.6 (3-C), 109.7, 113.7, 119.0, 127.2, 127.8, 128.5, 133.1, 137.0, 148.0, 149.8. FABMS 455 (M + H)$^+$. Anal. found: C 52.77%, H 5.42%; calcd for $C_{20}H_{23}O_4I$: C 52.88%, H 5.10%. 2-*epi*-**14**: colorless crystals, mp 112–113 °C (EtOAc/hexane = 1/1), $[\alpha]_D^{25}$ +3.9 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, d, *J* = 6.9 Hz, CH_3), 2.06 (1H, br s, OH), 2.13 (1H, m, 4-H), 3.35 (1H, dd, *J* = 9.8, 5.6 Hz, 2-C*H*H-I), 3.44 (1H, dd, *J* = 9.8, 7.5 Hz, 2-CH*H*-I), 3.90 (3H, s, OCH_3), 4.10 (1H, m, 3-H), 4.16 (1H, ddd, *J* = 7.4, 5.5, 5.5 Hz, 2-H), 4.29 (1H, d, *J* = 8.1 Hz, 5-H), 5.14 (2H, s, OCH_2Ph), 6.82 (2H, s), 7.03 (1H, s), 7.28 (1H, m), 7.35 (2H, m), 7.42 (2H, d, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.21 (CH_3), 15.3 (4-C), 50.3 (2-CH_2-I), 56.0 (OCH_3), 70.9 (OCH_2Ph), 79.4 (2-C), 80.2 (5-C), 86.5 (3-C), 109.9, 113.6, 118.7, 127.2, 127.7, 128.5, 133.5, 137.0, 147.8, 149.7. FABMS 455 (M + H)$^+$. HRMS (FAB): calculated $C_{20}H_{25}O_4I$: 455.0721, found: 455.0719.

ent-**14**. Colorless oil, $[\alpha]_D^{25}$ +30 (*c* 0.9, $CHCl_3$).

ent-2-*epi*-**14**. Colorless crystals, mp 112–114 °C, $[\alpha]_D^{25}$ −7 (*c* 0.6, $CHCl_3$).

(2*R*,3*R*,4*S*,5*S*)-5-(4-Benzyloxy-3-methoxyphenyl)-2,4-dimethyltetrahydro-3-furanol 3-*epi*-15. To an ice-cooled suspension of $LiAlH_4$ (0.19 g, 5.01 mmol) in THF (5 mL) was added a solution of iodide 3-*epi*-**14** (1.14 g, 2.50 mmol) in THF (10 mL). After the reaction mixture was stirred at room temperature for 30 min, sat. aq. $MgSO_4$ and K_2CO_3 were added. The mixture was filtered, and then the filtrate was concentrated. The residue was subjected to silica gel column chromatography (EtOAc/hexane = 1/1) to give 3-*epi*-**15** (0.58 g, 1.77 mmol, 71%) as colorless crystals, mp 100–102 °C, $[\alpha]_D^{25}$ +9 (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, d, *J* = 6.8 Hz, 4-CH_3), 1.33 (3H, d, *J* = 6.4 Hz, 2-CH_3), 1.63 (1H, br s, OH), 2.22 (1H, ddq, *J* = 10.2, 6.8, 3.8 Hz, 4-H), 3.90 (3H, s, OCH_3), 4.07 (1H, m, 3-H), 4.40 (1H, dq, *J* = 6.4, 3.0 Hz, 2-H), 4.58 (1H, d, *J* = 10.2 Hz, 5-H), 5.14 (2H, s, OCH_2Ph), 6.78 (1H, dd, *J* = 8.2, 1.9 Hz), 6.84 (1H, d, *J* = 8.2 Hz), 6.89 (1H, d, *J* = 1.9 Hz), 7.29 (1H, m), 7.35 (2H, br dd, *J* = 7.6, 6.9 Hz), 7.43 (2H, br d, *J* = 7.0 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1 (4-CH_3), 14.8 (2-CH_3), 48.5 (4-C), 56.0 (OCH_3), 71.0 (OCH_2Ph), 76.7 (2-C), 79.0 (5-C), 84.9 (3-C), 109.7, 113.9, 118.5, 127.2, 127.7, 128.5, 135.3, 137.2, 147.6, 149.7. FABMS 329 (M + H)$^+$. HRMS (FAB): calculated $C_{20}H_{25}O_4$: 329.1753, found: 329.1760.

ent-3-*epi*-**15**. $[\alpha]_D^{25}$ −9 (*c* 0.7, $CHCl_3$), colorless crystals, mp 100–102 °C.

(2*R*,3*S*,4*S*,5*S*)-5-(4-Benzyloxy-3-methoxyphenyl)-2,4-dimethyltetrahydro-3-furanol 15. 79% yield from **14**, colorless oil, $[\alpha]_D^{25}$ +0.2 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, d, *J* = 6.5 Hz, 4-CH_3), 1.35 (3H, d, *J* = 6.1 Hz, 2-CH_3), 2.01 (1H, br d, *J* = 5.1 Hz, OH), 2.06 (1H, m, 4-H), 3.53 (1H, m, 3-H), 3.90 (3H, s, OCH_3), 4.03 (1H, dq, *J* = 6.5, 6.1 Hz, 2-H), 4.43 (1H, d, *J* = 9.8 Hz, 5-H), 5.14 (2H, s, OCH_2Ph), 6.78 (1H, dd, *J* = 8.1, 1.6 Hz), 6.83 (1H, d, *J* = 8.1 Hz), 6.93 (1H, d, *J* = 1.6 Hz), 7.28 (1H, m), 7.35 (2H, m), 7.42 (2H, d, *J* = 7.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (4-CH_3), 19.1 (2-CH_3), 50.2 (4-C), 55.9 (OCH_3), 71.0 (OCH_2Ph), 79.8 (2-C), 84.1 (5-C), 84.9 (3-C), 109.6, 113.6, 118.7, 127.2, 127.7, 128.5, 134.6, 137.1, 147.7, 149.7; FABMS 329 (M + H)$^+$. Anal. found: C 73.26%, H 7.34%; calcd for $C_{20}H_{24}O_4$: C 73.15%, H 7.37%.

ent-**15**. Colorless oil, $[\alpha]_D^{25}$ −0.2 (*c* 0.2, $CHCl_3$).

(2*R*,4*R*,5*S*)-5-(4-Benzyloxy-3-methoxyphenyl)-2,4-dimethyl-3(2*H*)-furanone 16. A reaction mixture of alcohol 3-*epi*-**15** (0.45 g, 1.37 mmol), PCC (0.35 g, 1.62 mmol), and MS 4A (0.5 g) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 16 h. After the addition of ether, the mixture was filtered. The filtrate was concentrated and the residue was subjected to silica gel column chromatography (EtOAc/hexane = 1/4) to give ketone **16** (0.42 g, 1.29 mmol, 94%) as a colorless oil, $[\alpha]_D^{25}$ −52 (*c* 1.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, *J* = 7.0 Hz, 4-CH_3), 1.33 (3H, d, *J* = 7.3 Hz, 2-CH_3), 2.45 (1H, ddq, *J* = 10.1, 7.0, 1.5 Hz, 4-H), 3.91 (3H, s, OCH_3), 4.44 (1H, dq, *J* = 7.0, 1.5 Hz, 2-H), 4.67 (1H, d, *J* = 10.1 Hz, 5-H), 5.16 (2H, s, OCH_2Ph), 6.86–6.87 (2H, m), 7.01 (1H, d, *J* = 1.5 Hz), 7.28 (1H, m), 7.35 (2H, dd, *J* = 7.1, 7.1 Hz), 7.43 (2H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (4-CH_3), 16.2 (2-CH_3), 50.1 (4-H), 56.3 (OCH_3), 71.2 (OCH_2Ph), 76.7 (2-C), 83.5 (5-C), 109.7, 114.0, 119.0, 127.4, 128.1, 128.7, 132.8, 137.2, 148.5, 150.2, 218.0 (C=O). FABMS: 327 (M + H)$^+$. HRMS (FAB): calculated $C_{20}H_{23}O_4$: 327.1596, found: 327.1589. Alcohol **15** was converted to ketone **16** by PCC oxidation in 82% yield.

ent-**16**. Colorless oil, $[\alpha]_D^{25}$ +60 (*c* 0.7, $CHCl_3$).

(2*R*,3*S*,4*R*,5*S*)-3,5-Bis(4-benzyloxy-3-methoxyphenyl)-2,4-dimethyltetrahydro-3-furanol 17. To a solution of 1-benzyloxy-4-bromo-2-methoxybenzene (1.18 g, 4.03 mmol) in THF (10 mL) was added *n*-BuLi (1.92 mL, 2.7 M in hexane, 5.18 mmol) at −70 °C. The reaction solution was stirred at −70 °C for 10 min, and then a solution of ketone **16** (0.53 g, 1.62 mmol) in THF (10 mL) was added at −70 °C. After stirring at −70 °C for 1.5 h, sat. aq. NH_4Cl and EtOAc were added. The organic solution was separated and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave 3-furanol **17** (0.65 g, 1.20 mmol, 74%) as a colorless oil, $[\alpha]_D^{25}$ +27 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 6.8 Hz, 4-CH_3), 1.19 (3H, d, *J* = 6.3 Hz, 2-CH_3), 1.90 (1H, s, OH), 2.52 (1H, dq, *J* = 9.8, 6.8 Hz, 4-H), 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.44 (1H, q, *J* = 6.4 Hz, 2-H), 4.71 (1H, d, *J* = 9.8 Hz, 5-H), 5.14 (2H, s, OCH_2Ph), 5.15 (2H, s, OCH_2Ph), 6.86 (4H, s), 6.95 (1H, s), 7.07 (1H, s), 7.28 (2H, m), 7.34 (2H, dd, *J* = 7.2, 1.5 Hz), 7.36 (2H, dd, *J* = 7.2, 1.7 Hz), 7.43 (4H, d, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.7 (4-CH_3), 12.9 (2-CH_3), 53.5 (4-C), 56.06 (OCH_3), 56.12 (OCH_3), 70.9 (OCH_2Ph), 71.0 (OCH_2Ph), 83.1 (2-C), 83.7 (5-C), 85.2 (3-C), 109.6, 109.7, 113.5, 113.9, 117.2, 118.2, 127.2, 127.7, 127.8, 128.47, 128.50, 133.2, 135.3, 137.0, 137.1, 147.3, 147.6, 149.4, 149.7. FABMS: 541 (M + H)$^+$. HRMS (FAB): calculated $C_{34}H_{37}O_6$: 541.2591, found: 541.2594.

ent-**17**. Colorless oil, $[\alpha]_D^{25}$ −27 (*c* 1.1, $CHCl_3$).

(1*S*,2*R*,3*S*)-6-Benzyloxy-1-(4-benzyloxy-3-methoxyphenyl)-3-((*R*)-1-hydroxyeth-1-yl)-5-methoxy-2-methylindane, (7*S*,7′*S*,8*R*,8′*R*)-4,4′-dibenzyloxy-3′,5-dimethoxy-2,7′-cyclo-7,8′-neolignan-8-ol 18 and (2*S*,3*S*,4*R*,5*R*)-2,4-bis(4-benzyloxy-3-methoxyphenyl)-3,5-dimethyltetrahydrofuran, (7*S*,7′*R*,8*S*,8′*R*)-

4,4′-dibenzyloxy-3,3′-dimethoxy-7,8′-epoxy-8,7′-neolignan 19. To a solution of 3-furanol **17** (0.16 g, 0.30 mmol) and Et_3SiH (0.46 mL, 2.88 mmol) in CH_2Cl_2 (12 mL) was added $BF_3{\cdot}OEt_2$ (25 μL, 0.20 mmol) at 0 °C. After the reaction solution was stirred at 0–5 °C for 2 h, sat. aq. $NaHCO_3$ was added. The organic solution was separated and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave **18** (0.12 g, 0.23 mmol, 77%) as a colorless oil, $[\alpha]_D^{25}$ −75 (*c* 1.8, $CHCl_3$), and **19** (12 mg, 0.022 mmol, 8%) as a colorless oil, $[\alpha]_D^{25}$ −7 (*c* 0.2, $CHCl_3$). **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, d, *J* = 6.6 Hz, 9′-H), 1.29 (3H, d, *J* = 6.4 Hz, 9-H), 1.67 (1H, br s, OH), 2.12 (1H, m, 8′-H), 2.83 (1H, dd, *J* = 9.6, 5.9 Hz, 7-H), 3.65 (1H, d, *J* = 8.0 Hz, 7′-H), 3.76 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.08 (1H, m, 8-H), 4.95 (1H, d, *J* = 12.2 Hz, OC*H*HPh), 5.00 (1H, d, *J* = 12.2 Hz, OCH*H*Ph), 5.14 (2H, s, OCH_2Ph), 6.46 (1H, s), 6.58 (1H, dd, *J* = 8.2, 1.9 Hz), 6.62 (1H, d, *J* = 1.9 Hz), 6.80 (1H, d, *J* = 8.2 Hz), 6.99 (1H, s), 7.21–7.29 (4H, m), 7.30–7.38 (4H, m), 7.45 (2H, d, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (9′-C), 21.4 (9-C), 47.4 (8′-C), 55.9 (OCH_3), 56.2 (OCH_3), 58.0 (7-C), 58.5 (7′-C), 70.5 (8-C), 70.8 (OCH_2Ph), 71.0 (OCH_2Ph), 108.3, 110.7, 111.7, 113.7, 120.4, 127.2, 127.3, 127.6, 127.7, 128.3, 128.4, 136.0, 137.0, 137.3, 138.0, 138.2, 146.7, 147.7, 148.9, 149.5. FABMS 525 $(M + H)^+$. HRMS (FAB): calculated $C_{34}H_{37}O_5$: 525.2641, found: 525.2635. **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, *J* = 6.4 Hz, 9-H), 1.29 (3H, d, *J* = 6.0 Hz, 9′-H), 2.25 (1H, m, 8-H), 2.52 (1H, dd, *J* = 11.0, 9.5 Hz, 7′-H), 3.89 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.27 (1H, m, 8′-H), 4.54 (1H, d, *J* = 9.4 Hz, 7-H), 5.14 (2H, s, OCH_2Ph), 5.16 (2H, s, OCH_2Ph), 6.71 (1H, d, *J* = 1.7 Hz), 6.74 (1H, dd, *J* = 8.2, 1.7 Hz), 6.85 (1H, d, *J* = 8.2 Hz), 6.87 (2H, s), 6.99 (1H, s), 7.28–7.31 (2H, m), 7.34–7.38 (4H, m), 7.41–7.45 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (9′-C), 20.0 (9-C), 51.1 (8-C), 56.1 (OCH_3 × 2), 61.9 (7′-C), 71.1 (OCH_2Ph × 2), 81.8 (8′-C), 87.0 (7-C), 110.0, 111.6, 114.0, 114.1, 118.5, 120.0, 127.3, 127.8, 128.5, 132.3, 135.2, 137.2, 147.2, 147.7, 149.7; FABMS 525 $(M + H)^+$. HRMS (FAB): calculated $C_{34}H_{37}O_5$: 525.2641, found: 525.2637.

ent-**18**. Colorless oil, $[\alpha]_D^{25}$ +75 (*c* 0.2, $CHCl_3$).

ent-**19**. Colorless oil, $[\alpha]_D^{25}$ +7 (*c* 0.2, $CHCl_3$).

(2*S*,3*S*,4*S*,5*R*)-2,4-Bis(4-benzyloxy-3-methoxyphenyl)-3,5-dimethyltetrahydrofuran, (7*S*,7′*S*,8*S*,8′*R*)-(4,4′-dibenzyloxy-3,3′-dimethoxy-7,8′-epoxy-8,7′-neolignan 7′-*epi*-19. To a solution of 3-furanol **17** (70 mg, 0.13 mmol) and Et_3SiH (0.21 mL, 1.30 mmol) in CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (11 μL, 0.091 mmol) at −40 °C. After the reaction solution was stirred at −40 °C for 2 h, sat. aq. $NaHCO_3$ was added. The organic solution was separated and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave 7′-*epi*-**19** (15 mg, 0.029 mmol, 22%) as a colorless oil, $[\alpha]_D^{25}$ +34 (*c* 0.3, $CHCl_3$). 3-Furanol **17** (52 mg, 0.096 mmol, 74%) was recovered. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (3H, d, *J* = 6.8 Hz, 9-H), 1.19 (3H, d, *J* = 6.5 Hz, 9′-H), 2.58 (1H, m, 8-H), 3.15 (1H, dd, *J* = 6.5, 4.4 Hz, 7′-H), 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.62 (1H, d, *J* = 9.7 Hz, 7-H), 4.71 (1H, m, 8′-H), 5.15 (4H, s, OCH_2Ph), 6.71 (1H, dd, *J* = 8.2, 2.0 Hz), 6.82–6.87 (3H, m), 6.87 (1H, d, *J* = 8.2 Hz), 6.94 (1H, d, *J* = 1.5 Hz), 7.30 (2H, m), 7.33–7.39 (4H, m), 742–7.47 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0 (9-C), 16.8 (9′-C), 29.7 (8-C), 48.8 (7′-C), 55.6 (OCH_3), 56.1 (OCH_3), 71.1 (OCH_2Ph × 2), 79.2 (8′-C), 86.1 (7-C), 109.6, 113.6, 113.9, 114.0, 118.0, 122.4, 127.2, 127.3, 127.8, 128.5, 131.0, 136.7, 137.25, 137.32, 146.8, 147.5, 149.2, 149.7. FABMS 525 $(M + H)^+$. HRMS (FAB): calculated $C_{34}H_{37}O_5$: 525.2641, found: 525.2639.

ent-7′-*epi*-**19**. Colorless oil, $[\alpha]_D^{25}$ −39 (*c* 0.1, $CHCl_3$).

Conversion of 7′-*epi*-19 to indane 18. To a solution of 7′-*epi*-**19** (42 mg, 0.078 mmol) in CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (10 μL, 0.079 mmol) at 0 °C, and then the reaction solution was stirred at 0–3 °C for 1 h before the addition of sat. aq. $NaHCO_3$ and CH_2Cl_2. The organic solution was separated and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave **18** (31 mg, 0.059 mmol, 76%).

(2*S*,3*S*,4*R*,5*R*)-2,4-Bis(4-hydroxy-3-methoxyphenyl)-3,5-dimethyltetrahydrofuran, (7*S*,7′*R*,8*S*,8′*R*)-3,3′-dimethoxy-7,8′-epoxy-8,7′-neolignan-4,4′-diol 20. A reaction mixture of benzyl ether **19** (12 mg, 0.022 mmol) and 5% Pd/C (20 mg) in EtOAc (10 mL) was stirred under a H_2 atmosphere at room temperature for 2 h, and then the mixture was filtered. After concentration of the filtrate, the residue was subjected to silica gel column chromatography (EtOAc/hexane = 1/3) to give **20** (4 mg, 0.012 mmol, 53%) as a colorless oil, $[\alpha]_D^{25}$ +38 (*c* 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, d, *J* = 6.5 Hz, 9-H), 1.29 (3H, d, *J* = 6.0 Hz, 9′-H), 2.24 (1H, m, 8-H), 2.52 (1H, dd, *J* = 11.1, 9.5 Hz, 7′-H), 3.90 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.27 (1H, m, 8′-H), 4.54 (1H, d, *J* = 9.5 Hz, 7-H), 5.58 (1H, br s, OH), 5.59 (1H, br s, OH), 6.70 (1H, d, *J* = 1.8 Hz), 6.75 (1H, dd, *J* = 8.2, 1.8 Hz), 6.88 (1H, d, *J* = 8.2 Hz), 6.91 (2H, s), 6.95 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (9-C), 20.0 (9′-C), 51.2 (8-C), 56.0 (OCH_3 × 2), 62.0 (7′-C), 81.8 (8′-C), 87.1 (7-C), 108.7, 110.1, 114.2, 114.5, 119.3, 120.6, 131.0, 134.0, 144.6, 145.1, 146.55, 146.62; EIMS *m*/*z* (%): 344 (M^+, 33), 300 (100), 285 (56), 137 (80). HRMS (EI): calculated $C_{20}H_{24}O_5$: 344.1624, found: 344.1631. >99%ee (AD-H, 254 nm, 20% 2-propanol/hexane, 1 mL min^{-1}, t_R 20.6 min).

ent-**20**. Colorless oil, $[\alpha]_D^{25}$ −40 (*c* 0.04, $CHCl_3$). 97%ee (AD-H, 254 nm, 20% 2-propanol/hexane, 1 mL min^{-1}, t_R 33.8 min).

(2*S*,3*S*,4*S*,5*R*)-2,4-Bis(4-hydroxy-3-methoxyphenyl)-3,5-dimethyltetrahydrofuran, (7*S*,7′*S*,8*S*,8′*R*)-3,3′-dimethoxyl-7,8′-epoxy-8,7′-neolignan-4,4′-diol 7′-*epi*-20. 53% yield, colorless crystals, mp 84–85 °C, $[\alpha]_D^{25}$ +84 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (3H, d, *J* = 6.8 Hz, 9-H), 1.20 (3H, d, *J* = 6.4 Hz, 9′-H), 2.58 (1H, m, 8-H), 3.15 (1H, dd, *J* = 8.4, 5.3 Hz, 7′-H), 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.62 (1H, d, *J* = 9.7 Hz, 7-H), 4.71 (1H, m, 8′-H), 5.56 (1H, s, OH), 5.57 (1H, s, OH), 6.72 (1H, dd, *J* = 8.1, 1.5 Hz), 6.78 (1H, d, *J* = 1.5 Hz), 6.85 (1H, dd, *J* = 8.1, 1.7 Hz), 6.88–6.90 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9 (9-C), 16.9 (9′-C), 48.8 (8-C), 55.7 (7′-C), 55.9 (OCH_3), 56.0 (OCH_3), 79.2 (8′-C), 86.2 (7-C), 108.3, 112.4, 114.0, 114.2, 118.8, 123.2, 129.7, 135.4, 144.2, 144.9, 146.2, 146.6. EIMS *m*/*z* (%): 344 (M^+, 16), 300 (100), 284 (45). HRMS (EI): calculated $C_{20}H_{24}O_5$: 344.1624, found: 344.1613. >99%ee (AD-H, 254 nm, 20% 2-propanol/hexane, 1 mL min^{-1}, t_R 9.8 min).

ent-7′-*epi*-**20**. Colorless oil, $[\alpha]_D^{25}$ −84 (*c* 0.1, $CHCl_3$) >99%ee (AD-H, 254 nm, 20% 2-propanol/hexane, 1 mL min^{-1}, t_R 18.7 min).

(1*S*,2*S*,3*S*)-6-Benzyloxy-1-(4-benzyloxy-3-methoxyphenyl)-3-ethyl-5-methoxy-2-methylindane, (7*S*,7′*S*,8′*S*)-4,4′-dibenzyloxy-3′,5-dimethoxy-2,7′-cyclo-7,8′-neolignan 21. To an ice-cooled solution of alcohol **18** (96 mg, 0.18 mmol) and Et_3N (80 μL, 0.57 mmol) in CH_2Cl_2 (5 mL) was added MsCl (40 μL, 0.52 mmol). The reaction mixture was stirred at room temperature for 1 h, and then H_2O and CH_2Cl_2 were added. The organic solution was separated and dried (Na_2SO_4). Concentration followed by silica gel column chromatography gave crude mesylate. A reaction mixture of crude mesylate and $NaBH_4$ (0.10 g, 2.64 mmol) in HMPA (2 mL) was stirred at 80 °C for 12 h before the addition of sat. aq. NH_4Cl and EtOAc. The organic solution was separated and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/4) gave **21** (44 mg, 0.087 mmol, 48%, 2 steps) as a colorless oil, $[\alpha]_D^{25}$ −63 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, t, *J* = 7.5 Hz, 9-H), 1.15 (3H, d, *J* = 6.6 Hz, 9′-H), 1.78 (1H, m, 8-C*H*H), 1.87 (1H, m, 8-CH*H*), 1.97 (1H, m, 8′-H), 2.69 (1H, ddd, *J* = 8.9, 5.4, 5.4 Hz, 7-H), 3.59 (1H, d, *J* = 9.3 Hz, 7′-H), 3.77 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.94 (1H, d, *J* = 12.2 Hz, OC*H*HPh), 4.99 (1H, d, *J* = 12.2 Hz, OCH*H*Ph), 5.15 (2H, s, OCH_2Ph), 6.44 (1H, s), 6.61–6.63 (2H, m), 6.77 (1H, s), 6.82 (1H, d, *J* = 8.7 Hz), 7.24–7.26 (2H, m), 7.28–7.39 (6H, m), 7.46 (2H, d, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0 (9-C), 17.6 (9′-C), 24.9 (8-C), 51.0 (8′-C), 51.6 (7-C), 56.0 (OCH_3), 56.3 (OCH_3), 58.4 (7′-C), 71.0 (OCH_2Ph × 2), 107.1, 110.7, 111.9, 113.7, 120.7, 127.2, 127.4, 127.6, 127.7, 128.3, 128.5, 137.2, 137.4, 137.7, 138.0, 139.1, 146.7, 147.2, 149.0, 149.5. FABMS 509 $(M + H)^+$. HRMS (FAB): calculated $C_{34}H_{37}O_4$: 509.2692, found: 509.2688.

ent-**21**. Colorless oil, $[\alpha]_D^{25}$ +63 (*c* 0.1, $CHCl_3$).

(1*S*,2*S*,3*S*)-1-Ethyl-5-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-6-methoxy-2-methylindane, (7*S*,7′*S*,8′*S*)-3′,5-dimethoxy-2,7′-cyclo-7,8′-neolignan-4,4′-diol, (−)-γ-diisoeugenol 4. A reaction mixture of benzyl ether **21** (40 mg, 0.079 mmol) and 5% Pd/C (50 mg) in EtOAc (10 mL) was stirred under H_2 gas at room temperature for 2 h before filtration. The filtrate was concentrated, and then the residue was subjected to silica gel column chromatography (EtOAc/hexane = 1/1) to give (−)-γ-diisoeugenol (**4**) (24 mg, 0.073 mmol, 92%) as colorless crystals, mp 100–103 °C, $[\alpha]_D^{25}$ −24 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, t, *J* = 7.4 Hz, 9-H), 1.15 (3H, d, *J* = 6.5 Hz, 9′-H), 1.78 (1H, m, 8-*H*H), 1.88 (1H, m, 8-H*H*), 1.99 (1H, m, 8′-H), 2.68 (1H, ddd, *J* = 9.0, 5.3, 5.3 Hz, 7-H), 3.58 (1H, d, *J* = 9.4 Hz, 7′-H), 3.83 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.49 (1H, s, OH), 5.55 (1H, s, OH), 6.44 (1H, s), 6.64 (1H, d, *J* = 1.9 Hz), 6.70 (1H, dd, *J* = 7.9, 1.9 Hz), 6.72 (1H, s), 6.86 (1H, d, *J* = 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (9-C), 17.6 (9′-C), 24.9 (8-C), 50.9 (8′-C), 51.5 (7-C), 55.9 (OCH_3), 56.2 (OCH_3), 58.4 (7′-C), 105.7, 110.6, 110.7, 114.1, 121.5, 136.3, 137.7, 139.1, 144.1, 144.5, 145.7, 146.5; EIMS *m*/*z* (%): 328 (M^+, 70), 299 (100). HRMS (EI): calculated $C_{20}H_{24}O_4$: 328.1675, found: 328.1666. >99%ee (AD-H, 254 nm, 5% 2-propanol/hexane, 1 mL min^{-1}, t_R 45.8 min).

ent-**4** ((+)-diisoeugenol). Colorless crystals, mp 98–100 °C, $[\alpha]_D^{25}$ +24 (*c* 0.1, $CHCl_3$), >99%ee (AD-H, 254 nm, 5% 2-propanol/hexane, 1 mL min^{-1}, t_R 38.3 min).

(1*S*,2*S*,3*S*)-1-Ethyl-5,6-dimethoxy-3-(3,4-dimethoxyphenyl)-2-methylindane, (7*S*,7′*S*,8′*S*)-3′,4,4′,5-tetramethoxy-2,7′-cyclo-7,8′-neolignan, (−)-γ-diisohomogenol 5. A reaction mixture of (−)-γ-diisoeugenol (**4**) (73 mg, 0.22 mmol), MeI (1.00 mL, 16.1 mmol), K_2CO_3 (0.12 g, 0.87 mmol), and dibenzo-18-crown-6 (10 mg) in MeCN (20 mL) was heated under reflux for 16 h before filtration. Concentration of the filtrate followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave (−)-γ-diisohomogenol (**5**) (73 mg, 0.20 mmol, 91%) as a colorless oil, $[\alpha]_D^{25}$ −83 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, t, *J* = 7.5 Hz, 9-H), 1.17 (3H, d, *J* = 6.6 Hz, 9′-H), 1.79 (1H, m, 8-*H*H), 1.90 (1H, m, 8-H*H*), 2.00 (1H, m, 8′-H), 2.71 (1H, m, 7-H), 3.65 (1H, d, *J* = 9.3 Hz, 7′-H), 3.72 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.40 (1H, s), 6.68 (1H, d, *J* = 2.1 Hz), 6.77 (1H, dd, *J* = 8.1, 2.1 Hz), 6.77 (1H, s), 6.85 (1H, d, *J* = 8.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.9 (9-C), 17.7 (9′-C), 25.0 (8-C), 51.1 (8′-C), 51.7 (7-C), 55.9 (OCH_3 × 2), 56.0 (OCH_3), 56.1 (OCH_3), 58.6 (7′-C), 106.5, 107.8, 111.1, 111.5, 120.8, 137.3, 138.1, 138.4, 147.6, 148.2, 148.3, 149.0. EIMS *m*/*z* (%): 356 (M^+, 95), 327 (100). HRMS (EI): calculated $C_{22}H_{28}O_4$: 356.1988, found: 356.1985.

(2*S*,3*R*,4*R*,5*S*)-3,5-Bis(4-benzyloxy-3-methoxyphenyl)-2,4-dimethyltetrahydro-3-furanol 22. 2-*epi*-**15** was obtained by $LiAlH_4$ reduction of 2-*epi*-**14** in 74% yield as colorless crystals, mp 74–75 °C, $[\alpha]_D^{25}$ +17 (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, *J* = 6.9 Hz, 4-CH_3), 1.34 (3H, d, *J* = 6.4 Hz, 2-CH_3), 1.78 (1H, br s, OH), 2.06 (1H, m, 4-H), 3.86 (1H, m, 3-H), 3.89 (3H, s, OCH_3), 4.05 (1H, dq, *J* = 6.9, 5.0 Hz, 2-H), 4.21 (1H, d, *J* = 7.7 Hz, 5-H), 5.14 (2H, s, OCH_2Ph), 6.82–6.83 (2H, m), 6.97 (1H, s), 7.28 (1H, s), 7.35 (2H, m), 7.42 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 (4-CH_3), 15.7 (2-CH_3), 50.9 (4-C), 55.9 (OCH_3), 71.0 (OCH_2Ph), 77.0 (2-C), 80.4 (5-C), 86.4 (3-C), 110.0, 113.7, 118.7, 127.2, 127.7, 128.4, 134.2, 137.1, 147.7, 149.6; FABMS 328 (M^+). Anal. found: C 73.31%, H 7.42%; calcd for $C_{20}H_{24}O_4$: C 73.15%, H 7.37%. *ent*-2-*epi*-**15**. Colorless crystals, mp 73–74 °C, $[\alpha]_D^{25}$ −18 (*c* 0.5, $CHCl_3$). 2-*epi*-**16** was obtained by PCC oxidation of 2-*epi*-**15** at 0 °C in 94% yield as colorless crystals, mp 98–99 °C; $[\alpha]_D^{25}$ −63 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, *J* = 6.9 Hz, 4-CH_3), 1.45 (3H, d, *J* = 6.8 Hz, 2-CH_3), 2.36 (1H, dq, *J* = 10.4, 6.9 Hz, 4-H), 3.92 (3H, s, OCH_3), 3.98 (1H, q, *J* = 6.8 Hz, 2-H), 4.50 (1H, d, *J* = 10.4 Hz, 5-H), 5.17 (2H, s, OCH_2Ph), 6.88–6.89 (2H, m), 6.98 (1H, s), 7.30 (1H, m), 7.36 (2H, m), 7.43 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2 (4-CH_3), 16.4 (2-CH_3), 49.5 (4-C), 56.0 (OCH_3), 71.0 (OCH_2Ph), 77.8 (2-C), 84.5 (5-C), 109.9, 113.8, 118.9, 127.2, 127.8, 128.5, 132.0, 137.0, 148.3, 149.9, 217.9 (C═O). FABMS 326 (M^+). Anal. found: C 73.81%, H 6.88%; calcd for $C_{20}H_{22}O_4$: C 73.60%, H 6.79%. *ent*-2-*epi*-**16**. Colorless crystals, mp 98–99 °C, $[\alpha]_D^{25}$ +58 (*c* 0.6, $CHCl_3$). Furanol **22** was obtained by the reaction of 2-*epi*-**16** with 4-benzyloxy-3-methoxyphenyllithium at −70 °C in 94% yield as a colorless oil, $[\alpha]_D^{25}$ +36 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (3H, d, *J* = 7.1 Hz, 4-CH_3), 1.36 (3H, d, *J* = 6.3 Hz,

2-CH_3), 2.30–2.37 (1H, overlapped, 4-H), 2.35 (1H, s, OH), 3.90 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.35 (1H, d, J = 7.0 Hz, 5-H), 4.46 (1H, q, J = 6.3 Hz, 2-H), 5.146 (2H, s, OCH_2Ph), 5.155 (2H, s, OCH_2Ph), 6.82–6.90 (4H, m), 7.03 (1H, d, J = 1.8 Hz), 7.09 (1H, d, J = 1.8 Hz), 7.16 (1H, m), 7.30 (1H, m), 7.33–7.38 (4H, m), 7.42 (2H, d, J = 6.6 Hz), 7.44 (2H, d, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5 (4-CH_3), 15.7 (2-CH_3), 54.2 (4-C), 55.97 (OCH_3), 56.04 (OCH_3), 70.9 (OCH_2Ph), 71.0 (OCH_2Ph), 79.6 (2-C), 84.1 (5-C), 86.5 (3-C), 110.0, 110.5, 113.2, 113.9, 118.2, 118.5, 127.18, 127.23, 127.7, 127.8, 128.47, 128.50, 134.1, 134.7, 137.0, 137.1, 147.4, 147.7, 149.4, 149.7. FABMS 541 (M + H)$^+$. Anal. found: C 75.75%, H 6.84%; calcd for $C_{34}H_{36}O_6$: C 75.53%, H 6.71%.

ent-**22**. Colorless oil, $[\alpha]_D^{25}$ −37 (c 0.4, $CHCl_3$).

(2*S*,3*S*,4*S*,5*S*)-2,4-Bis(4-benzyloxy-3-methoxyphenyl)-3,5-dimethyltetrahydrofuran, (7*S*,7′*S*,8*S*,8′*S*)-4,4′-dibenzyloxy-3,3′-dimethoxyl-7,8′-epoxy-8,7′-neolignan 23. A reaction mixture of 3-furanol **22** (0.28 g, 0.52 mmol), ZnI_2 (0.25 g, 0.78 mmol), and $NaBH_3CN$ (0.24 g, 3.82 mmol) in 1,2-dichloroethane (15 mL) was heated under reflux for 4 h before adding to H_2O. The mixture was extracted with CH_2Cl_2. The organic solution was separated and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/4) gave **23** (73 mg, 0.14 mmol, 27%) as a colorless oil, $[\alpha]_D^{25}$ +44 (c 0.3, $CHCl_3$). 3-Furanol **22** (0.19 g, 0.37 mmol, 71%) was recovered. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (3H, d, J = 6.9 Hz, 9′-H), 1.43 (3H, d, J = 6.1 Hz, 9-H), 2.38 (1H, m, 8-H), 3.03 (1H, dd, J = 8.4, 5.7 Hz, 7′-H), 3.89 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.45 (1H, dq, J = 5.9, 5.9 Hz, 8′-H), 4.49 (1H, d, J = 8.7 Hz, 7-H), 5.15 (4H, s, OCH_2Ph × 2), 6.69 (1H, dd, J = 8.2, 1.8 Hz), 6.75 (1H, d, J = 1.8 Hz), 6.84–6.86 (3H, m), 6.96 (1H, d, J = 1.1 Hz), 7.27–7.32 (2H, m), 7.34–7.39 (4H, m), 7.42–7.46 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (9-C), 21.6 (9′-C), 46.0 (8-C), 55.7 (7′-C), 56.0 (OCH_3), 56.1 (OCH_3), 71.1 (OCH_2Ph × 2), 79.9 (8′-C), 87.2 (7-C), 109.9, 112.8, 113.7, 113.8, 118.4, 120.7, 127.2, 127.3, 127.7, 127.8, 128.5, 133.2, 135.4, 137.2, 146.8, 147.5, 149.4, 149.6. FABMS 525 (M + H)$^+$. HRMS (FAB): calculated $C_{34}H_{37}O_5$: 525.2641, found: 525.2632.

ent-**23**. Colorless oil, $[\alpha]_D^{25}$ −44 (c 0.2, $CHCl_3$).

(2*S*,3*S*,4*R*,5*S*)-2,4-Bis(4-benzyloxy-3-methoxyphenyl)-3,5-dimethyltetrahydrofuran, (7*S*,7′*R*,8*S*,8′*S*)-4,4′-dibenzyloxy-3,3′-dimethoxyl-7,8′-epoxy-8,7′-neolignan 7′-*epi*-23. To a solution of 3-furanol **22** (0.16 g, 0.30 mmol) and Et_3SiH (2.00 mL, 12.5 mmol) in CH_2Cl_2 (10 mL) was added $BF_3{\cdot}OEt_2$ (40 μL, 0.32 mmol) at 0 °C. The reaction solution was stirred at 0–3 °C for 30 min before the addition of sat. aq. $NaHCO_3$. The organic solution was separated and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/3) gave 7′-*epi*-**23** (87 mg, 0.17 mmol, 57%) as a colorless oil, $[\alpha]_D^{25}$ −55 (c 1.3, $CHCl_3$), and **23** (4.8 mg, 0.0091 mmol, 3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, d, J = 6.4 Hz, 9-H), 1.03 (3H, d, J = 6.5 Hz, 9′-H), 2.30 (1H, m, 8-H), 3.15 (1H, dd, J = 9.3, 8.3 Hz, 7′-H), 3.84 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.40–4.46 (1H, overlapped, 8′-H), 4.41 (1H, d, J = 9.2 Hz, 7-H), 5.12 (2H, s, OCH_2Ph), 5.15 (2H, s, OCH_2Ph), 6.66 (1H, dd, J = 8.2, 1.6 Hz), 6.70 (1H, d, J = 1.6 Hz), 6.83 (1H, d, J = 8.2 Hz), 6.86–6.92 (2H, m), 7.01 (1H, d, J = 1.6 Hz), 7.28 (2H, m), 7.35 (4H, dd, J = 7.3, 7.3 Hz), 7.43 (4H, d, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1 (9-C), 18.9 (9′-C), 46.5 (8-C), 56.0 (OCH_3 × 2), 56.5 (7′-C), 71.0 (OCH_2Ph × 2), 77.3 (8′-C), 87.4 (7-C), 110.0, 112.5, 113.7, 113.8, 118.4, 120.5, 127.16, 127.20, 127.7, 128.4, 132.5, 134.5, 137.2, 146.8, 147.6, 149.4, 149.6. FABMS 525 (M + H)$^+$. HRMS (FAB): calculated $C_{34}H_{37}O_5$: 525.2641, found: 525.2630.

ent-7′-*epi*-**23**. Colorless oil, $[\alpha]_D^{25}$ +55 (c 0.7, $CHCl_3$).

(2*S*,3*S*,4*S*,5*S*)-2,4-Bis(4-hydroxy-3-methoxyphenyl)-3,5-dimethyltetrahydrofuran, (7*S*,7′*S*,8*S*,8′*S*)-3,3′-dimethoxyl-7,8′-epoxy-8,7′-neolignan-4,4′-diol 24. The phenol **24** was obtained by the hydrogenolysis of **23** using 5% Pd/C in EtOAc under H_2 gas in 100% yield as a colorless oil, $[\alpha]_D^{25}$ +43 (c 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (3H, d, J = 7.0 Hz, 9-H), 1.43 (3H, d, J = 6.1 Hz, 9′-H), 2.36 (1H, m, 8-H), 3.02 (1H, dd, J = 8.4, 5.7 Hz, 7′-H), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.44 (1H, dq, J = 6.0, 6.0 Hz, 8′-H), 4.48 (1H, d, J = 8.1 Hz, 7-H), 5.59 (2H, br s, OH × 2), 6.68–6.71 (2H, m), 6.84 (1H, dd, J = 8.2, 1.6 Hz), 6.86–6.89 (2H, m), 6.92 (1H, d, J = 1.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (9-C), 21.6 (9′-C), 46.1 (8-C), 55.8 (7′-C), 55.9 (OCH_3), 56.0 (OCH_3), 80.0 (8′-C), 87.3 (7-C), 108.6, 111.3, 114.1, 119.1, 121.5, 132.0, 134.1, 144.1, 145.0, 146.3, 146.5. EIMS m/z (%): 344 (56), 300 (100), 285 (39). HRMS (EI): calculated $C_{20}H_{24}O_5$: 344.1624, found: 344.1617. >99%ee (AD-H, 254 nm, 20% 2-propanol/hexane, 1 mL min^{-1}, t_R 11.6 min).

ent-**24**. Colorless oil, $[\alpha]_D^{25}$ −45 (c 0.2, $CHCl_3$). >99%ee (AD-H, 254 nm, 20% 2-propanol/hexane, 1 mL min^{-1}, t_R 18.0 min).

(2*S*,3*S*,4*R*,5*S*)-2,4-Bis(4-hydroxy-3-methoxyphenyl)-3,5-dimethyltetrahydrofuran, (7*S*,7′*R*,8*S*,8′*S*)-3,3′-dimethoxyl-7,8′-epoxy-8,7′-neolignan-4,4′-diol 7′-*epi*-24. The phenol 7′-*epi*-**24** was obtained by the hydrogenolysis of 7′-*epi*-**23** using 5% Pd/C in EtOAc under H_2 gas in 96% yield as a colorless oil, $[\alpha]_D^{25}$ −69 (c 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, d, J = 6.4 Hz, 9-H), 1.04 (3H, d, J = 6.4 Hz, 9′-H), 2.29 (1H, m, 8-H), 3.16 (1H, dd, J = 9.7, 8.5 Hz, 7′-H), 3.87 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.41–4.47 (1H, overlapped, 8′-H), 4.42 (1H, d, J = 9.2 Hz, 7-H), 5.56 (2H, br s, OH × 2), 6.66 (1H, d, J = 1.6 Hz), 6.69 (1H, dd, J = 8.1, 1.6 Hz), 6.87 (1H, d, J = 8.1 Hz), 6.92 (2H, s), 6.98 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0 (9-C), 19.0 (9′-C), 46.5 (8-C), 55.9 (OCH_3), 56.6 (7′-C), 76.7 (8′-C), 87.6 (7-C), 108.8, 111.2, 114.1, 119.3, 121.3, 131.3, 133.4, 144.3, 145.1, 146.4, 146.5. EIMS m/z (%): 344 (28), 300 (100), 285 (34). HRMS (EI): calculated $C_{20}H_{24}O_5$: 344.1624, found: 344.1631. >99%ee (AD-H, 254 nm, 20% 2-propanol/hexane, 1 mL min^{-1}, t_R 23.4 min).

ent-7′-*epi*-**24**. Colorless oil, $[\alpha]_D^{25}$ +69 (c 0.4, $CHCl_3$). 97%ee (AD-H, 254 nm, 20% 2-propanol/hexane, 1 mL min^{-1}, t_R 29.6 min).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Part of this work was performed at ADRES (Johoku station) of Ehime University. We are grateful to Marutomo Co. for financial support.

Notes and references

1 (*a*) S. Fujisawa and Y. Kadoma, *Mini-Rev. Med. Chem.*, 2012, **12**, 477–490; (*b*) D. R. M. Arenas, A. M. Acevedo, L. Y. V. Méndez and V. V. Kouznetsov, *Sci. Pharm.*, 2011, **79**, 779–791; (*c*) T. Atsumi, K. Tonosaki and S. Fujisawa, *Arch. Oral Biol.*, 2006, **51**, 913–921; (*d*) T. Atsumi, Y. Murakami, K. Shibuya, K. Tonosaki and S. Fujisawa, *Anticancer Res.*, 2005, **25**, 4029–4036; (*e*) Y. Murakami, M. Shoji, A. Hirata, S. Tanaka, I. Yokoe and S. Fujisawa, *Arch. Biochem. Biophys.*, 2005, **434**, 326–332; (*f*) S. Fujisawa, T. Atsumi, Y. Murakami and Y. Kadoma, *Arch. Immunol. Ther. Exp.*, 2005, **53**, 28–38; (*g*) T. Atsumi, S. Fujisawa, K. Satoh, H. Sakagami, I. Iwakura, T. Ueha, Y. Sugita and I. Yokoe, *Anticancer Res.*, 2000, **20**, 2519–2524; (*h*) C.-H. Lin, Y.-H. Kuo, Y.-L. Lin and C.-M. Teng, *J. Pharm. Pharmacol.*, 1994, **46**, 54–57.

2 (*a*) T. Yamamoto, B. Riehi, K. Naba, K. Nakahara, A. Wiebe, T. Saitoh, S. R. Waldvogel and Y. Einaga, *Chem. Commun.*, 2018, **54**, 2771–2773; (*b*) N. Morita, R. Mashiko, D. Hakuta, D. Eguchi, S. Ban, Y. Hashimoto, I. Okamoto and O. Tamura, *Synthesis*, 2016, 1927–1933.

3 T. Nakato, S. Yamauchi, R. Tago, K. Akiyama, M. Maruyama, T. Sugahara, T. Kishida and Y. Koba, *Biosci. Biotechnol. Biochem.*, 2009, **73**, 1608–1617.

4 (*a*) H. Nishiwaki, K. Nakayama, Y. Shuto and S. Yamauchi, *J. Agric. Food Chem.*, 2014, **62**, 651–659; (*b*) S. Yamauchi, K. Nakayama, H. Nishiwaki and Y. Shuto, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4798–4803.

5 T. Wukirsari, H. Nishiwaki, K. Nishi, T. Sugahra, K. Akiyama, T. Kishida and S. Yamauchi, *Biosci. Biotechnol. Biochem.*, 2016, **80**, 669–675.

6 G. P. Moss, *Pure Appl. Chem.*, 2000, **72**, 1493–1523.

7 (*a*) Y. Lu, Y. Xue, J. Liu, G. Yao, D. Li, B. Sun, J. Zhang, Y. Liu, C. Qi, M. Xiang, Z. Luo, G. Du and Y. Zhang, *J. Nat. Prod.*, 2015, **78**, 2205–2214; (*b*) O. Muraoka, T. Sawada, E. Morimoto and G. Tanabe, *Chem. Pharm. Bull.*, 1993, **41**, 772–774; (*c*) T. Tsuruga, Y. Ebizuka, J. Nakajima, Y.-T. Chun, H. Noguchi, Y. Iitaka, U. Sankawa and H. Seto, *Tetrahedron Lett.*, 1984, **25**, 4129–4132.

8 E. Gao, Z.-Q. Zhou, J. Zou, Y. Yu, X.-L. Feng, G.-D. Chen, R.-R. He, X.-S. Yao and H. Gao, *J. Nat. Prod.*, 2017, **80**, 2923–2929.

9 (*a*) B. D. Dickson, N. Dittrich and D. Barker, *Tetrahedron Lett.*, 2012, **53**, 4464–4468; (*b*) B. M. Pérez, D. Schuch and J. Hartung, *Org. Biomol. Chem.*, 2008, **6**, 3532–3541; (*c*) M. Greb, J. Hartung, F. Köhler, K. Spehar, R. Kluge and R. Csuk, *Eur. J. Org. Chem.*, 2004, 3799–3812.

10 J. MacMillan, I. L. Martin and D. J. Morris, *Tetrahedron*, 1969, **25**, 905–914.

11 D. A. Evans, J. S. Tedrow, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2002, **124**, 392–393.

12 Y. Ogura, H. Sato and S. Kuwahara, *Org. Lett.*, 2016, **18**, 2399–2402.

13 F. A. Carey and H. S. Tremper, *J. Org. Chem.*, 1969, **34**, 4–6.

14 C. K. Lau, C. Dufresne, P. C. Belanger, S. Pietre and J. Scheigetz, *J. Org. Chem.*, 1986, **51**, 3038–3043.

