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Efficient Synthesis of Optically Active Neolignans Ligraminol D and E

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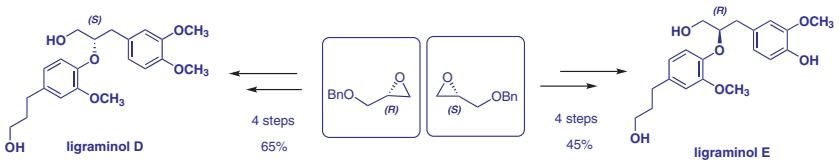

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Abstract Efficient syntheses of optically active neolignans ligraminol D and E were achieved in four simple steps starting from easily available chiral benzyl glycidyl ethers. The products were obtained in good overall yields and high enantioselectivities. The protocol might also be useful in the synthesis of other ligraminols or related neolignans.

Key words ligraminol, epoxide, lignan, benzyl glycidyl ether, Mitsunobu

Lignans and neolignans are important secondary metabolites, widespread in the plant kingdom and are produced from the shikimic acid pathway.[1] Further, they exhibit interesting biological activities such as anti-inflammatory,[2a] antiviral,[2b] antimalarial,[2c] antileishmanial,[2d] and anticancer.[2e] Hence, there is a lot of interest in synthesizing this class of compounds.[3] Ligraminol D and E (Figure 1) belong to the alkyl aryl ether class of neolignans, recently isolated from 80% aqueous methanolic extract of rhizomes of *Acorus gramineus*, also known as 'Japanese sweet flag'. These compounds were tested for their antiproliferative activities against three human cancer cell lines including SK-OV-3, SK-MEL-2, and A549 using SRB bioassay. Ligraminol D with few other lignans exhibited anticancer activity and were able to suppress the survival of cancer cells selectively (Figure 1). In addition, these compounds also showed good neuroprotective properties.[4]

However, methods available for the synthesis of ligraminols are very limited. There is only one method available for the synthesis of ligraminol E, employing imidazolidinone-

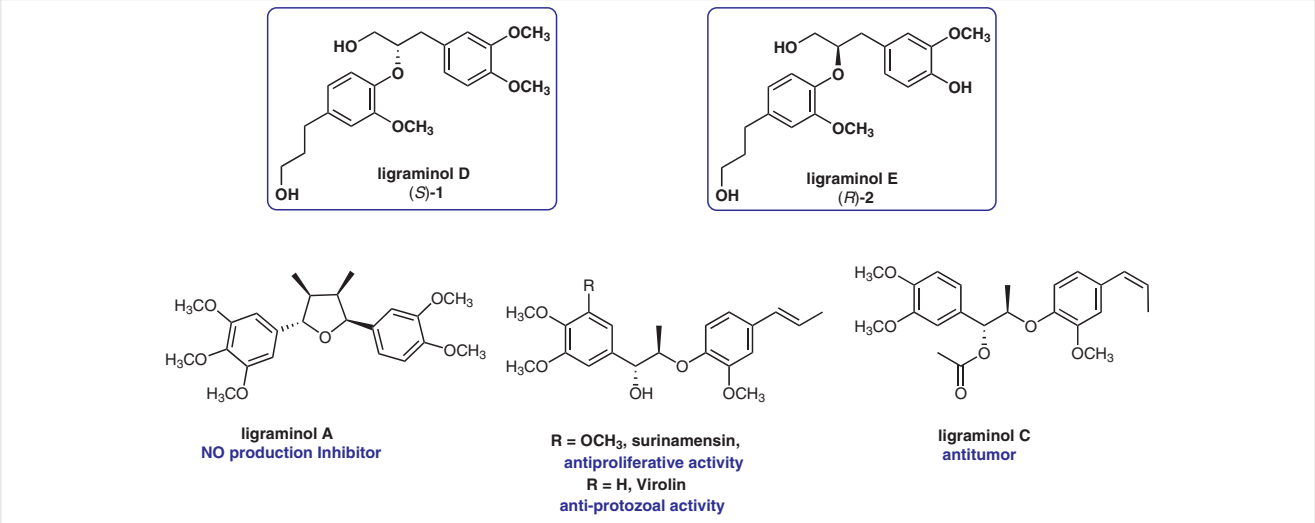

Figure 1 Representative bioactive neolignans

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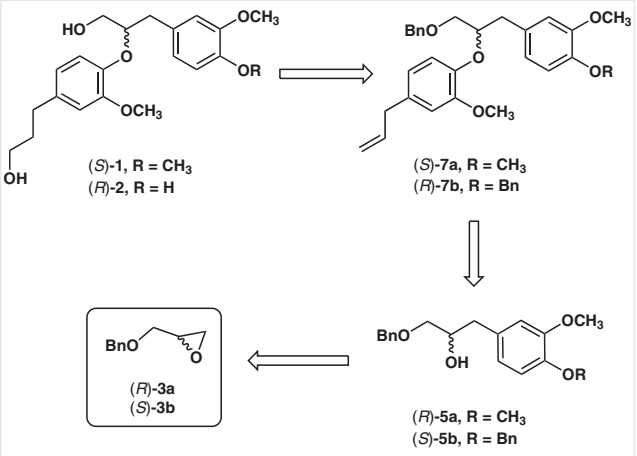


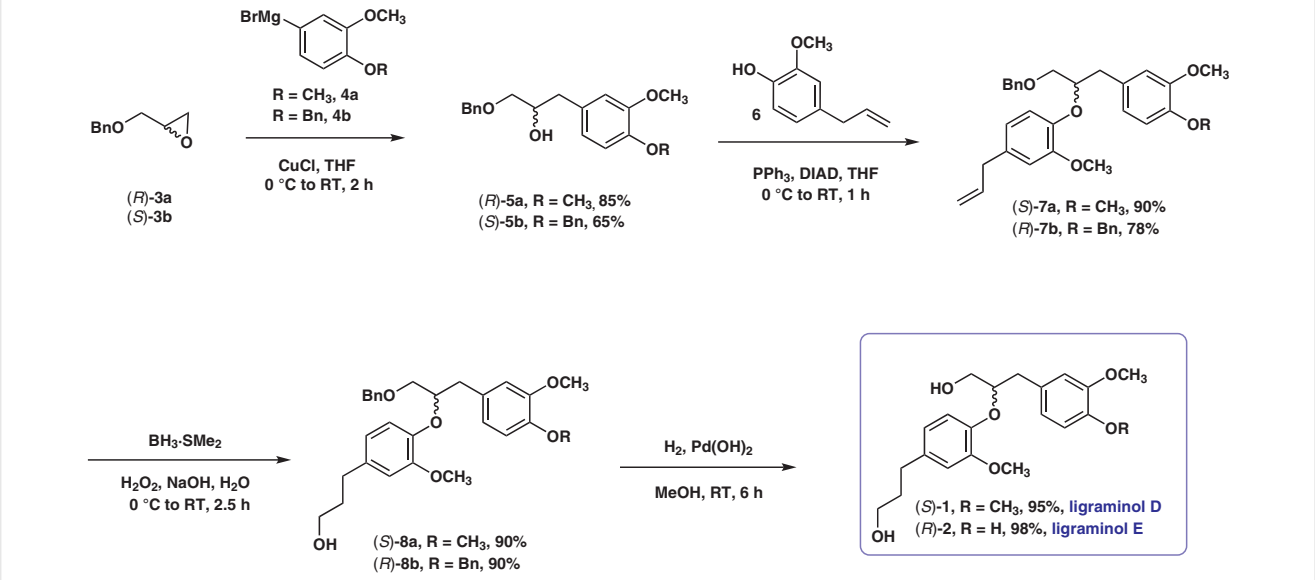
Scheme 1 Retrosynthetic analysis of ligraminol D [(*S*)-**1**] and ligraminol E [(*R*)-**2**]

based chiral auxiliary and the method requires eight steps with more protection/deprotection sequences.[5] In addition, no synthesis is reported particularly for ligraminol D. Therefore, the development of a robust method that can facilitate the easy access to ligraminol and its derivatives are highly desirable.

Epoxides represent a versatile functional group in organic synthesis. Due to their intrinsic propensity towards strain-induced ring-opening reactions, they are widely accepted as important building blocks for the industrial production of various chemicals.[6] Over the past few years, we demonstrated the potential utility of these epoxides for the synthesis of various biologically/pharmaceutically important compounds.[7] Herein, we report a concise and simple synthesis of ligraminol D [(*S*)-**1**] and E [(*R*)-**2**] from commercially available (*R*)- and (*S*)-benzyl glycidyl ethers, thereby devising a new approach that would enable the synthesis of other alkyl aryl ether class of neolignans.

A retrosynthetic analysis of the target compounds (*S*)-**1** and (*R*)-**2** is outlined in Scheme 1. Optically active ligraminols (*S*)-**1** and (*R*)-**2** could be readily obtained from precursors (*S*)-**7a** and (*R*)-**7b**, respectively, via alkene oxidation followed by the deprotection of benzyl group. The particular alkene derivatives (*S*)-**7a** and (*R*)-**7b** could be constructed by Mitsunobu coupling between the secondary alcohols (*R*)-**5a** and (*S*)-**5b** and 4-allyl-2-methoxyphenol (**6**). Enantiomerically pure alcohols (*R*)-**5a** and (*S*)-**5b** could be visualized as key intermediates and they can be easily obtained by the ring-opening reaction of chiral epoxides (*R*)-**3a** and (*S*)-**3b** using the corresponding Grignard reagent.

As shown in Scheme 2, the synthesis commenced with the commercially available chiral benzyl glycidyl ethers (*R*)-**3a** and (*S*)-**3b**. Alternatively, (*R*)-**3a** and (*S*)-**3b** enantiomers can be obtained by employing hydrolytic kinetic resolution (HKR) strategy on the corresponding *rac*-benzyl glycidyl ethers.[8] Glycidyl ethers (*R*)-**3a** and (*S*)-**3b** on regioselective ring opening with the respective Grignard reagent **4a**/**4b**, in the presence of catalytic amount of CuCl provided the key alcohols (*R*)-**5a** and (*S*)-**5b** in 85% and 65% yield, respectively. Next, the coupling between 4-allyl-2-methoxyphenol (**6**) and the key intermediates (*R*)-**5a** and (*S*)-**5b** was carried out using standard Mitsunobu conditions to furnish the desired alkene derivatives (*S*)-**7a** and (*R*)-**7b** in good yields. Subsequently, the alkene group of intermediates (*S*)-**7a** and (*R*)-**7b** was transformed to primary alcohols (*S*)-**8a** and (*R*)-**8b** using H_2O_2 in the presence of borane-DMS under basic conditions in high yields. Finally, $Pd(OH)_2$-catalyzed



Scheme 2 Synthesis of ligraminol D [(*S*)-**1**] and ligraminol E [(*R*)-**2**]

hydrogenolysis of compounds (*S*)-**8a** and (*R*)-**8b** furnished ligraminol D [(*S*)-**1**] and ligraminol E [(*R*)-**2**] in 95% and 98% yield, respectively. The structures of (*S*)-**1** and (*R*)-**2** were confirmed by means of ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic analyses.

In conclusion, we have developed a short synthesis of ligraminol D and E [(*S*)-**1** and (*R*)-**2**] from commercially available chiral benzyl glycidyl ethers. Simple procedures, high yields, and high enantioselectivities are some of the salient features of this strategy. Further, this simple approach offers flexibility in making other ligraminols or related neolignans.

Solvents were purified and dried by standard procedures prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 and AV-500 NMR spectrometers. Spectra were obtained in $CDCl_3$. The reactions were monitored by using TLC Merck silica gel 60 F254 plates and visualization with UV light (254 and 365 nm), or with $KMnO_4$ and anisaldehyde in EtOH as development reagents. Optical rotations were measured with a JASCO P 1020 digital polarimeter. High-resolution mass spectrometry (HRMS) was performed on a TOF/Q-TOF mass spectrometer.

(*R*)-1-(Benzyloxy)-3-(3,4-dimethoxyphenyl)propan-2-ol [(*R*)-5a]

To a pre-cooled (0 °C) solution of (*R*)-**3a** (1.0 g, 6.24 mmol) in anhyd THF (10 mL) was slowly added 3,4-dimethoxyphenylmagnesium bromide (**4a**; 2.20 g, 9.13 mmol) in the presence of a catalytic amount of CuCl under argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature and cautiously quenched with sat. aq NH_4Cl (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (anhyd Na_2SO_4) and the solvent was removed under reduced pressure to afford a crude mixture, which was purified by column chromatography (silica gel, PE/EtOAc 80:20) to afford (*R*)-**5a** as a yellow oil; yield: 1.6 g (85%); R_f = 0.3 (PE/EtOAc 70:30); $[\alpha]_D^{26}$ –5.4 (*c* 1.3, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.22 (m, 5 H), 6.83–6.78 (m, 1 H), 6.78–6.71 (m, 2 H), 4.56 (s, 2 H), 4.09–3.99 (m, 1 H), 3.86 (s, 6 H), 3.53 (dd, *J* = 2.1, 9.5 Hz, 1 H), 3.45–3.38 (m, 1 H), 2.76 (d, *J* = 6.1 Hz, 2 H), 2.09 (br s, 1 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 148.9, 147.6, 137.9, 130.4, 128.4, 127.8, 127.7, 121.2, 112.5, 111.3, 73.6, 73.4, 71.4, 55.9, 55.8, 39.4.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{18}H_{22}O_4Na$ [M + Na]$^+$: 325.1410; found: 325.1410.

(*S*)-4-Allyl-1-{[1-(benzyloxy)-3-(3,4-dimethoxyphenyl)propan-2-yl]oxy}-2-methoxybenzene [(*S*)-7a]

A solution of DIAD (0.7 mL, 3.97 mmol) was added dropwise to a solution of (*R*)-**5a** (1.0 g, 3.30 mmol), eugenol (**6**; 0.54 g, 3.30 mmol), and PPh_3 (1 g, 3.97 mmol) in anhyd THF (20 mL) at 0 °C under N_2 atmosphere. Then, the reaction mixture was stirred at RT for 1 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, PE/EtOAc 93:07) to afford (*S*)-**7a** as a colorless oil; yield: 1.33 g (90%); R_f = 0.6 (PE/EtOAc 80:20); $[\alpha]_D^{26}$ –17.61 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 4 H), 7.31–7.25 (m, 1 H), 6.86 (s, 1 H), 6.83–6.75 (m, 3 H), 6.71 (s, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 5.96 (tdd, *J* = 6.7, 10.1, 16.9 Hz, 1 H), 5.13–5.04 (m, 2 H), 4.60–4.53 (m, 2 H), 4.49 (quint, *J* = 5.5 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 6 H), 3.67–3.59 (m, 2 H), 3.33 (d, *J* = 6.5 Hz, 2 H), 3.11–2.99 (m, 2 H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 150.5, 148.6, 147.5, 145.9, 138.3, 137.5, 134.0, 130.7, 128.3, 127.6, 127.5, 121.5, 120.6, 117.4, 115.6, 113.0, 112.7, 111.0, 80.4, 73.3, 70.7, 55.8, 55.8, 55.7, 39.8, 37.5.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{28}H_{32}O_5Na$ [M + Na]$^+$: 471.2142; found: 471.2142.

(*S*)-3-(4-{[1-(Benzyloxy)-3-(3,4-dimethoxyphenyl)propan-2-yl]oxy}-3-methoxyphenyl)propan-1-ol [(*S*)-8a]

BH_3·SMe_2 complex (0.42 mL, 4.46 mmol) was slowly added to a solution of (*S*)-**7a** (1.0 g, 2.23 mmol) in THF (50 mL) at 0 °C under argon atmosphere. After stirring for 30 min, the reaction mixture was warmed to RT and stirred for another 2 h. The reaction was quenched at 0 °C with H_2O (100 mL), H_2O_2 (30%, 3.0 mL, 33.4 mmol), and NaOH (0.17 g, 4.46 mmol); then the mixture was stirred for 90 min. The resulting two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL), the combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried (anhyd Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, PE/acetone 83:17) to afford (*S*)-**8a** as a colorless liquid; yield: 0.94 g (90%); R_f = 0.4 (PE/EtOAc 80:20); $[\alpha]_D^{25}$ –22.27 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.30 (m, 4 H), 7.29 (d, *J* = 6.1 Hz, 1 H), 6.85 (s, 1 H), 6.83–6.75 (m, 3 H), 6.72 (s, 1 H), 6.66 (d, *J* = 7.9 Hz, 1 H), 4.61–4.52 (m, 2 H), 4.49 (t, *J* = 5.2 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 6 H), 3.67 (t, *J* = 6.4 Hz, 2 H), 3.65–3.58 (m, 2 H), 3.09–3.02 (m, 2 H), 2.99 (s, 1 H), 2.65 (t, *J* = 7.6 Hz, 2 H), 1.87 (quint, *J* = 7.0 Hz, 2 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.5, 148.6, 147.5, 145.8, 138.3, 135.8, 130.7, 128.3, 127.6, 127.5, 121.6, 120.4, 117.4, 113.0, 112.6, 111.0, 80.4, 73.4, 70.8, 62.2, 55.9, 55.7, 42.6, 37.5, 34.3, 31.7.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{28}H_{34}O_6Na$ [M + Na]$^+$: 489.2248; found: 489.2248.

(*S*)-3-(3,4-Dimethoxyphenyl)-2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]propan-1-ol [Ligraminol D, (*S*)-1]

To a solution of (*S*)-**8a** (0.5 g, 1.07 mmol) in EtOH (5 mL) was added $Pd(OH)_2$ on activated charcoal (50 mg, 10–20 wt%), and the reaction mixture was stirred under H_2 atmosphere (20 psi) for 6 h. After the completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of Celite bed (EtOAc eluent) and the solvent was evaporated under reduced pressure to give (*S*)-**1** as a colorless liquid; yield: 0.383 g (95%); R_f = 0.2 (PE/EtOAc 80:20); $[\alpha]_D^{25}$ –29.09 (*c* 0.1, MeOH) {Lit.[4] $[\alpha]_D^{25}$ +9.5 (*c* 0.1, MeOH)}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.81 (s, 3 H), 6.74 (s, 1 H), 6.67 (s, 2 H), 4.24–4.18 (m, 1 H), 3.89–3.82 (m, 9 H), 3.72–3.64 (m, 3 H), 3.63–3.58 (m, 1 H), 3.06 (dd, *J* = 6.7, 13.9 Hz, 1 H), 2.91 (dd, *J* = 6.9, 14.1 Hz, 1 H), 2.67–2.60 (m, 2 H), 2.42 (br s, 2 H), 1.91–1.82 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.9, 148.9, 147.7, 145.5, 137.2, 130.5, 121.5, 121.0, 119.7, 112.9, 112.4, 111.4, 84.9, 63.4, 62.0, 55.9, 55.8, 55.8, 37.2, 34.2, 31.7, 29.6.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{28}O_6Na$ [M + Na]$^+$: 399.1778; found: 399.1776.

(*S*)-1-(Benzyloxy)-3-[4-(benzyloxy)-3-methoxyphenyl]propan-2-ol [(*S*)-5b]

To a pre-cooled (0 °C) solution of (*R*)-**3b** (1.0 g, 6.24 mmol) in anhyd THF (10 mL) was slowly added [4-(benzyloxy)-3-methoxyphenyl]magnesium bromide (**4b**; 3.0 g, 9.14 mmol) in the presence of a catalytic amount of CuCl under argon atmosphere. The reaction mixture was stirred at the same temperature for 2 h and cautiously quenched with sat. aq NH_4Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (anhyd Na_2SO_4) and the solvent was removed under reduced pressure to afford a crude mixture, which was purified by column chromatography (silica gel, PE/EtOAc, 90:10) to yield (*S*)-**5b** as a yellow oil; yield: 1.53 g (65%); R_f = 0.4 (PE/EtOAc 70:30); $[\alpha]_D^{26}$ +4.2 (*c* 1.3, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.42 (m, 2 H), 7.41–7.28 (m, 8 H), 6.85–6.80 (m, 1 H), 6.79 (d, *J* = 2.3 Hz, 1 H), 6.68 (dd, *J* = 1.9, 8.0 Hz, 1 H), 5.14 (s, 2 H), 4.56 (s, 2 H), 4.08–4.00 (m, 1 H), 3.87 (s, 3 H), 3.52 (dd, *J* = 3.4, 9.5 Hz, 1 H), 3.45–3.39 (m, 1 H), 2.75 (d, *J* = 6.9 Hz, 2 H), 2.32 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 146.8, 137.9, 137.3, 131.1, 128.5, 128.4, 127.8, 127.7, 127.2, 121.2, 114.1, 113.0, 73.5, 73.4, 71.4, 71.1, 55.9, 39.5.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{24}H_{26}O_4Na$ [M + Na]$^+$: 401.1723; found: 401.1718.

(*R*)-4-Allyl-1-({1-(benzyloxy)-3-[4-(benzyloxy)-3-methoxyphenyl]propan-2-yl}oxy)-2-methoxybenzene [(*R*)-7b]

A solution of DIAD (0.64 mL, 3.16 mmol) was added dropwise to a solution of (*S*)-**5b** (1.0 g, 2.64 mmol), eugenol (**6**; 0.43 g, 2.64 mmol), and PPh_3 (0.830 g, 3.16 mmol) in anhyd THF (20 mL) at 0 °C under N_2 atmosphere. Then, the reaction mixture was stirred at RT for 1 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, PE/EtOAc 93:07) to afford (*R*)-**7b** as a colorless liquid; yield: 1.0 g (78%); R_f = 0.6 (PE/EtOAc, 80:20); $[\alpha]_D^{26}$ +18.61 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.42 (m, 2 H), 7.40–7.35 (m, 2 H), 7.35–7.28 (m, 6 H), 6.88 (d, *J* = 1.8 Hz, 1 H), 6.82–6.76 (m, 2 H), 6.76–6.70 (m, 2 H), 6.69–6.63 (m, 1 H), 5.97 (tdd, *J* = 6.7, 10.0, 16.9 Hz, 1 H), 5.16–5.09 (m, 3 H), 5.07 (dd, *J* = 1.8, 3.7 Hz, 1 H), 4.61–4.52 (m, 2 H), 4.52–4.45 (m, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.67–3.60 (m, 2 H), 3.34 (d, *J* = 6.4 Hz, 2 H), 3.08–2.98 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 149.3, 146.6, 145.9, 138.2, 137.5, 137.3, 133.9, 131.3, 128.4, 128.3, 127.7, 127.6, 127.5, 127.2, 121.5, 120.5, 117.3, 115.6, 113.9, 113.5, 112.6, 80.4, 73.3, 71.1, 70.7, 55.8, 55.8, 39.8, 37.5

HRMS (ESI-TOF): *m*/*z* calcd for $C_{34}H_{36}O_5Na$ [M + Na]$^+$: 547.2455; found: 547.2455.

(*R*)-3-[4-({1-(Benzyloxy)-3-[4-(benzyloxy)-3-methoxyphenyl]-propan-2-yl}oxy)-3-methoxyphenyl]propan-1-ol [(*R*)-8b]

$BH_3{\cdot}SMe_2$ complex (0.36 mL, 3.81 mmol) was slowly added to a solution of (*R*)-**7b** (1.0 g, 1.90 mmol) in THF (50 mL) at 0 °C under argon. After stirring for 30 min, the reaction mixture was warmed to RT and stirred for a further 2 h. The reaction was quenched with H_2O (100 mL), H_2O_2 (30%, 3.0 mL, 28.59 mmol), and NaOH (0.15 g, 3.81 mmol); then the mixture was stirred for 90 min. The resulting two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL), the combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried (anhyd Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, PE/acetone 70:30) to afford (*R*)-**8b** as a colorless thick liquid; yield: 0.93 g (90%); R_f = 0.3 (PE/EtOAc 70:30); $[\alpha]_D^{25}$ +18.13 (*c* 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.2 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 2 H), 7.32 (m, 4 H), 7.30 (d, *J* = 6.5 Hz, 2 H), 6.87 (s, 1 H), 6.82–6.75 (m, 2 H), 6.75–6.69 (m, 2 H), 6.66 (br s, 1 H), 5.13 (s, 2 H), 4.65–4.52 (m, 2 H), 4.48 (m, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.67 (t, *J* = 5.9 Hz, 2 H), 3.63 (m, 2 H), 3.12–3.01 (m, 2 H), 2.65 (t, *J* = 7.4 Hz, 2 H), 1.88 (t, *J* = 6.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.5, 149.3, 146.6, 145.7, 138.2, 137.3, 135.8, 131.4, 128.4, 128.3, 127.7, 127.6, 127.5, 127.2, 121.5, 120.3, 117.4, 114.0, 113.5, 112.5, 80.4, 73.3, 71.1, 70.7, 62.2, 55.8, 55.8, 37.6, 34.3, 31.7

HRMS (ESI-TOF): *m*/*z* calcd for $C_{34}H_{38}O_6Na$ [M + Na]$^+$: 565.2561; found: 565.2560.

(*R*)-4-{3-Hydroxy-2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]-propyl}-2-methoxyphenol [Ligraminol E, (*R*)-2]

To a solution of (*R*)-**8b** (0.5 g, 0.92 mmol) in EtOH (5 mL) was added $Pd(OH)_2$ on activated charcoal (50 mg, 10–20 wt%), and the reaction mixture was stirred under H_2 (20 psi) for 6 h. After the completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of Celite bed (EtOAc eluent) and the solvent was evaporated under reduced pressure to give (*R*)-**2** as a colorless liquid; yield: 0.32 g (98%); R_f = 0.3 (PE/EtOAc 60:40); $[\alpha]_D^{25}$ +18.84 (*c* 0.1, MeOH) {Lit.[4] $[\alpha]_D^{25}$ +18.3 (*c* 0.1, MeOH)}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, *J* = 8.4 Hz, 1 H), 6.80–6.72 (m, 3 H), 6.67 (s, 2 H), 5.83 (br s, 1 H), 4.20 (tdd, *J* = 3.2, 6.5, 9.2 Hz, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.74–3.56 (m, 4 H), 3.33 (br s, 1 H), 3.04 (dd, *J* = 6.5, 14.1 Hz, 1 H), 2.89 (dd, *J* = 6.9, 13.7 Hz, 1 H), 2.71–2.58 (m, 2 H), 1.96 (br s, 1 H), 1.90–1.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 146.5, 145.4, 144.2, 137.1, 129.6, 122.0, 120.9, 119.5, 114.4, 112.2, 112.1, 84.9, 63.3, 62.0, 55.8, 55.7, 37.1, 34.1, 31.7.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{20}H_{26}O_6Na$ [M + Na]$^+$: 385.1622; found: 385.1618.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611919.

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