First Total Synthesis of (−)-Ligustiphenol

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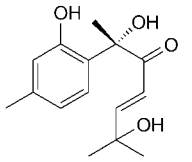
The first asymmetric total synthesis of (−)-ligustiphenol is reported. The key step was conducted by exploiting a steric hindrance effect to control the formation of the adduct in a nucleophilic α-Li-phenolate addition reaction to the intermediate α-oxo (−)-menthyl ester. The synthesis is concise and feasible for the construction of analogous compounds and investigation of their biological activity.

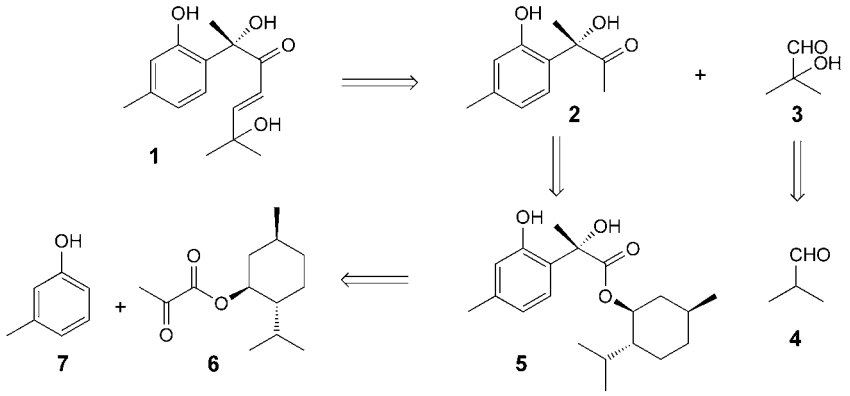
Introduction. – The natural product (−)-ligustiphenol (**1**) was isolated from *Ligusticum sinense* OLIV. [1], and it has been shown to exhibit significant immunosuppressive and anti-inflammatory activities [2]. (−)-Ligustiphenol has a rather uncomplicated structure and displays favorable '*Lipinski*'s rule of five' characteristics to encourage the investigation of its structure–activity relationship. *Huang* and *Yu* [3] reported the total synthesis of racemic ligustiphenol. However, the asymmetric total synthesis of (−)-ligustiphenol has not been reported yet. In this study, we report a concise and scalable asymmetric total synthesis of (−)-ligustiphenol.



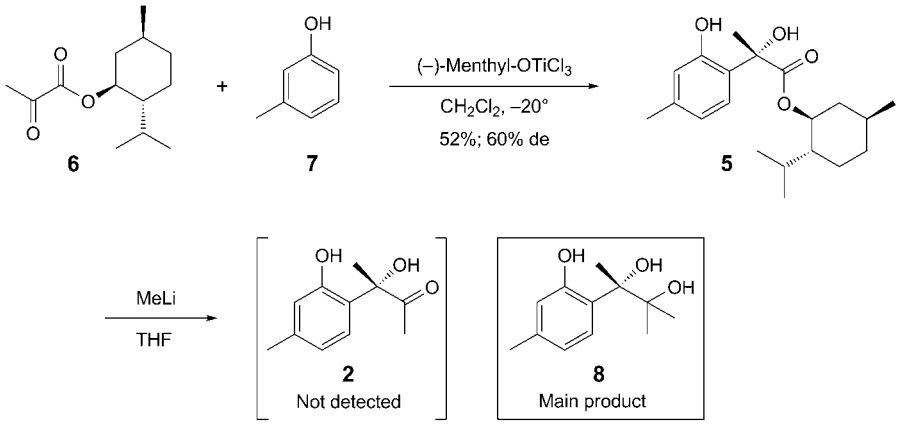
(−)-Ligustiphenol (**1**)

Results and Discussion. – According to the retrosynthetic analysis (*Scheme 1*), compound **3** could be prepared from compound **4**, with the key step being the preparation of α-hydroxymethyl ketone **2**. Although the reaction of α-hydroxy carboxylic acids and α-hydroxy amides with MeLi without protecting groups have been used for the synthesis of α-hydroxymethyl ketones [4–7], α-hydroxy esters in this type of reaction were rarely studied. In the synthetic protocol, we first treated a mixture of **6** [8] and **7** with (−)-menthyl-$OTiCl_3$ as promoter leading to **5** and its epimer (80:20 ratio), which could easily be separated with silica-gel chromatography [9]. Then, we attempted to treat α-hydroxy ester **5** with MeLi, but the main product was compound **8** instead of the desired methyl ketone **2**. The result could not be affected, neither by lowering the reaction temperature nor by reducing the amount of MeLi (*Scheme 2*).

Scheme 1. *Retrosynthetic Analysis of (–)-Ligustiphenol* (**1**)



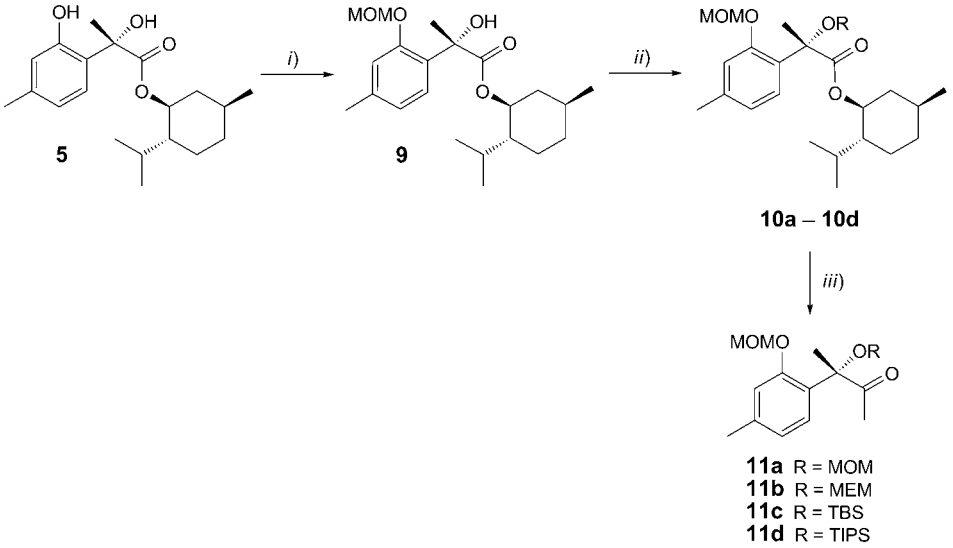
Scheme 2. *Synthesis of the Key Intermediate* **2**



The failure of the attempt was analyzed by comparing with analogous reactions with the cyclohexyl or propenyl group in the α-position of carboxylic acids and amides [4–7]. The Me group in the α-position of the ester **5** presumably exerts only a weak steric hindrance, thus leading to the unexpected product **8**. Our revised synthetic plan aimed at increasing the steric hindrance in the α-position of **5** by protecting the OH group (*Scheme 3*). After protecting the phenolic OH group with the methoxymethyl (MOM) group to give **9**, the alcoholic OH group was also protected with the MOM group. By treatment of **10a** with MeLi in THF, the expected methyl ketone **11a** was obtained in a moderate yield (50%).

Encouraged by the successful application of the MOM protecting group, larger protecting groups were introduced to attain higher yields. The alcoholic OH group was protected with the (2-methoxyethoxy)methyl (MEM), the (*tert*-butyl)(dimethyl)silyl (TBS), and the triisopropylsilyl (TIPS) protecting groups, respectively (*Scheme 3*).

Scheme 3. *Modified Synthetic Plan for Key Intermediate* **11**



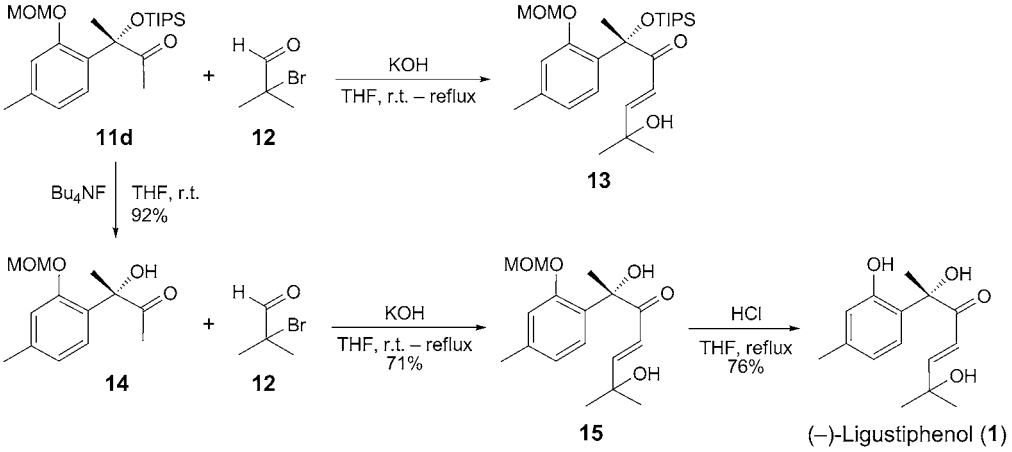
i) Methoxymethyl bromide (MOMBr; 1.2 equiv.), EtN^iPr_2 (3 equiv.), CH_2Cl_2, 0°, 2 h; quant. *ii*) For **10a** with MOMBr (1.2 equiv.), NaH (3 equiv.), THF, 0° to r.t., 2 h; quant.; for **10b** with (2-methoxyethoxy)-methyl chloride (MEMCl; 1.2 equiv.), NaH (3 equiv.), THF, 0° to r.t., 2 h; quant.; for **10c** with (*tert*-butyl)(dimethyl)silyl trifluoromethanesulfonate (TBSOTf; 3.5 equiv.), EtN^iPr_2 (7 equiv.), CH_2Cl_2, 0°, 2 h; quant.; for **10d** with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf; 3.5 equiv.), EtN^iPr_2 (7 equiv.), CH_2Cl_2, 0° to reflux, 2 h; quant. *iii*) MeLi (2 equiv.), THF, 0° to r.t., 1 h; **11a** (50%), **11b** (61%), **11c** (79%), and **11d** (94%).

Based on the above mentioned attempts, we confirmed that the steric hindrance was the key factor for the success of the reaction. With **10b**, **10c**, and **10d**, the reaction, under the same reaction conditions, furnished **11b** (61%), **11c** (79%), and **11d** (94%), respectively.

With the key step established for the preparation of methyl ketone **11d**, the synthesis of (−)-ligustiphenol was performed as outlined in *Scheme 4*. The attempt to react **11d** with **12** [10] *via* aldol condensation was unsuccessful, most likely due to the steric hindrance of the TIPS group. For this reason, the TIPS group was removed with Bu_4NF in THF at room temperature to afford **14**. Condensation of **14** with **12** by treatment with KOH in THF yielded **15**. Finally, (−)-ligustiphenol was obtained after removing the protecting group in **15**. The spectroscopic data (^{1}H- and ^{13}C-NMR, and HR-MS) of the synthetic product were identical with those of the natural product.

Conclusions. – The first asymmetric total synthesis of (−)-ligustiphenol (**1**) was completed in seven steps from commercially available starting materials in good overall yield (24.3%). The effect of steric hindrance was applied to transform the chiral ester **11** to the key intermediate methyl ketone **14** efficiently and successfully. Preparation of structural analogs and evaluation of activity are currently in progress in our laboratory.

Scheme 4. *Synthesis of (−)-Ligustiphenol* (**1**)



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Experimental Part

General. All reagents were obtained commercially and used without further purification. The solvents used were all of anal. grade, and were dried over standard drying agents and freshly distilled where necessary. TLC: Silica gel GF_{254} (*Qingdao Marine Chemical Company*, P. R. China). Column chromatography (CC): commercial silica gel (SiO_2, 200–300 mesh; *Qingdao Haiyang Chemical Group Co.*). Optical rotations: *JASCO P-2000* polarimeter; at 20°. IR Spectra: *Nicolet 5700* spectrometer, by the method of FT-IR microscope transmission; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian Mercury-300* at 300 (^1H) and 75 MHz (^{13}C); in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. HR-ESI-MS: *Agilent 1100* series LC/MSD; in m/z.

(1S,2R,5S)-5-Methyl-2-(1-methylethyl)cyclohexyl (2S)-2-Hydroxy-2-(2-hydroxy-4-methylphenyl)-propanoate (**5**). A soln. of $TiCl_4$ (1.0 g, 10 mmol) in CH_2C1_2 (10 ml) was added a soln. of (−)-menthol (1.56 g, 10 mmol) in CH_2C1_2 (15 ml) at −20°. After stirring the mixture for 20 min, a soln. of *m*-cresol (**7**; 1.08 g, 10 mmol) in 10 ml of CH_2Cl_2 was added. After additional 2 h at −20°, a soln. of *pyruvic acid (−)-menthyl ester* (**6**) [8] (2.26 g, 10 mmol) in CH_2C1_2 (10 ml) was added dropwise, and the deep brown soln. was stirred at −20° overnight. The reaction was quenched with sat. NH_4Cl soln., and the mixture was extracted with CH_2C1_2 (3 × 50 ml). After drying (Na_2SO_4), the solvent was removed under reduced pressure. The resulting crude was purified by CC (AcOEt/PE 1:20) to provide **5** (1.74 g, 52%). White solid. $[\alpha]_D^{20} = -62.2$ ($c = 0.1$, $CHCl_3$). IR: 3500, 3192, 2957, 2926, 2870, 1739, 1619, 1590, 1454, 1420, 1367, 1286, 1124, 1052, 913, 811. ^1H-NMR ($CDCl_3$): 8.51 (*s*, 1 H); 7.10 (*d*, $J = 7.8$, 1 H); 6.67 (*s*, 1 H); 6.65 (*d*, $J = 7.8$, 1 H); 4.79 (*td*, $J = 11.1, 4.2$, 1 H); 4.26 (br. *s*, 1 H); 2.26 (*s*, 3 H); 1.95 (*d*, $J = 12$, 1 H); 1.79 (*s*, 3 H); 0.88 (*s*, 3 H); 0.86 (*s*, 3 H); 0.75 (*d*, $J = 7.2$, 3 H): 0.8–1.80 (*m*, 8 H). ^{13}C-NMR ($CDCl_3$): 174.5; 155.4; 139.8; 126.2; 122.3; 120.5; 118.3; 77.8; 77.4; 46.8; 40.1; 34.0; 21.4; 26.5; 26.1; 23.1; 21.9; 20.9; 20.7; 15.9. HR-ESI-MS: 357.2032 ($[M + Na]^+$, $C_{20}H_{30}NaO_4^+$; calc. 357.2036).

(1S,2R,5S)-5-Methyl-2-(1-methylethyl)cyclohexyl (2S)-2-Hydroxy-2-[2-(methoxymethoxy)-4-methylphenyl]propanoate (**9**). To a soln. of **5** (1.67 g, 5 mmol) in dry CH_2Cl_2 (15 ml) was added EtN^iPr_2 (2.6 ml, 15 mmol) at 0°, followed by MOMBr (1.19 ml, 6 mmol). After 1 h stirring at r.t., the reaction was quenched with H_2O (20 ml), and the mixture was extracted with CH_2Cl_2 (3 × 15 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give **9** (1.89 g, quant.). Colorless oil. $[\alpha]_D^{20} = -27.8$ ($c = 0.176$, $CHCl_3$). IR: 3497, 2957, 2926, 2870, 1731, 1613, 1580, 1455, 1390, 1370, 1254,

1134, 1012, 924, 817. ^{1}H-NMR ($CDCl_3$): 7.31 (*d*, *J* = 8.1, 1 H); 6.94 (*s*, 1 H); 6.83 (*d*, *J* = 8.1, 1 H); 5.15 (*d*, *J* = 6.6, 1 H); 5.08 (*d*, *J* = 6.6, 1 H); 4.68 (*td*, *J* = 10.8, 4.2, 1 H); 3.48 (*s*, 3 H); 2.33 (*s*, 3 H); 1.93 (*d*, *J* = 11.1, 1 H); 1.77 (*s*, 3 H); 0.86 (*s*, 3 H); 0.84 (*s*, 3 H); 0.73 (*d*, *J* = 7.2, 3 H); 0.8–1.80 (*m*, 8 H). ^{13}C-NMR ($CDCl_3$): 176.0; 154.9; 1396.; 128.8; 126.4; 122.5; 115.5; 94.9; 75.7; 74.1; 56.4; 46.7; 40.2; 34.2; 31.4; 26.1; 24.6; 23.2; 22.1; 21.5; 20.9; 16.0. HR-ESI-MS: 401.2295 ($[M + Na]^+$, $C_{22}H_{34}NaO_5^+$; calc. 401.2298).

*(1*S*,2*R*,5*S*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*S*)-2-(Methoxymethoxy)-2-[2-(methoxymethoxy)-4-methylphenyl]propanoate* (**10a**). A soln. of **9** (1.89 g, 5 mmol) in THF (15 ml) was added dropwise to a stirred suspension of NaH (0.6 g, 15 mmol; 60% in mineral oil; prerinsed twice with dry hexanes) at 0°. The mixture was warmed to r.t. and stirred for 1 h, then MOMBr (0.47 ml, 6 mmol) was added, and the mixture was stirred for 1 h. The reaction was quenched with H_2O (20 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to furnish **10a** (2.11 g, quant.). Colorless oil. $[\alpha]_D^{20} = -45.8$ (*c* = 0.1, $CHCl_3$). IR: 2954, 2928, 2870, 1735, 1614, 1580, 1454, 1394, 1370, 1261, 1157, 1121, 1016, 926, 816. ^{1}H-NMR ($CDCl_3$): 7.41 (*d*, *J* = 7.8, 1 H); 6.90 (*s*, 1 H); 6.82 (*d*, *J* = 7.8, 1 H); 5.11 (*d*, *J* = 8.2, 1 H); 5.07 (*d*, *J* = 8.2, 1 H); 4.78 (*d*, *J* = 8.2, 1 H); 4.70 (*d*, *J* = 8.2, 1 H); 4.60 (*td*, *J* = 11.1, 4.2, 1 H); 3.43 (*s*, 3 H); 3.35 (*s*, 3 H); 2.31 (*s*, 3 H); 2.08 (*d*, *J* = 8, 1 H); 1.77 (*s*, 3 H); 0.86 (*d*, *J* = 4.8, 3 H); 0.79 (*d*, *J* = 5.4, 3 H); 0.71 (*d*, *J* = 5.1, 3 H); 0.76–1.80 (*m*, 8 H). ^{13}C-NMR ($CDCl_3$): 172.4; 154.3; 139.5; 127.5; 126.9; 122.3; 115.1; 94.5; 92.4; 79.5; 75.3; 56.4; 55.9; 46.8; 40.5; 34.4; 31.4; 25.8; 23.7; 23.2; 22.3; 21.6; 21.0; 16.2. HR-ESI-MS: 445.2545 ($[M + Na]^+$, $C_{24}H_{38}NaO_6^+$; calc. 445.2561).

*(1*S*,2*R*,5*S*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*S*)-2-[(2-Methoxyethoxy)methoxy]-2-[2-(methoxymethoxy)-4-methylphenyl]propanoate* (**10b**). A soln. of **9** (1.89 g, 5 mmol) in THF (15 ml) was added dropwise to a stirred suspension of NaH (0.6 g, 15 mmol; 60% in mineral oil; prerinsed twice with dry hexane) at 0°. The mixture was warmed to r.t. and stirred for 1 h, then MEMCl (0.68 ml, 6 mmol) was added, and the reaction was stirred for 1 h. The reaction was quenched with H_2O (20 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to afford **10b** (2.33 g, quant.). Colorless oil. $[\alpha]_D^{20} = -16.1$ (*c* = 0.1, $CHCl_3$). IR: 2954, 2926, 2870, 1734, 1614, 1580, 1455, 1393, 1370, 1261, 1157, 1122, 1015, 928, 816. ^{1}H-NMR ($CDCl_3$): 7.42 (*d*, *J* = 7.8, 1 H); 6.91 (*s*, 1 H); 6.82 (*d*, *J* = 7.8, 1 H); 5.09 (*d*, *J* = 6.6, 1 H); 5.05 (*d*, *J* = 6.6, 1 H); 4.87 (*d*, *J* = 8.2, 1 H); 4.76 (*d*, *J* = 8.2, 1 H); 4.63 (*td*, *J* = 10.5, 3.9, 1 H); 3.74 (*m*, 2 H); 3.49 (*t*, *J* = 4.8, 2 H); 3.45 (*s*, 3 H); 3.35 (*s*, 3 H); 2.32 (*s*, 3 H); 2.07 (*d*, *J* = 11.7, 1 H); 1.81 (*s*, 3 H); 0.87 (*d*, *J* = 6.3, 3 H); 0.77 (*d*, *J* = 6.9, 3 H); 0.70 (*d*, *J* = 6.9, 3 H); 0.8–1.80 (*m*, 8 H). ^{13}C-NMR ($CDCl_3$): 172.5; 154.3; 139.5; 127.4; 127.1; 122.3; 110.0; 94.5; 91.3; 79.6; 75.3; 71.9; 67.4; 59.1; 56.4; 46.8; 40.5; 34.3; 31.4; 29.9; 25.8; 23.6; 23.2; 22.3; 21.6; 21.0; 16.1. HR-ESI-MS: 489.2842 ($[M + Na]^+$, $C_{26}H_{42}NaO_7^+$; calc. 489.2823).

*(1*S*,2*R*,5*S*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*S*)-2-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-2-[2-(methoxymethoxy)-4-methylphenyl]propanoate* (**10c**). To a soln. of **9** (1.89 g, 5 mmol) in CH_2Cl_2 (20 ml), EtN^iPr_2 (1.22 ml, 35 mmol) and TBSOTf (4 ml, 17.5 mmol) were added at 0°. The mixture was stirred for 2 h at 0°. The reaction was quenched with H_2O (20 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give **10c** (2.46 g, quant.). Colorless oil. $[\alpha]_D^{20} = -60.0$ (*c* = 0.07, $CHCl_3$). IR: 2955, 2931, 2859, 1736, 1613, 1580, 1503, 1460, 1391, 1367, 1254, 1126, 1011, 928, 838, 816, 777. ^{1}H-NMR ($CDCl_3$): 7.46 (*d*, *J* = 7.8, 1 H); 6.88 (*s*, 1 H); 6.82 (*d*, *J* = 7.8, 1 H); 5.12 (*d*, *J* = 6.6, 1 H); 5.00 (*d*, *J* = 6.6 H); 4.59 (*td*, *J* = 10.5, 3.9, 1 H); 3.46 (*s*, 3 H); 2.32 (*s*, 3 H); 2.07 (*d*, *J* = 12, 1 H); 1.78 (*s*, 3 H); 0.92 (*s*, 9 H); 0.87 (*d*, *J* = 6.3, 3 H); 0.77 (*d*, *J* = 6.9, 3 H); 0.70 (*d*, *J* = 6.9, 3 H); 0.8–1.80 (*m*, 8 H); 0.13 (*s*, 3 H); 0.03 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 173.6; 154.1; 138.8; 130.6; 126.2; 122.1; 114.8; 94.5; 77.1; 74.9; 56.4; 46.9; 40.7; 34.4; 31.5; 26.2; 26.1; 25.5; 23.2; 22.3; 21.5; 21.1; 18.7; 16.2; −2.3; −2.6. HR-ESI-MS: 515.3181 ($[M + Na]^+$, $C_{28}H_{48}NaO_5Si^+$; calc. 515.3163).

*(1*S*,2*R*,5*S*)-5-Methyl-2-(1-methylethyl)cyclohexyl (2*S*)-2-[2-(Methoxymethoxy)-4-methylphenyl]-2-{[tris(1-methylethyl)silyl]oxy}propanoate* (**10d**). To a soln. of **9** (1.89 g, 5 mmol) in CH_2Cl_2 (20 ml), EtN^iPr_2 (1.22 ml, 35 mmol) and TIPSOTf (4.7 ml, 17.5 mmol) were added at 0°. The mixture was warmed to r.t. and refluxed for 6 h. The reaction was quenched with H_2O (20 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give **10d** (2.67 g, quant.). Colorless oil. $[\alpha]_D^{20} = -33.6$ (*c* = 0.137, $CHCl_3$). IR: 2950, 2923, 2868, 1734, 1614, 1580, 1503, 1464, 1390, 1368, 1252, 1157, 1128, 1013, 926, 883, 818. ^{1}H-NMR ($CDCl_3$): 7.46 (*d*,

$J = 7.8$, 1 H); 6.88 (*s*, 1 H); 6.82 (*d*, $J = 7.8$, 1 H); 5.13 (*d*, $J = 8.4$, 1 H); 4.98 (*d*, $J = 8.4$, 1 H); 4.54 (*td*, $J = 11.1, 4.5$, 1 H); 3.45 (*s*, 3 H); 2.32 (*s*, 3 H); 2.08 (*d*, $J = 14.1$, 1 H); 1.85 (*s*, 3 H); 1.07 (*m*, 3 H); 1.05 (*s*, 18 H); 0.86 (*d*, $J = 6.3$, 3 H); 0.71 (*d*, $J = 6.9$, 3 H); 0.63 (*d*, $J = 6.9$, 3 H); 0.7–1.80 (*m*, 8 H); 0.13 (*s*, 3 H); 0.03 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 173.5; 154.2; 138.8; 130.7; 126.4; 122.0; 114.8; 94.5; 77.2; 74.9; 56.4; 47.0; 40.7; 34.4; 31.5; 26.0; 25.4; 23.1; 22.3; 21.5; 21.1; 18.6; 16.2; 13.8. HR-ESI-MS: 557.3644 ($[M + Na]^+$, $C_{31}H_{54}NaO_5Si^+$; calc. 557.3633).

*(3*S*)-3-(Methoxymethoxy)-3-[2-(methoxymethoxy)-4-methylphenyl]butan-2-one* (**11a**). To a soln. of **10a** (2.11 g, 5 mmol) in THF (50 ml) was added MeLi (10 ml, 1M in Et_2O) dropwise at 0°. The mixture was warmed to r.t. and stirred for 1 h. The reaction was quenched with sat. NH_4Cl soln., and the mixture was extracted with AcOEt (3×15 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting crude was purified by CC (AcOEt/PE 1:20) to provide **11a** (0.71 g, 50%). Colorless oil. $[\alpha]_D^{20} = +28.3$ ($c = 0.12$, $CHCl_3$). IR: 2989, 2941, 2825, 1721, 1613, 1580, 1503, 1155, 1015, 924, 816. ^{1}H-NMR ($CDCl_3$): 7.46 (*d*, $J = 7.8$, 1 H); 6.89 (*s*, 1 H); 6.84 (*d*, $J = 8$, 1 H); 5.09 (*d*, $J = 6.6$, 1 H); 5.06 (*d*, $J = 6.6$, 1 H); 4.63 (*d*, $J = 7.2$, 1 H); 4.59 (*d*, $J = 7.2$, 1 H); 3.40 (*s*, 3 H); 3.35 (*s*, 3 H); 2.31 (*s*, 3 H); 2.16 (*s*, 3 H); 1.62 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 208.8; 153.9; 140.0; 127.6; 127.5; 122.5; 114.9; 94.3; 92.0; 83.2; 56.4; 55.9; 25.0; 21.6; 21.5. HR-ESI-MS: 305.1359 ($[M + Na]^+$, $C_{15}H_{22}NaO_5^+$; calc. 305.1359).

*(3*S*)-3-[(2-Methoxyethoxy)methoxy]-3-[2-(methoxymethoxy)-4-methylphenyl]butan-2-one* (**11b**). To a soln. of **10b** (2.33 g, 5 mmol) in THF (50 ml) was added MeLi (10 ml, 1M in Et_2O) dropwise at 0°. The mixture was warmed to r.t. and stirred for 1 h. The reaction was quenched with sat. NH_4Cl soln., and the mixture was extracted with AcOEt (3×15 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting crude was purified by CC (AcOEt/PE 1:10) to give **11b** (0.99 g, 61%). Colorless oil. $[\alpha]_D^{20} = +21.5$ ($c = 0.1$, $CHCl_3$). IR: 2955, 2926, 2825, 1721, 1613, 1579, 1503, 1157, 1014, 926, 816. ^{1}H-NMR ($CDCl_3$): 7.46 (*d*, $J = 8.1$, 1 H); 6.90 (*s*, 1 H); 6.84 (*d*, $J = 8.1$, 1 H); 5.09 (*d*, $J = 6.6$, 1 H); 5.06 (*d*, $J = 6.6$, 1 H); 4.71 (br. *s*, 2 H); 3.77 (*m*, 1 H); 3.64 (*m*, 1 H); 3.42 (*s*, 3 H); 3.36 (*s*, 3 H); 2.33 (*s*, 3 H); 2.18 (*s*, 3 H); 1.66 (*s*, 3 H); ^{13}C-NMR ($CDCl_3$): 208.8; 153.8; 140.0; 127.8; 127.5; 122.5; 115.0; 94.3; 91.0; 83.4; 71.9; 67.5; 59.2; 56.5; 25.1; 21.6; 21.5. HR-ESI-MS: 349.1619 ($[M + Na]^+$, $C_{17}H_{26}NaO_6^+$; calc. 349.1622).

*(3*S*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-3-[2-(methoxymethoxy)-4-methylphenyl]butan-2-one* (**11c**). To a soln. of **10c** (2.46 g, 5 mmol) in THF (50 ml) was added MeLi (10 ml, 1M in Et_2O) dropwise at 0°. The mixture was warmed to r.t. and stirred for 1 h. The reaction was quenched with sat. NH_4Cl soln., and the mixture was extracted with AcOEt (3×15 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting crude was purified by CC (AcOEt/PE 1:20) to provide **11c** (1.39 g, 79%). Colorless oil. $[\alpha]_D^{20} = -28.3$ ($c = 0.119$, $CHCl_3$). IR: 2955, 2932, 2857, 1725, 1613, 1579, 1503, 1254, 1157, 1124, 1014, 926, 837, 815, 776. ^{1}H-NMR ($CDCl_3$): 7.47 (*d*, $J = 7.8$, 1 H); 6.89 (*s*, 1 H); 6.84 (*d*, $J = 7.8$, 1 H); 5.11 (*d*, $J = 6.6$, 1 H); 5.02 (*d*, $J = 6.6$, 1 H); 3.42 (*s*, 3 H); 2.33 (*s*, 3 H); 2.16 (*s*, 3 H); 1.61 (*s*, 3 H); 0.93 (*s*, 3 H); 0.03 (*s*, 3 H); −0.10 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 209.9; 153.9; 139.5; 131.4; 126.7; 122.4; 114.7; 94.3; 80.6; 56.5; 26.2; 26.1; 24.9; 24.6; 21.6; −2.7; −2.9. HR-ESI-MS: 375.1977 ($[M + Na]^+$, $C_{19}H_{32}NaO_4Si^+$; calc. 375.1962).

*(3*S*)-3-[2-(Methoxymethoxy)-4-methylphenyl]-3-{[tris(1-methylethyl)silyl]oxy}butan-2-one* (**11d**). To a soln. of **10d** (2.67 g, 5 mmol) in THF (50 ml) was added MeLi (10 ml, 1M in Et_2O) dropwise at 0°. The mixture was warmed to r.t. and stirred for 1 h. The reaction was quenched with sat. NH_4Cl soln., and the mixture was extracted with AcOEt (3×15 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting crude was purified by CC (AcOEt/PE 1:25) to afford **11d** (1.85 g, 94%). White solid. $[\alpha]_D^{20} = -50.3$ ($c = 0.142$, $CHCl_3$). IR: 2943, 2921, 2868, 1726, 1612, 1578, 1503, 1468, 1155, 1134, 1000, 923, 886, 835, 773. ^{1}H-NMR ($CDCl_3$): 7.58 (*d*, $J = 7.8$, 1 H); 6.89 (*s*, 1 H); 6.86 (*d*, $J = 7.8$, 1 H); 5.10 (*d*, $J = 6.9$, 1 H); 5.04 (*d*, $J = 6.9$, 1 H); 3.42 (*s*, 3 H); 2.33 (*s*, 3 H); 2.07 (*s*, 3 H); 1.66 (*s*, 3 H); 1.07 (*s*, 18 H); 1.06 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 207.6; 153.5; 139.2; 131.0; 126.5; 122.5; 114.5; 94.2; 80.7; 56.5; 24.6; 24.0; 21.6; 18.5; 13.6. HR-ESI-MS: 417.2446 ($[M + Na]^+$, $C_{22}H_{38}NaO_4Si^+$; calc. 417.2432).

*(3*S*)-3-Hydroxy-3-[2-(methoxymethoxy)-4-methylphenyl]butan-2-one* (**14**). To a soln. of **11d** (0.78 g, 2 mmol) in THF (10 ml) was added Bu_4NF (1.04 g, 4 mmol) at r.t. The mixture was stirred at r.t. for 6 h. The reaction was quenched with sat. $NaHCO_3$ soln., and the mixture was extracted with AcOEt (3×15 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The

resulting crude was purified by CC (AcOEt/PE 1:10) to provide **11** (0.68 g, 79%). Colorless oil. $[\alpha]_D^{20} = -70.2$ ($c = 0.11$, $CHCl_3$). IR: 3449, 2955, 2924, 2852, 1713, 1613, 1579, 1503, 1354, 1252, 1158, 1009, 928, 812. ^{1}H-NMR ($CDCl_3$): 7.33 (*d*, *J* = 7.8, 1 H); 6.89 (*s*, 1 H); 6.83 (*d*, *J* = 8, 1 H); 5.11 (*d*, *J* = 6.9, 1 H), 5.07 (d, *J* = 6.9, 1 H); 3.40 (*s*, 3 H); 2.30 (*s*, 3 H); 2.06 (*s*, 3 H); 1.64 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 210.6; 154.6; 140.2; 128.1; 127.0; 122.8; 115.4; 94.5; 78.5; 56.5; 24.0; 23.8; 21.5; HR-ESI-MS: 261.1092 ($[M + Na]^+$, $C_{13}H_{18}NaO_4^+$; calc. 261.1097).

*(2*S*,4*E*)-2,6-Dihydroxy-2-[2-(methoxymethoxy)-4-methylphenyl]-6-methylhept-4-en-3-one* (**15**). To a soln. of **14** (0.46 g, 2 mmol) in THF (10 ml) was added α-bromoisobutyraldehyde (**12**; 0.22 g, 2 mmol) and KOH (0.11 g, 2 mmol) successively at r.t. The resulting mixture was heated to reflux for 2 h, cooled afterwards to r.t., and filtered, and the KOH cake was washed with excess CH_2Cl_2. The combined org. layer evaporated under reduced pressure. The resulting crude was purified by CC (AcOEt/PE 1:5) to give **15** (0.43 g, 71%). Colorless oil. $[\alpha]_D^{20} = -30.5$ ($c = 0.12$, $CHCl_3$). IR: 3450, 2974, 2925, 2859, 1698, 1632, 1613, 1579, 1503, 1460, 1156, 1010, 926, 821, 744. ^{1}H-NMR ($CDCl_3$): 7.35 (*d*, *J* = 7.8, 1 H); 7.03 (*d*, *J* = 15.6, 1 H); 6.86 (*s*, 1 H); 6.83 (*d*, *J* = 7.8, 1 H); 6.31 (*d*, *J* = 15.6, 1 H); 5.05 (*d*, *J* = 6.9, 1 H), 4.96 (*d*, *J* = 6.9, 1 H); 3.35 (*s*, 3 H); 2.30 (*s*, 3 H); 1.65 (*s*, 3 H); 1.27 (*s*, 3 H); 1.24 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 201.2; 155.0; 154.3; 140.3; 127.6; 127.2; 122.9; 119.5; 115.4; 94.4; 18.0; 71.3; 56.4; 29.5; 24.0; 21.6. HR-ESI-MS: 331.1506 ($[M + Na]^+$, $C_{17}H_{24}NaO_5^+$; calc. 331.1516).

(−)-Ligustiphenol (=*(2*S*,4*E*)-2,6-Dihydroxy-2-(2-hydroxy-4-methylphenyl)-6-methylhept-4-en-3-one*; **1**). To a soln. of **15** (0.31 g, 1 mmol) in THF (5 ml) was added HCl (5 ml, 1M) at r.t. The mixture was heated to reflux for 4 h. The reaction was quenched with sat. $NaHCO_3$ soln., and the mixture was extracted with AcOEt (3×5 ml). The org. layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting crude was purified by CC (AcOEt/PE 1:2) to afford **1** (0.2 g, 76%). Colorless oil. $[\alpha]_D^{20} = -73.5$ ($c = 0.26$, $CHCl_3$). IR: 3450, 3199, 2958, 2925, 2859, 1688, 1632, 1613, 1579, 1503, 1460, 1153, 1014, 925, 819, 734. ^{1}H-NMR ($CDCl_3$): 7.17 (*d*, *J* = 7.8, 1 H); 7.08 (*d*, *J* = 15.3, 1 H); 6.72 (*d*, *J* = 7.8, 1 H); 6.65 (*s*, 1 H); 6.36 (*d*, *J* = 15.3, 1 H); 2.26 (*s*, 3 H); 1.71 (*s*, 3 H); 1.27 (*s*, 3 H); 1.24 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 199.3; 156.0; 155.8; 128.3; 126.7; 124.4; 120.8; 117.9; 117.5; 80.2; 70.7; 29.2; 28.7; 24.8, 20.6. HR-ESI-MS: 287.1256 ($[M + Na]^+$, $C_{15}H_{20}NaO_4^+$; calc. 287.1254).

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