DOI: 10.1002/cjoc.201500315

Synthesis and Absolute Configuration of Two Natural Phenolic Homobenzyl Esters

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Two recently identified natural phenolic homobenzyl esters, isolated from *Phragmipedium calurum* (an orchid) and *Eupatorium fortunei* TURCZ (a perennial herb in the *Asteraceae* family), respectively, were synthesized in enantiopure forms. By comparison of the optical rotations for the synthetic and the natural samples, the absolute configurations for the natural products were reliably assigned. The synthesis also enables establishment of the absolute configuration of a closely related natural homobenzyl alcohol and provided for the first time complete physical and spectroscopic data for two other natural homobenzyl esters.

Keywords esters, alkylation, natural products, stereochemistry, phenols

Introduction

The subjects of this synthetic study, compounds **1** and **2** (Figure 1), were identified and characterized very recently by Guo *et al*.[1] and Starks *et al*.,[2] respectively. Compound **1** was isolated[1] from *Eupatorium fortunei* TURCZ, a perennial herb in the family *Asteraceae* widely distributed in China and has been used as a Chinese folk medicine for the treatment of dissipating dampness, diaphoresis relieving superficies, and relieving summer-heat. Compound **2** was isolated[2] from the orchid *Phragmipedium calurum,* which showed antitumor activity (non-small lung adenocarcinoma A549) in the preliminary screening.

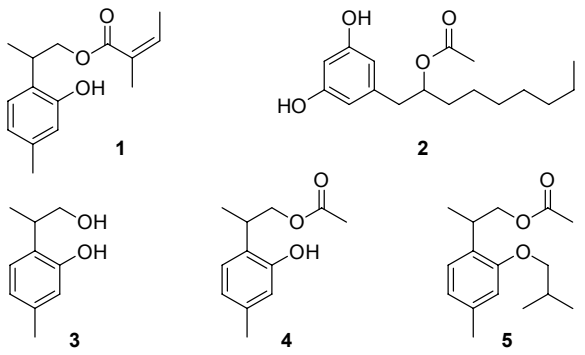

Figure 1 The planar structures for **1**, **2**, and three other natural products studied in this work (cf. text).

While the planar structures for **1** and **2** were assigned on the basis of spectroscopic analyses, their absolute configurations remain unknown. To confirm the assigned structures and to acquire the still missing information about the stereochemistry of these natural products, we performed the enantioselective syntheses described below.

Results and Discussion

The synthesis of **1** is shown in Scheme 1. Taking into consideration several factors including the commercial availability, experimental feasibility and overall cost, we chose the strategy developed by Snieckus[3] to gain the carbogenic framework of the target **1**. Thus, using the inexpensive 2,5-dimethylphenol (**6**) as the starting material, acylation[4] with diethylcarbamyl chloride (**7**) gave **8**. Selective deprotonation of the methyl group in vicinity of the amido group with lithium diisopropylamide (LDA) induced an intramolecular migration of the carbonyl group as reported by Snieckus, with addition of *t*-butyl-dimethylsilyl chloride (TBSCl) to prevent the reverse reaction caused by the resulting phenoxide. It was noticed in this work that use of a 5-fold excess of LDA could effectively raise the overall yield of **10**, probably due to effective suppression of the quenching of the intermediate carbanion by the moisture introduced with the addition of hygroscopic TBSCl.

The undesired amido functionality in **9** was then converted into lactone **10**[5] by treatment with trifluroacetic acid (TFA) as reported[3] in the literature. The lactone ring was subsequently cleaved via hydrolysis, with the newly freed phenol OH protected with methoxy-

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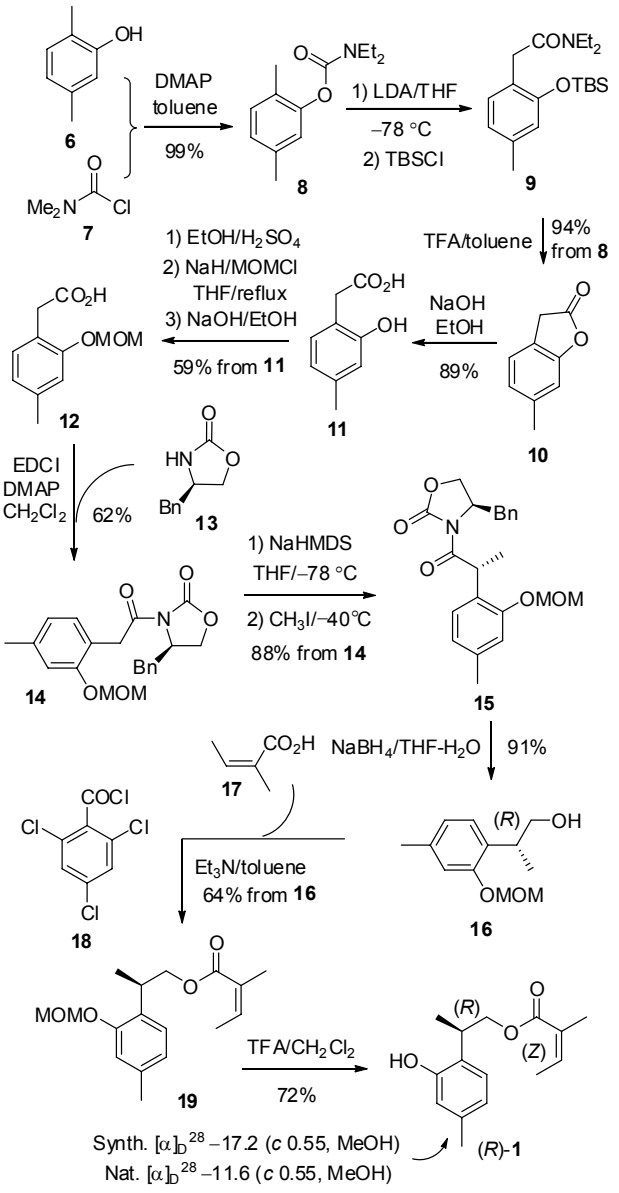
Received March 24, 2015; accepted April 17, 2015; published online June 2, 2015.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201500315 or from the author.

methyl chloride (MOMCl). The resulting mixture of **12** and its MOM ester was then exposed to refluxing NaOH/EtOH to afford pure **12** after careful neutralization. The free carboxylic acid group was connected to the known[6] chiral auxiliary oxazolidinone **13** under the EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)/DMAP (4-dimethylaminopyridine) conditions. An Evans[7] asymmetric methylation was then performed using $NaN(SiMe_3)_2$ (NaHMDS) as the base and MeI as the methylating agent, which delivered the desired enantiomer **15** in 88% isolated yield. It is noteworthy that use of LiHMDS under the otherwise the same conditions led to **15** in only 20%—30%.

Scheme 1 Synthesis of (*R*)-**1**

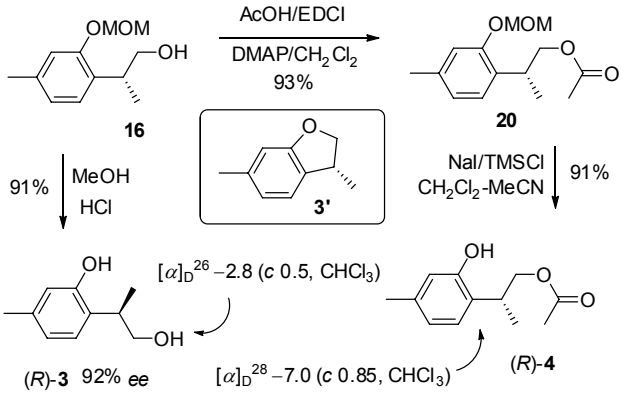


The chiral auxiliary was cleaved under the $NaBH_4$/THF-H_2O[8] conditions. The alcohol **16**, determined to be of 99% *ee* by chiral HPLC analysis, was acylated with angelic acid (**17**) to afford the desired ester **19**. The transformation first attempted under the EDCI/DMAP conditions. However, the desired **19** was obtained in only 20% yield; the undesired (*E*) isomer turned out to be the main product (80%). Addition of HOBt (1-hydroxybenzotriazole) or using DCC (dicyclohexylcarbodiimide)/DMAP conditions with different addition sequences and different amounts of DMAP at different temperatures led to essentially the same results. The inversion of the C—C double bond appeared uncontrollable. Fortunately, finally the Yamaguchi conditions worked reasonably well, giving ester **19** in 64% isolated yield.

It should be noted that the double bond inversion problem not only occurred in the acylation but also at the removal of the MOM group. For instance, under the NaI/TMSCl[9] conditions, the resulting **1** was heavily contaminated by the inseparable (*E*) isomer. However, if the cleavage of the MOM protecting group was carried out under the TFA/THF conditions, the isomerization of the double bond could be efficiently suppressed and pure (*R*)-(*Z*)-**1** could be acquired in 72% isolated yield.

The synthetic (*R*)-(*Z*)-**1** showed the ^{1}H NMR and ^{13}C NMR in full consistency with those reported for the natural **1**. The optical rotations were also consistent with each other. Therefore, the absolute configuration for the natural **1** must be (*R*).

Scheme 2 Conversion of **16** into (*R*)-**3** and (*R*)-**4**



Because of their closely related structures, three other natural products, *i.e.*, **3**, **4** and **5**, were also synthesized. To this end, acylation of **16** with acetic acid instead of angelic acid (Scheme 2) gave acetate **20** in 93% yield, which on removal of the MOM protecting group in **20** under the NaI/TMSCl[9] conditions afforded the end product (*R*)-**4**.

Alternatively, in an effort to gain access to (*R*)-**3**,[10] alcohol **16** was subjected to the often employed TFA/CH_2Cl_2[11] conditions. However, instead of the well-expected (*R*)-**3**, the totally unexpected **3'** was formed. Fortunately, the desired transformation eventually could be achieved smoothly under the aq. HCl/MeOH[12] conditions, providing diol (*R*)-**3** in 91% yield.

It should be noted that neither of the originally reported **3**[13a,13b] and **4**[13b] was fully characterized because of the small quantities of the samples. It is therefore

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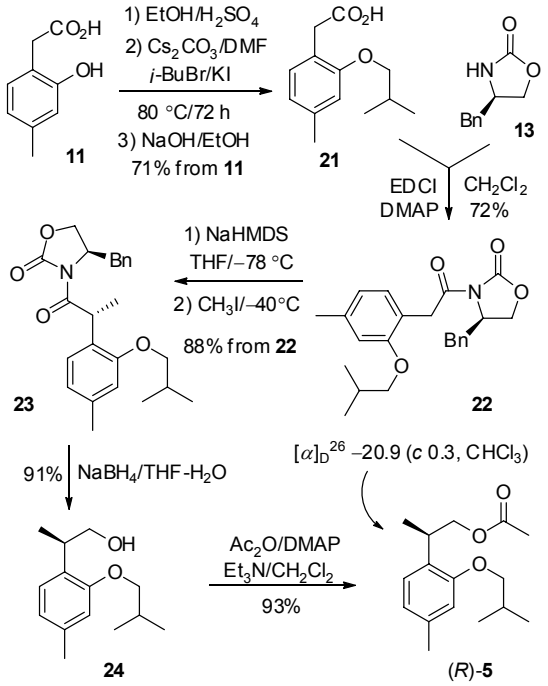
impossible to establish the absolute configurations for those compounds. However, the complete sets of physical and spectroscopic data acquired in this work may provide reliable references of comparison for future studies.

Apart from the first report, there have been several other ones on the isolation of **3** (or its antipode) from other natural sources. One[13c] of them came with complete ^{1}H and ^{13}C NMR (fully consistent with those for the synthetic **3**, cf. the Supporting Information) and optical rotation data. By comparison of the signs for the natural and synthetic **3**, the absolute configuration of the natural **3** can be assigned as (*S*).

Like compound **4**, acetate **5** was also isolated[13b] in very small quantity. Only the GC-MS data were collected. Therefore, a synthesis of **5**, which would provide the so far missing ^{1}H NMR and ^{13}C NMR data, appeared to be warranted.

Scheme 3 Elaboration of **11** into (*R*)-**5**

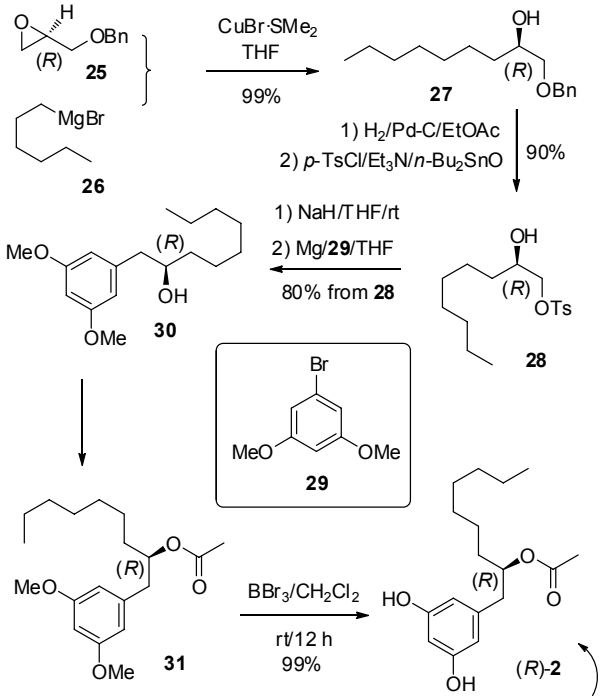


The synthesis of compound **5** is outlined in Scheme 3. Starting with the acid **11** via esterification, alkylation and hydrolysis afforded acid **21**. Connection of this acid with the chiral auxiliary **13** under the same conditions for conversion of **12** into **14** delivered **22** in 72% yield. The stereogenic center was then installed by the Evans asymmetric methylation. The resulting **23** was exposed to the $NaBH_4/THF/H_2O$ conditions to remove the chiral auxiliary, affording alcohol **24** in 91% yield. Finally, an acetylation of the homobenzyl alcohol furnished (*R*)-**5**.

The synthesis of target **2** was first attempted as shown in Scheme 4. The commercially available (*R*)-**25** was treated with *n*-hexyl Grignard reagent in the presence of $CuBr•SMe_2$ leading to **27** in 99% yield.[14] Removal of the benzyl protecting group by catalytic hydrogenolysis over Pd—C afforded the intermediate diol, which on treatment with *p*-TsCl in the presence of *n*-Bu_2SnO furnished tosylate **28**.

The aromatic moiety of the target was then installed via the intermediate epoxide derived from **28** with the Grignard reagent derived *in situ* from the commercially available bromide **29**. The resulting alcohol **30** was acetylated with Ac_2O to furnish acetate **31**, which on treatment[15] with BBr_3 delivered the end product (*R*)-**2**.

Scheme 4 Synthesis of (*R*)-**2**



nat. $[\alpha]_D^{25}$ −223 (*c* 0.10, $CHCl_3$); synth. $[\alpha]_D^{26}$ −4.14 (*c* 0.80, $CHCl_3$)

The spectroscopic data for the synthetic (*R*)-**2** were in full consistence with those reported for the natural **2**, while the optical rotation[16] had the same sign as that for the natural **2**. Therefore, the natural **2** must be an (*R*) isomer.

Conclusions

In summary, the absolute configurations of two recently identified natural homobenzyl esters (**1** and **2**) along with a natural homobenzyl alcohol (**3**) were established through enantioselective synthesis. The adequate amount of synthetic (*R*)-**2** allowed for acquisition of a more reliable optical rotation data. En route to the target molecules, complete physical and spectroscopic data for another two closely related natural products (**4** and **5**), long-known yet still under-characterized, were also made available for the first time.

Experimental

The NMR spectra were recorded on either an Agilent 500/54 NMR spectrometer (operating at 500 MHz for ^{1}H) or a Bruker Avance 400 (operating at 400

MHz for ^{1}H) NMR spectrometer. IR spectra were measured on a Nicolet 380 Infrared spectrophotometer. ESI-MS data were acquired on a Shimadzu LCMS-2010EV mass spectrometer. HRMS data were obtained with a Bruker APEXIII 7.0 Tesla FT-MS spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. Melting points were uncorrected (measured on a hot stage melting point apparatus equipped with a microscope). CH_2Cl_2 was dried with activated 4 Å MS (molecular sieves). Dry THF was obtained by distillation over Ph_2CO/Na under argon prior to use. All chemicals were reagent grade and used as purchased. Column chromatography was performed on silica gel (300−400 mesh) under slightly positive pressure. PE= petroleum ether (b.p. 60−90 ℃).

Acylation of 6 with 7 to afford 8

A solution of phenol **6** (4.00 g, 32.74 mmol), DMAP (8.00 g, 65.48 mmol) and diethylcarbamoyl chloride **7** (8.3 mL, 65.48 mmol) in dry toluene (164 mL) was stirred at refluxing temperature for 7 h (TLC showed completion of the reaction). The heating bath was removed. The mixture was partitioned between water and EtOAc. The organic layer was washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (5∶1, PE∶EtOAc) on silica gel gave **8** as a colorless oil (7.20 g, 32.56 mmol, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.07 (d, J=7.6 Hz, 1H), 6.90 (d, J=7.7 Hz, 1H), 6.88 (s, 1H), 3.46−3.38 (m, 4H), 2.30 (s, 3H), 2.17 (s, 3H), 1.26 (t, J=6.3 Hz, 3H), 1.20 (t, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.2, 149.9, 136.7, 130.7, 127.3, 126.2, 122.9, 42.3, 42.0, 21.0, 16.0, 14.4, 13.6; FT-IR (film) v: 2974, 2931, 1717, 1509, 1473, 1457, 1421, 1405, 1379, 1274, 1246, 1223, 1158, 1117, 1097, 996, 962, 806, 757 cm^{-1}. ESI-MS m/z: 222.5 ([M+H]$^+$). ESI-HRMS calcd for $C_{13}H_{20}NO_2$ ([M+H]$^+$): 222.1483, found 222.1489.

Conversion of 8 into 10[3]

n-BuLi (2.5 mol/L, in hexanes, 18.1 mL, 45.2 mmol) was added to a solution of *i*-Pr_2NH (8.0 mL, 45.2 mmol) in dry THF (30 mL) stirred at –20 ℃ under N_2 (balloon). After completion of the addition, the mixture was stirred for 30 min before the bath temperature was lowered to –78 ℃. At that temperature stirring was continued for another 30 min. A solution of **8** (2.00 g, 9.04 mmol) in dry THF (37 mL) was introduced very slowly so that the inner temperature did not exceed –72 ℃. After completion of the addition, the mixture was stirred at –78 ℃ for 1 h. TBSCl (1.63 g, 10.8 mmol) was then added. The mixture was stirred at –20 ℃ for 30 min and at 0 ℃ for 1 h. Aq. saturated NH_4Cl was added to quench the reaction. The mixture was extracted with EtOAc. The organic layer was washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation left an oily residue, which was dissolved in toluene (23 mL) and CF_3CO_2H (2.1 mL). The mixture was refluxed for 1.5 h. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (6∶1, PE/EtOAc) on silica gel to give the known[5] lactone **10** as a red-brown solid (maybe recrystalized to remove the color but not really necessary here, 1.255 g, 8.47 mmol, 94%): m.p. 78−80 ℃ (lit.[3] m.p. 73−74.5 ℃; lit.[5a] m.p. 68−70 ℃; lit.[5b] m.p. 73 ℃); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.14 (d, J=7.6 Hz, 1H), 6.93 (d, J=7.7 Hz, 1H), 6.90 (s, 1H), 3.67 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.7, 154.9, 139.4, 124.8, 124.3, 120.0, 111.4, 32.9, 21.7; FT-IR (film) v: 2924, 1804, 1630, 1595, 1501, 1427, 1391, 1326, 1280, 1259, 1223, 1200, 1151, 1128, 1056, 946, 860, 835, 807, 760, 683, 668, 590, 567, 547, 427 cm^{-1}. EI-MS m/z (%): 148 (90), 51 (11), 65 (14), 91 (100), 92 (67), 120 (57), 121 (18), 149 (11).

Hydrolysis of lactone 10 to afford acid 11

A solution of **10** (200 mg, 1.35 mmol) in EtOH (6.8 mL) and aq. NaOH (1 N, 1.4 mL) was stirred at ambient temperature for 3 h. Water was added, followed by EtOAc. The phases were separated. The aqueous layer was acidified to pH 1 with HCl (1 N) and extracted with EtOAc. The organic layer was concentrated on a rotary evaporator to dryness to give a yellowish solid (200 mg, 1.2 mmol, 89%): m.p. 121−123 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.00 (d, J=7.5 Hz, 1H), 6.71 (d, J=10.7 Hz, 1H), 6.69 (s, 1H), 3.63 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.8, 154.3, 139.7, 131.1, 122.1, 117.8, 117.2, 36.7, 21.2; FT-IR (KBr) v: 3312, 2922, 1698, 1626, 1588, 1525, 1432, 1336, 1238, 1197, 1179, 1155, 1115, 957, 915, 866, 798, 726, 677, 459 cm^{-1}. ESI-MS (negative) m/z: 165.0 ([M–H]$^-$). ESI-HRMS (negative) calcd for $C_9H_9O_3$ ([M–H]$^-$): 165.0554, found 165.0557.

Conversion of 11 into 12

Concentrated H_2SO_4 (4 drops from a pipette) was added to a solution of **11** (190 mg, 1.14 mmol) in EtOH (99.5%, 2 mL). The mixture was refluxed for 4 h. After being cooled down to ambient temperature, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left a yellowish oil (205.2 mg, 1.06 mmol, 93% from **11**), which was dissolved in dry THF (1.8 mL) and added to a mixture of NaH (60%, in mineral oil, 48 mg, 1.2 mmol) in dry THF (2 mL). The resulting mixture was stirred at ambient temperature for 15 min. With cooling (0 ℃ bath), MOMCl (90 μL, 2.08 mmol) was added. The mixture was then stirred at 0 ℃ for 5 min and then at ambient temperature for 30 min. Aq. NaOH (2 N) was added to quench the reaction. The mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (4∶1, PE/EtOAc) on silica gel afforded a pale

yellow oil (the intermediate ethyl ester, 179 mg, 0.75 mmol, 66% from **11**), which was dissolved in EtOH (2 mL) and aq. NaOH (2 N, 0.4 mL). The mixture was stirred at reflux temperature for 1.5 h. The mixture was allowed to cool down to ambient temperature before being diluted with water and washed with EtOAc. The aqueous layer was then acidified with HCl (1 N) to pH 1 and extracted with EtOAc. The organic layer was concentrated to dryness on a rotary evaporator to give acid **12** as a white solid (42.8 mg, 0.68 mmol, 60% overall from **11**): m.p. 41−43 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.06 (d, J=7.6 Hz, 1H), 6.92 (s, 1H), 6.78 (d, J=7.5 Hz, 1H), 5.16 (s, 2H), 3.63 (s, 2H), 3.44 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.3, 155.1, 139.1, 130.9, 122.6, 120.1, 114.9, 94.4, 56.1, 35.7, 21.6; FT-IR (film) v: 2923, 1718, 1616, 1585, 1510, 1400, 1283, 1260, 1210, 1154, 1122, 1079, 1016, 940, 922, 803, 669 cm^{-1}. ESI-MS *m/z*: 233.1 ([M+Na]$^+$). ESI-HRMS calcd for $C_{13}H_{20}NO_2$ ([M+Na]$^+$): 233.0779, found 233.0784.

Condensation of acid 12 with chiral auxiliary 13 to give 14

A solution of acid **12** (31.5 mg, 0.15 mmol), chiral auxilary **13** (40 mg, 0.025 mmol), DMAP (28 mg, 0.025 mmol) and EDCI (58 mg, 0.3 mmol) in dry CH_2Cl_2 (1 mL) was stirred at ambient temperature for 2 h. Aq. HCl (1 N) was added to quench the reaction. The mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (4∶1, PE/EtOAc) 2−3 times (to remove the purple impurities) on silica gel gave **14** as an almost colorless oil (34 mg, 0.092 mmol, 61%): $[\alpha]_D^{28}$ –82.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34−7.20 (m, 5H), 7.06 (d, J=7.6 Hz, 1H), 6.96 (s, 1H), 6.82 (d, J=8.2 Hz, 1H), 5.18 (dd, J=6.7, 10.8 Hz , 2H), 4.69−4.67 (m, 1H), 4.31 (d, J=17.7 Hz, 1H), 4.24 (dd, J=8.7, 8.7 Hz, 1H), 4.20 (dd, J=9.1, 3 Hz, 1H), 4.19 (d, J=18.1 Hz, 1H), 3.46 (s, 3H), 3.29 (dd, J=13.4, 3.1 Hz, 1H), 2.81 (dd, J=13.4, 9.4 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.3, 155.3, 153.8, 139.0, 135.5, 131.1, 129.6, 129.1, 127.5, 122.6, 120.3, 115.0, 94.5, 66.4, 56.2, 55.5, 38.0, 37.4, 21.7; FT-IR (film) v: 2922, 1781, 1701, 1616, 1511, 1454, 1390, 1365, 1298, 1248, 1211, 1153, 1121, 1077, 1012, 922, 761, 703, 508, 427, 719, 404 cm^{-1}. ESI-MS *m/z*: 392.3 ([M + Na]$^+$). ESI-HRMS calcd for $C_{21}H_{23}NNaO_5$ ([M+Na]$^+$): 392.1478, found 392.1468.

Asymmetric methylation of 14 to afford 15

NaHMDS (1.0 mol/L, in THF, 0.33 mL, 0.33 mmol) was added to a solution of **14** (100 mg, 0.27 mmol) in dry THF (2.7 mL) stirred at –78 ℃ under argon (balloon). After completion of the addition, the mixture was stirred at the same temperature for 1 h. MeI (50 μL, 0.81 mmol) was added. Stirring was continued at –78 ℃ for 10 min, then at –40 ℃ for 1 h. Aq. saturated NH_4Cl was added. The mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (4∶1, PE/EtOAc) on silica gel afforded **15** as a colorless oil (91 mg, 0.24 mmol, 88% from **14**): $[\alpha]_D^{28}$ –98.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35−7.21 (m, 5H), 7.11 (d, J=7.8 Hz, 1H), 6.88 (s, 1H), 6.80 (d, J=10.8 Hz, 1H), 5.29 (q, J=7 Hz , 1H), 5.17 (dd, J=15.8, 6.6 Hz, 2H), 4.66−4.61 (m, 1H), 4.14 (dd, J=9.0, 2.7 Hz, 1H), 4.11 (dd, J=9.0, 7.3 Hz, 1H), 3.48 (s, 3H), 3.33 (dd, J=13.3, 3.2 Hz, 1H), 2.79 (dd, J=13.3, 9.7 Hz, 1H), 2.31 (s, 3H), 1.51 (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.7, 154.4, 152.9, 138.4, 135.6, 129.6, 129.1, 127.4, 127.2, 126.8, 122.6, 114.9, 94.7, 66.1, 56.3, 56.0, 38.2, 37.7, 21.6, 17.1; FT-IR (film) v: 2924, 1782, 1699, 1613, 1507, 1454, 1378, 1358, 1288, 1210, 1153, 1125, 1078, 1012, 924, 762, 748, 702, 668, 594, 536, 509, 427, 404 cm^{-1}. ESI-MS *m/z*: 406.3 ([M+Na]$^+$). ESI-HRMS calcd for $C_{22}H_{25}NNaO_5$ ([M+Na]$^+$): 406.1626, found 406.1625.

Reductive cleavage of the chiral auxiliary in 15 to afford alcohol 16

$NaBH_4$ (44.5 mg, 1.17 mmol) was added small portions to a solution of **15** (90 mg, 0.235 mmol) in THF (1.9 mL) and H_2O (0.5 mL) stirred at ambient temperature. After completion of the addition, the mixture was stirred at the same temperature for 10 h (when TLC showed completion of the reaction). Aq. saturated NH_4Cl was added to quench the reaction. The mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (4∶1, PE/EtOAc) on silica gel afforded **15** as a colorless oil (45 mg, 0.21 mmol, 91%): $[\alpha]_D^{28}$ –0.35 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.09 (d, J=7.7 Hz, 1H), 6.92 (s, 1H), 6.82 (d, J=7.8 Hz, 1H), 5.19 (dd, J=8.2, 6.8 Hz, 1H), 3.73 (dd, J=10.5, 7 Hz, 1H), 3.68 (dd, J=10.5, 6.2 Hz, 1H), 3.49 (s, 3H), 3.44−3.37 (m, 1H), 2.32 (s, 3H), 1.25 (d, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.1, 137.6, 129.5, 127.3, 122.9, 115.2, 94.7, 68.0, 56.3, 35.2, 21.4, 17.0; FT-IR (film) v: 3398, 2958, 2925, 1613, 1578, 1507, 1451, 1398, 1250, 1209, 1153, 1133, 1075, 1015, 925, 812, 594 cm^{-1}. ESI-MS *m/z*: 233.2 ([M+Na]$^+$). ESI-HRMS calcd for $C_{12}H_{18}NaO_3$ ([M + Na]$^+$): 233.1146, found 233.1148.

Acylation of 16 to afford 19

2,4,6-Trichlorobenzoyl chloride **18** (30 μL, 0.189 mmol) was added to a solution of angelic acid **17** (18.9 mg, 0.189 mmol) and Et_3N (14 μL, 0.189 mmol) in dry toluene (120 μL). The mixture was stirred at ambient temperature for 2 h. A solution of alcohol **16** (20 mg, 0.095 mmol) in toluene (0.15 mL) was added. The mixture was stirred in a 70 ℃ bath for 6 h (when TLC showed completion of the reaction). The heating bath

was removed. The mixture was diluted with EtOAc. Solids were filtered. The filtrate was concentrated on a rotary evaporator to give a residue, which was purified by column chromatography (8∶1, PE/EtOAc) on silica gel to afford ester **19** as a colorless oil (17.7 mg, 0.06 mmol, 64%): $[\alpha]_D^{28}$ –12.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.09 (d, J=7.7 Hz, 1H), 6.91 (s, 1H), 6.79 (d, J=7.8 Hz, 1H), 6.04−5.99 (m, 1H), 5.19 (dd, J=10.7, 6.7 Hz, 2H), 4.31 (dd, J=10.7, 6.1 Hz, 1H), 4.20 (dd, J=10.7, 7.5 Hz, 1H), 3.59−3.52 (m, 1H), 3.49 (s, 3H), 2.31 (s, 3H), 1.92−1.90 (dq, J=7.3, 1.6 Hz, 3H), 1.85−1.84 (m, 3H), 1.31 (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.3, 154.9, 137.7, 137.6, 129.0, 128.2, 127.5, 122.6, 114.9, 94.6, 68.4, 56.2, 32.2, 21.5, 20.8, 17.5, 15.8; FT-IR (film) *v*: 2958, 1715, 1613, 1579, 1508, 1455, 1389, 1351, 1254, 1231, 1209, 1078, 1043, 1014, 926, 848, 811, 595, 431, 416 cm^{-1}. ESI-MS *m/z*: 351.3 ([M+Na]$^+$). ESI-HRMS calcd for $C_{17}H_{24}NaO_4$ ([M+Na]$^+$): 315.1567, found 315.1568.

Removal of the MOM in 19 to afford (*R*)-1

A solution of **19** (10 mg, 0.034 mmol) in CH_2Cl_2 (1.8 mL) and CF_3CO_2H (10 μL) was stirred at ambient temperature overnight. The mixture was concentrated to dryness on a rotary evaporator. The residue was purified by column chromatography (6∶1, PE/EtOAc) on silica gel to give (*R*)-**1** as a colorless oil (6.1 mg, 0.025 mmol, 72%): $[\alpha]_D^{28}$ –17.2 (*c* 0.55, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.05 (d, J=7.8 Hz, 1H), 6.72 (d, J=7.8 Hz, 1H), 6.68 (s, 1H), 6.14−6.08 (m, 1H), 4.38 (dd, J=11, 4.7 Hz, 1H), 3.96 (dd, J=11, 8.2 Hz, 1H), 3.37 (d quint, J=4.8, 7.5 Hz, 1H), 2.28 (s, 3H), 1.98 (dq, J=7.3, 1.5 Hz, 3H), 1.90−1.89 (m, 3H), 1.37 (d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.0, 154.1, 139.2, 138.0, 127.7, 127.0, 125.1, 121.5, 116.9, 69.7, 32.4, 21.1, 20.7, 16.6, 16.0; FT-IR (film) *v*: 3415, 2963, 2925, 1691, 1644, 1619, 1587, 1520, 1457, 1421, 1391, 1378, 1351, 1291, 1235, 1162, 1085, 1043, 980, 947, 851, 806, 669, 594 cm^{-1}. ESI-MS *m/z*: 271.3 ([M+Na]$^+$). ESI-HRMS calcd for $C_{15}H_{20}NaO_3$ ([M+Na]$^+$): 271.1306, found 271.1305.

Acetylation of 16 to afford 20

A solution of **16** (21 mg, 0.1 mmol), CH_3CO_2H (1 μL, 0.12 mmol), DMAP (6.1 mg, 0.05 mmol) and EDCI (28.8 mg, 0.15 mmol) in dry CH_2Cl_2 (1 mL) was stirred at ambient temperature for 2 h (when TLC showed completion of the reaction). Aq. saturated NH_4Cl was added. The mixture was extracted with EtOAc. The organic layer was concentrated to dryness on a rotary evaporator. The residue was purified by column chromatography (4∶1, PE/EtOAc) on silica gel to furnish acetate **20** as a colorless oil (23.4 mg, 0.093 mmol, 93%): $[\alpha]_D^{28}$ –15.6 (*c* 0.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.07 (d, J=7.8 Hz, 1H), 6.91 (s, 1H), 6.80 (d, J=8.3 Hz, 1H), 5.19 (s, 2H), 4.22 (dd, J=10.6, 6.2 Hz, 1H), 4.13 (dd, J=10.6, 7.5 Hz, 1H), 3.52−3.50 (m, 1H), 3.49 (s, 3H), 2.31 (s, 3H), 2.01 (s, 3H), 1.27 (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.3, 154.9, 137.6, 128.9, 127.3, 122.6, 115.0, 94.6, 68.7, 56.2, 32.1, 21.5, 21.1, 17.3; FT-IR (film) *v*: 2965, 1733, 1614, 1578, 1508, 1452, 1387, 1371, 1234, 1155, 1077, 1014, 926, 812 cm^{-1}. ESI-MS *m/z*: 275.3 ([M+Na]$^+$). ESI-HRMS calcd for $C_{14}H_{20}NaO_4$ ([M+Na]$^+$): 275.1254, found 275.1254.

Removal of the MOM in 20 to furnish (*R*)-4

A solution of **20** (20 mg, 0.08 mmol), NaI (11.9 mg, 0.08 mmol) and TMSCl (10 μL, 0.12 mmol) in dry CH_3CN (210 μL) was stirred at ambient temperature for 15 min (when TLC showed completion of the reaction). Aq. saturated $Na_2S_2O_3$ was added. The mixture was extracted with EtOAc. The organic layer was concentrated to dryness on a rotary evaporator. The residue was purified by column chromatography (4∶1, PE/EtOAc) on silica gel to furnish (*R*)-**4** as a colorless oil (16.4 mg, 0.08 mmol, 99%): $[\alpha]_D^{28}$ –7.0 (*c* 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.03 (d, J=7.8 Hz, 1H), 6.72 (d, J=7.8 Hz, 1H), 6.65 (s, 1H), 5.88 (br. s, 1H), 4.27 (dd, J=10.9, 5.5 Hz, 1H), 3.98 (dd, J=10.9, 7.8 Hz, 1H), 3.39−3.32 (m, 1H), 2.27 (s, 3H), 2.07 (s, 3H), 1.33 (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.1, 153.9, 138.0, 127.1, 125.4, 121.6, 116.8, 69.8, 32.3, 21.2, 21.1, 16.6; FT-IR (film) *v*: 3402, 2968, 1736, 1686, 1676, 1654, 1618, 1586, 1460, 1421, 1390, 1372, 1266, 1028, 947, 807 cm^{-1}. ESI-MS *m/z*: 231.1 ([M + Na]$^+$). ESI-HRMS calcd for $C_{12}H_{16}NaO_3$ ([M + Na]$^+$): 231.0988, found 231.0992.

Removal of the MOM in 16 to afford (*R*)-3

A solution of **16** (26 mg, 0.124 mmol) in MeOH (12 mL) and HCl (10 N, 0.5 mL) was stirred at ambient temperature overnight. Water was added (2 mL). The mixture was extracted with EtOAc (5 mL×3). The organic layer was concentrated on a rotary evaporator. The residue was purified by column chromatography (2∶1 PE/EtOAc) on silica gel to give (*R*)-**3** as a colorless oil (19.6 mg, 0.118 mmol, 95%): $[\alpha]_D^{26}$ –2.8 (*c* 0.5, $CHCl_3$), $[\alpha]_D^{26}$ –4.8 (*c* 0.25, $CHCl_3$), $[\alpha]_D^{26}$ –6.4 (*c* 0.13, $CHCl_3$) (lit.[13c] $[\alpha]_D$ +21.2 (*c* 0.25, MeOH), but **3** turned out to be almost insoluble in MeOH); of 92% *ee* as shown by HPLC analysis on a Chiralcel IC column (4.6 mm×250 mm, particle size 5 μm) eluting with 95∶5 *n*-hexane/*i*-PrOH at a flow rate of 0.7 mL/min with the UV detector set to 214 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.00 (d, J=8.2 Hz, 1H), 6.72 (s, 1H), 6.71 (d, J=4.7 Hz, 1H), 3.93 (dd, J=9.7, 3.7 Hz ,1H), 3.71 (dd, J=9.7, 7.9 Hz, 1H), 3.23−3.18 (m, 1H), 2.28 (s, 3H), 1.30 (d, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 154.8, 138.0, 127.8, 127.7, 121.6, 118.0, 69.7, 36.7, 21.1, 15.9; FT-IR (film) *v*: 3344, 2962, 2923, 2877, 1619, 1576, 1508, 1452, 1422, 1380, 1288, 1263, 1127, 1013, 946, 861, 808 cm^{-1}. ESI-MS *m/z*: 167.1 ([M + H]$^+$). ESI-HRMS calcd for $C_{10}H_{15}O_2$ ([M+H]$^+$): 167.1067, found 167.1066.

Conversion of 11 into 21

A solution of acid **11** (110 mg，0.67 mmol) and conc. H_2SO_4 (4 drops from a pipette) in EtOH (2 mL) was refluxed for 4 h. Water was added. The mixture was extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The yellowish oily residue (crude ethyl ester, 120 mg, 0.62 mmol, 93%) was dissolved in dry DMF (1.4 mL). Cs_2CO_3 (303 mg, 0.93 mmol) and KI (154 mg, 0.93 mmol) were then added. The mixture was stirred at ambient temperature under argon (balloon) for 1 h. 1-Bromo-2-methylpropane (1.8 mL, 1.55 mmol) was then introduced. The mixture was stirred under argon in an 80 ℃ bath for 72 h. The heating bath was removed. The solids were filtered off. The filtrate was partitioned between aq. NaOH (2 N, 2 mL). The mixture was extracted with EtOAc (5 mL×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was purified by column chromatography (8∶1 PE/EtOAc) on silica gel to give the intermediate ethyl ester-phenol ether (120 mg, 0.48 mmol, 72% from **11**), which was dissolved in EtOH (2.4 mL) and aq. NaOH (2 N, 0.5 mL) and stirred at reflux temperature for 1 h. The heat bath was removed. Water (2 mL) was added, followed by EtOAc (5 mL). The mixture was washed with EtOAc (5 mL×3). The aqueous layer was acidified with HCl (1 N) to pH 1 and extracted with EtOAc (15 mL×3). The combined organic layers were concentrated to dryness on a rotary evaporator to afford **21** as a yellowish solid (106 mg, 0.48 mmol, 71% overall from **11**): m.p. 64−66 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.06 (d, J=7.5 Hz, 1H), 6.72 (d, J=7.6 Hz, 1H), 6.68 (s, 1H), 3.73 (d, J=6.3 Hz, 2H), 3.63 (s, 2H), 2.33 (s, 3H), 2.10−2.04 (m, 1H), 1.01 (d, J=6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.4, 156.9, 139.0, 130.8, 121.0, 120.0, 112.2, 74.4, 35.9, 28.5, 21.7, 19.4; FT-IR (film) v: 2959, 2924, 2873, 1710, 1615, 1585, 1509, 1469, 1415, 1286, 1267, 1158, 1125, 1037, 947, 800 cm^{-1}. ESI-MS m/z: 245.2 ([M+Na]$^+$). ESI-HRMS calcd for $C_{13}H_{18}NaO_3$ ([M+Na]$^+$): 245.1153, found 245.1148.

Condensation of 21 with 13 to furnish 22

This was done using the same procedure given above for the condensation of acid **12** with chiral auxiliary **13** to give **14** (except using acid **21** to replace acid **11**). Yield: 72% (83 mg, chromatography eluting with 8∶1 PE/EtOAc). Data for **22** (a yellowish oil): $[\alpha]_D^{25}$ –31.6 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34−7.20 (m, 5H), 7.05 (d, J=7.2 Hz, 1H), 6.74 (d, J=7.4 Hz, 1H), 6.70 (s, 1H), 4.67−4.63 (m, 1H), 4.28−4.18 (m, 4H), 3.75 (dd, J=9, 6.7 Hz, 1H), 3.71 (dd, J=8.8, 7 Hz, 1H), 3.34 (dd, J=13.2, 2.9 Hz, 1H), 2.74 (dd, J=13.3, 9.9 Hz, 1H), 2.34 (s, 3H), 2.07−2.02 (m, 1H), 1.00 (d, J=6.7 Hz, 3H), 0.98 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.6, 157.0, 153.8, 138.8, 135.6, 131.0, 129.6, 129.1, 127.4, 121.1, 119.8, 112.3, 74.3, 66.4, 55.7, 38.1, 37.2, 29.8, 28.5, 21.8, 19.4; FT-IR (film) v: 2957, 2921, 2872, 1781, 1703, 1614, 1584, 1510, 1469, 1454, 1391, 1365, 1287, 1247, 1200, 1124, 1105, 1035, 988, 762, 703 cm^{-1}. ESI-MS m/z: 404.3 ([M+Na]$^+$). ESI-HRMS calcd for $C_{23}H_{27}NaO_4$ ([M+Na]$^+$): 404.1837, found 404.1832.

Asymmetric methylation of 22 to afford 23

This was done using the same procedure given above for the conversion of **14** into **15** (except using **22** to replace **14**). Yield: 51% (chromatography eluting with 4∶1, PE/EtOAc). Data for **23** (a colorless oil): $[\alpha]_D^{27}$ –86.0 (c 0.68, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34−7.21 (m, 5H), 7.14 (d, J=7.7 Hz, 1H), 6.76 (d, J=7.7 Hz, 1H), 6.64 (s, 1H), 5.25 (q, J=7.1 Hz, 1H), 4.66−4.62 (m, 1H), 4.16 (dd, J=9.1, 2.5 Hz, 1H), 4.11 (dd, J=8.5, 8.5 Hz, 1H), 3.74 (dd, J=8.7, 6.2 Hz, 1H), 3.67 (dd, J=8.7, 6.4 Hz, 1H), 3.32 (dd, J=13.3, 3.1 Hz, 1H), 2.77 (dd, J=13.3, 9.9 Hz, 1H), 2.32 (s, 3H), 2.07−1.99 (m, 1H), 1.55 (d, J=7.1 Hz, 3H), 1.01 (d, J=6.9 Hz, 3H), 1.00 (d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.0, 156.2, 152.9, 138.2, 135.7, 129.6, 129.1, 127.4, 127.2, 125.9, 121.0, 112.0, 74.3, 66.1, 55.9, 38.2, 37.7, 28.7, 21.6, 19.43, 19.40, 16.3; FT-IR (film) v: 2960, 2872, 1781, 1698, 1611, 1582, 1506, 1454, 1416, 1380, 1358, 1288, 1260, 1237, 1209, 1130, 1104, 1036, 965, 817, 762, 744, 702 cm^{-1}. ESI-MS m/z: 418.4 ([M+Na]$^+$). ESI-HRMS calcd for $C_{24}H_{29}NaO_4$ ([M+Na]$^+$): 418.1995, found 418.1989.

Reductive cleavage of the chiral auxiliary in 23 to afford alcohol 24

This was done using the same procedure given above for the reductive cleavage of the chiral auxiliary in **15** to afford alcohol **16** (except using **23** to replace **15**). Yield: 91% (7.1 mg, chromatography eluting with 4∶1 PE/EtOAc). Data for **24** (a colorless oil): $[\alpha]_D^{26}$ –5.6 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.07 (d, J=7.7 Hz, 1H), 6.75 (d, J=7.6 Hz, 1H), 6.68 (s, 1H), 3.76−3.68 (m, 4H), 3.44−3.37 (m, 1H), 2.32 (s, 3H), 2.15−2.07 (m, 1H), 1.52 (br, s, 1H), 1.26 (d, J=7 Hz, 3H), 1.05 (d, J=6.7 Hz, 3H), 1.04 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 156.9, 137.4, 128.8, 127.4, 121.2, 112.5, 74.5, 68.0, 35.5, 28.6, 21.6, 19.60, 19.59, 16.8; FT-IR (film) v: 2960, 2921, 2873, 1611, 1505, 1470, 1414, 1393, 1287, 1260, 1164, 1137, 1039, 1017, 809, 772 cm^{-1}. ESI-MS m/z: 223.1 ([M+H]$^+$). ESI-HRMS calcd for $C_{14}H_{23}O_2$ ([M+H]$^+$): 223.1693, found 223.1698.

Acetylation of 24 to afford (*R*)-5

A solution of alcohol **24** (7 mg, 0.03 mmol), Ac_2O (3 μL, 0.036 mmol), DMAP (1 mg, 0.006 mmol) and Et_3N (6 μL, 0.045 mmol) in dry CH_2Cl_2 (0.3 mL) was stirred at ambient temperature for 2 h. Water was added (1 mL). The mixture was extracted with EtOAc (5 mL×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed

on a rotary evaporator. The residue was purified by column chromatography (2∶1, PE/EtOAc) on silica gel to give (*R*)-**5** as a colorless oil (7.8 mg, 0.03 mmol, 99%): $[\alpha]_D^{26}$ –20.9 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.05 (d, J=7.7 Hz, 1H), 6.72 (d, J=7.3 Hz, 1H), 6.66 (s, 1H), 4.23 (dd, J=10.6, 6.0 Hz,1H), 4.14 (dd, J=10.5, 7.5 Hz, 1H), 3.72 (d, J=6.4 Hz, 2H), 3.52−3.47 (m, 1H), 2.32 (s, 3H), 2.13−2.08 (m, 1H), 2.02 (s, 3H), 1.27 (d, J=7 Hz, 3H), 1.04 (d, J=6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.4, 156.7, 137.5, 128.3, 127.3, 121.0, 112.3, 74.4, 68.7, 32.2, 28.6, 21.6, 21.2, 19.59, 19.57, 17.2; FT-IR (film) v: 2962, 2874, 1741, 1613, 1581, 1507, 1469, 1415, 1388, 1369, 1287, 1233, 1166, 1039, 809, 669 cm^{-1}. ESI-MS *m/z*: 287.3 ($[M+Na]^+$). ESI-HRMS calcd for $C_{16}H_{25}O_3$ ($[M+H]^+$): 265.1798, found 265.1798.

Conversion of epoxide 25 into alcohol 27

n-Hexyl bromide (2.1 mL, 15 mmol) added slowly (first only a small part to induce the reaction, with the main part added after the yellow-brown color faded) to a suspension of Mg turnings (828 mg, 34.5 mmol) and a small grain of solid I_2 in dry THF (15 mL) stirred at ambient temperature under argon (balloon). The mixture was then heated in a 60 ℃ bath for 2 h to give a dark-grey yet clear solution. This Grignard reagent (after being cooled down to ambient temperature) was then added to a mixture of CuBr•Me_2S (65 mg, 0.32 mmol) in dry THF (25 mL) stirred at –78 ℃ under argon (balloon). The mixture was stirred at the same temperature for 30 min. A solution of epoxide **25** (1.00 g, 6.1 mmol) in dry THF (5 mL) was added slowly. The mixture was stirred at –78 ℃ for 1 h (TLC showed completion of the reaction). Aq. sat. NH_4Cl (15 mL) was added. The mixture was extracted with EtOAc (15 mL ×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (8∶1, PE/EtOAc) on silica gel gave alcohol **27** as a colorless oil (1.51 g, 6.0 mmol, 99% from **25**): $[\alpha]_D^{24}$ –6.1 (*c* 1.00, $CHCl_3$) (lit.[14] $[\alpha]_D$ –3.6 (*c* 1.03, $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36−7.26 (m, 5H), 4.54 (s, 2H), 3.82−3.77 (m, 1H), 3.49 (dd, J=9.4, 3.1 Hz, 1H), 3.31 (dd, J=9.4, 7.9 Hz, 1H), 2.42 (br. s, 1H), 1.48−1.39 (m, 2H), 1.31−1.27 (m, 10H), 0.87 (t, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.1, 128.5, 127.83, 127.81, 74.8, 73.4, 70.5, 33.3, 31.9, 29.7, 29.3, 25.6, 22.8, 14.2.

Conversion of alcohol 27 into tosylate 28

A mixture of **27** (1.51 g, 6.0 mmol) and 10% Pd-C (150 mg) in anhydrous EtOH (99.5%, 60 mL) was stirred at 40 ℃ (bath) under H_2 (1 atm) atmosphere for 4 h (TLC showed completion of the reaction). The solids were filtered off. The filtrate and washings were combined and concentrated on a rotary evaporator to afford the intermediate diol as a white solid (960 mg, 99% from **27**), which was dissolved in CH_3CN (27 mL). To the solution were added n-Bu_2SnO (116 mg, 0.6 mmol), DMAP (73 mg, 0.6 mmol), Et_3N (0.9 mL, 6.6 mmol) and *p*-TsCl (1.26 g, 6.6 mmol). The mixture was stirred at ambient temperature for 3 h. Et_2O (20 mL) was added. The solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed (4∶1, PE/EtOAc) on silica gel to give a white solid (the intermediate primary tosylate, 1.86 g, 5.9 mmol, 99%): m.p. 32−33 ℃. $[\alpha]_D^{25}$ +2.47 (*c* 2.55, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80 (d, J=8.3 Hz, 2H), 7.35 (d, J=8.2 Hz, 2H), 4.03 (dd, J=10, 3.0 Hz, 1H), 3.89 (dd, J=10, 7 Hz, 1H), 3.84−3.80 (m, 1H), 2.45 (s, 3H), 2.29 (br. s, 1H), 1.43−1.39 (m, 2H), 1.30−1.24 (m, 10H), 0.87 (t, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.1, 132.8, 130.0, 128.0, 74.1, 69.5, 32.8, 31.8, 29.5, 29.2, 25.3, 22.7, 21.7, 14.1; FT-IR (film) v: 3535, 2927, 2856, 1598, 1496, 1458, 1360, 1308, 1189, 1176, 1097, 1020, 968, 814, 667, 555 cm^{-1}. ESI-MS *m/z*: 337.2 ($[M+Na]^+$). ESI-HRMS calcd for $C_{16}H_{26}NaO_4S$ ($[M+Na]^+$): 337.1452, found 337.1444.

Conversion of 28 into 30

NaH (60%, 20 mg, 0.8 mmol) and a magnetic stirring bar were placed in a three-neck flask. One of the necks was equipped with a condenser while another sealed with an uninflated balloon containing CuBr•Me_2S (which was needed in the next step, *vide infra*). PE (petroleum ether) was added through the third neck. The mixture was stirred for a few minutes. The liquid/emulsion phase was removed with a pipette and another portion of PE was added. The process was repeated three times. And then using dry THF to replace PE to repeat the washing two times. The flask was sealed with a rubber septum and cooled in an ice-water bath under argon (balloon). Dry THF (1 mL) was added, followed by a solution of tosylate **28** (100 mg, 0.32 mmol) in dry THF (1 mL). The mixture was stirred at ambient temperature overnight (when TLC showed completion of the reaction).

A solution of 1-bromo-3,5-dimethoxy-benzene **29** (1.08 g, 5mmol) in dry THF (3 mL) was added slowly (first only a small part to induce the reaction, with the main part added after the brown-yellow color faded) to a suspension of Mg turnings (276 mg, 11.5 mmol) and a small grain of solid I_2 in dry THF (2 mL) stirred at ambient temperature under argon (balloon). The mixture was then heated in a 60 ℃ bath for 2 h to give a dark-grey yet clear solution. A portion of this Grignard reagent (cooled to ambient temperature, 3.2 mL, *ca*. 3.2 mmol) was then added to the above mentioned reaction mixture (containing the epoxide prepared from **28**) stirred under argon (balloon) in a –78 ℃ bath (acetone-dry ice). CuBr•Me_2S (placed in an uninflated balloon sealed onto a side neck of the three-neck flask for the above mentioned epoxidation from the beginning, 132 mg, 0.64 mmol) was then added. The mixture was stirred at –78 ℃ for 5 h (TLC showed completion of

the reaction). Aq. sat. NH_4Cl (5 mL) was added. The mixture was extracted with EtOAc (15 mL×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (8∶1, PE/EtOAc) on silica gel gave alcohol **30** as a colorless oil (48 mg, 0.17 mmol, 53% overall from **28**): $[\alpha]_D^{25}$ –6.36 (*c* 1.00, $CHCl_3$), 98% *ee* as determined by HPLC on a Chiralcel OD-H column (4.6 mm×250 mm, particle size 5 μm) eluting with 80∶20 *n*-hexane/*i*-PrOH at a flow rate of 0.7 mL/min with the UV detector set to 214 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.37 (d, J=2.1 Hz, 2H), 6.34 (t, J=2.1 Hz, 1H), 3.84−3.80 (m, 1H), 3.78 (s, 6H), 2.77 (dd, J=13.4, 3.9 Hz, 1H), 2.57 (dd, J=13.4, 8.6 Hz, 1H), 1.61 (br. s, 1H), 1.53−1.51 (m, 2H), 1.30−1.28 (m, 10H), 0.88 (t, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.1, 141.1, 107.5, 98.6, 72.7, 55.4, 44.6, 37.0, 32.0, 29.8, 29.4, 25.9, 22.8, 14.2; FT-IR (film) *v*: 3448, 3998, 2927, 2854, 1596, 1462, 1429, 1343, 1323, 1293, 1205, 1150, 1068, 925, 829, 700, 456 cm^{-1}. ESI-MS *m/z*: 281.4 ($[M+H]^+$). ESI-HRMS calcd for $C_{17}H_{29}O_3$ ($[M+H]^+$): 281.2110, found 281.2111.

Acetylation of 30 to afford acetate 31

A solution of **30** (20 mg, 0.07 mmol), Ac_2O (7 μL, 0.084 mmol), DMAP (2 mg, 0.014 mmol) and Et_3N (12 μL, 0.11 mmol) in dry CH_2Cl_2 (0.7 mL) was stirred at ambient temperature for 1.5 h. Water was added. The mixture was extracted with EtOAc (5 mL×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (10∶1, PE/EtOAc) on silica gel gave acetate **31** as a colorless oil (22.3 mg, 0.069 mmol, 99%): $[\alpha]_D^{26}$ –4.14 (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.35 (d, J=2 Hz, 2H), 6.33 (t, J=2.1 Hz, 1H), 5.09−5.03 (m, 1H), 3.77 (s, 6H), 2.82 (dd, J=13.7, 6.8 Hz, 1H), 2.72 (dd, J=13.7, 6.3 Hz, 1H), 2.01 (s, 3H), 1.54−1.50 (m, 2H), 1.29−1.25 (m, 10H), 0.87 (t, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.8, 160.8, 140.1, 107.6, 98.6, 74.8, 55.4, 41.0, 33.7, 31.9, 29.6, 29.3, 25.5, 22.8, 21.4, 14.2; FT-IR (film) *v*: 2930, 2857, 1737, 1608, 1597, 1464, 1430, 1374, 1326, 1292, 1240, 1206, 1152, 1069, 1023, 939, 831, 772, 703, 608 cm^{-1}. ESI-MS *m/z*: 323.4 ($[M+H]^+$). ESI-HRMS calcd for $C_{19}H_{31}O_4$ ($[M+H]^+$): 323.2216, found 323.2217.

Conversion of 31 into (*R*)-2

BBr_3 (0.22 mL, 0.24 mmol) was added to a solution of **31** (20 mg, 0.06 mmol) in CH_2Cl_2 (0.6 mL) stirred at –78 ℃ under argon (balloon). After completion of the addition, the mixture was stirred at ambient temperature overnight (when TLC showed completion of the reaction). Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc (5 mL×3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (2∶1, PE/EtOAc) on silica gel gave (*R*)-**2** as a yellowish oil (17.4 mg, 0.059 mmol, 99%): $[\alpha]_D^{26}$ –4.14 (*c* 0.80, $CHCl_3$), $[\alpha]_D^{26}$ –9.4 (*c* 0.10, $CHCl_3$) (lit.[2] $[\alpha]_D^{25}$ –223 (*c* 0.10, $CHCl_3$), measured on 0.34 mg of the natural sample); ^{1}H NMR (500 MHz, CD_3OD) δ: 6.15 (d, J=2.1 Hz, 2H), 6.12 (t, J=2.1 Hz, 1H), 5.02−4.97 (m, 1H), 2.69 (dd, J=13.5, 7.0 Hz, 1H), 2.63 (dd, J=13.6, 6.1 Hz, 1H), 1.99 (s, 3H), 1.54−1.51 (m, 2H), 1.29−1.27 (m, 10H), 0.89 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ: 172.7, 159.4, 141.3, 108.9, 101.7, 76.4, 41.6, 34.6, 32.9, 30.4, 30.3, 26.5, 23.7, 21.1, 14.4; FT-IR (film) *v*: 3381, 2926, 2856, 1736, 1706, 1602, 1456, 1378, 1269, 1148, 1026, 999, 841, 705, 669, 609 cm^{-1}. ESI-MS (negative) *m/z*: 293.3 ($[M–H]^-$). ESI-HRMS calcd for $C_{17}H_{25}O_4$ ($[M-H]^-$): 293.1751, found 293.1758.

Acknowledgement

This work was supported by the National Natural Science Foundation of China (21172247, 21032002) and the Chinese Academy of Sciences.

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(Lu, Y.)

