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Asymmetric Synthesis of 2-Substituted Dihydrobenzofurans and 3-Hydroxydihydrobenzopyrans through the Enantioselective Epoxidation of *O*-Silyl-Protected *ortho*-Allylphenols

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Abstract: The Shi-type epoxidation of *O-tert*-butyldiphenylsilyl (TBDPS) protected *o*-allylphenols serves as an efficient strategy to construct the dihydrobenzofurans and dihydrobenzopyrans in up to 97% *ee*. This methodology led to the enantioselective synthesis of (+)-marmesin, (−)-(3′*R*)-decursinol, and (+)-lomatin.

Keywords: dihydrobenzofurans; dihydrobenzopyrans; lomatin; marmesin; Shi-type epoxidation

Introduction

2-Substituted dihydrobenzofurans **1** are important structural motifs, which are often found in a variety of natural products and exhibit a wide range of biological activities (Figure 1).[1] Although a number of methods have been developed for the preparation of the dihydrobenzofurans,[2–6] a simple and reliable method for the construction of optically active dihydrobenzofurans is scarce and remains to be developed. Previous investigations from this laboratory have demonstrated the highly enantioselective synthesis of angelmarin (**2**),[7] a dihydrobenzofuran natural product bearing a strong activity against PANC-1 cancer cells under a nutrient-starved environment, using our developed asymmetric synthesis as a key step.[8–10] As an extention of this synthesis, we now describe the successful asymmetric synthesis of 2-substituted dihydrobenzofurans and 3-hydroxydihydrobenzopyrans through the enantioselective epoxidation of *O*-silyl-protected *o*-allylphenols using the Shi-type asymmetric epoxidation as the key step.

As illustrated in Scheme 1, the 2-substituted dihydrobenzofurans **4** and 3-hydroxydihydrobenzopyrans **5** can be constructed from the same epoxide **3**, which would be obtained from the enantioselective epoxidation of the corresponding *ortho*-allylphenols. The starting *ortho*-allylphenols can be prepared by the direct alkylation of phenols or the Claisen rearrangement of *O*-allylphenyl ethers.

Results and Discussion

Our synthesis commenced with the preparation of the starting *ortho*-allylphenols. For the *ortho*-3-methylbut-2-enylation, the Claisen rearrangement of a corresponding *O*-2-methylbut-3-en-2-yl aryl ether is the most efficient. The required rearrangement precursor can be prepared by the palladium-catalyzed direct al-

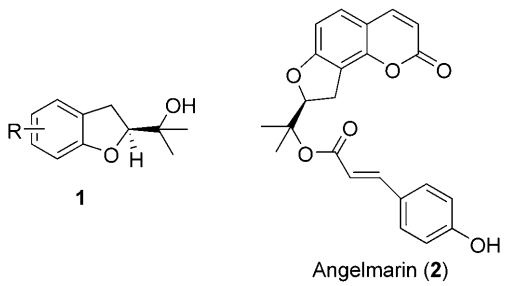
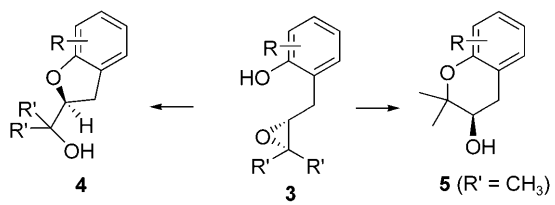
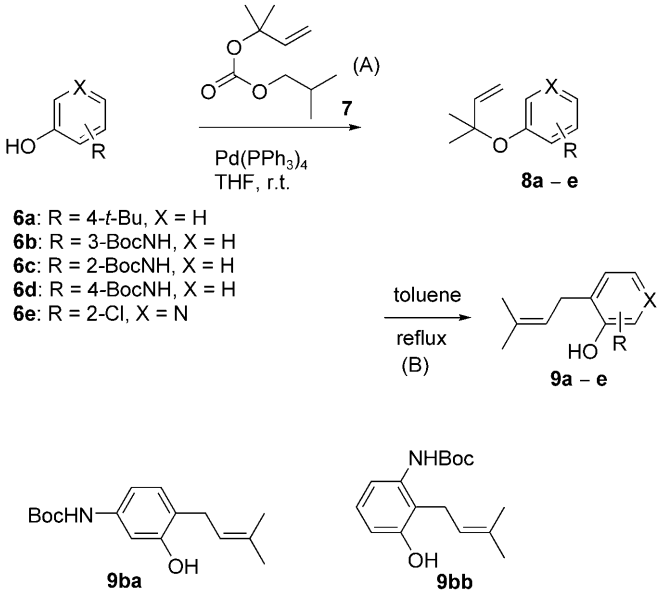


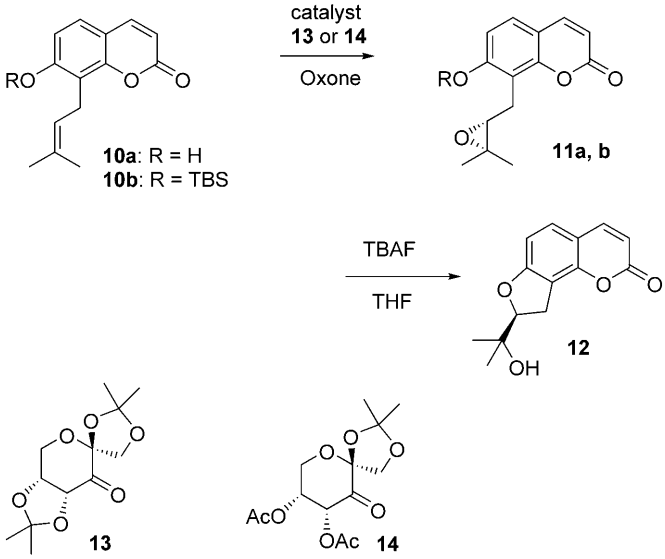
Figure 1. Dihydrobenzofurans.



Scheme 1. Synthetic route.



Scheme 2. Preparation of *ortho*-prenylphenols.



Scheme 3. Reaction conditions of epoxidation

lylation of a phenol, i.e., Kaiho's procedure.[11] Scheme 2 and Table 1 summarize the synthesis of *ortho*-allylphenols. The reaction of the corresponding phenols with a slight excess amount of 2-(2-methyl)-but-3-enyl 2-methylpropyl carbonate (**7**) in the presence of tetrakis(triphenylphosphine)palladium (1–1.5 mol%) in tetrahydrofuran at room temperature for 1.5–7.5 h smoothly proceeded to give allyl ethers **8a–e** in 89–98% yields. The exposure of **8a–e** to refluxing conditions in toluene for 24 h–2 d furnished the *ortho*-allylphenols **9a–e** in 67–85% yields. In the case of **8b**, the regioselective control of the Claisen rearrangement was difficult and an equal amount of the products, **9ba** and **9bb**, was obtained in 44% and 42% yields, respectively (entry 2).

The asymmetric epoxidation conditions of *ortho*-allylphenols were optimized using *ortho*-prenylcoumarins **10a** and **10b** as shown in Scheme 3 and Table 2. When the protection-free phenol **10a** was epoxidated using the Shi ketone **13** at −10 °C for 4 h, the intermediately formed epoxide **11a** spontaneously cyclized and directly formed benzofuran **12**, columbianetin, in 28% yield with 21% *ee* (entry 1). The yield and enantioselectivity were poor. While the reaction of the silyl-protected phenol **10b** provided the stable epoxide **11b** and the deprotection of the epoxide with tetra-*n*-butylammonium fluoride (TBAF) occurred with *in situ* cyclization to afford the benzofuran **12** in 27% yield with 77% *ee* (entry 2). The yield was still unsatisfactory. Finally, the use of Shi's other ketone **14**,[12] designed for less reactive substrates, maximized

Table 2. Reaction conditions of epoxidation.[a)]

Entry	Alkene	Ketone (equiv.)	Conditions	Yield [%][b]	% *ee*[c]
1	**10a**	13 (0.3)	−10 °C, 4 h	28	21
2	**10b**	13 (0.3)	0 °C, 3 h	27	77
3	**10b**	14 (0.15)	0 °C, 23 h	88	97

[a] The reaction was carried out using **13** or **14** in the presence of $(n\text{-Bu})_4NHSO_4$ (0.04 equiv.), oxone (1.63 equiv.), and potassium carbonate (2.4 equiv.) in CH_3CN-DMM buffer.
[b] Isolated yield of two steps.
[c] Enantiomeric excess of **12** determined by HPLC.

Table 1. Preparation of *ortho*-prenylphenols.

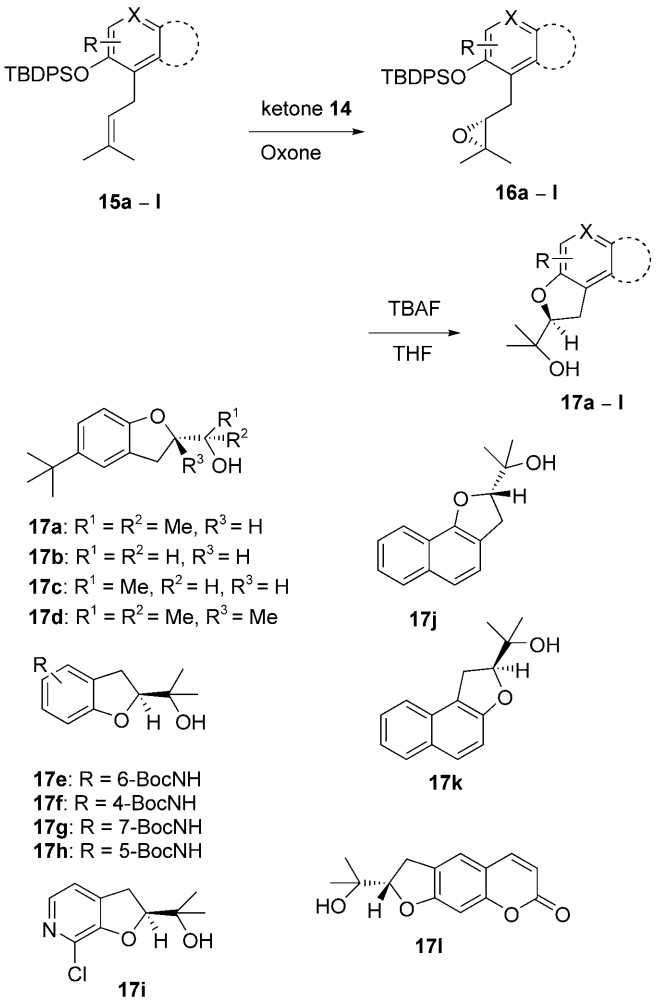
Entry	Substrate	Conditions of (A)	Yield of **8**	Time of (B)	Yield of **9**
1	**6a**	1 mol%, 7.5 h	89%	24 h	85%
2	**6b**	1 mol%, 3 h	92%	2 d	44%,[a] 42%[b]
3	**6c**	1.5 mol%, 3 h	98%	13 h	85%
4	**6d**	1.3 mol%, 3 h	94%	24 h	70%
5	**6e**	1 mol%, 1.5 h	92%	24 h	67%

[a] Yield of **9ba**.
[b] Yield of **9bb**.

Table 3. Asymmetric synthesis of dihydrobenzofurans.[a]

Entry	Substrate	Product	Yield [%][b]	% *ee*[c]
1	**15a**	**17a**	95	96
2	**15b**	**17b**	38	39
3	**15c**[d]	**17c**[e]	85	92[f]
4	**15d**	**17d**	96	40
5	**15e**	**17e**	84	91
6	**15f**	**17f**	89	96
7	**15g**	**17g**	96	89
8	**15h**	**17h**	94	90
9	**15i**	**17i**	86	97
10	**15j**	**17j**	83	97
11	**15k**	**17k**	84	97
12	**15l**	**17l**	83	96 (68)[g]

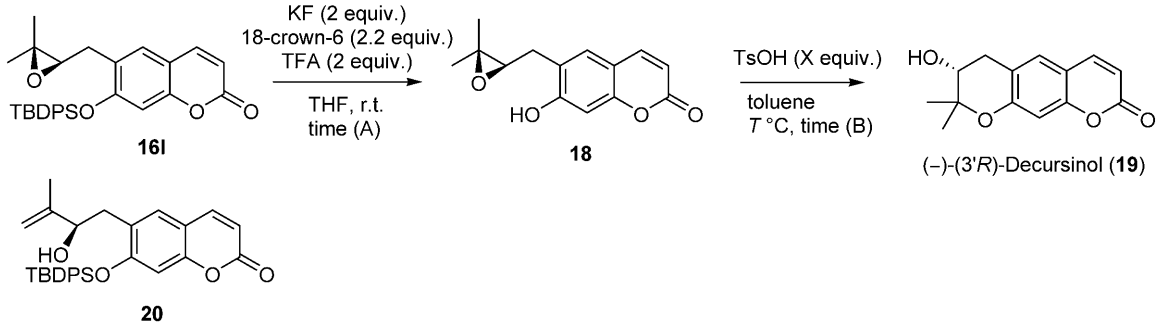
[a] The reaction was carried out by two-step sequence: (1) the epoxidation of **15** using **14** (0.15 equiv.) in the presence of $(n\text{-Bu})_4NHSO_4$ (0.04 equiv.), oxone (1.63 equiv.), and potassium carbonate (2.4 equiv.) in CH_3CN-DMM-buffer and (2) the conversion of **16** to **17** by the treatment with TBAF (1.2 equiv.) in THF.
[b] Isolated yield of two steps.
[c] Enantiomeric excess of **17** was determined by HPLC.
[d] The ratio of *trans/cis* is 97:3.
[e] Diastereomeric ratio = 96:4.
[f] Enantiomeric excess of the major diastereomer.
[g] The enantiomeric excess in parenthesis is for the TBS derivative of **15l**.



Scheme 4. Asymmetric synthesis of dihydrobenzofurans.

the yield and enantioselectivity to 88% and 97% *ee*, respectively (entry 3). The absolute configuration of **12** was established by comparison to the known compound in the literature.[13] It is interesting to note, in contrast to Shi's conditions, that the Shi ketone **14** is not only highly reactive and enantioselective, but is also robust and we were able to decrease the catalytic amount to 15 mol%.

Using the optimized reaction conditions, we set out to explore its generality and scope. Table 3 and Scheme 4 summarize the synthesis of dihydrobenzofurans from various *ortho*-allylphenols, which were prepared as described above or by the reported procedures.[14] The silyl-protected phenols **15a–l** were prepared by the reaction of the corresponding phenols with *tert*-butylchlorodiphenylsilane and imidazole. The reaction of **15a–l** was carried out by using the ketone **14** (15 mol%) and oxone (1.63 mol equiv.) in the presence of tetra-*n*-butylammonium hydrogen sulfate and potassium carbonate in 1:2 acetonitrile/dimethoxymethane (v/v) and buffer solution (pH 6) at 0 °C. The exposure of the resulting epoxides **16a–l** to a slightly excess amount of TBAF in THF provided dihydrobenzofurans **17a–l**. The enantiomeric excess was determined by the HPLC analysis of **17a–l**. First, the substituent effects of the allyl moiety were examined. The reaction of *ortho*-prenylphenol **15a**, a trisubstituted substrate, provided the corresponding dihydrobenzofuran **17a** with a very high enantioselectivity and in 95% yield (entry 1). The disubstituted olefin **15c** (*trans/cis* = 96/4) was also a good substrate for this asymmetric epoxidation and furnished the dihydrobenzofuran **17c** with a 96/4 diastereomeric ratio and 92% *ee* (major diastereomer) and in 85% yield (entry 3). However, the reaction of the monosubstituted and tetrasubstituted olefins **15b** and **15d** resulted in fair enantioselectivities (entries 2 and 4). For all the trisubstituted substrates, excellent enantioselectivities of up to 97% *ee* were obtained (entries 5–12). To demonstrate this methodology, we chose (+)-marmesin (**17l**), a naturally occurring dihydrobenzofuran. In this case, the effect of the silyl protecting groups was briefly examined and the bulkiness was found to affect the enantioselectivity. The sequential reaction of **15l** with a bulky protecting group furnished (+)-marmesin (**17l**) with a high enantiomeric purity (96% *ee*) and in 83% yield (entry 12). The specific optical rotation and the spectroscopic data of our synthetic sample matched those of the reported values.[15] On the other hand, the *tert*-butyl dimethylsilyl derivative



Scheme 5. Synthesis of (−)-(3′*R*)-decursinol (**19**).

Table 4. Reaction conditions of (−)-(3′*R*)-decursinol (**19**).

Entry	A	Ratio of **18:17l**	X	T [°C]	B	Ratio of **19:17l**
1	17 h	94/6	0.1	0	6 h	92/8
2	2 h	>98/2	0.1	−50	5 d	>98/2
3	20 min	>99/1	1	−50	19 h	>99/1

of **15l** provided a decreased enantioselectivity of 68% *ee*.

Next, we investigated the formation of a dihydrobenzopyran, (−)-(3′*R*)-decursinol (**19**), using **16l** as shown in Scheme 5 and Table 4.[16,17] The direct transformation of **16l** under several conditions, such as hydrogen chloride-dioxane, trimethylsilyl triflate-dichloromethane, and potassium fluoride-18-crown-6-TsOH, failed to afford **19** and resulted in the ring-cleavage product **20**. However, TBAF-trifluoroacetic acid (TFA) was promising and provided **18** as a major product together with **19** in a 9:1 ratio. These results were still unsatisfactory. Therefore, we decided to employ a two-step procedure for this transformation. Although the chemoselective removal of the TBDPS group was difficult for the *in situ* cyclization, a combination of potassium fluoride (KF, 2 equiv.)-18-crown-6 (2.2 equiv.)-TFA (2 equiv.) in tetrahydrofuran was very effective, affording **19** with 96% *ee* in 67% yield (two steps). For the TBS-protected **11b**, low temperature was necessary to avoid the benzofuran formation. Finally, the treatment of **11b** with KF-18-crown-6-TFA at −40 °C for 19 h followed by TsOH at −50 °C for 22 h furnished (+)-lomatin (**22**) with 96% *ee* in 70% yield (two steps) as shown in Scheme 6, of which the physical values were identical to those of the natural (+)-lomatin.[18,19]

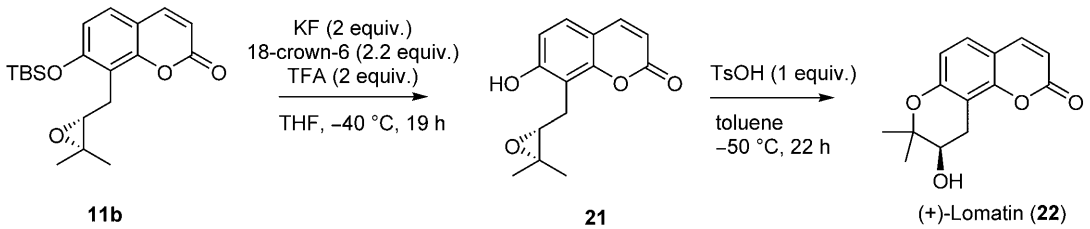
Conclusions

The Shi-type epoxidation of the *O*-TBDPS-protected *ortho*-allylphenols serves as an efficient method to construct dihydrobenzofurans and dihydrobenzopyrans with up to 97% *ee*. This methodology led to the enantioselective synthesis of (+)-marmesin, (−)-(3′*R*)-decursinol, and (+)-lomatin.

Experimental Section

General Procedure for the Synthesis of *o*-Allylphenols

To a stirred solution of a phenol (0.31 mmol) and isobutyl 2-methylbut-3-en-2-yl carbonate (101.4 mg, 0.46 mmol, 85% purity, 1.5 equiv.) in THF (2 mL) at room temperature was added tetrakis(triphenylphosphine)palladium (3.6 mg, 0.003 mmol, 1 mol%) and the mixture was stirred at 23 °C for 1.5–7.5 h. The reaction mixture was diluted with ethyl acetate and the whole was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography to give an *O*-allyl ether, which was used for next reaction. A solution of the *O*-allyl ether in toluene was heated



Scheme 6. Synthesis of (+)-lomatin (**22**).

to reflux for 13 h–2 d. After cooling the reaction mixture to room temperature, the mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography to give the *ortho*-allylphenol.

General Procedure for the Asymmetric Synthesis of 2-Substituted Dihydrobenzofurans through the Enantioselective Epoxidation of *O*-Silyl-protected *ortho*-Allylphenols

An *O*-silyl-protected *ortho*-allylphenol (0.1 mmol) and ketone **14** (9.1 mg, 0.03 mmol) were dissolved in acetonitrile/dimethoxymethane (1.98 mL, 1:2 v/v). A pH 6 buffer solution (0.36 mL) and tetra-*n*-butylammonium hydrogen sulfate (1.4 mg, 0.004 mmol) were slowly added with stirring, and the mixture was cooled to 0 °C. The flask was equipped with two syringe pumps; one of them was filled with a solution of Oxone (100.2 mg, 0.163 mmol) in pH 6 buffer solution (0.63 mL), and the other one with a solution of K_2CO_3 (33.2 mg, 0.24 mmol) in water (0.63 mL). The two solutions were added dropwise over a 2 h period. The solution was stirred at 0 °C for 24 h. The crude material was quenched by addition of water (3 mL) and hexane (3 mL). The reaction mixture was extracted with hexane (5 mL × 2). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum to give a crude epoxide. The residue was used in next step without any purification.

To a solution of the crude epoxide in THF (1 mL) at 0 °C was added TBAF (0.12 mL, 0.12 mmol, 1.0 M in THF) and then the mixture was allowed to gradually warmed to room temperature. After being stirred for 4 h, the reaction was quenched with water. The residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography to give a dihydrobenzofuran.

(*S*)-2-(5-*tert*-Butyl-2-methyl-2,3-dihydrobenzofuran-2-yl)-propan-2-ol (17a): Yield: 95%; 96% *ee*; colorless oil; $[\alpha]_D^{22}$: +42.4 (*c* 0.97, $CHCl_3$) for 96% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 3H), 1.29 (s, 9H), 1.34 (s, 3H), 3.14 (m, 2H), 4.58 (t, *J* = 9.2 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 26.3, 30.8, 31.7, 34.2, 71.7, 89.3, 108.2, 121.9, 124.6, 126.7, 143.5, 157.2; IR (KBr): ν = 3429, 2961, 1734, 1616, 1541, 1494, 1362, 1295, 1267, 1230, 1175, 1152, 1119, 963, 882, 862, 814, 731, 688 cm^{-1}; HR-MS (FAB): *m/z* = 234.1616, calcd. for $C_{15}H_{22}O_2$ $[M]^+$: 234.1620; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 85/15, flow rate = 0.3 mL min^{-1}): retention time = 14.7 min (minor), 16.2 min (major).

(*S*)-(5-*tert*-bBtyl-2-methyl-2,3-dihydrobenzofuran-2-yl)methanol (17b): Yield: 79%; 39% *ee*; colorless oil; $[\alpha]_D^{24}$: +17.8 (*c* 0.29, $CHCl_3$) for 39% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 9H), 2.11 (brs, 1H), 3.00 (dd, *J* = 15.6, 7.6 Hz, 1H), 3.23 (dd, *J* = 15.6, 9.2 Hz, 1H), 3.73 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.84 (d, *J* = 11.6 Hz, 1H), 4.89 (m, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 7.14 (dm, *J* = 8.4 Hz, 1H), 7.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4, 31.7, 34.2, 65.0, 83.1, 108.6, 122.1, 124.8, 126.1, 143.7, 156.9; IR (KBr): ν = 3394, 2953, 1492, 1362, 1266, 1233, 1174, 1119, 1047, 814, 729 cm^{-1}; HR-MS (FAB): *m/z* = 229.1210, calcd. for $C_{13}H_{18}O_2Na$ $[M+Na]^+$: 229.1204; HPLC (CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 92/8, flow rate = 0.5 mL min^{-1}): retention time = 12.9 min (major), 15.2 min (minor).

(*R*)-1-[(*S*)-5-*tert*-Butyl-2,3-dihydrobenzofuran-2-yl]ethanol (17c): Yield: 85%; diastereomeric ratio = 96:4, 92% *ee* (major isomer); colorless oil; $[\alpha]_D^{23}$: +17.5 (*c* 0.56, $CHCl_3$) for 92% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.4 Hz, 3H), 1.29 (s, 9H), 1.97 (brs, 1H), 3.08 (dd, *J* = 15.6, 9.6 Hz, 1H), 3.24 (dd, *J* = 15.6, 8.8 Hz, 1H), 4.17 (m, *J* = 6.4, 3.2 Hz, 1H), 4.69 (td, *J* = 8.8, 3.6 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 7.13 (dm, *J* = 8.4 Hz, 1H), 7.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 29.4, 31.7, 34.2, 68.1, 86.6, 108.3, 122.1, 124.6, 126.5, 143.7, 157.2; IR (KBr): ν = 3420, 2960, 1493, 1362, 1266, 1235, 1174, 1119, 992, 898, 814, 730 cm^{-1}; HRMS (FAB): m/z = 220.1466, calcd for $C_{14}H_{20}O_2$ $[M]^+$: 220.1463; HPLC (CHIRALCEL OD-H, *n*-hexane/*i*-PrOH = 98/2, flow rate = 0.5 mL min^{-1}): retention time = 20.1 min (minor), 21.6 min (major).

(*S*)-2-(5-*tert*-Butyl-2-methyl-2,3-dihydrobenzofuran-2-yl)-propan-2-ol (17d): Yield: 96%; 40% *ee*; colorless oil; $[\alpha]_D^{24}$: +2.5 (*c* 0.82, $CHCl_3$) for 40% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 3H), 1.29 (s, 9H), 1.36 (s, 3H), 1.39 (s, 3H), 2.04 (brs, 1H), 2.75 (d, *J* = 15.6 Hz, 1H), 3.50 (d, *J* = 15.6 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6, 24.2, 24.8, 31.7, 34.2, 37.7, 74.2, 93.7, 108.6, 122.2, 124.6, 126.7, 143.3, 156.4; IR (KBr): ν = 3437, 2962, 1492, 1363, 1252, 1176, 1113, 1061, 957, 897, 849, 814 cm^{-1}; HR-MS (FAB): *m/z* = 248.1788, calcd. for $C_{16}H_{24}O_2$ $[M]^+$: 248.1776; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.3 mL min^{-1}): retention time = 13.3 min (major), 14.9 min (minor).

(*S*)-*tert*-Butyl 2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-6-ylcarbamate (17e): Yield: 84%; 91% *ee*; white solid; mp 127–128.5 °C (*n*-hexane/ethyl acetate); $[\alpha]_D^{23}$: +12.0 (*c* 1.075, $CHCl_3$) for 91% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 3H), 1.30 (s, 3H), 1.50 (s, 9H), 2.20 (brs, 1H), 3.07 (d, *J* = 9.2 Hz, 2H), 4.59 (t, *J* = 9.2 Hz, 1H), 6.71 (brs, 1H), 6.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.94 (brs, 1H), 7.00 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 26.0, 28.3, 30.1, 71.8, 80.4, 89.8, 100.4, 110.8, 121.6, 124.7, 138.3, 152.7, 160.2; IR (KBr): ν = 3284, 2976, 1715, 1605, 1541, 1500, 1419, 1364, 1233, 1154, 1109, 1052, 962, 889, 853, 772 cm^{-1}; HR-MS (FAB): *m/z* = 293.1619, calcd. for $C_{16}H_{23}NO_4$ $[M]^+$: 293.1627; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 85:15, flow rate = 0.3 mL min^{-1}): retention time = 36.4 min (minor), 54.2 min (major).

(*S*)-*tert*-Butyl 2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-4-ylcarbamate (17f): Yield: 89%; 96% *ee*; yellow oil; $[\alpha]_D^{22}$: +43.7 (*c* 1.35, $CHCl_3$) for 96% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 3H), 1.34 (s, 3H), 1.52 (s, 9H), 3.06 (m, 2H), 4.63 (t, *J* = 8.8 Hz, 1H), 6.24 (brs, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 7.08 (t, 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 26.0, 28.3, 28.6, 71.7, 80.7, 89.3, 104.5, 111.9, 116.2, 128.8, 135.0, 152.5, 160.0; IR (KBr): ν = 3447, 3281, 2979, 2925, 1689, 1605, 1533, 1446, 1366, 1291, 1229, 1157, 1094, 1061, 979, 892, 872, 772, 753 cm^{-1}; HR-MS (FAB): *m/z* = 293.1604, calcd. for $C_{16}H_{23}NO_4$ $[M]^+$: 293.1627; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 85:15, flow rate = 0.3 mL min^{-1}): retention time = 22.0 min (minor), 23.9 min (major).

(*S*)-*tert*-Butyl 2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-7-ylcarbamate (17g): Yield: 96%; 89% *ee*; colorless oil; $[\alpha]_D^{22}$: +15.0 (*c* 1.355, $CHCl_3$) for 89% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 3H), 1.36 (s, 3H), 1.52 (s, 9H), 3.18 (m, 2H), 4.61 (t, *J* = 8.8 Hz, 1H), 6.57 (brs, 1H), 6.82 (m, 1H), 7.71 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 26.2, 28.3, 31.3, 71.7, 80.6, 90.0, 117.8, 118.9, 121.1, 122.4, 126.7, 148.1, 152.7; IR (KBr, cm^{-1}): ν = 3291, 2979, 1718, 1627, 1540, 1440, 1389, 1363, 1305, 1239, 1150, 1085, 984, 944, 864, 754, 729; HR-MS (FAB): *m/z* = 293.1634, calcd. for $C_{16}H_{23}NO_4$ $[M]^+$: 293.1627; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 85:15, flow rate = 0.3 mL min^{-1}): retention time = 17.3 min (minor), 18.7 min (major).

(*S*)-*tert*-Butyl 2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-5-ylcarbamate (17h): Yield: 94%; 90% *ee*; colorless solid; mp 118.5–119.5 °C (*n*-hexane/ethyl acetate); $[\alpha]_D^{23}$: +36.6 (*c* 1.37, $CHCl_3$) for 90% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 3H), 1.32 (s, 3H), 1.50 (s, 9H), 3.12 (m, 2H), 4.58 (t, *J* = 8.8 Hz, 1H), 6.41 (brs, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.31 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 26.0, 28.3, 30.9, 71.7, 80.2, 89.5, 108.8, 117.0, 119.3, 127.7, 131.3, 153.3, 155.7; IR (KBr): ν = 3368, 2974, 2926, 1714, 1617, 1539, 1497, 1438, 1367, 1289, 1227, 1163, 1119, 1048, 1027, 967, 942, 875, 819, 800, 756 cm^{-1}; HR-MS (FAB): *m/z* = 293.1619, calcd. for $C_{16}H_{23}NO_4$ $[M]^+$: 293.1627; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 85:15, flow rate = 0.3 mL min^{-1}): retention time = 27.8 min (minor), 36.1 min (major).

(*S*)-2-(7-Chloro-2,3-dihydrofuro[2,3-*c*]pyridin-2-yl)propan-2-ol (17i): Yield: 86%; 97% *ee*; colorless solids; mp 140–141 °C (*n*-hexane/ethyl acetate); $[\alpha]_D^{22}$: +27.2 (*c* 0.715, $CHCl_3$) for 97% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 3H), 1.40 (s, 3H), 3.24 (dd, *J* = 16.8, 9.6 Hz, 1H), 3.35 (dd, *J* = 16.8, 8.4 Hz, 1H), 4.74 (t, *J* = 9.2 Hz, 1H), 7.08 (dd, *J* = 4.8, 0.4 Hz, 1H), 7.92 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 26.1, 31.0, 71.4, 89.9, 119.5, 132.0, 138.5, 141.5, 152.9; IR (KBr): ν = 3337, 2977, 1572, 1458, 1420, 1380, 1321, 1240, 1209, 1183, 1148, 1067, 1039, 949, 921, 869, 834, 777 cm^{-1}; HR-MS (FAB): *m/z* = 214.0642, calcd. for $C_{10}H_{13}O_2NCl$ $[M+H]^+$: 214.0635; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 85:15, flow rate = 0.3 mL min^{-1}): retention time = 24.9 min (minor), 27.4 min (major).

(*S*)-2-(2,3-Dihydronaphtho[1,2-*b*]furan-2-yl)propan-2-ol (17j): Yield: 83%; 97% *ee*; colorless oil; $[\alpha]_D^{21}$: +5.3 (*c* 0.65, $CHCl_3$) for 97% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3H), 1.42 (s, 3H), 3.33 (m, 2H), 4.82 (t, *J* = 9.6 Hz, 1H), 7.27 (d, *J* = 19.2 Hz, 1H), 7.34 (d, *J* = 18.4 Hz, 1H), 7.42 (m, 2H), 7.80 (dd, *J* = 7.2, 3.2 Hz, 1H), 7.96 (dd, *J* = 9.2 , 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 26.0, 31.4, 71.9, 89.9, 120.09, 120.18, 120.21, 121.2, 122.8, 125.2, 125.4, 127.8, 133.8, 154.6; IR (KBr): 3420, 2973, 2926, 1734, 1594, 1575, 1519, 1466, 1441, 1398, 1375, 1280, 1260, 1233, 1170, 1067, 1042, 1004, 941, 876, 800, 772, 742 cm^{-1}; HR-MS (FAB): *m/z* = 228.1157, calcd. for $C_{15}H_{16}O_2$ $[M]^+$: 228.1150; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 85:15, flow rate = 0.3 mL min^{-1}): retention time = 17.0 min (minor), 20.7 min (major).

(*S*)-2-(1,2-Dihydronaphtho[2,1-*b*]furan-2-yl)propan-2-ol (17k): Yield: 84%; 97% *ee*; colorless oil; $[\alpha]_D^{22}$: +79.3 (*c* 0.835, $CHCl_3$) for 97% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 3H), 1.39 (s, 3H), 3.42 (m, 2H), 4.80 (t, *J* = 9.2 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 25.9, 29.6, 71.9, 90.0, 111.7, 118.7, 122.6, 122.9, 126.6, 128.6, 128.9, 129.1, 130.6, 156.9; IR (KBr): ν = 3416, 2974, 2932, 1631, 1599, 1577, 1520, 1465, 1374, 1321, 1240, 1206, 1150, 1065, 965, 858, 806, 768, 743 cm^{-1}; HR-MS (FAB): *m/z* = 228.1148, calcd. for $C_{15}H_{16}O_2$ $[M]^+$: 228.1150; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 85:15, flow rate = 0.3 mL min^{-1}): retention time = 21.0 min (minor), 23.5 min (major).

Synthetic (+)-marmesin (17l): Yield: 83%; 96% *ee*; white solid; mp 180.5–181.5 °C (*n*-hexane/ethyl acetate); $[\alpha]_D^{21}$: +22.9 (*c* 0.885, $CHCl_3$) for 96% *ee* {lit.[15a] $[\alpha]_D^{23}$: +21.7 (*c* 0.9, $CHCl_3$), lit.[15b] $[\alpha]_D^{21}$: +20.3 (*c* 1.2, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 3H), 1.38 (s, 3H), 3.24 (m, 2H), 4.74 (t, *J* = 8.8 Hz, 1H), 6.20 (d, *J* = 9.6 Hz, 1H), 6.72 (s, 1H), 7.22 (s, 1H), 7.59 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 26.0, 29.3, 71.5, 91.1, 97.7, 111.9, 112.5, 123.3, 125.1, 143.7, 155.4, 161.5, 163.1; IR (KBr): ν = 3476, 2977, 2930, 1698, 1629, 1569, 1487, 1446, 1402, 1365, 1309, 1267, 1227, 1183, 1130, 1000, 960, 946, 860, 834, 818, 754, 726 cm^{-1}; HR-MS (FAB): *m/z* = 247.0959 calcd. for $C_{14}H_{15}O_4$ $[M+H]^+$: 247.0970; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 75:25, flow rate = 0.5 mL min^{-1}): retention time = 15.5 min (minor), 28.3 min (major).

Synthetic (−)-(3′*R*)-Decursinol (19)

18-Crown-6 (120.0 mg, 0.454 mmol), trifluoroacetic acid (47.1 mg, 0.413 mmol), and potassium fluoride (24.0 mg, 0.413 mmol) were dissolved in THF (4 mL). Epoxide **16l** (100 mg, 0.206 mmol, 96% *ee*) was added in one portion at room temperature. After being stirred at room temperature for 20 min, the reaction was quenched by addition of water (5 mL). The reaction mixture was extracted with ethyl acetate, washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to give crude epoxide **18** that was used in next step without further purification; yield: 103.0 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3H), 1.50 (s, 3H), 2.80 (m, 1H), 3.07 (m, 2H), 6.22 (d, *J* = 9.2 Hz, 1H), 6.91 (s, 1H), 7.24 (s, 1H), 7.61 (d, *J* = 9.6 Hz, 1H), 8.25 (brs, 1H).

The epoxide **18** (0.206 mmol) was dissolved in toluene (4 mL). The solution was cooled to −50 °C, and *p*-toluenesulfonic acid monohydrate (39.2 mg, 0.206 mmol) was added. After being stirred at −50 °C for 19 h, the reaction was quenched by addition of water (5 mL). The whole was extracted with ethyl acetate, washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 1/1) to give (−)-decursinol (**19**) as a white solids; yield: 33.9 mg (67%); mp 180–180.5 °C (*n*-hexane/ethyl acetate) (lit.[17] mp 180.5–181.5 °C); $[\alpha]_D^{18}$: −10.8 (*c* 1.015, $CHCl_3$) for 96% *ee* {lit.[17] $[\alpha]_D^{23}$: −11 (*c* 0.7, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s,3H), 1.40 (s, 3H), 2.34 (brs, 1H), 2.84 (dd, *J* = 16.8, 6.0 Hz, 1H), 3.11 (dd, *J* = 16.8, 4.8 Hz, 1H), 3.88 (dd, *J* = 6.0, 4.8 Hz, 1H), 6.19 (d, *J* = 9.6 Hz, 1H), 6.75 (s, 1H), 7.17 (s, 1H), 7.57 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 25.0, 30.6, 68.9, 78.2, 104.6,

112.8, 113.0, 116.6, 129.0, 143.2, 154.0, 156.5, 161.5; IR (KBr): $\nu = 3447$, 1698, 1625, 1561, 1390, 1134, 1070, 820, 750 cm^{-1}; HR-MS (FAB): $m/z = 247.0966$, calcd. for $C_{14}H_{15}O_4$ $[M+H]^+$: 247.0970; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 90:10, flow rate = 1.0 mL min^{-1}): retention time = 29.6 min (minor), 38.2 min (major).

Synthetic (+)-Lomatin (22)

Epoxide **11b** (158.0 mg, 0.434 mmol, 97% *ee*) and 18-crown-6 (252.5 mg, 0.955 mmol) were dissolved in THF (4 mL). Trifluoroacetic acid (99.0 mg, 0.869 mmol) was slowly added with stirring, and the mixture was cooled to −40 °C. Potassium fluoride (50.5 mg, 0.869 mmol) was added in one pot. The solution was stirred at −40 °C for 19 h. The reaction was quenched by addition of water (5 mL). The reaction mixture was extracted with ethyl acetate, washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated under vacuum to give crude **21** that was used for next step without any purification; yield: 164.7 mg. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.40$ (s, 3H), 1.56 (s, 3H), 2.50 (dd, $J = 15.2$, 10.4 Hz, 1H), 3.09 (dd, $J = 10.4$, 2.0 Hz, 1H), 3.90 (dd, $J = 15.2$, 1.6 Hz, 1H), 6.25 (d, $J = 9.6$ Hz, 1H), 6.92 (d, $J = 8.8$ Hz, 1H), 7.30 (d, $J = 8.8$ Hz, 1H), 7.66 (d, $J = 9.6$ Hz, 1H), 8.10 (brs, 1H).

The epoxide **21** (164.7 mg, 0.434 mmol) was dissolved in toluene (4 mL). The solution was cooled to −50 °C, and *p*-toluenesulfonic acid monohydrate (82.6 mg, 0.434 mmol) was added in one portion. After being stirred at −50 °C for 22 h, the reaction was quenched by addition of water (5 mL). The reaction mixture was extracted with ethyl acetate, washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 1/1) to give (+)-lomatin **22** as a colorless solid; yield: 75.2 mg (0.305 mmol, 70.3%); 96% *ee*; mp 182–183 °C (*n*-hexane/ethyl acetate) (lit.[17] mp 182.5–183.5 °C); $[\alpha]_D^{17}$: +49.1 (*c* 0.375, EtOH) for 99.2% *ee* {lit.[17] $[\alpha]_D^{23}$: +52 (*c* 0.4, EtOH)}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 1.36 (s, 3H), 1.42 (s, 3H), 2.22 (d, $J = 6.0$ Hz, 1H), 2.98 (dd, $J = 17.6$, 5.2 Hz, 1H), 3.15 (dd, $J = 17.6$, 4.8 Hz, 1H), 3.93 (dd, $J = 10.8$, 5.2 Hz, 1H), 6.23 (d, $J = 9.2$ Hz, 1H), 6.79(d, J=8.8 Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 7.63 (d, $J = 9.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.1$, 24.6, 25.8, 68.3, 78.1, 107.5, 112.1, 112.3, 114.4, 126.6, 144.0, 153.5, 156.4, 161.5; IR (KBr): $\nu = 3492$, 1695, 1600, 1493, 1227, 1125, 1070, 827, 760 cm^{-1}; HR-MS (FAB): $m/z = 247.0973$, calcd. for $C_{14}H_{15}O_4$ $[M+H]^+$: 247.0970; HPLC (CHIRALPAC AD, *n*-hexane/*i*-PrOH = 75:25, flow rate = 0.5 mL min^{-1}): retention time = 13.6 min (minor), 16.2 min (major).

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