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A concise synthetic route to optically active *cis*-β,γ-disubstituted-γ-butyrolactones via tandem Michael–MPV reaction: new total synthesis of (−)-*cis*-whisky lactone and (−)-*cis*-cognac lactone

Minoru Ozeki, Daisuke Hashimoto, Kiyoharu Nishide, Tetsuya Kajimoto and Manabu Node*

Department of Pharmaceutical Manufacturing Chemistry, 21st Century COE Program, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8414, Japan

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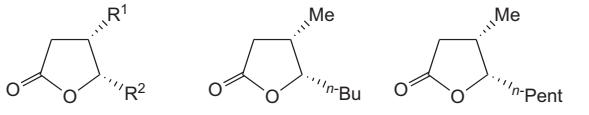
Abstract—Optically active *cis*-β,γ-disubstituted-γ-butyrolactones, for example, *cis*-whisky lactone and *cis*-cognac lactone, were readily synthesized by using tandem Michael–Meerwein–Ponndorf–Verley reactions that employed (−)-10-mercapto-isoborneol as a chiral template in the key step.

1. Introduction

γ-Butyrolactones occur in nature as pheromones and flavor components,[1] and their enantiomeric purity and absolute configuration often affect physiological activities.[2] In addition, optically active γ-butyrolactones are useful as the chiral synthons for the synthesis of versatile bioactive compounds.[3] Thus, much attention has been paid to asymmetric syntheses of γ-butyrolactones. However, reports on the synthesis of *cis*-β,γ-disubstituted-γ-butyrolactones **I** (Fig. 1) compared with that of the *trans* form are limited.[4] Moreover, construction of the two stereogenic centers in β,γ-disubstituted-γ-butyrolactone has required tedious, stepwise procedures.[5] Herein we report a facile synthetic route that can construct the contiguous stereogenic centers of optically active *cis*-β,γ-disubstituted-γ-butyrolactones **I** in one step.



I (-)-*cis*-whisky lactone **9** (-)-*cis*-cognac lactone **10**

Figure 1.

2. Result and discussion

We have recently developed a tandem Michael addition-Meerwein–Ponndorf–Verley (MPV) reduction of α,β-unsaturated ketones **2** with (−)-10-mercaptoisoborneol **1** to give the optically active alcohols **3** (Scheme 1).[6a,b]

Alcohols **3** having three contiguous stereogenic carbons were obtained with high stereoselectivity and good yield when the α,β-unsaturated ketones **2** ($R^1 \neq H$, R^2 = aryl group) were employed as substrates.[6c] An increase in the stereoselectivity of the reaction was observed by adding pentafluorobenzoic acid (PFBA) when substrate **2** ($R^1 \neq H$, R^2 = alkyl group) was treated in the reaction; almost no diastereoselectivity was observed without the addition of PFBA (Table 1).[6c]

Based on these results, we planned to take advantage of the tandem reaction for an asymmetric synthesis of *cis*-β,γ-disubstituted-γ-butyrolactones **I**, as shown in the retro-synthetic analysis (Scheme 2). γ-Butyrolactones **I** can be cyclized by acidic treatment of γ-hydroxycarboxylic acid **II**, which could in turn be obtained from 3-arylpropanol derivative **III** by oxidative degradation of

* Corresponding author. Tel.: +81 75 595 4639; fax: +81 75 595 4775; e-mail: node@mb.kyoto-phu.ac.jp

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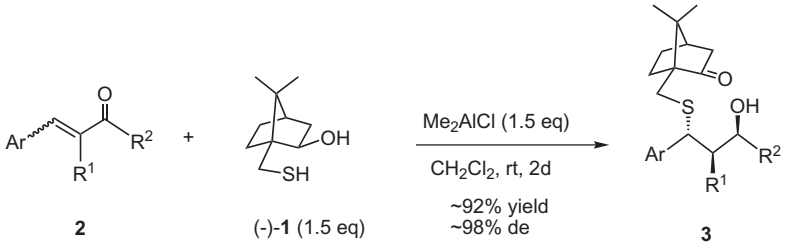
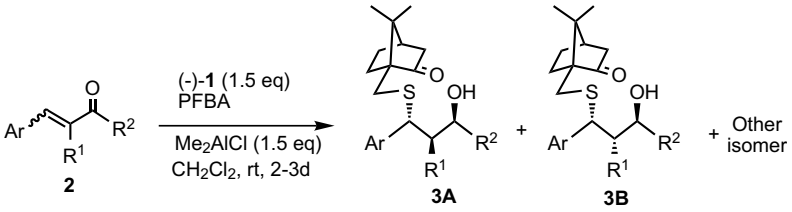


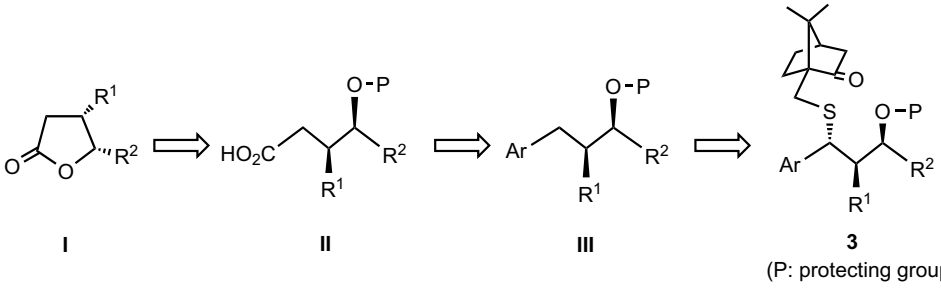
Scheme 1. Tandem Michael–MPV reaction of **2** with (−)-**1**.

Table 1. Tandem Michael–MPV reaction of (−)-**l** with **2**



Entry		Substrate			PFBA [equiv]	Yield[a] (Ratio)[b]	
		Ar	R^1	R^2		**3A/3B**	Other isomer
1	a	4-MeO-Ph	Me	Ph	—	67 (94:6)	—
2	b	4-MeO-Ph	Et	Ph	—	67 (94:6)	—
3	c	4-MeO-Ph	Me	4-ClPh	—	84 (97:3)	—
4	d	Ph	Me	*n*-Bu	—	72 (53:47)	—
5					1.5	62 (71:29)	13
6	e	Ph	Me	*n*-Pen	—	64 (51:49)	—
7					1.5	61 (73:27)	14
8	f	Ph	Me	*c*-Hex	1.5	50 (98:2)	5

[a] Isolated yield.
[b] Ratio was determined by ^{1}H NMR spectroscopy.

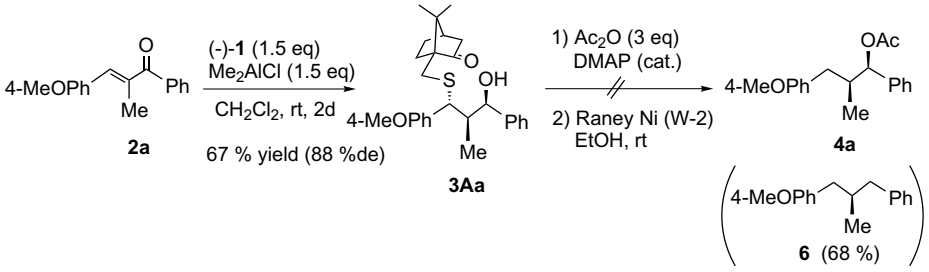


Scheme 2. Retro-synthetic strategy for asymmetric synthesis of *cis*-β,γ-disubstituted-γ-butyrolactones.

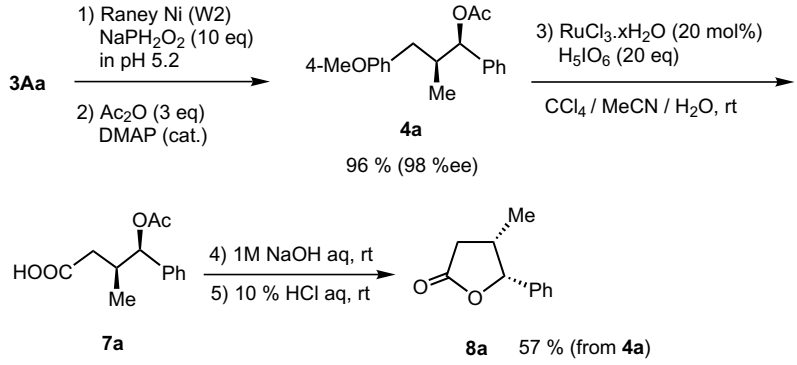
the aryl ring with $RuCl_3/NaIO_4$ (or H_5IO_6).[7] Furthermore, introduction of a methoxy group on the phenyl ring is known to be effective in the oxidation to carboxylic acid.[8] Alcohol **III** could be derived by the reductive desulfurization of **3**, the product of the tandem Michael–MPV reaction. Taking the above background into consideration, we chose α,β-unsaturated ketones **2** having a 4-methoxyphenyl group at the β-position as the starting material for the tandem Michael–MPV reaction.

We first attempted the conversion of **3Aa** (Table 1)[9] into acetate **4a** (Scheme 3). Unfortunately, acetyl protection of the hydroxyl group of **3Aa**, followed by the reductive removal of the chiral moiety under the conventional Raney Ni (W2) conditions afforded the undesired product **6** instead of the desired acetate **4a** due to the hydrogenolysis of the benzylic acetate.

In order to obtain the desired secondary acetate **4a**, we reversed the reaction sequence of the acetylation and the reductive desulfurization of **3Aa**. Namely, the desired acetate **4a** was obtained quantitatively by the treatment of **3Aa** with the milder Raney Ni (W2)–$NaPH_2O_2$ combination system[10,11] to remove the chiral moiety, followed by acetyl protection of the hydroxyl group (Scheme 4). The resulting acetate **4a** was oxidized to carboxylic acid **7a** with $RuCl_3xH_2O/H_5IO_6$.[7,8] Successive treatment of carboxylic acid **7a** with 1 M NaOH and 10% HCl afforded the desired *cis*-β,γ-disubstituted-γ-butyrolactone **8a**[12] in 57% yield from **4a**.



Scheme 3.



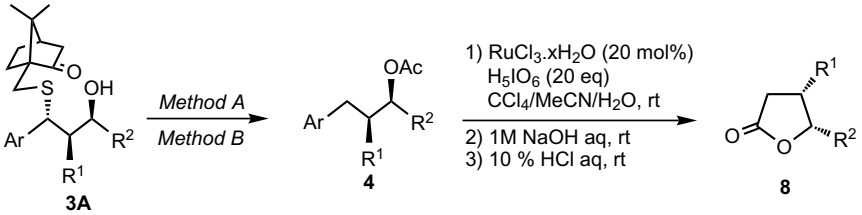
Scheme 4. Asymmetric synthesis of *cis*-β,γ-disubstituted-β-butyrolactone.

Next, we tried to generalize the above method for the synthesis of a broad range of *cis*-β,γ-disubstituted-γ-butyrolactones **8** (Table 2). Compounds **3Ab-c**, which were obtained by using the tandem Michael–MPV reaction with high diastereoselectivity and in good yield (Table 1, entries 2 and 3), were successfully converted into the desired *cis*-β,γ-disubstituted-γ-butyrolactones **8b** and **c** (Table 2, entries 2 and 3). Differing from these instances, the preparation of **8f** (R^2 = alkyl group instead of aryl group) gave a satisfactory result (Table 2, entry 4) by a sequence of acetylation of **3Af** and the conventional Raney Ni (W2) reduction since no undesired compound, such as **6**, was formed (Method B).

Finally, we focused our attention on the synthesis of natural products as a practical application of the newly developed methodology. Whisky and cognac lactones were identified as essential flavor components of aged alcoholic beverages such as whisky, cognac, brandy and wine, and exist as *cis*- and *trans*-forms in nature (Fig. 1).[13] Although many enantioselective total syntheses of *trans*-isomers have been reported,[14] there are few reports of enantioselective total syntheses of *cis*-isomers **9** and **10**.[5b,15]

According to our retro-synthetic strategy (Scheme 2), the key compound **3Ad**, obtained by the tandem

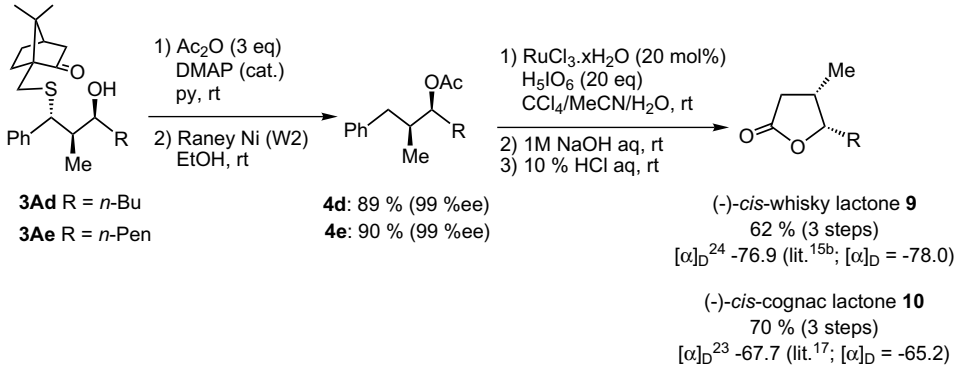
Table 2. Asymmetric syntheses of *cis*-β,γ-disubstituted-γ-butyrolactones **8**



Method A ; 1) Raney Ni (W-2), $NaPH_2O_2$ (10 eq). 2) Ac_2O, DMAP.
Method B ; 1) Ac_2O, DMAP. 2) Raney Ni (W-2).

Entry		3A			Method	4		8
		Ar	R^1	R^2		Yield (%)	Ee (%)	Yield (%)
1	a	4-MeO-Ph	Me	Ph	A	99	98[a]	57
2	b	4-MeO-Ph	Et	Ph	A	95	98[a]	56
3	c	4-MeO-Ph	Me	4-Cl-Ph	A	95	99[a]	60
4	f	Ph	Me	*c*-Hex	B	97	99	67

[a] Ee value was determined for the corresponding free alcohol.



Scheme 5. Asymmetric total syntheses of (−)-*cis*-whisky lactone and (−)-*cis*-cognac lactone.

Michael–MPV reaction (Table 1, entry 4) was acetylated and followed by reductive removal of the chiral moiety with Raney Ni (W2) to afford a secondary acetate **4d** in 89% yield (Scheme 5). After ruthenium-catalyzed oxidative degradation of the phenyl group on **4d** to carboxylic acid, (−)-*cis*-whisky lactone **9** was obtained readily by hydrolysis under basic conditions (1 M NaOH) and lactonization under an acidic condition (10% HCl) in 62% yield from **4d**. The specific rotations $\{[\alpha]_D^{24} = -76.9$ (*c* 1.73, MeOH), lit.[15b] $[\alpha]_D = -78.0$ (MeOH)$\}$ and spectroscopic data of synthetic (−)-*cis*-whisky lactone **9** were identical with those reported in the literature.[16] According to the same synthetic procedure, we achieved asymmetric total synthesis of (−)-*cis*-cognac lactone **10** (Scheme 5).[15c,17]

3. Conclusion

We have developed a highly enantio- and diastereoselective synthetic route to *cis*-β,γ-disubstituted-γ-butyrolactones by using the tandem Michael–MPV reaction with a chiral reagent (−)-**1** as the key step to construct the two required stereogenic centers in one step. As an application of our lactone synthesis, we have succeeded in the asymmetric total synthesis of (−)-*cis*-whisky lactone **9** and (−)-*cis*-cognac lactone **10**, which had hardly been reported so far.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO IR-810 or a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer while ^{1}H NMR spectra were obtained on a JEOL JNM-AL300, a Varian XL-300, a Varian Unity INOVA-400 spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on a Varian Unity INOVA-400 spectrometer with $CDCl_3$ as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Optical rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Chiral HPLC analyses were performed with a Shimadzu LC-9A and LC-10A Liquid Chromatograph series using a Daicel chiral column (CHIRALCEL OD, OF). Their data were recorded on Shimadzu C-R6A Chromatopac. Acetate buffer was adjusted by using a Horiba pH meter F-13. Wakogel C-200 (silica gel) (100–200 mesh, Wako) was used for open column chromatography. Flash column chromatography was performed by using Silica Gel 60N (Kanto Chemical Co., Inc.) as a solid support of immobile phase. Kieselgel 60 F-254 plates (Merck) were used for thin layer chromatography (TLC). Preparative TLC (PTLC) was conducted with Kieselgel 60 F-254 plate (0.25 mm, Merck) or Silica gel 60 F-254 plate (0.5 mm, Merck). Unless purification with silica gel gave compound being pure enough, the compounds were further treated with a recycle HPLC (JAI LC-908) on GPC column (JAIGEL 1H and 2H). When possible, diastereomeric mixtures were also separated by a recycle HPLC (JAI LC-908) on silica gel column (Kusano Si-10) after the purification mentioned above.

4.2. Materials

Most of the reagents were obtained from Wako Pure Chemical Industries, Ltd., Nakalai Tesque, Inc., Aldrich Chemical Inc. Raney Ni (W-2) (suspension in ethanol) was prepared according to general procedure. (−)-10-Mercaptoisoborneol (−)-**1** was prepared by Eliel's procedure.[18,6a,b] A typical procedure for the tandem Michael–MPV reaction of (−)-**1** with **2** should be referred to the previous report.[6c] Mixtures of the diastereomers of **3** were also separated to each diastereomer by the recycle HPLC. The characterized data for **3a**, **3b**, and **3f** have been reported.[6c]

4.2.1. (1*R*,2*R*,3*R*)-1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-2-methyl-3-[(1*S*,4*R*)-2-oxobornane-10-sulfanyl]-1-propanol 3Ac. Colorless oil; $[\alpha]_D^{23} = +173.2$ (*c* 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.28 (m, 4H), 7.24 (dt type, $J = 8.8$, 2.6 Hz, aromatic 2H), 6.84 (dt type, $J = 8.8$, 2.6 Hz, aromatic 2H), 5.53 (dd, $J = 4.2$, 2.6 Hz, 1H), 3.92 (d, $J = 10.6$ Hz, 1H), 3.80 (s, 3H), 3.11 (d, $J = 4.4$ Hz, 1H), 2.56 (d, A part of AB, $J_{AB} = 13.3$ Hz, 1H), 2.34 (ddd, A part of AB, $J_{AB} = 18.4$ Hz, $J = 4.8$, 3.2 Hz, 1H), 2.27 (d, B part of AB, $J_{AB} = 13.3$ Hz, 1H), 2.11–2.03 (m, 2H), 1.96–1.87 (m, 1H), 1.86 (d, B part of AB, $J_{AB} = 18.4$ Hz, 1H), 1.79–1.71 (m, 1H), 1.65–1.58 (m, 1H), 1.38–1.31 (m,

1H), 0.89 (s, 3H), 0.79 (s, 3H), 0.50 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.7, 158.5, 142,1, 134.6, 132.1, 129.5 (2C), 128.1 (2C), 127.1 (2C), 113.7 (2C), 72.3, 61.0, 55.7, 55.2, 48.0, 45.8, 43.3, 43.2, 28.2, 27.0, 26.8, 19.9, 19.8, 10.9; IR ($CHCl_3$): 3500, 3026, 3006, 2964, 2937, 1735, 1610, 1583, 1510, 1490, 1465, 1456, 1251 cm^{-1}; MS (20 eV) *m/z*: 472 (M^+, 0.3), 288 (29), 148 (100), 139 (37), 121 (65), 105 (8), 91 (6); HRMS calcd for $C_{27}H_{33}ClO_2S$ (M^+): 472.1839, found 472.1836.

4.2.2. (1*R*,2*R*,3*S*)-2-Methyl-1-[(1*S*,4*R*)-2-oxobornane-10-sulfanyl]-1-phenyl-3-heptanol 3Ad. Colorless oil; $[\alpha]_D^{18} = +174.4$ (*c* 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.19 (m, 5H), 4.29–4.24 (br m, 1H), 3.82 (d, $J = 10.6$ Hz, 1H), 2.57 (d, A part of AB, $J_{AB} = 13.3$ Hz, 1H), 2.37 (d, $J = 4.8$ Hz, 1H), 2.30 (ddd, A part of AB, $J_{AB} = 18.3$ Hz, $J = 4.6$, 3.3 Hz, 1H), 2.14 (d, B part of AB, $J_{AB} = 13.3$ Hz, 1H), 2.02–1.99 (m, 1H), 1.94–1.84 (m, 2H), 1.83 (d, B part of AB, $J_{AB} = 18.3$ Hz, 1H), 1.73–1.23 (m, 9H), 0.92 (t, $J = 7.0$ Hz, 3H), 0.85 (s, 3H), 0.73 (s, 3H), 0.70 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.1, 143.0, 128.7 (2C), 128.3 (2C), 126.8, 71.4, 60.8, 56.1, 47.8, 43.3, 43.2, 43.1, 34.4, 28.7, 27.8, 26.8, 26.7, 22.8, 19.8 (2C), 14.1, 11.1; IR ($CHCl_3$): 3529, 3062, 3035, 2993, 2958, 2862, 1735, 1600, 1488, 1454, 1377, 1319, 1299 cm^{-1}; MS (70 eV) *m/z*: 388 (M^+, 6), 273 (85), 204 (35), 185 (46), 151 (43), 147 (37), 118 (89), 105 (17), 91 (100), 77 (23), 69 (55), 57 (55); HRMS calcd for $C_{24}H_{36}O_2S$ (M^+): 388.2436, found 388.2434.

4.2.3. (1*R*,2*S*,3*S*)-2-Methyl-1-[(1*S*,4*R*)-2-oxobornane-10-sulfanyl]-1-phenyl-3-heptanol 3Bd. Colorless oil; $[\alpha]_D^{26} = +133.1$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.45 (m, 2H), 7.35–7.30 (m, 2H), 7.26–7.20 (m, 1H), 4.40 (d, $J = 4.6$ Hz, 1H), 3.63–3.57 (br m, 1H), 3.10 (d, $J = 5.1$ Hz, 1H), 2.44 (d, A part of AB, $J_{AB} = 13.0$ Hz, 1H), 2.32 (d, B part of AB, $J_{AB} = 13.0$ Hz, 1H), 2.31 (ddd, A part of AB, $J_{AB} = 18.3$ Hz, $J = 4.8$, 2.9 Hz, 1H), 2.04–2.02 (m, 1H), 2.00–1.82 (m, 3H), 1.86 (d, B part of AB, $J_{AB} = 18.3$ Hz, 1H), 1.68–1.24 (m, 8H), 0.92 (s, 3H), 0.90 (t, $J = 7.3$ Hz, 3H), 0.83 (d, $J = 7.0$ Hz, 3H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.1, 142.2, 128.8 (2C), 128.2 (2C), 126.7, 73.8, 60.7, 55.4, 47.9, 46.5, 43.2, 43.1, 33.7, 28.6, 28.2, 26.8, 26.6, 22.8, 19.9, 19.8, 14.1, 11.8; IR ($CHCl_3$): 3506, 3062, 3028, 2993, 2958, 2873, 1735, 1600, 1492, 1454, 1415, 1377, 1319, 1299 cm^{-1}; MS (70 eV) *m/z*: 388 (M^+, 6), 273 (100), 204 (48), 185 (57), 151 (51), 118 (95), 105 (11), 91 (91), 77 (13), 69 (55), 57 (43); HRMS calcd for $C_{24}H_{36}O_2S$ (M^+): 388.2436, found 388.2434.

4.2.4. (1*R*,2*R*,3*S*)-2-Methyl-1-[(1*S*,4*R*)-2-oxobornane-10-sulfanyl]-1-phenyl-3-octanol 3Ae. Colorless oil; $[\alpha]_D^{23} = +168.6$ (*c* 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.19 (m, 5H), 4.27 (br m, 1H), 3.82 (d, $J = 10.6$ Hz, 1H), 2.57 (d, A part of AB, $J_{AB} = 13.2$ Hz, 1H), 2.37 (d, $J = 4.6$ Hz, 1H), 2.30 (ddd, A part of AB, $J_{AB} = 18.3$ Hz, $J = 4.6$, 3.3 Hz, 1H), 2.14 (d, B part of AB, $J_{AB} = 13.2$ Hz, 1H), 2.01–1.99 (m, 1H), 1.94–1.83 (m, 2H), 1.83 (d, B part of AB, $J_{AB} = 18.3$ Hz, 1H), 1.73–1.26 (m, 11H), 0.90 (t, $J = 6.9$ Hz, 3H), 0.85 (s, 3H), 0.73 (s, 3H), 0.69 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.1, 143.0, 128.7 (2C), 128.2 (2C), 126.8, 71.4, 60.8, 56.1, 47.8, 43.3, 43.2, 43.1, 34.7, 32.0, 27.8, 26.8, 26.7, 26.2, 22.6, 19.8 (2C), 14.1, 11.1; IR ($CHCl_3$): 3525, 2958, 2935, 2858, 1735, 1600, 1488, 1454, 1415, 1377 cm^{-1}; MS (70 eV) *m/z*: 402 (M^+, 5), 273 (79), 218 (18), 151 (31), 118 (100), 91 (77), 64 (46), 55 (65); HRMS calcd for $C_{25}H_{38}O_2S$ (M^+): 402.2592, found 402.2594.

4.2.5. (1*R*,2*S*,3*S*)-2-Methyl-1-[(1*S*,4*R*)-2-oxobornane-10-sulfanyl]-1-phenyl-3-octanol 3Be. Colorless oil; $[\alpha]_D^{24} = +128.3$ (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.45 (m, 2H), 7.35–7.31 (m, 2H), 7.25–7.21 (m, 1H), 4.40 (d, $J = 4.6$ Hz, 1H), 3.63–3.57 (br m, 1H), 3.09 (d, $J = 5.1$ Hz, 1H), 2.44 (d, A part of AB, $J_{AB} = 13.0$ Hz, 1H), 2.32 (d, B part of AB, $J_{AB} = 13.0$ Hz, 1H), 2.31 (ddd, A part of AB, $J_{AB} = 18.3$ Hz, $J = 5.1$, 3.0 Hz, 1H), 2.04–2.02 (m, 1H), 1.99–1.82 (m, 3H), 1.86 (d, B part of AB, $J_{AB} = 18.3$ Hz, 1H), 1.67–1.48 (m, 3H), 1.42–1.20 (m, 7H), 0.92 (s, 3H), 0.88 (t, $J = 7.0$ Hz, 3H), 0.83 (d, $J = 7.0$ Hz, 3H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.1, 142.2, 128.8 (2C), 128.2 (2C), 126.7, 73.8, 60.7, 55.4, 47.9, 46.4, 43.2, 43.1, 33.9, 32.0, 28.6, 26.8, 26.6, 25.6, 22.7, 19.9, 19.8, 14.1, 11.8; IR ($CHCl_3$): 3506, 3062, 2993, 2958, 2931, 2858, 1735, 1596, 1492, 1454, 1415, 1377 cm^{-1}; MS (70 eV) *m/z*: 402 (M^+, 5), 273 (100), 233 (19), 218 (32), 185 (46), 151 (40), 147 (32), 118 (96), 91 (94), 64 (66), 55 (79); HRMS calcd for $C_{25}H_{38}O_2S$ (M^+): 402.2592, found 402.2599.

4.3. Asymmetric synthesis of γ-butyrolactone 8

The synthetic procedure of γ-butyrolactone **8a** is shown below as a typical procedure. Compounds **8b** and **c** were synthesized in the same way as **8a**.

4.3.1. (1*R*,2*S*)-1-Acetoxy-3-(4-methoxyphenyl)-2-methyl-1-phenylpropane 4a. Freshly prepared Raney Ni (W-2) (suspension in ethanol, 7 mL) was added to a solution of **3Aa** (30 mg, 0.67 mmol) in a mixed medium (7 mL) of an acetate buffer (pH 5.2) and ethanol (1:2), followed by the immediate addition of aqueous solution (2 mL) of sodium hypophosphite monohydrate (710 mg, 6.70 mmol), and the reaction mixture stirred for another 0.5 h at room temperature. The reaction mixture was filtered through Celite (washing with methanol), and the filtrate evaporated. The residue was poured into water, and then extracted with ethyl acetate three times. The combined organic layer was washed with brine, and dried over magnesium sulfate, filtered and concentrated in vacuo. Purification of the residue by the preparative TLC (hexane/ethyl acetate = 5:1) gave (1*R*,2*S*)-3-(4-methoxyphenyl)-2-methyl-1-phenyl-1-propanol (17.3 mg, 99%). Pale yellow oil; $[\alpha]_D^{21} = +9.4$ (*c* 0.64, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H), 7.08–7.06 (m, 2H), 6.84–6.81 (m, 2H), 4.60 (d, $J = 4.9$ Hz, 1H), 3.78 (s, 3H), 2.72 (dd, A part of AB, $J_{AB} = 13.4$ Hz, $J = 5.9$ Hz, 1H), 2.33 (dd, B part of AB, $J_{AB} = 13.4$ Hz, $J = 9.0$ Hz, 1H), 2.10–2.01 (m, 1H), 1.80 (br, 1H), 0.85 (d, $J = 6.7$ Hz, 3H); IR ($CHCl_3$): 3607, 3032, 3010, 2934, 1610, 1512, 1454, 1300, 1250, 1178, 1035 cm^{-1};

MS (70 eV) *m/z*: 256 (M^+, 27), 238 (76), 223 (23), 149 (56), 121 (92), 107 (100), 79 (19); HRMS calcd for $C_{17}H_{20}O_2$ (M^+): 256.1463, found 256.1471. [98% ee, chiral HPLC analysis; DAICEL CHIRALCEL OF (25 × 0.46); eluent: hexane/isopropanol = 99/1; flow rate: 0.5 mL/min; Temp.: 25 °C; detector: 254 nm, (−): 43.9 min, (+): 49.3 min].

Next acetic anhydride (193 mg, 1.89 mmol) was added to a solution of (1*R*,2*S*)-3-(4-methoxyphenyl)-2-methyl-1-phenyl-1-propanol (161 mg, 0.63 mmol) and 4-dimethylaminopyridine (catalytic amount) in pyridine (3 mL), and the reaction mixture stirred for 30 min at room temperature. The reaction mixture was added into methanol at 0 °C, and concentrated in vacuo to give a residue, which was purified by silica gel column chromatography (hexane/ethyl acetate = 3:1) to give **4a** (188.0 mg, 100%). Colorless oil; $[\alpha]_D^{24} = +17.7$ (*c* 0.82, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.25 (m, 5H), 7.00 (dt type, $J = 8.6$, 2.5 Hz, aromatic 2H), 6.81 (dt type, $J = 8.6$, 2.5 Hz, aromatic 2H), 5.65 (d, $J = 5.7$ Hz, 1H), 3.78 (s, 3H), 2.63 (dd, $J = 12.8$, 4.4 Hz, 1H), 2.26–2.10 (m, 2H), 2.12 (s, 3H), 0.86 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 157.9, 139.7, 132.3, 129.9 (2C), 128.2 (2C), 127.6, 126.7 (2C), 113.7 (2C), 78.8, 55.2, 41.1, 38.4, 21.2, 14.5; IR ($CHCl_3$): 3035, 3026, 1732, 1612, 1512, 1465, 1456, 1371, 1244, 1178, 1020 cm^{-1}; MS (70 eV) *m/z*: 298 (M^+, 4), 238 (31), 223 (27), 121 (51), 107 (15), 105 (4), 91 (12), 83 (100), 77 (11); HRMS calcd for $C_{19}H_{22}O_3$ (M^+): 298.1569, found 298.1567.

4.3.2. (3*S*,4*R*)-3-Methyl-4-phenylbutan-4-olide 8a.[12] Ruthenium(III) chloride hydrate (12 mg, 0.06 mmol) and orthoperiodic acid (1.3 g, 5.50 mmol) were added to a biphasic solution of **4a** (82 mg, 0.28 mmol) in $CCl_4/CH_3CN/H_2O$ = 5:5:8 (9 mL), and the reaction mixture stirred for 2 h at room temperature. The reaction mixture was acidified with 1 M HCl aq to pH 1, and the solution extracted with ethyl acetate three times. The combined organic layer was successively washed with a saturated aqueous solution of sodium thiosulfate and brine, dried over magnesium sulfate, filtered and concentrated in vacuo to give crude (3*S*,4*R*)-4-acetoxy-3-methyl-4-phenylbutyric acid. Then, it was hydrolyzed with 1 M NaOH (5 mL) at room temperature for 2 h, and the reaction mixture acidified with 10% HCl aq to pH 1, and stirred for another 18 h. The reaction mixture was neutralized with saturated aqueous solution of sodium bicarbonate, and extracted with ethyl acetate three times. The combined organic layer was successively washed with saturated aqueous solution of sodium thiosulfate and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give a residue. The residue was purified with silica gel column chromatography (hexane/ethyl acetate = 3:1) to give **8a** (28 mg, 57% yield from **4a**). Colorless oil; $[\alpha]_D^{25} = +56.7$ (*c* 1.19, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.30 (m, 3H), 7.25–7.22 (m, 2H), 5.60 (d, $J = 6.2$ Hz, 1H), 2.94–2.80 (m, 2H), 2.40–2.31 (m, 1H), 0.70 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.7, 136.1, 128.5 (2C), 128.0, 125.4 (2C), 84.0, 37.0, 34.9, 15.1; IR ($CHCl_3$): 3035, 1774, 1604, 1496, 1454, 1089, 1008, 989 cm^{-1}; MS (20 eV) *m/z*: 176 (M^+, 35), 107 (100), 105 (41), 79 (11), 70 (16); HRMS calcd for $C_{11}H_{12}O_2$ (M^+): 176.0837, found 176.0840.

4.3.3. (1*R*,2*S*)-1-Acetoxy-2-ethyl-3-(4-methoxyphenyl)-1-phenylpropane 4b. Colorless oil; $[\alpha]_D^{23} = +29.2$ (*c* 1.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.22 (m, 5H), 7.00 (dt type, $J = 8.7$, 2.5 Hz, aromatic 2H), 6.81 (dt type, $J = 8.7$, 2.5 Hz, aromatic 2H), 5.72 (d, $J = 5.9$ Hz, 1H), 3.78 (s, 3H), 2.49 (dd, A part of AB, $J_{AB} = 13.8$ Hz, $J = 6.6$ Hz, 1H), 2.42 (dd, B part of AB, $J_{AB} = 13.8$ Hz, $J = 7.9$ Hz, 1H), 2.10 (s, 3H), 2.09–2.01 (m, 1H), 1.44–1.30 (m, 2H), 0.89 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 157.8, 139.7, 132.5, 129.9 (2C), 128.2 (2C), 127.5, 126.7 (2C), 113.7 (2C), 76.7, 55.2, 47.1, 34.7, 21.2, 20.9, 11.0; IR ($CHCl_3$): 3026, 3010, 2964, 2935, 2877, 2837, 1732, 1612, 1512, 1496, 1463, 1456, 1245 cm^{-1}; MS (70 eV) *m/z*: 312 (M^+, 4), 252 (19), 223 (83), 121 (100), 105 (6), 77 (16); HRMS calcd for $C_{20}H_{24}O_3$ (M^+): 312.1725, found 312.1727.

4.3.4. (3*S*,4*R*)-3-Ethyl-4-phenylbutan-4-olide 8b. Colorless oil; $[\alpha]_D^{21} = +42.6$ (*c* 1.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.03 (m, 3H), 7.23–7.20 (m, 2H), 5.62 (d, $J = 6.6$ Hz, 1H), 2.75 (ddd, A part of AB, $J_{AB} = 16.7$ Hz, $J = 8.1$, 0.4 Hz, 1H), 2.73–2.63 (m, 1H), 2.45 (dd, B part of AB, $J_{AB} = 16.7$ Hz, $J = 5.7$ Hz, 1H), 1.18–1.09 (m, 1H), 0.93–0.78 (m, 1H), 0.80 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 136.3, 128.4 (2C), 128.1, 125.7 (2C), 84.2, 42.1, 33.9, 22.5, 11.9; IR ($CHCl_3$): 3033, 2964, 2935, 1778, 1602, 1496, 1456, 1315, 1303, 1163 cm^{-1}; MS (70 eV) *m/z*: 190 (M^+, 34), 107 (100), 105 (59), 77 (32), 56 (70); HRMS calcd for $C_{12}H_{14}O_2$ (M^+): 190.0994, found 190.0995.

4.3.5. (1*R*,2*S*)-1-Acetoxy-1-(4-chlorophenyl)-3-(4-methoxyphenyl)-2-methylpropane 4c. Colorless oil; $[\alpha]_D^{22} = +27.1$ (*c* 1.57, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.31(dt type, $J = 8.6$, 2.2 Hz, aromatic 2H), 7.22–7.19 (m, 2H), 6.98 (dt type, $J = 8.6$, 2.5 Hz, aromatic 2H), 6.80 (dt type, $J = 8.6$, 2.5 Hz, aromatic 2H), 5.59 (d, $J = 5.7$ Hz, 1H), 3.78 (s, 3H), 2.61 (dd, A part of AB, $J_{AB} = 13.4$ Hz, $J = 5.1$ Hz, 1H), 2.33 (dd, B part of AB, $J_{AB} = 13.4$ Hz, $J = 9.3$ Hz, 1H), 2.17–2.07 (m, 1H), 2.12 (s, 3H), 0.85 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 174.7, 151.0, 145.0, 143.4, 140.8 (2C), 139.1 (2C), 138.6 (2C), 121.3 (2C), 78.3, 50.7, 33.6, 30.4, 9.5, 1.5; IR ($CHCl_3$): 3033, 3024, 3006, 2966, 2935, 2912, 1733, 1612, 1583, 1512, 1492, 1463, 1371, 1299, 1249, 1178, 1024, 1014 cm^{-1}; MS (70 eV) *m/z*: 332 (M^+, 5), 334 (2), 274 (7), 272 (22), 257 (24), 121 (70), 83 (100), 77 (12); HRMS calcd for $C_{19}H_{21}ClO_3$ (M^+): 332.1179, found 332.1178.

4.3.6. (3*S*,4*R*)-4-(4-Chlorophenyl)-3-methylbutan-4-olide 8c. Colorless prism; mp 50–52 °C (hexane/ethyl acetate); $[\alpha]_D^{22} = +52.7$ (*c* 1.46, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (dt type, $J = 6.6$, 2.2 Hz, aromatic 2H), 7.21–7.17 (m, 2H), 5.57 (d, $J = 5.9$ Hz, 1H), 2.93–2.82 (m, 2H), 2.39–2.30 (m, 1H), 0.70 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3,

134.6, 133.9, 128.7 (2C), 126.8 (2C), 83.3, 37.1 34.8, 15.1; IR ($CHCl_3$): 3020, 2970, 1782, 1600, 1494, 1456, 1305, 1161 cm^{-1}; MS (70 eV) *m/z*: 210 (M^+, 35), 212 (9), 175 (10), 141 (85), 139 (91), 115 (15), 85 (68), 83 (100), 70 (48), 51 (19); HRMS calcd for $C_{11}H_{11}ClO_2$ (M^+): 210.0447, found 210.0452; Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.63; H, 5.41.

4.3.7. (1*R*,2*S*)-1-Acetoxy-1-cyclohexyl-2-methyl-3-phenylpropane 4f. Acetic anhydride (341 μL, 3.61 mmol) was added to a solution of **3Af** (300 mg, 0.72 mmol) and 4-dimethylaminopyridine (catalytic amount) in pyridine (3 mL), and the reaction mixture stirred for 2 h at room temperature. The reaction mixture was added into methanol at 0 °C, and concentrated in vacuo to give a crude material. It was subsequently added into a suspension of freshly prepared Raney Ni (W-2) in ethanol (30 mL), and the mixture stirred for 0.5 h at room temperature, and then the reaction mixture filtered through Celite (washing with methanol). The filtrate was concentrated in vacuo to give a residue, which was purified with silica gel column chromatography (hexane/ethyl acetate = 50:1) to give **4f** (192 mg, 97% over two steps). Colorless oil; $[\alpha]_D^{24} = -9.4$ (*c* 1.49, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.24 (m, 2H), 7.20–7.11 (m, 3H), 4.78 (dd, $J = 8.0$, 3.7 Hz, 1H), 2.68 (dd, A part of AB, $J_{AB} = 13.5$ Hz, $J = 4.9$ Hz, 1H), 2.28 (dd, B part of AB, $J_{AB} = 13.5$ Hz, $J = 9.4$ Hz, 1H), 2.11 (s, 3H), 2.11–2.02 (m, 1H), 1.76–1.53 (m, 6H), 1.27–1.06 (m, 3H), 1.04–0.89 (m, 2H), 0.82 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 140.7, 129.1 (2C), 128.2 (2C), 125.9, 80.4, 40.5, 39.2, 35.9, 29.4, 28.7, 26.3, 26.0, 25.9, 21.0, 13.0; IR ($CHCl_3$): 3010, 2933, 2854, 1724, 1602, 1494, 1450, 1371, 1251, 1018, 970 cm^{-1}; MS FAB(+) *m/z*: 297 (M^++Na, 100); HRMS calcd for $C_{18}H_{26}O_2Na$ (M^++Na): 297.1830, found 297.1834. [99% ee, chiral HPLC analysis; DAICEL CHIRALCEL OD (25 × 0.46); eluent: hexane/isopropanol = 500:1; flow rate: 1.0 mL/min; temp.: 27 °C; detector: 254 nm, (−): 8.6 min, (+): 9.8 min].

4.3.8. (3*S*,4*R*)-4-Cyclohexyl-3-methylbutan-4-olide 8f. Colorless prism; mp 74–75 °C (hexane); $[\alpha]_D^{24} = -53.2$ (*c* 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.02 (dd, $J = 9.8$, 4.7 Hz, 1H), 2.72 (dd, A part of AB, $J_{AB} = 16.8$ Hz, $J = 7.5$ Hz, 1H), 2.59–2.50 (m, 1H), 2.19 (dd, B part of AB, $J_{AB} = 16.8$ Hz, $J = 1.2$ Hz, 1H), 2.09–2.02 (m, 1H), 1.79–1.56 (m, 5H), 1.34–1.13 (m, 3H), 1.10–0.88 (m, 2H), 1.00 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 87.7, 38.7, 37.4, 32.0, 30.3, 28.0, 26.2, 25.4, 25.3, 13.5; IR ($CHCl_3$): 3035, 2931, 2856, 1770, 1463, 1450, 1421, 1176, 983, 975, 935 cm^{-1}; MS (70 eV) *m/z*: 182 (M^+, 1), 154 (13), 111 (17), 99 (100), 83 (53), 71 (41), 55 (57); HRMS calcd for $C_{11}H_{18}O_2$ (M^+): 182.1307, found 182.1305; Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.44; H, 9.94.

4.4. The asymmetric total synthesis of (−)-*cis*-whisky lactone 9

4.4.1. (2*S*,3*S*)-3-Acetoxy-2-methyl-1-phenylheptane 4d. Acetic anhydride (184 μL, 1.95 mmol) was added to a solution of **3Ad** (253 mg, 0.65 mmol) and 4-dimethylaminopyridine (catalytic amount) in pyridine (2 mL), and the reaction mixture stirred for 1 h at room temperature. The reaction mixture was added into methanol at 0 °C, and concentrated in vacuo to give a crude material. This was subsequently added into a suspension of freshly prepared Raney Ni (W-2) in ethanol (14 mL), and the mixture stirred for 0.5 h at room temperature and filtered through Celite (washing with methanol). The filtrate was concentrated in vacuo to give a residue, which was purified by silica gel column chromatography (hexane/ethyl acetate = 50:1) to give **4d** (145 mg, 89% over two steps). Colorless oil; $[\alpha]_D^{23} = -29.2$ (*c* 1.72, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.12 (m, 5H), 4.88 (ddd, $J = 8.2$, 4.8 and 4.0 Hz, 1H), 2.75 (dd, A part of AB, $J_{AB} = 13.4$ Hz, $J = 5.1$ Hz, 1H), 2.31 (dd, B part of AB, $J_{AB} = 13.4$ Hz, $J = 9.5$ Hz, 1H), 2.07 (s, 3H), 2.00–1.91 (m, 1H), 1.66–1.48 (m, 2H), 1.35–1.19 (m, 4H), 0.89 (t, $J = 7.0$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 140.7, 129.1 (2C), 128.2 (2C), 125.9, 77.0, 39.5, 38.5, 31.0, 27.9, 22.6, 21.2, 14.0, 13.9; IR ($CHCl_3$): 3035, 3012, 2958, 2935, 2826, 1724, 1600, 1496, 1454, 1373, 1257, 1018 cm^{-1}; MS FAB(+) *m/z*: 249 (M^++H, 57); HRMS calcd for $C_{16}H_{25}O_2$ (M^++H): 249.1855, found 249.1850. [99% ee, chiral HPLC analysis; DAICEL CHIRALCEL OD (25 × 0.46); eluent: hexane/isopropanol = 500:1; flow rate: 0.2 mL/min; temp.: 27 °C; detector: 254 nm, (−): 37.8 min, (+): 40.1 min].

4.4.2. (−)-*cis*-Whisky lactone 9.[15b,16] Ruthenium(III) chloride hydrate (21 mg, 0.10 mmol) and orthoperiodic acid (2.30 g, 10.01 mmol) were added to a biphasic solution of **4d** (125 mg, 0.50 mmol) in $CCl_4/CH_3CN/H_2O$ = 5:5:8 (9 mL), and the reaction mixture stirred for 20 h at room temperature. The reaction mixture was acidified with 1 M HCl aq to pH 1, and extracted with ethyl acetate three times. The combined organic layer was successively washed with saturated aqueous solution of sodium thiosulfate and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give crude (3*S*,4*S*)-4-acetoxy-3-methyloctanoic acid. Then, it was hydrolyzed with 1 M NaOH (5 mL) at room temperature for 1.5 h, and the reaction mixture acidified with 10% HCl aq to pH 1, and stirred for a further 2.5 h. The reaction mixture was neutralized with saturated aqueous solution of sodium bicarbonate, and extracted with ethyl acetate three times. The combined organic layer was successively washed with saturated aqueous solution of sodium thiosulfate and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give a residue. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1) to give (−)-*cis*-whisky lactone (63 mg, 62% yield from **4d**). Colorless oil; $[\alpha]_D^{24} = -76.9$ (*c* 1.73, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 4.46–4.41 (m, 1H), 2.69 (dd, A part of AB, $J_{AB} = 16.9$ Hz, $J = 7.9$ Hz, 1H), 2.63–2.53 (m, 1H), 2.20 (dd, B part of AB, $J_{AB} = 16.9$ Hz, $J = 4.0$ Hz, 1H), 1.71–1.30 (m, 6H), 1.01 (d, $J = 7.0$ Hz, 3H), 0.92 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 83.7, 37.5, 33.0, 29.5, 28.0, 22.5, 13.9, 13.8; IR ($CHCl_3$): 3006, 2960, 2873, 2862, 1770, 1456 cm^{-1}; MS CI(+) *m/z*: 157

(M^++H, 54); HRMS calcd for $C_9H_{17}O_2$ (M^++H): 157.1228, found 157.1237.

4.5. The asymmetric total synthesis of (−)-*cis*-cognac lactone 10

(−)-*cis*-Cognac lactone **10** was synthesized in the same way as (−)-*cis*-whisky lactone **9**.

4.5.1. (2*S*,3*S*)-3-Acetoxy-2-methyl-1-phenyloctane 4e. Ninety percent yield from **3Ae**. Colorless oil; $[\alpha]_D^{25} = -26.6$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.11 (m, 5H), 4.88 (ddd, J = 8.4, 4.8 and 3.8 Hz, 1H), 2.75 (dd, A part of AB, J_{AB} = 13.5 Hz, J = 5.1 Hz, 1H), 2.31 (dd, B part of AB, J_{AB} = 13.5 Hz, J = 9.4 Hz, 1H), 2.07 (s, 3H), 2.00–1.91 (m, 1H), 1.63–1.47 (m, 2H), 1.33–1.22 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 140.7, 129.1 (2C), 128.2 (2C), 125.9, 77.0, 39.5, 38.4, 31.7, 31.2, 25.3, 22.5, 21.2, 14.0, 13.9; IR ($CHCl_3$): 3062, 3035, 3012, 2954, 2931, 2858, 1724, 1600, 1496, 1458, 1373, 1253 cm^{-1}; MS FAB(+) *m*/*z*: 263 (M^++H, 39); HRMS calcd for $C_{17}H_{27}O_2$ (M^++H): 263.2011, found 263.2016. [99% ee, chiral HPLC analysis; DAICEL CHIRALCEL OD (25 × 0.46); eluent: hexane/isopropanol = 500:1; flow rate: 0.2 mL/min; temp.: 28 °C; detector: 254 nm, (−): 44.4 min, (+): 46.9 min].

4.5.2. (−)-*cis*-Cognac lactone 10.[15c,17] Seventy percent yield from **4e**. Colorless oil; $[\alpha]_D^{23} = -67.7$ (*c* 1.78, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46–4.41 (m, 1H), 2.69 (dd, A part of AB, J_{AB} = 16.8 Hz, J = 7.8 Hz, 1H), 2.63–2.53 (m, 1H), 2.20 (dd, B part of AB, J_{AB} = 16.8 Hz, J = 4.0 Hz, 1H), 1.69–1.25 (m, 8H), 1.01 (d, J = 7.1 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 83.7, 37.5, 33.0, 31.6, 29.8, 25.6, 22.5, 13.9, 13.8; IR ($CHCl_3$): 3035, 2954, 2931, 2862, 1766, 1461 cm^{-1}; MS CI(+) *m*/*z*: 171 (M^++H, 20); HRMS calcd for $C_{10}H_{19}O_2$ (M^++H): 171.1385, found 171.1393.

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