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Enantiodivergent synthesis of the key intermediate for a marine natural furanoterpene by chemoenzymatic process

Toshio Honda * and Tomoko Ogino

Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

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Abstract

A short chemoenzymatic route to both enantiomers of the key intermediate in the preparation of a marine natural furanoterpene was developed by employing a prochiral malonate derivative as a starting material.

1. Introduction

Many biologically active compounds containing a furan subunit with a benzylic quaternary carbon center have been discovered as natural products. For example, hippospongin A **1**,[1] and furanoterpenes **2**[2] and **3**[3] contain 7-methyl-7-substituted 4,5,6,7-tetrahydrobenzofuran units as part of their structures (Fig. 1). In searching the general synthetic route for these furanoterpenes, we concentrated our attention on the construction of a potential key intermediate **4** in an optically active form, since this unit seems to function as a common starting material. Recently we reported[4] an asymmetric synthetic procedure for the alcohol **5**, the key intermediate for the synthesis of a marine natural product, (−)-aphanorphine **6**, by a chemoenzymatic process using PLE as shown in Scheme 1. We thought that this procedure would be applicable to the synthesis of the target molecule **4**, because of the structural similarity between **4** and **5**. Our synthesis began with the preparation of dimethyl 4,5,6,7-tetrahydrofuran-7,7-dicarboxylate **11** having a prochiral center at the benzylic position as follows.

2. Results and discussion

Treatment of methyl 2-oxocyclohexanecarboxylate **7**[5] with methyl chloroformate in the presence of magnesium perchlorate[6] and sodium hydride in refluxing tetrahydrofuran afforded the dicarboxylate **8** in

* Corresponding author. E-mail: honda@hoshi.ac.jp

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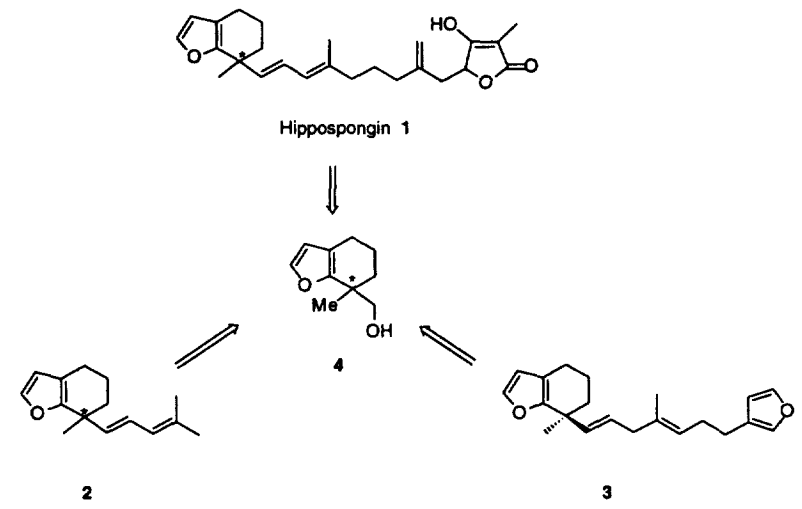
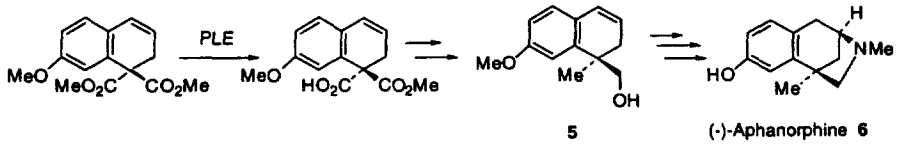


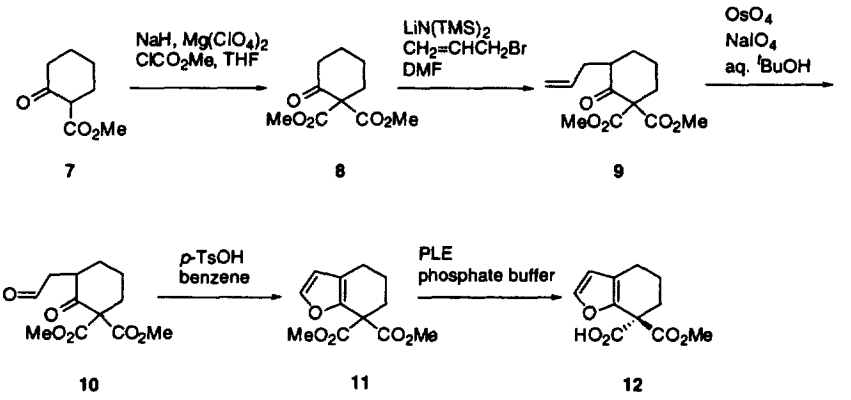
Fig. 1.



Scheme 1.

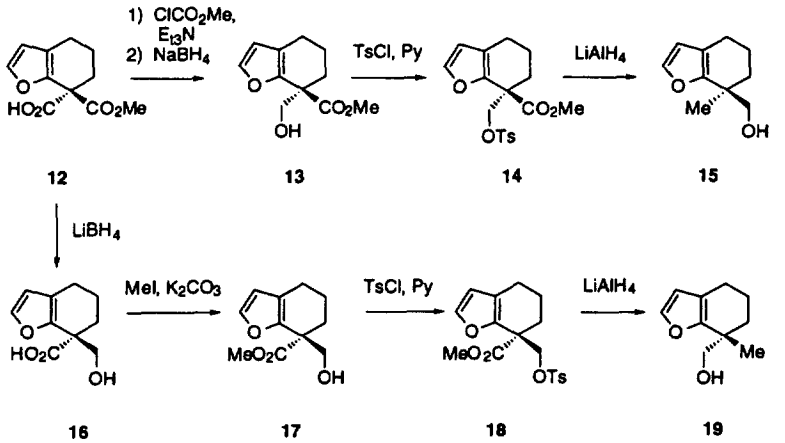
72% yield. Alkylation of the ketone **8** with allyl bromide in the presence of lithium hexamethyldisilazide in *N,N*-dimethylformamide at −30°C gave the allylated compound **9**, which on oxidative cleavage with osmium tetroxide and sodium periodate in *tert*-butyl alcohol–water afforded the aldehyde **10** in 92% yield from **8**. Treatment of the aldehyde **10** with *p*-toluenesulfonic acid in refluxing toluene in a Dean–Stark apparatus brought about furan formation to provide the desired starting material **11** in 83% yield. Incubation with PLE of the malonate derivative **11** in a 0.2 M phosphate buffer solution with 5% acetone between 15 and 20°C resulted in the desired acid–ester **12** in quantitative yield (Scheme 2). Although the absolute configuration at the newly created stereogenic center of **12** could not be determined at this stage, it was assumed to be *R* based on the proposed models for PLE hydrolysis of malonate derivatives[7] and also on our earlier work.[4] Because of the relative instability of **12** at room temperature, the enantiomeric excess from the enzymatic hydrolysis was determined after the reduction to the corresponding alcohol–ester **13**. The selective reduction of both acid and ester groups enabled the synthesis divergence for the preparation of both enantiomers of the product alcohol. Thus, reduction of the acid was carried out using sodium borohydride *via* the mixed anhydride, prepared from the acid with methyl chloroformate, to give the (*S*)-alcohol–ester **13**, mp: 56.5–56.8°C, $[\alpha]_D$ +17.9 (c=1.0, $CHCl_3$), in 71% yield.

The enantiomeric excess of **13** was determined to be 94% using Chiralcel OD. Whereas the reduction of the ester group of **12** was achieved by employing lithium borohydride to afford the (*R*)-alcohol–acid **16**, in 82% yield, which on esterification with methyl iodide and potassium carbonate furnished the (*R*)-alcohol–ester **17**, mp: 55–56°C; $[\alpha]_D$ −17.2 (c=0.8, $CHCl_3$), in 84% yield with 89% e.e. Both alcohols **13** and **17** were successfully converted into the corresponding primary alcohols **15** and **19**, by two steps involving tosylation with *p*-toluenesulfonyl chloride, followed by lithium aluminum hydride reduction of the tosylates **14** and **18** in 85% and 84% yields, respectively (Scheme 3). By comparison of the sign of rotations for the synthetic products **15**, $[\alpha]_D$ −13.5 (c=0.5, $CHCl_3$), and **19**, $[\alpha]_D$ +12.7 (c=0.1, $CHCl_3$),



Scheme 2.

with that of the known compound [lit.,[8] $[\alpha]_D$ +15.6 (c=0.87, $CHCl_3$)], their absolute stereochemistries can now be unambiguously assigned. The compound **19** has already been transformed to the antipode of **3**,[9] this synthesis thus constitutes its formal synthesis.



Scheme 3.

In summary, we have disclosed a short procedure for the preparation of both enantiomers of the key intermediate, in very high enantiomeric excess and chemical yield, for the synthesis of the furanoterpene **3** *via* asymmetric enzymatic hydrolysis and selective reduction. The synthesis of other furanoterpenes using the alcohol **15** or **19** is under investigation.

3. Experimental

3.1. General procedures

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded for thin films on a JASCO FT/IR-200 Fourier transform infrared spectrophotometer. ^1H and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX 270 instrument (270 MHz), and chemical shifts are reported in ppm on the δ-scale from internal Me_4Si. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter. All new compounds described in the Experimental section were homogeneous on TLC. E.e. determinations

were carried out using a 5% iso-propanol in *n*-hexane mobile phase with a Chiralcel OD (Daicel Chemical Industries Limited) on a Senshu HPLC.

3.2. *Dimethyl 2-oxocyclohexane-1,1-dicarboxylate* **8**

Compound **8**[6] was prepared from methyl 2-oxocyclohexanecarboxylate[5] and methyl chloroformate according to a previous report using NaH and magnesium perchlorate as the base in THF.

3.3. *Dimethyl 2-oxo-3-(2′-propenyl)cyclohexane-1,1-dicarboxylate* **9**

To a stirred solution of the ketone **8** (3 g, 14 mmol) in dry DMF (30 ml) was added 1 M solution of lithium hexamethyldisilazide in THF (15.5 ml, 15.5 mmol) at −30°C and the mixture was stirred at the same temperature for a further 1 h. To this solution was added allyl bromide (1.3 ml, 15.4 mmol) and the resulting mixture was stirred for 30 min at −30°C. The solution was poured into a saturated $KHSO_4$ solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:ethyl acetate (5:1, by volume) afforded the allylated compound **9** (3.4 g, 94%) as a colorless oil; IR ν_{max}: 2955, 1736, 1435, 1257 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.35–1.44 (1H, m, 4-H), 1.51–1.61 (1H, m, 5-H), 1.86–1.90 (1H, m, 5-H), 1.98–2.01 (1H, m, 1′-H), 2.09–2.15 (1H, m, 4-H), 2.28 (1H, ddd, J=4.0, 13.7, and 14.0 Hz, 6-H), 2.55–2.61 (1H, m, 1′-H), 2.62–2.67 (1H, m, 6-H), 2.67–2.73 (1H, m, 3-H), 3.79 (3H, s, OMe), 3.83 (3H, s, OMe), 5.01–5.09 (2H, m, 3′-H), 5.70–5.85 (1H, m, 2′-H); MS *m/z* (M^+) 254.1154. $C_{13}H_{18}O_5$ (M^+) requires 254.1155. Anal. calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.24; H, 7.13.

3.4. *Dimethyl 2-oxo-3-(2′-formylmethyl)cyclohexane-1,1-dicarboxylate* **10**

To a stirred solution of **9** (2.0 g, 7.9 mmol) in *tert*-butyl alcohol (10 ml) were successively added pyridine (2 ml, 23.7 mmol), osmium tetroxide [200 mg in *tert*-butyl alcohol (40 ml)], and 0.5 M $NaIO_4$ solution in water (47 ml, 23.7 mmol) at ambient temperature and the resulting mixture was stirred for 10 h at the same temperature. The mixture was treated with saturated $KHSO_4$ solution and extracted with chloroform. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:Et_2O (1:1, by volume) afforded the aldehyde **10** (2.0 g, 98%) as a colorless oil; IR ν_{max}: 2955, 2928, 2866, 2340, 1732, 1435, 1262 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.46–1.54 (1H, m, 4-H), 1.60–1.69 (1H, m, 5-H), 1.86–1.91 (1H, m, 5-H), 2.10–2.15 (1H, m, 4-H), 2.26–2.36 (2H, m, 6-H_2), 2.66–2.70 (1H, m, 1′-H), 2.98–3.01 (1H, m, 1′-H), 3.26–3.33 (1H, m, 3-H), 3.75 (3H, s, OMe), 3.77 (3H, s, OMe), 9.79 (1H, s, CHO); MS *m/z* (M^+-H_2O) 238.0845. $C_{12}H_{14}O_5$ (M^+-H_2O) requires 238.0842. Anal. calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.04; H, 6.29.

3.5. *Dimethyl 4,5,6,7-tetrahydrobenzofuran-7,7-dicarboxylate* **11**

A solution of the aldehyde **10** (184 mg, 0.7 mmol) in benzene (46 ml) in the presence of *p*-toluenesulfonic acid (137 mg, 0.7 mmol) was heated at reflux for 1 h. The mixture was treated with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:Et_2O (4:1, by volume) afforded **11** (142 mg, 83%)

as a colorless oil; IR ν_{max}: 2958, 1733, 1502, 1435, 1259 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.75–1.85 (2H, m, 5-H_2), 2.47–2.51 (2H, m, 6-H_2), 2.49 (2H, t, J=6.2 Hz, 4-H_2), 3.78 (6H, s, 2×OMe), 6.25 (1H, d, J=2.0 Hz, 3-H), 7.38 (1H, d, J=2.0 Hz, 2-H); MS *m/z* (M^+) 238.0840. $C_{12}H_{14}O_5$ (M^+) requires 238.0840. Anal. calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.66; H, 6.06.

3.6. (7R)-7-Methoxycarbonyl-4,5,6,7-tetrahydrobenzofuran-7-carboxylic acid 12

The diester **11** (100 mg, 0.42 mmol) was incubated with PLE (Amano, 29 mg) in a solution of 5% acetone in 0.2 M phosphate buffer (pH 7.2, 10 ml) at 15–20°C. After the stirring had been continued for 3 days, the reaction mixture was acidified by addition of 1 M $KHSO_4$ with ethyl acetate. The precipitated enzyme was removed by filtration and the filtrate was extracted with ethyl acetate. The organic layer was washed with 1 M $NaHCO_3$ solution to remove the acidic components and the aqueous layer was again acidified as before and re-extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was used in the next step without further purification; (*R*)-**12** (94 mg, 100%); IR ν_{max}: 3700–2220, 1732, 1503, 1437, 1260 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.80–1.88 (2H, m, 5-H_2), 2.35–2.43 (2H, m, 6-H_2), 2.50 (2H, t, J=6.3 Hz, 4-H_2), 3.80 (3H, s, OMe), 6.26 (1H, d, J=1.5 Hz, 3-H), 7.39 (1H, d, J=1.5 Hz, 2-H); MS *m/z* (M^+-44) 180.0782. $C_{10}H_{12}O_3$ (M^+-44) requires 180.0786.

3.7. (7S)-Methyl 7-hydroxymethyl-4,5,6,7-tetrahydrobenzofuran-7-carboxylate 13

To a stirred solution of the acid **12** (660 mg, 2.9 mmol) in dry THF (10 ml) were added triethylamine (0.45 ml, 3.2 mmol) and methyl chloroformate (0.25 ml, 3.2 mmol) dropwise at 0°C and the mixture was stirred for a further 1 h. After removal of the precipitated triethylamine hydrochloride by filtration, the filtrate was concentrated to give a residue, which was dissolved in MeOH (10 ml). $NaBH_4$ (120 mg, 3.2 mmol) was added portionwise to this solution at 0°C and the mixture was stirred for a further 1 h at the same temperature. After quenching the reaction by addition of saturated $KHSO_4$ solution, the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane:ethyl acetate (10:1, by volume) as eluent to give the alcohol–ester **13** (618 mg, 71%) as needles; mp: 56.5–56.8°C; $[\alpha]_D$ +17.9 (c=1.0, $CHCl_3$); IR ν_{max}: 3475, 2950, 1734, 1505, 1435, 1233, 1055, 893 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.74–1.97 (3H, m, 5-H_2 and 6-H), 2.17–2.25 (1H, m, 6-H), 2.46–2.56 (3H, m, 4-H_2 and OH), 3.73 (3H, s, OMe), 3.82 (1H, dd, J=9.5 and 10.2 Hz, C*H*HOH), 4.03 (1H, dd, J=4.7 and 10.2 Hz, C*H*HOH), 6.26 (1H, d, J=1.6 Hz, 3-H), 7.32 (1H, d, J=1.6 Hz, 2-H); ^{13}C-NMR ($CDCl_3$); 20.0, 21.7, 29.6, 49.7, 52.1, 66.4, 110.0, 119.6, 141.6, 147.7, 174.2; MS *m/z* (M^+) 210.0893. $C_{11}H_{14}O_4$ (M^+) requires 210.0885. Anal. calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.72; H, 6.68. The enantiomeric excess of **13** was determined to be 94% by using a 5% iso-propanol in *n*-hexane mobile phase with a Chiralcel OD (Daicel Chemical Industries Limited) on a Senshu HPLC.

3.8. (7S)-Methyl 7-p-tosyloxymethyl-4,5,6,7-tetrahydrobenzofuran-7-carboxylate 14

A solution of the alcohol **13** (100 mg, 0.48 mmol), triethylamine (0.2 ml, 1.44 mmol), *p*-toluenesulfonyl chloride (272 mg, 1.44 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (3 ml) was stirred for 2 h at room temperature. The mixture was diluted with CH_2Cl_2 and washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane:ethyl acetate (10:1, by volume) as eluent to give the tosylate

14 (618 mg, 71%) as an oil; IR ν_{max}: 2950, 1740, 1598, 1503, 1475, 1364, 1236, 1178, 1097, 992 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.75–1.90 (2H, m, 5-H_2), 2.25–2.43 (4H, m, 6-H_2 and 4-H_2), 2.46 (3H, s, Me), 3.64 (3H, s, OMe), 4.17 (1H, d, J=10.2 Hz, C*H*HOTs), 4.52 (1H, d, J=10.2 Hz, C*H*HOTs), 6.19 (1H, d, J=1.6 Hz, 3-H), 7.22 (1H, d, J=1.6 Hz, 2-H), 7.34 (2H, d, J=8.1 Hz, PhH), 7.74 (2H, d, J=8.1 Hz, PhH); ^{13}C-NMR ($CDCl_3$); 19.8, 21.4, 21.5, 29.5, 47.4, 52.4, 71.6, 110.3, 121.0, 127.8, 129.6, 132.4, 142.1, 144.7, 144.8, 171.1; MS *m/z* (M^+) 364.0978. $C_{18}H_{20}O_6S$ (M^+) requires 364.0980. Anal. calcd for $C_{18}H_{20}O_6S$: C, 59.33; H, 5.53. Found: C, 59.27; H, 5.74.

3.9. (7S)-4,5,6,7-Tetrahydro-7-methylbenzofuran-7-methanol **15**

To a stirred suspension of lithium aluminum hydride (100 mg, 2.76 mmol) in refluxing THF (5 ml) was slowly added a solution of the tosylate **14** (156 mg, 0.43 mmol) in THF (2 ml) and the mixture was stirred for a further 6 h. The mixture was treated with ethyl acetate and then with water, and the precipitate formed was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:ethyl acetate (10:1, by volume) gave the alcohol **15** (61 mg, 85%) as an oil; $[\alpha]_D$ −13.5 (c=0.5, $CHCl_3$); lit.,[8] $[\alpha]_D$ +15.6 (c=0.87, $CHCl_3$) for its antipode; IR ν_{max}: 3380, 2933, 1504, 1456, 1152, 1101, 1036, 891, 733 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.24 (3H, s, Me), 1.48–1.60 (2H, m, 5-H_2), 1.68–1.89 (3H, m, 6-H_2 and OH), 2.41 (2H, t, J=7.6 Hz, 4-H_2), 3.57 (1H, d, J=10.7 Hz, C*H*HOH), 3.68 (1H, d, J=10.7 Hz, C*H*HOH), 6.18 (1H, d, J=1.6 Hz, 3-H), 7.25 (1H, d, J=1.6 Hz, 2-H); ^{13}C-NMR ($CDCl_3$); 20.0, 22.4, 22.5, 33.6, 37.9, 70.1, 110.3, 117.9, 140.9, 154.4; MS *m/z* (M^+) 166.0995. $C_{18}H_{20}O_6$ (M^+) requires 166.0994.

3.10. (7R)-Hydroxymethyl-4,5,6,7-tetrahydrobenzofuran-7-carboxylic acid **16**

To a stirred solution of the ester **12** (416 mg, 1.8 mmol) in dry Et_2O (5 ml) was added lithium borohydride (400 mg, 18 mmol) portionwise at 0°C and the resulting mixture was stirred for a further 5 h at the same temperature. After addition of 1 M $KHSO_4$, the mixture was extracted with Et_2O and the extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using chloroform:MeOH (10:1, by volume) as eluent to give the acid **16** (299 mg, 82%) as an oil. This compound was used in the next step without further purification because of its instability.

3.11. (7R)-Methyl 7-hydroxymethyl-4,5,6,7-tetrahydrobenzofuran-7-carboxylate **17**

To a stirred solution of potassium carbonate (11 mg, 0.088 mmol) in HMPA (1 ml) was added a solution of iodomethane (0.02 ml, 0.32 mmol) and the acid **16** (15.6 mg, 0.08 mmol) in HMPA (1 ml) at room temperature and the resulting mixture was stirred for a further 2 h at ambient temperature. After treatment with water, the mixture was extracted with Et_2O and the extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane:ethyl acetate (3:1, by volume) as eluent to give the ester **17** (14.1 mg, 84%) as needles; mp: 55–56°C; $[\alpha]_D$ −17.2 (c=0.8, $CHCl_3$). The spectroscopic data except for the specific optical rotation were identical to those of **13**. The enantiomeric excess of **17** was determined to be 89% by using a 5% iso-propanol in *n*-hexane mobile phase with a Chiralcel OD (Daicel Chemical Industries Limited) on a Senshu HPLC.

3.12. (7R)-Methyl 7-p-tosyloxymethyl-4,5,6,7-tetrahydrobenzofuran-7-carboxylate **18**

Tosylation of **17** was carried out by using the same procedure as for the preparation of **14** to give **18** in 70% yield, whose spectroscopic data except for the specific optical rotation were identical with those of **14**.

3.13. (7R)-4,5,6,7-Tetrahydro-7-methylbenzofuran-7-methanol **19**

Reduction of **18** was carried out by using the same procedure as for the preparation of **15** to give **19**, $[\alpha]_D$ +12.7 (c=0.1, $CHCl_3$), lit.,[8] $[\alpha]_D$ +15.6 (c=0.87, $CHCl_3$), as an oil, in 84% yield, whose spectroscopic data except for the specific optical rotation were identical with those of **15**.

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References

1. Kato, Y.; Fesetani, N.; Matsunaga, S.; Hashimoto, K., *Experientia*, **1986**, *42*, 1299; Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y., *Tetrahedron Lett.*, **1986**, *27*, 2113.
2. Dimitriadis, E.; Massy-Westropp, R. A., *Aust. J. Chem.*, **1980**, *33*, 2729.
3. Kobayashi, M.; Chavakula, R.; Murata, O.; Sarma, N. S., *Chem. Pharm. Bull.*, **1992**, *40*, 599.
4. Hallinan, K. O.; Honda, T., *Tetrahedron*, **1995**, *51*, 12211.
5. Alderdice, M.; Sum, F. W.; Weiler, L., *Org. Synth. Coll. Vol. 7*, **1990**, 351.
6. Ferris, J. P.; Wright, B. G.; Crawford, C. C., *J. Org. Chem.*, **1965**, *30*, 2367.
7. De Jeso, B.; Belair, N.; Deleuze, H.; Rascle, M.-C.; Maillard, B., *Tetrahedron Lett.*, **1990**, *31*, 653; Toone, E. J.; Jones, J. B., *Tetrahedron: Asymmetry*, **1991**, *2*, 1041.
8. Shishido, K., personal communication.
9. Bando, T.; Shishido, K., *J. Chem. Soc., Chem. Commun.*, **1996**, 1357.