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Preparation of chiral building blocks for the enantioselective total synthesis of *ent*-kauranoids by the pig liver esterase-catalyzed asymmetric hydrolysis of a dialkyl malonate-type prochiral diester

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ABSTRACT

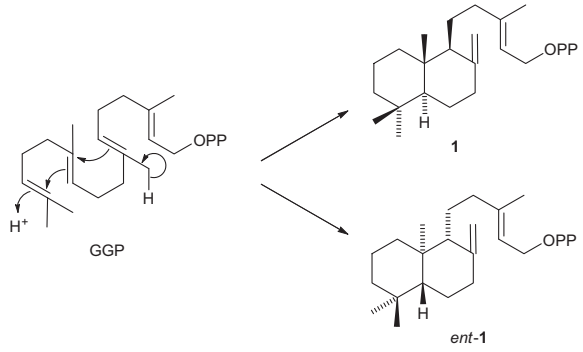
The preparation of chiral building blocks, suitable for use in the enantioselective total synthesis of kauranoids and *ent*-kauranoids, is reported herein. The pig liver esterase-catalyzed asymmetric hydrolysis of dimethyl 3,3-dimethyl-2-methylenecyclohexane-1,2-dicarboxylate, a malonate-type prochiral diester, afforded the corresponding half-ester in 96% yield and with 99% enantiomeric excess. The absolute configuration of the half-ester was determined by X-ray crystallographic analysis of its derivative and its enantiodivergent transformations are also described herein.

1. Introduction

Isodon is a genus of the Lamiaceae family; it has been traditionally used in Chinese folk medicine. Terpenoids with diverse structures and interesting biological activities, such as antibacterial, anti-inflammatory, and antitumor activities, have been isolated from *Isodon*. More than 60 *Isodon* species from China have been phytochemically investigated while more than 600 new diterpenoids, such as abietanes, labdanes, pimaranes, isopimaranes, gibberellanes, and clerodanes, but mainly *ent*-kauranoids, have been isolated and characterized.[1]

In biogenetics, the protonation of a terminal trisubstituted alkene of geranylgeranyl pyrophosphate (GGP) leads to a cascade cyclization to afford two enantiomeric *trans*-decalin derivatives (Scheme 1, compounds **1** and *ent*-**1**). Furthermore, the divergent biogenetic conversions of compound **1** afford diterpenes such as beyeranes, kauranes, and pimaranes, whereas those from compound *ent*-**1** afford the corresponding enantiomers (Fig. 1).[2]

Certain *ent*-kauranoids possess the common polycarbocyclic scaffold, featuring a unique carbocyclic ring system consisting of a *trans*-decalin skeleton with a *cis*-fused bicyclo[3.2.1]octane core (Fig. 1). The ABC-ring of the *ent*-kaurane scaffold has a *trans–anti–cis* tricyclic ring system with three all-carbon quaternary centers, two of which are stereogenic and embedded at the ring junctions.



Scheme 1. Proposed biogenetic formation of **1** and *ent*-**1** from geranylgeranyl pyrophosphate (GGP).

Xerophilusin B **2** and macrocalin B **3** (Fig. 2), isolated from *Isodon xerophylus*, belong to *ent*-kauranoids, and their structures have been established by various spectroscopic and X-ray crystallographic analyses.[3–5] Compounds **2** and **3** significantly inhibit the proliferation of some tumor cell lines such as K562, HL-60, A549, MKN, HCT, and CA in vitro.[6] Compounds **2** and **3** markedly inhibit the telomerase activity in K562 cells below a concentration of 10^{-4}–10^{-8} mol/L; this effect is exhibited in a dose-dependent manner.

The unique structure and potent cytotoxic activity of compounds **2** and **3** inspired us to study their synthesis. Compound **3** has the same structure as compound **2** except for an extra hydroxyl group. Therefore, we decided to pursue the total synthesis of

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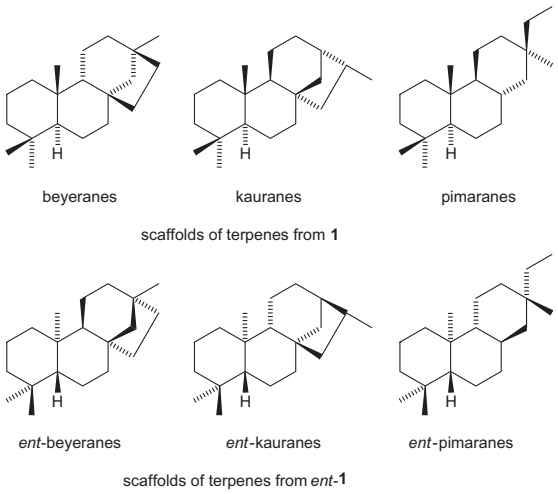


Figure 1. Scaffolds of terpenes from **1** and *ent*–**1**.

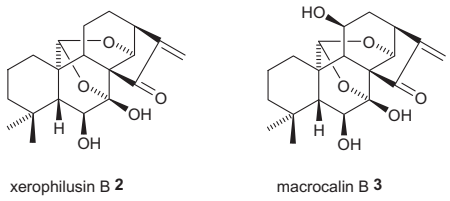


Figure 2. Structures of xerophilsin B **2** and macrocalin B **3**.

compounds **2** and **3** via a divergent approach; that is, by employing the same starting material or intermediate for both syntheses. It is important to synthesize a bioactive compound in an enantiopure form because of the close relationship between the chirality and the corresponding bioactivity. In general, chiral compounds, suitable for use in the enantioselective total synthesis of complex molecules, are limited; therefore, when unsuitable chiral compounds are used as starting materials, many steps are inevitably required to complete the total synthesis.

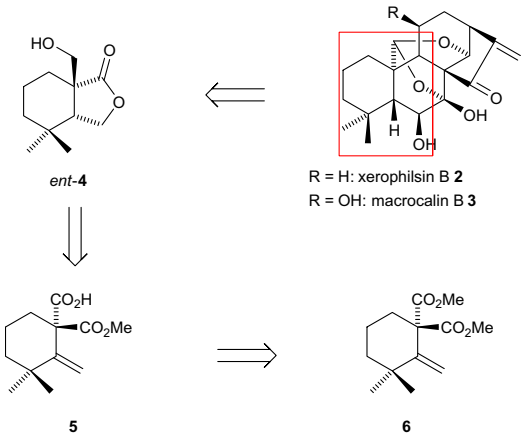
Thus, the preparation of a new enantiopure compound that is suitable for use in a planned total synthesis should reduce the number of steps in the total synthesis, thereby improving the efficiency. For this purpose, we have prepared new chiral building blocks and demonstrated their utility for the enantioselective total synthesis of certain natural products. Herein we report the preparation of new chiral building blocks via the pig liver esterase (PLE)-catalyzed asymmetric hydrolysis of dimethyl 3,3-dimethyl-2-methylenecyclohexane-1,2-dicarboxylate, which are suitable for use in the enantioselective total synthesis of compounds **2** and **3**, and other bioactive terpenes.

2. Results and discussion

Chiral compounds have been prepared by diverse methods, for example, (i) from chiral pools such as amino acids, sugars, and terpenes; (ii) asymmetric synthesis from prochiral compounds; and (iii) resolution of racemic compounds.[7] Among these methods, biocatalytic transformations are advantageous because of the mild reaction conditions that do not require anhydrous or toxic reagents, organic solvents, or an inert atmosphere. They also meet the requirements of environmentally benign processes because they do not produce toxic effluents or by-products.[8] Enzyme-catalyzed transformations are easy to scale-up; therefore, they have also been utilized in industrial-scale syntheses. An enzyme usually catalyzes the reaction of a specific substrate; however, certain enzymes exceptionally catalyze diverse substrates and have been utilized to prepare many new chiral compounds. Among the many biocatalysts, lipase and PLE have been widely used in the preparation of chiral compounds;[9,10] baker's yeast also shows a broad applicability although it is a single-celled microorganism.[11]

PLE shows low substrate specificity and has been utilized in the catalytic asymmetric hydrolysis of prochiral diesters and in the kinetic resolution of racemic esters.[12] Although many successful applications of PLE have been reported, further improvements are possible. In this regard, when a new prochiral diester is designed, it may be possible to prepare the corresponding half-ester by the PLE-catalyzed asymmetric hydrolysis.

We envisioned that the structures of **2** and **3** are comprised of a common chiral unit (the moiety surrounded by the red line in Scheme 2) with a hidden σ-symmetry. Therefore, lactone *ent*-**4** was expected to be a good intermediate because it possesses appropriate functionality that can be independently converted into other functional groups. Lactone *ent*-**4** can be formed by the stereoselective transformation of compound **5**, which can be retrosynthetically converted into the corresponding prochiral diester **6**. Thus, the PLE-catalyzed asymmetric hydrolysis of **6** may afford the corresponding chiral half-ester.

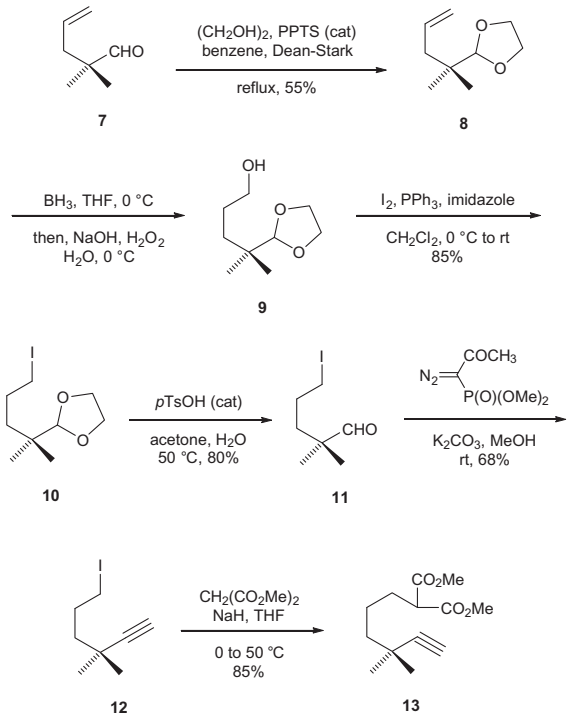


Scheme 2. Retrosynthetic analysis of xerophilsin B **2** and macrocalin B **3**.

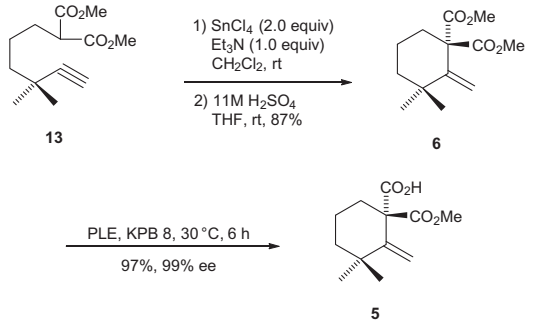
The yield and enantioselectivity of the PLE-catalyzed reaction are difficult to predict. However, we have previously observed that the PLE-catalyzed asymmetric hydrolysis of malonate-type diesters proceeds in quantitative yield and with excellent enantioselectivity.[13] Therefore, we decided to examine the PLE-catalyzed asymmetric hydrolysis of the prochiral diester **6**, which can be obtained by the intramolecular cyclization of compound **13** (Scheme 3). Consequently, the preparation of **13** was first examined.

The preparation of compound **13** commenced with the ethylene acetal formation of the known aldehyde **7**, which was prepared by the Claisen rearrangement of the allyl alkenyl ether generated by the acid-catalyzed reaction of 2-methylpropyl aldehyde and allyl alcohol under dehydrative conditions.[14] Aldehyde **7** was converted into ethylene acetal **8**. Next, the hydroboration and subsequent work-up with hydrogen peroxide under basic conditions afforded alcohol **9**, which was then converted into iodide **10** under standard reaction conditions. Next, the ethylene acetal of compound **10** was removed to afford aldehyde **11**, followed by reaction with an Ohira–Bestmann reagent to afford compound **12**. The subsequent reaction with dimethyl malonate and sodium hydride afforded compound **13**.

Next, the 6-*exo*-*dig* cyclization of compound **13** was examined (Scheme 4). The Tamura protocol[15] was employed for the



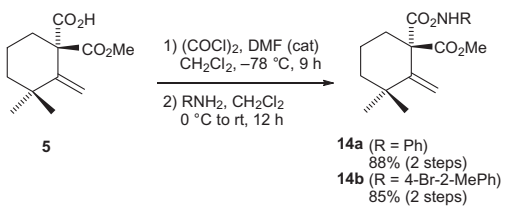
Scheme 3. Preparation of **13**.



Scheme 4. Preparation and the PLE-catalyzed asymmetric hydrolysis of **6**.

cyclization of compound **13** to efficiently afford prochiral diester **6**. The PLE-catalyzed asymmetric hydrolysis of prochiral diester **6** under standard reaction conditions[13] smoothly afforded half-ester **5** in 96% yield. No decarboxylation was observed during the reaction or work-up.

Half-ester **5** was converted into the corresponding anilide **14a** to determine the enantiomeric excess (ee) by HPLC analysis using a chiral column (Scheme 5); the half-ester was found to be formed with 99% ee. Next, half-ester **5** was converted into 4-bromo-2-methyl anilide **14b**. The recrystallization of **14b** afforded a crystal suitable for X-ray crystallographic analysis.[16] The crystal structure of compound **14b** (Fig. 3) indicated the absolute configuration of the half-ester **5** as shown in Scheme 5.



Scheme 5. Preparation of **14a** and **14b** from **5**.

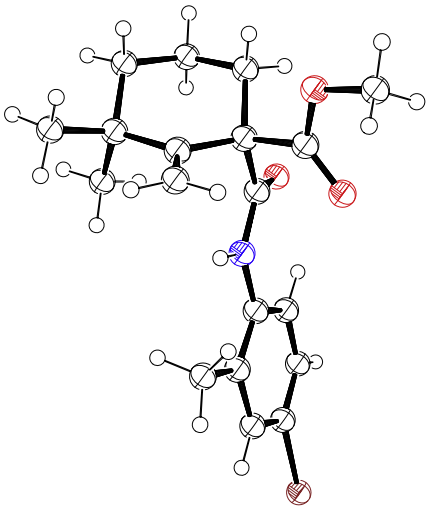
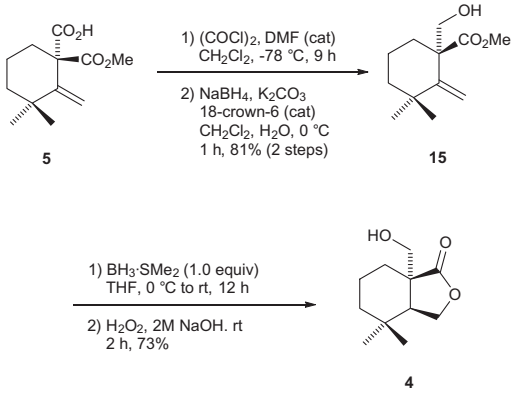


Figure 3. X-ray crystallographic structure of **14b**.

In order to utilize compound **5** for the total synthesis of the kauranoids, its functionalities were transformed in further conversions (Scheme 6). Compound **5** was successfully converted into the corresponding alcohol **15** by the formation of the corresponding acid chloride and subsequent reduction with sodium borohydride.

In order to generate the stereogenic center adjacent to the quaternary stereogenic center in compound **15**, the stereoselective transformation of the alkene in compound **15** was examined. After several experiments, the hydroboration of compound **15** with borane–dimethyl sulfide complex followed by treatment with an aqueous hydrogen peroxide solution under basic conditions afforded lactone **4** as the sole product. This high stereoselectivity is attributed to the directing effect of the hydroxyl group.

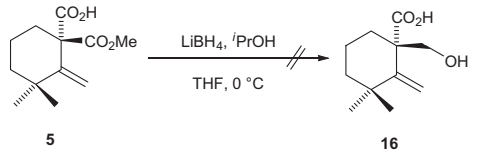


Scheme 6. Transformation of **5** into **4**.

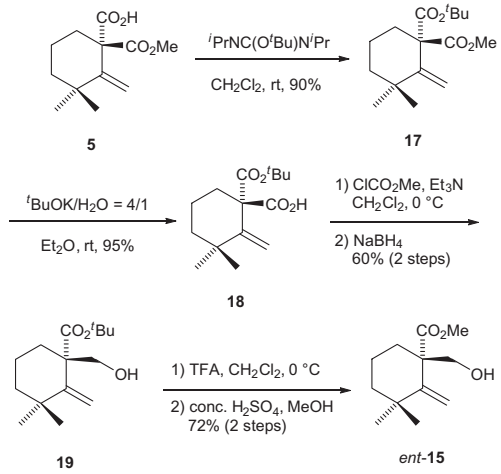
Next, we examined an enantiodivergent approach from **5** to *ent*-**4**. The chemoselective reduction of the methyl ester **5** using $LiBH_4$ and $^{i}PrOH$[17] in THF to prepare **16** was attempted (Scheme 7); however, the reaction only afforded the compound derived from decarboxylation and reduction. Consequently, compound **5** was converted into the corresponding *tert*-butyl ester **17** via reaction

with the reported reagent[18] (Scheme 8), and then the selective hydrolysis of the methyl ester in compound **17** was examined. In general, hydrolysis of methyl esters at an all-carbon quaternary stereogenic center proceeds sluggishly under basic conditions; moreover, in this case, a bulky *tert*-butyl ester group was one of the substituents at the all-carbon quaternary center. Therefore, the hydrolysis of compound **17** required special conditions.

Indeed, the reaction of compound **17** under the usual basic conditions failed with the starting material being quantitatively recovered. After an extensive survey of reaction conditions, the hydrolysis of compound **17** with 'anhydrous KOH'[19] efficiently afforded compound **18** in 95% yield. No decarboxylation was observed during the hydrolysis.



Scheme 7. Attempted chemoselective reduction of **5** to prepare **16**.



Scheme 8. Transformation of **5** to *ent*-**15**.

Compound **18** was successfully converted into alcohol **19** by reduction of the mixed acid anhydride, which was formed by the reaction of compound **18** with methyl chloroformate. The mixed acid anhydride was relatively stable and observed as a single spot on the TLC plate, probably because of the diminished reactivity of the mixed acid anhydride caused by the steric hindrance arising from the all-carbon quaternary center and the *tert*-butyl ester. Treatment of compound **19** with trifluoroacetic acid and subsequent conversion into the methyl ester *ent*-**15** was successfully carried out under conventional reaction conditions as shown in Scheme 8. Transformation of *ent*-**15** into *ent*-**4** can be carried out according to the procedure in Scheme 6. Therefore, the formal preparation of *ent*-**4**, which is a synthetic intermediate for the total synthesis of *ent*-kauranoids, was achieved.

3. Conclusion

In conclusion, we found that the PLE-catalyzed asymmetric hydrolysis of dimethyl 3,3-dimethyl-2-methylenecyclohexane-1,2-dicarboxylate, a prochiral diester, afforded the corresponding half-ester in 96% yield and with 99% ee. The absolute configuration of the half-ester was successfully established by X-ray crystallographic analysis. The transformations of the half-ester into (3a*S*,7a*R*)-7a-hydroxymethyl-4,4-dimethylhexahydroisobenzofuran-1(3*H*)-one and its enantiomeric synthetic intermediate were successfully established. The chiral building blocks prepared herein will be useful for the enantioselective total synthesis of *ent*-kauranoids and other natural products.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on JEOL AL-400 spectrometers. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as the internal standards. The following abbreviations are used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; br, broad. IR spectra were recorded on a JASCO FT/IR-8300. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a JASCO DIP-1000. Chiral HPLC analysis was performed on a JASCO PU-980 and UV-970. Mass spectra and elemental analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254). Pig liver esterase was purchased from Sigma–Aldrich, and all other reagents were purchased from Aldrich, TCI, or Kanto Chemical Co. Ltd.

4.2. Preparation of 6

Di-ester **6** was prepared from known **9**.[20]

4.2.1. 2-(5-Iodo-2-methylpentan-2-yl)-1,3-dioxolane 10

To a stirred solution of imidazole (3.91 g, 57.4 mmol, 2.0 equiv) and PPh_3 (9.03 g, 34.4 mmol, 1.2 equiv) in CH_2Cl_2 (140 mL) was added I_2 (8.01 g, 31.6 mmol, 1.1 equiv), and the reaction mixture was stirred at room temperature for 5 min. Then, to the reaction mixture was added **9**[15] (5.00 g, 28.7 mmol) in CH_2Cl_2 (8 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 2 h. After the disappearance of the starting material, to the reaction mixture was added H_2O (140 mL), the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2), and the combined organic layer was washed with brine (50 mL × 1), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 40:1) to afford product **10** (6.93 g, 24.4 mmol, 85%) as a colorless oil: R_f = 0.72 (hexane/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (1H, s), 3.93 (1H, m), 3.86 (1H, m), 3.16 (2H, t, J = 7.2 Hz), 1.91–1.36 (2H, m), 1.43–1.36 (2H, m), 0.90 (6H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 109.7, 65.2, 38.6, 36.8, 28.4, 21.6, 7.7; IR (neat) ν_{max} 2957, 2874, 1474, 1397, 1360, 1294, 1210, 1161, 1106, 1037, 1003, 950 cm^{-1}.

4.2.2. 5-Iodo-2,2-dimethylpentanal 11

To a stirred solution of **10** (6.72 g, 23.7 mmol) in acetone/H_2O (1:1 volume, 120 mL) was added *p*-toluenesulfonic acid (1.80 g, 9.46 mmol, 0.4 equiv), and the reaction mixture was stirred at 50 °C for 10 h. After the disappearance of the starting material, to the reaction mixture was added saturated aqueous $NaHCO_3$

solution (100 mL). The aqueous layer was extracted with Et_2O (50 mL × 2), and the combined organic layer was washed with brine (50 mL × 1), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 40:1) to afford product **11** (4.55 g, 19.0 mmol, 80%) as a colorless oil: R_f = 0.69 (benzene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (1H, s), 3.16 (2H, t, J = 6.8 Hz), 1.80–1.70 (2H, m), 1.61–1.52 (2H, m), 1.07 (6H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 205.6, 45.4, 37.8, 28.4, 21.6, 21.4, 6.5; IR (neat) ν_{max} 2960, 2700, 2153, 1985, 1725, 1469, 1397, 1207, 1109, 1008, 947 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_7H_{13}IO$: 241.0084, found: 241.0084.

4.2.3. Dimethyl 2-(4,4-dimethylhex-5-ynyl)malonate 13

To a stirred solution of **11** (1.67 g, 6.96 mmol) in methanol (140 mL) were added potassium carbonate (1.92 g, 13.9 mmol, 2.0 equiv) and Ohira–Bestmann reagent (1.45 g, 8.37 mmol, 1.2 equiv), and the reaction mixture was stirred at room temperature for 12 h. After the disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (140 mL). The aqueous layer was extracted with Et_2O (50 mL × 2), and the combined organic layer was washed with brine (50 mL × 1), dried over Na_2SO_4, and evaporated. The residue was purified by short flash chromatography (hexane/ethyl acetate = 50:1) to afford product **12** (1.12 g, 4.74 mmol, 68%) as a colorless oil, which was immediately used for the next reaction: R_f = 0.8 (hexane/ethyl acetate=10:1). To a stirred solution of NaH (0.145 g, 6.04 mmol, 1.3 equiv) in THF (40 mL) was added dimethyl malonate (0.69 mL, 6.04 mmol, 1.3 equiv) at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min. To the reaction mixture was added **12** (1.10 g, 4.65 mmol) in THF (20 mL), after which the reaction mixture was stirred at 50 °C for 4 h. After the disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (40 mL). The aqueous layer was extracted with Et_2O (20 mL × 2), and the combined organic layer was washed with brine (20 mL × 1), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 20:1) to afford the product **13** (0.951 g, 3.96 mmol, 85%) as a colorless oil: R_f = 0.6 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (6H, s), 3.40 (2H, t, J = 7.6 Hz), 2.07 (1H, s), 1.95 (2H, m), 1.52–1.34 (4H, m), 1.19 (6H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.9, 91.5, 68.0, 52.4, 51.6, 42.5, 30.8, 29.1, 29.0, 23.1; IR (neat) ν_{max} 3303, 2955, 1733, 1436, 1355, 1260, 1238, 1198, 1154, 1051, 1015, 912 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{13}H_{20}O_4Na$: 263.1253, found: 263.1254.

4.2.4. Dimethyl 3,3-dimethyl-2-methylenecyclohexane-1,1-dicarboxylate 6

To a stirred solution of **13** (0.105 g, 0.435 mmol) in CH_2Cl_2 (4.4 mL) were added triethylamine (0.061 mL, 0.435 mmol, 1.0 equiv) and $SnCl_4$ (0.1 mL, 0.871 mmol, 2.0 equiv), and the reaction mixture was stirred at room temperature for 14 h. To the reaction mixture were added THF (5.0 mL) and 5.5 M H_2SO_4 (2.5 mL), after which the reaction mixture was stirred at room temperature for 1 h. Next, the aqueous layer was extracted with Et_2O (10 mL × 2), and the combined organic layer was washed with brine (10 mL × 1), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 25:1) to afford product **6** (0.091 g, 0.379 mmol, 87%) as a colorless oil: R_f = 0.7 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, s), 4.79 (1H, s), 3.75 (6H, s), 2.22 (2H, t, J = 5.9 Hz), 1.65 (2H, tt, J = 5.9, 5.4 Hz), 1.44 (2H, t, J = 5.4 Hz), 1.05 (6H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.2, 151.0, 113.5, 62.2, 52.6, 40.1, 36.8, 33.2, 29.7, 18.7; IR (neat) ν_{max} 2950, 1726, 1634, 1433, 1383, 1363, 1245, 1225, 1206, 1140, 1113, 1062, 1032, 1019, 991 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{13}H_{20}O_4Na$: 263.1254, found: 263.1254.

4.3. PLE-catalyzed asymmetric hydrolysis of 6

To a stirred solution of **6** (0.0174 g, 0.0724 mmol) in potassium phosphate buffer (KPB, pH 8.0, 1.5 mL) was added PLE (165 units), and the reaction mixture was stirred at 30 °C for 6 h. To the reaction mixture was added 2 M HCl to make the pH of the solution equal to pH 1. The aqueous layer was extracted with ethyl acetate (5 mL × 2), and the combined organic layer was washed with brine (5 mL × 1), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 3/1) to afford product **5** (0.016 g, 0.0707 mmol, 97%) as a white solid. R_f = 0.3 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (1H, s), 4.93 (1H, s), 3.76 (3H, s), 2.31 (1H, ddd, J = 13.3, 6.0, 6.0 Hz), 2.18 (1H, ddd, J = 13.3, 6.4, 6.4 Hz), 1.72–1.63 (2H, m), 1.48–1.40 (2H, m), 1.11 (3H, s), 1.05 (3H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.6, 171.7, 150.4, 113.8, 62.0, 52.7, 39.8, 36.7, 32.8, 29.9, 29.4, 18.5; IR (neat) ν_{max} 2950, 1731, 1702, 1633, 1435, 1383, 1364, 1244, 1204, 1165, 1141, 1111, 1061, 1019, 989 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{12}H_{18}O_4Na$: 249.1097, found: 249.1097; $[\alpha]_D^{23} = -18.6$ (c 0.80, $CHCl_3$), mp 72.4 °C.

4.3.1. (*S*)-Methyl 3,3-dimethyl-2-methylene-1-(phenylcarbamoyl) cyclohexanecarboxylate 14a

To a stirred solution of **5** (0.0255 g, 0.113 mmol) in CH_2Cl_2 (1.1 mL) were added $(COCl)_2$ (0.019 mL, 0.225 mmol, 2.0 equiv) and DMF (1 drop) at −78 °C, and the reaction mixture was stirred at −78 °C for 9 h. The reaction mixture was dried under reduced pressure, and to the residue were added CH_2Cl_2 (1.1 mL) and aniline (0.021 mL, 0.225 mmol, 2.0 equiv), and the reaction mixture was stirred at room temperature for 8 h. Next, to the reaction mixture was added saturated aqueous NH_4Cl solution (5.0 mL). The aqueous layer was extracted with Et_2O (10 mL × 2), and the combined organic layer was washed with 2 M HCl (10 mL × 1), saturated aqueous $NaHCO_3$ solution (10 mL × 1), brine (10 mL × 1), dried over Na_2SO_4, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 4:1 × 2) to afford product **14a** (0.030 g, 0.0996 mmol, 88%) as a white solid: R_f = 0.7 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, br), 7.50 (2H, d, J = 7.7 Hz), 7.33 (2H, dd, J = 7.7, 7.7 Hz), 7.11 (2H, d, J = 7.7 Hz), 5.42 (1H, s), 5.07 (1H, s), 3.76 (3H, s), 2.63 (1H, ddd, J = 13.6, 4.5, 4.5 Hz), 2.09 (1H, ddd, J = 13.6, 5.0, 5.0 Hz), 1.82–1.62 (2H, m), 1.51–1.46 (2H, m), 1.18 (3H, s), 1.10 (3H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.0, 167.2, 154.7, 137.5, 129.0, 124.4, 119.7, 113.8, 63.3, 52.9, 40.0, 37.4, 31.9, 31.5, 30.6, 29.8, 29.7, 18.5; IR (neat) ν_{max} 3397, 2950, 2917, 2849, 2150, 2027, 1728, 1691, 1598, 1527, 1500, 1463, 1440, 1382, 1364, 1313, 1242, 1177, 1143, 1111, 1079, 1061, 1029, 960 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{18}H_{23}O_3NNa$: 324.1569, found: 324.1570; $[\alpha]_D^{22} = +77.7$ (c 0.39, $CHCl_3$), mp 57.4 °C. HPLC: chiralpak OD-3 (hexane/2-PrOH = 9:1, 0.5 mL/min); t_R 12.1, 15.1 min, 99% ee. The peaks were confirmed by HPLC of the racemic sample.

4.3.2. (*S*)-Methyl 1-(4-bromo-2-methylphenylcarbamoyl)-3,3-dimethyl-2-methylenecyclohexanecarboxylate 14b

To a stirred solution of **5** (0.0226 g, 0.0999 mmol) in CH_2Cl_2 (1.0 mL) were added $(COCl)_2$ (0.017 mL, 0.200 mmol, 2.0 equiv) and DMF (1 drop) at −78 °C, and the reaction mixture was stirred at −78 °C for 9 h. The reaction mixture was dried under reduced pressure, and to the residue were added CH_2Cl_2 (1.0 mL), triethylamine (0.028 mL, 0.200 mmol, 2.0 equiv), and 4-bromo-2-methyl aniline (0.0372 mg, 0.200 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 10 h. Then, to the reaction mixture was added saturated aqueous NH_4Cl solution (10 mL), and the aqueous layer was extracted with Et_2O (10 mL × 2), and the combined organic layer was washed with 2 M HCl (10 mL × 1), saturated aqueous $NaHCO_3$ solution (10 mL × 1),

brine (10 mL × 1), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 10:1) to afford product **14b** (0.0335 g, 0.0849 mmol, 85%) as a white solid: R_f = 0.8 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, s), 7.95 (1H, d, J = 8.6 Hz), 7.36–7.29 (2H, m), 5.41 (1H, s), 5.11 (1H, s), 3.77 (3H, s), 2.63 (1H, ddd, J = 13.6, 4.5, 4.5 Hz), 2.20 (3H, s), 2.09 (1H, ddd, J = 13.6, 5.0, 5.0 Hz), 1.83–1.63 (2H, m), 1.52–1.46 (2H, m), 1.19 (3H, s), 1.10 (3H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.0, 167.0, 155.1, 135.1, 133.0, 129.8, 122.7, 117.2, 113.5, 63.3, 52.9, 39.8, 37.4, 31.2, 30.5, 30.1, 18.4, 17.4; IR (neat) ν_{max} 3411, 2949, 1961, 1739, 1724, 1694, 1625, 1602, 1578, 1518, 1437, 1397, 1364, 1301, 1242, 1185, 1143, 1124, 1060, 1029, 960 cm^{-1}; HRMS-ESI [M+Na]$^+$ calculated for $C_{19}H_{24}O_3NBrNa$: 416.0830, found: 416.0832; $[\alpha]_D^{23} = +100.7$ (c 0.60, $CHCl_3$), mp 112.2 °C.

4.3.3. (*R*)-Methyl 1-hydroxymethyl-3,3-dimethyl-2-methylenecyclohexanecarboxylate 15

To a stirred solution of **5** (0.020 g, 0.0884 mmol) in CH_2Cl_2 (1.0 mL) were added $(COCl)_2$ (0.015 mL, 0.177 mmol, 2.0 equiv) and DMF (1 drop) at −78 °C, and the reaction mixture was stirred at −78 °C for 9 h. The reaction mixture was dried under reduced pressure, and the residue in CH_2Cl_2 (1.0 mL) was added to a mixture of 18-crown-6 (0.0047 mg, 0.0177 mmol, 0.2 equiv), K_2CO_3 (0.0244 g, 0.177 mmol, 2.0 equiv), and $NaBH_4$ (0.0074 g, 0.194 mmol, 2.2 equiv) in CH_2Cl_2/H_2O (1:1 volume, 2.0 mL). The reaction mixture was stirred for 1 h at 0 °C. Then, to the reaction mixture was added H_2O (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL × 2), and the combined organic layer was washed with brine (5 mL × 1), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5:1) to afford product **15** (0.0152 g, 0.0716 mmol, 81%) as a white solid: R_f = 0.5 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (1H, s), 4.88 (1H, s), 3.91 (1H, d, J = 10.9 Hz), 3.72 (1H, d, J = 10.9 Hz), 5.41 (1H, s), 3.69 (3H, s), 2.30 (1H, ddd, J = 13.1, 5.0, 5.0 Hz), 2.19 (1H, br), 1.83 (1H, m), 1.60 (1H, m), 1.53–1.43 (2H, m), 1.35 (1H, m), 1.12 (3H, s), 1.00 (3H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 176.0, 153.4, 110.3, 68.6, 53.7, 52.2, 40.5, 36.9, 31.2, 31.0, 28.7, 18.6; IR (neat) ν_{max} 3467, 2950, 2846, 1728, 1628, 1434, 1381, 1302, 1269, 1202, 1134, 1055, 1032, 1012, 990 cm^{-1}; HRMS-ESI [M+Na]$^+$ calculated for $C_{12}H_{20}O_3Na$: 235.1305, found: 235.1305; $[\alpha]_D^{23} = -61.9$ (c 1.5, $CHCl_3$).

4.3.4. (3a*S*,7a*R*)-7a-Hydroxymethyl-4,4-dimethyl-hexahydroisobenzofuran-1(3H)-one 4

To a stirred solution of **15** (0.0139 g, 0.0614 mmol) in THF (1.0 mL) was added BH_3SMe_2 (0.002 mL, 0.0614 mmol, 1.0 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 10 h. To the reaction mixture were added H_2O (2 drops) and 30% H_2O_2 (0.5 mL), 2 M NaOH (0.5 mL), and the reaction mixture was stirred at room temperature for 2 h. Then, to the reaction mixture was added saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with ethyl acetate (5 ml × 2), washed with saturated aqueous $Na_2S_2O_3$ solution (5 mL × 1), brine (5 mL × 1), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 6:1) to afford product **4** (0.009 g, 0.0455 mmol, 73%) as a colorless oil; R_f = 0.4 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (1H, dd, J = 9.1, 8.6 Hz), 4.10 (1H, dd, J = 11.3, 9.1 Hz), 3.97 (1H, d, J = 11.3 Hz), 3.76 (1H, d, J = 11.3 Hz), 2.54 (1H, br), 2.40 (1H, m), 1.84 (1H, m), 1.62–1.31 (5H, m), 1.05 (3H, s), 0.90 (3H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 182.2, 67.4, 64.3, 46.7, 44.9, 34.7, 30.0, 28.7, 25.2, 17.7; IR (neat) ν_{max} 3445, 2932, 2869, 2028, 1759, 1460, 1390, 1367, 1345, 1224, 1154, 1121, 1046, 1022, 998 cm^{-1}; HRMS-ESI [M+Na]$^+$ calculated for $C_{11}H_{18}O_3Na$: 221.1149, found: 221.1148; $[\alpha]_D^{23} = -19.4$ (c 0.17, $CHCl_3$).

4.3.5. (*S*)-1-*tert*-Butyl 1-methyl 3,3-dimethyl-2-methylenecyclohexane-1,1-dicarboxylate 17

To a stirred solution of **5** (0.032 g, 0.141 mmol) in CH_2Cl_2 (1.4 mL) was added *N*,*N*′-diisopropyl-*O*-*tert*-butyl isourea (0.0085, 0.424 mmol, 3.0 equiv), and the reaction mixture was stirred at room temperature for 18 h, then stirred at 50 °C for 3 h. The reaction mixture was evaporated and dried under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20:1) to afford product **17** (0.036 g, 0.128 mmol, 90%) as a white solid: R_f = 0.4 (hexane/ethyl acetate = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, s), 4.85 (1H, s), 3.72 (3H, s), 2.22 (1H, m), 2.13 (1H, m), 1.68–1.58 (2H, m), 1.46 (9H, s), 1.47–1.39 (2H, m), 1.10 (3H, s), 1.03 (3H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.6, 170.5, 151.3, 113.0, 82.0, 62.7, 52.3, 39.9, 36.7, 33.0, 30.2, 29.5, 27.7, 18.7; IR (neat) ν_{max} 2948, 1724, 1633, 1456, 1392, 1367, 1300, 1251, 1213, 1161, 1138, 1062, 1022, 991, 952 cm^{-1}; HRMS-ESI [M+Na]$^+$ calculated for $C_{16}H_{26}O_4Na$: 305.1723, found: 305.1723; $[\alpha]_D^{19} = -6.8$ (c 0.65, $CHCl_3$).

4.3.6. (*S*)-1-*tert*-Butoxycarbonyl-3,3-dimethyl-2-methylenecyclohexane-1-carboxylic acid 18

To a stirred suspension of *t*-BuOK (0.0668 g, 0.595 mmol, 8.0 equiv) in Et_2O (1.5 ml) was added H_2O (0.003 ml, 0.149 mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred at 0 °C for 5 min. To the resulting mixture was added **17** (0.021 g, 0.0744 mmol) in Et_2O. The mixture was stirred at room temperature for 46 h. Then, to the reaction mixture were added ice cold water (5.0 mL) and 2 M HCl (2 mL). The aqueous layer was extracted with ethyl acetate (5 mL × 2) and the combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 4:1) to afford product **18** (0.0189 g, 0.704 mmol, 95%) as a white solid: R_f = 0.4 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (1H, s), 4.98 (1H, s), 2.24–2.16 (2H, m), 1.71–1.62 (2H, m), 1.50–1.40 (2H, m), 1.47 (9H, s), 1.10 (6H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 177.8, 170.0, 150.9, 113.6, 82.4, 62.6, 39.7, 36.7, 32.7, 30.1, 29.9, 27.7, 18.6; IR (neat) ν_{max} 2968, 2003, 1727, 1702, 1632, 1458, 1393, 1368, 1255, 1163, 1144, 1061, 1020, 953 cm^{-1}; HRMS-ESI [M+Na]$^+$ calculated for $C_{15}H_{24}O_4Na$: 291.1566, found: 291.1567; $[\alpha]_D^{20} = +7.6$ (c 0.75, $CHCl_3$), mp 107.4 °C.

4.3.7. (*S*)-*tert*-Butyl 1-hydroxymethyl-3,3-dimethyl-2-methylenecyclohexane-1-carboxylate 19

To a stirred solution of **18** (0.0386 g, 0.1438 mmol) in THF (1.5 mL) were added triethylamine (0.04 ml, 0.288 mmol, 2.0 equiv) and $ClCO_2{}^iPr$ (0.025 mL, 0.216 mmol, 1.5 equiv) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. After the disappearance of the starting material, to the reaction mixture was added saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with Et_2O (5 mL × 2), and the combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. To the residue were added MeOH (1.0 mL) and $NaBH_4$ (0.0163 g, 0.431 mmol, 3.0 equiv) at 0 °C, and the mixture was stirred at 0 °C for 2 h. After the disappearance of the starting material, to the mixture was added H_2O (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL × 2), and the combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 4:1) to afford product **19** (0.0218 g, 0.0863 mmol, 60%) as a colorless oil: R_f = 0.58 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (1H, s), 4.91 (1H, s), 3.82 (1H, d, J = 10.5 Hz), 3.68 (1H, d, J = 10.5 Hz), 2.22–2.14 (2H, m), 1.87–1.74 (2H, m), 1.63–1.47 (2H, m), 1.44 (9H, s), 1.11 (3H, s), 1.07 (3H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.6, 153.5, 110.3, 81.0, 68.7, 54.1, 40.1, 36.6, 31.0, 30.7, 29.5, 27.8, 18.4; IR (neat) ν_{max}

3478, 2965, 2931, 1723, 1628, 1458, 1392, 1367, 1247, 1156, 1056, 1031, 1013, 949, 901 cm^{-1}; HRMS-ESI $[M+Na]^+$ calculated for $C_{15}H_{26}O_3Na$: 277.1774, found: 277.1774; $[\alpha]_D^{20} = +28.8$ (*c* 0.21, $CHCl_3$).

4.3.8. (*S*)-Methyl 1-hydroxymethyl-3,3-dimethyl-2-methylenecyclohexanecarboxylate *ent*-15

To a stirred solution of **19** (0.0066 g, 0.0259 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (1.0 mL), and the reaction mixture was stirred for 3 h at room temperature. After the disappearance of the starting material, the reaction mixture was concentrated and dried under reduced pressure. To the residue were added MeOH (1.0 mL) and conc. H_2SO_4 (cat.), and the mixture was stirred at 70 °C for 20 h. After disappearance of the starting material, to the reaction mixture was added saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with Et_2O (5 mL × 2), and the combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 4:1) to afford product *ent*-**15** (0.0044 g, 0.0188 mmol, 72%) as a colorless oil: $R_f = 0.5$ (hexane/ethyl acetate = 2:1); $[\alpha]_D^{20} = +60.0$ (*c* 0.21, $CHCl_3$).

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