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Practical method for crystalline-liquid resolution of chrysanthemic acids utilizing chiral 1,1′-binaphthol monoethyl ethers directed for process chemistry

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ABSTRACT

We have developed an efficient practical resolution method for (1*R*,3*R*)-*trans*-chrysanthemic acid **1** and (1*R*,3*S*)-*trans*-2,2-dimethyl-3-(2,2-dichloroethenyl)cyclopropanecarboxylic acid **2**, based on the preliminary results of the simpler analogues, (1*R*)-2,2-dichlorocyclopropanecarboxylic acid **3** and (1*R*)-2,2-dimethylcyclopropanecarboxylic acid **4**, using a crystalline-liquid separation procedure (without column chromatography) with chiral 1,1′-binaphthol monoethyl ethers (*R*)-**5b** as the key auxiliary. Direct esterifications of **1**, **2**, **3**, and **4** with (*R*)-**5b** gave four sets of (1*R*)- and (1*S*)-diastereomeric esters **8**, **9**, **6**, and **7**, respectively, with markedly different melting points. All of these diastereomers were easily obtained using a simple and one-step crystalline-liquid separation. The separated diastereomers **8** and **9** were easily hydrolyzed to the desired enantiopure acids **1** (>98%) and **2** (>99%), respectively, with recovery of (*R*)-**5b** (>90%).

1. Introduction

Synthetic pyrethroids are well-recognized insecticides.[1] The original natural (1*R*,3*R*)-*trans*-chrysanthemic acid **1** and its remarkable synthetic analogues, such as (1*R*,3*S*)-*trans*-2,2-dimethyl-3-(2,2-dichloroethenyl)cyclopropanecarboxylic acid **2** [due to the operation of the sequence rules, these structures are geometrically equivalent but differ in their (3*R*) and (3*S*) descriptors], are a strong commodity in the agricultural industry and commonly used daily amenities (Fig. 1). Because chiral discrimination between all four stereoisomers of each chrysanthemic acid analogue is generally observed, a number of syntheses have been exploited[1,2] to obtain insecticidally active (1*R*,3*R* or 3*S*)-*trans* isomers utilizing resolutions together with racemizations[3] or direct asymmetric reactions.

Resolution is a major method used for industrial scale production, because complementary racemization of useless stereoisomers is well established.[4] There are several reported resolutions of (±)-(1*R**,3*R**)-*trans*-**1**′ and (±)-(1*R**,3*S**)-*trans*-**2**′, utilizing chiral amines such as α-phenenylethylamine, α-naphthylethylamine, and *threo*-1-aryl-2-dimethylamino-1,3-propanediols.[2b,3] These methods, however, lack generality with regard to the structures of the amine resolving agents and the resolution efficiency is not clearly disclosed except for Rosini group's recent extensive studies on the resolution of (1*R**,3*R**)-*trans*-**1**′.[3c–e] Our longstanding interests in process chemistry[5] and synthetic studies of cyclopropane

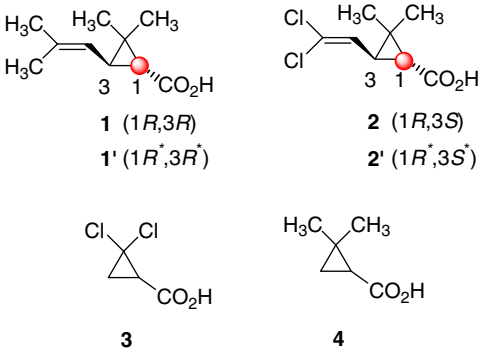

Figure 1.

transformations[6] led us to investigate a practical method for the resolution of **1** and **2** by crystalline-liquid separation.

2. Results and discussion

Chiral 1,1′-binaphthol derivatives are well established as readily available chiral catalysts and auxiliaries for the production of various useful optically active compounds. Monoalkyl ethers **5** are easily prepared from (*R*)-1,1′-binaphthol and alcohols utilizing

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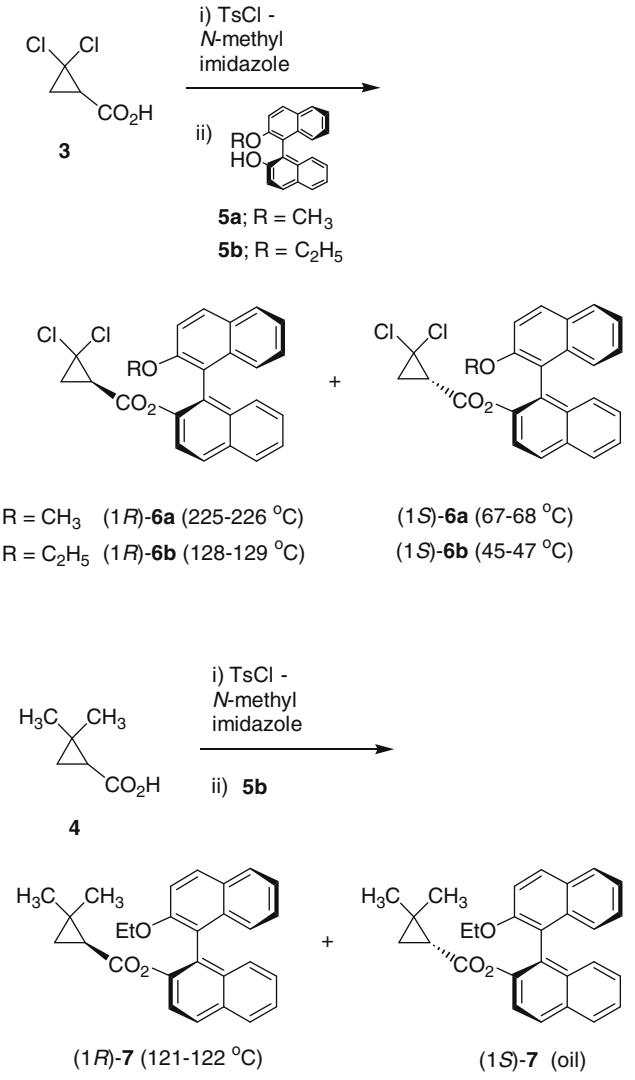
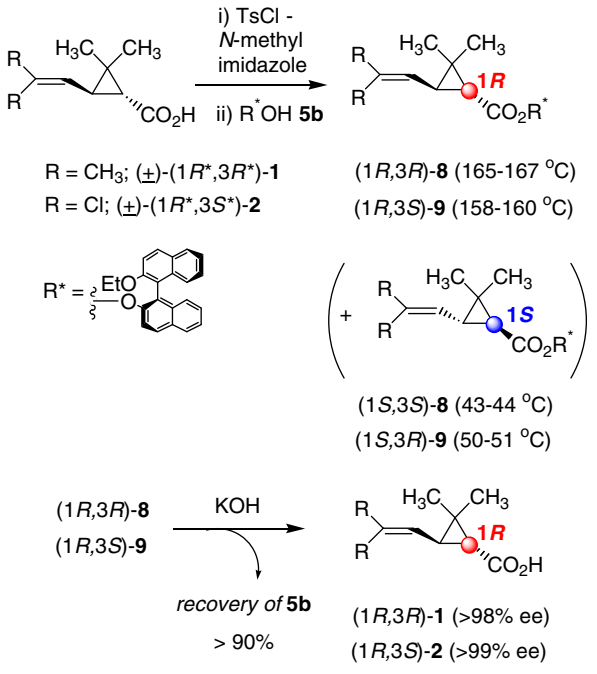
the Mitsunobu reaction in one step.[7] Recently, we reported a general and systematic method for the chromatographic resolution of *gem*-dihalo- and monohalo-cyclopropanecarboxylic acids containing a 1-Me group on a cyclopropane ring, wherein the monomethyl ether of (*R*)-1,1′-binaphthol **5a** is the key chiral auxiliary.[8] Another notable feature of this method is that the absolute configuration of cyclopropanecarboxylic acids can be predicted based on the different R_f values; R_f (1*S*) > R_f (1*R*). In view of process chemistry, however, this method is disadvantageous because it requires chromatographic separation. We report herein a practical resolution of 1-Me-lacking derivatives, (1*R**,3*R**)-*trans*-chrysanthemic acid **1**, (1*R**,3*S**)-*trans*-2,2-dimethyl-3-(2,2-dichloroethenyl)cyclopropanecarboxylic acid **2**, (±)-2,2-dichlorocyclopropanecarboxylic acid **3**,[9] and (±)-2,2-dimethylcyclopropanecarboxylic acid **4**, directed for process chemistry, that utilized readily accessible crystalline-liquid separation without the need for column chromatography.

Based on a previous report,[8] our initial attempt was guided by the condensation of 2,2-dichlorocyclopropanecarboxylic acid **3** with the monomethyl ether of (*R*)-binaphthol **5a** and monoethyl ether of (*R*)-binaphthol **5b** using the TsCl–*N*-methylimidazole reagent[10] to give the corresponding two sets of ester diastereomers; (1*R*)-**6a** and (1*S*)-**6a**, and (1*R*)-**6b** and (1*S*)-**6b** (Scheme 1). The melting points were significantly different between the corresponding diastereomers; (1*R*)-**6a**, **b** ≫ (1*S*)-**6a**, **b**. We chose monoethyl ether analogue **5b** giving (1*R*)-**6b** and (1*S*)-**6b** for the present study, because of its easy solid–liquid separation (degree of crystallinity) at ambient temperature. Moreover, the critical racemization tendency in the final hydrolysis step was sufficiently retarded (vide infra). The use of ester **7** derived from 2,2-dimethylcyclopropanecarboxylic acid **4** and **5b** showed a similar degree of crystallinity. Notably, a difference in the R_f value was not observed in the present case; R_fs of (1*R*)-**6a** = (1*S*)-**6a** = 0.54 and (1*R*)-**6b** = (1*S*)-**6b** = 0.56, (1*R*)-**7** = (1*S*)-**7** = 0.55 (silica gel; hexane–AcOEt = 5:1).

This preliminary successful result led us to investigate a crystalline-liquid resolution of useful (1*R**,3*R**)-*trans*-chrysanthemic acid **1**′ and (1*R**,3*S**)-*trans*-2,2-dimethyl-3-(2,2-dichloroethyl) cyclopropanecarboxylic acid **2**′. As expected, the two diastereomeric esters **8** derived from **1**′ and **5b** showed a significant degree of crystallinity; the desired (1*R*,3*R*)-**8** diastereomer exhibited a much higher melting point compared with diastereomer (1*S*,3*S*)-**8** and these two diastereomers were easily obtained using a simple and one-step crystalline-liquid separation procedure (Scheme 2). A similar result was obtained using two diastereomeric esters (1*R*,3*S*)- and (1*S*,3*R*)-**9** derived from **2**′ and **5b**. Also in these cases, the R_f values of the two diastereomer sets were almost the same; R_fs of (1*R*,3*R*)-**8** = (1*S*,3*S*)-**8** = 0.70 and (1*R*,3*S*)-**9** = (1*S*,3*R*)-**9** = 0.59 (silica gel; hexane–AcOEt = 5:1). Eventually, all five (1*R*)-enantiomers examined, **6a**, **6b**, **7**, **8**, and **9**, had consistently higher melting points.



Scheme 1.



Scheme 2.

To achieve the present resolution method, hydrolysis leading to chiral acids **1** and **2** was investigated. The separated diastereomers (1*R*,3*S*)-**8** and (1*R*,3*S*)-**9** were readily hydrolyzed under conventional conditions (KOH/THF–H_2O, 60–65 °C, 2 h) to give the desired chiral *trans*-chrysanthemic acid **1** [(1*R*,3*S*)] and *trans*-2,2-dimethyl-3-(2,2-dichloroethenyl)cyclopropanecarboxylic acid **2** [(1*R*,3*S*)], respectively, which were isolated by a facile extraction procedure in good to excellent yields. The aqueous reaction phase obtained was washed with ether, and then acidified with aq HCl, followed by re-extraction with AcOEt. The organic phase contained sufficiently pure products **1** and **2** with nearly complete retention of enantiomeric purity (~99% ee). Two favorable features should be

noted: (i) chiral auxiliary **5b** was recovered in ca. 90% yield by the initial ether extraction step, and (ii) mild reaction conditions did not cause undesirable epimerization of the (1*R*)-position: HPLC analysis of phenyl ester derivatives (1*R*,3*S*)-**1** and (1*R*,3*S*)-**2** confirmed this result. On the other hand, there was considerable epimerization in ca. 50% using the methyl analogue derived from **1′** or **2′** and **5a**, because harsh reaction conditions were required for the hydrolysis of these esters.

3. Conclusion

We have developed a practical resolution method for two important *trans*-chrysanthemic acids directed for process chemistry using a crystalline-liquid separation procedure. The present method will be a promising candidate for the systematic resolution of cyclopropanecarboxylic acids, because the (1*R*)- or (1*S*)-configuration on the cyclopropane is predictable.

4. Experimental

4.1. General

Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and are uncorrected. NMR spectra were recorded on a JEOL DELTA300 spectrometer, operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (=0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts on a scale relative to 77.00 ppm were used as an internal reference. IR spectra were recorded on JASCO FT/IR-5300 spectrophotometer. Optical rotations were measured on a JASCO DIP-370 (λ 589 nm). Mass spectra were measured on a JEOL JMS-T100LC spectrometer. Flash column chromatography was performed with Silica Gel Merck 60 (230–400 mesh ASTM). HPLC data were obtained on a SHIMADZU HPLC system (consisting of the following: SLC-10A, DGU-12A, LC-10AD, SIL-10A, CTO-10A, and detector SPD-10AV, measured at 254 nm) using DAICEL Chiralpak OD-H column (0.46 cm × 25 cm) at 35 °C.

The monoalkyl ethers of (*R*)-binaphthols **5a**, **b** were known compounds.[6]

4.1.1. (1*R*)- and (1*S*)-[(*R*)-2′-Ethoxy-1,1′-binaphth-2-yl] 2, 2-dichlorocyclopropanecarboxylates (1*R*)-6b and (1*S*)-6b

TsCl (364 mg, 1.91 mmol) in CH_3CN (1.0 mL) was added to a stirred solution of (±)-2,2-dichlorocyclopropanecarboxylic acid **3** (296 mg, 1.91 mmol) and *N*-methylimidazole (392 mg, 4.77 mmol) in CH_3CN (1.0 mL) at 0–5 °C under an Ar atmosphere, followed by being stirred at the same temperature for 0.5 h. The (*R*)-monoethyl ether of 1,1′-binaphthol **5b** (500 mg, 1.59 mmol) in CH_3CN (1.0 mL) was added to the reaction mixture at 0–5 °C, followed by being stirred at 20–25 °C for 2 h. The mixture was quenched with water, which was extracted with AcOEt (5 mL × 3). The combined organic phase was washed with 10% NaOH aqueous solution (5 mL), water, brine, dried (Na_2SO_4), and concentrated. The obtained crude solids were collected using a glass filter, followed by being washed with cooled heptane–AcOEt (3.5:1; 3 mL). The resultant solids were purified by recrystallization twice from AcOEt to give the desired product (1*R*)-**6b** (220 mg, 31%). The filtrate was concentrated and purified by silica gel column chromatography (hexane–AcOEt = 40:1) to give the antipode (1*S*)-**6b** (249 mg, 35%).

(1*R*)-**6b** (99% de based on ^{1}H NMR): Colorless crystals; mp 128–129 °C; R_f = 0.56 (hexane–AcOEt = 5:1); $[\alpha]_D^{23} = +34.1$ (*c* 1.80, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, t, *J* = 6.9 Hz), 1.67 (1H, dd, *J* = 7.2 Hz, J_{gem} = 9.6 Hz), 1.79 (1H, t, *J* = 7.2 Hz), 2.33 (1H, dd, *J* = 7.2 Hz, J_{gem} = 9.6 Hz), 4.05 (2H, q, *J* = 6.9 Hz), 7.08 (1H, d, *J* = 8.3 Hz) 7.16–7.34 (4H, m), 7.37–7.50 (3H, m), 7.83 (1H, d, *J* = 8.3 Hz), 7.90–8.02 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 26.2, 32.7, 57.2, 65.0, 115.0, 117.9, 121.4, 123.6, 125.4, 125.6, 126.4, 126.4, 126.5, 127.7, 128.1, 129.0, 129.1, 130.0, 131.8, 133.7, 133.8, 146.5, 154.2, 164.9. IR (KBr) 3489, 3057, 2982, 2930, 1763, 1620, 1593, 1508, 1472, 1366, 1246, 1150, 1111, 810, 750 cm^{-1}.

(1*S*)-**6b** (99% de based on ^{1}H NMR): Colorless crystals; mp 45–47 °C; R_f = 0.56 (hexane–AcOEt = 5:1); $[\alpha]_D^{23} = -38.6$ (*c* 0.90, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, t, *J* = 6.9 Hz), 1.59 (1H, dd, *J* = 7.9 Hz, J_{gem} = 10.0 Hz), 1.70 (1H, t, *J* = 7.9 Hz), 2.25 (1H, dd, *J* = 7.9 Hz, J_{gem} = 10.0 Hz), 3.98–4.18 (2H, m), 7.07–7.56 (8H, m), 7.81–8.08 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 26.4, 32.6, 57.4, 65.0, 115.1, 118.0, 121.5, 123.7, 125.3, 125.6, 126.3, 126.4, 126.5, 127.7, 128.0, 129.0, 129.9, 131.8, 133.6, 133.7, 146.5, 154.2, 165.1. IR (KBr) 3490, 3059, 2980, 2930, 1759, 1622, 1593, 1508, 1472, 1366, 1238, 1150, 1111, 808, 750 cm^{-1}.

4.1.2. (1*R*)- and (1*S*)-[(*R*)-2′-Methoxy-1,1′-binaphth-2-yl] 2, 2-dichlorocyclopropanecarboxylate (1*R*)-6a and (1*S*)-6a

Following the procedure for the preparation of (1*R*)-**6b** and (1*S*)-**6b**, the use of **5a** instead of **5b** gave the desired products (1*R*)-**6a** and (1*S*)-**6a**.

(1*R*)-**6a** (98% de based on ^{1}H NMR)**:** Colorless crystals; mp 225–226 °C; R_f = 0.22 (hexane–AcOEt = 10:1); $[\alpha]_D^{23} = +36.9$ (*c* 1.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (1H, dd, *J* = 7.6 Hz, J_{gem} = 9.6 Hz), 1.77 (1H, t, *J* = 7.6 Hz), 2.33 (1H, dd, *J* = 7.6 Hz, J_{gem} = 9.6 Hz), 3.77 (3H, s), 7.08 (1H, d, *J* = 7.6 Hz), 7.17–7.34 (4H, m), 7.39–7.49 (3H, m), 7.84 (1H, d, *J* = 7.6 Hz), 7.90–8.03 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 32.6, 56.7, 57.4, 113.6, 117.3, 121.5, 123.6, 125.1, 125.2, 125.7, 126.2, 126.5, 126.6, 127.8, 128.1, 128.9, 129.1, 130.1, 131.9, 133.6, 146.5, 154.9, 165.1. IR (KBr) 3428, 3092, 3063, 3009, 2965, 2841, 2359, 1757, 1620, 1593, 1507, 1462, 1362, 1263, 1142, 1107, 957, 816, 752 cm^{-1}.

(1*S*)-**6a** (95% de based on ^{1}H NMR)**:** Pale yellow crystals; mp 67–68 °C; R_f = 0.22 (hexane–AcOEt = 10:1); $[\alpha]_D^{24} = -39.7$ (*c* 4.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (1H, dd, *J* = 7.6 Hz, J_{gem} = 9.6 Hz), 1.70 (1H, t, *J* = 7.6 Hz), 2.26 (1H, dd, *J* = 7.6 Hz, J_{gem} = 9.6 Hz), 3.77 (3H, s), 7.11 (1H, d, *J* = 7.6 Hz), 7.17–7.35 (4H, m), 7.38–7.50 (3H, m), 7.85 (1H, d, *J* = 7.6 Hz), 7.89–8.03 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 32.6, 56.6, 57.4, 113.5, 117.2, 121.5, 123.6, 125.1, 125.6, 126.2, 126.5, 126.6, 127.8, 128.1, 128.9, 129.1, 130.1, 131.9, 133.6, 146.5, 154.9, 165.1. IR (KBr) 3449, 3059, 2936, 2839, 1759, 1622, 1593, 1508, 1473, 1364, 1263, 1150, 1111, 957, 808, 750 cm^{-1}.

4.1.3. (1*R*)-[(*R*)-2′-Ethoxy-1,1′-binaphth-2-yl] 2, 2-dimethylcyclopropanecarboxylate (1*R*)-7

Following the procedure for the preparation of (1*R*)-**6b**, the reaction using (±)-2,2-dimethylcyclopropanecarboxylic acid **4** (179 mg, 1.57 mmol), TsCl (358 mg, 1.88 mmol), *N*-methylimidazole (386 mg, 4.70 mmol), and **5b** (494 mg, 1.57 mmol), gave the crude solids. These were collected using a glass filter, followed by being washed with cooled hexane–AcOEt (15:1; 12 mL) to give the desired product (1*R*)-**7** (188 mg, 30%).

Colorless crystals (90% de based on ^{1}H NMR); mp 121–122 °C; R_f = 0.55 (hexane–AcOEt = 5:1); $[\alpha]_D^{25} = +7.4$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.41 (3H, s), 0.67 (1H, dd, *J* = 4.1, 7.9 Hz), 0.80–0.88 (1H, m), 0.86 (3H, s), 1.10 (3H, t, *J* = 6.9 Hz), 1.29 (1H, dd, *J* = 5.5, 7.9 Hz), 4.07 (2H, q, *J* = 6.9 Hz), 7.08 (1H, d, *J* = 8.4), 7.13–7.33 (4H, m), 7.35–7.49 (3H, m), 7.82 (1H, d, *J* = 8.4), 7.87–7.98 (3H, m) ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 17.6, 22.0, 29.1, 23.6, 26.4, 26.6, 115.3, 118.8, 122.2, 123.6, 125.2, 125.4, 125.8, 126.2, 126.3, 127.5, 128.0, 128.7, 129.1, 129.6, 131.6,

133.6, 133.9, 147.0, 154.2, 170.8. IR (KBr) 3062, 2949, 2930, 1748, 1620, 1593, 1509, 1393, 1263, 1219, 1136 cm^{-1}.

4.1.4. (1*R*,3*R*)- and (1*S*,3*S*)-[(*R*)-2′-Ethoxy-1,1′-binaphth-2-yl]3-(2′,2′-dimethylethenyl)-2,2-dimethylcyclopropanecarboxylates (1*R*,3*R*)-8 and (1*S*,3*S*)-8

Following the procedure for the preparation of (1*R*)-**6b**, the reaction using (1*R**,3*R**)-*trans*-chrysanthemic acid **1**′ (385 mg, 2.29 mmol), TsCl (437 mg, 2.29 mmol), *N*-methylimidazole (470 mg, 5.73 mmol), and **5b** (600 mg, 1.91 mmol), gave the crude solids. These were collected using a glass filter, followed by being washed with cooled hexane–AcOEt (15:1; 8 mL) to give the desired product (1*R*,3*R*)-**8** (284 mg, 32%).

(1*R*,3*R*)-**8** (99% de based on ^{1}H NMR): Colorless crystals; mp 165–167 °C; R_f = 0.70 (hexane–AcOEt = 5:1); $[\alpha]_D^{24} = +88.5$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, s), 0.95 (3H, s), 1.04 (3H, t, *J* = 6.9 Hz), 1.10 (1H, d, *J* = 5.5 Hz), 1.36 (3H, s), 1.62 (3H, s), 1.69–1.76 (1H, m), 4.01 (2H, q, *J* = 7.2 Hz), 4.68 (1H, d, *J* = 6.9 Hz), 7.12–7.33 (5H, m), 7.35–7.46 (3H, m), 7.82 (1H, d, *J* = 8.3 Hz), 7.87–8.00 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 18.2, 20.0, 21.9, 25.4, 28.9, 32.8, 34.4, 65.1, 115.4, 118.8, 120.5, 122.2, 123.6, 125.2, 125.5, 126.1, 126.2, 126.4, 127.6, 128.0, 128.7, 129.1, 129.7, 131.5, 133.7, 133.8, 135.8, 147.0, 154.2, 170.6. IR (KBr) 3449, 2926, 2857, 1738, 1620, 1593, 1508, 1458, 1246, 1142, 1113, 862, 810 cm^{-1}. HRMS (ESI) calcd for $C_{32}H_{32}O_3$ ($M+Na^+$) 487.2249, found 487.2246.

(1*S*,3*S*)-**8** (99% de based on ^{1}H NMR): Colorless oil; mp 43–44 °C; R_f = 0.70 (hexane–AcOEt = 5:1); $[\alpha]_D^{23} = -53.5$ (*c* 1.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48 (3H, s), 0.83 (3H, s), 1.08 (3H, t, *J* = 6.9 Hz), 1.17 (1H, d, *J* = 5.5 Hz), 1.55 (3H, s), 1.65 (3H, s), 1.75–1.88 (1H, m), 4.05 (2H, q, *J* = 6.9 Hz), 4.73 (1H, d, *J* = 7.9 Hz), 7.09 (1H, d, *J* = 8.3), 7.13–7.32 (4H, m), 7.34–7.47 (3H, m), 7.81 (1H, d, *J* = 8.3 Hz), 7.87–7.99 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 18.4, 19.3, 21.8, 25.5, 29.1, 32.5, 34.2, 65.1, 115.3, 118.8, 120.8, 122.2, 123.6, 125.2, 125.4, 125.7, 126.2, 126.2, 126.3, 127.5, 128.0, 128.7, 129.1, 129.6, 131.6, 133.7, 133.9, 135.4, 147.1, 154.2, 170.4. IR (KBr) 3420, 3059, 2978, 2926, 1743, 1622, 1593, 1508, 1460, 1431, 1244, 1136, 1111, 856, 808 cm^{-1}.

4.1.5. (1*R*,3*S*)- and (1*S*,3*R*)-[(*R*)-2′-Ethoxy-1,1′binaphth-2-yl] 3-(2′,2′-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylates (1*R*,3*S*)-9 and (1*S*,3*R*)-9

TsCl (6.33 g, 33.3 mmol) in CH_3CN (25 mL) was added to a stirred solution of (1*R**,3*S**)-*trans*-(2′,2′-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylic acid **2** (5.80 g, 27.7 mmol) and *N*-methylimidazole (6.83 g, 83.2 mmol) in CH_3CN (25 mL) at 0–5 °C under an Ar atmosphere, followed by being stirred at the same temperature for 0.5 h. Compound **5b** (8.72 g, 27.7 mmol) in CH_3CN (25 mL) was added to the reaction mixture at 0–5 °C, followed by being stirred at 20–25 °C for 2 h. The mixture was quenched with water, which was extracted with AcOEt (20 mL × 3). The combined organic phase was washed with 10% NaOH aqueous solution (50 mL), water, brine, dried (Na_2SO_4), and concentrated. The crude solids obtained were collected using a glass filter, followed by being washed with cooled hexane–AcOEt (15:1; 120 mL). The obtained solids were recrystallized from AcOEt to give the desired product (1*R*,3*S*)-**9** (5.33 g, 36%). The filtrate was concentrated and purified by SiO_2 column chromatography (hexane–AcOEt = 10:1) to give pure (1*S*,3*R*)-**9**.

(1*R*,3*S*)-**9**: Colorless crystals (97% de); mp 158–160 °C; R_f = 0.59 (hexane–AcOEt = 5:1); $[\alpha]_D^{29} = +77.4$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, s), 0.96 (3H, s), 1.03 (3H, t, *J* = 6.9 Hz), 1.29 (1H, d, *J* = 5.5 Hz), 1.86 (1H, dd, *J* = 5.5, 7.9 Hz), 4.01 (2H, q, *J* = 6.9 Hz), 5.35 (1H, d, *J* = 7.9 Hz), 7.14 (1H, d, *J* = 8.3 Hz), 7.18–7.49 (7H, m), 7.84 (1H, d, *J* = 8.3 Hz), 7.88–8.01 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 19.6, 22.3, 29.1, 32.8, 34.3, 65.1, 115.3, 118.6, 121.9, 122.3, 123.7, 125.3, 126.2, 126.3, 126.5, 127.7, 128.0, 128.8, 129.1, 129.8, 131.6, 133.7, 133.8, 146.8, 154.2, 169.2. IR (KBr) 3459, 3057, 2988, 2953, 1740, 1620, 1593, 1507, 1154 cm^{-1}. HRMS (ESI) calcd for $C_{30}H_{26}Cl_2O_3$ ($M+Na^+$) 527.1159, found 527.1155.

(1*S*,3*R*)-**9**: Colorless crystals; mp 50–51 °C; R_f = 0.59 (hexane–AcOEt = 5:1); $[\alpha]_D^{25} = -40.2$ (*c* 4.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53 (3H, s), 0.88 (3H, s), 1.08 (3H, t, *J* = 6.9 Hz), 1.36 (1H, d, *J* = 5.5 Hz), 1.96 (1H, dd, *J* = 5.5, 8.3 Hz), 4.06 (2H, q, *J* = 6.9 Hz), 5.41 (1H, d, *J* = 8.6 Hz), 7.08 (1H, d, *J* = 8.3 Hz), 7.13–7.46 (7H, m), 7.82 (1H, d, *J* = 8.3 Hz), 7.87–7.99 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 18.9, 22.1, 29.2, 32.7, 34.1, 65.0, 115.1, 118.4, 121.8, 123.5, 125.3, 125.4, 125.5, 126.2, 126.2, 126.4, 126.7, 127.6, 128.0, 128.8, 129.0, 129.7, 131.6, 133.6, 133.8, 146.8, 154.2, 169.0. IR (KBr) 3436, 3057, 2978, 2928, 1745, 1620, 1593, 1508, 1334, 1271, 1244, 1151, 1111 cm^{-1}.

4.1.6. (1*R*,3*S*)-2,2-Dimethyl-3-(2′,2′-dichloroethenyl) cyclopropanecarboxylic acid (1*R*,3*S*)-2 with recovery of (*R*)-monoethyl ether of 1,1′-binaphthol 5b

1 M KOH aqueous solution (25 mL) was added to a stirred solution of (1*R*,3*S*)-**9** (3.89 g, 7.7 mmol) in THF (77 mL) and MeOH (15 mL) at room temperature. After stirring at 60–65 °C for 2 h, the mixture was cooled down and concentrated ca. 10 mL to give the residue, which was extracted with ether (30 mL × 3). The aqueous phase was adjusted to ca. pH 1 using 6 M HCl aqueous solution, which was re-extracted with AcOEt (30 mL × 3). The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give the desired product (1*R*,3*S*)-**2** (1.48 g, 92%). The separated ether solution was washed with water, brine, dried (Na_2SO_4), and concentrated to recover (1*R*)-**5b** (2.25 g, 93%).

(1*R*,3*S*)-**2**: Colorless crystals (99% ee); mp 70–71 °C; $[\alpha]_D^{24} = +35.7$ (*c* 1.45, $CHCl_3$). Lit., $[\alpha]_D^{25} = +36.3$ (*c* 1.00, $CHCl_3$).[3b]

4.1.7. (1*R*,3*S*)-2,2-Dimethyl-3-(2′,2′-dimethylethenyl) cyclopropanecarboxylic acid (1*R*,3*R*)-1 and recovery of (*R*)-5b

Following the procedure for the preparation of (1*R*,3*S*)-**2**, the reaction using (1*R*,3*S*)-**8** (465 mg, 1.0 mmol) gave the desired (1*R*,3*R*)-**1** (151 mg, 90%) with the recovery of (*R*)-**5b** (292 g, 93%).

Colorless oil (98% ee); $[\alpha]_D^{24} = +25.1$ (*c* 1.10, $CHCl_3$). Lit., $[\alpha]_D^{24} = +25.9$ (*c* 3.00, $CHCl_3$).[11]

4.1.8. Determination of enantiomeric purity of (1*R*,3*R*)-1 using the phenyl ester derivative

A mixture of (1*R*,3*R*)-**1** (25 mg, 0.15 mmol), $SOCl_2$ (22 mg, 19 mmol), and a catalytic amount of DMF (1 drop) in hexane (0.5 mL) was stirred at 60 °C for 1.5 h. Evaporation of the mixture under reduced pressure gave the intermediary (1*R*,3*R*)-acid chloride (35 mg). This acid chloride in toluene (0.30 ml) was added to a stirred solution of phenol (10 mg, 13 mmol) and pyridine (13 mg, 0.15 mmol) in toluene (0.20 mL) at 0–5 °C, and the mixture was stirred at room temperature for 2 h. Water was added to the mixture, which was extracted with ether. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The crude product obtained was purified by silica gel column chromatography (hexane–AcOEt = 80:1) to give the phenyl ester of (1*R*,3*R*)-**1** (20 mg, 77% based on phenol).

Colorless oil; $[\alpha]_D^{24} = +21.8$ (*c* 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, s), 1.35 (3H, s), 1.63 (1H, d, *J* = 5.5 Hz), 1.74 (3H, s), 1.75 (3H, s), 2.18 (1H, dd, *J* = 5.5, 7.6 Hz), 4.97 (1H, d, *J* = 7.6 Hz), 7.04–7.11 (2H, m), 7.15–7.25 (1H, m), 7.31–7.40 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 20.4, 22.2, 25.6, 29.6, 33.5, 34.6, 120.8, 121.7, 125.5, 129.3, 136.0, 151.0, 171.1. IR (KBr) 3355, 3044, 2926, 1746, 1595, 1493, 1198, 1134, 1111 cm^{-1}.

98% ee by HPLC analysis [flow rate 0.50 ml/min, solvent: hexane–2-propanol = 99.5:0.5, t_R(racemic) = 18.29 min and 19.19 min. t_R[(1*R*,3*R*)-**1**] = 19.11 min.

4.1.9. Determination of enantiomeric purity of (1*R*,3*S*)-2 using the phenyl ester derivative

Following the procedure for the preparation of phenyl ester of (1*R*,3*R*)-**1**, the reaction using (1*R*,3*R*)-**2** (29 mg, 0.14 mmol) gave the phenyl ester of (1*R*,3*S*)-**2** (21 mg, 78% based on phenol) as the desired product.

Colorless crystals (99% ee); mp 67–68 °C; $[\alpha]_D^{23} = +28.7$ (*c* 0.65, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (3H, s), 1.38 (3H, s), 1.84 (1H, d, *J* = 5.5 Hz), 2.35 (1H, dd, *J* = 5.5, 8.3 Hz), 5.69 (1H, d, *J* = 8.3 Hz), 7.05–7.12 (2H, m), 7.19–7.27 (1H, m), 7.31–7.42 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 22.6, 29.8, 33.4, 34.6, 121.6, 122.5, 125.8, 126.6, 129.4, 150.7, 169.7. IR (KBr) 3071, 2953, 2926, 1740, 1589, 1279, 1165, 1140, 1113, 933, 885, 874 cm^{-1}.

99% ee by HPLC analysis [flow rate 0.50 ml/min, solvent: hexane–2-propanol = 99.5:0.5, t_R(racemic) = 11.53 min and 14.42 min. t_R[(1*R*,3*S*)-**2**] = 14.40 min.

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