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The resolution of *trans*-2,2-dichloro-3-methylcyclopropanecarboxylic acid via crystallization of its salts with (+)- and (−)-α-phenylethylamine, and the transformation of the resulting enantiomers into (*R*)- and (*S*)-dimethyl 2-methylsuccinates

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ABSTRACT

The resolution of *trans*-2,2-dichloro-3-methylcyclopropanecarboxylic acid *trans*-**1** was achieved by crystallization of its salts with (+)- and (−)-α-phenylethylamine. The chiral acids were converted into methyl esters **9**, which upon reaction with sodium methoxide in methanol underwent a three-carbon ring cleavage, leading to the corresponding *mono*-orthoester derivatives **10**. Acidic hydrolysis then gave the known (*R*)- and (*S*)-dimethyl 2-methylsuccinates **12**.

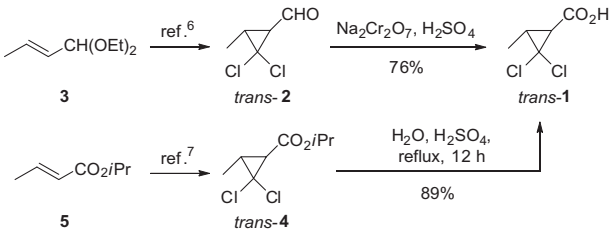
1. Introduction

Ring-opening reactions of the cyclopropane derivatives have found wide application in organic synthesis.[1] For the halogen substituted cyclopropanes, the cationic cyclopropyl–allyl[1b] and cyclopropylidene–allene[1c] isomerizations are the most often used. The direct nucleophilic substitution of the halogen atoms in cyclopropane derivatives is inhibited by I-strain, however the reactions can proceed smoothly via an elimination–addition mechanism when the hydrogen atom acidified with a π-electron acceptor substituent is present at the vicinal position to the halogen.[2] In the case of oxygen and other heteroatomic nucleophiles it leads to the corresponding donor–acceptor cyclopropanes, which under the reaction conditions are usually transformed into acyclic 1,4-bifunctional compounds or five-membered heterocycles via heterolytic cleavage of the cyclopropane ring.[2,3]

In view of the results on the efficient resolution of racemic α-methyl-β-halogen-substituted cyclopropanecarboxylic acids by crystallizations of their salts with (+)-dehydroabietylamine,[4a] (+)-cinchonine[4b] and (−)-α-(1-naphthyl)ethylamine,[4b] we decided to study the ability of the resolution for *trans*-2,2-dichloro-3-methylcyclopropanecarboxylic acid *trans*-**1**. The development of a convenient procedure for the preparation of acid *trans*-**1** in enantiomerically pure form could provide a new pathway to chiral bifunctional compounds with isopentane carbon chain, because the esters and *N*,*N*-dialkyl amides of the α-unsubstituted dichlorocyclopropanecarboxylic acids could be involved in the nucleophilic substitution of the halogen atoms and subsequent cleavage of the activated cyclopropane ring.[5] Enantiomerically pure acids **1** could also be used as sources of the corresponding chiral aldehydes and ketones which are even more easily involved in such transformations.[3]

2. Results and discussion

Racemic acid *trans*-**1** was obtained by the oxidation of *trans*-2,2-dichloro-3-methylcyclopropanecarbaldehyde *trans*-**2** prepared from crotonic aldehyde diethyl acetal **3** in two steps.[6] Acid *trans*-**1** could also be synthesized by acidic hydrolysis of the isopropyl ester *trans*-**4** (Scheme 1). The latter was obtained by cyclopropanation of isopropyl crotonate **5** under two-phase conditions according to the described procedure.[7] Although the cyclopropanation proceeds in high yield for acetal **3**, the obtaining of acid *trans*-**1** from ester **5** seemed to be the method of choice because one is shorter and less toxic reagents are used. Due to the simplicity of the preparation and purification of acid *trans*-**1** by crystallization,



Scheme 1.

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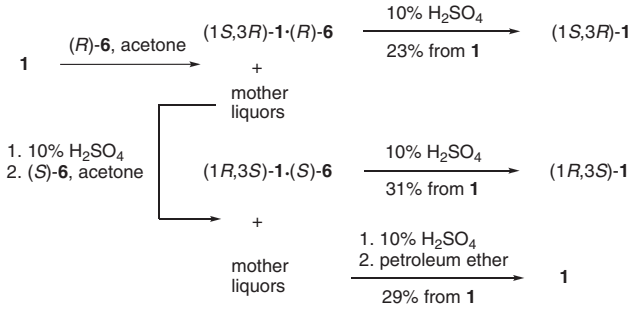
this approach can be used to obtain the target compound in multigram quantities.

We found that the addition of slightly more than 0.5 equiv of inexpensive (*R*)-(+)-α-phenylethylamine (*R*)-**6** to acid **1** in acetone led to the formation of the crystalline salt which was considerably enriched with the levorotary enantiomer of acid **1**. After two crystallizations of this salt from 90% aqueous acetone and subsequent treatment with dilute sulfuric acid, the levorotary enantiomer (1*S*,3*R*)-**1** {$[\alpha]_D = -119.5$ (*c* 2.0, $CHCl_3$)} was obtained in 23% yield, based on the starting racemate (Scheme 2). The addition of amine (*S*)-**6** to an acetone solution of acid **1** recovered from the combined mother liquors led to the salt, which was recrystallized in the same manner and then decomposed. As a result, the dextrorotary isomer (1*R*,3*S*)-**1**, with a specific rotation of $[\alpha]_D = +120.5$ (*c* 2.0, $CHCl_3$) was isolated in 31% yield. After all these manipulations, the acid **1** slightly enriched with the levorotary enantiomer {$[\alpha]_D = -19.0$ (*c* 2.0, $CHCl_3$)} was recovered from the combined mother liquors. This compound was recrystallized from petroleum ether to give racemic acid **1** {$[\alpha]_D = 0$ (*c* 2.0, $CHCl_3$)} in 29% yield, based on its initial quantity. Thus, the yields of the enantiomers (1*S*,3*R*)-**1** and (1*R*,3*S*)-**1** calculated from the acid **1** utilized were 32% and 44%, respectively.



Scheme 2.

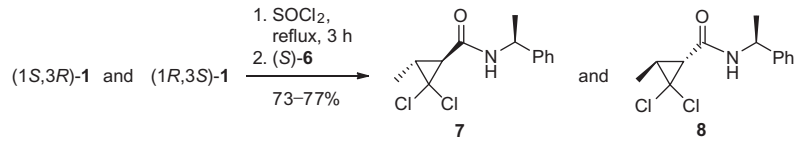
The enantiomeric purities of compounds (1*S*,3*R*)-**1** and (1*R*,3*S*)-**1** were determined from their transformation into a diastereomeric derivative by successive treatment with thionyl chloride and (*S*)-(−)-α-phenylethylamine and by comparison of the ^{1}H NMR spectroscopic data of the unpurified amides **7** and **8** obtained (Scheme 3). The ratio between the integral intensity of the doublet signals at δ 1.84 and 1.91 ppm of the cyclopropane protons at the α-position to the amide groups showed that both samples contained less than 1% impurity of diastereomers [after the first and second crystallizations, the ee of acid (1*S*,3*R*)-**1** was 62% and 92%, and the ee of acid (1*R*,3*S*)-**1** was 86% and 95%, respectively].

The absolute configurations at the C-3 stereogenic centers in the compounds (1*S*,3*R*)-**1** and (1*R*,3*S*)-**1** were determined by their transformations into the known (*R*)- and (*S*)-dimethyl 2-methylsuccinates **12** (Scheme 4). Acid (1*S*,3*R*)-**1** was converted into methyl ester (1*S*,3*R*)-**9**, which then reacted with sodium methylate in methanol to give, after aqueous work-up at reduced temperature, orthoester (3*R*)-**10**. Acidic hydrolysis of the *mono*-orthoester (3*R*)-**10**, which was formed via methanolysis of the corresponding donor–acceptor cyclopropane intermediate **11**, led to the methyl branched dimethyl succinate (2*R*)-**12**. In the same manner, acid (1*R*,3*S*)-**1** was converted into diester (2*S*)-**12** via *mono*-orthoester (3*S*)-**10**. The measured specific rotations of diesters (2*R*)-**12** {$[\alpha]_D = +5.0$ (*c* 3.2, $CHCl_3$)} and (2*S*)-**12** {$[\alpha]_D = -5.0$ (*c* 3.2, $CHCl_3$)} were in accordance with the literature data for (2*R*)-**12** {$[\alpha]_D = +4.75$ (*c* 2.9, $CHCl_3$)} and for (2*S*)-**12** {$[\alpha]_D = -4.9$ (*c* 2.9, $CHCl_3$)}.[8] As a result, the absolute configurations of the methyl branched stereogenic centers in compounds **1**, **9**, and **10** were established.

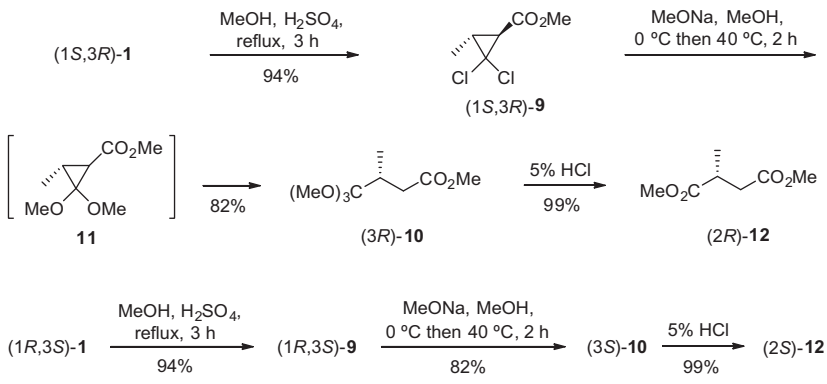
For the determination of the enantiomeric purity, (2*R*)- and (2*S*)-2-methylsuccinates **12** were reduced with $LiAlH_4$ to give the (2*R*)- and (2*S*)-2-methylbutane-1,4-diols **13**, which were then converted into MTPA-esters **14** by acylation with an excess of (*S*)-(−)-Mosher acid chloride[9] (Scheme 5). The comparison of the intensity of the signals of the methyl groups at δ 0.91 and 0.94 ppm in the ^{1}H NMR spectra of compounds **14** showed that both enantiomers were obtained with up to 99% ee.

3. Conclusion

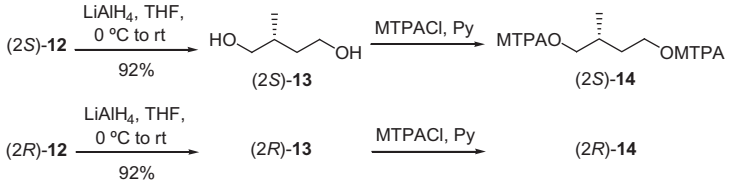
The optical resolution of racemic acid *trans*-**1** was efficiently achieved via crystallization of its salts with (+)- and (−)-α-phenylethylamine. The transformation of the enantiomers obtained into (2*R*)- and (2*S*)-dimethyl 2-methylsuccinates demonstrates that chiral acids **1** can serve as precursors of bifunctional building blocks with an isopentane carbon skeleton which are widely used in the synthesis of natural products and other biologically active compounds.[10]



Scheme 3.



Scheme 4.



Scheme 5.

4. Experimental

4.1. General methods

Melting points of the compounds **1**, **7**, **8**, and salts (1*S*,3*R*)-**1**·(*R*)-**6**, (1*R*,3*S*)-**1**·(*S*)-**6** were determined with a capillary apparatus. Petroleum ether of boiling point 40–60 °C was used for crystallizations. Optical rotations were measured with a CM-3 polarimeter (scale factor: 0.05°) at room temperature. IR spectra were recorded on a Vertex 70 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 400 instrument at 400 and 100 MHz, respectively, $CHCl_3$ was used as internal standard (δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR).

4.2. *trans*-2,2-Dichloro-3-methylcyclopropanecarboxylic acid *trans*-1

4.2.1. Preparation from *trans*-2,2-dichloro-3-methylcyclopropanecarbaldehyde 2

A solution of sodium dichromate dihydrate (47.7 g, 160 mmol) and 96% H_2SO_4 (36 mL, 650 mmol) in water (200 mL) was added dropwise to a stirred and ice cooled solution of *trans*-2,2-dichloro-3-methylcyclopropanecarbaldehyde[6] **2** (61.2 g, 400 mmol) in acetone (500 mL). After the addition was complete, the cooling bath was removed and stirring was continued at room temperature for 6 h. The reaction mixture was diluted with water (1000 mL) and extracted with Et_2O (5 × 200 mL). The combined organic phases were washed with brine (2 × 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from petroleum ether (150 mL) afforded acid *trans*-**1** as white crystals (51.4 g, 76%, mp 66–67 °C).

4.2.2. Preparation from isopropyl *trans*-2,2-dichloro-3-methylcyclopropanecarboxylate 4

A mixture of ester **4**[7] (27.5 g, 130 mmol) and 40% aqueous H_2SO_4 (500 mL) was refluxed with vigorous stirring for 12 h. The reaction mixture was then cooled to room temperature and extracted with Et_2O (5 × 100 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from petroleum ether (50 mL) afforded acid *trans*-**1** as white crystals (19.6 g, 89%, mp 66–67 °C). IR (CCl_4): ν_{max} = 3526, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (d, J = 6.6 Hz, 3H), 2.11 (d, J = 7.9 Hz, 1H), 2.23 (dq, J = 7.9, 6.6 Hz, 1H), 11.54 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 31.8, 38.5, 63.5, 173.5. Anal. Calcd for $C_5H_6Cl_2O_2$ (169.01): C, 35.53; H, 3.58. Found: C, 35.56; H, 3.59.

4.3. Resolution of acid 1

4.3.1. The salt of (1*S*,3*R*)-2,2-dichloro-3-methylcyclopropanecarboxylic acid with (*R*)-(+)-α-phenylethylamine (1*S*,3*R*)-1·(*R*)-6

At first, (*R*)-(+)-α-phenylethylamine (13.3 g, 110 mmol) was added to a solution of acid **1** (33.8 g, 200 mmol) in acetone (150 mL) and the mixture was heated to reflux and then cooled to +5 °C. After being kept at this temperature for 12 h, the crystalline salt formed was separated by filtration and washed with cold acetone (80 mL). Two crystallizations of the obtained salt (22.8 g) from refluxing 90% aqueous acetone afforded the salt of acid (1*S*,3*R*)-**1** with (*R*)-(+)-α-phenylethylamine as white crystals (13.4 g, 23%, mp 155–157 °C); $[\alpha]_D$ = −37.7 (*c* 1.3, MeOH). IR (KBr): ν_{max} = 3450, 1559 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, J = 6.1 Hz, 3H), 1.50 (d, J = 8.0 Hz, 1H), 1.56 (d, J = 6.7 Hz, 3H), 1.72 (dq, J = 8.0, 6.1 Hz, 1H), 4.24 (q, J = 6.7 Hz, 1H), 7.29–7.42 (m, 5H), 6.38 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 21.6, 30.0, 41.1, 51.1, 64.1, 126.6 (2C), 128.3, 128.9 (2C), 139.5, 172.9. Anal. Calcd for $C_{13}H_{17}Cl_2NO_2$ (290.19): C, 53.81; H, 5.90. Found: C, 53.84; H, 5.91.

4.3.2. (1*S*,3*R*)-2,2-Dichloro-3-methylcyclopropanecarboxylic acid (1*S*,3*R*)-1

The salt of acid (1*S*,3*R*)-**1** with (*R*)-(+)-α-phenylethylamine (13.35 g, 46.00 mmol) was treated with 10% aqueous H_2SO_4 (100 mL), and the resulting mixture was extracted with Et_2O (5 × 50 mL). The combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, acid (1*S*,3*R*)-**1** was obtained as white crystals (7.77 g, quantitative yield, mp 66–67 °C); $[\alpha]_D$ = −119.5 (*c* 2.0, $CHCl_3$). The IR and NMR spectroscopic data corresponded to those of racemic acid *trans*-**1**.

4.3.3. The salt of (1*R*,3*S*)-2,2-dichloro-3-methylcyclopropanecarboxylic acid with (*S*)-(−)-α-phenylethylamine (1*R*,3*S*)-1·(*S*)-6

The combined mother liquors obtained after the crystallization of acid **1** with (*R*)-(+)-α-phenylethylamine were evaporated under reduced pressure. To the residue, 10% aqueous H_2SO_4 (100 mL) and Et_2O (100 mL) were added, and the mixture was vigorously stirred until the residue was dissolved. The organic layer was separated and the aqueous layer was extracted with diethyl ether (4 × 100 mL). The combined organic phases were washed with 10% aqueous H_2SO_4 (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in acetone (300 mL), and then (*S*)-(−)-α-phenylethylamine (13.3 g, 110 mmol) was added. The resulting mixture was heated at reflux and then cooled to +5 °C. After keeping at this temperature for 12 h, the formed crystalline salt was separated by filtration and washed with cold acetone (80 mL). Two crystallizations of the obtained salt (24.5 g) from refluxing 90% aqueous acetone afforded the salt of acid (1*R*,3*S*)-**1** with (*S*)-(−)-α-phenylethylamine as white crystals (18.0 g, 31%, mp 157–158 °C); $[\alpha]_D$ = +38.0 (*c* 1.3, MeOH). The IR and NMR spectroscopic data corresponded to those of the salt of acid (1*S*,3*R*)-**1** with (*R*)-(+)-α-phenylethylamine.

4.3.4. (1*R*,3*S*)-2,2-Dichloro-3-methylcyclopropanecarboxylic acid (1*R*,3*S*)-1

The salt of acid (1*R*,3*S*)-**1** with (*S*)-(+)-α-phenylethylamine (18.0 g, 62.0 mmol) was treated with 10% aqueous H_2SO_4 (100 mL), and the resulting mixture was extracted with Et_2O (5 × 80 mL). The combined organic phases were washed with brine (50 mL) and dried over $MgSO_4$. After the removal of the solvent under reduced pressure, the acid (1*R*,3*S*)-**1** was obtained as white

crystals (10.45 g, quantitative yield, mp 66–67 °C); $[\alpha]_D$ = +120.5 (*c* 2.0, $CHCl_3$). The IR and NMR spectroscopic data corresponded to those of racemic acid *trans*-**1**.

4.3.5. Isolation of racemic acid *trans*-1 from the mother liquors

The combined mother liquors after crystallizations of acid *trans*-**1** with (*S*)-(+)-α-phenylethylamine were evaporated under reduced pressure. To the residue 10% aqueous H_2SO_4 (100 mL) and Et_2O (100 mL) were added, and the mixture was vigorously stirred until the residue was dissolved. The organic layer was separated and the aqueous layer was extracted with Et_2O (4 × 100 mL). The combined organic phases were washed with 10% aqueous H_2SO_4 (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give the acid *trans*-**1** as a viscous oil (15.0 g); $[\alpha]_D$ = −19.0 (*c* 2.0, $CHCl_3$). The residue was dissolved upon heating in petroleum ether (30 mL). The resulting solution was cooled to −10 °C and kept at this temperature for 12 h. The crystals formed were separated by filtration and washed with cold petroleum ether (20 mL). The acid *trans*-**1** was obtained as white crystals (9.85 g, 29%, mp 66–67 °C); $[\alpha]_D$ = 0 (*c* 2.0, $CHCl_3$).

4.4. (1*S*,3*R*)-2,2-Dichloro-3-methyl-*N*-[(1*S*)-1-phenylethyl] cyclopropanecarboxamide 7

A mixture of acid (1*S*,3*R*)-**1** (0.17 g, 1.0 mmol) and thionyl chloride (0.3 mL, 4.1 mmol) was refluxed for 3 h, the excess thionyl chloride was removed under reduced pressure (20 mmHg), the residue was dissolved in CH_2Cl_2, and (*S*)-(−)-α-phenylethylamine (0.25 g, 2.1 mmol) was added. After keeping at room temperature for 1 h, the mixture was diluted with Et_2O (5 mL), washed with 10% H_2SO_4 (1 mL), water (1 mL), saturated aqueous $NaHCO_3$ (1 mL), and then dried with Na_2SO_4. Evaporation of the solvent under reduced pressure gave crude amide **7** as a white solid (0.21 g, 77%, mp 160–163 °C). IR (CCl_4): ν_{max} = 3437, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, *J* = 6.3 Hz, 3H), 1.51 (d, *J* = 6.9 Hz, 3H), 1.84 (d, *J* = 7.8 Hz, 1H), 2.19 (dq, *J* = 7.8, 6.3 Hz, 1H), 5.10–5.17 (m, 1H), 6.38 (br s, 1H), 7.23–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 21.8, 29.1, 40.3, 49.7, 63.2, 126.3 (2C), 127.4, 128.6 (2C), 142.8, 164.3.

4.5. (1*R*,3*S*)-2,2-Dichloro-3-methyl-*N*-[(1*S*)-1-phenylethyl]cyclopropanecarboxamide 8

Compound **8** was obtained from acid (1*R*,3*S*)-**1** in accordance with the procedure for amide **7** (yield 73%, white solid, mp 130–133 °C). IR (CCl_4): ν_{max} = 3437, 1688 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, *J* = 6.3 Hz, 3H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.91 (d, *J* = 7.9 Hz, 1H), 2.19 (dq, *J* = 7.9, 6.3 Hz, 1H), 5.10–5.17 (m, 1H), 6.43 (br s, 1H), 7.23–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 21.4, 29.1, 40.5, 49.4, 63.2, 126.2 (2C), 127.4, 128.6 (2C), 142.5, 164.4.

4.6. Methyl (1*S*,3*R*)-2,2-dichloro-3-methylcyclopropanecarboxylate (1*S*,3*R*)-9

To a solution of acid (1*S*,3*R*)-**1** (7.60 g, 45.0 mmol) in MeOH (20 mL), 96% H_2SO_4 (3 mL, 54 mmol) was added. The mixture was refluxed for 3 h, then cooled to room temperature, diluted with water (50 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure (100–150 mmHg). Distillation of the residue afforded methyl ester (1*S*,3*R*)-**9** as a colorless liquid (7.75 g, 94%, bp 72–73 °C, 12–13 mmHg); $[\alpha]_D$ = −118.0 (*c* 1.2, $CHCl_3$). IR (CCl_4): ν_{max} = 3026, 1745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, *J* = 6.3 Hz, 3H), 2.09 (d, *J* = 7.9 Hz, 1H), 2.20 (dq, *J* = 7.9, 6.3 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 31.2, 38.8, 52.7, 63.5, 168.2. The ^1H and ^{13}C NMR spectroscopic data corresponded to those reported in the literature[11] for racemic ester **9**. Anal. Calcd for $C_6H_8Cl_2O_2$ (183.03): C, 39.37; H, 4.41. Found: C, 39.46; H, 4.44.

4.7. Methyl (1*R*,3*S*)-2,2-dichloro-3-methylcyclopropanecarboxylate (1*R*,3*S*)-9

Compound (1*R*,3*S*)-**9** was obtained from acid (1*R*,3*S*)-**1** in accordance with the procedure for ester (1*S*,3*R*)-**9** (yield 94%); $[\alpha]_D$ = +118.5 (*c* 1.2, $CHCl_3$). The IR and NMR spectroscopic data corresponded to those of compound (1*S*,3*R*)-**9**.

4.8. Methyl (3*R*)-4,4,4-trimethoxy-3-methylbutanoate (3*R*)-10

A solution of MeONa (90 mmol) in MeOH (45 mL) was added dropwise to a stirred and ice cooled solution of ester (1*S*,3*R*)-**9** (7.50 g, 41.0 mmol) in MeOH (30 mL). After the addition was complete, the cooling bath was removed, and the mixture was heated to 40 °C and stirred for 2 h. The reaction was then cooled to 0 °C, quenched with cold water (200 mL) and extracted with CH_2Cl_2 (5 × 40 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure (100–150 mmHg). Distillation of the residue afforded compound (3*R*)-**10** as a colorless liquid (6.93 g, 82%, bp 48–50 °C, 1 mmHg); $[\alpha]_D$ = +9.2 (*c* 7.5, Et_2O). IR (CCl_4): ν_{max} = 1741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, *J* = 6.8 Hz, 3H), 2.13 (dd, *J* = 15.4, 9.5 Hz, 1H), 2.45–2.54 (m, 1H), 2.63 (dd, *J* = 15.4, 4.1 Hz, 1H), 3.29 (s, 9H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 35.5, 36.4, 50.4 (3C), 51.4 114.6, 173.8. Anal. Calcd for $C_9H_{18}O_5$ (206.24): C, 52.41; H, 8.80. Found: C, 52.49; H, 8.82.

4.9. Methyl (3*S*)-4,4,4-trimethoxy-3-methylbutanoate (3*S*)-10

Compound (3*S*)-**10** was obtained from ester (1*R*,3*S*)-**9** in accordance with the procedure for *mono*-orthoester (3*R*)-**10** (yield 82%); $[\alpha]_D$ = −9.2 (*c* 7.5, Et_2O). Spectroscopic data corresponded to those of compound (3*R*)-**10**.

4.10. Dimethyl (2*R*)-2-methylsuccinate (2*R*)-12

A solution of compound (3*R*)-**10** (3.00 g, 14.5 mmol) in Et_2O (30 mL) was vigorously stirred with 5% aqueous HCl (30 mL) for 10 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with water (10 mL), saturated aqueous $NaHCO_3$, brine (10 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave diester (2*R*)-**12** as a colorless liquid which was pure by NMR (2.30 g, 99%); $[\alpha]_D$ = +5.0 (*c* 3.2, $CHCl_3$) {lit.[8] $[\alpha]_D$ = +4.75 (*c* 2.9, $CHCl_3$), >95% ee}.

4.11. Dimethyl (2*S*)-2-methylsuccinate (2*S*)-12

Compound (2*S*)-**12** was obtained from *mono*-orthoester (3*S*)-**10** in accordance with the procedure for diester (2*R*)-**12** (yield 99%); $[\alpha]_D$ = −5.0 (*c* 3.2, $CHCl_3$) {lit.[8] $[\alpha]_D$ = −4.9 (*c* 2.9, $CHCl_3$), >96% ee}. The NMR spectroscopic data corresponded to those of compound (2*R*)-**12**.

4.12. (2*R*)-2-Methylbutane-1,4-diol (2*R*)-13

A solution of diester (2*R*)-**12** (10 mg, 62 μmol) in THF (0.5 mL) was added under argon to a stirred and ice cooled solution of $LiAlH_4$ (5.0 mg, 0.13 mmol) in THF (0.5 mL). The cooling bath was removed, and the mixture was stirred at room temperature for

1 h. Then, the reaction mixture was quenched with 10% aqueous NaOH (50 μL) at 0 °C. The mixture was diluted with CH_2Cl_2 (3 mL) and filtered. The filtrate was dried with Na_2SO_4 and evaporated under reduced pressure to give crude diol (2*R*)-**13** (6.0 mg, 92%). The ^1H and ^{13}C NMR spectroscopic data were in full accordance to those reported in the literature.[12]

4.13. (2*S*)-2-Methylbutane-1,4-diol (2*S*)-13

Compound (2*S*)-**13** was obtained from diester (2*S*)-**12** in yield 92% in the same way.

4.14. (2*R*)-2-Methylbutane-1,4-diyl (2*S*,2′*S*)-bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (2*R*)-14

^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, J = 6.8 Hz, 3H), 1.48–1.57 (m, 1H), 1.72–1.81 (m, 1H), 1.88–1.97 (m, 1H), 3.52 (s, 3H), 3.52 (s, 3H), 4.09 (dd, J = 10.8, 5.8 Hz, 1H), 4.18 (dd, J = 10.8, 5.7 Hz, 1H), 4.26–4.38 (m, 2H), 7.35–1.43 (m, 6H), 7.46–7.50 (m, 4H).

4.15. (2*S*)-2-Methylbutane-1,4-diyl (2*S*,2′*S*)-bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (2*S*)-14

^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (d, J = 6.7 Hz, 3H), 1.47–1.56 (m, 1H), 1.74–1.83 (m, 1H), 1.87–1.96 (m, 1H), 3.52 (s, 3H), 3.52 (s, 3H), 4.09 (dd, J = 10.7, 5.8 Hz, 1H), 4.18 (dd, J = 10.7, 5.8 Hz, 1H), 4.28–4.40 (m, 2H), 7.36–1.41 (m, 6H), 7.46–7.50 (m, 4H).

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