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Synthesis of (1*S*)-1-amino-2,2-dimethylcyclopropane-1-carboxylic acid via PLE mediated hydrolysis of bis(2,2,2-trifluoroethyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate

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Abstract—Hydrolysis of bis(2,2,2-trifluoroethyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate with pig liver esterase afforded (1*R*)-2,2-dimethyl-1-(2,2,2-trifluoroethoxycarbonyl)-cyclopropane-1-carboxylic acid in high enantiomeric excess. This compound was rearranged to (1*S*)-2,2,2-trifluoroethyl-2,2-dimethyl-1-[(*N*-ethoxycarbonyl)amino]-cyclopropane-1-carboxylate via a Curtius type reaction with DPPA. Final alkaline hydrolysis gave (1*S*)-1-amino-2,2-dimethylcyclopropane-1-carboxylic acid.

1. Introduction

Cyclopropane containing amino acids are found to inhibit some amino acid processing enzymes.[1] This may be due to the fact that cyclopropane amino acids, as strained moieties in peptides, can restrict the conformational freedom and thus render those peptides more resistant to hydrolysis and other enzyme cleavage processes. 1-Aminocyclopropane-1-carboxylic acid (**1**) is known to be the biochemical precursor of the plant hormone ethylene in a process catalysed by the ethylene forming enzyme (EFE).[2] Ethylene, once liberated, induces acceleration of most of the plant development processes, such as flowering, ripening, germination and senescence.[3] Substances that inhibit the ethylene forming enzyme would allow an effective control on the growth of plants, therefore being of greatest importance to agriculture.[4]

1-Amino-2-substituted-cyclopropane-1-carboxylic acids (**2**) have received growing interest due to their proven physiological effect as inhibitors of the ethylene forming enzyme,[5] thus justifying their role as plant growth regulators. However, little attention has been paid to the geminally substituted 1-amino-2,2-dialkylcyclopropane-1-carboxylic acids (**3**).

Most of the described syntheses of 1-amino-2,2-dialkylcyclopropane-1-carboxylic acids (**3**), in particular 1-amino-2,2-dimethylcyclopropane-1-carboxylic acid (**4**), are limited to the preparation of the racemate.[6,7] Only in few cases syntheses of optically active 1-amino-2,2-dimethylcyclopropane-1-carboxylic acid (**4**) have been reported.[8–11] These syntheses consist of the fractional crystallisation of the diastereoisomeric salts of 2,2-dimethyl-1-formylaminocyclopropane-1-carboxylic acid with (−)-quinine,[8] the Strecker-type reaction of a dimethylcyclopropanone hemiacetal with chiral amines,[9] the cycloaddition of isopropylidene triphenylphosphorane to (2*S*)-*N*-benzoyl-2-*tert*-butyl-4-methylene-1,3-oxazolidin-5-one, followed by the separation and hydrolysis of the two formed diastereoisomers,[10] and base induced cyclisation of diastereomeric methyl (4-bromo-2-(dihydro-3-methoxy-1-oxo-1*H*-isoindol-2-yl)-4-methylpentanoates, prepared from (*S*)-*N*-phthaloyl-4-bromoleucine methyl ester.[11] All the reported syntheses rely on the use of chiral precursors and auxiliaries, and in the resolution of racemic mixtures. Here, we report the first enantioselective synthesis of (1*S*)-1-amino-2,2-dimethylcyclopropane-1-carboxylic acid (**4**) by an enzymatic asymmetrisation of a prochiral precursor (Fig. 1).

2. Results and discussion

We describe a facile and highly stereoselective synthesis of (1*S*)-1-amino-2,2-dimethylcyclopropane-1-carboxylic acid (**4**) via pig liver esterase (PLE) catalysed hydrolysis of

Keywords: 1-aminocyclopropane-1-carboxylic acid; enzymatic hydrolysis; Curtius rearrangement; 2,2-dimethylACC.

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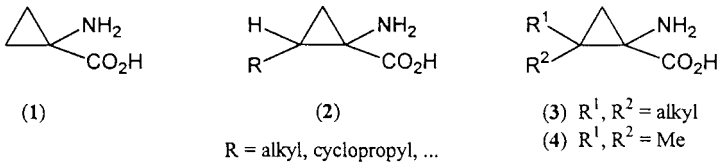


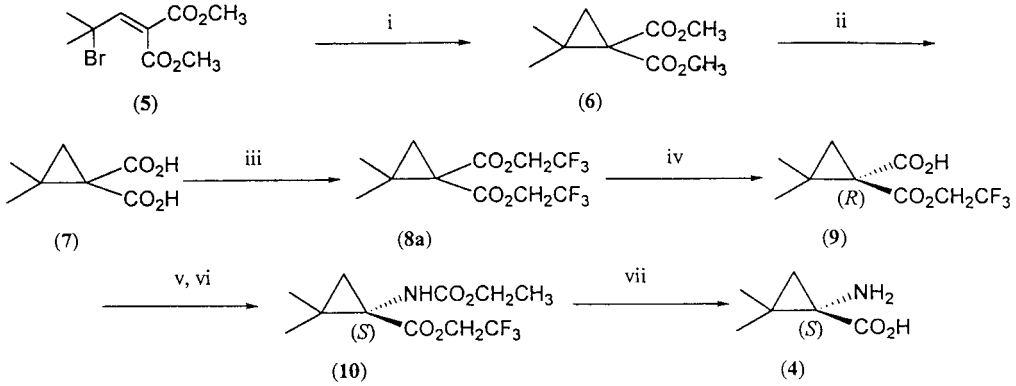
Figure 1.

bis(2,2,2-trifluoroethyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate (**8a**) as the key step, affording (1*R*)-2,2-dimethyl-1-(2,2,2-trifluoroethoxycarbonyl)cyclopropane-1-carboxylic acid (**9**) in high enantiomeric excess (>95%, Scheme 1). The diester (**8a**) was prepared by Michael-induced ring closure (MIRC) of the brominated alkylidene malonate (**5**) with sodium borohydride in methanol,[12] followed by double saponification of dimethyl 2,2-dimethylcyclopropane-1,1-dicarboxylate (**6**) with sodium hydroxide at room temperature for five days. The resulting 2,2-dimethylcyclopropane-1,1-dicarboxylic acid (**7**)[13] was esterified with 2,2,2-trifluoroethanol in dichloromethane in the presence of dicyclohexylcarbodiimide (DCC) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP).[14]

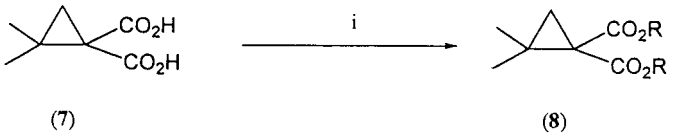
We attempted the enzymatic asymmetrisation of the prochiral C-1 position of 2,2-dimethylcyclopropane-1,1-dicarboxylic esters (**8**). The enzymatic hydrolysis of dimethyl 2,2-dimethylcyclopropane-1,1-dicarboxylate (**6**) with pig liver esterase gave the corresponding monoacid in low enantiomeric excess (ca. 65%).[15] Accordingly, a set of activated esters derived from β-halogenated alcohols was evaluated as prochiral precursors for the PLE hydrolysis. The inductive effect of the halogen atoms would render the corresponding diesters (**8**) more labile towards enzymatic hydrolysis. It is noteworthy that pig liver esterase has been reported to selectively hydrolyse some conformationally rigid, prochiral malonic esters.[16] Although some authors report the resolution of racemic mixtures of chiral acetylated alcohols with bromine or fluorine atoms at the adjacent position of that of the alcohol function,[17] to the best of our knowledge no prochiral bis(2,2,2-trifluoroethyl) malonates have been attempted as substrates in asymmetrisation reactions. As only a few β-halogenated alcohols were commercially available, some novel 2,2-dichloroalkanols were prepared, the details of their syntheses are discussed elsewhere.[18] The diester precursors (**8**) were prepared by condensation of the appropriate β-halogenated alcohol and 2,2-dimethylcyclopropane-1,1-dicarboxylic acid (**7**) with DCC/DMAP.[14] In this respect, the esterification process gave access to the novel cyclopropane-1,1-dicarboxylic esters (**8a**–**d**) (Scheme 2).

Entry	R	Diester	Yield (%)
1	CF_3CH_2	**8a**	60
2	CCl_3CH_2	**8b**	62
3	$CH_3CH_2CCl_2CH_2$	**8c**	20
4	$CH_3(CH_2)_3CCl_2CH_2$	**8d**	51

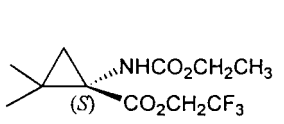
The enzymatic asymmetrisation at the prochiral C-1 position was further attempted with the trifluoroethyl (**8a**) and dichlorobutyl (**8c**) derivatives. The enzymatic hydrolysis of the bis(2,2,2-trichloroethyl) dicarboxylate (**8b**) gave problems as it is a solid with a relatively high melting point and thus presenting dispersion problems. In a phosphate buffer with PLE it was not converted at all, while the



Scheme 1. (i) $NaBH_4$, MeOH, 0°C to rt, 16 h, 58%; (ii) 1 M NaOH, MeOH, 0°C to rt, 6 days, 87%; (iii) CF_3CH_2OH, DCC, DMAP, CH_2Cl_2, 0°C to rt, 16 h, 50%; (iv) PLE, phosphate buffer pH 7.0, 28–30°C, 30 h, 62%; (v) DPPA, Et_3N, toluene, reflux, 2 h; (vi) EtOH, rt, 16 h, 34%; (vii) 6 M NaOH, reflux, 16 h, 75%.



Scheme 2. Preparation of diesters (**8**). (i) ROH, DCC, DMAP, CH_2Cl_2, 16 h, 0°C to rt.



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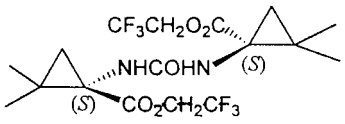

(11)

Figure 2.

addition of DMF to the medium solubilised the solid, but still did not give any conversion. In each case, the diester precursor (ca. 1 mmol) was dispersed in pH 7.0 phosphate buffer (0.1 M) at 30°C and enzyme (pig liver esterase) was added with stirring. Only the hydrolysis of bis(2,2,2-trifluoroethyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate (**8a**) with pig liver esterase succeeded, resulting in (1*R*)-2,2-dimethyl-1-(2,2,2-trifluoroethoxycarbonyl)-cyclopropane-1-carboxylic acid (**9**) in 62% yield after 30 h. The enantiomeric excess (>95%) of the monoacid (**9**) was determined by chiral GC (cyclodextrose capillary column) after esterification of the carboxylic acid group with an excess of diazomethane.[19] These results were supported by ^{1}H NMR measurements (500 MHz) using (*R*)-2,2,2-trifluoro-1-(9-anthranyl)ethanol ((*R*)-Pirkle's chiral alcohol).[20]

The next step was the Curtius rearrangement of (1*R*)-2,2-dimethyl-1-(2,2,2-trifluoroethoxycarbonyl)-cyclopropane-1-carboxylic acid (**9**) with diphenylphosphoroazidate (DPPA).[21] After work-up with ethanol, this reaction afforded a mixture containing the optically active carbamate (1*S*)-2,2,2-trifluoroethyl 2,2-dimethyl-1-(*N*-ethoxycarbonylamino)-cyclopropane-1-carboxylate (**10**, 34%) and *N*,*N*′-bis[1-[(1*S*)-2,2-dimethyl-1-(2,2,2-trifluoroethoxycarbonyl)-cyclopropyl]] urea (**11**, 12%). Both compounds (**10**) and (**11**) were separated by column chromatography (Fig. 2).

Finally, hydrolysis of the carbamate (**10**) with 6 M sodium hydroxide under reflux and purification through cationic ion exchange resin (H form) gave (1*S*)-1-amino-2,2-dimethylcyclopropane-1-carboxylic acid (**4**) in 75% yield. All spectroscopic data of (**4**) were consistent with the literature.[7,9] The absolute stereochemistry of the compound obtained was assessed by direct comparison to reported data of its optical rotation (see Section 3).[9] The enantiomeric excess (>84%) was also determined by analytical reverse phase HPLC after derivatisation with (*R*)-Mosher's acid chloride.[22] The decrease of enantiomeric excess can be explained by partial epimerisation during Curtius rearrangement as there are precedents in the literature.[23,24]

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 NMR spectrometer operating at 270 and 67.5 MHz, respectively. The determination of the enantiomeric excess of (1*R*)-2,2-dimethylcyclopropane-1-(2,2,2-trifluoroethoxycarbonyl)-1-carboxylic acid (**9**) by NMR was done with a Bruker AM500 spectrometer, operating at 500 MHz. FT-IR spectra were recorded on a Perkin–Elmer model 1310 spectrophotometer. Optical rotations were measured with a Optical Activity AA-10 polarimeter. GC analysis was carried out with a DELSI Intersmat IGC 120 ML gas chromatograph. The electron impact (EI) mode mass spectra were obtained with a Varian MAT 112 mass spectrometer, operating at 70 eV. The electrospray mass spectrum of (1*R*)-2,2-dimethylcyclopropane-1-(2,2,2-trifluoroethoxycarbonyl)-1-carboxylic acid (**9**) was got with a Hewlett Packard 1100 MSD mass spectrometer. Melting points were measured with a Büchi 535 melting point apparatus. Boiling and melting points are uncorrected. Chromatographic separations were performed using Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F_{254} precoated tlc plates (0.25 mm thickness). All chemicals and solvents were used as supplied.

3.1.1. Preparation of 2,2-dimethylcyclopropane-1,1-dicarboxylic acid (7). In a 500 ml round-bottomed flask, provided with a magnetic stirrer, dimethyl 2,2-dimethylcyclopropane-1,1-dicarboxylate[12] (**6**, 7.81 g, 0.042 mol) was dissolved in methanol (80 ml) and the solution was cooled to 0°C. To this solution, 1 M sodium hydroxide (126 ml, 0.126 mol) was added at 0°C in one portion and the mixture was left stirring at room temperature for 5 days. Ice (ca. 50 g) was added and the reaction mixture was carefully acidified with 1 M hydrochloric acid until pH 3–4, and washed with chloroform (3×50 ml). The organic extracts were discarded and the aqueous phase was acidified with 1 M hydrochloric acid until pH 1–2 and then extracted with ethyl acetate (3×50 ml). The combined organic phases were washed with water (20 ml), dried over sodium sulphate, filtered and the solvent was evaporated. 2,2-Dimethylcyclopropane-1,1-dicarboxylic acid (**7**)[13] was obtained as a waxy white solid (5.77 g, 36 mmol, 87%), which was used without further purification. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 10.5 (s, 2H, CO_2H); 1.90 (s, 2H, H-3); 1.39 (s, 6H, Me). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 173.66 (CO_2H); 38.22 (C-1); 37.65 (C-2); 28.05 (C-3); 21.29 (Me). IR (NaCl, cm^{-1}): 3500–2500 (COOH); 1658 (CO). MS (70 eV, *m*/*z*, %): 158 (M^+, 0.3); 140 (19); 123 (11); 122 (100); 99 (18); 97 (11); 94 (33); 69 (13); 68 (10); 67 (30); 66 (39); 59 (45); 55 (24); 54 (18); 53 (16); 45 (13); 43 (21); 42 (11); 41 (42).

3.1.2. Preparation of bis(2,2,2-trifluoroethyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate (8a). In a 100 ml round bottomed flask, provided with magnetic stirrer, ice bath and nitrogen inlet, 2,2-dimethylcyclopropane-1,1-dicarboxylic acid (**7**, 3.07 g, 19.4 mmol) was dissolved in freshly distilled dichloromethane (70 ml). 2,2,2-Trifluoroethanol (10.24 g, 102.4 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 0.96 g, 7.87 mmol) were added and the mixture was cooled to 0°C. Dicyclohexylcarbodiimide (DCC, 7.99 g, 38.8 mmol) was added portionwise at 0°C over

5 min. The ice bath was removed and the reaction mixture was further stirred at room temperature for 16 h. The precipitate formed was filtered off and washed with dichloromethane (10 ml). The filtrate was evaporated and the residue was purified by column chromatography (silica gel, column dimensions 44.0 cm×2.4 cm, hexane–ethyl acetate 50:1). Pooling and evaporation of the appropriate fractions gave bis(2,2,2-trifluoroethyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate (**8a**) as a viscous colourless liquid (3.73 g, 11.57 mmol, 60%). R_f: 0.52 (silica gel, hexane–AcOEt 4:1). Bp 54–55°C/0.15 mm Hg. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 4.42–4.61 (m, 4H, CH_2CF$_3$); 1.61 (s, 2H, H-3); 1.30 (s, 6H, Me). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 167.24 (*C*O$_2$R); 123.20 (q, J_{C-F}=277 Hz, *C*F$_3$); 61.48 (q, J_{C-C-F}=37.9 Hz, *C*H$_2$CF$_3$); 38.83 (C-1); 31.99 (C-2); 28.99 (C-3); 21.87 (Me). IR (NaCl, cm^{-1}): 1752 (C=O). MS (70 eV, *m/z*, %): 254 (M$^+$, 2); 239 (2); 223 (6); 155 (5); 154 (6); 123 (29); 122 (100); 95 (11); 94 (19); 83 (10); 73 (12); 67 (16); 66 (10); 59 (11); 55 (18); 54 (7); 53 (6); 43 (7); 41 (12); 40 (7); 39 (8). HRMS (EI, *m/z*): $C_{11}H_{12}F_6O_4$ requires 322.0640; found 322.0637 (M$^+$).

3.1.3. Preparation of bis(2,2,2-trichloroethyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate (8b). In a 100 ml round bottomed flask, provided with magnetic stirrer, ice bath and nitrogen inlet, 2,2-dimethylcyclopropane-1,1-dicarboxylic acid (**7**, 2.01 g, 12.73 mmol), 2,2,2-trichloroethanol (7.61 g, 50.9 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 0.62 g, 5.09 mmol) were dissolved in freshly distilled dichloromethane (60 ml). The mixture was cooled to 0°C and dicyclohexylcarbodiimide (DCC, 5.78 g, 28.01 mmol) was added portionwise at 0°C over 5 min. The ice bath was removed after 1 h and the reaction mixture was further stirred at room temperature for 15 h. The precipitate formed was filtered off and washed with dichloromethane (10 ml) and the filtrate was evaporated. The residue was purified by column chromatography (silica gel, column dimensions 42.0 cm×2.4 cm, hexane–ethyl acetate 50:1). Pooling and evaporation of the appropriate fractions gave bis(2,2,2-trichloroethyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate (**8b**) as an amorphous white solid (3.32 g, 7.90 mmol, 62%). R_f: 0.52 (silica gel, hexane–AcOEt 4:1). Mp: 49–50°C (powder-like crystalline solid from MeOH). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 4.86 and 4.74 (each d, J=12.0 Hz, each 2H, AB system, 2× CH_2CCl$_3$); 1.64 (s, 2H, H-3); 1.37 (s, 6H, Me). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 166.76 (*C*O$_2$R); 94.54 (CH$_2$*C*Cl$_3$); 74.79 (*C*H$_2$CCl$_3$); 38.78 (C-1); 31.36 (C-2); 28.57 (C-3); 21.96 (Me). IR (NaCl, cm^{-1}): 1749 (C=O ester). Elem. Anal.: $C_{11}H_{12}Cl_6O_4$ requires C 31.89%, H 2.87%; found C 31.71%, H 2.81%. HRMS (EI, *m/z*): $C_{11}H_{12}Cl_6O_4$ requires 417.8867; found 417.8861 (M$^+$).

3.1.4. Preparation of bis(2,2-dichlorobutyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate (8c). In a 100 ml round bottomed flask, provided with magnetic stirrer, ice bath and nitrogen inlet, 2,2-dimethylcyclopropane-1,1-dicarboxylic acid (**7**, 2.23 g, 14.10 mmol), 2,2-dichlorobutanol[18] (10.09 g, 70.60 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 0.69 g, 5.64 mmol) were dissolved in freshly distilled dichloromethane (60 ml). The mixture was cooled to 0°C and dicyclohexylcarbodiimide (DCC, 6.39 g, 31.0 mmol) was added portionwise at 0°C over 5 min. The ice bath was removed after 1 h and the reaction mixture was further stirred at room temperature for 16 h. The precipitate formed was filtered off and washed with dichloromethane (20 ml) and the filtrate was evaporated. The residue was purified by column chromatography (silica gel, column dimensions 48.0 cm×2.4 cm, hexane–ethyl acetate 50:1). Pooling and evaporation of the appropriate fractions gave bis(2,2-dichlorobutyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate (**8c**) as a colourless liquid (1.20 g, 2.94 mmol, 20%). R_f: 0.53 (silica gel, hexane–AcOEt 4:1). Bp: 87–88°C/0.15 mm Hg. ^{1}H NMR (270 MHz, $CDCl_3$, δ): 4.58 and 4.51 (each d, J=11.0 Hz, each 2H, AB system, 2× CH_2CCl$_2$R); 2.24 (q, J=7.3 Hz, 4H, CCl$_2$CH_2CH$_3$); 1.57 (s, 2H, H-3); 1.32 (s, 6H, Me); 1.19 (t, J=7.3 Hz, 6H, CCl$_2$CH$_2$CH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 167.35 (*C*O$_2$R); 90.28 (CH$_2$*C*Cl$_2$R); 71.66 (*C*H$_2$CCl$_2$R); 37.66 (CCl$_2$*C*H$_2$CH$_3$); 37.57 (C-1); 30.67 (C-2); 28.21 (C-3); 21.96 (Me); 9.22 (CCl$_2$CH$_2$*C*H$_3$). IR (NaCl, cm^{-1}): 1744 (C=O ester). HRMS (EI, *m/z*): $C_{15}H_{22}Cl_4O_4$ requires 406.0272; found 406.0271 (M$^+$).

3.1.5. Preparation of bis(2,2-dichlorohexyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate (8d). In a 50 ml round-bottomed flask, provided with magnetic stirrer and nitrogen inlet, 2,2-dimethylcyclopropane-1,1-dicarboxylic acid (**7**, 0.95 g, 6.0 mmol) was dissolved in dichloromethane (15 ml). To this solution, 2,2-dichlorohexanol[18] (4.90 g, 28.8 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 0.29 g, 2.4 mmol) were added and the mixture was cooled to 0°C. Then dicyclohexylcarbodiimide (DCC, 2.72 g, 13.2 mmol) was added portionwise and the mixture was left stirring at room temperature for 18 h. The precipitate formed was filtered off and the filtrate was evaporated. The residue was chromatographed (silica gel, column dimensions 21 cm×2,4 cm, hexane–AcOEt 50:1). Bis(2,2-dichlorohexyl) 2,2-dimethylcyclopropane-1,1-dicarboxylate (**8d**) was obtained as a colourless liquid (1.43 g, mmol, 51%). R_f: 0.16 (silica gel, hexane–AcOEt 50:1). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 4.57 and 4.49 (each d, J=11.9 Hz, each 2H, AB system, CH_2CCl$_2$R); 2.20 (q, J=7.3 Hz, 4H, CCl$_2$CH_2(CH$_2$)$_2$CH$_3$); 1.63 (pent, J=7.3 Hz, 4H, CH_2CH$_2$CH$_3$); 1.57 (s, 2H, H-3); 1.39 (sextet, J=7.3 Hz, 4H, CH_2CH$_3$); 1.32 (s, 6H, Me); 0.95 (t, J=7.3 Hz, 6H, CCl$_2$CH$_2$CH_3). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 167.35 (*C*O$_2$R); 89.47 (CH$_2$*C*Cl$_2$C$_4$H$_9$); 71.81 (*C*H$_2$CCl$_2$C$_4$H$_9$); 44.12 (CCl$_2$*C*H$_2$(CH$_2$)$_2$CH$_3$); 38.98 (C-1); 30.62 (C-2); 28.18 (C-3); 26.81 (CCl$_2$CH$_2$*C*H$_2$C$_2$H$_5$); 22.14 (CCl$_2$(CH$_2$)$_2$*C*H$_2$CH$_3$); 21.96 (Me); 13.84 (CCl$_2$(CH$_2$)$_3$*C*H$_3$). IR (NaCl, cm^{-1}): 1740 (C=O ester). MS (70 eV, *m/z*, %): 462/4/6/8/470 (M$^+$, 4); 295 (10); 293 (11); 159 (10); 141 (67); 140 (41); 123 (89); 122 (70); 117 (11); 116 (10); 114 (83); 113 (49); 112 (42); 111 (13); 103 (11); 97 (20); 96 (28); 95 (100); 94 (20); 89 (11); 86 (10); 84 (11); 81 (46); 79 (18); 78 (13); 77 (13); 76 (36); 75 (25); 71 (11); 69 (22); 67 (35); 65 (11); 57 (13); 56 (14); 55 (52); 53 (23); 51 (11); 49 (27); 44 (32); 43 (42); 42 (26); 41 (79). HRMS (EI, *m/z*): $C_{19}H_{30}Cl_4O_4$ requires 462.0898; found 462.0890 (M$^+$).

3.1.6. Preparation of (1*R*)-2,2-dimethylcyclopropane-1-(2,2,2-trifluoroethoxycarbonyl)-1-carboxylic acid (9). In a 50 ml beaker flask, provided with a magnetic stirrer, heating plate set at 30°C and a potentiometric titrator fitted with a calomel electrode, bis(2,2,2-trifluoroethyl)

2,2-dimethylcyclopropane-1,1-dicarboxylate (**8a**, 501 mg, 1.556 mmol) was dispersed in pH 7.0 phosphate buffer (0.1 M, 30 ml). Porcine liver esterase (PLE, from Sigma, in 2.5 M ammonium sulphate, 35 μl) was added. The mixture was kept under vigorous stirring at 28–30°C for 30 h and was then transferred to a separating funnel and extracted with dichloromethane (2×20 ml). The combined organic phases were dried, filtered and the solvent was evaporated, giving a recovery of unreacted bis(2,2,2-trifluoroethyl)-2,2-dimethylcyclopropane-1,1-dicarboxylate (**8a**, 48.8 mg, 0.152 mmol, 9.7%). The aqueous phase was then carefully acidified with 1 M HCl until pH 3–4 and extracted with ethyl acetate (5×20 ml). Drying ($MgSO_4$), filtration and evaporation of the solvent afforded (1*R*)-2,2-dimethylcyclopropane-1-(2,2,2-trifluoroethoxycarbonyl)-1-carboxylic acid (**9**, 231.2 mg, 0.963 mmol, 62%) as a colourless oil. R_f: 0.30 (silica gel, CH_2Cl_2–MeOH–HOAc 20:1:0.1). $[\alpha]_D^{20}$ =+7.51 (*c*=0.67, $CHCl_3$). ee: >95%.[19] ^{1}H NMR (270 MHz, $CDCl_3$, δ): 4.55 (m, 2H, CH_2CF_3); 1.78 and 1.70 (each d, *J*=5.1 Hz, AB system, 1H, H-3); 1.27 and 1.36 (each s, 3H, Me). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 171.03 (CO_2H); 169.40 ($CO_2CH_2CF_3$); 122.64 (q, J_{C-F}= 277 Hz, CH_2CF_3); 61.25 (q, J_{C-C-F}=36.6 Hz, CH_2CF_3); 34.28 (C-1); 29.72 (C-2); 27.98 (C-3); 22.12, 20.79 (Me_2). IR (KBr, cm^{-1}): 3430 (O–H acid); 1730 (C=O ester); 1610 (C=O acid). MS (ES^+, *m/z*, %): 240.9 ($M+1^+$, 100).

3.1.7. Preparation of (1*S*)-2,2,2-trifluoroethyl 2,2-dimethylcyclopropane-1-(*N*-ethoxycarbonylamino)-1-carboxylate (10). In a 50 ml round-bottomed flask equipped with a magnetic stirrer and a reflux condenser (1*R*)-2,2-dimethylcyclopropane-1-(2,2,2-trifluoroethoxycarbonyl)-1-carboxylic acid (**9**, 82 mg, 0.34 mmol) was dissolved in toluene (4 ml). Triethylamine (39 mg, 0.386 mmol) and diphenylphosphoroazidate (DPPA, 113 mg, 0.411 mmol) were added and the mixture was refluxed for 2 h. After cooling to room temperature, absolute ethanol (28.4 mg, 32 μl, 0.54 mmol) was added and stirring was continued for 16 h at room temperature. Saturated citric acid solution (10 ml) was added and the organic phase was then washed with 10% sodium bicarbonate (10 ml), dried, filtered and the solvent was evaporated. The residue was purified by column chromatography (silica gel, column dimensions 8.0 cm× 2.4 cm, hexane–ethyl acetate 5:1). A first eluting compound, *N*,*N*′-bis[1-[(1*S*)-2,2-dimethyl-1-(2,2,2-trifluoroethoxycarbonyl)-cyclopropyl]] urea (**11**), was obtained as a colourless oil (18.0 mg, 0.040 mmol, 12%). The second eluting compound, (1*S*)-2,2,2-trifluoroethyl 2,2-dimethylcyclopropane-1-(*N*-ethoxycarbonylamino)-1-carboxylate (**10**), was obtained as a colourless liquid (33 mg, 0.117 mmol, 34%). *N*,*N*′-Bis[1-[(1*S*)-2,2-dimethyl-1-(2,2,2-trifluoroethoxy-carbonyl)cyclopropyl]] urea (**11**): R_f: 0.28 (silica gel, hexane–AcOEt 4:1). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 5.63 (broad s, 2H, NH); 4.54 and 4.47 (each d, *J*=7.6 Hz, 2H, AB system, CH_2CF_3); 1.84 (d, *J*=6.0 Hz, 2H, H-3); 1.29 and 1.26 (each s, 3H, CH_3); 1.16 (d, *J*=6.0 Hz, 2H, H-3′). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 169.35 ($CO_2CH_2CF_3$); 157.43 (NHCONH); 122.70 (q, J_{C-F}=278 Hz, CH_2CF_3); 61.05 (q, J_{C-C-F}=36.6 Hz, CH_2CF_3); 42.82 (C-1); 29.83, 29.72 (C-2, C-3); 21.96, 19.41 (2×CH_3). IR (NaCl, cm^{-1}): 3321 (N–H); 1749 (C=O ester); 1705 (C=O urea). HRMS (EI, *m/z*): $C_{17}H_{22}F_6N_2O_5$ requires 448.1433; found 448.1423 (M^+). (1*S*)-2,2,2-Trifluoroethyl 2,2-dimethylcyclopropane-1-(*N*-ethoxycarbonylamino)-1-carboxylate (**10**): R_f: 0.22 (silica gel, hexane–AcOEt 4:1). $[\alpha]_D^{20}$ =−21.03 (*c*=0.17, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$, δ): 5.25 (broad s, 1H, N*H*CO_2R); 4.49 (m, 2H, CH_2CF_3); 4.13 (q, *J*=7.0 Hz, 2H, OCH_2CH_3); 1.77 (m, 1H, H-3); 1.30 and 1.24 (each s, 3H, Me); 1.25 (t, *J*=7.0 Hz, OCH_2CH_3); 1.12 (m, 1H, H-3). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 170.33 (CO_2R); 156.87 (NHCO_2Et); 122.80 (q, J_{C-F}=277 Hz, CH_2CF_3); 61.29 (OCH_2CH_3); 60.8 (q, J_{C-C-F}=36.6 Hz, CH_2CF_3); 42.95 (C-1); 29.87, 29.69 (C-2, C-3); 21.92, 19.52 (2×CH_3); 14.41 (CH_2CH_3). IR (NaCl, cm^{-1}): 3327 (N–H); 1745 (C=O ester); 1720 (C=O carbamate). HRMS (EI, *m/z*): $C_{11}H_{16}F_3NO_4$ requires 283.1031; found 283.1038 (M^+).

3.1.8. Preparation of (1*S*)-1-amino-2,2-dimethylcyclopropane-1-carboxylic acid (4). In a 10 ml round-bottomed flask provided with a magnetic stirrer and a reflux condenser, (1*S*)-2,2,2-trifluoroethyl 2,2-dimethyl-1-(*N*-ethoxycarbonylamino)cyclopropane-1-carboxylate (**10**, 30 mg, 0.106 mmol) was mixed with 6 M NaOH solution (1.0 ml). After refluxing for 16 h, the mixture was cooled to 0°C and acidified with 2 M HCl (ca. 3.0 ml). The acidic solution was chromatographed over ion exchange resin DOWEX 50-8 (H form, column dimensions 7.0 cm× 2.0 cm) eluting with 1 M HCl, water and then 5% aqueous ammonia. Pooling and evaporation of the appropriate fractions afforded (1*S*)-1-amino-2,2-dimethylcyclopropane-1-carboxylic acid (**4**, 10.2 mg, 0.079 mmol, 75%) as an amorphous white solid. R_f: 0.41 (silica gel, *n*-butanol–water–HOAc 4:1:1). $[\alpha]_D^{20}$ =−50 (*c*=0.52, MeOH), lit. 9 $[\alpha]_D^{20}$ =−55 (*c*=0.95, MeOH). ee: >84%.[22] ^{1}H NMR (270 MHz, D_2O, δ): 1.29 (d, *J*=6.6 Hz, AX system, H-3b); 1.14 and 1.10 (each s, 3H, $(CH_3)_2$); 0.91 (d, *J*= 6.6 Hz, AX system, H-3a). ^{13}C NMR (67.5 MHz, D_2O, δ): 178.20 (CO_2H); 46.43 (C-1); 24.94 (C-3); 23.68 (C-2); 20.97 and 20.77 (2×CH_3).

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19. Racemic and enantiomerically enriched samples of compound (**9**) were reacted with an excess of diazomethane in diethyl ether. After five minutes at room temperature, mixtures were evaporated. The resulting methyl ester derivatives were analysed by isothermic (90°C) chiral GC, using a cyclodextrose B SDE 25QC2/CYDEX-B 0.25 column, length 25 m, and with H_2 (10 psi) as carrier gas. The determination of the enantiomeric excess of (**9**) was thus done by direct comparison of the areas in the chromatograms.
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22. Racemic and enantiomerically enriched samples of (**4**) were mixed with (*R*)-α-methoxy-α-trifluoromethyl phenyl acetyl chloride (ca. 1.5 equiv.) and pyridine and refluxed for 16 h. Conventional work-up, drying and evaporation of the solvent afforded the corresponding *N*-acyl derivatives, already suitable for HPLC purposes. Samples were analysed by isocratic reverse phase HPLC (MeCN:0.05% TFA 40:60, flow 1 ml min^{-1}), using a μBondapack C18, 3.9×300 mm column (10 μm particle size). The enantiomeric excess of (**4**) was determined by direct comparison of the areas in the chromatograms.
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