Isomorphic supramolecular structures *via* one-dimensional hydrogen bonding motifs in crystals of chiral difluorolactates, trichlorolactates and trifluorolactates

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Electronic Supplementary Information (ESI)

(i) Experimental procedures.

(ii) Figure 1S ORTEP plots for 4, 5a, 6, 7b, and 21 at 50% probability

level.

(iii) Figure 2S Additional figures for 2a and 2b

Experimental procedures General

Reagents and solvents were obtained from TCI Co., Ltd., WAKO Pure Chemical Industries Ltd., and Aldrich Chemical., Ltd. Chlorotrimethylsilane was distilled prior to use. Tetrahydrofuran (THF) was distilled from sodium and benzophenone under nitrogen atmosphere. Furfural was distilled under reduced pressure prior to use. Chloroform was distilled from CaH₂. Other reagents were used without further purification. IR spectra were measured on a Hitachi Model 270-30 Infrared Spectrophotometer. Elemental analyses were performed on a Perkin Elmer series II CHNS/O Analyzer 2400. GC/MS analyses were carried out on a Shimadzu GCMS-QP5050A. Melting points were recorded by a Yanako MP-S3 melting point measurement apparatus. ¹H (300 MHz) and ¹⁹F (282 MHz) NMR spectra were recorded by a Varian MERCURY 300 instrument. ¹H (500 MHz) NMR spectra were recorded by a Varian VXR500 instrument. ¹H (600 MHz), ¹⁹F (564 MHz) and ¹³C (150 MHz) NMR spectra were recorded by a Varian UNITY INOVA 600 instrument. The chemical shifts are reported in δ (ppm) values relative to TMS (δ 0 ppm for ¹H NMR), C₆F₆ (δ 0 ppm for ¹⁹F NMR), CDCl₃ or acetone-*d*₆ or CD₃OD (δ 77.0 ppm or 29.8 ppm or 49.0 ppm for ¹³C NMR, respectively). Coupling constants are reported in hertz (Hz). Optical rotation was measured in a cell with 50 mm length and 1 mL capacity using a Horiba SEPA-300 highly sensitive polarimeter. Chiral GC analysis was performed on a Shimadzu GC-14B equipped with a Varian Chrompack CP-cyclodexB236-M19 capillary column (50 m) using N₂ career gas.

5-Methyl-2-(2,2,2-trifluoroacetyl)furan (9): To a mixture of 2-methylfuran (68 mL, 750 mmol) in dry *n*-hexane (500 mL) was added trifluoroacetic anhydride (70.6 mL, 500 mmol) dropwise (30 min) at 0 °C under argon atmosphere. The reaction mixture was stirred for additional 2 h at 0 °C. After evaporation of *n*-hexane under reduced pressure, the reaction mixture was added to saturated NaHCO₃ aq. (150 mL) at 0 °C. The reaction mixture was extracted with ether (20 mL x 5). The combined organic phase was washed with brine, dried (MgSO₄), filtrated, and concentrated to give a crude oil, which was purified by distillation under reduced pressure (20 Torr, 70 °C) to afford **9** (67.0 g, 78% yield based on TFAA). Colorless oil. IR (neat): 1694, 1512 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.44 (m, 1H), 6.32 (m, 1H), 2.47 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃) δ 88.6 (s, 3F). ¹³C NMR (150 MHz, CDCl₃): δ 167.6, 145.7, 126.4, 116.4, 110.4, 14.1. MS: m/z 178(28), 109(100), 69(17), 53(35), 51(11).

5-Methyl-2-(2,2-difluoroacetyl)furan (11): A suspension of Mg (2.43 g, 100 mmol) and chlorotrimethylsilane (25.4 mL, 200 mmol) in freshly distilled dry THF (200 mL) was cooled down to 0 °C under an argon atmosphere. To the mixture was added **9** (8.95 g, 50 mmol) in dry THF (50 mL) dropwise (1.5 h) at 0 °C under an argon atmosphere. The reaction mixture was stirred for additional 20 min. After evaporation of excess chlorotrimethylsilane and THF under reduced pressure, then *n*-hexane was added to the residue, and the resulting salt was separated by filtration through Celite with *n*-hexane and the filtrate was concentrated to give crude difluoroenol silyl diethyl ether **10**. Purity of **10**: 90% (determined by ¹H NMR). ¹H NMR (300 MHz, CDCl₃): δ 6.24 (m, 1H), 6.00 (m, 1H), 2.31 (s, 3H), 0.22 (s, 9H). ¹⁹F NMR (282 MHz, CDCl₃): δ 58.7 (d, J = 65 Hz, 1F), 51.0 (d, J = 65 Hz, 1F). A solution of **10** in THF (50 mL) was poured into suspension of 35 wt% HCl aq. (8 mL) in THF (50mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and the reaction mixture was neutralized with saturated NaHCO₃ aq. (80 mL) at 0 °C and then THF was removed from the mixture under reduced pressure. The resulting mixture was extracted with ether (10 mL x 5). The combined organic phase was washed with brine, dried (MgSO₄), filtrated, and concentrated to give a crude oil, which was purified by distillation under reduced pressure (20 Torr,

90 °C) to afford **11** (5.59 g, 70%). Colorless oil. IR (neat): 1694, 1512 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.43 (m, 1H), 6.28 (m 1H), 6.15 (t, $J_{H,F}$ = 54 Hz, 1H), 2.46 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ 38.1 (d, $J_{F,H}$ = 54 Hz, 2F). ¹³C NMR (150 MHz, CDCl₃): δ 175.0, 161.3, 146.9, 124.9, 110.4, 110.0, 14.1. MS: m/z 160(23), 109(100), 53(34), 51(21).

rac-1-(5-methyl-2-furyl)-2,2-difluoroethyl acetate (12): To a stirred solution of 11 (14.8 g, 93 mmol) and EtOH (93 mL) at 0 °C was added NaBH₄ (21.0 g, 56 mmol) for 10 min. The reaction mixture was stirred for 3 h at room temperature. After removal of the EtOH under reduced pressure, the residue was dissolved in water (50 mL), the aqueous phase was extracted with ether. The organic phase was dried (MgSO₄), filtrated, and concentrated to give a crude alcohol. To a mixture of the crude alcohol and dry pyridine (47 mL) was added acetic anhydride (13.1 mL, 139 mmol) at 0 °C. The reaction mixture was stirred 10 h at room temperature. After the reaction mixture was added to 35% HCl aq. (50 mL) at 0 °C for removing excess amount of pyridine, the aqueous solution was extracted with ether (20 mL x 5). The combined organic phase was concentrated. The residue was added to saturated NaHCO₃ aq. (50 mL) at 0 °C, the resulting mixture was extracted with ether (20 mL x 5) again. The combined organic phase was washed with brine, then dried (MgSO₄), filtrated, and concentrated to give crude oil, which was purified by distillation under reduced pressure (20 Torr, 110 °C) to afford **12** (16.4 g, 87%). Colorless oil. IR (neat): 1760 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 64.1 (d, *J* = 3 Hz, 1H), 6.06 (dt, *J*_{H,H} = 5 Hz, *J*_{H,F} = 54 Hz, 1H), 5.98 (m, 1H), 5.97 (m, 1H), 2.30 (d, *J* = 1 Hz, 3H), 2.14 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ 34.7 (dd, *J*_{EH} = 12, 56 Hz, 1F), 36.7 (dd, *J*_{EH} = 9, 56 Hz, 1F). ¹³C NMR (150 MHz, CDCl₃): δ 169.2, 153.8, 144.3, 112.7, 112.5, 106.7, 66.9, 20.6, 13.4. MS: m/z 204(7), 184(6), 145(32), 142(52), 111(100), 95(25), 51(43).

rac-2-Acetoxy-3,3-difluoropropanoic acid (13): The acetate 12 (16.4 g, 80 mmol) was dissolved in CCl₄/CH₃CN/H₂O (2:2:3, 800 mL). To this mixture were added NaIO₄ (137 g, 640 mmol) and RuCl₃·3H₂O (0.42 g, 1.6 mmol) at 5 °C, and the mixture was vigorously stirred using a mechanical stirrer (200 rpm) for 3 h. The white precipitate was filtered off through a pad of Celite with ether (300 mL). The organic phase was separated, and the aqueous phase was extracted with ether (20 mL x 5). The combined organic phase was dried (MgSO₄), filtrated, and concentrated to give a crude oil, which purified by distillation under reduced pressure (5 Torr, 60 °C) to afford **13** (12.1 g, 90%). Colorless oil. IR (neat): 3196, 1756 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 6.17 (dt, $J_{H,H}$ = 3 Hz, $J_{E,H}$ = 54 Hz, 1H), 5.41 (ddd, $J_{H,H}$ = 3 Hz, $J_{H,F}$ = 9, 17 Hz, 1H), 2.25 (s, 3H), COOH was not observed. ¹⁹F NMR (282 MHz, CDCl₃): δ 34.4 (ddd, $J_{E,H}$ = 9, 54 Hz, $J_{E,F}$ = 289 Hz, 1F), 33.6 (ddd, $J_{E,H}$ = 17, 54 Hz, $J_{E,F}$ = 289 Hz, 1F). ¹³C NMR (150 MHz, CDCl₃): δ 169.9, 169.6, 111.7, 70.3, 20.1.

rac-3,3-Difluoro-2-hydroxypropanoic acid (3,3-difluorolactic acid) (14): To a stirred solution of 13 (12.1 g, 72 mmol) and H₂O (72 mL) at 0 °C was added K₂CO₃ for 10 min. The reaction mixture was stirred for 3 h at room temperature and then treated with 35% HCl aq. (60 mL) at 0 °C, and the resulting mixture was extracted with ether (10 mL x 20). The combined organic phase was dried (MgSO₄), filtrated, and concentrated to give a crude oil, which was purified by kugelrohr distillation (5 Torr, 60 °C) to afford a hygroscopic solid 14 (5.16 g, 57%). IR (KBr): 3400, 1738 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 6.04 (dt, $J_{H,H} = 2$ Hz, $J_{F,H} = 54$ Hz, 1H), 4.48 (ddd, $J_{H,H} = 2$ Hz, $J_{H,F} = 12$, 16 Hz, 1H), 2.8-3.4 (brs, 1OH), COOH was not observed. ¹⁹F NMR (282 MHz, CDCl₃): δ 32.7 (ddd, $J_{F,H} = 12$, 54 Hz, $J_{F,F} = 286$ Hz, 1F), 31.0 (ddd, $J_{F,H} = 16$, 54 Hz, $J_{E,F} = 286$ Hz, 1F). ¹³C NMR (150 MHz, acetone- d_6): 170.1, 115.4, 71.3.

stirred solution of *rac*-14 (1.95 g, 34 mmol) and AcOEt (34 mL) was added to suspension of (1*S*,2*S*)-2-amino-1-phyenyl-1,3-propanediol (5.53 g 34 mmol) and AcOEt (60 mL) at 80 °C. The reaction mixture was stirred for 30 min at 80 °C. Then, the reaction mixture was rested for 5 h at room temperature to give a yellow solid 15 (4.10 g, 42%, 53% de). The solid was separated from the mother liquor and then recrystallized from AcOEt/MeOH solution (3 times) to give optically pure yellow solid 15 (0.754 g, 8%, >99% de). Mp = 154-155 °C. ¹H NMR (300 MHz, methanol-*d*₄): δ 7.3-7.5 (m, 5H), 5.99 (dt, *J*_{*H*,*H*} = 2 Hz, *J*_{*E*,*H*} = 55 Hz, 1H), 4.73 (d, *J* = 9 Hz, 1H), 4.02 (ddd, *J*_{*H*,*H*} = 2 Hz, *J*_{*H*,*F*} = 8, 23 Hz, 1H), 3.52 (dd, *J* = 4, 6 Hz, 1H), 3.40 (dd, *J* = 6, 12 Hz, 1H), 3.2-3.3 (m, 1H), OHs and NH₃ were not observed. ¹⁹F NMR (282 MHz, methanol-*d*₄): δ 37.2 (ddd, *J*_{*E*,*H*} = 7, 56 Hz, *J*_{*E*,*F*} = 280 Hz, 1F), 30.8 (ddd, *J*_{*E*,*H*} = 23, 56 Hz, *J*_{*E*,*F*} = 280 Hz, 1F), 30.8 (ddd, *J*_{*E*,*H*} = 23, 56 Hz, *J*_{*E*,*F*} = 280 Hz, 1F). [α]²⁵_D = +22.1 (*c* 1.16, EtOH). The diastereomeric excess of **15** was confirmed as follows: the salt was treated with 6 N HCl aq. (10 equiv. of HCl) to give a optically active difluorolactic acid (+)-14, then its methyl ester derivative (+)-16 was analyzed by chiral GC. Absolution configuration of the 3,3-difluorolactate moiety was confirmed to be *R*.

(+)-(*R*)-3,3-Difluorolactic acid [(*R*)-14]: Optically pure (*S*,*S*)-(*R*)-15 was dissolved in 6 N HCl aq. and the aqueous solution was extracted with ether. The combined organic phase was dried (Na₂SO₄) and ether was removed under reduced pressure to give (+)-14 quantitatively. [α]²⁵_D = +4.57° (*c* 1.10, MeOH). Absolution configuration was confirmed to be *R*. IR (KBr): 3400, 1738 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 6.04 (dt, $J_{H,H}$ = 2 Hz, $J_{F,H}$ = 54 Hz, 1H), 4.48 (ddd, $J_{H,H}$ = 2 Hz, $J_{H,F}$ = 12, 16 Hz, 1H), 2.8-3.4 (brs, 1OH), COOH was not observed. ¹⁹F NMR (282 MHz, CDCl₃): δ 32.7 (ddd, $J_{F,H}$ = 12, 54 Hz, $J_{F,F}$ = 286 Hz, 1F), 31.0 (ddd, $J_{F,H}$ = 16, 54 Hz, $J_{F,F}$ = 286 Hz, 1F). ¹³C NMR (150 MHz, acetone- d_6): 170.1, 115.4, 71.3.

(+)-Methyl (*R*)-3,3-difluorolactate [(*R*)-16]: To stirred solution of (+)-14 (0.061 g, 0.48 mmol) in MeOH (1.0 mL) was added 1 drop of H₂SO₄. The reaction mixture was stirred for 12 h at 50 °C and then MeOH was removed from the mixture under reduced pressure. The resulting mixture was purified by column chromatography on silica gel (*n*-hexane:ether = 1:1) to give optically pure (+)-16 (0.036 g, 53%). Colorless needle crystal. ¹H NMR (300 MHz, CDCl₃): δ 5.96 (dt, *J*_{*H*,*H*} = 2 Hz, *J*_{*H*,*F*} = 54 Hz , 1H), 4.40 (m, 1H), 3.90 (s, 3H), 3.06 (d, *J* = 7 Hz, 1OH). ¹⁹F NMR (282 MHz, CDCl₃): δ 32.1 (ddd, *J*_{*E*,*H*} = 14, 54 Hz, *J*_{*E*,*F*} = 286 Hz, 1F), 31.4 (ddd, *J*_{*E*,*H*} = 16, 54 Hz, *J*_{*E*,*F*} = 286 Hz, 1F). [α] ²⁵_D = +8.32 (*c* 1.72, ether). Absolution configuration was confirmed to be *R*. Chiral GC analysis: >99% ee (t_S = 12.6 min, t_R = 13.1 min, column temp 90 °C isothermal, injector temp 100 °C, detector temp 200 °C, inlet pressure 100 kPa).

(-)-Methyl (*R*)-2-benzyloxy-3,3-difluoropropanoate [(*R*)-17]: To a suspension of silver oxide (0.042 g, 0.18 mmol) in ether (0.5 mL) under Ar was added (+)-16 (0.012 g, 0.09 mmol) in ether (0.2 mL) and benzyl bromide (36 μ L, 0.30 mmol). The reaction mixture was stirred for 48 h at room temperature then filtered through a pad of Celite and concentrated. The resulting residue was purified by column chromatography on silica gel (*n*-hexane:ether = 1:1) to afford (-)-17 (0.012 g, 58%). Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.2-7.4 (m, 5H), 5.97 (dt, $J_{H,H}$ = 4 Hz, $J_{H,F}$ = 54 Hz , 1H), 4.81 (d, J = 12 Hz, 1H), 4.65 (d, J = 12 Hz, 1H), 4.15 (ddd, $J_{H,H}$ = 4 Hz, $J_{H,F}$ = 9, 13 Hz, 1H), 3.81 (s, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ 34.5 (dd, J_{EH} = 9, 54 Hz, 1F), 34.41 (dd, $J_{F,H}$ = 13, 54 Hz, 1F). [α] ¹⁹_D = -61 (*c* 0.44, MeOH). Absolute configuration of (-)-17 was confirmed to be *R* by comparison of optical rotation with a known compound (*S*)-(+)-17. Lit. [α] ¹⁹_D = +61.07 (*c* 1.45, MeOH) [>95% ee (*S*)] (K. Murata and T. Kitazume, *Tetrahedron: Asymmetry*, 1993, 4, 889-892.). Thus, (+)-14 and its derivatives (-)-16, (-)-4, and (-)-5a had the same *R* configuration as (*R*)-(-)-17.

(-)-Isopropyl (*R*)-3,3-difluorolactate [(*R*)-4]: A mixture of (*R*)-14 (0.674 g, 5.35 mmol), sulfuric acid (0.5 mL), molecular sieves 4A (0.28 g) in 2-propanol (15 mL) was stirred under reflux condition for 48 h and then 2-propanol was removed under reduced pressure. The resulting mixture was purified by column chromatography on silica gel (*n*-hexane:ether = 1:1) to give optically pure (*R*)-4 (0.522 g, 58%). Colorless crystal. Mp 61-62 °C. IR (KBr) 3472, 1746 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 5.93 (dt, $J_{H,H}$ = 2 Hz, $J_{H,F}$ = 54 Hz, 1H), 5.19 (sept, J = 6 Hz, 1H), 4.33 (dddd, $J_{H,H}$ = 2, 7 Hz, $J_{H,F}$ = 12, 16 Hz, 1H), 3.11 (d, J = 7 Hz, 1OH), 1.33 (d, J = 6 Hz, 3H), 1.31 (d, J = 6 Hz, 3H). ¹⁹F NMR (282 MHz, CDCl₃): δ 32.1 (ddd, $J_{F,H}$ = 12, 54 Hz, $J_{F,F}$ = 286 Hz, 1F), 31.4 (ddd, $J_{F,H}$ = 16, 54 Hz, $J_{F,F}$ = 286 Hz, 1F). ¹³C NMR (150 MHz, CDCl₃): δ 168.4, 113.5, 71.2, 70.7, 21.5. MS: m/z 169(18), 125(70), 117(23), 107(16), 81(53), 62(100), 51(80). Anal. Calcd for C₆H₁₀F₂O₃ C 42.86, H 5.99, Found: C 42.82, H 5.93. [α] ²⁵_D = -2.21 (*c* 1.38, MeOH). Chiral GC analysis: >99% ee (t_R = 17.1 min, t_S = 18.0 min, column temp 100 °C isothermal, injector temp 100 °C, detector temp 200 °C, inlet pressure 100 kPa).

(-)-Hexamethylene-(*R*,*R*)-bis(3,3-difluorolactate) [(*R*,*R*)-5a]: Two-necked round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and Dean-Stark apparatus surmounted by reflux condenser was charged with 1,6-hexanediol (0.0777 g, 0.66 mmol), a optically pure (*R*)-14 (0.214 g, 1.7 mmol) and 1 drop of sulfuric acid as a catalyst in benzene (5 mL). The mixture was brought to reflux with the removal water. After 6 h resulting mixture was cooled to ambient temperature and water (1 mL) was added to the mixture, which was extracted with ether (1 mL x 5). The organic phase was dried over MgSO₄, filtrated, and concentrated to give a crude product. The crude product was purified by column chromatography on silica gel (*n*-hexane:ether = 1:1) to afford (*R*,*R*)-5a (0.159 g, 73% yield based on 1,6-hexanediol). Colorless crystal. Mp 82-83 °C. IR (KBr) 3460, 1754 cm⁻¹: ¹H NMR (500 MHz, CDCl₃): δ 5.94 (dt, *J*_{*H*,*H*} = 2 Hz, *J*_{*H*,*F*} = 55 Hz, 2H), 4.38 (dddd, *J*_{*H*,*H*} = 2, 7 Hz, *J*_{*H*,*F*} = 14, 14 Hz, 2H), 4.33 (dt, *J* = 7, 11 Hz, 2H), 4.27 (dt, *J* = 7, 11 Hz, 2H), 3.08 (d, *J* = 7 Hz, 2CH), 1.72 (m, 4H), 1.41 (m, 4H). ¹⁹F NMR (564 MHz, CDCl₃): δ 32.15 (dd, *J* = 7.0, 14.0 Hz, 2F). ¹³C NMR (150 MHz, CDCl₃): δ 169.0, 113.5, 70.7, 66.6, 28.2, 25.1. MS: *m*/z 127(10), 111(9), 99(4), 91(4), 83(54), 81(98), 73(5), 67(18), 62(19), 61(66), 55(100), 51(25). Anal. Calcd for C₁₂H₁₈F₄O₆ C 43.12, H 5.43, Found: C 43.28, H 5.33. [α]²⁰_D = -5.7 (*c* 0.81, acetone).

rac-1-(2-Furyl)-2,2,2-trichloroethanol (18): To a mixture of furfural (16.6 mL, 200 mmol) and chloroform (32.1 mL, 400 mmol) was added DBU (200 mmol) dropwise under nitrogen at 15 °C. The reaction mixture was stirred for 6 h and then diluted with chloroform (500 mL) and washed with 2 N HCl aq. (3 x 200 mL). The organic phase was dried (Na₂SO₄), filtrated, and concentrated. The residue was distilled under reduced pressure (0.6 Torr, 80 °C) to give **18** in 74% yield (96% purity by GCMS). ¹H NMR (500MHz, CDCl₃): δ 7.47 (dd, $J_1 = 2$ Hz, $J_2 = 1$ Hz, 1H), 6.61 (d, J = 3 Hz, 1H), 6.43 (dd, $J_1 = 3$ Hz, $J_2 = 2$ Hz, 1H), 5.24 (d, J = 7 Hz, 1H), 3.32 (d, J = 7 Hz, 1OH). MS: m/z 217.9 (0.2), 215.9 (0.6), 143 (5), 97 (100), 69 (8), 51 (6), 41 (27).

rac-2-Acetoxy-3,3,3-trichloropropanoic acid (19): A mixture of 18 (26.8 g, 124 mmol), acetic anhydride (14.1 mL, 150 mmol), DMAP (0.61 g, 5 mmol) and pyridine (60 mL) was stirred at room temperature for 12 h. Saturated NaHCO₃ aq. (60 mL) was added, and the mixture was extracted with *n*-hexane (2 x 100 mL). The combined organic phase was dried (MgSO₄) and concentrated to give the crude acetate. This acetate was dissolved in $CCl_4/CH_3CN/H_2O$ (2:2:3, 800 mL). To

this mixture were added NaIO₄ (197 g, 920 mmol) and RuCl₃·3H₂O (0.60 g, 2.3 mmol) at 5 °C, and the mixture was vigorously stirred using a mechanical stirrer (200 rpm) for 2.5 h. The white precipitate was filtered off through a pad of Celite with AcOEt (500 mL). The organic phase was separated, and the aqueous phase was extracted with AcOEt (2 x 200 mL). The combined organic phase was dried (MgSO₄), filtrated, and concentrated to give a crude oil, which purified by distillation under reduced pressure (1 Torr, 90 °C) to afford **19** (23.6 g, 80%). Colorless oil. IR (neat): 3208, 1768 cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 5.67 (s, 1H), 2.28 (s, 3H), COOH was not observed. ¹³C NMR (150 MHz, CDCl₃): δ 169.4, 168.6, 93.1, 79.8, 20.3. MS: m/z 117 (3), 60 (2), 43 (100).

rac-3,3,3-Trichloro-2-hydroxypropanoic acid (3,3,3-trichlorolactic acid) (20): A mixture of **19** (23.5 g, 100 mmol), potassium carbonate (13.8 g, 100 mmol) and methanol (150 mL) was stirred for 4 h and then treated with 6N HCl aq. (100 mL) and the mixture was extracted with ether (4 x 200 mL). The combined organic phase was dried (Na₂SO₄), filtrated, and concentrated to give crude yellow solid, which purified by recrystallization from chloroform solution at freezer to afford **20** (72%). White solid. IR (KBr): 3400, 1746 cm⁻¹. ¹H NMR (600 MHz, acetone-*d*₆): δ 6.07 (brs, 10H), 4.79 (brs, 1H), COOH was not observed. ¹³C NMR (150 MHz, acetone-*d*₆): δ 168.4, 99.4, 81.9.

(+)-(*S*)-1-Phenylethylammonium (*S*)-3,3,3-trichlorolactate [(*S*,*S*)-21]: To a mixture of *rac*-20 (3.18 g, 16.4 mmol) and ethanol (30 mL) was added (*S*)-1-phenylethylamine (1.98 g, 16.4 mmol) at room temperature. The white precipitate was dissolved at 50 °C and the ethanol solution was cooled in room temperature and then cooled to 0 °C to give colorless crystal (*S*,*S*)-21 (2.10 g, 40%, 43% de). The crystal was separated from the mother liquor. Recrystallization of the diastereomeric salt was repeated twice to give the optically pure (*S*,*S*)-21 (0.74 g, 14%). Colorless block crystal. Mp 125-126 °C. IR (KBr): 3448, 3040, 1642, 1632, 1602 cm⁻¹. ¹H NMR (300 MHz, CD₃CN): δ 7.35-7.57 (m, 5H), 4.46 (q, *J* = 7 Hz, 1H), 1.65 (d, *J* = 7 Hz, 3H), NH and OH were not observed. ¹³C NMR (150 MHz, CD₃OD): δ 172.1, 139.8, 130.2, 130.1, 127.7, 101.8, 84.2, 52.3, 20.8. Anal. Calcd for C₁₁H₁₄Cl₃N₁O₃: C 42.00, H 4.49, N 4.45, Found: C 42.25, H 4.22, N 4.70. [α]²⁰_D +18.62 (*c* 1.3, MeOH). Absolute configuration of the 3,3,3-trichlorolactate moiety was determined to be *S* by single crystal X-ray diffraction technique. The diastereomeric excess of (*S*,*S*)-21 was confirmed as follows: the salt was treated with 6 N HCl aq. (10 equiv. of HCl) to give a optically active trichlorolactic acid (–)-20, then its ethyl ester derivative was analyzed by chiral GC (t_s = 18.0 min, t_R = 18.3 min, column temp: 150 °C isothermal, injector and detector temp: 200 °C, inlet pressure 50 kPa).

(-)-(*S*)-3,3,3-trichlorolactic acid [(*S*)-20]: Optically pure (*S*,*S*)-21 (0.70 g, 2.2 mmol) was dissolved in 6 N HCl aq. (22 mmol, 3.6 mL) and the aqueous solution was extracted with ether (3 x 3.0 mL). The combined organic phase was dried (Na₂SO₄) and ether was removed under reduced pressure to give (*S*)-20 (0.40 g, 95%). White solid. Mp 106-110 °C. $[\alpha]^{25}_{D}$ –18.55 (*c* 2.5, EtOH). IR (KBr): 3400, 1746 cm⁻¹. ¹H NMR (600 MHz, acetone-*d*₆): δ 6.07 (brs, 10H), 4.79 (brs, 1H), COOH was not observed. ¹³C NMR (150 MHz, acetone-*d*₆): δ 168.4, 99.4, 81.9.

(-)-Isopropyl-(*S*)-3,3,3-trichlorolactate [(*S*)-6]: A mixture of (*S*)-20 (0.364 g, 1.87 mmol), sulfuric acid (0.02 g, 0.2 mmol), molecular sieves 3A (0.5 g), and 2-propanol (1.5 mL) was stirred at 60 °C for 24 h. The reaction mixture was cooled and washed with brine (1.5 mL) and extracted with ether (3 x 2.0 mL). The combined organic phase was dried (Na₂SO₄), filtrated, and concentrated to give crude oil, which purified by kugelrohr distillation (13 mmHg, 80 °C) to give (*S*)-6 (0.158 g, 36%). Colourless needle crystal. Mp 42-43 °C. IR (KBr): 3364, 1722 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ

5.21 (heptet, J = 6 Hz, 1H), 4.60 (d, J = 9 Hz, 1H), 3.98 (d, J = 9 Hz, 1OH), 1.34 (t, J = 6 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃): δ 167.3, 98.0, 80.9, 72.0, 21.6, 21.5. MS m/z 197 (0.08), 195 (0.37), 193 (0.79), 191 (0.6), 119 (1), 117 (4), 116 (1), 114 (5), 113 (1), 112 (8), 111 (1), 85 (1), 83 (2), 59 (2.5), 43(100). Anal. Calcd for C₆H₉FCl₃O₃: C 30.60, H 3.85, Found: C 30.40, H 3.74. [α]²⁰_D –23.0 (*c* 0.50, MeOH). Chiral GC analysis: >99% ee (t_s = 18.3 min, t_R = 18.6 min, column temp: 150 °C isothermal, injector and detector temp: 200 °C, inlet pressure 50 kPa).

(-)-Octamethylene-(*S*,*S*)-bis(3,3,3-trichlorolactate) [(*S*,*S*)-7b]: Two-necked round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a pressure-equalized addition funnel acting as Soxhlet extractor (containing a cotton plug and g of molecular sieves 4A) surmounted by reflux condenser was charged with 1,8-octanediol (0.146 g, 1.0 mmol), (*S*)-**20** (0.580 g, 3.0 mmol) and sulfuric acid (0.049 g, 0.5 mmol) as a catalyst in heptane (5 ml). The mixture was brought to reflux with the removal of water. After 12 h, the resulting mixture was cooled to ambient temperature and water was added to the mixture, which was extracted with ether. The combined organic phase was washed with brine, dried (MgSO₄), filtrated, and concentrated under reduced pressure. The crude oil was purified by silica-gel column chromatography (*n*-hexane/AcOEt = 5/1) to give the double-headed ester (*S*,*S*)-7b (0.253 g, 0.51 mmol, 51% yield based on 1,8-octanediol). Mp 83-84 °C. IR (KBr): 3416, 1742 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 4.64 (d, *J* = 10 Hz, 2H), 4.35 (dt, *J*₁ = 11 Hz, *J*₂ = 7 Hz, 2H), 4.27 (dt, *J*₁ = 11 Hz, *J*₂ = 7 Hz, 2H), 3.98 (d, *J* = 10 Hz, 2OH), 1.65-1.75 (m, 4H), 1.30-1.42 (m, 8H). ¹³C NMR (150 MHz, CDCl₃): δ 168.0, 97.8, 80.9, 67.4, 28.8, 28.2, 25.6. Anal. Calcd for C₁₄H₂₀Cl₆O₆ C 33.83, H 4.06, Found: C 34.10, H 3.93. [α]²⁰D -12.74 (*c* 0.63, MeOH).

Figure 1S ORTEP plots for (*R*)-4, (*R*,*R*)-5a, (*S*)-6, (*S*,*S*)-7b, and (*S*,*S*)-21 at 50% probability level.











(*S*)-6

(*S*,*S*)-7b





and green spheres represent carbon, hydrogen, oxygen, and fluorine atoms, respectively. Hash bonds indicate intermolecular hydrogen bonds. (a) (b) Two-dimensional hydrogen bonding networks along with the c axes; (c) (d) perspective views of three-dimensional layered crystal structures. Hydrogen atoms of polymethyelene chains are omitted for clarity. (e) (f) the space-filling representations as viewd down along the b axes.





