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REGULAR ARTICLE

Chiral syntheses of methyl (*R*)-2-Sulfanylcarboxylic esters and acids with optical purity determination using HPLC

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Abstract

Accessible chiral syntheses of 3 types of (*R*)-2-sulfanylcarboxylic esters and acids were performed: (*R*)-2-sulfanylpropanoic (thiolactic) ester (53%, 98%ee) and acid (39%, 96%ee), (*R*)-2-sulfanylsucciinic diester (59%, 96%ee), and (*R*)-2-mandelic ester (78%, 90%ee) and acid (59%, 96%ee). The present practical and robust method involves (i) clean S_N2 displacement of methanesulfonates of (*S*)-2-hydroxyesters by using commercially available AcSK with tris(2-[2-methoxyethoxy])ethylamine and (ii) sufficiently mild deacetylation. The optical purity was determined by the corresponding (2*R*,5*R*)-*trans*-thiazolidin-4-one and (2*S*,5*R*)-*cis*-thiazolidin-4-one derivatives based on accurate high-performance liquid chromatography analysis with high-resolution efficiency. Compared with the reported method utilizing AcSCs (generated from AcSH and $CsCO_3$), the present method has several advantages, that is, the use of odorless AcCOSK reagent, reasonable reaction velocity, isolation procedure, and accurate, reliable optical purity determination.

The use of accessible AcSK has advantages because of easy-to-handle odorless and hygroscopic solid that can be used in a bench-top procedure. The $Ti(OiPr)_4$ catalyst promoted smooth *trans*-cyclo-condensation to afford (2*R*,5*R*)-*trans*-thiazolidin-4-one formation of (*R*)-2-sulfanylcarboxylic esters with available *N*-(benzylidene)methylamine under neutral conditions without any racemization, whereas (2*S*,5*R*)-*cis*-thiazollidin-4-ones were obtained via *cis*-cyclo-condensation and no catalysts. Direct high-performance liquid chromatography analysis of methyl (*R*)-mandelate was also performed; however, the resolution efficiency was inferior to that of the thaizolidin-4-one derivatizations.

KEYWORDS

2-sulfanylmandelic ester, 2-sulfanylsuccinic ester, drug discovery, HPLC analysis, process chemistry, SN2 inversion, thiazolidin-4-one, thiolactic acid

1 | INTRODUCTION

Considerable attention has been focused on the chemistry of ubiquitous optically pure secondary and tertiary thiols.[1,2] Among them, chiral 2-sulfanyl (classically, α-mercapto) carboxylic esters **1** and acids **2** (Figure 1) serve as well-recognized synthetic building blocks for the isoster of chiral 2-hydroxycarboxylic esters and acids in natural product and pharmaceutical syntheses.

Figure 2 displays representative natural products and biologically active agents/compounds installing the chiral thiol segments **1** and **2**.[1,2] Tiopronin,[3,4] thiolactomycin,[5-7]

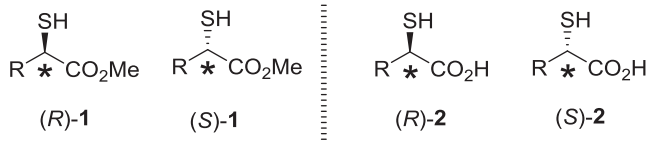


FIGURE 1 Chiral 2-sulfanylcarboxylic esters **1** and acids **2**

and gliotoxin[8] are leading natural antibiotic compounds. Other representative agents/compounds are listed in chronologic order: antiplatelet activating factor (*anti*-PAF) antagonists (1991),[9] IMP-1 metallo-β-lactamase inhibitor (1999),[10] vasopeptidase inhibitor (2003),[11] methionine aminopeptidase active cite probes (2004),[12] specific substrate for Streptomyces R61 D,D-peptidases (2005),[13] nonsteroidal farnesoid X receptor agonist (2013),[14] (CNS)-penetrant thiazolidinone CGRP receptor antagonists (2014),[15] agonist for muscarinic M_1 acetylcoline receptor (2015),[16] and fructosyl peptide oxidases inhibitor (2015).[17]

Two notable synthetic utilities are addressed (Scheme 1). One is the chiral template methodology[18] using 1,3-oxathiolan-4-ones for synthesizing chiral 2-alkyl-2-methylsulfanyl acids (self-regeneration of stereocenters[19]), which were representatively applied for the asymmetric synthesis of (5*R*)-thiolactomycin and its analogues.[20,21] Another is thiazolidin-4-one type chiral ligand derived from **2** for a Cu(I)-catalyzed asymmetric conjugate addition to enones, developed by Feringa's group.[22] Recently, synthesis of Au-nanocluster of (*R*)/(*S*)-sulfanylsuccinic acid and its chiroptical response property was disclosed.[23]

Due to the high demand, several synthetic methods of chiral thiols **1** and **2** have been developed to date. Transformation starting from chiral amino acids to **2** is a traditional synthetic protocol by the following sequences: diazotization, stereoretentive double clean S_N2 displacements using AcSM, and deprotection of AcS-group.[24] The pioneering and reliable method for obtaining **1** and

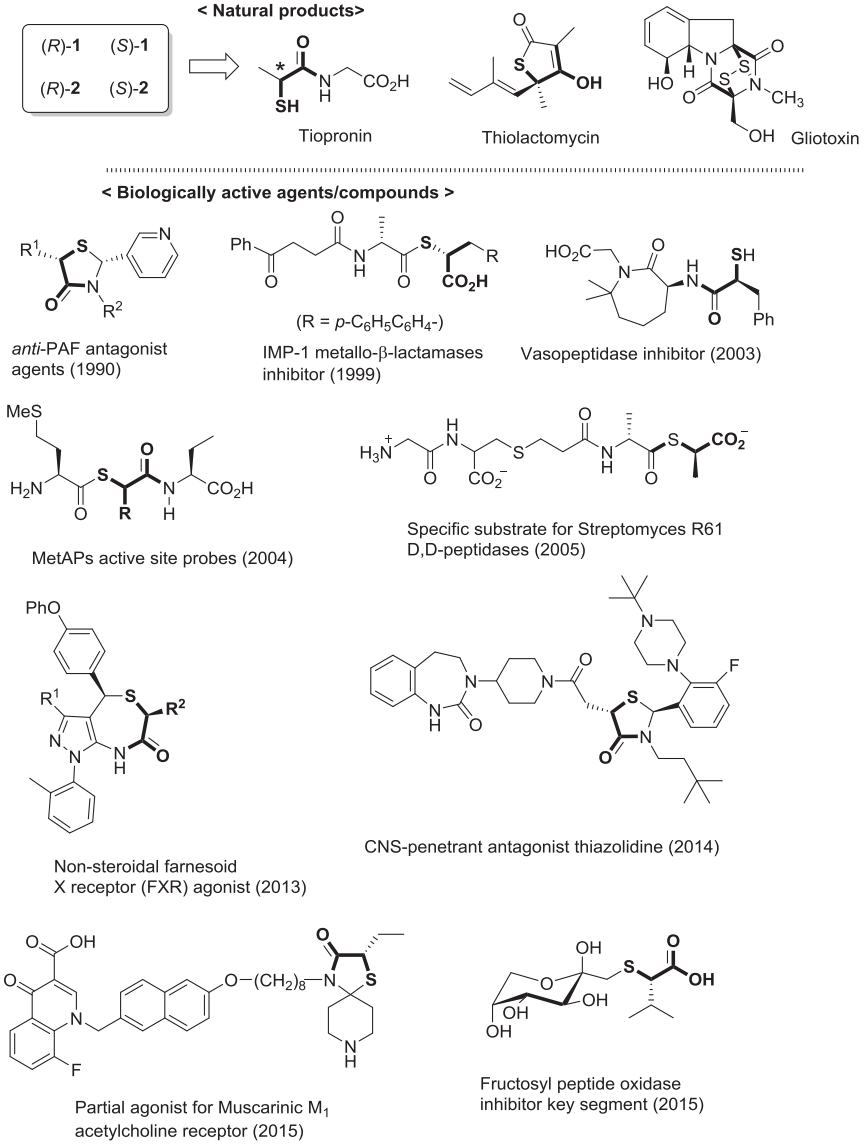
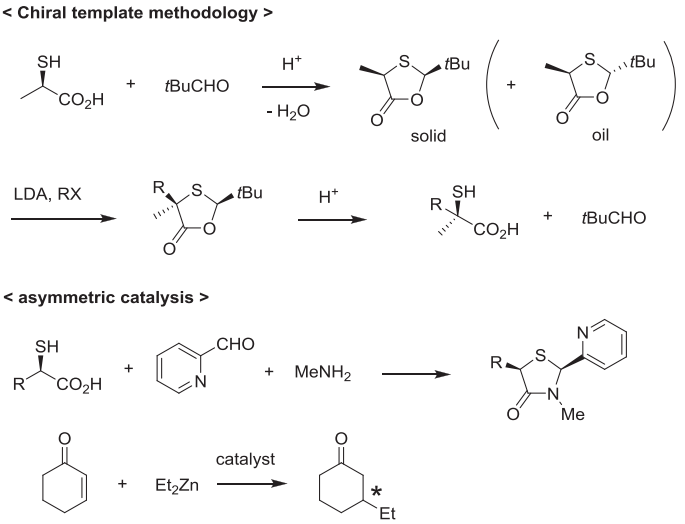


FIGURE 2 Representative natural products and pharmaceuticals incorporating **1** and **2**



SCHEME 1 Representative synthetic utility of chiral 2-sulfanylcarboxylic acids **2**

2 was developed by Kellogg and Strijtveen[25]; mesylates of readily available chiral 2-hydroxyesters are converted to **1** and **2** through clean S_N2 displacement by using AcSCs (generated in situ from AcSH and $CsCO_3$), followed by mild NH_4OH and acid treatments to produce **1** and **2**, respectively. This paper also pointed out critical racemization prone during the synthesis of **1** and **2**, due to the high acidity compared with lactates.[25] Later, the author reported a pig liver esterase-catalyzed optical resolution of **1** and **2**.[26] These privileged methods have been successfully applied to syntheses for natural products, biologically active agents/compounds, and functional materials containing α-sulfur substituted carbonyl moieties.

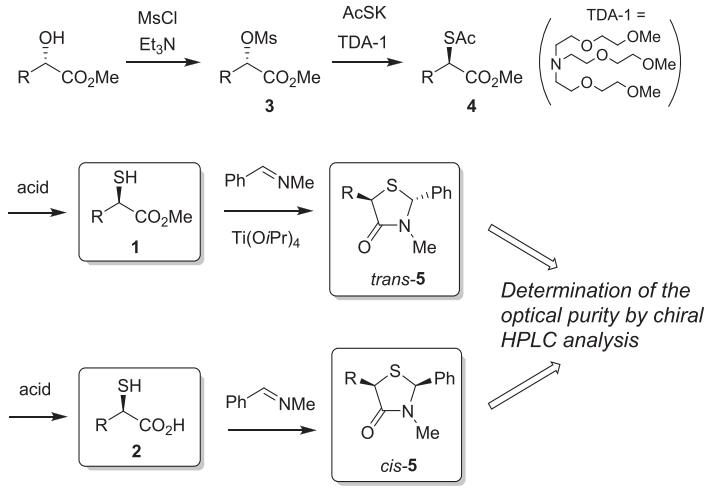
There are another noticeable synthetic studies leading to chiral 2-sulfanylpropanoic acid (unless otherwise noted), which are listed in chronologic order: (i) solid-phase Mitsunobu inversion followed by NH_4OH hydrolysis,[10] (ii) S_N2 displacement of 2-bromosuccinic acids derived from chiral aspartic acids specifically leading to 2-sulfanylsuccinic acid,[27] (iii) esterase-catalyzed hydrolysis of 2-(*S*-acetylsulfanyl)propanoate,[28] (iv) S_N2 displacement using tritylthiol followed by reductive deprotection,[29] (v) dynamic resolution method using *N*-methyl pseudoephedrine 2-bromoesters leading to 2-sulfanylpropane amide,[30] (vi) Cu-chiral spiro(bisoxazoline) complex-catalyzed enantioselective carbenoid insertion into S–H bonds,[31] and (vii) Rh_2 complexes and chiral spiro phosphoric acid-catalyzed enantioselective S–H bond insertion.[32]

On the other hand, the optical purity determination of **1** and **2** is another crucial subject. The first seminal method was developed by Kellogg and Feringa's group by utilizing ^{13}C and ^{31}P NMR determination techniques of phosphonoditiolate derivatives and/or chiral shift reagents.[33] The second more accurate method was reported by 1 of the authors (Y.T.) and his coworkers: simple derivatization of **1** and **2** to thiazolidin-4-ones under neutral conditions and reliable chiral HPLC analysis of these derivatives.[34,35] The second method, however, is limited to rather specific 2-(3-pyridyl)thiazolidin-4-ones, that is, lacks generality. Moreover, high-performance liquid chromatography (HPLC) resolution efficiency is considerably unsatisfactory.

This background led us to investigate a general, practical, and accessible synthetic method for **1** and **2** and a new method for accurate HPLC analysis. The outline is depicted in Scheme 2.

2 | MATERIALS AND METHODS

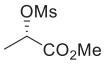
Flash column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM). Thin-liquid chromatography analysis was performed on 0.25-mm Silicagel Merck $60F_{254}$ plates. Melting points were determined on a hot stage microscope apparatus (AS ONE, ATM-01) and were uncorrected. Nuclear magnetic resonance spectra were recorded on a JEOLRESONANCE ECX-500 spectrometer, operating at 500 MHz for ^1H-NMR and 126 MHz for ^{13}C-NMR. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (=0) for ^1H-NMR. For ^{13}C-NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. Infrared spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. Mass spectra were measured on a JEOL JMS-T100LC spectrometer. Stains for developing thin-layer chromatography plates were carried out by I_2 for **3b** and others for UV light. High-performance liquid chromatography data were obtained on a SHIMADZU HPLC system (consisting of the following: LC-20AT, CMB20A, CTO-20AC, and detector SPD-20A measured at 254 nm) by using Daicel Chiracel AD-3, IA, or OD-H column (25 cm) at 25°C. Optical rotations were measured on a JASCO DIP-370 (Na lamp, 589 nm).



SCHEME 2 General procedures of the present approach

3 | GENERAL METHODS

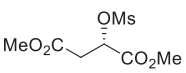
3.1 | Methyl (2*S*)-2-[(methylsulfonyl)oxy] propanoate (3a)[36]



$MeSO_2Cl$ (6.87 g, 60.0 mmol) was added dropwise to a stirred solution of methyl (*S*)-lactate (5.20 g, 50.0 mmol) and Et_3N (6.07 g, 60.0 mmol) in AcOEt (50 mL) at 0 to 5°C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 hour. *N*,*N*-Dimethylethylenediamine (1.1 mL) and water (50 mL) were successively added to the mixture, which was extracted with AcOEt (100 mL ×2). The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was distilled under reduced pressure to give the desired product (**3a**; 7.71 g, 85%).

Colorless oil; bp 113 to 115°C/3.0 mmHg [lit.[36] bp 80-82°C/0.5 mmHg]; $[\alpha]_D^{22}$ −55.5 (*c* 1.00, EtOH) [lit. [36] $[\alpha]_D^{27}$ − 55.5 (*c* 1.91, EtOH)]; ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 1.62 (d, *J* = 7.5 Hz, 3H), 3.15 (s, 3H), 3.81 (s, 3H), 5.15 (q, *J* = 7.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 18.3, 39.0, 52.7, 74.0, 169.8.

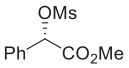
3.2 | Dimethyl (2*S*)-2-[(methylsulfonyl) oxy]succinate (3b)



Following a similar procedure for the preparation of mesylate **3a**, the reaction of dimethyl (*S*)-malate (1.62 g, 10.0 mmol) with $MeSO_2Cl$ (2.29 g, 20.0 mmol) and Et_3N (2.02 g, 20.0 mmol) in AcOEt (20 mL) at −20°C for 1 hour gave the crude product, which was purified by silica-gel column chromatography (hexane/AcOEt = 2:1) to give the desired product (**3b**; 1.59 g, 66%).

Colorless oil; $[\alpha]_D^{19}$–49.7 (*c* 1.00, $CHCl_3$); R_f value = 0.25 (hexane/AcOEt = 2:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.97 (dd, *J* = 7.5 Hz, 16.61 Hz, 1H), 3.02 (dd, *J* = 4.6 Hz, 16.6 Hz, 1H), 3.18 (s, 3H), 3.75 (s, 3H), 3.84 (s, 3H), 5.39 (dd, *J* = 4.6 Hz, 7.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 36.6, 38.9, 52.3, 53.1, 73.7, 168.3, 169.1; IR (neat): ν = 1735, 1438, 1359, 1284, 1168; HRMS (ESI, *m*/*z*): $[M + Na]^+$ calcd for $C_7H_{12}O_7SNa^+$, 263.0201; found, 263.0193.

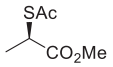
3.3 | Methyl (2*S*)-2-[(methylsulfonyl)oxy]-2-phenylacetate (3c)[37,38]



Following a similar procedure for the preparation of mesylate **3a**, the reaction of methyl (*S*)-mandelate (1.66 g, 10.0 mmol) with $MeSO_2Cl$ (2.29 g, 20.0 mmol) and Et_3N (2.02 g, 20.0 mmol) in AcOEt (20 mL) at −20°C for 1 hour gave the crude product, which was purified by silica-gel column chromatography (hexane/AcOEt = 2:1) to give the desired product (**3c**; 2.28 g, 88%). Alternatively, the reaction of methyl (*S*)-mandelate (14.7 g, 88.5 mmol) with $MeSO_2Cl$ (20.3 g, 177 mmol) and Et_3N (17.9 g, 177 mmol) in AcOEt (180 mL) at −20°C for 1 hour yielded the crude product, which was purified by recrystallization with 2-propanol (180 mL) to give the desired product (**3c**; 18.6 g, 81%).

Colorless crystals; mp 113 to 115°C [lit.[38] mp 113-114°C]; $[\alpha]_D^{21}$ + 108.9 (*c* 1.00, CH_2Cl_2) [lit.[38] $[\alpha]_D^{25}$ + 112.6 (*c* 2.00, CH_2Cl_2)]; R_f value = 0.54 (hexane/AcOEt = 4:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 3.09 (s, 3H), 3.78 (s, 3H), 5.95 (s, 1H), 7.39 to 7.48 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 39.3, 53.0, 78.9,127.7 (2C), 129.0 (2C), 130.0, 132.7, 168.1.

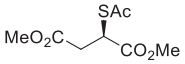
3.4 | Methyl (2*R*)-2-(acetylthio)propanoate (4a)[24]



Mesylate **3a** (5.47 g, 30.0 mmol) in AcOEt (10 mL) was added to a stirred suspension of AcSK (3.77 g, 33.0 mmol) and tris[2-(2-methoxyethoxy)-ethyl] amine (TDA-1) (10.7 g, 33.0 mmol) in AcOEt (50 mL) at room temperature, and the mixture was stirred at the same temperature for 1 hour. Approximately 1 M aqueous HCl (20 mL) was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was distilled under reduced pressure to give the desired product (**4a**; 3.50 g, 72%).

Pale yellow oil; bp 36 to 38°C/2.2 mmHg [lit.[35] bp 108-109°C/30 mmHg]; $[\alpha]_D^{19}$ + 144.7 (*c* 1.00, EtOH) [lit.[35] $[\alpha]_D^{25}$ + 145.3 (*c* 0.73, EtOH)]; R_f value = 0.53 (hexane/AcOEt = 4:1). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 1.51 (d, *J* = 7.5 Hz, 3H), 2.35 (s, 3H), 3.74 (s, 3H), 4.25 (q, *J* = 7.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 17.5, 30.0, 40.6, 52.6, 172.3, 193.6.

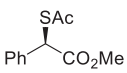
3.5 | Dimethyl (2*R*)-2-(acetylthio) succinate (4b)



Following a similar procedure for the preparation of thioester **4a**, the reaction of mesylate **3b** (1.20 g, 5.00 mmol) with AcSK (628 mg, 5.50 mmol) and TDA-1 (1.78 g, 5.50 mmol) in AcOEt (10 mL) at room temperature for 1 hour gave the crude product, which was purified by silica-gel column chromatography (hexane/AcOEt = 4:1) to give the desired product (**4b**; 877 mg, 80%).

Colorless oil; $[\alpha]_D^{22}$ + 102.9 (*c* 1.00, $CHCl_3$); R_f value = 0.34 (hexane/AcOEt = 4:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.38 (s, 3H), 2.88 (dd, *J* = 5.2 Hz, 17.2 Hz, 1H), 3.00 (dd, *J* = 8.0 Hz, 17.2 Hz, 1H), 3.71 (s, 3H), 3.75 (s, 3H), 4.56 (dd, *J* = 5.2 Hz, 8.0 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 30.0, 36.4, 40.8, 52.0, 52.9, 170.6, 170.8, 192.9; IR (KBr): ν = 1732, 1695, 1435, 1359, 1209; HRMS (ESI, *m*/*z*): $[M + Na]^+$ calcd for $C_8H_{12}O_5S\ Na^+$, 243.0303; found, 243.0295.

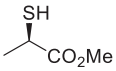
3.6 | Methyl (2*R*)-2-(acetylthio)-2-phenylacetate (4c)[39]



Following a similar procedure for the preparation of thioester **4a**, the reaction of mesylate **3c** (1.81 g, 7.00 mmol) with AcSK (879 mg, 7.70 mmol) and TDA-1 (2.49 g, 7.70 mmol) in AcOEt (20 mL) at 0 to 5°C for 4 hours gave the crude product, which was purified by silica-gel column chromatography (hexane/AcOEt = 10:1) gave the desired product (**4c**; 1.40 g, 89%).

Colorless oil; $[\alpha]_D^{19}$ − 236.5 (*c* 1.00, $CHCl_3$) [lit.[39] $[\alpha]_D^{20}$ − 236.5 (*c* 3.37, $CHCl_3$)]; R_f value = 0.53 (hexane/AcOEt = 4:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.35 (s, 3H), 3.74 (s, 3H), 5.32 (s, 1H), 7.29 to 7.40 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 29.8, 50.9, 53.0, 128.2 (2C), 128.4, 128.8 (2C), 134.7, 170.3, 193.7.

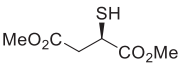
3.7 | Methyl (*R*)-2-sulfanylpropanoate (1a)[35,40]



Thioester **4a** (324 mg, 2.00 mmol) with conc. HCl aqueous solution (0.3 mL) in MeOH (3.7 mL) was stirred at 55 to 60°C under an Ar atmosphere for 4 hours. Water was added to the mixture, which was extracted with Et_2O (50 mL ×2). The combined organic phase was washed with water (10 mL ×3), brine, dried (Na_2SO_4), and concentrated. The obtained desired product was sufficiently pure (**1a**; 170 mg, 71%).

Colorless oil; $[\alpha]_D^{19}$ + 65.5 (*c* 0.83, $CHCl_3$) [lit.[35] $[\alpha]_D^{25}$ + 55.1 (*c* 1.81, $CHCl_3$)]; R_f value = 0.59 (hexane/AcOEt = 4:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 1.53 (d, *J* = 6.9 Hz, 3H), 2.17 (d, *J* = 8.6 Hz, 1H), 3.52 (dq, *J* = 6.9, 8.6 Hz, 1H), 3.75 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 21.0, 35.4, 52.5, 174.1.

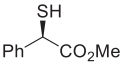
3.8 | Dimethyl (2*R*)-2-sulfanylsuccinate (1b)[41]



Following a similar procedure for the preparation of 2-sulfanyl ester **1a**, the reaction of thioester **4b** (440 mg, 2.00 mmol) with conc. HCl aqueous solution (0.3 mL) in MeOH (3.7 mL) at 55 to 60°C under an Ar atmosphere for 4 hours gave the desired product (**1b**; 282 mg, 79%).

Colorless oil; $[\alpha]_D^{17}$ + 70.9 (*c* 1.00, $CHCl_3$) [lit.[41] $[\alpha]_D^{20}$ + 14.1 (*c* 1.92, $CHCl_3$)]; R_f value = 0.44 (hexane/AcOEt = 4:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.22 (d, *J* = 9.2 Hz, 1H), 2.78 (dd, *J* = 6.3 Hz, 17.2 Hz, 1H), 3.03 (dd, *J* = 9.2 Hz, 17.2 Hz, 1H), 3.70 (s, 3H), 3.77 (dt, *J* = 6.3, 9.2 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 35.9, 39.6, 52.0, 52.8, 170.7, 172.7.

3.9 | Methyl (2*R*)-2-sulfanyl-2-phenylacetate (1c)[18]



AcCl (7.1 mL, 100 mmol) was added to a stirred solution of thioester **4c** (2.24 g, 10.0 mmol) in MeOH (20 mL) at 0 to 5°C under an Ar atmosphere, and the mixture was stirred at room temperature for

7 hours. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained desired product was sufficiently pure (**1c**; 1.48 g, 88%).

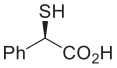
Colorless oil; $[\alpha]_D^{17}$ − 99.1 (*c* 1.00, $CHCl_3$); R_f value = 0.63 (hexane/AcOEt = 4:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.60 (d, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 4.70 (d, *J* = 8.0 Hz, 1H), 7.28–7.39 (m, 3H), 7.42 to 7.46 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 45.6, 53.0, 127.6 (2C), 128.1, 128.7 (2C), 138.1, 171.8.

3.10 | (2*R*)-2-Sulfanylpropanoic acid (2a)[24,35]

Sulfanyl ester **1a** (648 mg, 4.00 mmol) in 6 M HCl aqueous solution (8 mL) was stirred at 75 to 80°C under Ar atmosphere for 4 hours. After the mixture was concentrated under reduced pressure (~11 mmHg), remained water and AcOH was removed under azeotropic conditions by using toluene (2 mL ×3). The obtained desired product was sufficient pure (**2a**; 225 mg, 53%).

Colorless oil; $[\alpha]_D^{20}$ + 60.1 (*c* 1.00, EtOH) [lit.[35] $[\alpha]_D^{25}$ + 45.0 (*c* 0.728, EtOH)]; R_f value = 0.19 (hexane/AcOEt = 4:1) (tailing). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 1.55 (d, *J* = 6.9 Hz, 3H), 2.24 (d, *J* = 8.6 Hz, 1H), 3.55 (dq, *J* = 6.9, 8.6 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 20.6, 35.5, 180.2.

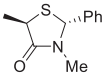
3.11 | (2*R*)-2-Sulfanylpropanoic acid (2c)[42]



Sulfanyl ester **1c** (1.48 g, 8.12 mmol) with conc. HCl aqueous solution (12 mL) in CH_3CN (8 mL) was stirred at 75 to 80°C under Ar atmosphere for 4 hours. After cooling down, the mixture was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give the crude product (1.29 g, 94%, $[\alpha]_D^{24}$ − 85.0 (*c* 1.00, EtOH)). The obtained crude product (898 mg, 5.34 mmol) was washed 3 times with hexane (10 mL ×3) to give the desired product (**2c**; 716 mg, 80%).

Colorless crystals; mp 86 to 88°C [lit.[42] mp 88-88.5°C]; $[\alpha]_D^{23}$–104.1 (*c* 1.00, EtOH) [lit.[43] $[\alpha]_D^{25}$ − 106.2 (*c* 0.5, 95% EtOH)]; R_f value = 0.13 (hexane/AcOEt = 5:1) (tailing). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.62 (d, *J* = 7.5 Hz, 1H), 4.71 (d, *J* = 7.5 Hz, 1H), 7.29 to 7.41 (m, 3H), 7.43 to 7.49 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 45.4, 127.8 (2C), 128.5, 128.8 (2C), 137.1, 177.7.

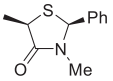
3.12 | (2*R*,5*R*)-3,5-Dimethyl-2-phenylthiazolidin-4-one (*trans*-5a)



Ti(O*i*Pr)$_4$ (0.78 mL, 2.65 mmol) was added to a stirred solution of sulfanyl ester **1a** (265 mg, 2.21 mmol) and *N*-benzylidenemethylamine (316 mg, 2.65 mmol) in CH_2Cl_2 (4.4 mL) at room temperature under an Ar atmosphere, and the mixture was stirred at the same temperature for 2 hours. Water was added to the stirred mixture, and the obtained micelle was filtered by using celite washing with $CHCl_3$. The separated organic phase was dried (Na_2SO_4) and concentrated. The obtained crude product (*cis*/*trans* = 12:88) was purified by silica-gel column chromatography (hexane/AcOEt = 6:1-2:1) to give the desired product (*trans*-**5a**; 306 mg, 68%, *cis*-**5a**, 41 mg, 13%).

Colorless crystals; mp 47 to 48°C; 98% ee, by HPLC analysis (Daicel Chiralcel AD-3 column, hexane/2-propanol = 40:1, 1.0 mL/min, 254 nm UV detector), t_R = 29.48 min for [(2*R*,5*R*)-*trans*] and t_R = 16.17 min for [(2*S*,5*S*)-*trans*]; $[\alpha]_D^{18}$ + 144.5 (*c* 1.00, $CHCl_3$); R_f value = 0.29 (hexane/AcOEt = 4:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 1.60 (d, 7.5 Hz, 3H), 2.76 (s, 3H), 4.07 (dq, *J* = 1.7 Hz, 7.5 Hz, 1H), 5.46 (d, *J* = 1.7 Hz, 1H), 7.25 to 7.29 (m, 2H), 7.32 to 7.41 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 19.8, 30.3, 41.5, 63.3, 126.5 (2C), 128.9, 129.0 (2C), 139.5, 173.9. The racemic compound was reported (Johnson MR, Fazio MJ, Ward DL, Sousa LR, Synthesis of β-lactams by the photochemical extrusion of sulfur dioxide from 1,1-dioxo-4-thiazolidinones. *J. Org. Chem*. 1983, *48*, 494-499).

3.13 | (2*S*,5*R*)-3,5-Dimethyl-2-phenylthiazolidin-4-one (*cis*-5a)

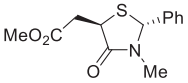


N-(Benzylidene)methylamine (303 mg, 2.54 mmol) in tetrahydrofuran (THF; 1 mL) was added to a stirred solution of 2-sulfanylpropanoic acid **2a** (225 mg, 2.12 mmol) in THF (3 mL) at room temperature under an Ar atmosphere, and the mixture was stirred at the same temperature for 6 hours. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product (*cis*/*trans* = 82:18) was purified by silica-gel column chromatography (hexane/AcOEt = 5:1-4:1) and gave the desired product (*cis*-**5a**; 132 mg, 30%, *trans*-**5a**; 33 mg, 8%).

Pale yellow oil; 96% ee, by HPLC analysis (Daicel Chiralcel AD-3 column, hexane/2-propanol = 40:1,

1.0 mL/min, 254-nm UV detector), t_R = 13.77 min for [(2*S*,5*R*)-*cis*] and t_R = 19.06 min for [(2*R*,5*S*)-*cis*]; $[\alpha]_D^{18}$ − 38.5 (*c* 0.73, $CHCl_3$); R_f value = 0.23 (hexane/AcOEt = 4:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 1.66 (d, *J* = 6.9 Hz, 3 H), 2.71 (s, 3H), 3.96 (q, *J* = 6.9 Hz, 1H), 5.47 (s, 1H), 7.30 to 7.42 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 20.3, 30.4, 42.3, 63.6, 127.2 (2C), 128.9 (2C), 129.1, 138.8, 173.9.

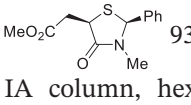
3.14 | Methyl 2-[(2*R*,5*R*)-3-methyl-4-oxo-2-phenylthiazolidin-5-yl]acetate (*trans*-5b)



Following a similar procedure for the preparation of thiazolidine-4-one *trans*-**5a**, the reaction of 2-sulfanyl ester **1b** (276 mg, 1.55 mmol) with *N*-benzylidenemethylamine (222 mg, 1.86 mmol) and $Ti(OiPr)_4$ (0.55 mL, 1.86 mmol) in CH_2Cl_2 (3.7 mL) at room temperature for 2 hours gave the crude product, which was purified by silica-gel column chromatography (hexane/AcOEt = 4:1-3:1), and gave the desired product (**5b**; 302 mg, 73%, *trans/cis* = 87:13).

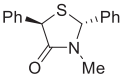
Pale yellow oil; 93% ee, by HPLC analysis (Daicel Chiralcel IA column, hexane/2-propanol = 10:1, 1.0 mL/min, 254 nm UV detector), t_R = 26.34 min for [(2*R*,5*R*)-*trans*] and t_R = 19.46 min for [(2*S*,5*S*)-*trans*]; R_f value = 0.27 (hexane/AcOEt = 2:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.75 (s, 3H), 2.95 (dd, *J* = 8.0 Hz, 17.2 Hz, 1H), 3.15 (dd, *J* = 4.0 Hz, 17.2 Hz, 1H), 3.73 (s, 3H), 4.35 (ddd, *J* = 2.3 Hz, 4.0 Hz, 8.0 Hz, 1H), 5.50 (d, *J* = 2.3 Hz, 1H), 7.23 to 7.43 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 30.4, 38.5, 43.0, 51.9, 64.3, 126.9 (2C), 128.9 (2C), 129.0, 138.8, 171.1, 172.2; IR (neat): ν = 1735, 1674, 1435, 1394, 1174, 1049; HRMS (ESI, *m/z*): $[M + Na]^+$ calcd for $C_{13}H_{15}N_1O_3SNa^+$, 288.0670; found, 288.0679.

3.15 | Methyl 2-[(2*S*,5*R*)-3-methyl-4-oxo-2-phenylthiazolidin-5-yl]acetate (*cis*-5b)



93% ee, by HPLC analysis (Daicel Chiralcel IA column, hexane: 2-propanol = 10:1, 1.0 mL/min, 254 nm UV detector), t_R = 20.77 min for [(2*S*,5*R*)-*cis*] and t_R = 40.63 min for [(2*R*,5*S*)-*cis*]; R_f value = 0.27 (hexane/AcOEt = 2:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.73 (s, 3H), 2.83 (dd, *J* = 10.3 Hz, 17.2 Hz, 1H), 3.36 (dd, *J* = 3.4 Hz, 17.2 Hz, 1H), 3.72 (s, 3H), 4.30 (dd, *J* = 4.0 Hz, 10.3 Hz, 1H), 5.49 to 5.51 (m, 1H), 7.29 to 7.43 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 30.3, 39.4, 43.6, 51.9, 63.8, 127.1 (2C), 129.0 (2C), 129.1, 138.5, 171.0, 171.7.

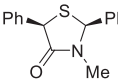
3.16 | (2*R*,5*R*)-3-methyl-2,5-diphenylthiazolidin-4-one (*trans*-5c)



Following a similar procedure for the preparation of thiazolidine-4-one *trans*-**5a**, the reaction of 2-sulfanyl ester **1c** (83 mg, 0.46 mmol) with *N*-benzylidenemethylamine (65 mg, 0.55 mmol) and $Ti(OiPr)_4$ (0.16 mL, 0.55 mmol) in CH_2Cl_2 (1 mL) at room temperature for 2 hours gave the crude product (*cis*/*trans* = 6:94), which was purified by silica-gel column chromatography (hexane/AcOEt = 5:1), and gave the desired product (*trans*-**5c**; 63 mg, 51%).

Pale yellow crystals; mp 91 to 93°C; 90% ee, by HPLC analysis (Daicel Chiralcel OD-H column, hexane/2-propanol = 15:1, 1.0 mL/min, 254 nm UV detector), t_R = 14.79 minutes for [(2*R*,5*R*)-*trans*] and t_R = 19.94 minutes for [(2*S*,5*S*)-*trans*]; $[\alpha]_D^{22}$ + 75.0 (*c* 0.72, $CHCl_3$); R_f value = 0.55 (hexane/AcOEt = 2:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.80 (s, 3H), 5.15 (d, *J* = 2.3 Hz, 1H), 5.68 (d, *J* = 2.3 Hz, 1H), 7.29 to 7.48 (m, 10H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 31.2, 52.0, 64.8, 127.4 (2C), 128.6, 128.7 (2C), 129.3 (2C), 129.71 (2C), 129.75, 138.8, 139.5, 172.4; IR (neat): ν = 1674, 1454, 1419, 1390, 1257; HRMS (ESI, *m/z*): $[M + Na]^+$ calcd for $C_{16}H_{15}NOSNa^+$, 292.0772; found, 292.0764.

3.17 | (2*S*,5*R*)-3-Methyl-2,5-diphenylthiazolidin-4-one (*cis*-5c)



Following a similar procedure for the preparation of thiazolidine-4-one *cis*-**5a**, the reaction of 2-sulfanyl carboxylic acid **2c** (168 mg, 1.00 mmol) with *N*-benzyli denemethylamine (143 mg, 1.20 mmol) in THF at room temperature for 4 hours gave the crude product (*cis*/*trans* = 89:11), which was purified by silica-gel column chromatography (hexane/AcOEt = 3:1) gave the desired product (*cis*-**5c**; 200 mg, 74%).

Colorless oil; 96% ee, by HPLC analysis (Daicel Chiralcel OD-H column, hexane/2-propanol = 15:1, 1.0 mL/min, 254 nm UV detector), t_R = 28.08 min for [(2*S*,5*R*)-*cis*] and t_R = 22.83 min for [(2*R*,5*S*)-*cis*]; $[\alpha]_D^{20}$ − 29.1 (*c* 0.62, $CHCl_3$); R_f value = 0.42 (hexane/AcOEt = 2:1). ^{1}H-NMR (500 MHz, $CDCl_3$, δ): 2.78 (s, 3H), 5.09 (s, 1H), 5.58 (s, 1H), 7.29 to 7.34 (m, 1H), 7.3 to 7.46 (m, 7H), 7.47–7.54(m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$, δ): 30.8 52.1, 63.6, 127.3 (2C), 128.0, 128.6 (2C), 128.7 (2C), 129.0 (2C), 129.2, 137.5, 138.4, 171.9; IR (neat): ν = 1678, 1454, 1418, 1389, 1350, 1261, 1101.

4 | RESULTS AND DISCUSSION

In connection with our continuing synthetic studies of process chemistry and biologically active sulfur- and nitrogen-containing heterocyclic compounds,[44-46] we envisage a practical and robust synthesis of chiral building blocks **1** and **2**. The basic concept of the present protocol is based on Kellogg's original procedure[25] and our collaborations.[35] The initial screening for a clean S_N2 displacement of methyl (*S*)-2-(methanesulfonyloxy) propanoate (**3a**) to obtain methyl (*R*)-acetylthiolactate (**4a**) was guided by the reaction by using commercially available AcSK, which is an easy-to-handle bench-top procedure, and an odorless and less hygroscopic than liquid AcSH and Cs_2CO_3.[25] Table 1 shows the successful results. As pointed out in the literature,[25,35] the use of polar solvents such as DMF and DMSO produced better yields with excellent enantiomeric excesses (ee) than less polar solvents such as THF, toluene, CH_2Cl_2, and EtOAc (entries 4-6).

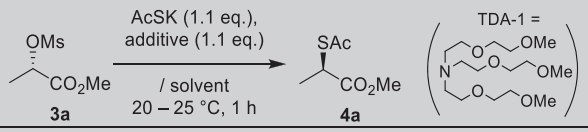
Notably, the use of AcOEt, a favorable solvent for process chemistry, produced desirable results to afford (*R*)-**4a** in 74% yield with 98% ee (HPLC analysis of the thiazolidin-4-one derivatives, vide infra) with the aid of a commercially available TDA-1 additive, an inexpensive and less toxic cryptand modified for 18-crown-6 (entry 8).

Based on this procedure, Table 2 compiles not only the S_N2 reactions <Step 1> but also the deacetylations <Step 2> starting from (*S*)-**3a**, dimethyl (*S*)-2-(methane sulfonyloxy)succinate (**3b**), and methyl (*S*)-2-(methane sulfonyloxy)mandelate (**3c**). The S_N2 reactions proceeded smoothly to give the corresponding (*R*)-2-(acetylthio)lactates **4a**, **4b**, and **4c** in good yield (entries 1, 3, and 5). Deacetylation under modified Kellogg's conditions[25] (*methods A* and *B*) were investigated next, and the salient features are as follows. (i) **4a**-**c** underwent the reaction smoothly to give the desired deacetylated methyl (*R*)-esters **1a**-**c** under mild acidic (*method A*) and basic (*method B*) conditions in good yield. (ii) **1a** and **1b** were produced in good yield and with excellent ee using *method A* (entries 1-3). (iii) In clear contrast, the ee of **1c** was considerably decreased when using either *method A* or *B* due to the high racemization tendency of **4c** (entries 5 and 6).

To overcome the critical racemization problem for preparing **1c**, we screened the appropriate conditions for both the S_N2 reaction and acid hydrolysis. A lower temperature (0-5°C) in Step 1 and AcCl/MeOH (in situ generation of HCl) reagent in Step 2 produced 90% ee satisfactory results (cf. 93% ee in the literature[25] using ^{31}P NMR method developed by Feringa's group[43]), as shown in Scheme 3.

The precise enantiomeric excesses of **1a**-**c** were determined by HPLC (DAICEL AD-3, column with chiral stationary phase) analyses of (2*R*,5*R*)-*trans*-thiazolidin-4-ones **5a**-**c** derived from **1a** to **1c** (Table 3). The present $Ti(OiPr)_4$-mediated neutral *trans*-selective cyclo-condensation[34,35] with *N*-(benzylidene)methylamine proceeded smoothly to afford (2*R*,5*R*)-*trans*-**5a** and **5c** in good yield. Minor (2*S*,5*R*)-*cis*-**5a** and **5c** diastereomers could be separated by column chromatography, but this chromatographic separation was otherwise unnecessary, because the four enantiomers could be directly analyzed by HPLC. Notably, the chirality of the labile stereogenic 5-position in **5** was completely maintained during the transformation; excellent 98%ee was obtained for *trans*-

TABLE 1 Optimization of clean S_N2 reaction of methyl (*S*)-2-(methanesulfonyloxy)propanoate **3a**

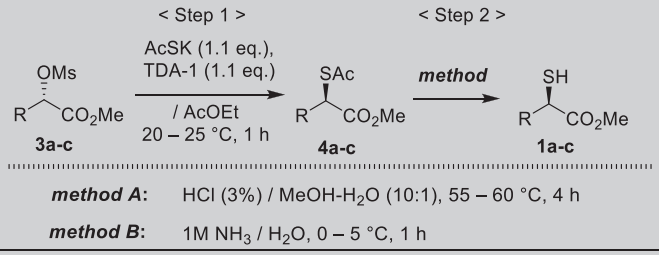


Entry	Solvent	Additive	Yield/%[a]	ee/%[b]
1	DMF	None	56	97
2	DMSO		59	98
3	CH_3CN		52	98
4	THF		27	98
5	Toluene, CH_2Cl_2		Trace	—
6	AcOEt		26	98
7		18-Crown-6	20	94
8		TDA-1	74	99

[a]Determined by ^1H-NMR analysis by using ethylene carbonate IS.

[b]Determined by high-performance liquid chromatography analysis of thiazolidin-4-one derivatives (2*R*,5*R*)-*trans*-**5a**-**5c** (see Table 3).

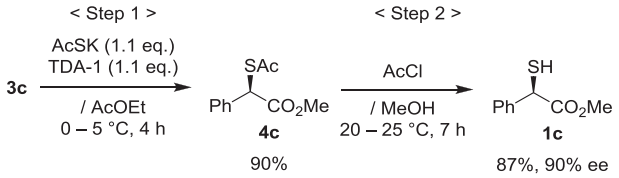
TABLE 2 Synthesis of methyl (*R*)-sulfanylcarboxylates **1** from methyl (*S*)-2-(methanesulfonyloxy)carboxylates **3**



Entry	*R*	Product	Yield/%[a] <Step 1>	Method	Product	Yield/% <Step 2>	ee/%[ba]
1	Me	**4a**	74	*A*	**1a**	71	98
2				*B*		71	96
3	CH_2CO_2Me	**4b**	78	*A*	**1b**	97	93
4				*B*		97	78
5	Ph	**4c**	89	*A*	**1c**	89	75
6				*B*		96	31

[a]Isolated.

[b]Determined by high-performance liquid chromatography analysis of thiazolidin-4-one derivatives (2*R*,5*R*)-*trans*-**5a**-**5c** (see Table 3).



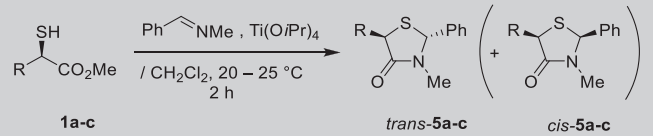
SCHEME 3 Mild S_N2 reaction and deacetylation for the synthesis of methyl (*R*)-mandelate **1c**

5a (entry 1), which confirmed the high optical purity of the parent ester **1a** compared with that obtained by using the previously reported method[25] (90% ee: ^{31}P NMR technique of the phosphonodithioate derivative). High-performance liquid chromatography analysis of *trans*-**5b** and *trans*-**5c** derived from **1b**, **1c** revealed 93% ee and 90% ee, respectively.

Next, syntheses of (*R*)-2-sulfanylcarboxylic acids **2a** and **2c** from (*R*)-2-(acetylthio)carboxylate **4a** and (*R*)-2-(sulfanyl)carboxylate **1c**, respectively, were investigated (Scheme 4). The former conversion to **2a** involved both deacetylation and hydrolysis of **4a** in a one-pot manner, and the latter one involved hydrolysis of **1c**. Both processes were carried out under somewhat harsh conditions (6 M HCl, 75-80°C, 4 h) to afford **2a** and **2c** in good yield. **2a** and **2c** were successfully transformed to (2*S*,5*R*)-*cis*-thiazolidin-4-ones **5a** and **5c** by neutral *cis*-selective cyclo-condensation[34,35] by using *N*-(benzylidene)methylamine without catalyst.

In a similar procedure of (2*R*,5*R*)-*trans*-thiazolidin-4-ones, HPLC analysis was performed to determine precise ee of (2*S*,5*R*)-*cis*-**5a** (96% ee) and **5c** (85% ee). The previously reported method[25] of acid deacetylation and hydrolysis of **4c** (6 M HCl, rt, 4 days) yielded parent acid

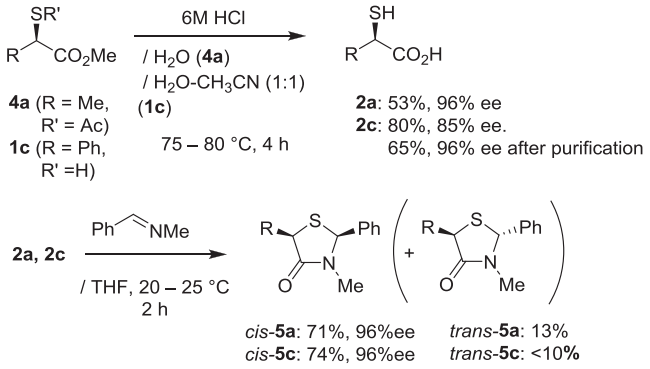
TABLE 3 $Ti(OiPr)_4$-promoted derivatization to (2*R*,5*R*)-*trans*-thiazolidin-4-one **5**



Entry	*R*	Product	Yield/%[a] (trans/cis)	ee/%[b] Trans
1	Me	**5a**	51 (93/7)	98
2	CH_2CO_2Me	**5b**	73 (87/13)	93
3	Ph	**5c**	76 (95/5)	90

[a]Isolated.

[b]Determined by high-performance liquid chromatography analysis.



SCHEME 4 Synthesis of (*R*)-2-sulfanylcarboxylic acids **2**

2c with 86% ee (comparison with optical rotation value); this racemization tendency led the authors to abandon their attempts to acquire **2c** with higher optical purity. To our delight, the obtained crude product **2c** was solid and could be enriched by washing with hexane: 65% isolated yield, 96% ee by HPLC analysis of (2*S*,5*R*)-*cis*-**5c** derivative.

As a final note, direct HPLC analysis of methyl (*R*)-thiomandelate **1c** was investigated, but the resolution efficiency was inferior to that of the thiazolidin-4-one derivatizations.

5 | CONCLUSION

Practical chiral syntheses of 3 kinds of (*R*)-2-sulfanylcarboxylic esters and acids were performed. The present accessible and robust method involves (i) clean S_N2 displacement of methanesulfonates of methyl (*S*)-2-hydroxy carboxylic esters by using convenient AcCOSK with TDA-1 and (ii) sufficiently mild deacetylation for ester synthesis and deacetylation-hydrolysis for acid synthesis.

The optical purity was determined by distinctive HPLC analysis of the corresponding (2*R*,5*R*)-*trans*-thiazolidin-4-ones by using Ti(O*i*Pr)$_4$-promoted *trans*-cyclo-condensation and (2*S*,5*R*)-*cis*-thiazolidin-4-ones by *cis*-cyclo-condensation without a catalyst. This protocol will be a useful contribution to synthetic chemists engaged in drug discovery and process chemistry.

ACKNOWLEDGMENTS

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One of the authors (Y.T.) appreciates the collaboration with Prof Richard M. Kellogg on this work and offers his warmest congratulations to Prof Ben L. Feringa (University of Groningen, the Netherlands) on being awarded the 2016 Nobel Prize in Chemistry. Dedication to Professor Teruaki Mukaiyama on the celebration of his 90th birthday (Sotuju).

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SUPPORTING INFORMATION

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