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# Benzyl (*R*)-2-(Acetylthio)Propanoate: A Promising Sulfur Isoster of (*R*)-Lactic Acid and Ester Precursors

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Received: 6 July 2018; Accepted: 24 July 2018; Published: 29 July 2018

**Abstract:** In this paper, an accessible chiral pool synthesis of benzyl (*R*)-2-(acetylthio)propanoate (acetylthiolactate), which is less odorous than the methyl or ethyl analogue, was performed through a clean $S_N2$ displacement reaction using available AcSK with tris[2-(2-methoxyethoxy)]ethylamine (TDA-1), starting from commercially available benzyl (*S*)-lactate in 76%, 94% ee (2 steps). Deprotection of the acetyl group using *N*,*N*-dimethylethylenediamine afforded benzyl (*R*)-2-sulfanylpropanoate in 93% yield with 90% ee. These two sulfur-containing benzyl esters were sufficiently odorless to be purified by column chromatography. Direct HPLC analysis was applied to determine the enantiomeric excess without thiazolidin-4-one derivatizations. A complementary debenzylation of benzyl (*R*)-2-(acetylthio)propanoate was also performed using HBr/AcOH to afford (*R*)-2-(acetylthio)propanoic acid without critical racemization in 92% yield with 92% ee.

**Keywords:** thiolactic ester; benzyl (*S*)-lactate; (*R*)-2-(acetylthio)propanoate; $S_N2$ displacement; potassium thioacetate; benzyl (*R*)-2-sulfanylpropanoate; HPLC analysis; odorless

## 1. Introduction

Synthetic chemistry of optically pure secondary thiols as the isoster of the corresponding chiral alcohols has attracted much attention [1,2]. Chiral 2-sulfanyl (classically, α-mercapto) carboxylic acids, and esters are well-recognized synthetic building blocks for distinctive derivatives of chiral 2-hydroxycarboxylic acids and esters in natural products and pharmaceutical syntheses. Among them, chiral 2-sulfanylpropanoic acid and esters **1** (thiolactic acid and esters) serve as the most fundamental chiral synthons (Figure 1). In this paper, we report a straightforward and accessible synthesis of novel benzyl (2*R*)-2-(acetylthio)propanoate [(*R*)-**2**] starting from inexpensive and commercially available benzyl (*S*)-lactate through mesylation and a clean $S_N2$ displacement reaction using available AcSK with tris[2-(2-methoxyethoxy)]ethylamine (TDA-1) [3]. In addition, convenient direct HPLC analysis was performed to determine the accurate optical purities of (*R*)-**2** and their analogues.

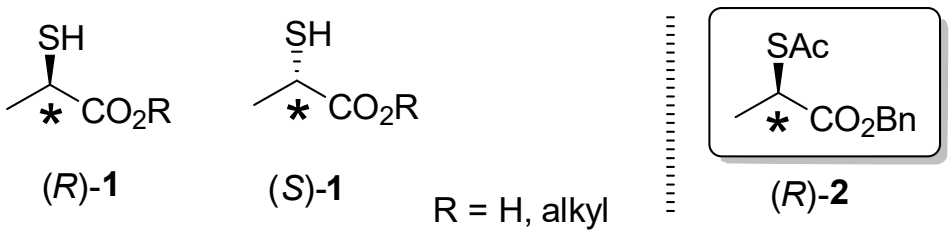



**Figure 1.** Chiral thiolactic acid and esters (*R*)-**1**, (*S*)-**1**, and benzyl (2*R*)-2-(acetylthio)propanoate (*R*)-**2**.

Representative natural products and biologically active agents/compounds installing the chiral thiol segments (*R*)- and (*S*)-**1** are listed in our recent report along with the display of their structures [3]. Tiopronin [4,5] and thiolactomycin [6–9] are leading natural antibiotic compounds (Figure 2). Other biologically active agents/compounds are described in chronologic order of their development: antiplatelet activating factor (anti-PAF) antagonists [10,11]; IMP-1, a metallo-β-lactamase inhibitor [12]; vasopeptidase inhibitors [13]; methionine aminopeptidases (MetAPs) active site probes [14]; specific substrates for Streptomyces R61 D,D-peptidases [15]; and a nonsteroidal farnesoid X receptor (FXR) agonist [16].

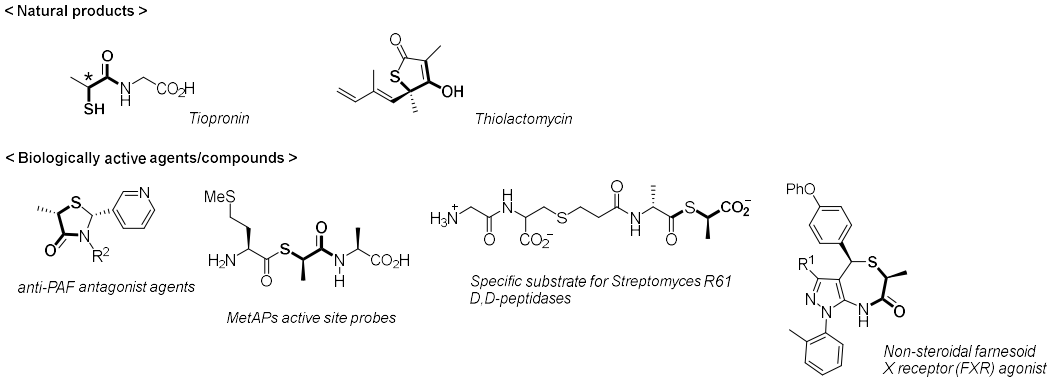
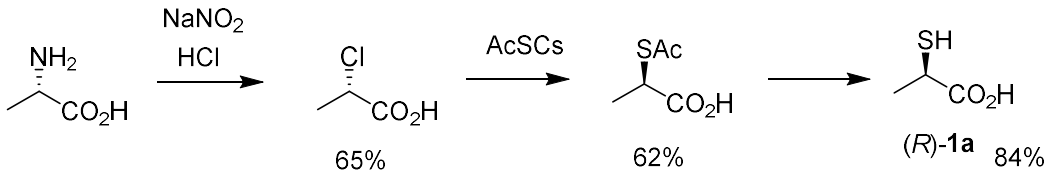



**Figure 2.** Representative natural products containing chiral thiol segments (*R*)- or (*S*)-**1**.

Chiral acid and esters **1** have two characteristic synthetic utilities. One is the chiral template methodology [17] using 1,3-oxathiolan-4-ones derived from **1**, which involves distinct self-regeneration of the stereocenter [18]. This protocol was successfully applied for the asymmetric synthesis of (5*R*)-thiolactomycin and its analogues [9,19,20]. Another is a thiazolidin-4-one type chiral ligand derived from **1**, which was utilized for a Cu(I)-catalyzed asymmetric conjugate addition to enones, developed by Feringa's group [20].

Due to the demand, several synthetic methods to access **1** have been developed to date. Scheme 1 shows the most traditional synthesis of (*R*)-**1a** starting from chiral alanine, developed by Owen's [21] and Kellogg's groups [22]; stereoretentive diazotization-chlorination; $S_N2$ displacement with AcSCs (generated in situ from AcSH and $Cs_2CO_3$); and deacetylation sequences. The addressed yields are referred from Townsend and co-workers' total synthesis of (*R*)-thiolactomycin [9]. However, this reliable method requires a somewhat tedious step for in situ generation of odorous and hygroscopic AcSCs from AcSH and $Cs_2CO_3$, and results in moderate overall yield.



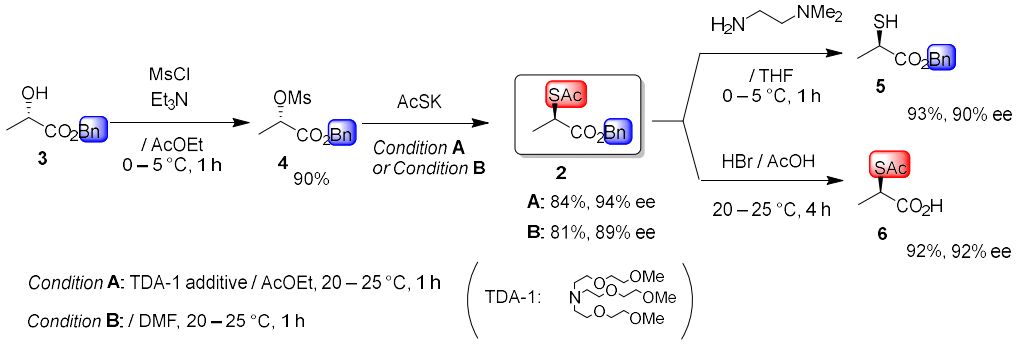

**Scheme 1.** Traditional synthesis of chiral thiolactic acid (*R*)-**1a**.

Another notable synthesis is copper-catalyzed enantioselective carbenoid insertion to α-diazopropanoate; this method afforded the desired benzyl ester **5** with 77% ee using a chiral bisoxazoline ligand [23]. In connection with our continuing studies on process chemistry and biologically active sulfur- and nitrogen-containing heterocyclic compounds [24–27], we planned to develop a practical and robust synthesis of chiral building blocks **1**.

## 2. Results

Our previous report described the synthesis of **1** as well as the related α-sulfanyl succinate and mandelate and their accurate HPLC optical purity determinations by derivatization under nearly neutral conditions [Ti(O*i*-Pr)$_4$/*N*-benzylidenemethylamine] to thiazolidin-4-ones [3]. However, in the case of **1,** this method required the isolation of methyl acetylthiolactate and methyl thiolactate, both of which have a highly unpleasant odor due to their high volatility. To address this problem, we investigated an alternative protocol using benzyl analogues. Scheme 2 outlines the reaction sequence. Cheap and available benzyl (*S*)-lactate **3** was converted to benzyl (*S*)-methanesulfonate **4**. The key clean $S_N2$ displacement reaction of **4** was conducted using commercially available AcSK—an odorless, less hygroscopic, easy-to handle solid in bench-top procedures—and compared with liquid AcSH and $Cs_2CO_3$ [22]. Condition A (TDA-1, tris[2-(2-methoxyethoxy)]ethylamine additive, AcOEt solvent) is slightly superior to conventional condition B (no additive, DMF solvent) with regard to yield, enantiomeric excess, and well-equalized suspension formation during the reaction. TDA-1 is an inexpensive and less toxic cryptand modified for 18-crown-6.

Benzyl (*R*)-acetylthioester **2** was considerably less odorous than the corresponding methyl or ethyl acetylthioester and, therefore, readily purified by column chromatography. Mild deacetylation of **2** with *N*,*N*-dimethylethylenediamine afforded benzyl (*R*)-2-sulfanylpropanoate (**5**) in 93% yield with 90% ee. Complementary debenzylation of **2** afforded (*R*)-2-(acetylthio)propanoic acid (**6**) upon treatment with HBr/AcOH in 92% yield, also without significant racemization (92% ee). Catalytic hydrogenation to remove the benzyl group failed to proceed (no reaction or decomposition) in any of the cases examined ($H_2$, 10% Pd/C; TBS-H, $Pd(OAc)_2$, $Et_3N$; $Et_3SiH$, $Pd(OAc)_2$, $Ph_3P$; $PdCl_2$).




**Scheme 2.** Synthesis of benzyl (*R*)-2-(acetylthio)propanoate (**2**) and derivatization leading to (*R*)-benzyl 2-sulfanyl ester **5** and (*R*)-2-acetylthio acid **6**.

The enantiomeric purity determination of **2** and **5** is a crucial subject. Two methods of determining the optical purity have been reported to date. The seminal method was developed by Kellogg and Feringa's group utilizing $^{13}C$ and $^{31}P$-NMR determination techniques of phosphonodithiolate derivatives and/or chiral shift reagents [28]. The other more accurate method utilized the neutral derivatization of 2-sulfanylcarboxylic acids and esters to thiazolidin-4-ones, which were subjected to HPLC analyses [3,11]. Notably, direct HPLC analysis of **2** and **5** to determine the enantiomeric excess was performed with the aid of UV detection of the benzyl group; derivatization to the corresponding thiazolidin-4-ones was omitted.

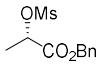
## 3. Experimental Section

*General*

All reactions were carried out in oven-dried glassware under an argon atmosphere. Flash column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM, Tokyo, Japan). TLC analysis was performed on 0.25 mm Silicagel Merck 60 $F_{254}$ plates (Tokyo, Japan). Melting points

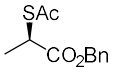
were determined on a hot stage microscope apparatus (AS ONE, ATM-01, Tokyo, Japan) and were uncorrected. NMR spectra were recorded on a JEOL DELTA 300 or JEOLRESONANCE ECX-500 spectrometer (Tokyo, Japan), operating at 300 MHz or 500 MHz for $^{1}$H-NMR and 75 MHz or 120 MHz for $^{13}$C-NMR. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (=0) for $^{1}$H-NMR. For $^{13}$C-NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR Spectra were recorded on a JASCO FT/IR-5300 spectrophotometer (Tokyo, Japan). Mass spectra were measured on a JEOL JMS-T100LC spectrometer (Tokyo, Japan).

*Benzyl (S)-2-[(methylsulfonyl)oxy]propanoate* (**4**)




MsCl (7.01 g, 61.2 mmol) was added dropwise to a stirred solution of benzyl (*S*)-2-hydroxypropanoate (**3**; 7.35 g, 40.8 mmol) and $Et_3N$ (6.19 g, 61.2 mmol) in AcOEt (40 mL) at 0–5 °C for 20 min, and the mixture was stirred at the same temperature for 1 h. Then, *N*,*N*-dimethylethylenediamine (2.2 mL) and water (ca. 40 mL) were successively added to the mixture, which was extracted with AcOEt (40 mL × 2). The combined organic phase was washed with water, brine, dried ($Na_2SO_4$), and concentrated. The obtained crude oil was purified by $SiO_2$ column chromatography (hexane/AcOEt = 4:1) to give the desired product (9.45 g, 90%). Colorless oil; $[\alpha]_D^{21}$ + 49.2 (*c* 1.00, $CHCl_3$); $^{1}$H-NMR (500 MHz, $CDCl_3$): δ = 1.62 (d, *J* = 6.9 Hz, 3H), 3.10 (s, 3H), 5.18 (q, *J* = 6.9 Hz, 1H), 5.20 (d, *Jgem* = 12.6 Hz, 1H), 5.25 (d, *Jgem* = 12.6 Hz, 1H), 7.33–7.43 (m, 5H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 18.2, 39.0, 67.6, 74.1, 128.2 (2C), 128.6 (3C), 134.7, 169.3; IR (neat): $\nu_{max}$ = 1751, 1456, 1352, 1175, 1120, 1086, 1030 cm$^{-1}$; HRMS (ESI): *m*/*z* calcd. for $C_{11}H_{14}O_5S$ $[M + Na]^+$ 281.0460; found: 281.0462.

*Benzyl (R)-2-(acetylthio)propanoate* (**2**)

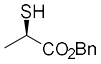



(Condition **A**) Benzyl (*S*)-2-[(methylsulfonyl)oxy]propanoate (**4**; 9.04 g, 35.0 mmol) in AcOEt (5 mL) was added dropwise to a stirred suspension of AcSK (4.40 g, 38.5 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) (12.5 g, 38.5 mmol) in AcOEt (100 mL) at 20–25 °C for 5 min, and the mixture was vigorously stirred at the same temperature for 1 h to maintain well-equalized suspension formation during the reaction. 1 M HCl aqueous solution (ca. 20 mL) was added to the mixture, which was extracted with AcOEt (40 mL × 2). The combined organic phase was washed with water, brine, dried ($Na_2SO_4$), and concentrated. The obtained crude oil was purified by $SiO_2$ column chromatography (hexane/AcOEt = 20:1) to give the desired product (**2**; 6.98 g, 84%).

Colorless oil; 94% ee, by HPLC analysis (Daicel Chiralcel OD-H column, hexane/2-propanol = 100:1, 1.0 mL/min, 254 nm UV detector), tR = 12.28 min (*R*) and tR = 11.80 min (*S*); $[\alpha]_D^{24}$ + 95.9 (*c* 1.00, $CHCl_3$) $^{1}$H-NMR (500 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 7.5 Hz, 3H), 2.34 (s, 3H), 4.29 (q, *J* = 7.5 Hz, 1H), 5.17 (s, 2H), 7.31–7.39 (m, 5H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 17.5, 30.0, 40.9, 67.2, 127.9 (2C), 128.5 (2C), 135.4, 171.7, 193.7 cm$^{-1}$; HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{14}O_3S$ $[M + Na]^+$ 261.0562; found: 261.0559.

(Condition **B**) In a similar procedure, the use of **4** (1.29 g, 5.0 mmol) and AcSK (0. 69 g, 6.0 mmol) in DMF (10 mL) under the identical conditions gave the desired product (**2**; 0.95 g, 80%, 89% ee by HPLC analysis).

*Benzyl (R)-2-sulfanylpropanoate* (**5**) [23]

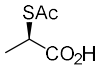



*N*,*N*-Dimethylethylenediamine (5.77 mL, 7.12 g, 53.0 mmol) was added dropwise to a stirred solution of benzyl (*R*)-2-(acetylthio)propanoate (**2**; 6.31 g, 26.5 mmol) in THF (53 mL) at 0–5 °C for

5 min, and the mixture was stirred at the same temperature for 1 h. 1 M HCl aqueous solution (ca. 20 mL) was added to the mixture, which was extracted with AcOEt (30 mL × 2). The combined organic phase was washed with water, brine, dried ($Na_2SO_4$), and concentrated. The obtained crude oil was purified by $SiO_2$ column chromatography (hexane/AcOEt = 20:1) to give the desired product (**5**; 5.30 g, 93%).

Colorless oil; 90% ee, by HPLC analysis (Daicel Chiralcel OJ-H column, hexane/2-propanol = 150:1, 1.0 mL/min, 254 nm UV detector), tR = 27.20 min (*R*) and tR = 24.07 min (*S*); $[\alpha]_D^{23}$ + 15.7 (*c* 1.00, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 6.9 Hz, 3H), 2.17 (d, *J* = 8.0 Hz, 1H), 3.55 (dq, *J* = 6.9, 8.0 Hz, 1H), 5.16 (d, *Jgem* = 12.0 Hz, 1H), 5.19 (d, *Jgem* = 12.0 Hz, 1H), 7.31–7.41 (m, 5H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 21.0, 35.6, 67.0, 128.1 (2C), 128.5 (2C), 135.5, 173.4.

*(R)-2-(acetylthio)propanoic acid* (**6**) [29]




A mixture of benzyl (*R*)-2-(acetylthio)propanoate (**2**; 0.48 g, 2.0 mmol) and HBr (ca. 5.1 M in AcOH, 2 mL) was stirred at 20–25 °C for 4 h. Toluene (1 mL) was added to the mixture and was evaporated (azeotropic removal) to give the residue, which was purified by $SiO_2$ column chromatography (hexane/AcOEt = 5:1) to give the desired product (**6**; 0.27 g, 92%).

Pale yellow oil; $[\alpha]_D^{25}$ + 104.6 (*c* 1.05, MeOH); [(*S*)-form; lit. [29] − 114 (*c* 0.50, MeOH)]. $^1$H-NMR (500 MHz, $CDCl_3$): δ = 1.53 (d, *J* = 7.5 Hz, 3H), 2.38 (s, 3H), 4.24 (q, *J* = 7.5 Hz, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ = 17.1, 30.0, 40.6, 177.6, 194.2.

## 4. Conclusions

Chiral pool synthesis of novel and less odorous benzyl (*R*)-2-(acetylthio)propanoate was performed through a clean $S_N2$ displacement reaction using available AcSK with tris[2-(2-methoxyethoxy)]ethylamine (TDA-1) starting from commercially available benzyl (*S*)-lactate in two steps. Deprotection of the acetyl group using *N,N*-dimethylethylenediamine afforded benzyl (*R*)-2-sulfanylpropanoate in good yield without undesirable racemization. These two sulfur-containing benzyl esters were sufficiently odorless to be purified by column chromatography. Benzyl (*R*)-2-(acetylthio)propanoate (acetylthiolactate) is less odorous than the corresponding methyl or ethyl analogue. Direct HPLC analysis was applied to determine the enantiomeric excess without thiazolidin-4-one derivatizations. Upon treatment with HBr/AcOH, complementary debenzylation of benzyl (*R*)-2-(acetylthio)propanoate afforded (*R*)-2-(acetylthio)propanoic acid without significant racemization.

**Supplementary Materials:** All materials (substrates and reagents) in this work are commercially available with inexpensive price. Copies of the $^1$H, $^{13}$C-NMR spectra for compounds **2**, **4**, **5**, and **6** and copies of HPLC analyses data of **2** and **5** are available in the supplementary information. They and molfiles can be found on line.

**Author Contributions:** M.K. and S.I. contributed the whole syntheses and assisted literature survey. Y.T. prepared the whole manuscript.

**Funding:** This research was partially supported by Grant-in-Aids for Scientific Research on Basic Areas (B) "18350056" and (C) 15K05508, Priority Areas (A) "17035087" and "18037068", and Exploratory Research "17655045" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

**Conflicts of Interest:** The authors declare no conflict of interest. One of the author (Y.T.) offers his warmest congratulations to Ben L. Feringa (University of Groningen, The Netherlands) on being awarded the 2016 Nobel Prize in Chemistry. Dedication to Teruaki Mukaiyama on the celebration of his 90th birthday (Sotuju).

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**Sample Availability:** Samples of the compounds **2**, **5** and **6** are available from the authors.