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Synthesis, antibacterial activities, and sustained perfume release properties of optically active5-hydroxy- and 5-acetoxyalkanethioamide analogues

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Abstract: 5-Acetoxy- and 5-hydroxyalkanethioamide analogues showed high antibacterial activity against *Staphylococcus aureus*. Antibacterial thioamides were prepared from 5-alkyl-*δ*-lactones by amidation, thionation, and subsequent deacetylation. Optically active thioamides with 99% diastereomeric excesses were prepared by diastereomeric resolution using Cbz-L-proline as the resolving agent. Antibacterial thioamides were slowly lactonized by a lipase catalyst. Therefore, these thioamides are potential sustained-release perfume compounds having antibacterial properties.

Keywords: thioamide, antibacterial activity, *Staphylococcus aureus*, optically active, diastereomeric resolution

Introduction

In the past few decades, there has been growing concern about the health hazards and infections caused by pathogenic microorganisms [1]. Currently used antibiotics are effective in treating numerous infectious diseases [2]. However, the widespread use and abuse of antibiotics has led to the emergence of various multidrug resistant strains and superbugs, resulting in a potential threat to human health and survival. The rapid increase in multidrug resistant pathogenic bacteria is surprising. Examples of multidrug-resistant bacteria include the methicillin-resistant *Staphylococcus aureus* (MRSA) and the vancomycin-resistant enterococci (VRE). *S. aureus* (SA) is a historically major human pathogen that continues to be one of the most common disease-causing bacteria in humans [3]. Every year, approximately 50% of the hospitalized patients around the world suffer from nosocomial infections due to drug-resistant bacteria [4]. Therefore, there is an urgent requirement to develop new drugs and materials that can combat drug-resistant bacteria [5-8]. Over the past few decades, the treatment of bacterial infections has become more complicated due to their resistance mechanism. In light of the increasing incidence of antibiotic resistance, the research and development of novel antimicrobial agents with excellent antibacterial activity is highly desirable and is of great scientific significance. We have synthesized various optically active *δ*-lactones [9-11] and found that *N*-methyl-5-acetoxydodecanamide, *N*-methyl-5-acetoxytridecanamide, and *N*-methyl-5-acetoxytetradecanamides, which are precursors of *δ*-lactones, have antibacterial activities [12]. *N*-Methyl-5-acetoxyalkanamides showed high antibacterial activities against Gram positive bacteria such as *S. aureus* and *Pneumococcus pneumoniae*. It is known that thioamide compounds have higher biological activities than the corresponding amide compounds [13-18]. Fortuna *et al*. and Xue *et al*. also reported that thioamide compounds have higher antibacterial activity than the corresponding amide compounds [19, 20]. Based on these facts, we synthesized various *N*-methyl-5-acetoxyalkanethioamides and attempted to improve their antibacterial activities and establish the structure-activity relationship.

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In many cases, there is a difference in biological activity between stereoisomers [21-25]. Therefore, optically active *N*-methyl-5-acetoxyalkanethioamides were synthesized, and their antibacterial activities were evaluated. Furthermore, *N*-methyl-5-acetoxyalkanethioamides are precursors of *δ*-lactones. Many 5-alkyl-*δ*-lactones have a sweet and fruity odor [26-30]. Therefore, if fungal lipase catalyzes its lactonization, it can be used as a sustained-release perfume compound having antibacterial properties. The lipase-catalyzed lactonization of alkanethioamide analogues showing antibacterial activities was investigated.

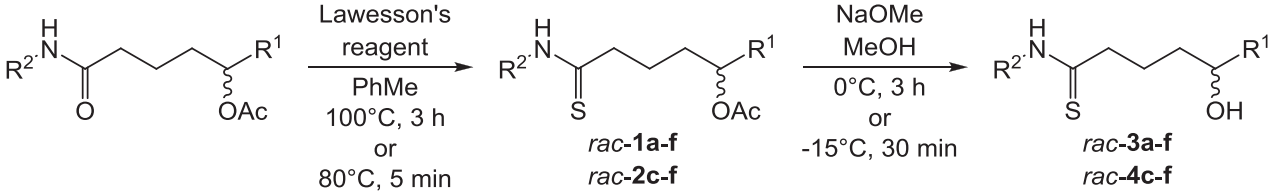
Results and discussion

Preparation of *N*-methyl-5-hydroxyalkanethioamides (*rac*-3) and 5-hydroxyalkanethioamides (*rac*-4)

We had previously reported the synthesis of optically active 5-alkyl-*δ*-lactones with >99% enantiomeric excesses *via* diastereomeric resolution of racemic *N*-methyl-5-hydroxyalkanamides using amino acid derivatives as the optical resolving agent [9]. We hypothesized that optically active 5-acetoxyalkanethioamides could be synthesized by the same method (Scheme 1). Therefore, diastereomeric resolution of 5-hydroxyalkanethioamides was planned using amino acid derivatives. *N*-Methyl-5-acetoxyalkanamides and 5-acetoxyalkanamides were prepared from the corresponding 5-alkyl-*δ*-lactones by a previous method [31]. Racemic 5-hydroxyalkanethioamides were prepared by thionation of 5-acetoxyalkanamides with Lawesson's reagent and subsequent deacetylation under basic conditions. The thionation of *N*-methyl-5-acetoxyalkanamides was carried out using Lawesson's reagent in toluene at 100 °C for 3 h. *N*-Methyl-5-acetoxyalkanethioamides (*rac*-**1**) were obtained in approximately 90% yields, regardless of the difference in the R^1 group. In contrast, when 5-acetoxytetradecanamide was thionized under the same conditions, 5-acetoxytetradecanethioamide (*rac*-**2e**) was obtained in 40% yield. In order to improve the yield, thionation of 5-acetoxytetradecanamide was performed at 40, 60, 80 and 100 °C for 5 min, respectively, and *rac*-**2e** was obtained in 61%, 80%, 83%, and 62% yields. We decided to perform the thionation of 5-acetoxyalkanamides at 80 °C for 5 min, as prolonged thionation at high temperature reduced the yield. 5-Acetoxydodecanethioamide (*rac*-**2c**) and 5-acetoxytridecanethioamide (*rac*-**2d**) were obtained in approximately 70% yields, and 5-acetoxyhexadecanethioamide (*rac*-**2f**) was obtained in 99% yield. The deacetylation of *N*-methyl-5-acetoxyalkanethioamides (*rac*-**1**) was then performed at 0 °C for 3 h using sodium methoxide to give *N*-methyl-5-hydroxyalkanethioamides (*rac*-**3**) in approximately 90% yield. However, deacetylation of 5-acetoxyalkanethioamides (*rac*-**2**) at 0 °C gave 5-hydroxyalkanethioamides (*rac*-**4**) in approximately 40% yield. When the reaction was performed at -15 °C, *rac*-**4** was obtained in approximately 70% yield, regardless of the difference in the R^1 group. The antibacterial activities of the synthesized 5-acetoxyalkanethioamide analogues (*rac*-**1** and *rac*-**2**) and 5-hydroxyalkanethioamide analogues (*rac*-**3** and *rac*-**4**) were investigated (Table 1).

Antibacterial activities of racemic 5-aetoxy- and 5-hydroxyalkanethioamide analogues

The antibacterial activity value was calculated, compounds with a value of 2.0 or more (≥99% killing ratio) were considered antibacterial substances (see experimental section). At antibacterial activity values of ≥7.0, the bacteria were almost completely killed. Antibacterial activities against *S. aureus* and *E. coli* were tested, and none of the thioamide compounds showed activities against *E. coli*. Several thioamides showed high antibacterial activities against *S. aureus* (Table 1). Among the *N*-methyl-5-acetoxyalkanethioamides (*rac*-**1**), of the primary thioamides *rac*-**1b** and *rac*-**1c** showed high activities, with *rac*-**1c** showing higher activity than *rac*-**1b**. Among the 5-acetoxyalkanethioamides (*rac*-**2**), which are



R^1= *n*-C_5H_{11}: **a**, *n*-C_6H_{13}: **b**, *n*-C_7H_{15}: **c**, *n*-C_8H_{17}: **d**, *n*-C_9H_{19}: **e**, *n*-$C_{11}H_{23}$: **f**
R^2= Me: **1**, **3**, H: **2**, **4**

Scheme 1 Synthesis of racemic 5-hydroxyalkanthioamide analogues.

Table 1 Antibacterial activities of racemic thioamide analogues against *S. aureus*[a)]

Sample	R^1	R^2	Antibacterial activity value [-][b)]	Sample	R^1	R^2	Antibacterial activity value [-][b)]
rac-**1a**	*n*-C_5H_{11}	Me	<0.1	*rac*-**3a**	*n*-C_5H_{11}	Me	<0.1
rac-**1b**	*n*-C_6H_{13}		5.0	*rac*-**3b**	*n*-C_6H_{13}		1.9
rac-**1c**	*n*-C_7H_{15}		6.7	*rac*-**3c**	*n*-C_7H_{15}		>7.0
rac-**1d**	*n*-C_8H_{17}		1.9	*rac*-**3d**	*n*-C_8H_{17}		6.4
rac-**1e**	*n*-C_9H_{19}		0.5	*rac*-**3e**	*n*-C_9H_{19}		0.5
rac-**1f**	*n*-$C_{11}H_{23}$		0.3	*rac*-**3f**	*n*-$C_{11}H_{23}$		0.3
rac-**2c**	*n*-C_7H_{15}	H	5.1	*rac*-**4c**	*n*-C_7H_{15}	H	5.1
rac-**2d**	*n*-C_8H_{17}		6.4	*rac*-**4d**	*n*-C_8H_{17}		4.3
rac-**2e**	*n*-C_9H_{19}		6.3	*rac*-**4e**	*n*-C_9H_{19}		4.8
rac-**2f**	*n*-$C_{11}H_{23}$		1.6	*rac*-**4f**	*n*-$C_{11}H_{23}$		<0.1

[a)] Final concentration of synthetic compounds is 500 μg/mL.

[b)] Data An antibacterial activity value of ≥2.0 indicates that the bacterial killing ratio is ≥99%.

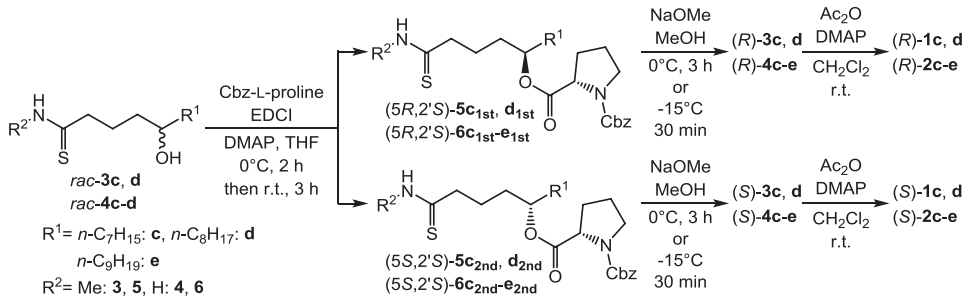
secondary thioamides, all *rac*-**2** except *rac*-**2f** showed high antibacterial activity. The antibacterial activities appeared to be related to the chain length, as **1b** and **2c**, and **1c** and **2d**, which have the same number of carbons respectively, showed similar activities. Moreover, high activities were observed for *rac*-**3c** and *rac*-**3d** among *N*-methyl-5-hydroxyalkanethioamides (*rac*-**3**). Among the tested thioamides in Table 1, *rac*-**3c** had the highest antibacterial activity. These *N*-methyl-5-hydroxyalkanethioamides (*rac*-**3c** and **3d**) showed higher activity than the corresponding *N*-methyl-5-acetoxyalkanethioamides (*rac*-**1c** and **1d**). All 5-hydroxyalkanethioamides (*rac*-**4**) except *rac*-**4f** showed antibacterial activities, which were lower than those of the corresponding 5-acetoxyalkanethioamides (*rac*-**2**). From these results, it was found that an acetyl group is not necessary for the expression of antibacterial activity in these thioamides. It is assumed that appropriate polarity to penetrate the cell membrane of *S. aureus* is required to express antibacterial activities.

Diastereomeric resolution of racemic 5-hydroxyalkanethioamide analogues (*rac*-3 and *rac*-4)

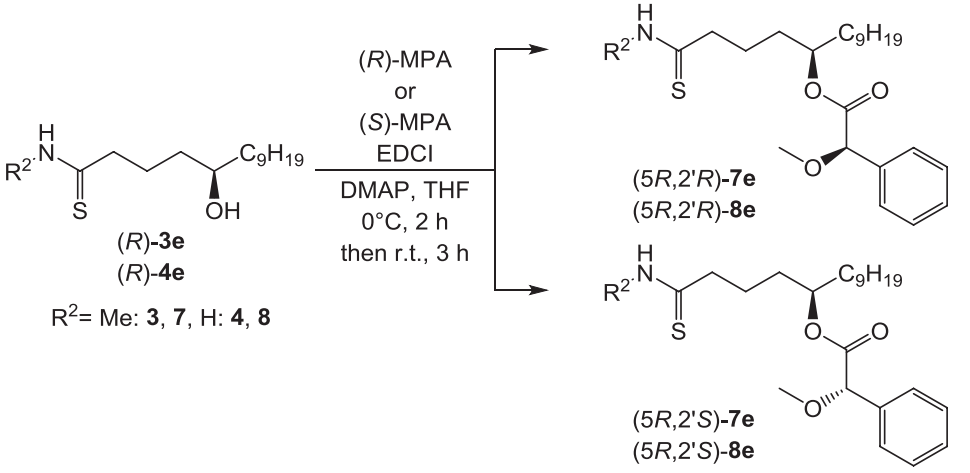
It is known that organic compounds having biological activities differ in these activities between stereoisomers [21-25]. As thioamides showing antibacterial activities have an asymmetric center at the C-5 position, it is considered that there is a difference in antibacterial properties between the stereoisomers. 5-Acetoxyalkanethioamide analogues (**1** and **2**) and 5-hydroxyalkanethioamide analogues (**3** and **4**) with high antibacterial activities were converted to the corresponding optically active forms (Scheme 2). We have previously reported the diastereomeric resolution of various amide compounds using amino acid derivatives as resolving agents [9, 32]. We found that Cbz-L-proline is an efficient resolving agent to obtain both the diastereomeric esters with high diastereomeric excesses. TLC analysis of the diastereomeric esters revealed a polarity difference, regardless of the difference between R^1 and R^2 (**5** and **6**), and it was easy to obtain both the diastereomers with over 99% diastereomeric excesses by silica gel column chromatography separation. We named the high polarity diastereomers as **1st** and the low polarity diastereomers as **2nd**. Subsequently, each of the obtained diastereomeric esters (**5** and **6**) was deacylated to give optically active 5-hydroxyalkanethioamide analogues (**3** and **4**) with approximately 90% and 70% yields for **3** and **4**, respectively. Acetylation of both **3** and **4** afforded optically active 5-acetoxyalkanethioamide analogues (**1** and **2**) almost quantitatively. The absolute configuration at the C-5 position of the diastereomeric esters was determined by ^{1}H NMR, using the Trost method [33, 34]. Diastereomer esters (**7e** and **8e**) were prepared from optically active **3e** and **4e** obtained by deacylation of $\mathbf{5e_{1st}}$ and $\mathbf{6e_{1st}}$, using (*R*)- or (*S*)-α-methoxyphenylacetic acid (Scheme 3). From the ^{1}H NMR analysis, the absolute configuration at the C-5 position in $\mathbf{5e_{1st}}$ and $\mathbf{6e_{1st}}$ was found to be the (*R*)-configuration regardless of the difference in R^2 group. Moreover, no decrease in optical purity could be confirmed in the deacylation of diastereomeric esters (**5** and **6**) under basic conditions. Antibacterial activity tests were carried out on these thioamide analogues (**1**-**4**).

Evaluation of antibacterial activities for optically active 5-acetoxy- and 5-hydroxyalkanethioamide analogues

Table 2 shows the results of antibacterial activity tests against *S. aureus* for the optically active forms. There



Scheme 2 Preparation of optically active thioamide analogues.



Scheme 3 Esterification of (R)-3e and 3e using (R)- or (S)-MPA.

were no great differences in the antibacterial activities between the enantiomers of *N*-methyl-5-acetoxydodecanethioamide (**1c**). In the 5-acetoxyalkanethioamides (**2**), both **2d** and **2e** showed higher activities in (*S*)-form than in (*R*)-form. On the other hand, in the *N*-methyl-5-hydroxyalkanethioamides (**3**) no great difference was observed in the activity value between each enantiomer. The antibacterial activity values of 5-hydroxyalkanethioamides (**4**) tended to be slightly higher in the (*R*)-form as compared to the (*S*)-form. Although a difference in antibacterial activity depending on the absolute configuration could be observed, the consistency of the absolute configuration could not be confirmed. The antibacterial activity values of (*S*)-**2d** and **3c** at a final sample concentration of 500 μg/mL were equal to or greater than seven. These samples were also tested for antibacterial activity at a final sample concentration of 200 μg/mL (noted in brackets). The antibacterial activity of **3c** decreased slightly in both enantiomers, but the activity of the (*R*)-enantiomer was slightly higher than that of (*S*)-enantiomer. In contrast, **2d** showed almost no reduction in the antibacterial activity values when the sample concentration decreased. Of all the samples evaluated, (*S*)-**2d** showed the highest antibacterial activity.

Evaluation of lipase-catalyzed lactonization for use as a sustained-release perfume

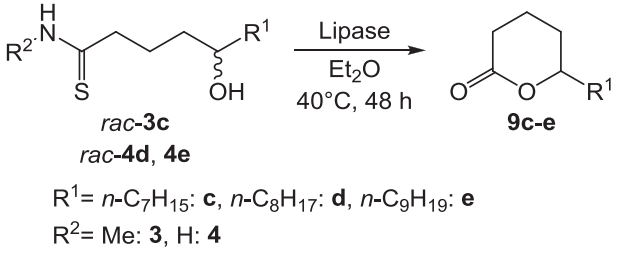
5-Hydroxyalkanethioamide analogues which have antibacterial activities against *S. aureus* are precursors of 5-alkyl-*δ*-lactones. Many 5-alkyl-*δ*-lactones have a sweet and fruity odor [26-30]. We have also reported that *δ*-tridecalactone has a walnut-like odor [11]. Therefore, if a fungal-derived lipase catalyzes lactonization, it can be expected to be used as a sustained-release perfume having antibacterial properties [35]. Lipase-catalyzed lactonization was confirmed for 5-hydroxyalkanethioamide analogues (**3c**, **4d** and **4e**) that showed antibacterial activities (Scheme 4, Table 3). 5-Hydroxytridecanethioamide (*rac*-**4d**) was stirred for 48 h at 40 °C in diethyl ether with each lipase derived from different sources. The yield of *δ*-tridecalactone (**9d**) was 0.4% in the absence of lipase. On the other hand, all lipases catalyzed lactonization regardless of the origin. All lipases showed no stereoselectivity for lactonization. Although Novozym 435 gave the highest yield of 13.1%, the other lipases catalyzed lactonization with approximately 4-5% yields. All lipases similarly catalyzed lactonization for 5-hydroxytetradecanethioamide (*rac*-**4e**) and *N*-methyl-5-hydroxydodecanethioamide

Table 2 Antibacterial activities of optically active thioamide analogues against *S. aureus*[a)]

Sample	Config.	Antibacterial activity value [-][b)]	Sample	Config.	Antibacterial activity value [-][b)]
1c	*Racemate*	6.7	**3d**	*Racemate*	6.4 (6.4)[c)]
	5*R*	6.4		5*R*	5.9 (5.9)[c)]
	5*S*	7.0		5*S*	6.0 (6.1)[c)]
2d	*Racemate*	6.4 (5.2)[c)]	**4c**	*Racemate*	5.1
	5*R*	5.8 (5.7)[c)]		5*R*	5.9
	5*S*	>7.0 (>7.0)[c)]		5*S*	5.7
2e	*Racemate*	6.3 (5.8)[c)]	**4d**	*Racemate*	4.3
	5*R*	6.3 (5.9)[c)]		5*R*	4.8
	5*S*	6.3 (5.9)[c)]		5*S*	4.2
3c	*Racemate*	>7.0 (6.4)[c)]	**4e**	*Racemate*	4.8
		>7.0 (6.6)[c)]		5*R*	5.3
		>7.0 (6.3)[c)]		5*S*	5.0

[a)] Final concentration of synthetic compounds is 500 μg/mL.
[b)] An antibacterial activity value of ≥2.0 indicates that the bacterial killing ratio is ≥99%.
[c)] Final concentration of synthetic compounds is 200 μg/mL.

(*rac*-**3c**), although with varying yields. The antibacterial activity value was evaluated after incubation for 20 h. The yield after 48 h of lipase-catalyzed lactonization was at most approximately 13%. It seems that if the catalytic activity of lipase is strong, all thioamides convert to lactones before they show antibacterial properties. Previously we have confirmed that *δ*-dodeca-, *δ*-trideca-, and *δ*-tetradecalactone showed no antibacterial activities against *S. aureus*. Catalytic lactonization would preferably be slow in order for these thioamides to exhibit antibacterial activity. From these results, it was shown that these thioamides showing antibacterial activities can be expected to be used as a sustained-release perfume.



Scheme 4 Lipase-catalyzed lactonization of thioamide derivatives.

Conclusions

5-Acetoxy- and 5-hydroxyalkanethioamide analogues prepared from 5-alkyl-*δ*-lactones showed high antibacterial activities against *S. aureus*. 5-Acetoxyalkanethioamide analogues (**1** and **2**) had a higher antibacterial activity in the (*S*)-form than in the (*R*)-form. Conversely, 5-hydroxyalkanethioamide analogues (**3** and **4**) showed only a slightly higher antibacterial activity in the (*S*)-form than in the (*R*)-form. Among the samples evaluated, (*S*)-**2d** showed the highest antibacterial activity. In addition, lipase catalytic activity for these thioamides was tested. All lipases slowly catalyzed the lactonization of thioamides regardless of their origin. Therefore, we propose that these thioamides can be used as sustained-release perfume compounds having antibacterial activity.

Experimental

General

NMR spectra were recorded on a JNM-ECA-600 spectrometer (JEOL, Tokyo, Japan). Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in Hz. Structural determination of all compounds was performed by the use of COSY, HMQC, and HMBC NMR techniques. Infrared spectra were obtained on an FT-IR 460plus spectrometer (JASCO Corp., Tokyo, Japan). ESI high resolution mass spectra were provided on an AccuTOF GCv 4G instrument (JEOL). Melting points (mp) were recorded on a MP-500D micro-melting-point apparatus from Yanaco Technical Science Co., Ltd. (Kyoto, Japan) and are uncorrected.

General procedure for thionation

To a solution of *N*-methyl-5-acetoxyalkanamides (1.0 mmol) or 5-acetoxyalkanethioamide (1.0 mmol) in dry

Table 3 Effect of source on lipase-catalyzed lactonization[a)]

Entry	Substrate	Lipase	Source	Yield [%]
1	*rac*-**4d**	None	-	0.4
2		Novozym 435	*Candida antarctica* B	13.1
3		Lipase AK	*Pseudomonas fluorescens*	3.8
4		Lipase AS	*Aspergillus niger*	5.4
5		Lipase AYS	*Candida cylindracea*	6.0
6		Lipase F-AP15	*Rhizopus oryzae*	5.2
7		Lipase G	*Penicillium camemberti*	4.7
8		Lipase M	*Mucor javanicus*	4.6
9		Lipase PS	*Burkholderia cepacia*	3.5
10		PPL	Porcine pancreas	6.3
11	*rac*-**4e**	Novozym 435	*Candida antarctica* B	7.9
12		Lipase AS	*Aspergillus niger*	1.8
13		Lipase G	*Penicillium camemberti*	3.3
14		Lipase PS	*Burkholderia cepacia*	2.6
15	*rac*-**3c**	Novozym 435	*Candida antarctica* B	4.3
16		Lipase AS	*Aspergillus niger*	12.7
17		Lipase G	*Penicillium camemberti*	12.8
18		Lipase PS	*Burkholderia cepacia*	7.3

[a)] Substrate: 1.0 mmol, Novozym 435: 0.4 g, other lipase: 0.5 w/w, Et_2O: 20 mL, 40 °C, 48 h.

toluene (20 mL), Lawesson's reagent (0.4 g, 1.0 mmol) was added. The reaction mixture was heated for 3 h at 100 °C for the preparation of *rac*-**1**, and for 5 min at 80 °C for the preparation of *rac*-**2**. After cooling, the solvent was evaporated under vacuum, and the remaining residue was applied to a chromatographic column on silica (eluent; *n*-hexane/EtOAc= 9/1) to afford the corresponding *N*-methyl-5-acetoxyalkanethioamides (**1**) or 5-acetoxyalkanethioamides (**2**).

***N*-Methyl-5-acetoxydecanethioamide (1a)** Yield: 89%; Colorless oil. R_f= 0.19 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3255 (N-H), 2953 (CH_3, C-H), 2929 (CH_2, C-H), 2858 (CH_2, C-H), 1732 (OC=O), 1543 (NHC=S), 1458 (C-H), 1375 (NHC=S), 1242 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-10), 1.28 (m, 6H, H-7, H-8, H-9), 1.53 (m, 2H, H-6), 1.57 (m, 2H, H-4), 1.73 (m, 1H, H-3), 1.84 (m, 1H, H-3), 2.06 (s, 3H, -OC(=O)CH_3), 2.67 (m, 2H, H-2), 3.16 (d, *J*= 4.8 Hz, 3H, CH_3NHC(=S)-), 4.86 (m, 1H, H-5), 7.91 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.0 (C-10), 21.4 (-OC(=O)CH_3), 22.6 (-CH_2-), 25.1 (C-3), 31.7 (-CH_2-), 33.0 (CH_3NHC(=S)-), 33.2 (C-4), 34.0 (C-6), 46.0 (C-2), 73.8 (C-5), 171.5 (-OC(=O)CH_3), 205.8 (C-1). HRMS (FD). Calcd for $C_{13}H_{25}NO_2S$ (M): *m*/*z* 259.1606. Found: *m*/*z* 259.1608.

***N*-Methyl-5-acetoxyundecanethioamide (1b)** Yield: 91%; Colorless oil. R_f= 0.19 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3256 (N-H), 2953 (CH_3, C-H), 2930 (CH_2, C-H), 2858 (CH_2, C-H), 1734 (OC=O), 1541 (NHC=S), 1458 (C-H), 1375 (NHC=S), 1246 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-11), 1.26 (m, 8H, H-7, H-8, H-9, H-10), 1.53 (m, 2H, H-6), 1.57 (m, 2H, H-4), 1.73 (m, 1H, H-3), 1.84 (m, 1H, H-3), 2.05 (s, 3H, -OC(=O)CH_3), 2.67 (m, 2H, H-2), 3.16 (d, *J*= 4.8 Hz, 3H, CH_3NHC(=S)-), 4.85 (m, 1H, H-5), 7.83 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1 (C-11), 21.4 (-OC(=O)CH_3), 22.6 (-CH_2-), 25.1 (C-3), 25.4 (-CH_2-), 29.2 (-CH_2-), 31.8 (-CH_2-), 33.0 (CH_3NHC(=S)-), 33.2 (C-4), 34.1 (C-6), 46.0 (C-2), 73.8 (C-5), 171.5 (-OC(=O)CH_3), 205.8 (C-1). HRMS (FD). Calcd for $C_{14}H_{27}NO_2S$ (M): *m*/*z* 273.1762. Found: *m*/*z* 273.1756.

***N*-Methyl-5-acetoxydodecanethioamide (1c)** Yield: 94%; Colorless oil. R_f= 0.20 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3254 (N-H), 2953 (CH_3, C-H), 2928 (CH_2, C-H), 2856 (CH_2, C-H), 1736 (OC=O), 1545 (NHC=S), 1458 (C-H), 1377 (NHC=S), 1244 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-12), 1.26 (m, 10H, H-7, H-8, H-9, H-10, H-11), 1.53 (m, 2H, H-6), 1.56 (m, 2H, H-4), 1.73 (m, 1H, H-3), 1.84 (m, 1H, H-3), 2.05 (s, 3H, -OC(=O)CH_3), 2.67 (m, 2H, H-2), 3.16 (d, *J*= 4.8 Hz, 3H, CH_3NHC(=S)-), 4.85 (quin, *J*= 6.2 Hz, 1H, H-5), 7.80 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1 (C-12), 21.4 (-OC(=O)CH_3), 22.7 (-CH_2-), 25.1 (C-3), 25.4 (-CH_2-), 29.2 (-CH_2-), 29.5 (-CH_2-), 31.8 (-CH_2-), 33.0 (CH_3NHC(=S)-), 33.2 (C-4), 34.1 (C-6), 46.0 (C-2), 73.8 (C-5), 171.5 (-OC(=O)CH_3), 205.8 (C-1). HRMS (FD). Calcd for $C_{15}H_{29}NO_2S$ (M): *m*/*z* 287.1919. Found: *m*/*z* 287.1890.

***N*-Methyl-5-acetoxytridecanethioamide (1d)** Yield: 90%; Colorless oil. R_f= 0.21 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3252 (N-H), 2953 (CH_3, C-H), 2927 (CH_2, C-H), 2856 (CH_2, C-H), 1735 (OC=O), 1545 (NHC=S), 1458 (C-H), 1377 (NHC=S), 1243 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 7.6 Hz, 3H, H-13), 1.26 (m, 12H, H-7, H-8, H-9, H-10, H-11, H-12), 1.53 (m, 2H, H-6), 1.56 (m, 2H, H-4), 1.73 (m, 1H, H-3), 1.84 (m, 1H, H-3), 2.05 (s, 3H, -OC(=O)CH_3), 2.67 (m, 2H, H-2), 3.16 (d, *J*= 4.8 Hz, 3H, CH_3NHC(=S)-), 4.85 (quin, *J*= 6.2 Hz, 1H, H-5), 7.80 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1 (C-13), 21.4 (-OC(=O)CH_3), 22.7 (-CH_2-), 25.1 (C-3), 25.4 (-CH_2-), 29.3 (C-6), 29.5 (-CH_2-), 31.9 (-CH_2-), 33.0 (CH_3NHC(=S)-), 33.2 (C-4), 34.1 (-CH_2-), 46.0 (C-2), 73.8 (C-5), 171.5 (-OC(=O)CH_3), 205.6 (C-1). HRMS (FD). Calcd for $C_{16}H_{31}NO_2S$ (M): *m*/*z* 301.2075. Found: *m*/*z* 301.2075.

***N*-Methyl-5-acetoxytetradecanethioamide (1e)** Yield: 89%; Colorless oil. R_f= 0.22 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3254 (N-H), 2952 (CH_3, C-H), 2929 (CH_2, C-H), 2856 (CH_2, C-H), 1734 (OC=O), 1546 (NHC=S), 1458 (C-H), 1377 (NHC=S), 1244 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-14), 1.26 (m, 14H, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 1.53 (m, 2H, H-6), 1.56 (m, 2H, H-4), 1.73 (m, 1H, H-3), 1.84 (m, 1H, H-3), 2.05 (s, 3H, -OC(=O)CH_3), 2.67 (m, 2H, H-2), 3.16 (d, *J*= 4.1

Hz, 3H, C$\underline{H}_3$NHC(=S)-), 4.85 (quin, *J*= 6.2 Hz, 1H, H-5), 7.84 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2 (C-14), 21.4 (-OC(=O)$\underline{C}H_3$), 22.7 (-$\underline{C}H_2$-), 25.1 (C-3), 25.4 (-$\underline{C}H_2$-), 29.3 (C-6), 29.5 (-$\underline{C}H_2$-), 29.6 (-$\underline{C}H_2$-), 31.9 (-$\underline{C}H_2$-), 33.0 ($\underline{C}H_3$NHC(=S)-), 33.2 (C-4), 34.1 (-$\underline{C}H_2$-), 46.0 (C-2), 73.8 (C-5), 171.5 (-O$\underline{C}$(=O)CH_3), 205.8 (C-1). HRMS (FD). Calcd for $C_{17}H_{33}NO_2S$ (M): *m*/*z* 315.2232. Found: *m*/*z* 315.2191.

***N*-Methyl-5-acetoxyhexadecanethioamide (1f)** Yield: 90%; Pale yellow oil. R_f= 0.23 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3252 (N-H), 2954 (CH_3, C-H), 2928 (CH_2, C-H), 2856 (CH_2, C-H), 1737 (O$\underline{C}$=O), 1545 (NH$\underline{C}$=S), 1458 (C-H), 1376 (NH$\underline{C}$=S), 1244 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-16), 1.25 (m, 18H, H-7, H-8, H-9, H-10, H11, H-12, H-13, H-14, H-15), 1.53 (m, 2H- H-6), 1.56 (m, 2H, H-4), 1.72 (m, 1H, H-3), 1.84 (m, 2H, H-3), 2.05 (s, 3H, -OC(=O)C$\underline{H}_3$), 2.67 (m, 2H, H-2), 3.16 (d, *J*= 4.8 Hz, 3H, C$\underline{H}_3$NHC(=S)-), 4.85 (quin, *J*= 6.2 Hz, 1H, H-5), 7.80 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2 (C-16), 21.4 (-OC(=O)$\underline{C}H_3$), 22.7 (-$\underline{C}H_2$-), 25.1 (C-3), 25.5 (-$\underline{C}H_2$-), 29.4 (-$\underline{C}H_2$-), 29.5 (-$\underline{C}H_2$-), 29.6 (-$\underline{C}H_2$-), 29.6 (-$\underline{C}H_2$-), 29.7 (-$\underline{C}H_2$-), 29.7 (-$\underline{C}H_2$-), 32.0 (-$\underline{C}H_2$-), 33.0 ($\underline{C}H_3$NHC(=S)-), 33.2 (C-4), 34.1 (C-6), 46.0 (C-2), 73.8 (C-5), 171.5 (-O$\underline{C}$(=O)CH_3), 205.9 (C-1). HRMS (FD). Calcd for $C_{19}H_{37}NO_2S$ (M): *m*/*z* 343.2545. Found: *m*/*z* 343.2479.

5-Acetoxydodecanethioamide (2c) Yield: 72%; Pale yellow oil. R_f= 0.16 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3186 (N-H), 3310 (N-H), 2928 (CH_3, C-H), 2856 (CH_2, C-H), 1715 (O$\underline{C}$=O), 1456 (NH$\underline{C}$=S), 1375 (NH$\underline{C}$=S), 1259 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-12), 1.26 (m, 10H, H-7, H-8, H-9, H-10, H-11), 1.53 (m, 2H, H-6), 1.60 (m, 2H, H-4), 1.73 (m, 1H, H-3), 1.84 (m, 1H, H-3), 2.06 (s, 3H, -OC(=O)C$\underline{H}_3$), 2.64 (m, 1H, H-2), 2.70 (m, 1H, H-2), 4.87 (quin, *J*= 6.9 Hz, 1H, H-5), 7.26 (br s, 1H, NH), 7.80 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1 (C-12), 21.4 (-OC(=O)$\underline{C}H_3$), 22.7 (-$\underline{C}H_2$-), 25.0 (C-3), 25.5 (-$\underline{C}H_2$-), 29.2 (-$\underline{C}H_2$-), 29.5 (-$\underline{C}H_2$-), 31.8 (-$\underline{C}H_2$-), 33.2 (C-6), 34.2 (C-4), 44.7 (C-2), 73.8 (C-5), 171.5 (-O$\underline{C}$(=O)CH_3), 210.5 (C-1). HRMS (FD). Calcd for $C_{14}H_{27}NO_2S$ (M): *m*/*z* 273.1762. Found: *m*/*z* 273.1734.

5-Acetoxytridecanethioamide (2d) Yield: 73%; Pale yellow oil. R_f= 0.17 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3185 (N-H), 3309 (N-H), 2928 (CH_3, C-H), 2856 (CH_2, C-H), 1714 (O$\underline{C}$=O), 1456 (NH$\underline{C}$=S), 1375 (NH$\underline{C}$=S), 1259 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-13), 1.26 (m, 12H, H-7, H-8, H-9, H-10, H-11, H-12), 1.53 (m, 2H, H-6), 1.60 (m, 2H, H-4), 1.73 (m, 1H, H-3), 1.84 (m, 1H, H-3), 2.06 (s, 3H, -OC(=O)C$\underline{H}_3$), 2.64 (m, 1H, H-2), 2.69 (m, 1H, H-2), 4.87 (m, 1H, H-5), 7.29 (br s, 1H, NH), 7.87 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1 (C-13), 21.4 (-OC(=O)$\underline{C}H_3$), 22.7 (-$\underline{C}H_2$-), 24.9 (-$\underline{C}H_2$-), 25.4 (-$\underline{C}H_2$-), 29.2 (-$\underline{C}H_2$-), 29.5 (-$\underline{C}H_2$-×2), 31.8 (-$\underline{C}H_2$-), 33.1 (C-4), 34.1 (C-6), 44.8 (C-2), 73.7 (C-5), 171.5 (-O$\underline{C}$(=O)CH_3), 210.4 (C-1). HRMS (FD). Calcd for $C_{15}H_{29}NO_2S$ (M): *m*/*z* 287.1919. Found: *m*/*z* 287.1877.

5-Acetoxytetradecanethioamide (2e) Yield: 83%; Pale yellow oil. R_f= 0.19 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3186 (N-H), 3309 (N-H), 2928 (CH_3, C-H), 2856 (CH_2, C-H), 1716 (O$\underline{C}$=O), 1456 (NH$\underline{C}$=S), 1373 (NH$\underline{C}$=S), 1258 (C-C(=O)-O). ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.86 (t, *J*= 6.9 Hz, 3H, H-14), 1.24 (m, 14H, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 1.49 (m, 4H, H-4, H-6), 1.63 (m, 2H, H-3), 1.99 (s, 3H, -OC(=O)C$\underline{H}_3$), 2.45 (t, *J*= 7.3 Hz, 2H, H-2), 4.77 (quin, *J*= 5.5, 6.9 Hz, 1H, H-5), 9.05 (br s, 1H, NH), 9.24 (br s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 14.4 (C-14), 21.4 (-OC(=O)$\underline{C}H_3$), 22.6 (-CH_2-), 24.9 (C-3), 25.2 (-CH_2-), 29.2 (-CH_2-), 29.3 (-CH_2-), 29.4 (-CH_2-), 31.8 (-CH_2-), 33.2 (C-6), 34.0 (C-4), 44.5 (C-2), 73.6 (C-5), 170.6 (-O$\underline{C}$(=O)CH_3), 208.6 (C-1). HRMS (FD). Calcd for $C_{16}H_{31}NO_2S$ (M): *m*/*z* 301.2075. Found: *m*/*z* 301.2033.

5-Acetoxyhexadecanethioamide (2f) Yield: 99%; Colorless solid; Mp= 47-48 °C. R_f= 0.20 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (KBr): cm^{-1} 3185 (N-H), 3310 (N-H), 2928 (CH_3, C-H), 2855 (CH_2, C-H), 1715 (O$\underline{C}$=O), 1456 (NH$\underline{C}$=S), 1374 (NH$\underline{C}$=S), 1257 (C-C(=O)-O). ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.86 (t, *J*= 6.9 Hz, 3H, H-16), 1.24 (m, 18H, H-7, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15), 1.48 (m, 4H, H-4, H-6), 1.62 (m, 2H, H-3), 1.99 (s, 3H, -OC(=O)C$\underline{H}_3$), 2.44 (t, *J*= 7.3 Hz, 2H, H-2), 4.76 (quin, *J*= 6.0, 6.0 Hz, 1H, H-5), 9.11 (br s, 1H, NH), 9.32 (br s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 14.5 (C-16), 21.4 (-OC(=O)C$\underline{H}_3$), 22.6 (-CH_2-), 25.0 (C-3), 25.3 (-CH_2-), 29.3 (-CH_2-), 29.4 (-CH_2-), 29.5 (-CH_2-), 29.5 (-CH_2-), 29.6 (-CH_2-), 31.8 (-CH_2-), 33.2 (C-6), 34.0 (C-4), 44.5 (C-2), 73.6 (C-5), 170.6 (-O$\underline{C}$(=O)CH_3), 208.5 (C-1). HRMS (FD). Calcd for $C_{18}H_{35}NO_2S$ (M): *m*/*z* 329.2389. Found: *m*/*z* 329.2340.

General procedure for deacetylation of *rac*-1 and 2

To a solution of *rac*-**1** (1.0 mmol) or *rac*-**2** (1.0 mmol) in methanol (1.0 mL) was added a solution of sodium methoxide in methanol (5.0 M, 10 mL). The reaction mixture was stirred for 3 h at 0 °C for the deacetylation of *rac*-**1**, and for 30 min at -15 °C for the deacetylation of *rac*-**2**. The reaction was quenched by adding H_2O (30 mL) and $CHCl_3$ (10 mL). The resultant mixture was extracted with $CHCl_3$, and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification of crude product by silica gel column chromatography (eluent; *n*-hexane/EtOAc= 1/1) gave the corresponding *N*-methyl-5-hydroxyalkanethioamides (*rac*-**2**) or 5-hydroxyalkanethioamides (*rac*-**4**).

***N*-Methyl-5-hydroxydecanethioamide (3a)** Yield: 92%; Colorless solid; Mp= 35-36 °C. R_f= 0.26 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). IR (KBr): cm^{-1} 3243 (O-H, N-H), 2928 (CH_2, C-H), 2855 (CH_2, C-H), 1539 (NHC=S), 1456 (C-H), 1378 (NHC=S). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.89 (t, *J*= 6.9 Hz, 3H, H-10), 1.30 (m, 5H, H-7, H-8, H-9), 1.44 (m, 4H, H-4, H-6, H-7), 1.52 (m, 1H, H-4), 1.89 (m, 2H, H-3), 2.31 (br s, 1H, OH), 2.72 (m, 2H, H-2), 3.16 (d, *J*= 6.2 Hz, 3H, CH_3NHC(=S)-), 3.63 (m, 1H, H-5), 8.12 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1 (C-10), 22.7 (-CH_2-), 25.4 (C-3), 25.5 (C-7), 31.9 (-CH_2-), 33.0 (CH_3NHC(=S)-), 35.8 (C-4), 37.7 (C-6), 46.3 (C-2), 71.8 (C-5), 206.2 (C-1). HRMS (FD). Calcd for $C_{11}H_{23}NOS$ (M): *m*/*z* 217.1500. Found: *m*/*z* 217.1505.

***N*-Methyl-5-hydroxyundecanethioamide (3b)** Yield: 90%; Colorless solid; Mp= 40-41 °C. R_f= 0.27 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). IR (KBr): cm^{-1} 3242 (O-H, N-H), 2928 (CH_2, C-H), 2856 (CH_2, C-H), 1539 (NHC=S), 1456 (C-H), 1379 (NHC=S). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-11), 1.28 (m, 7H, H-7, H-8, H-9, H-10), 1.43 (m, 3H, H-4, H-6, H-7), 1.52 (m, 1H, H-4), 1.88 (m, 2H, H-3), 2.51 (br s, 1H, OH), 2.72 (m, 2H, H-2), 3.16 (t, *J*= 4.8 Hz, 3H, CH_3NHC(=S)-), 3.62 (m, 1H, H-5), 8.27 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2 (C-11), 22.7 (-CH_2-), 25.6 (C-3), 25.8 (C-7), 29.4 (-CH_2-), 31.9 (-CH_2-), 33.0 (-CH_2-), 35.9 (C-4), 37.7 (C-6), 46.3 (C-2), 71.8 (C-5), 206.1 (C-1). HRMS (FD). Calcd for $C_{12}H_{25}NOS$ (M): *m*/*z* 231.1657. Found: *m*/*z* 231.1651.

***N*-Methyl-5-hydroxydodecanethioamide (3c)** Yield: 94%; Colorless solid; Mp= 53-54 °C. R_f= 0.27 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). IR (KBr): cm^{-1} 3242 (O-H, N-H), 2928 (CH_2, C-H), 2855 (CH_2, C-H), 1539 (NHC=S), 1373 (NHC=S). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-12), 1.28 (m, 9H, H-7, H-8, H-9, H-10, H-11), 1.43 (m, 3H, H-4, H-6, H-7), 1.52 (m, 1H, H-4), 1.89 (m, 2H, H-3), 2.43 (br s, 1H, OH), 2.72 (m, 2H, H-2), 3.16 (d, *J*= 4.8 Hz, 3H, CH_3NHC(=S)-), 3.62 (m, 1H, H-5), 8.22 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2 (C-12), 22.7 (-CH_2-), 25.6 (C-3), 25.8 (C-7), 29.4 (-CH_2-), 29.7 (-CH_2-), 31.9 (-CH_2-), 33.1 (CH_3NHC(=S)-), 35.9 (C-4), 37.8 (C-6), 46.3 (C-2), 71.8 (C-5), 206.2 (C-1). HRMS (FD). Calcd for $C_{13}H_{27}NOS$ (M): *m*/*z* 245.1813. Found: *m*/*z* 245.1804.

***N*-Methyl-5-hydroxytridecanethioamide (3d)** Yield: 89%; Colorless solid; Mp= 54-55 °C. R_f= 0.27 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). IR (KBr): cm^{-1} 3242 (O-H, N-H), 2929 (CH_2, C-H), 2856 (CH_2, C-H), 1539 (NHC=S), 1456 (C-H), 1379 (NHC=S). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-13), 1.27 (m, 11H, H-7, H-8, H-9, H-10, H-11, H-12), 1.43 (m, 3H, H-4, H-6, H-7), 1.52 (m, 1H, H-4), 1.89 (m, 2H, H-3), 2.41 (br s, 1H, OH), 2.72 (m, 2H, H-2), 3.16 (d, *J*= 4.8 Hz, 3H, CH_3NHC(=S)-), 3.62 (m, 1H, H-5), 8.20 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2 (C-13), 22.8 (-CH_2-), 25.6 (C-3), 25.8 (C-7), 29.4 (-CH_2-), 29.7 (-CH_2-), 29.8 (-CH_2-), 32.0 (-CH_2-), 33.1 (CH_3NHC(=S)-), 35.9 (C-4), 37.8 (C-6), 46.3 (C-2), 71.8 (C-5), 206.2 (C-1). HRMS (FD). Calcd for $C_{14}H_{29}NOS$ (M): *m*/*z* 259.1970. Found: *m*/*z* 259.1972.

***N*-Methyl-5-hydroxytetradecanethioamide (3e)** Yield: 90%; Colorless solid; Mp= 62-63 °C. R_f= 0.30 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). IR (KBr): cm^{-1} 3242 (O-H, N-H), 2929 (CH_2, C-H), 2856 (CH_2, C-H), 1538 (NHC=S), 1456 (C-H), 1379 (NHC=S). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-14), 1.26 (m, 13H, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 1.43 (m, 4H, H-4, H-6, H-7), 1.52 (m, 1H, H-4), 1.88 (m, 2H, H-3), 2.27 (br s, 1H, OH), 2.72 (m, 2H, H-2), 3.16 (d, *J*= 4.8 Hz, 3H, CH_3NHC(=O)-), 3.63 (m, 1H, H-5), 8.11 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2 (C-14), 22.8 (-CH_2-), 25.6 (C-3), 29.4 (C-7), 29.7 (-CH_2-), 29.8 (-CH_2-), 29.9 (-CH_2-), 32.0 (-CH_2-), 33.1 (CH_3NHC(=O)-), 35.9 (C-4), 37.8 (C-6), 46.4 (C-2), 71.9 (C-5), 206.2 (C-1). HRMS (FD). Calcd for $C_{15}H_{31}NOS$ (M): *m*/*z* 273.2126. Found: *m*/*z* 273.2137.

***N*-Methyl-5-hydroxyhexadecanethioamide (3f)** Yield: 91%; Colorless solid; Mp= 70-71 °C. R_f= 0.30 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). IR (KBr): cm^{-1} 3242 (O-H, N-H), 2928 (CH_2, C-H), 2858 (CH_2, C-H), 1539 (NHC=S), 1455 (C-H), 1379 (NHC=S). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.89 (t, *J*= 6.9 Hz, 3H, H-16), 1.26 (m, 17H, H-7, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15), 1.44 (m, 4H, H-4, H-6, H-7), 1.53 (m, 1H, H-4), 1.89 (m, 2H, H-3), 2.22 (br s, 1H, OH), 2.72 (m, 2H, H-2), 3.17 (d, *J*= 4.8 Hz, 3H, CH_3NHC(=S)-), 3.63 (m, 1H, H-5), 8.07 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2 (C-16), 22.8 (-CH_2-), 25.5 (C-3), 25.8 (C-7), 29.4 (-CH_2-), 29.7 (-CH_2-×3), 29.8 (-CH_2-×2), 32.0 (-CH_2-), 33.0 (CH_3NHC(=S)-), 35.8 (C-4), 37.8 (C-6), 46.3 (C-2), 71.9 (C-5), 206.2 (C-1). HRMS (FD). Calcd for $C_{17}H_{35}NOS$ (M): *m*/*z* 301.2439. Found: *m*/*z* 301.2365.

5-Hydroxydodecanethioamide (4c) Yield: 71%; Colorless solid; Mp= 70-71 °C. R_f= 0.25 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). IR (KBr): cm^{-1} 3306 (N-H), 3152 (N-H), 2920 (CH_2, C-H), 2849 (CH_2, C-H), 1456 (NHC=S), 1394 (NHC=S). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-12), 1.28 (m, 9H, H-7, H-8, H-9, H-10, H-11), 1.41 (m, 1H, H-4), 1.44 (m, 3H, H-6, H-7), 1.55 (m, 1H, H-4), 1.88 (m, 2H, H-3), 2.49 (br s, 1H, OH), 2.71 (m, 2H, H-2), 3.64 (m, 1H, H-5), 7.72 (br s, 1H, NH), 8.07 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2 (C-12), 22.7 (-CH_2-), 25.4 (C-3), 25.8 (-CH_2-), 29.4 (-CH_2-), 29.7 (-CH_2-), 31.9 (-CH_2-), 35.8 (C-6), 37.7 (C-4), 45.1 (C-2), 71.8 (C-5), 210.8 (C-1). HRMS (FD). Calcd for $C_{12}H_{25}NOS$ (M): *m*/*z* 231.1657. Found: *m*/*z* 231.1645.

5-Hydroxytridecanethioamide (4d) Yield: 73%; Colorless solid; Mp= 72-73 °C. R_f= 0.26 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). IR (KBr): cm^{-1} 3306 (N-H), 3153 (N-H), 2919 (CH_2, C-H), 2849 (CH_2, C-H), 1456 (NHC=S), 1394 (NHC=S). ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.88 (t, *J*= 6.8 Hz, 3H, H-13), 1.27 (m, 16H, H-4, H-6, H-7, H-8, H-9, H-10, H-11, H-12), 1.65 (m, 1H, H-3), 1.77 (m, 1H, H-3), 2.47 (t, *J*= 6.9 Hz, 2H, H-2),

3.39 (m, 1H, H-5), 4.29 (d, *J*= 5.0 Hz, 1H, OH), 9.10 (br s, 1H, NH), 9.29 (br s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 14.5 (C-13), 22.7 (-CH_2-), 25.7 (C-3), 25.8 (-CH_2-), 29.3 (-CH_2-), 29.7 (-CH_2-), 29.8 (-CH_2-), 31.9 (-CH_2-), 36.8 (C-6), 37.7 (C-4), 45.1 (C-2), 69.9 (C-5), 209.1 (C-1). HRMS (FD). Calcd for $C_{13}H_{27}NOS$ (M): *m*/*z* 245.1813. Found: *m*/*z* 245.1805.

5-Hydroxytetradecanethioamide (4e) Yield: 69%; Colorless solid; Mp= 76-77 °C. R_f= 0.27 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). IR (KBr): cm^{-1} 3305 (N-H), 3152 (N-H), 2919 (CH_2, C-H), 2849 (CH_2, C-H), 1456 (NHC=S), 1394 (NHC=S). ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.88 (t, *J*= 6.6 Hz, 3H, H-14), 1.27 (m, 18H, H-4, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 1.66 (m, 1H, H-3), 1.76 (m, 1H, H-3), 2.47 (t, *J*= 7.1 Hz, 2H, H-2), 3.39 (m, 1H, H-5), 4.20 (d, *J*= 5.0 Hz, 1H, OH), 9.04 (br s, 1H, NH), 9.22 (br s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 14.4 (C-14), 22.6 (-CH_2-), 25.7 (C-3), 25.8 (-CH_2-), 29.2 (-CH_2-), 29.5 (-CH_2-), 29.7 (-CH_2-), 29.8 (-CH_2-), 31.8 (-CH_2-), 36.9 (C-6), 37.7 (C-4), 45.1 (C-2), 69.9 (C-5), 209.2 (C-1). HRMS (FD). Calcd for $C_{14}H_{29}NOS$ (M): *m*/*z* 259.1970. Found: *m*/*z* 259.1934.

5-Hydroxyhexadecanethioamide (4f) Yield: 77%; Colorless solid; Mp= 85-86 °C. R_f= 0.29 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). IR (KBr): cm^{-1} 3306 (N-H), 3152 (N-H), 2920 (CH_2, C-H), 2848 (CH_2, C-H), 1456 (NHC=S), 1393 (NHC=S). ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.86 (t, *J*= 7.3 Hz, 3H, H-16), 1.24 (m, 22H, H-4, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13, H-14, H-15), 1.63 (m, 1H, H-3), 1.73 (m, 1H, H-3), 2.45 (t, *J*= 7.3 Hz, 2H, H-2), 3.36 (m, 1H, H-5), 4.18 (d, *J*= 5.5 Hz, 1H, OH), 9.02 (br s, 1H, NH), 9.20 (br s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 14.4 (C-16), 22.6 (-CH_2-), 25.7 (C-3), 25.8 (-CH_2-), 29.2 (-CH_2-), 29.5 (-CH_2-), 29.6 (-CH_2-×2), 29.7 (-CH_2-), 29.8 (-CH_2-), 31.8 (-CH_2-), 36.9 (C-6), 37.7 (C-4), 45.2 (C-2), 69.9 (C-5), 209.2 (C-1). HRMS (FD). Calcd for $C_{16}H_{33}NOS$ (M): *m*/*z* 287.2283. Found: *m*/*z* 287.2238.

General procedure for esterification of *rac*-3 and 4

To a solution of *rac*-**3** or **4** (1.0 mmol) in THF (10 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (0.31 g, 2.0 mmol), 4-dimethylaminopyridine (DMAP) (0.12 g, 1.0 mmol), and *N*-carbobenzoxy-L-proline (0.50 g, 2.0 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, and then for 3 h at room temperature. The reaction was quenched with aqueous 0.1 M HCl (5 mL). The resultant mixture was extracted with EtOAc, and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (eluent; *n*-hexane/EtOAc= 3/1) gave the corresponding $\mathbf{5}_{1st}$ and $\mathbf{5}_{2nd}$ or $\mathbf{6}_{1st}$ and $\mathbf{6}_{2nd}$, respectively.

(5*R*)-*N*-Methyl-5-[(2*S*)-*N*-(benzyloxy)carbonyl-2-pyrrolidinylmethanoyloxy]dodecanethioamide [(5*R*,2'*S*)-5c$_{1st}$] Yield: 47%; Colorless oil; $[\alpha]^{24}_D$= -20.0 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.25 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3308 (N-H), 2930 (CH_2, C-H), 2856 (CH_2, C-H), 1742 (OC=O), 1659 (NC(=O)O), 1541 (NHC=S), 1456 (Ar, C=C), 1418 (NHC=S), 1120 (C-C(=O)-O), 698 (Ar, C-H). ^{1}H NMR (600 MHz, $CDCl_3$): (rotamer observed) δ 0.88 (t, *J*= 6.9 Hz, 3H, H-12), 1.20-1.32 (m, 10H, H-7, H-8, H-9, H-10, H-11), 1.47-1.59 (m, 2H, H-6), 1.63-1.69 (m, 2H, H-4), 1.81-1.87 (m, 2H, H-3), 1.90-2.09 (m, 3H, -CH$_2$- at pyrrolidine), 2.23-2.32 (m, 1H, -CH$_2$- at pyrrolidine), 2.46-2.52, 2.55-2.61 and 2.65-2.76 (m, 2H, H-2), 3.06 and 3.11 (d, *J*= 4.6 Hz, 3H, CH$_3$NHC(=S)-), 3.47-3.57 and 3.62-3.69 (m, 2H, -CH$_2$- at pyrrolidine), 4.29-4.32 and 4.35-4.38 (dd, *J*= 4.0, 4.0 Hz, 1H, -CH- at pyrrolidine), 4.82-4.87 and 4.99-5.04 (m, 1H, H-5), 5.09 (d, *J*= 12.0 Hz, 1H, -C(=O)OCH$_2$Ph), 5.18 (d, *J*= 12.0 Hz, 1H, -C(=O)OCH$_2$Ph), 7.29-7.39 (m, 5H, Ph), 7.47 and 8.83 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): (rotamer observed) δ 14.1 (C-12), 22.6 (-CH$_2$-), 23.4 and 24.4 (-CH$_2$- at pyrrolidine), 24.7 and 25.4 (-CH$_2$-), 25.5 (-CH$_2$-), 29.2 (-CH$_2$-), 29.3 (-CH$_2$-), 30.0 (-CH$_2$-), 31.1 and 31.7 (C-4), 32.9 and 33.1 (-CH$_2$- at pyrrolidine), 33.9 and 35.1 (C-1'), 45.7 and 45.9 (C-2), 46.8 and 47.0 (-CH$_2$- at pyrrolidine), 59.1 and 59.4 (-CH- at pyrrolidine), 66.9 and 67.2 (-C(=O)OCH$_2$Ph), 74.1 and 74.6 (C-5), 127.4 and 127.7 (Ph), 128.0 and 128.2 (Ph), 128.5 and 128.6 (Ph), 136.1 and 136.5 (Ph), 154.3 and 155.2 (-C(=O)OCH$_2$Ph), 172.6 and 173.2 (-OC(=O)CH-), 205.7 (C-1). HRMS (FD). Calcd for $C_{26}H_{40}N_2O_4S$ (M): *m*/*z* 476.2709. Found: *m*/*z* 476.2700.

(5*S*)-*N*-Methyl-5-[(2*S*)-*N*-(benzyloxy)carbonyl-2-pyrrolidinylmethanoyloxy]dodecanethioamide [(5*S*,2'*S*)-5c$_{2nd}$] Yield: 49%; Colorless oil; $[\alpha]^{24}_D$= -19.3 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.16 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3304 (N-H), 2930 (CH_2, C-H), 2856 (CH_2, C-H), 1738 (OC=O), 1695 (NC(=O)O), 1541 (NHC=S), 1456 (Ar, C=C), 1418 (NHC=S), 1120 (C-C(=O)-O), 696 (Ar, C-H). ^{1}H NMR (600 MHz, $CDCl_3$): (rotamer observed) δ 0.88 (t, *J*= 6.8 Hz, 3H, H-12), 1.21-1.32 (m, 10H, H-7, H-8, H-9, H-10, H-11), 1.41-1.78 (m, 6H, H-3, H-4, H-6), 1.89-1.99 (m, 2H, -CH$_2$- at pyrrolidine), 2.01-2.08 (m, 1H, -CH$_2$- at pyrrolidine), 2.22-2.32 (m, 1H, -CH$_2$- at pyrrolidine), 2.47-2.58 and 2.65-2.71 (m, 2H, H-2), 3.13 (t, *J*= 4.6 Hz, 3H, CH$_3$NHC(=S)-), 3.50-3.57 (m, 1H, -CH$_2$- at pyrrolidine), 3.58-3.64 (m, 1H, -CH$_2$- at pyrrolidine), 4.37-4.40 (m, 1H, -CH- at pyrrolidine), 4.80-4.85 and 4.91-4.96 (m, 1H, H-5), 5.05-5.18 (m, 2H, -C(=O)OCH$_2$Ph), 7.28-7.38 (m, 5H, Ph), 7.68 and 8.31 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): (rotamer observed) δ 14.1 (C-12), 22.6 (-CH$_2$-), 23.5 and 24.1 (C-4), 24.4 and 24.5 (-CH$_2$-), 25.3 and 25.4 (-CH$_2$-), 29.1 (-CH$_2$-), 29.4 (-CH$_2$-),

30.3 and 31.0 (-$\underline{C}H_2$-), 31.7 and 31.8 (-$\underline{C}H_2$-), 32.7 (C-4), 33.0 and 33.1 (-$\underline{C}H_2$- at pyrrolidine), 33.7 and 34.5 ($\underline{C}H_3$NHC(=S)-), 45.9 (C-2), 46.7 and 47.0 (-$\underline{C}H_2$- at pyrrolidine), 59.4 and 60.0 (-$\underline{C}$H- at pyrrolidine), 66.9 and 67.0 (-O$\underline{C}H_2$Ph), 74.2 and 74.7 (C-5), 127.4 and 127.7 (Ph), 128.1 and 128.2 (Ph), 128.5 and 128.6 (Ph), 136.3 and 136.4 (Ph), 154.6 and 155.1 (-N$\underline{C}$(=O)OCH$_2$Ph), 172.5 and 172.7 (-O$\underline{C}$(=O)CH-), 205.4 (C-1). HRMS (FD). Calcd for $C_{26}H_{40}N_2O_4S$ (M): *m*/*z* 476.2709. Found: *m*/*z* 476.2697.

(5*R*)-*N*-Methyl-5-[(2*S*)-*N*-(benzyloxy)carbonyl-2-pyrrolidinylmethanoyloxy]tridecanethioamide [(5*R*,2'*S*)-5d$_{1st}$] Yield: 46%; Colorless oil; $[\alpha]^{20}_D$= -36.2 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.24 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3308 (N-H), 2929 (CH$_2$, C-H), 2856 (CH$_2$, C-H), 1742 (O$\underline{C}$=O), 1658 (N$\underline{C}$(=O)O), 1542 (NH$\underline{C}$=S), 1456 (Ar, C=C), 1418 (NH$\underline{C}$=S), 1119 (C-C(=O)-O), 698 (Ar, C-H). ^{1}H NMR (600 MHz, CDCl$_3$): (rotamer observed) δ 0.88 (t, *J*= 7.3 Hz, 3H, H-13), 1.25-1.31 (m, 12H, H-7, H-8, H-9, H-10, H-11, H-12), 1.41-1.62 (m, 2H, H-6), 1.64-1.71 (m, 2H, H-4), 1.80-1.88 (m, 2H, H-3), 1.92-2.08 (m, 3H, -C$\underline{H}_2$- at pyrrolidine), 2.22-2.33 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.46-2.60 and 2.64-2.76 (m, 2H, H-2), 3.06 and 3.10 (d, *J*= 4.6 Hz, 3H, C$\underline{H}_3$NHC(=S)-), 3.50-3.58 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 3.61-3.71 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 4.30 and 4.37 (dd, *J*= 4.6, 4.1 Hz, 1H, -C$\underline{H}$- at pyrrolidine), 4.81-4.87 and 4.98-5.04 (m, 1H, H-5), 5.09 (d, *J*= 12.4 Hz, 1H, -OC$\underline{H}_2$Ph), 5.18 (d, *J*= 12.4 Hz, 1H, -OC$\underline{H}_2$Ph), 7.29-7.40 (m, 5H, Ph), 7.52 and 8.81 (br s, 1H, NH). ^{13}C NMR (150 MHz, CDCl$_3$): (rotamer observed) δ 14.2 (C-13), 22.7 (-$\underline{C}H_2$-), 24.5 (-$\underline{C}H_2$- at pyrrolidine), 25.4 (-$\underline{C}H_2$-), 25.5 (-$\underline{C}H_2$-), 29.3 (-$\underline{C}H_2$-), 29.4 (-$\underline{C}H_2$-), 29.5 (-$\underline{C}H_2$-), 30.1 (-$\underline{C}H_2$-), 31.9 (C-4), 33.2 (-$\underline{C}H_2$- at pyrrolidine), 35.2 ($\underline{C}H_3$NHC(=S)-), 45.9 (C-2), 46.9 (-$\underline{C}H_2$- at pyrrolidine), 59.5 (-$\underline{C}$H- at pyrrolidine), 67.2 (-O$\underline{C}H_2$Ph), 74.2 (C-5), 127.5 and 127.7 (Ph), 128.3 (Ph), 128.5 and 128.7 (Ph), 136.2 (Ph), 155.2 (-N$\underline{C}$(=O)OCH$_2$Ph), 172.7 (-O$\underline{C}$(=O)CH-), 205.8 (C-1). HRMS (FD). Calcd for $C_{27}H_{42}N_2O_4S$ (M): *m*/*z* 490.2865. Found: *m*/*z* 490.2816.

(5*S*)-*N*-Methyl-5-[(2*S*)-*N*-(benzyloxy)carbonyl-2-pyrrolidinylmethanoyloxy]tridecanethioamide [(5*S*,2'*S*)-5d$_{2nd}$] Yield: 46%; Colorless oil; $[\alpha]^{20}_D$= -41.7 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.15 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3303 (N-H), 2929 (CH$_2$, C-H), 2856 (CH$_2$, C-H), 1738 (O$\underline{C}$=O), 1695 (N$\underline{C}$(=O)O), 1541 (NH$\underline{C}$=S), 1455 (Ar, C=C), 1418 (NH$\underline{C}$=S), 1120 (C-C(=O)-O), 696 (Ar, C-H). ^{1}H NMR (600 MHz, CDCl$_3$): (rotamer observed) δ 0.88 (t, *J*= 6.9 Hz, 3H, H-13), 1.19-1.33 (m, 12H, H-7, H-8, H-9, H-10, H-11, H-12), 1.40-1.80 (m, 6H, H-3, H-4, H-6), 1.88-1.99 (m, 2H, -C$\underline{H}_2$- at pyrrolidine), 2.00-2.08 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.21-2.31 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.46-2.57 and 2.64-2.71 (m, 2H, H-2), 3.13 (t, *J*= 4.6 Hz, 3H, C$\underline{H}_3$NHC(=S)-), 3.50-3.56 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 3.57-3.64 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 4.36-4.41 (m, 1H, -C$\underline{H}$- at pyrrolidine), 4.79-4.85 and 4.90-4.96 (m, 1H, H-5), 5.05-5.18 (m, 2H, -OC$\underline{H}_2$Ph), 7.28-7.39 (m, 5H, Ph), 7.71 and 8.31 (br s, 1H, NH). ^{13}C NMR (150 MHz, CDCl$_3$): (rotamer observed) δ 14.1 (C-13), 22.7 (-$\underline{C}H_2$-), 23.5 and 24.2 (-$\underline{C}H_2$- at pyrrolidine), 24.5 (-$\underline{C}H_2$-), 25.3 (-$\underline{C}H_2$-), 29.2 (-$\underline{C}H_2$-), 29.4 (-$\underline{C}H_2$-), 30.3 (-$\underline{C}H_2$-), 31.0 and 31.8 (-$\underline{C}H_2$-), 32.7 (C-4), 33.1 and 32.9 (-$\underline{C}H_2$- at pyrrolidine), 33.7 and 34.5 ($\underline{C}H_3$NHC(=S)-), 45.9 (C-2), 46.7 and 47.0 (-$\underline{C}H_2$- at pyrrolidine), 59.4 and 60.0 (-$\underline{C}$H- at pyrrolidine), 67.0 (-O$\underline{C}H_2$Ph), 74.3 and 74.7 (C-5), 127.4 and 127.7 (Ph), 128.0 and 128.2 (Ph), 128.5 and 128.6 (Ph), 136.3 and 136.4 (Ph), 154.6 and 155.1 (-N$\underline{C}$(=O)OCH$_2$Ph), 172.5 and 172.7 (-O$\underline{C}$(=O)CH-), 205.5 and 205.6 (C-1). HRMS (FD). Calcd for $C_{27}H_{42}N_2O_4S$ (M): *m*/*z* 490.2865. Found: *m*/*z* 490.2803.

(5*R*)-5-[(2*S*)-*N*-(benzyloxy)carbonyl-2-pyrrolidinylmethanoyloxy]dodecanethioamide [(5*R*,2'*S*)-6c$_{1st}$] Yield: 40%; Colorless oil; $[\alpha]^{18}_D$= -39.1 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.15 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3312 (N-H), 3204 (N-H), 2930 (CH$_2$, C-H), 2856 (CH$_2$, C-H), 1740 (O$\underline{C}$=O), 1693 (N$\underline{C}$(=O)O), 1418 (NH$\underline{C}$=S), 1120 (C-C(=O)-O), 696 (Ar, C=C). ^{1}H NMR (600 MHz, CDCl$_3$): (rotamer observed) δ 0.88 (t, *J*= 6.9 Hz, 3H, H-12), 1.23-1.31 (m, 10H, H-7, H-8, H-9, H-10, H-11), 1.42-1.59 (m, 2H, H-6), 1.64-1.68 (m, 2H, H-4), 1.80-1.87 (m, 2H, H-3), 1.90-1.99 (m, 2H, -C$\underline{H}_2$- at pyrrolidine), 2.01-2.08 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.23-2.29 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.45-2.49 and 2.61-2.66 (m, 1H, H-2), 2.53-2.58 and 2.72-2.77 (m, 1H, H-2), 3.50-3.56 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 3.61-3.67 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 4.29 and 4.37 (dd, *J*= 8.6, 4.1 Hz, 1H, -C$\underline{H}$- at pyrrolidine), 4.85 and 4.99 (quin, *J*= 5.5, 6.9 Hz, 1H, H-1), 5.05 and 5.16 (d, *J*= 12.4 Hz, 1H, -C(=O)OC$\underline{H}_2$Ph), 5.10 and 5.20 (d, *J*= 12.4 Hz, 1H, -C(=O)OC$\underline{H}_2$Ph), 7.31-7.33 (m, 2H, Ph), 7.36-7.38 (m, 3H, Ph), 7.09 and 7.41 (br s, 1H, NH), 7.51 and 8.34 (br s, 1H, NH). ^{13}C NMR (150 MHz, CDCl$_3$): (rotamer observed) δ 14.2 (C-12), 22.7 (-$\underline{C}H_2$-), 24.5 and 24.7 (-$\underline{C}H_2$- at pyrrolidine), 25.0 (-$\underline{C}H_2$-), 25.3 and 25.4 (-$\underline{C}H_2$-), 29.3 (-$\underline{C}H_2$-), 29.4 (-$\underline{C}H_2$-), 30.1 (-$\underline{C}H_2$- at pyrrolidine), 31.1 and 31.8 (-$\underline{C}H_2$-), 34.0 and 35.0 (-$\underline{C}H_2$-), 44.4 and 44.8 (C-2), 46.8 and 47.1 (-CH$_2$- at pyrrolidine), 59.2 and 59.5 (-$\underline{C}$H- at pyrrolidine), 67.1 and 67.3 (-C(=O)O$\underline{C}H_2$Ph), 74.1 and 74.7 (C-5), 127.4 and 127.8 (Ph), 128.0 and 128.2 (Ph), 128.6 and 128.7 (Ph), 136.4 (Ph), 155.2 (-N$\underline{C}$(=O)OCH$_2$Ph), 172.9 (-O$\underline{C}$(=O)CH-), 210.9 (C-1). HRMS (FD). Calcd for $C_{25}H_{38}N_2O_4S$ (M): *m*/*z* 462.2552. Found: *m*/*z* 462.2534.

(5*S*)-5-[(2*S*)-*N*-(Benzyloxy)carbonyl-2-pyrrolidinylmethanoyloxy]dodecanethioamide [(5*S*,2'*S*)-6c$_{2nd}$] Yield: 40%; Colorless oil; $[\alpha]^{19}_D$= -40.5 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.08 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3310 (N-H), 3204 (N-H), 2928 (CH$_2$, C-H), 2856 (CH$_2$, C-H), 1740 (O$\underline{C}$=O), 1693 (N$\underline{C}$(=O)O), 1416 (NH$\underline{C}$=S), 1120 (C-C(=O)-O), 696 (Ar, C=C). ^{1}H NMR (600 MHz, CDCl$_3$):

(rotamer observed) δ 0.87 (t, *J*= 6.9 Hz, 3H, H-12), 1.21-1.32 (m, 10H, H-7, H-8, H-9, H-10, H-11), 1.45-1.77 (m, 6H, H-3, H-4, H-6), 1.88-2.00 (m, 2H, -C$\underline{H}_2$- at pyrrolidine), 2.02-2.07 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.22-2.31 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.46-2.51 (m, 1H, H-2), 2.53-2.58 and 2.64-2.68 (m, 1H, H-2), 3.50-3.55 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 3.59-3.62 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 4.36-4.39 (m, 1H, -C$\underline{H}$- at pyrrolidine), 4.82-4.86 and 4.92-4.96 (m, 1H, H-5), 5.12 (m, 2H, -C(=O)OC$\underline{H}_2$Ph), 7.29-7.38 (m, 5H, Ph), 7.54 (br s, 1H, NH), 7.92 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): (rotamer observed) δ 14.2 (C-12), 22.7 (-$\underline{C}H_2$-), 23.6 and 24.2 (-$\underline{C}H_2$-), 24.4 and 24.5 (-$\underline{C}H_2$- at pyrrolidine), 25.3 and 25.4 (-$\underline{C}H_2$-), 29.2 (-$\underline{C}H_2$-), 29.4 (-$\underline{C}H_2$-), 30.3 and 31.1 (-$\underline{C}H_2$- at pyrrolidine), 31.8 (-$\underline{C}H_2$-), 32.8 and 32.9 (-$\underline{C}H_2$-), 33.8 and 34.5 (-$\underline{C}H_2$-), 44.5 and 44.9 (C-2), 46.7 and 47.1 (-$\underline{C}H_2$- at pyrrolidine), 59.4 and 60.0 (-$\underline{C}$H- at pyrrolidine), 67.1 (-C(=O)O$\underline{C}H_2$Ph), 74.4 and 74.8 (C-5), 127.5 (Ph), 127.8 (Ph), 128.1 and 128.2 (Ph), 128.6 and 128.7 (Ph), 136.5 and 136.6 (Ph), 155.1 (-N$\underline{C}$(=O)OCH$_2$Ph), 172.5 and 172.7 (-O$\underline{C}$(=O)CH-), 210.3 and 210.5 (C-1). HRMS (FD). Calcd for $C_{25}H_{38}N_2O_4S$ (M): *m*/*z* 462.2552. Found: *m*/*z* 462.2533.

(5*R*)-5-[(2*S*)-*N*-(Benzyloxy)carbonyl-2-pyrrolidinylmethanoyloxy]tridecanethioamide [(5*R*,2'*S*)-6d$_{1st}$] Yield: 48%; Colorless oil; $[\alpha]^{19}_D$= -33.0 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.16 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3312 (N-H), 3203 (N-H), 2929 (CH_2, C-H), 2856 (CH_2, C-H), 1739 (O$\underline{C}$=O), 1693 (N$\underline{C}$(=O)O), 1418 (NH$\underline{C}$=S), 1120 (C-C(=O)-O), 696 (Ar, C=C). ^{1}H NMR (600 MHz, $CDCl_3$): (rotamer observed) δ 0.88 (t, *J*= 6.9 Hz, 3H, H-13), 1.25-1.29 (m, 12H, H-7, H-8, H-9, H-10, H-11, H-12), 1.50-1.60 (m, 2H, H-6), 1.64-1.67 (m, 2H, H-4), 1.80-1.86 (m, 2H, H-3), 1.88-2.00 (m, 2H, -C$\underline{H}_2$- at pyrrolidine), 2.01-2.06 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.22-2.28 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.44-2.49 and 2.61-2.66 (m, 1H, H-2), 2.52-2.57 and 2.71-2.77 (m, 1H, H-2), 3.49-3.55 (m, 1H- -C$\underline{H}_2$- at pyrrolidine), 3.61-3.67 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 4.28-4.30 and 4.35-4.37 (m, 1H, -C$\underline{H}$- at pyrrolidine), 4.84 and 4.99 (m, 1H, H-5), 5.05 (d, *J*= 12.4 Hz, 1H, -C(=O)OC$\underline{H}_2$Ph), 5.10 (d, *J*= 12.4 Hz, 1H, -C(=O)OC$\underline{H}_2$Ph), 7.31-7.38 (m, 5H, Ph), 7.18 and 7.54 (br s, 1H, NH), 7.66 and 8.34 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): (rotamer observed) δ 14.2 (C-13), 22.7 and 23.5 (-$\underline{C}H_2$-), 24.5 and 24.7 (-$\underline{C}H_2$- at pyrrolidine), 25.0 (-$\underline{C}H_2$-), 25.3 and 25.4 (-$\underline{C}H_2$-), 29.2 (-$\underline{C}H_2$-), 29.4 (-$\underline{C}H_2$-), 29.5 (-$\underline{C}H_2$-), 30.1 (-$\underline{C}H_2$- at pyrrolidine), 31.2 and 31.9 (-$\underline{C}H_2$-), 33.0 and 33.3 (-$\underline{C}H_2$-), 34.0 and 35.0 (-$\underline{C}H_2$-), 44.4 and 44.8 (C-2), 46.8 and 47.1 (-$\underline{C}H_2$- at pyrrolidine), 59.2 and 59.5 (-$\underline{C}$H- at pyrrolidine), 67.0 and 67.3 (-C(=O)O$\underline{C}H_2$Ph), 74.1 and 74.7 (C-5), 127.5 and 127.7 (Ph), 128.0 and 128.2 (Ph), 128.5 and 128.7 (Ph), 136.4 and 136.6 (Ph), 154.5 and 155.2 (-$\underline{C}$(=O)OCH$_2$Ph), 172.8 (-O$\underline{C}$(=O)CH-), 210.7 and 210.8 (C-1). HRMS (FD). Calcd for $C_{26}H_{40}N_2O_4S$ (M): *m*/*z* 476.2709. Found: *m*/*z* 476.2706.

(5*S*)-5-[(2*S*)-*N*-(Benzyloxy)carbonyl-2-pyrrolidinylmethanoyloxy]tridecanethioamide [(5*S*,2'*S*)-6d$_{2nd}$] Yield: 47%; Colorless oil; $[\alpha]^{20}_D$= -34.9 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.09 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3310 (N-H), 3202 (N-H), 2928 (CH_2, C-H), 2855 (CH_2, C-H), 1740 (O$\underline{C}$=O), 1693 (N$\underline{C}$(=O)O), 1417 (NH$\underline{C}$=S), 1120 (C-C(=O)-O), 696 (Ar, C=C). ^{1}H NMR (600 MHz, $CDCl_3$): (rotamer observed) δ 0.88 (t, *J*= 7.6 Hz, 3H, H-13), 1.21-1.29 (m, 12H, H-7, H-8, H-9, H-10, H-11, H-12), 1.44-1.77 (m, 6H, H-3, H-4, H-6), 1.88-2.00 (m, 2H, -C$\underline{H}_2$- at pyrrolidine), 2.02-2.07 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.22-2.31 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.46-2.51 (m, 1H, H-2), 2.53-2.58 and 2.63-2.68 (m, 1H, H-2), 3.50-3.55 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 3.59-3.62 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 4.37-4.39 (m, 1H, -C$\underline{H}$- at pyrrolidine), 4.82-4.86 and 4.93-4.94 (m, 1H, H-5), 5.12 (m, 2H, -C(=O)OC$\underline{H}_2$Ph), 7.29-7.38 (m, 5H, Ph), 7.65 (br s, 1H, NH), 7.93 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): (rotamer observed) δ 14.2 (C-13), 22.7 (-$\underline{C}H_2$-), 23.6 and 24.4 (-$\underline{C}H_2$-), 24.2 and 24.5 (-$\underline{C}H_2$- at pyrrolidine), 25.3 and 25.4 (-$\underline{C}H_2$-), 29.2 and 29.3 (-$\underline{C}H_2$-), 29.4 and 29.5 (-$\underline{C}H_2$-), 30.3 and 31.1 (-$\underline{C}H_2$- at pyrrolidine), 31.9 (-$\underline{C}H_2$-), 32.8 and 32.9 (-$\underline{C}H_2$-), 33.8 and 34.5 (-$\underline{C}H_2$-), 44.5 and 44.9 (C-2), 46.7 and 47.1 (-$\underline{C}H_2$- at pyrrolidine), 59.4 and 60.0 (-$\underline{C}$H- at pyrrolidine), 67.1 (-C(=O)O$\underline{C}H_2$Ph), 74.4 and 74.8 (C-5), 127.5 (Ph), 127.8 (Ph), 128.1 and 128.2 (Ph), 128.5 and 128.6 (Ph), 136.5 and 136.6 (Ph), 154.6 and 155.1 (-$\underline{C}$(=O)OCH$_2$Ph), 172.6 and 172.7 (-O$\underline{C}$(=O)CH-), 210.2 and 210.4 (C-1). HRMS (FD). Calcd for $C_{26}H_{40}N_2O_4S$ (M): *m*/*z* 476.2709. Found: *m*/*z* 476.2676.

(5*R*)-5-[(2*S*)-*N*-(Benzyloxy)carbonyl-2-pyrrolidinylmethanoyloxy]tetradecanethioamide [(5*R*,2'*S*)-6e$_{1st}$] Yield: 45%; Colorless oil; $[\alpha]^{20}_D$= -38.6 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.14 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3312 (N-H), 3204 (N-H), 2928 (CH_2, C-H), 2856 (CH_2, C-H), 1740 (O$\underline{C}$=O), 1692 (N$\underline{C}$(=O)O), 1418 (NH$\underline{C}$=S), 1119 (C-C(=O)-O), 696 (Ar, C=C). ^{1}H NMR (600 MHz, $CDCl_3$): (rotamer observed) δ 0.88 (t, *J*= 6.9 Hz, 3H, H-14), 1.25-1.32 (m, 14H, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 1.48-1.59 (m, 2H, H-6), 1.64-1.68 (m, 2H, H-4), 1.80-1.87 (m, 2H, H-3), 1.89-1.99 (m, 2H, -C$\underline{H}_2$- at pyrrolidine), 2.01-2.08 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.22-2.29 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 2.45-2.49 and 2.61-2.66 (m, 1H, H-2), 2.54-2.58, 2.72-2.77 (m, 1H, H-2), 3.50-3.56 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 3.61-3.68 (m, 1H, -C$\underline{H}_2$- at pyrrolidine), 4.29 and 4.99 (m, 1H, H-5), 5.05 and 5.17 (d, *J*= 12.4 Hz, 1H, -C(=O)OC$\underline{H}_2$Ph), 5.10 and 5.19 (d, *J*= 12.4 Hz, 1H, -C(=O)OC$\underline{H}_2$Ph), 7.05 (br s, 1H, NH), 7.29-7.38 (m, 5H, Ph), 7.46 and 8.33 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): (rotamer observed) δ 14.2 (C-14), 22.7 and 23.5 (-$\underline{C}H_2$-), 24.5 and 24.7 (-$\underline{C}H_2$- at pyrrolidine), 25.1 (-$\underline{C}H_2$-), 25.4 and 25.5 (-$\underline{C}H_2$-), 29.3 (-$\underline{C}H_2$-), 29.4 (-$\underline{C}H_2$-), 29.6 (-$\underline{C}H_2$-), 30.1 (-$\underline{C}H_2$- at pyrrolidine), 31.1 and 31.9 (-$\underline{C}H_2$-), 33.3 (-$\underline{C}H_2$-), 34.0 and 35.0 (-$\underline{C}H_2$-), 44.4 and 44.8 (C-2), 46.8 and 47.1

(-CH_2- at pyrrolidine), 59.2 and 59.5 (-CH- at pyrrolidine), 67.1 and 67.3 (-C(=O)OCH_2Ph), 74.1 and 74.7 (C-5), 127.4 and 127.8 (Ph), 128.0 and 128.2 (Ph), 128.6 and 128.7 (Ph), 136.4 (Ph), 155.2 (-NC(=O)OCH_2Ph), 172.8 and 173.1 (-OC(=O) CH-), 210.9 (C-1). HRMS (FD). Calcd for $C_{27}H_{42}N_2O_4S$ (M): *m*/*z* 490.2865. Found: *m*/*z* 490.2879.

(5*S*)-5-[(2*S*)-*N*-(Benzyloxy)carbonyl-2-pyrrolidinyl-methanoyloxy]tetradecanethioamide [(5*S*,2'*S*)-6e$_{2nd}$] Yield: 48%; Colorless oil; $[\alpha]^{20}_D$= -41.9 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.09 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3309 (N-H), 3204 (N-H), 2928 (CH_2, C-H), 2856 (CH_2, C-H), 1739 (OC=O), 1693 (NC(=O)O), 1416 (NHC=S), 1118 (C-C(=O)-O), 696 (Ar, C=C). ^{1}H NMR (600 MHz, $CDCl_3$): (rotamer observed) δ 0.88 (t, *J*= 6.9 Hz, 3H, H-14), 1.21-1.32 (m, 14H, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 1.44-1.76 (m, 6H, H-3, H-4, H-6), 1.88-2.00 (m, 2H, -CH_2- at pyrrolidine), 2.02-2.07 (m, 1H, -CH_2- at pyrrolidine), 2.22-2.31 (m, 1H, -CH_2- at pyrrolidine), 2.46-2.51 (m, 1H, H-2), 2.53-2.58 and 2.64-2.69 (m, 1H, H-2), 3.50-3.56 (m, 1H, -CH_2- at pyrrolidine), 3.59-3.63 (m, 1H, -CH_2- at pyrrolidine), 4.36-4.39 (m, 1H, -CH-, at pyrrolidine), 4.82-4.86 and 4.92-4.96 (m, 1H, H-5), 5.12 (m, 2H, -C(=O)OCH_2Ph), 7.28-7.38 (m, 5H, Ph), 7.52 (br s, 1H, NH), 7.91 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): (rotamer observed) δ 14.2 (C-14), 22.4 (-CH_2-), 24.2 and 24.4 (-CH_2-), 23.8 and 24.5 (-CH_2- at pyrrolidine), 25.3 and 25.4 (-CH_2-), 29.3 (-CH_2-), 29.5 (-CH_2-), 29.6 (-CH_2-), 30.3 and 31.1 (-CH_2- at pyrrolidine), 32.0 (-CH_2-), 32.8 and 32.9 (-CH_2-), 33.8 and 34.5 (-CH_2-), 44.5 and 44.9 (C-2), 46.7 and 47.1 (-CH_2- at pyrrolidine), 59.4 and 60.0 (-CH- at pyrrolidine), 67.1 (-C(=O)OCH_2Ph), 74.4 and 74.8 (C-5), 127.5 (Ph), 127.8 (Ph), 128.1 and 128.2 (Ph), 128.6 and 128.7 (Ph), 136.5 and 136.6 (Ph), 154.7 and 155.1 (-C(=O)OCH_2Ph), 172.7 and 172.5 (-OC(=O)CH-), 210.3 and 210.5 (C-1). HRMS (FD). Calcd for $C_{27}H_{42}N_2O_4S$ (M): *m*/*z* 490.2865. Found: *m*/*z* 490.2868.

General procedure for deacylation of diastereomeric esters (5 and 6)

To a solution of **5** (1.0 mmol) or **6** (1.0 mmol) in methanol (1.0 mL) was added a solution of sodium methoxide in methanol (5.0 M, 10 mL). The reaction mixture was stirred for 3 h at 0 °C for the deacylation of **5**, and for 30 min at –15 °C for the deacylation of **6**. The reaction was quenched by adding H_2O (30 mL) and $CHCl_3$ (10 mL). The resultant mixture was extracted with $CHCl_3$, and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification of the crude product by silica gel column chromatography (eluent; *n*-hexane/EtOAc= 1/1) gave the corresponding optically active *N*-methyl-5-hydroxyalkanethioamides (**3**) with over 90% yields or 5-hydroxyalkanethioamides (**4**) with about 70% yields. The data for each spectrum was reported above.

General procedure for acetylation of optically active 3 and 4

Acetic anhydride (1.0 mmol, 0.10 g) and 4-dimethylaminopyridine (0.1 mmol, 0.01 g) were added to a stirred solution of each of optically active **3** or **4** in anhydrous CH_2Cl_2 (5 mL) at room temperature. After 24 h, CH_2Cl_2 was removed under reduced pressure. Distilled water (10 mL) was then added, and the solution was neutralized with Na_2CO_3. CH_3Cl was added to the mixture and the organic layer was separated, washed with distilled water, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (eluent; *n*-hexane/EtOAc= 3/1) gave the optically active **1** and **2** with over 95% yields.

General procedure for the preparation of (*R*)- or (*S*)-MPA ester

A mixture of the resolved (*R*)-**3e** (55 mg, 0.2 mmol) or (*R*)-**4e** (52 mg, 0.2 mmol), EDCI (62 mg, 0.4 mmol), DMAP (24 mg, 0.2 mmol) and (*R*)- or (*S*)-α-methoxyphenylacetic acid (MPA) (66 mg, 0.4 mmol) in anhydrous THF (10 mL) was stirred for 2 h at 0 °C, and then stirred for 3 h at room temperature. The reaction was quenched with aqueous 0.1 M HCl (5 mL). The resultant mixture was extracted with EtOAc, and the combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography (eluent; *n*-hexane/EtOAc= 3/1) to afford the corresponding MPA ester [(5*R*,2'*R*)- or (5*R*,2'*S*)-**7e**, **8e**], respectively.

(5*R*)-*N*-Methyl-5-[(2*R*)-2-methoxy-2-phenylethanoyloxy]tetradecanethioamide [(5*R*,2'*R*)-7e] Yield: 89%; Colorless oil; $[\alpha]^{22}_D$= -36.5 (*c*= 0.3, MeOH, 99% d.e.). R_f= 0.17 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3314 (N-H), 2926 (CH_2, C-H), 2854 (CH_2, C-H), 1732 (OC=O), 1456 (Ar, C=C), 697 (Ar, C-H). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-14), 1.22-1.25 (m, 12H, H-7, H-8, H-9, H-10, H-11, H-12), 1.28-1.31 (m, 2H, H-13), 1.34-1.42 (m, 1H, H-3), 1.43-1.52 (m, 3H, H-3, H-4), 1.53-1.58 (m, 2H, H-6), 2.47 (m, 2H, H-2), 3.09 (d, *J*= 4.8 Hz, 3H, CH_3NHC(=S)-), 3.41 (s, 3H, -OCH_3), 4.76 (s, 1H, -OC(=O)CH(OCH_3)Ph), 4.92 (m, 1H, H-5), 7.32-7.38 (m, 3H, Ph), 7.44-7.45 (m, 2H, Ph), 7.47 (br s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.2 (C-14), 22.7 (C-13), 24.7 (C-3, C-4), 25.3 (-CH_2-), 29.3 (-CH_2-), 29.4

(-$\underline{C}H_2$-), 29.5 (-$\underline{C}H_2$-), 31.9 (-$\underline{C}H_2$-), 32.5 ($\underline{C}H_3$NHC(=S)-), 32.9 (-$\underline{C}H_2$-), 34.2 (C-6), 45.7 (C-2), 57.3 (-O$\underline{C}H_3$), 75.1 (C-5), 82.8 (-OC(=O)$\underline{C}$H(OCH$_3$)Ph), 127.2 (Ph), 128.7 (Ph), 128.8 (Ph), 136.5 (Ph), 170.9 (-O$\underline{C}$(=O)CH(OCH$_3$)Ph), 205.6 (C-1). HRMS (FD). Calcd for $C_{24}H_{39}NO_3S$ (M): *m*/*z* 421.2651. Found: *m*/*z* 421.2677.

(5*R*)-*N*-Methyl-5-[(2*S*)-2-methoxy-2-phenylethanoyloxy]tetradecanethioamide [(5*R*,2'*S*)-7e] Yield: 84%; Colorless oil; $[\alpha]^{23}_D$= +45.8 (*c*= 0.3, MeOH, 99% d.e.). R_f= 0.15 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3312 (N-H), 2925 (CH$_2$, C-H), 2854 (CH$_2$, C-H), 1731 (O$\underline{C}$=O), 1455 (Ar, C=C), 697 (Ar, C-H). ^{1}H NMR (600 MHz, CDCl$_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-14), 0.92 (m, 2H, H-7), 1.06 (m, 4H, H-8, H-10), 1.13 (m, 2H, H-11), 1.22 (m, 4H, H-9, H-12), 1.28 (m, 2H, H-13), 1.42 (m, 2H, H-6), 1.57 (m, 2H, H-4), 1.68 (m, 1H, H-3), 1.80 (m, 1H, H-3), 2.60 (m, 1H, H-2), 2.66 (m, 1H, H-2), 3.12 (d, *J*= 4.8 Hz, 3H, C$\underline{H}_3$NHC(=S)-), 3.40 (s, 3H, -OC$\underline{H}_3$), 4.76 (s, 1H, -OC(=O)C$\underline{H}$(OCH$_3$)Ph), 4.89 (m, 1H, H-5), 7.32-7.37 (m, 3H, Ph), 7.42-7.43 (m, 2H, Ph), 7.72 (br s, 1H, NH). ^{13}C NMR (150 MHz, CDCl$_3$): δ 14.2 (C-14), 22.7 (C-13), 25.0 (C-7), 25.1 (C-3), 29.2 (-$\underline{C}H_2$-), 29.3 (-$\underline{C}H_2$-), 29.4 (-$\underline{C}H_2$-), 29.5 (C-11), 31.9 (-$\underline{C}H_2$-), 33.0 (C-4), 33.1 ($\underline{C}H_3$NHC(=S)-), 34.1 (C-6), 45.8 (C-2), 57.3 (-O$\underline{C}H_3$), 74.9 (C-5), 82.7 (-OC(=O)$\underline{C}$H(OCH$_3$)Ph), 127.7 (Ph), 128.7 (Ph), 128.8 (Ph), 136.4 (Ph), 171.2 (-O$\underline{C}$(=O)CH(OCH$_3$)Ph), 205.7 (C-1). HRMS (FD). Calcd for $C_{24}H_{39}NO_3S$ (M): *m*/*z* 421.2651. Found: *m*/*z* 421.2677.

(5*R*)-5-[(2*R*)-2-Methoxy-2-phenylethanoyloxy]tetradecanethioamide [(5*R*,2'*R*)-8e] Yield: 61%; Colorless oil; $[\alpha]^{24}_D$= -40.5 (*c*= 0.3, MeOH, 99% d.e.). R_f= 0.10 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3313 (N-H), 3174 (N-H), 3036 (Ar, C-H), 2927 (CH$_2$, C-H), 2856 (CH$_2$, C-H), 1738 (O$\underline{C}$=O), 1626 (NH$\underline{C}$=S), 1491 (Ar, C=C), 1457 (C-N), 1378 (Ar, C=C), 1179 (C-C(=O)-O), 737 (Ar, C-H), 699 (Ar, C=C). ^{1}H NMR (600 MHz, CDCl$_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-14), 1.23-1.25 (m, 12H, H-7, H-8, H-9. H-10, H-11, H-12), 1.28-1.32 (m, 2H, H-13), 1.34-1.41 (m, 1H, H-3), 1.43- 1.51 (m, 3H, H-3, H-4), 1.54-1.59 (m, 2H, H-6), 2.41-2.51 (m, 2H, H-2), 3.40 (s, 3H, -OC$\underline{H}_3$), 4.76 (m, 1H, -OC(=O)C$\underline{H}$(OCH$_3$)Ph), 4.93 (m, 1H, H-5), 6.92 (br s, 1H, NH), 7.32-7.38 (m, 3H, Ph), 7.44-7.45 (m, 2H, Ph), 7.58 (br s, 1H, NH). ^{13}C NMR (150 MHz, CDCl$_3$): δ 14.2 (C-14), 22.7 (C-13), 24.4 (C-3, C-4), 25.3 (-$\underline{C}H_2$-), 29.3 (-$\underline{C}H_2$-), 29.4 (-$\underline{C}H_2$-), 29.5 (-$\underline{C}H_2$-), 31.9 (-$\underline{C}H_2$-), 32.6 (-$\underline{C}H_2$-), 34.2 (C-6), 44.4 (C-2), 57.3 (-O$\underline{C}H_3$), 75.0 (C-5), 82.8 (-OC(=O)C$\underline{H}$(OCH$_3$)Ph), 127.3 (Ph), 128.8 (Ph), 128.9 (Ph), 136.5 (Ph), 170.9 (-O$\underline{C}$(=O)CH(OCH$_3$)Ph), 210.2 (C-1). HRMS (FD). Calcd for $C_{23}H_{37}NO_3S$ (M): *m*/*z* 407.2494. Found: *m*/*z* 407.2451.

(5*R*)-5-[(2*S*)-2-Methoxy-2-phenylethanoyloxy]tetradecanethioamide [(5*R*,2'*S*)-8e] Yield: 66%; Colorless oil; $[\alpha]^{24}_D$= +44.7 (*c*= 0.2, MeOH, 99% d.e.). R_f= 0.08 (eluent; *n*-hexane-EtOAc, 3:1, *v*/*v*). IR (NaCl): cm^{-1} 3313 (N-H), 3201 (N-H), 2925 (CH$_2$, C-H), 2856 (CH$_2$, C-H), 1732 (O$\underline{C}$=O), 1628 (NH$\underline{C}$=S), 1494 (Ar, C=C), 1456 (C-N), 1377 (Ar, C=C), 1193 (C-C(=O)-O), 734 (Ar, C-H), 698 (Ar, C=C). ^{1}H NMR (600 MHz, CDCl$_3$): δ 0.88 (t, *J*= 6.9 Hz, 3H, H-14), 0.92 (m, 2H, H-7), 1.06 (m, 4H, H-8, H-10), 1.13 (m, 2H, H-11), 1.22 (m, 4H, H-9, H-12), 1.28 (m, 2H, H-13), 1.42 (m, 2H, H-6), 1.60 (m, 2H, H-4), 1.69 (m, 1H, H-3), 1.78 (m, 1H, H-3), 2.57-2.62 (m, 1H, H-2), 2.64-2.69 (m, 1H, H-2), 3.40 (s, 3H, -OC$\underline{H}_3$), 4.77 (s, 1H, -OC(=O)C$\underline{H}$(OCH$_3$)Ph), 4.90 (m, 1H, H-5), 7.22 (br s, 1H, NH), 7.32-7.37 (m, 3H, Ph), 7.42-7.43 (m, 2H, Ph), 7.66 (br s, 1H, NH). ^{13}C NMR (150 MHz, CDCl$_3$): δ 14.2 (C-14), 22.7 (C-13), 24.9 (C-3), 25.0 (C-7), 29.2 (-$\underline{C}H_2$-), 29.3 (-$\underline{C}H_2$-), 29.4 (-$\underline{C}H_2$-), 29.5 (C-11), 31.9 (-$\underline{C}H_2$-), 33.1 (C-4), 34.1 (C-6), 44.5 (C-2), 57.3 (-O$\underline{C}H_3$), 74.8 (C-5), 82.7 (-OC(=O)$\underline{C}$H(OCH$_3$)Ph), 127.2 (Ph), 128.7 (Ph), 128.9 (Ph), 136.4 (Ph), 171.2 (-O$\underline{C}$(=O)CH(OCH$_3$)Ph), 210.3 (C-1). HRMS (FD). Calcd for $C_{23}H_{37}NO_3S$ (M): *m*/*z* 407.2494. Found: *m*/*z* 407.2444.

Specific rotation of optically active 5-acetoxy- and 5-hydroxyalkanethioamide analogues

N-Methyl-5-acetoxydodecanethioamide (**1c**): $[\alpha]^{20}_D$= +8.3 [*c* 0.2, MeOH for (*R*)-**1c**], $[\alpha]^{20}_D$= -5.3 [*c* 0.2, MeOH for (*S*)-**1c**]. *N*-Methyl-5-acetoxytridecanethioamide (**1d**): $[\alpha]^{20}_D$= +9.7 [*c* 2.0, MeOH for (*R*)-**1d**], $[\alpha]^{20}_D$= -6.7 [*c* 2.0, MeOH for (*S*)-**1d**]. 5-Acetoxydodecanethioamide (**2c**): $[\alpha]^{25}_D$= +2.4 [*c*= 0.2, MeOH for (*R*)-**2c**], $[\alpha]^{25}_D$= -2.5 [*c*= 0.2, MeOH for (*S*)-**2c**]. 5-Acetoxytridecanethioamide (**2d**): $[\alpha]^{20}_D$= +5.7 [*c* 0.2, MeOH for (*R*)-**2d**], $[\alpha]^{20}_D$= -8.5 [*c* 0.2, MeOH for (*S*)-**2d**]. 5-Acetoxytetradecanethioamide (**2e**): $[\alpha]^{20}_D$= +3.9 [*c* 0.2, MeOH for (*R*)-**2e**], $[\alpha]^{20}_D$= -2.1 [*c* 0.2, MeOH for (*S*)-**2e**]. *N*-Methyl-5-hydroxydodecanethioamide (**3c**): $[\alpha]^{20}_D$= +2.6 [*c* 0.2, MeOH for (*R*)-**3c**], $[\alpha]^{20}_D$= +3.3 [*c* 0.2, MeOH for (*S*)-**3c**]. *N*-Methyl-5-hydroxytridecanethioamide (**3d**): $[\alpha]^{20}_D$= +6.3 [*c* 0.2, MeOH for (*R*)-**3d**], $[\alpha]^{20}_D$= -5.2 [*c* 0.2, MeOH for (*S*)-**3d**]. 5-Hydroxydodecanethioamide (**4c**): $[\alpha]^{20}_D$= -5.2 [*c* 0.2, MeOH for (*R*)-**4c**], $[\alpha]^{20}_D$= +5.0 [*c* 0.2, MeOH for (*S*)-**4c**]. 5-Hydroxytridecanethioamide (**4d**): $[\alpha]^{20}_D$= -1.7 [*c* 0.2, MeOH for (*R*)-**4d**], $[\alpha]^{20}_D$= +2.4 [*c* 0.2, MeOH for (*S*)-**4d**]. 5-Hydroxytetradecanethioamide (**4e**): $[\alpha]^{20}_D$= -3.4 [*c* 0.2, MeOH for (*R*)-**4e**], $[\alpha]^{20}_D$= +3.9 [*c* 0.2, MeOH for (*S*)-**4e**].

Lipase screening for enzyme-catalyzed lactonization of 3 and 4

Novozym 435 (0.4 g, from *Candida antarctica* B) or other lipase (0.5 w/w, AK from *Pseudomonas fluorescens*, AS from *Aspergillus niger*, AYS from *Candida cylindracea*, F-AP 15 from *Rhizopus oryzae*, G from *Penicillium camemberti*, M from *Mucor javanicus*, PS from *Burkholderia*

cepacia, PPL from porcine pancreas) was added to a solution of each substrate (1.0 mmol) in Et_2O (20 mL), and the mixture was stirred at 40 °C for 48 h. After stirring, the lipase was filtered off and the crude product was purified by flash chromatography (eluent; *n*-hexane/EtOAc= 4:1). All lactones obtained did not show enantioselectivities, which was confirmed by chiral GC.

***δ*-Dodecalactone (9c)** Colorless oil; R_f= 0.85 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). GC conditions [9]: CycloSil-B (30 m × 0.25 mm i.d. 0.25 μm film thickness) column; oven temperature, 130 °C (isothermal), injector temperature, 280 °C, detector temperature, 290 °C, He flow rate : 2.0 mL/min, t_R= 73.2 min, t_S= 74.4 min. IR (NaCl): cm^{-1} 2953 (CH_3), 2927 (CH_2), 2872 (CH_3), 2857 (CH_2), 1738 (OC=O), 1240 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 6.8 Hz, 3H, H-12), 1.22-1.40 (m, 8H, H-8, H-9, H-10, H-11), 1.42-1.62 (m, 4H, H-6, H-7), 1.68 (m, 1H, H-4), 1.78-1.96 (m, 3H, H-3, H-4), 2.38-2.62 (m, 2H, H-2), 4.28 (m, 1H, H-5). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1 (C-12), 18.5 (C-3), 22.6 (-CH_2-), 24.9 (-CH_2-), 27.8 (C-10), 29.2 (C-11), 29.4 (-CH_2-), 29.5 (C-4), 31.8 (C-6), 35.9 (C-2), 80.6 (C-5), 172.0 (C-1). HRMS (FI) calcd. for $C_{12}H_{22}O_2$ $(M)^+$, 198.1620; found: $(M)^+$, 198.1612.

***δ*-Tridecalactone (9d)** Colorless oil; R_f= 0.87 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). GC conditions [11]: CycloSil-B (30 m × 0.25 mm i.d. 0.25 μm film thickness) column; oven temperature, 130 °C (isothermal), injector temperature, 280 °C, detector temperature, 290°C, He flow rate: 2.0 mL/min, t_R= 124.7 min, t_S= 126.9 min. IR (NaCl): cm^{-1} 2953 (CH_3), 2926 (CH_2), 2872 (CH_3), 2855 (CH_2), 1734 (OC=O), 1241 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, *J*= 7.0 Hz, 3H, H-13), 1.22-1.34 (m, 10H, H-8, H-9, H-10, H-11, H-12), 1.42-1.62 (m, 4H, H-6, H-7), 1.68 (m, 1H, H-4), 1.79-1.94 (m, 3H, H-3, H-4), 2.40-2.62 (m, 2H, H-2), 4.28 (m, 1H, H-5). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.1 (C-13), 18.5 (C-3), 22.6 (-CH_2-), 24.9 (-CH_2-), 27.8 (-CH_2-), 29.2 (C-11), 29.3 (C-12), 29.4 (-CH_2-), 29.5 (C-4), 31.8 (C-6), 35.8 (C-2), 80.6 (C-5), 172.0 (C-1). HRMS (FI) calcd. for $C_{13}H_{24}O_2$ $(M)^+$, 212.1776; found: $(M)^+$, 212.1776.

***δ*-Tetradecalactone (9e)** Colorless oil; R_f= 0.88 (eluent; *n*-hexane-EtOAc, 1:1, *v*/*v*). GC conditions [11]: CycloSil-B (30 m × 0.25 mm i.d. 0.25 μm film thickness) column; oven temperature, 140 °C (isothermal), injector temperature, 280 °C, detector temperature, 290 °C, He flow rate: 2.0 mL/min, t_R= 118.8 min, t_S= 120.8 min. IR (NaCl): cm^{-1} 2954 (CH_3), 2925 (CH_2), 2870 (CH_3), 2855 (CH_2), 1734 (OC=O), 1248 (C-C(=O)-O). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, *J*= 6.8 Hz, 3H, H-14), 1.22-1.34 (m, 12H, H-8, H-9, H-10, H-11, H-12, H-13), 1.45-1.62 (m, 4H, H-6, H-7), 1.70 (m, 1H, H-4), 1.77-1.96 (m, 3H, H-3, H-4), 2.38-2.62 (m, 2H, H-2), 4.28 (m, 1H, H-5). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1 (C-14), 18.5 (C-3), 22.7 (-CH_2-), 24.9 (-CH_2-×2), 27.8 (-CH_2-), 29.3 (-CH_2-), 29.4 (C-12), 29.5 (C-13), 29.5 (-CH_2-), 31.9 (C-4), 35.9 (C-6), 80.6 (C-5), 172.0 (C-1). HRMS (FI) calcd. for $C_{14}H_{26}O_2$ $(M)^+$, 226.1933; found: $(M)^+$, 226.1938.

Antibacterial activity test

The antibacterial assay was performed according to the protocol of the Clinical and Laboratory Standards Institute (Wayne, PA, USA). In the protocol, *Escherichia coli* ATCC25922 and *Staphylococcus aureus* ATCC29213 are defined as the quality control strains and were therefore used for our antibacterial assay. In the assay, 10 μL of a bacterial cell suspension containing 1×10^5 colony forming units (CFU) bacteria was inoculated into 1 mL of Mueller-Hinton broth (Becton Dickinson and Company, Sparks, MD, USA) supplemented with 0.5 mg/mL of the test compound. The culture was incubated for 20 h at 35 °C under aerobic conditions, and the viable cells in the culture were counted with the modified Miles and Misra method [36], 10 μL aliquots of serial-diluted bacterial suspensions were inoculated into a trypticase soy agar broth. After 20 h incubation at 35 °C under aerobic conditions, the numbers of colonies recovered from the diluted suspensions on the agar broth were counted, and the number of viable bacterial cells in the source culture was determined. The antibacterial activity value is defined as follows:

$$\textit{Antibacterial activity value}\ [-] = \log \frac{\textit{viable cell count of nagative control}\ [\mathrm{CFU/mL}]}{\textit{viable cell count of sample}\ [\mathrm{CUF/mL}]}$$

An antibacterial activity value of >2.0 (≥99% killing ratio) of a sample treated with synthetic compounds might be considered as “Antibacterial agent”.

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