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EFFECTIVE METHOD OF LIPASE-CATALYZED ENANTIORESOLUTION OF 6-ALKYLSULFANYL-1,4-DIHYDROPYRIDINES

Zigmars Andzans,[1,2*] Ilze Adlere,[1] Aleksandrs Versilovskis,[1] Laura Krasnova,[1] Signe Grinberga,[1] Gunars Duburs,[1] and Aivars Krauze[1]

[1]Latvian Institute of Organic Synthesis, Aizkraukles 21, Riga LV-1006, Latvia;
E-mail: andzans@osi.lv
[2]University of Latvia, 19 Raina Blvd., Riga LV 1586, Latvia

Abstract – A series of 6-alkylsulfanyl-1,4-dihydropyridines **(±)-2** bearing a methoxycarbonylethyl group as a mild easily removable protecting group at S atom have been prepared by alkylation of 6-thioxo-1,4-dihydropyridines **1** with methyl bromopropionate. *Candida antarctica* lipase B (Novozyme 435®, CAL-B) - and Amano Acylase (*Aspergillus mellus*)-catalyzed kinetic resolution has been investigated in water-saturated diisopropyl ether (IPE) at 25 and 45 °C. After acrylic acid methyl ester as leaving group cleavage and alkylation of formed enantioenriched 1,4-dihydropyridine-6-thiolates (-)-**4** and (+)-**4**, optically active 1,4-dihydropyridines (-)-**2**, (+)-**2**, (-)-**5** and (+)-**5** were obtained in 85-99% enantiomeric excess. The experiments present the 6-(methoxycarbonylethyl)-sulfanyl group as an essentially new enzymatically labile (activating) group. The ester group being 6 bonds remote from the chiral center undergoes easy enzymatic hydrolysis and could be used for kinetic resolution of racemic 1,4-DHPs. This developed method offers access to mild optically active nucleophilic tiolates, which could be easily derivatized with electrophilic reagents.

INTRODUCTION

1,4-Dihydropyridine (DHP) scaffold represents a heterocyclic unit of remarkable pharmacological efficiency.[1-4] DHP derivatives depending on their structure may bind to the L-, T- and N-types calcium,

* Corresponding author. Tel.: +371 26309236; fax: +371 67550338; *e-mail adress:* zigmars.andzans@inbox.lv.

sodium, potassium or chloride channels and act as selective or multifunctional molecules for the various pharmacobiological activities such as bioprotective,[5] neurotropic,[6] membrane protecting,[7-9] radioprotecting,[10] antidiabetic,[11] gene-transfection,[12] and antibacterial.[13]

6-Alkylsulfanyl-1,4-DHPs display cardiovascular,[14-15] hepatoprotective,[16] antioxidant,[17] and antiradical[18] activities (in addition to the above mentioned activities), however, these compounds are still insufficiently studied.

Chirality plays an important role in the activity of 1,4-DHPs and both quantitative and qualitative differences between different stereoisomers (enantiomers) have been reported.[19,20] Pharmaceutical evaluations of chiral 1,4-DHPs revealed that their strereoisomers usually have different biological activities. Sometimes the undesired enantiomer caused serious side effects, while in other cases enantiomers were reported to have even the opposite action profile (calcium antagonist - calcium agonist; hypotensive activity - hypertensive activity).[21]

Chemoenzymatic methods for preparation of chiral drugs have a number of distinct advantages: they are simple, direct, efficient, mild, and cheap in case of multiple (repeated) use of the enzyme. The standard resolution technique, such as incorporation of an enzymatically labile group for the resolution of monocyclic 1,4-DHPs has been in use for the last decade. This approach has been pioneered by groups of Sih[22] and Achiwa,[23] applied to 6-derivatised 1,4-DHPs[24-26] and also used by our research group.[27-32]

It is worth mentioning that many activating groups applicable to enantioselective lipase-catalyzed kinetic resolution of 1,4-dihydropyridine-3-carboxylates have been screened. An asymmetric 1,4-DHPs alkoxycarbonylmethoxycarbonyl (double esters),[27,28] alkylcarboxymethyloxycarbonyl (reverse esters) in position 5[25,30-33] and acetoxymethyl group in position 6[24,26,34,35] were the best characterised.

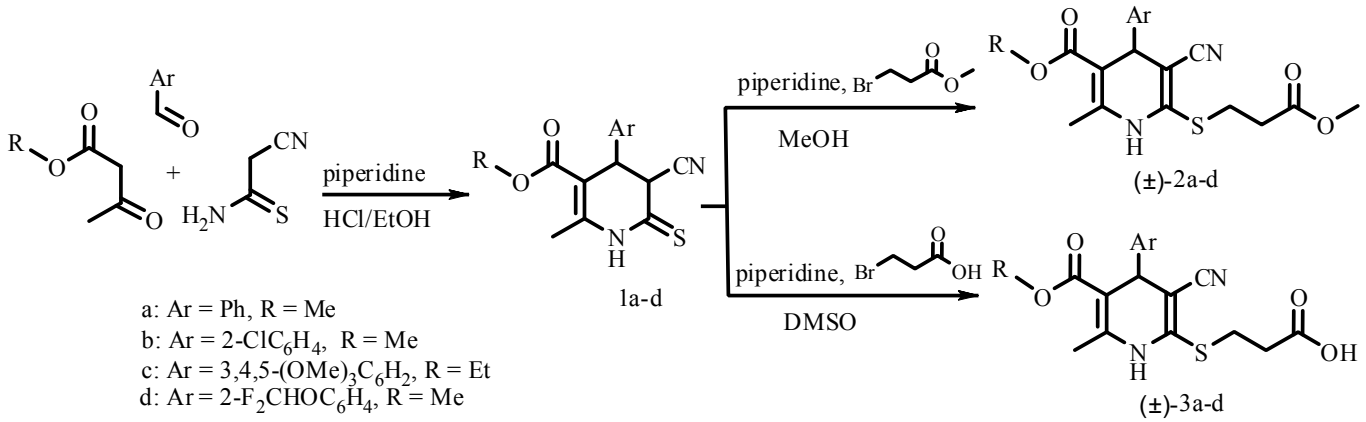
Esters are good substrates for the lipases and nowadays a lot of enzymes are commercially available. Lipases such as CAL-B and Amano acylase were evaluated for the resolution of esters and often possitive results are achieved.[33-37]

RESULTS AND DISCUSSION

The aim of our research was the synthesis of new 1,4-DHPs containing lipophilic methoxycarbonylethylsulfanyl group at position 6, which could act as mild and easily removable protecting group at S atom. Though the ester group is 6 bonds remote from the chiral center (stereogenic carbon at the 4 position), we expected that the enzymatic hydrolysis of this group could promote kinetic resolution of the target 1,4-DHPs. It is worth mentioning that our efforts to prepare optically active 6-alkylsulfanyl-1,4-DHPs by carrying out enzyme catalyzed hydrolysis of so called activated double esters - ethoxycarbonylmethyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates were unsuccessful,[40]

at the same time enantioresolution of 6-(methoxycarbonylmethyl)sulfanyl-1,4-dihydropyridines gave target products with up to 70% enantiomeric excess.[32]

The starting substrates 3-alkoxycarbonyl-5-cyano-2-methyl-4-aryl-1,4-dihydropyridine-6-thiones **1** were prepared by a one-pot three-component condensation of alkyl acetoacetate, aromatic aldehyde and 2-cyanothioacetamide according to the synthesis protocol mentioned previously.[41]



Scheme 1

Alkylation of thiones **1** bearing several nucleophilic reaction centres (5-C, S, N) in basic (alkaline) medium under mild reaction conditions with methyl bromopropionate proceeds preferably at the sulfur atom giving rise to methyl 4-aryl-6-methoxycarbonylethylsulfanyl-1,4-dihydropyridine-3-carboxylates (±)-**2** in 71-87% yields.

Carboxylic acids (±)-**3**, as authentic samples for investigation of enzyme catalyzed hydrolysis, were prepared by alkylation of thiones **1** with bromopropionic, acid in the presence of piperidine, in 64-85% yields.

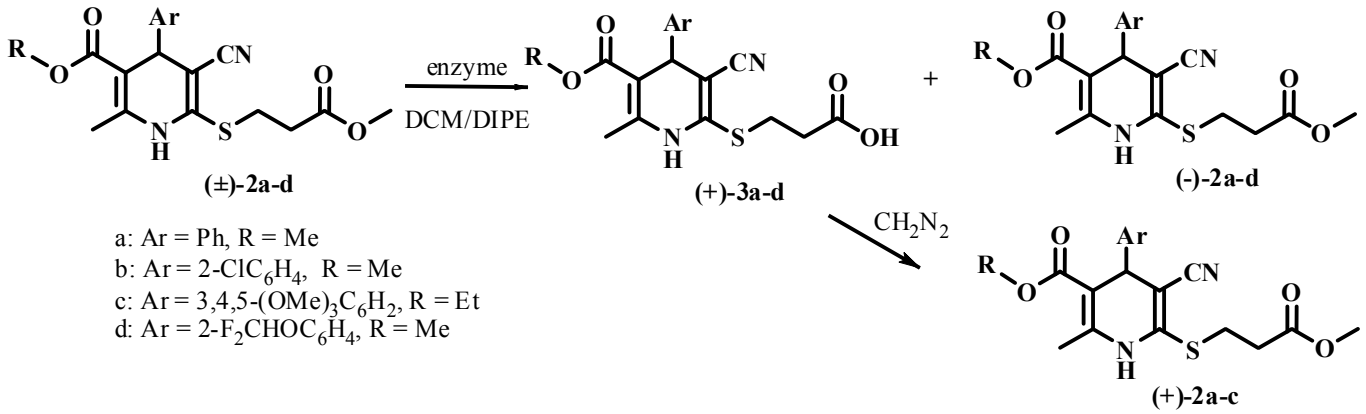
Enzymatic screening of the substrates (±)-**2** was performed in water-saturated (maximal water concentration was approximately 4 g/L) diisopropyl ether (IPE) (was found to be the best solvent) by using an Amano Acylase (*Aspergillus mellus*) and *Candida antarctica* lipase B (CAL-B, Novozyme 435®). The reaction was monitored by HPLC and when ~50% of acid (+)-**3** was formed the reaction was stopped, enzyme was filtered off, washed with IPE and the filtrate was evaporated. The mixture of acid (+)-**3** and the remaining ester (-)-**2** was separated by column chromatography. The enantiomeric excess (*ee*) of the remaining esters (-)-**2** were determined by HPLC using chiral column (Table 1).

Due to usage of water-saturated IPE as a solvent, the concentration of substrate needs to be less than 0.01 mol/L, otherwise precipitation takes place. To increase the solubility of

6-methoxycarbonylethylsulfanyl-1,4-dihydropyridines **(±)-2**, 0.5-10% of dichloromethane (DCM) was added to the reaction mixture and provided that remains substrate concentration 0.0025 mol/L. It increased the reaction rate, but enantioselectivity of the reaction decreased. When the ratio between DCM and water-saturated IPE was 1:10, *ee* of ester (-)-**2a** was 83%, but when the content of DCM was decreased from 9% (entry 5) to 5%, *ee* of (-)-**2a** was increased to 95% (entries 6).

To hydrolyze 6-methoxycarbonylethylsulfanyl-1,4-DHPs (±)-**2** an Amano Acylase was used. To our surprise, hydrolysis of DHPs (±)-**2a** and (±)-**2b** in water-saturated IPE did not take place at 45 °C (entries 14 and 15). In case of substrate (±)-**2d** hydrolysis yielding racemic acid (±)-**3d** and ester (±)-**2d** (entry 17) was observed, but in case of DHP (±)-**2c** just 20% *ee* of unreacted ester (-)-**2c** was reached. By carrying out hydrolysis of the ester (±)-**2b** with Amano Acylase at 25 °C 89% *ee* of (-)-**2b** was reached. In case of DHPs (-)-**2a**, (-)-**2c** and (-)-**2d** (entries 10, 12, 13) 38-52% *ee* was reached.

Table 1 shows that CAL-B gave better results and in case of 4-(3,4,5-trimethoxyphenyl)substituted 6-(2-methoxycarbonylethylsulfanyl)-1,4-DHP (±)-**2c** enzyme catalyzed hydrolysis carried out at 45 °C over 26 h provided 99% *ee* of (-)-**2c**.



Scheme 2

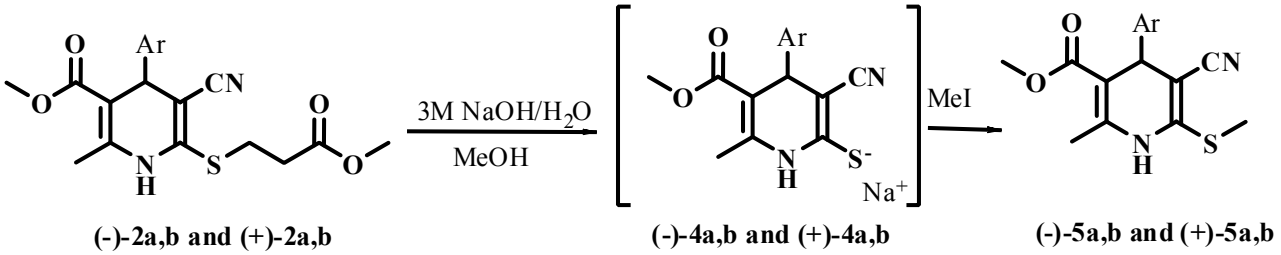
Table 1 shows that in contrast to Amano Acylase, better results for CAL-B were reached by raising the temperature from 25 °C (65-82% *ee*) to 45 °C (86-99% *ee*).

Table 1 Yields of enzymatic hydrolysis (reaction conditions)

Entry	Substrate	Enzyme	Ratio between DCM and IPE/H_2O, v/v	Temp., °C	Time, h	Yield of product (-)-2	Enantio-meric excess of (-)-2, %	Yield of product (+)-3
1	**(±)-2a**	CAL-B	1:20	25	48	49	82	47
2	**(±)-2b**	CAL-B	1:20	25	165	46	80	48
3	**(±)-2c**	CAL-B	1:200	25	51	46	77	47
4	**(±)-2d**	CAL-B	1:60	25	264	46	65	46
5	**(±)-2a**	CAL-B	1:10	45	40	48	83	47
6	**(±)-2a**	CAL-B	1:20	45	18	49	95	47
7	**(±)-2b**	CAL-B	1:20	45	48	46	92	48
8	**(±)-2c**	CAL-B	1:200	45	26	46	99	46
9	**(±)-2d**	CAL-B	1:60	45	168	46	86	46
10	**(±)-2a**	Amano Acylase	1:20	25	96	47	52	48
11	**(±)-2b**	Amano Acylase	1:20	25	310	45	89	48
12	**(±)-2c**	Amano Acylase	1:200	25	100	48	38	47
13	**(±)-2d**	Amano Acylase	1:60	25	336	45	48	48
14	**(±)-2a**	Amano Acylase	1:20	45	*	-	-	-
15	**(±)-2b**	Amano Acylase	1:20	45	*	-	-	-
16	**(±)-2c**	Amano Acylase	1:200	45	90	46	20	47
17	**(±)-2d**	Amano Acylase	1:60	45	336	47	racemate	48

* Reaction doesn`t take place within 6 weeks

We did not succeed to find out an appropriate HPLC conditions for enantioseparation of carboxylic acids (+)-**3** nor on Whelk O1, nor Lux Cellulose-2 chiral HPLC columns. To characterize the opposite enantiomer optically active acids (+)-**3b** and (+)-**3c** were methylated with diazomethane and enantiomeric excess of the corresponding methyl 6-methoxycarbonylethylsulfanyl-1,4-dihydropyridine-3-carboxylates (+)-**2b** and (+)-**2c** were determined (Table 2).



a) Ar = Ph; **b)** Ar = 2-ClC_6H_4

Scheme 3

Enantioenriched thiolates (-)-**4** and (+)-**4** were prepared by deacrylation of mercaptopropionates (-)-**2** and (+)-**2** with 3N NaOH water solution. Even after alkylation of (-)-**4** and (+)-**4** with methyl iodide enantioenriched methyl 6-methylsulfanyl-1,4-dihydropyridine-3-carboxylates (-)-**5** and (+)-**5** were still obtained (Table 2).

Table 2. Enantiomeric excess and optical yields of compounds (-)-**2**, (+)-**2**, (+)-**3**, (-)-**5** and (+)-**5**

Entry	Compound	*ee*, %	$[\alpha]^{20}$, deg, (c 1, MeOH)
1	**(+)-3a**	-	+168.6
2	**(+)-3b**	-	+171.9
3	**(+)-3c**	-	+182.1
4	**(-)-2a**	95	-127.8
5	**(-)-2b**	92	-134.9
6	**(-)-2c**	99	-152.9
7	**(+)-2a**	93	+120.3
8	**(+)-2b**	92	+133.9
9	**(+)-2c**	94	+134.9
10	**(-)-5a**	93	-104.8
11	**(+)-5a**	85	+92.6
12	**(-)-5b**	92	-110.4
13	**(+)-5b**	92	+80.5

Candida antarctica lipase B and Amano Acylase catalyzed kinetic resolution has been investigated in water-saturated diisopropylether at 25 and 45 °C. Further deacrylation and alkylation of enantioenriched 1,4-dihydropyridine-6-thiolates gave rise to optically active 1,4-dihydropyridines with 85-99% enantiomeric excess.

Experiments performed by our group allow characterisation of the 6-(methoxycarbonylethyl)sulfanyl group as an essentially new enzymatically labile (*activating*) group. The ester group being 6 bonds remote from chiral center undergoes easy enzymatic hydrolysis and could be used for kinetic resolution of racemic 1,4-DHPs. Since methoxycarbonylethylsulfanyl group at position 6 of 1,4-DHP ring acts as a mild, easily removable protecting group at sulfur atom, the method developed by our group becomes effective because it offers an access to mild synthesis of optically active nucleophilic thiolates, which could be easily derivatized with electrophilic reagents.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 580 B spectrometer in Nujol, or in thin layer. NMR spectra were recorded with a Varian 400-MR (400 MHz). Chemical shifts are reported in ppm relative to hexamethyldisiloxane (δ 0.055). Mass spectral data and chromatographic separation were obtained by using an Q-TOF mass spectrometer (Micromass) operating in the ESI positive or negative ion mode connected to an Acquity UPLC system (Waters) with Acquity UPLC BEH C18 column (1.7 μm, 2.1 × 50 mm). A gradient elution with MeCN–HCO_2H (0.1%) in water was used to separate analytes. The enantiomeric excesses were determinated by HPLC on a Lux Cellulose-2 column (4 μm, 4.6 × 150 mm), as a mobile phase a 0.1% acetic acid in 2-PrOH: hexane (50: 50, v/v) was used, flow rate was 1 mL/min, UV detector was operated at 254 nm. Melting points were determined using OptiMelt (SRS Stanford Research Systems). Elemental analyses were performed by using an EA 1106 (Carlo Erba Instruments). Optical rotation values were measured with a Rudolph Research Analytical autopol VI automatic polarimeter. TLC was performed on 20 × 20 cm Silica gel TLC-PET F254 foils (Fluka) by using different elution solvent systems. All reagents were purchased from Aldrich, Acros, Fluka or Merck and used without further purification.

Preparation of compounds **1a**, (±)-**2a** and (±)-**3a** was described in,[41] **1b** in,[40] and **1d** in.[32]

1.1. Methyl 5-cyano-2-methyl-6-thioxo-4-(3,4,5-trimethoxyphenyl)-1,4,5,6-tetrahydropyridine-3-carboxylate (1c)

A mixture of 3,4,5-trimethoxybenzaldehyde (0.20 g, 1.0 mmol), ethyl acetoacetate (0.13 g, 1.0 mmol) and piperidine (0.03 mL, 0.3 mmol) in EtOH (20 mL) was stirred for 5 min at room temperature. Then 2-cyanothioacetamide (0.1 g, 1.0 mmol) and piperidine (0.1 mL, 1.0 mmol) were added and reaction mixture was stirred for 30 min at room temperature. The resulting reaction mixture was acidified with 0.6 mL of 3M hydrochloric acid in EtOH. The precipitate was separated by filtration, washed with cold (-10 °C) MeOH (5 mL) and water (20 mL) to give 0.28 g (58%) of thione **1c** as yellow powder, mp

174-176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1,06 (t, *cis*-, J = 7.0 Hz, 3H), 1,08 (t, *trans*-, J = 7.0 Hz, 3H); 2.32 (s, *cis*-, 3H), 2.39 (s, *trans*-, 3H), 3.73-3.76 (m, 9H), 3.93 (q, *cis*-, J = 7.0 Hz, 3H), 4.03 (q, *trans*-, J = 7.0 Hz, 3H); 4.16 (d, *cis*-, J = 6.3 Hz, 1H); 4.27 (d, *cis*-, J = 6.3 Hz, 1H), 4.53 (d, *trans*-, J = 2.7 Hz, 1H), 5.03 (d, *trans*-, J = 2.7 Hz, 1H), 6.39-6.46 (m, 2H), 12.10 (br s, *cis*-, 1H), 12.26 (br s, *trans*-, 1H). IR (Nujol) 1706 (C=O), 2260 (C≡N), 3220 (br s, NH, OH) cm^{-1}. Anal. Calcd for $C_{19}H_{22}N_2O_5S$: C 58.45, H 5.68, N 7.17. Found: C 58.59; H 5.54; N 7.11.

1.2. Methyl 5-cyano-6-(2-methoxycarbonylethylsulfanyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate ((±)-2a)

A mixture of thione **1a** (0.29 g, 1.0 mmol) and piperidine (0.1 mL, 1.0 mmol) in MeOH (20 mL) was stirred for 10 min at room temperature. Then methyl bromopropionate (0.14 mL, 1.3 mmol) was added and the reaction mixture was stirred at 80 °C for 1 h. The precipitate was separated by filtration, washed with cold (-10 °C) MeOH (5 mL) and water (20 mL) to give 0.30 g (80%) of ester (±)-**2a** as white powder, mp 109-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.60-2.76 (m, 2H), 2.97-3.20 (m, 2H), 3.58 (s, 3H), 3.76 (s, 3H), 4.64 (s, 1H), 7.17–7.29 (m, 4H), 7.99 (s, 1H). IR (Nujol) 171 (C=O), 2198 (C≡N), 3309 (NH) cm^{-1}. MS *m/z* 373 (M^+), 342, 296, 287. Anal. Calcd for $C_{19}H_{20}N_2O_4S$: C 61.27; H 5.41; N 7.52. Found: C 61.20; H 5.44; N 7.49.

1.3. Methyl 4-(2-chlorophenyl)-5-cyano-6-(2-methoxycarbonylethylsulfanyl)-2-methyl-1,4-dihydropyridine-3-carboxylate ((±)-2b)

Compound (±)-**2b** was prepared in the same manner as (±)-**2a** using thione **1b** instead of **1a**. Yield 0.29 g (71%) of ester (±)-**2b** as white powder, mp 109-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H); 2.67-2.75 (m, 2H), 2.96-3.25 (m, 2H), 3.56 (s, 3H), 3.79 (s, 3H), 5.29 (s, 1H), 7.10–7.35 (m, 4H), 8.15 (s, 1H). IR (Nujol) 1714 (C=O), 2198 (C≡N), 3309 (NH) cm^{-1}. MS *m/z* 407 (M^+), 377, 343, 295, 289, 209. Anal. Calcd for $C_{19}H_{19}ClN_2O_4S$: C 56.09; H 4.70; N 6.88. Found: C 55.95; H 4.58; N 6.78.

1.4. Ethyl 5-cyano-6-(2-methoxycarbonylethylsulfanyl)-2-methyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine-3-carboxylate ((±)-2c)

Compound (±)-**2c** was prepared in the same manner as (±)-**2a** using thione **1c** instead of **1a**. Yield 0.38 g (79%) of ester (±)-**2c** as white powder, mp 138-139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, J = 7.0 Hz, 3H), 2.39 (s, 3H), 2.58-2.68 (m, 2H), 2.94-3.10 (m, 2H), 3.71 (s, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 3.99 (q, J = 7.0 Hz, 3H), 4.58 (s, 1H), 6.39 (s, 2H), 7.88 (s, 1H). IR (Nujol) 1684, 1712 (C=O), 2198 (C≡N); 3240 (NH) cm^{-1}. MS *m/z* (rel. int.) 499 (M+Na^+), 447, 432, 309, 277, 223. Anal. Calcd for $C_{23}H_{28}N_2O_7S$: C 57.97, H 5.92, N 5.88. Found: C 57.89, H 5.91, N 5.81.

1.5. Methyl 5-cyano-4-(2-difluoromethoxyphenyl)-6-(2-methoxycarbonylethylsulfanyl)-2-methyl-1,4-dihydropyridine-3-carboxylate ((±)-2d)

Compound (±)-**2d** was prepared in the same manner as (±)-**2a** using thione **1d** instead of **1a**. Yield 0.38 g (87%) of ester (±)-**2d** as white powder, mp 134-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 2.67-2.74 (m, 2H), 2.96-3.24 (m, 2H), 3.55 (s, 3H), 3.78 (s, 3H), 5.06 (s, 1H), 6.54 (q, J = 73.2 Hz, 1H), 6.96–7.27 (m, 4H), 8.03 (s, 1H). IR (Nujol) 1710 (C=O), 2201 (C≡N), 3183 (NH) cm^{-1}. MS *m/z* 439 (M^+), 420, 399, 333, 296. Anal. Calcd for $C_{20}H_{20}F_2N_2O_5S$: C 54.79; H 4.60; N 6.39. Found: C 54.79; H 4.47; N 6.26.

1.6. Methyl 6-carboxyethylsulfanyl-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate ((±)-3a)

A mixture of thione **1a** (0.29 g, 1.0 mmol) and piperidine (0.1 mL, 1.0 mmol) in DMSO (20 mL) was stirred for 10 min at room temperature. Then bromopropionic acid (0.15 g, 1.0 mmol) was added and the reaction mixture was stirred at 70 °C for 30 min. Resulting mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were evaporated and crystallized from CH_2Cl_2. The precipitate was separated by filtration, washed with cold (-10 °C) MeOH (5 mL) and water (20 mL) to give 0.31 g (85%) of acid (±)-**3a** as white powder, mp 165-167 °C. ^{1}H NMR (400 MHz, DMSO): δ 2.30 (s, 3H), 2.40-2.50 (m, 2H), 2.97-3.17 (m, 2H), 3.48 (s, 3H), 4.46 (s, 1H), 7.10-7.30 (m, 3H), 10.33 (s, 1H), 12.42 (s, 1H). IR (Nujol) 1685 (C=O), 2216 (C≡N), 3175 and 3225 (NH and OH) cm^{-1}. MS *m/z* 359 (M^+), 327, 281, 209. Anal. Calcd for $C_{18}H_{18}N_2O_4S$: C 60.32 H, 5.06; N 7.82. Found: C 60.25, H 5.17, N 7.88.

1.7. Methyl 6-carboxyethylsulfanyl-4-(2-chlorophenyl)-5-cyano-2-methyl-1,4-dihydro-pyridine-3-carboxylate ((±)-3b)

Compound (±)-**3b** was prepared in the same manner as (±)-**3a** using thione **1b** instead of **1a**. Yield 0.29 g (69%) of acid (±)-**3b** as white powder, mp 177-180 °C. ^{1}H NMR (400 MHz, DMSO): δ 2.30 (s, 3H), 2.51-2.44 (m, 2H), 2.98-3.18 (m, 2H), 3.42 (s, 3H), 5.07 (s, 1H), 7.21-7.37 (m, 4H), 9.54 (s, 1H), 12.42 (s, 1H), IR (Nujol) 1685 (C=O), 2216 (C≡N), 3175, 3225 (NH and OH) cm^{-1}. MS *m/z* 393 (M^+), 375, 281, 209. Anal. Calcd for $C_{18}H_{17}ClN_2O_4S$: C 55.03; H 4.36; N 7.13. Found: C 54.48; H 4.32; N 6.90.

1.8. Ethyl 6-carboxyethylsulfanyl-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl-1,4-dihydro-pyridine-3-carboxylate ((±)-3c)

Compound (±)-**3c** was prepared in the same manner as (±)-**3a** using thione **1c** instead of **1a**. Yield 0.31 g

(85%) of acid (±)-**3c** as white powder, mp 105-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, J = 7.0 Hz, 3H), 2.27 (s, 3H), 2.46-2.52 (m, 2H), 3.01-3.22 (m, 2H), 3.60 (s, 3H), 3.69 (s, 3H), 3.77 (s, 3H), 3.99 (q, J = 7.0 Hz, 3H), 4.44 (s, 1H), 6.39 (s, 2H), 9.51 (s, 1H), 12.40 (s, 1H). IR (Nujol) 1685 (C=O), 2216 (C≡N), 3175, 3225 (NH and OH) cm^{-1}. MS *m/z* 462 (M^+), 447, 432, 309, 277, 223. Anal. Calcd for $C_{22}H_{26}N_2O_7S$: C 57.13, H 5.67, N 6.06. Found: C 57.25, H 5.49, N 6.32.

1.9. Methyl 6-carboxyethylsulfanyl-5-cyano-4-(2-difluoromethoxyphenyl-2-methyl-1,4-dihydro-pyridine-3-carboxylate ((±)-3d)

Compound (±)-**3d** was prepared in the same manner as (±)-**3a** using thione **1d** instead of **1a**. Yield 0.27 g (64%) of acid (±)-**3d** as white powder, mp 157-158 °C. ^{1}H NMR (400 MHz, DMSO): δ 2.26 (s, 3H), 2.43-2.48 (m, 2H), 2.95-3.17 (m, 2H), 3.40 (s, 3H), 4.87 (s, 1H), 7.17-7.39 (m, 3H), 9.49 (s, 1H), 12.37 (s, 1H). IR (Nujol) 1685 (C=O), 2216 (C≡N), 3175 and 3225 (NH and OH) cm^{-1}. MS *m/z* 425 (M^+), 405, 385, 333, 281. Anal. Calcd for $C_{19}H_{18}F_2N_2O_5S$: C 53.77, H 4.27, N 6.60. Found: C 53.84, H 4.20, N 6.51.

1.10. General procedure of preparative *Candida antarctica* lipase B, Novozyme 435 (CAL-B) catalyzed hydrolysis of esters (±)-2.

1 mmol of ester (±)-**2** was dissolved in 2 mL of CH_2Cl_2 and appropriate amount of water-saturated diisopropyl ether was added as mentioned in Table 1 to give substrate concentration (0.0025 mol/L) and ratio between d CH_2Cl_2 and water-saturated diisopropyl ether. Then 0.4 g of Novozyme 435® (≥10,000 U/g) was added and the reaction mixture was placed in an incubator – shaker (45 °C) and stirred at 300 rpm. Every 10-20 min a 10-20 μL samples were taken with a syringe from the reaction mixture, transferred into the 1 mL vial containing 75% of MeCN - water solution. Obtained solution was stirred for 15 sec and analysed by HPLC. Reaction was stopped when ~ 50% of acid **4** was formed. Blank reactions without enzyme showed no conversion of substrate. The enzyme was separated from the reaction mixture by filtration. Filtrate was evaporated to dryness under reduced pressure at 50 °C and the residue was purified by flash chromatography. Purified acids (+)-**3** and esters (-)-**2** were analyzed by HPLC.

1.11. (+)-Methyl 6-carboxyethylsulfanyl-5-cyano-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate ((+)-3a)

0.17 g (47%) of acid (+)-**3a** as white powder, mp 165-167 °C. ^{1}H NMR (400 MHz, DMSO): δ 2.30 (s, 3H), 2.40-2.50 (m, 2H), 2.97-3.17 (m, 2H), 3.48 (s, 3H), 4.46 (s, 1H), 7.10-7.30 (m, 3H), 10.33 (s, 1H), 12.42 (s, 1H). IR (Nujol) 1685 (C=O), 2216 (C≡N), 3175, 3225 (NH and OH) cm^{-1}. MS *m/z* 359 (M^+),

327, 281, 209. Anal. Calcd for $C_{18}H_{18}N_2O_4S$: C 60.32 H, 5.06; N 7.82. Found: C 60.22, H 5.19, N 7.88. $[\alpha]^{20}_D$ +168.6 (c 1.0, MeOH).

1.12. (+)-Methyl 6-carboxyethylsulfanyl-4-(2-chlorophenyl)-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylate ((+)-3b)

0.19 g (48%) of acid (+)-**3b** as white powder, mp 177-180 °C. ^{1}H NMR (400 MHz, DMSO): δ 2.30 (s, 3H), 2.51-2.44 (m, 2H), 2.98-3.18 (m, 2H), 3.42 (s, 3H), 5.07 (s, 1H), 7.21–7.37 (m, 4H), 9.54 (s, 1H), 12.42 (s, 1H). IR (Nujol) 1685 (C=O), 2216 (C≡N), 3175, 3225 (NH and OH) cm^{-1}. MS *m/z* 393 (M^+), 375, 281, 209. Anal. Calcd for $C_{18}H_{17}ClN_2O_4S$: C 55.03; H 4.36; N 7.13. Found: C 54.86; H 4.25; N 6.88. $[\alpha]^{20}_D$ +171.9 (c 1.0, MeOH).

1.13. (+)-Ethyl 6-carboxyethylsulfanyl-5-cyano-2-methyl-4-(3,4,5-trimethoxyphenyl-1,4-dihydropyridine-3-carboxylate ((+)-3c)

0.21 g (46%) of acid (+)-**3c** as white powder, mp 105-107 °C. ^{1}H NMR (400 MHz, DMSO): δ 1.11 (t, J = 7.0 Hz, 3H), 2.27 (s, 3H), 2.46-2.52 (m, 2H), 3.01-3.22 (m, 2H), 3.60 (s, 3H), 3.69 (s, 3H), 3.77 (s, 3H), 3.99 (q, J = 7.0 Hz, 3H), 4.44 (s, 1H), 6.39 (s, 2H), 9.51 (s, 1H), 12.40 (s, 1H). IR (Nujol) 1684, 1712 (C=O), 2198 (C≡N), 3240 (NH) cm^{-1}. MS *m/z* 462 (M^+), 447, 432, 309, 277, 223. Anal. Calcd for $C_{22}H_{26}N_2O_7S$: C 57.13, H 5.67, N 6.06. Found: C 57.29, H 5.51, N 6.38. $[\alpha]^{20}_D$ +182.1 (c 1.0, MeOH).

1.14. (-)-Methyl 5-cyano-6-(2-methoxycarbonylethylsulfanyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate ((-)-2a)

0.30 g (49%) of ester (-)-**2a** as white powder, mp 109-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.60-2.76 (m, 2H), 2.97-3.20 (m, 2H), 3.58 (s, 3H), 3.76 (s, 3H), 4.64 (s, 1H), 7.17–7.29 (m, 4H), 7.99 (s, 1H). IR (Nujol) 1714 (C=O), 2198 (C≡N), 3309 (NH) cm^{-1}. MS *m/z* 373 (M^+), 342, 296, 287. Anal. Calcd for $C_{19}H_{20}N_2O_4S$: C 61.27; H 5.41; N 7.52. Found: C 61.20; H 5.44; N 7.49. $[\alpha]^{20}_D$ -127.8 (c 1.0, MeOH), 95% *ee*.

1.15. (-)-Methyl 4-(2-chlorophenyl)-5-cyano-6-(2-methoxycarbonyl-ethylsulfanyl)-2-methyl-1,4-dihydropyridine-3-carboxylate ((-)-2b)

0.29 g (46%) of ester (-)-**2b** as white powder, mp 109-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.67-2.75 (m, 2H), 2.96-3.25 (m, 2H), 3.56 (s, 3H), 3.79 (s, 3H), 5.29 (s, 1H), 7.10-7.35 (m, 4H), 8.15 (s, 1H). IR (Nujol) 1714 (C=O), 2198 (C≡N), 3309 (NH) cm^{-1}. MS *m/z* 407 (M^+), 377, 343, 295, 289, 209. Anal. Calcd for $C_{19}H_{19}ClN_2O_4S$: C 56.09; H 4.70; N 6.88. Found: C 55.95; H 4.58; N 6.78. $[\alpha]^{20}_D$

-134.9 (c 1.0, MeOH), 92% *ee*.

1.16. (-)-Ethyl 5-cyano-6-(2-methoxycarbonylethylsulfanyl)-2-methyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine-3-carboxylate ((-)-2c)

0.38 g (46%) of ester (-)-**2c** as white powder, mp 138-139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, J = 7.0 Hz, 3H), 2.39 (s, 3H), 2.58-2.68 (m, 2H), 2.94-3.10 (m, 2H), 3.71 (s, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 3.99 (q, J = 7.0 Hz, 3H), 4.58 (s, 1H), 6.39 (s, 2H), 7.88 (s, 1H). IR (Nujol) 1684, 1712 (C=O); 2198 (C≡N); 3240 (NH) cm^{-1}. MS *m/z* 499 (M+Na$^+$), 447, 432, 309, 277, 223. Anal. Calcd for $C_{23}H_{28}N_2O_7S$: C 57.97, H 5.92, N 5.88. Found: C 57.89, H 5.91, N 5.81. $[\alpha]^{20}_D$ -152.9 (c 1.0, MeOH), 92% *ee*.

1.17. (+)-Methyl 5-cyano-6-methoxycarbonylethylsulfanyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate ((+)-2a)

A mixture of acid (+)-**3a** (0.11 g, 0.3 mmol) and 0.5M diazomethane ether solution (1.0 mL) in CH_2Cl_2 (7 mL) was stirred for a 10 min at room temperature. After 10 min reaction mixture was evaporated to dryness under reduced pressure at 50 °C to give 0.10 g (97%) of ester (+)-**2a** as oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.60-2.76 (m, 2H), 2.97-3.20 (m, 2H), 3.58 (s, 3H), 3.76 (s, 3H), 4.64 (s, 1H), 7.17-7.29 (m, 4H), 7.99 (s, 1H). IR (Nujol) 1714 (C=O), 2198 (C≡N), 3309 (NH) cm^{-1}. MS *m/z* 373 (M$^+$), 342, 296, 287. Anal. Calcd for $C_{19}H_{20}N_2O_4S$: C 61.27; H 5.41; N 7.52. Found: C 61.18; H 5.47; N 7.43. $[\alpha]^{20}_D$ +120.3 (c 1.0, MeOH), 93% *ee*.

1.18. (+)-Methyl 4-(2-chlorophenyl)-5-cyano-6-methoxycarbonylethylsulfanyl-2-methyl-1,4-dihydropyridine-3-carboxylate (+)-2b

Compound (+)-**2b** was prepared in the same manner as (+)-**2a**. Yield 0.10 g (97%) of ester (+)-**2b** as oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H); 2.67-2.75 (m, 2H); 2.96-3.25 (m, 2H); 3.56 (s, 3H); 3.79 (s, 3H); 5.29 (s, 1H); 7.10–7.35 (m, 4H); 8.15 (s, 1H). IR (Nujol) 1714 (C=O); 2198 (C≡N); 3309 (NH) cm^{-1}. MS *m/z* 407 (M$^+$), 377, 343, 295, 289, 209. $[\alpha]^{20}_D$ +133.9 (c 1.0, MeOH), *ee* 92%.

1.19. (+)-Ethyl 5-cyano-6-methoxycarbonylethylsulfanyl-2-methyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine-3-carboxylate (+)-2c

Compound (+)-**2c** was prepared in the same manner as (+)-**2a**. Yield 0.10 g (95%) of ester **(+)-2c** as oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, J = 7.0 Hz, 3H); 2.39 (s, 3H); 2.58-2.68 (m, 2H); 2.94-3.10 (m, 2H); 3.71 (s, 3H); 3.75 (s, 3H); 3.76 (s, 3H); 3.77 (s, 3H); 3.99 (q, J = 7.0 Hz, 3H); 4.58 (s, 1H); 6.39 (s,

2H); 7.88 (s, 1H); IR (Nujol) 1684, 1712 (C=O); 2198 (C≡N); 3240 (NH) cm^{-1}. MS *m/z* 499 ($M+Na^+$), 447, 432, 309, 277, 223. $[\alpha]^{20}_D$ +134.9 (c 1.0, MeOH), 94% *ee*.

1.20. (-)-Methyl 5-cyano-2-methyl-6-methylsulfanyl-4-phenyl-1,4-dihydropyridine-3-carboxylate ((-)-5a)

A mixture of ester (-)-**2a** (0.37g, 1.0 mmol) and 3N $NaOH/H_2O$ (0.34 mL, 1.0 mmol) in MeOH (20 mL) was stirred for 30 min at room temperature. Then iodomethane (0.08 mL, 1.3 mmol) was added and the reaction mixture was stirred at 40 °C for 1 h. The precipitate was separated by filtration, washed with cold (-10 °C) MeOH (5 mL) and water (20 mL) to give 0.29 g (95%) of ester (-)-**5a** as white powder, mp 120-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.45 (s, 3H), 3.55 (s, 3H), 5.27 (s, 1H), 5.98 (s, 1H), 7.12-7.34 (m, 5H). IR (Nujol) 1685 (C=O), 2216 (C≡N), 3175 (NH) cm^{-1}. MS *m/z* 301 (M^+), 269, 223. Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C 63.98, H 5.37, N 9.33. Found: C 64.12, H 5.31, N 9.24. $[\alpha]^{20}_D$ -104.8 (c 1.0, MeOH), 93% *ee*.

1.21. (-)-Methyl 4-(2-chlorophenyl)-5-cyano-2-methyl-6-methylsulfanyl-1,4-dihydropyridine-3-carboxylate (-)-5b

Compound (-)-**5b** was prepared in the same manner as (-)-**5a**. Yield 0.32 g (94%) of ester (-)-**5b** as white powder, mp 120-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H); 2.45 (s, 3H), 3.55 (s, 3H), 5.27 (s, 1H), 5.98 (s, 1H), 7.12-7.34 (m, 4H). IR (Nujol) 1685 (C=O), 2216 (C≡N), 3225 (NH) cm^{-1}. MS *m/z* 335 (M^+), 303, 223. Anal. Calcd for $C_{16}H_{15}ClN_2O_2S$: C 57.40, H 4.52, N 8.37. Found: C 57.29, H 4.63, N 8.38. $[\alpha]^{20}_D$ -110.4 (c 1.0, MeOH), 92% *ee*.

1.22. (+)-Methyl 5-cyano-2-methyl-6-methylsulfanyl-4-phenyl-1,4-dihydropyridine-3-carboxylate ((+)-5a)

Compound (+)-**5a** was prepared in the same manner as (-)-**5a**. Yield 0.29 g (96%) of ester (+)-**5a** as white powder, mp 120-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.45 (s, 3H), 3.55 (s, 3H), 5.27 (s, 1H), 5.98 (s, 1H), 7.12-7.34 (m, 5H). IR (Nujol) 1685 (C=O), 2216 (C≡N), 3175 (NH) cm^{-1}. MS *m/z* 301 (M^+), 269, 223. Anal. Calcd for $C_{16}H_{16}N_2O_2S$: C 63.98, H 5.37, N 9.33. Found: C 64.20, H 5.30, N 9.19. $[\alpha]^{20}_D$ +92.6 (c 1.0, MeOH), 85% *ee*.

1.23. (+)-Methyl 4-(2-chlorophenyl)-5-cyano-2-methyl-6-methylsulfanyl-1,4-dihydropyridine-3-carboxylate ((+5)-b)

Compound (+)-**5b** was prepared in the same manner as (-)-**5a**. Yield 0.32 g (95%) of ester (+)-**5b** as white

powder, mp 120-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.45 (s, 3H), 3.55 (s, 3H), 5.27 (s, 1H), 5.98 (s, 1H), 7.12-7.34 (m, 4H). IR (Nujol) 1685 (C=O), 2216 (C≡N), 3225 (NH) cm^{-1}. MS *m/z* 335 (M^+), 303, 223. Anal. Calcd for $C_{16}H_{15}ClN_2O_2S$: C 57.40, H 4.52, N 8.37. Found: C 57.29, H 4.63, N 8.38. $[\alpha]^{20}_D$ +80.5 (c 1.0, MeOH), 92% *ee*.

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