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Efficient dynamic kinetic resolution method for the synthesis of enantiopure 6-hydroxy- and 6-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid

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ABSTRACT

Enantiomeric 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (*ee* >99%), useful in the synthesis of modulators of nuclear receptors, including liver X receptor and its analogue 6-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (*ee* >99%), a source of the above enantiomer was synthesized through *Candida antarctica* lipase B-catalysed dynamic kinetic hydrolysis of the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylic esters (±)-**4**·HCl and (±)-**5**. (*R*)-Selective hydrolysis in both organic solvents and an aqueous NH_4OAc buffer at pH 8.5 was observed and the amino acids were obtained in good chemical yields (>87%).

1. Introduction

Isoquinolines are an important class of compounds from both biological[1] and chemical[2] aspects. Some of them, for example 1-tetrahydroisoquinoline carboxylic acid can be used in the synthesis of promising matrix metalloproteinase inhibitors,[3] while 6,7-dimethoxy-1-tetrahydroisoquinoline carboxylic acid has been successfully applied in the synthesis of β-site amyloid precursor protein-cleaving enzyme inhibitors, which are useful for Alzheimer's disease.[4] Significant antitumor activity was reported for 8-methoxy-4,5-dihydropirrolo[2,1-*a*]isoquinolines with 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid as a key intermediate in its synthesis.[5] (*R*)-2-*tert*-Butyl-1-methyl-6-(3-chloro-2,6-difluorobenzyloxy)-3,4-dihydroisoquinoline-1,2(1*H*)-dicarboxylate, prepared from (*R*)-2-*tert*-butyl-1-methyl-6-hydroxy-3,4-dihydroisoquinoline-1,2(1*H*)-dicarboxylate, is useful as a modulator of nuclear receptors, including liver X receptor.[6]

Only a few enzymatic methods have been developed for the synthesis of valuable enantiopure isoquinolines,[7–10] such as chemoenzymatic kinetic resolution for the preparation of Crispine A,[7a] calicotomine[7b] and homocalicotomine[7c] enantiomers, the kinetic resolution for the preparation of enantiomeric 1-tetrahydroisoquinoline carboxylic acid,[8] the directed (*R*)- or (*S*)-selective dynamic kinetic enzymatic hydrolysis of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic esters,[9] and the Seaprose *S*-catalysed hydrolysis of methyl (±)-*N*-*tert*-Boc-6-hydroxy-3,4-dihydro-1*H*-isoquinoline-1-carboxylate.[10]

Over last few years, a large number of dynamic kinetic resolution methods for the preparation of enantiomeric compounds, important in terms of both biological and chemical aspects have been published and most of them reviewed.[11]

Herein our aim was to develop a dynamic kinetic resolution strategy for the synthesis of enantiopure 6-hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, with the appropriate (1*R*)-absolute configuration, essential for the biological activity of the above-mentioned (*R*)-2-*tert*-butyl-1-methyl-6-(3-chloro-2,6-difluorobenzyloxy)-3,4-dihydroisoquinoline-1,2(1*H*)-dicarboxylate. Our earlier extensive investigations of the CAL-B-catalysed dynamic kinetic resolution of 1-tetrahydroisoquinoline carboxylic acid[8] and 6,7-dimethoxy-1-tetrahydroisoquinoline carboxylic acid[9] prompted us to explore the possibility of the dynamic kinetic hydrolysis of (±)-**4** and (±)-**5** catalyzed by CAL-B.

2. Results and discussion

Racemic 6-methoxy-1-tetrahydroisoquinoline carboxylic acid ethyl ester (±)-**4** was synthesized via Bischler–Napieralski cyclisation of 3-methoxyphenethylamine hemioxalamide ethyl ester **2** (formed by heating 3-methoxyphenethylamine **1** and diethyl oxalate at reflux) and subsequent hydrogenation of compound **3** (Scheme 1).[12] Demethylation[13] of (±)-**4** followed by esterification furnished (±)-**5**.

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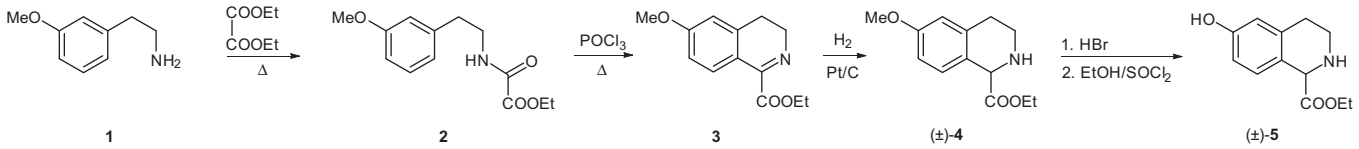
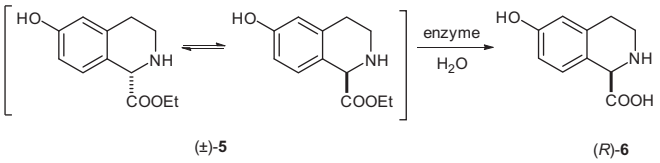


Scheme 1. Synthesis of (±)-**4** and (±)-**5**.

The resolution of (±)-**5** (Scheme 2) was first attempted in the presence of CAL-B (20 mg mL^{-1}) with H_2O (1 equiv) in toluene/MeCN (4:1) at 25 °C (Table 1, entry 1).



Scheme 2. Enzymatic dynamic kinetic resolution of (±)-**5**.

In an attempt to increase the reaction rate, preliminary experiments were performed with higher amounts of added H_2O (Table 1, entries 2 and 3). As the amount of H_2O was increased, only slightly faster reactions were observed, without a drop in ee_p (entries 2 and 3 vs entry 1).

Increasing the proportion of MeCN in the reaction medium, led to only slight differences in the reaction rates (entries 1 and 4–6). Next, iPr$_2$O/MeCN was used instead of toluene/MeCN (3:2) affording a marginally faster reaction (entry 7 vs 5). Nevertheless, because of toxicity reasons, iPr$_2$O/MeCN (3:2) was selected for further reactions.

When the CAL-B-catalysed hydrolysis of (±)-**5** was performed with 2 equiv of H_2O together with Pr$_2$NH (0.25 equiv) as a basic additive (base-catalysed racemisation of the unreacted amino ester enantiomer), a considerable enhancement in the reaction rate was observed (entry 8 vs entry 7) in accordance with our earlier observation.[9]

Hoping to further enhance the reaction rate and, at the same time, preserve the (*R*)-selectivity, the hydrolysis of (±)-**5** was performed in an aqueous NH_4OAc buffer at pH 8.5, at 25 °C. Much faster (*R*)-selective reactions, but lower *ee* values for the amino acid were observed, when using either CAL-B or α-chymotrypsine as the enzyme (Table 2, entries 1 and 6).

In order to improve the ee_p, the reaction was carried out at 3 °C (Table 2, entry 2) without much success (the ee_p did not change, the reaction became slower). An increase in reaction temperature to 45 °C resulted in a significant increase in reaction rate with the concomitant drop of the *ee* value (entry 3). A slight increase in the reaction rate was observed when using an increased amount of enzyme (Table 2, entries 4 and 5 vs entry 1).

As an alternative strategy to prepare (*R*)-**6** (Scheme 3), (±)-**4** was subjected to enzymatic resolution. When the CAL-B-catalysed hydrolysis of (±)-**4** was performed under the above optimized conditions for (±)-**5** [2 equiv of H_2O, 0.25 equiv of Pr$_2$NH, iPr$_2$O/MeCN (3:2), 25 °C], only traces of enantiomeric **7** were formed (*ee* of 91%, conversion of 35%, 2 days).

Hydrolysis of (±)-**4** in aqueous NH_4OAc buffer at pH 8.5, at 25 °C gave amino acid **7** (only traces) with an *ee* of 66% (90% conversion, 2 days). The major part of the starting amino ester underwent degradation (Table 2, entry 7).

In order to overcome the above-mentioned degradation, (±)-**4**·HCl rather than (±)-**4** was subjected to CAL-B-catalysed hydrolysis (Table 2, entry 8). Compound (*R*)-**7** was obtained as the sole product with an excellent *ee* value of >99%. This may be due to the relatively slow in situ liberation of basic amino ester from its hydrochloric salt followed by a relatively fast enzymatic hydrolysis.

The preparative-scale dynamic kinetic resolution of (±)-**4**·HCl[14] and (±)-**5**[15] was performed under the optimised conditions (footnotes of Table 3), and the results are summarized in Table 3. Demethylation of (*R*)-**7** with 48% aqueous HBr[16] resulted in the desired (*R*)-**6**·HBr with a significant decrease in *ee* (80%).

The analysed chromatograms indicated that the corresponding enantiomers of both compounds (±)-**4** and (±)-**5** reacted preferentially on CAL-B catalysis similar to ethyl 1,2,3,4-tetrahydroiso-

Table 1
Conversion and enantiomeric excess values (*ee*) of the hydrolysis of (±)-**5** in organic solvents[a]

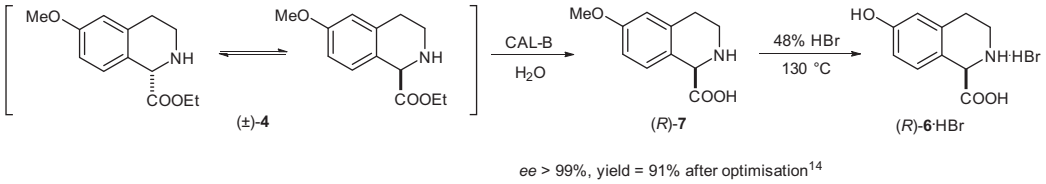
Entry	Solvent mixtures (*V*:*V*)	H_2O (equiv)	Reaction time (day)	Conversion (%)	ee_S[b] (%)	ee_P[c] (%)
1	Toluene:MeCN (4:1)	1	2	22	15	>99
			7	35	27	
2	Toluene:MeCN (4:1)	2	2	20	15	>99
			7	37	27	
3	Toluene:MeCN (4:1)	4	2	30	19	>99
			7	37	29	
4	Toluene:MeCN (7:3)	1	2	16	9	>99
			7	32	19	
5	Toluene:MeCN (3:2)	1	2	16	9	>99
			7	38	17	
6	Toluene:MeCN (1:1)	1	2	20	6	>99
			7	33	14	
7	iPr$_2$O:MeCN (3:2)	1	2	14	10	>99
			7	32	20	
8	iPr$_2$O:MeCN (3:2) Pr$_2$NH (0.25 equiv)	2	2	87	nd	>99

[a] 20 mg mL^{-1} CAL-B, at 25 °C.
[b] According to HPLC on a Chiralpak IA chiral column, (a 3,5-dimethylphenylcarbamate derivative of amylose, immobilized onto silica), eluent *n*-Hex/EtOH (80:20), Et$_2$NH (0.1%), flow: 1 mL min^{-1}, 25 °C, 232 nm {retention times [min], (*R*)-**5**: 7.62 and (*S*)-**5**: 23.09.
[c] According to HPLC by using a Chiralpak IA column (for *N*-Boc-protected derivative), eluent: *n*-Hex/*i*PA (90:10), TFA (0.1%), flow: 0.5 mL min^{-1}, 25 °C, 232 nm {retention times [min], (*R*)-**6**: 25.52 and (*S*)-**6**: 28.26}.

Table 2
Conversion and enantiomeric excess values (*ee*) of the hydrolysis in aqueous NH_4OAc buffer at pH 8.5

Entry	Substrate	Enzyme (mg mL^{-1})	Temperature (°C)	Time (h)	ee_S (%)	ee_P (%)
1[a]	(±)-**5**	CAL-B (30)	25	3	8[b]	80[c]
				24 (conv. >99%)	–	81[c]
2[a]	(±)-**5**	CAL-B (30)	3	3	24[b]	–
				168 (conv. >99%)	–	81[c]
3[a]	(±)-**5**	CAL-B (30)	45	3	5[b]	–
				24 (conv. >99%)	–	67[c]
4[a]	(±)-**5**	CAL-B (50)	25	3	14[b]	76[c]
				18 (conv. >99%)	–	82[c]
5[a]	(±)-**5**	CAL-B (90)	25	3	19[b]	78[c]
				14 (conv. >99%)	–	81[c]
6[a]	(±)-**5**	α-Chymotrypsine (10)	25	3	–	–
				50 (conv. >99%)	–	84[c]
7[a]	(±)-**4**	CAL-B (30)	25	48 (conv. = 90%)	27[d]	66[e,f]
8[g]	(±)-**4**·HCl	CAL-B (30)	25	3 (conv. = 89%)	5[d]	>99%[e]

[a] Racemic amino ester in aqueous NH_4OAc buffer at pH 8.5.
[b] According to HPLC (footnote of Table 1).
[c] According to HPLC (footnote of Table 1).
[d] According to HPLC on a Chiralpak IA chiral column, eluent: *n*-Hex/*i*PA (90:10), DEA (0.1%), flow: 0.5 mL min^{-1}, 25 °C, 232 nm {retention times [min], (*R*)-**4**: 26.6 and (*S*)-**4**: 28.17}.
[e] According to HPLC by using a Chiralpak IA column (for *N*-Boc-protected derivative), eluent: *n*-Hex/*i*PA (90:10), TFA (0,1%), flow: 0.5 mL min^{-1}, 25 °C, 232 nm {retention times [min], (*R*)-**7**: 19.37 and (*S*)-**7**: 21.29}.
[f] Only trace amounts of amino acid.
[g] (±)-**4**·HCl in aqueous NH_4OAc buffer at pH 8.5.



Scheme 3. Preparation of (*R*)-**6**·HBr through enzymatic dynamic kinetic resolution of (±)-**4**.

Table 3
Preparative-scale hydrolysis of (±)-**4**·HCl[a] and (±)-**5**[b]

Substrate	Time (h)	Product amino acid			
		Yield (%)	Isomer	*ee* (%)	$[\alpha]_D^{25}$ H_2O
(±)-**4**·HCl	3	91	(*R*)-**7**	>99[c]	−58 (*c* 0.2)
(±)-**5**	48	87	(*R*)-**6**	>99[d]	−51 (*c* 0.3)

[a] 100 mg (0.37 mmol) substrate, 25 mL aqueous NH_4OAc buffer at pH 8.5 (NH_4OH), 750 mg CAL-B (30 mg mL^{-1}), 25 °C.
[b] 200 mg (0.9 mmol) substrate, 2 equiv of H_2O, 0.25 equiv Pr_2NH, 25 mL iPr_2O/MeCN (3:2), 25 °C, 600 mg CAL-B (20 mg mL^{-1}), 25 °C.
[c] According to HPLC (footnote of Table 1).
[d] According to HPLC (footnote of Table 2).

quinoline carboxylate[8] and ethyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline carboxylate.[9] Thus the enantiomer hydrolysing with higher reactivity has the (*R*)-absolute configuration; consequently, the (*S*)-configuration was assigned to the racemizing enantiomer (*S*)-**4** and (*S*)-**5**.

3. Conclusion

In conclusion, an efficient dynamic kinetic resolution technique was carried out for the preparation of (1*R*)-6-hydroxy- and (1*R*)-6-methoxy-subsituted 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (*ee* >99%, chemical yields >87%), which are useful in the synthesis of modulators of nuclear receptors. The (*R*)-selective hydrolysis of the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylates took place with *Candida antarctica* lipase B as the catalyst and the reactions were performed in either organic solvents or aqueous NH_4OAc buffer at pH 8.5. It is important to note that the present dynamic kinetic resolution using the hydrochloric salt as starting racemate might provide an extra possibility for the resolution of such racemates, which are stable only as salts.

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14. (*R*)-Selective preparative-scale dynamic kinetic resolution of (±)-**4**·HCl: Compound (±)-**4**·HCl (100 mg, 0.37 mmol) was dissolved in an aqueous solution of NH_4OAc (0.1 M, 25 mL), after which CAL-B (750 mg, 30 mg mL^{-1}) was added. The pH was set to 8.5 (with 25% aqueous NH_4OH at the start of the reaction). The mixture was shaken at 25 °C for 3 h to attain a conversion of >99%. The enzyme was filtered off and washed with warm H_2O. The solvent and NH_4OAc were evaporated under vacuum, and after a wash of the residue with Me_2CO (*R*)-**7** was isolated (69 mg, 91% yield). M.p. 247–250 °C, (recrystallised from H_2O/Me_2CO), $[\alpha]_D^{25} = -58$ (*c* 0.2, H_2O), *ee* > 99%. ^1H NMR (400 MHz, D_2O): δ = 3.09–3.12 (m, 2H, H-4), 3.39–3.70 (m, 2H, H-3), 3.86 (s, 3H, CH_3), 4.94 (s, 1H, H-1), 6.82–7.55 (m, 3H, Ph) ppm. Elemental analysis for $C_{11}H_{13}NO_3$ (207.09): calcd. C 63.76, H 6.32, N 6.76; found C 63.74, H 6.20, N 6.79.
15. (*R*)-Selective preparative-scale dynamic kinetic resolution of (±)-**5**: Compound (±)-**5** (200 mg, 0.9 mmol), dipropylamine (30.84 μL, 0.23 mmol), water (32.46 μL, 1.8 mmol) and CAL-B (600 mg, 20 mg mL^{-1}) were added to a mixture of iPr_2O:MeCN (3:2) (30 mL). The mixture was shaken at 25 °C for 2 days, then the enzyme was filtered off at a conversion of 87%. A wash with iPr_2O and then with H_2O, followed by evaporation of the aqueous phase resulted in amino acid (*R*)-**6** as a yellowish oil (151 mg, 87% yield), $[\alpha]_D^{25} = -51$ (*c* 0.3, H_2O), *ee* >99%. ^1H NMR for (*R*)-**6**·HBr (400 MHz, D_2O): δ = 3.04–3.20 (t, *J* = 6.5 Hz, 2H, H-4), 3.51–3.76 (m, 2H, H-3), 5.20 (s, 1H, H-1), 6.82–7.00 (m, 2H, Ph) 7.47–7.57 (d, *J* = 8.4 Hz, 1H, Ph) ppm. Elemental analysis for $C_{10}H_{12}BrNO_3$ (274.11): calcd. C 43.82, H 4.41, N 5.11; found C 43.66, H 4.33, N 5.00.
16. Demethylation of (*R*)-**7**: Compound (*R*)-**7** (20 mg, 0.09 mmol, *ee* = 98%) was dissolved in 48% HBr (5 ml) and kept at reflux temperature for 4 h. The solvent was then evaporated and the product was recrystallized from EtOH and Et_2O to afford beige crystals of (*R*)-**6**·HBr (18 mg, 58% yield), M.p. 257-258 °C, $[\alpha]_D^{25} = -47$ (*c* 0.1, H_2O), *ee* = 80%.
The ^1H NMR (400 MHz, D_2O) data were similar to those given in the literature.[14] Elemental analysis calcd. for $C_{10}H_{12}BrNO_3$: C 43.82, H 4.41, N 5.11; found C 43.78, H 4.60, N 5.11.