Tetrahedron: *Asymmetry* 28 (2017) 1829–1833

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Efficient lipase-catalysed route for the kinetic resolution of salsolidine and its ß-carboline analogue

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ARTICLE INFO

Article history:
Received 19 October 2017
Accepted 24 October 2017
Available online 10 November 2017

ABSTRACT

Racemic 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **1** and 1-methyl-1,2,3,4-tetrahydro-ß-carboline **3** were resolved through lipase-catalysed asymmetric acylation on the secondary amino group. High enantioselectivities (*E* >200) were observed when the acylation of racemic **1** was performed with phenyl allyl carbonate in the presence of *Candida rugosa* lipase in toluene at 40 °C or with *Candida antarctica* lipase B in *tert*-butyl methyl ether at 50 °C. Excellent enantioselectivity (*E* >200) characterised the CAL-B-catalysed acylation of racemic **3** with phenyl allyl carbonate in the presence of triethylamine in *tert*-butyl methyl ether at 50 °C. The product (*R*)-carbamates (*ee* >97%) were hydrolysed into the corresponding (*R*)-enantiomers of the free amines **1** and **3** (*ee* = 99%) with the use of $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst.

1. Introduction

Interest in the research of compounds containing the 1-substituted 1,2,3,4-tetrahydroisoquinoline ring system has recently come into view, since compounds bearing this skeleton exert major biological activities. Several derivatives possess a common nucleus of synthetic structures, while other compounds are extracted from natural sources. All of them are associated with important pharmacological effects. The naturally occurring (*S*)-norcoclaurine [(1*S*)-1-(4-hydroxybenzyl)-1,2,3,4-tetrahydro-6,7-isochinolindiol] is an intermediate in the synthesis of morphine, papaverine or the antibacterial berberine.[1] Racemic norcoclaurine has α- and ß-adrenoreceptor activity.[2] Solifenacin [(1*S*,3′*R*)-3′quinuclidinyl-1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate] containing a 1-phenyl-substituted tetrahydroisoquinoline core is an example of synthetic compounds. It shows urinary antispasmodic effect.[3] Both enantiomers of 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **1** (salsolidine) are naturally occurring compounds.[4] The (*R*)-enantiomer was isolated from *Genista pungens*,[4] while the (*S*)-enantiomer was found in *Salsola richteri*.[4] Many pharmacological properties have been described to salsolidine; *e.g.*, it inhibits the uptake of 5-hydroxytryptamine by human blood platelets.[4] The (*R*)-enantiomer has a monoamine oxidase A (MAO A) inhibitoring effect.[4] On the other hand, as a structural feature of a trimethoprim analogue, it acts as a dihydrofolate reductase inhibitor.[4] The pharmaceutically valuable 1-substituted 1,2,3,4-tetrahydro-ß-carboline skeleton is also a common building block of several alkaloids, including the naturally occurring reserpine, which shows antitumor activity, as well as antihypertensive and neuroprotective effects.[5] Synthetic 1-substituted *N*-acylated tetrahydro-ß-carbolines have inhibitory activity against the Breast Cancer Resistance Protein (ABCG2).[6] The (*S*)-enantiomer of salsolidine analogue 1-methyl-1,2,3,4-tetrahydro-ß-carboline **3** (eleagnine) was isolated from *Eleagnus angustifolia* and *Petalostyles labicheoides*.[7] The racemic form can bind to the $GABA_A$ receptors in the benzodiazepine binding site, but it has an inverse agonist effect.[8]

It is not surprising, therefore, that a large number of synthetic routes have been developed for the preparation of **1** and **3**, in particular, in enantiomeric forms.[7,9–13] As an example, enantiomeric **1** was synthesized by Ding and et al. through enantioselective acylation of the racemic mixture in a batch process.[14]

In this work, our aim was to devise a new enzymatic strategy for the preparation of enantiomeric **1** and **3**, through lipase-catalysed kinetic resolution (Scheme 1). In addition to the batch reactions, we planned to examine the possibilities for their enzymatic reactions in a continuous-flow system. The use of this novel method has clear advantages, such as short reaction times, rapid heating and pressure screening.[15] In the literature, there are various examples using this innovative technique for resolution. For example, the asymmetric acylation of 1-phenylethylamine[16,17] and an imidazole derivative[18] as well as the esterification of flurbiprofen[19] have been reported.

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https://doi.org/10.1016/j.tetasy.2017.10.019
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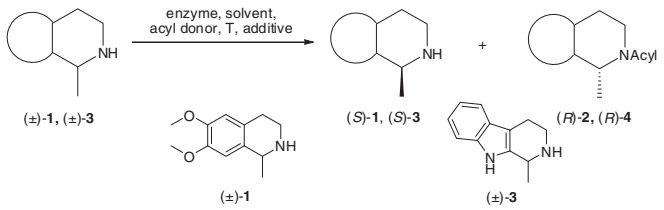


Scheme 1. Kinetic resolution of (±)-**1** and (±)-**3** through lipase-catalysed *N*-acylation on the secondary amino group.

2. Results and discussion

2.1. Synthesis of (±)-1 and (±)-3

1-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (±)-**1** was prepared from 3,4-dimethoxyphenylethylamine and acetic anhydride through Bischler–Napieralski cyclization followed by reduction, while racemic 1-methyl-1,2,3,4-tetrahydro-ß-carboline (±)-**3** was synthesized utilizing the Pictet–Spengler reaction via a microwave-assisted procedure according to known literature methods.[9,11]

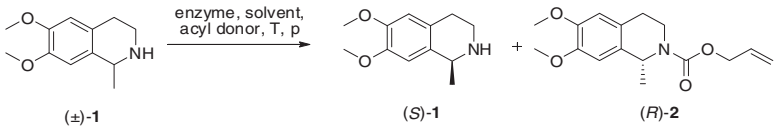
2.2. Enzymatic resolution of (±)-1 and (±)-3

Ding et al. reported the asymmetric *N*-acylation of racemic **1** ($E > 200$, conv. = 50% in 72 h, yield > 46%) by using CAL-A (*Candida antarctica* lipase A), 3-methoxyphenyl allyl carbonate in toluene at 40 °C.[14] The dynamic kinetic resolution of (±)-**1** was also described by Page *et al.* using a combination of catalysts AY (*Candida rugosa* lipase) and pentamethylcyclopentadienyliridium(III) iodide dimer in the presence of 3-methoxyphenyl propyl carbonate at 40 °C (conv. = 90% in 23 h, *ee* = 96%, yield = 82%).[20]

We started the resolution of (±)-**1** by an enzyme screening. First, the reaction was performed in batch with phenyl allyl carbonate in toluene at 40 °C (Scheme 2, Table 1, entries 1–4). Low enantioselectivity was observed with CAL-A ($E = 9$, entry 1) and with PS-IM (*Burkholderia cepacia* lipase) ($E = 2$, entry 2). In contrast, an improved $E = 46$ was found with CAL-B (*Candida antarctica* lipase B) 49% conversion in 4 days (entry 4). Lipase AY was the best catalyst with a conversion of 50% in 72 h and an excellent E (>200) (entry 3). Since the tested CAL-B was purchased as an immobilized enzyme (from Sigma) and also in view of its potential use in continuous-flow system, CAL-B was chosen for further optimization.

Next, the CAL-B-catalysed reaction was performed at 50 and then 60 °C (Table 1, entries 5 and 6). As the temperature was increased, the reaction rate increased considerably (entries 4–6). However, the best combination of reaction rate and enantioselectivity was found at 50 °C (entry 5). When toluene was replaced with *t*-BuOMe, a much faster reaction with excellent E (>200) was observed (entry 7).

Having the optimized conditions in the batch process (CAL-B, phenyl allyl carbonate, *t*-BuOMe, 50 °C, 1 bar), we decided to perform a reaction under these conditions in a continuous-flow reactor (an *H*-Cube in 'no H_2 mode'). A 70-mm-long heat- and pressure-resistant stainless-steel CatCart was filled with CAL-B. Unfortunately, only 20% conversion was reached after a cycle, although an excellent E (>200) was observed (Table 2, entry 1).



Scheme 2. Kinetic resolution of (±)-**1** through enantioselective *N*-acylation.

Table 1
N-Acylation of (±)-**1** in batch[a]

Entry	Enzyme	T (°C)	Solvent	Reaction time (h)	Conv. (%)	ee_s[b] (%)	ee_p[c] (%)	E
1	CAL-A	40	Toluene	96	42	50	68	9
2	PS-IM	40	Toluene	96	3	13	25	2
3	AY	40	Toluene	72	50	99	98	>200
4	CAL-B	40	Toluene	96	49	85	89	46
5	CAL-B	50	Toluene	48	50	96	95	154
6	CAL-B	60	Toluene	48	51	96	92	94
7	CAL-B	50	*t*-BuOMe	2.5	50	99	97	>200

[a] 0.025 M (±)-**1**, phenyl allyl carbonate.
[b] According to HPLC after a derivatisation with Ac_2O.
[c] According to HPLC.

Table 2
Effect of pressure and temperature on the acylation of (±)-**1** with phenyl allyl carbonate in a continuous-flow system[a]

Entry	p (bar)	T (°C)	Conv. (%)	ee_s[b] (%)	ee_p[c] (%)	E
1	1	50	20	24	99	>200
2	30	50	3	3	99	>200
3	60	50	9	10	99	>200
4	1	60	21	26	99	>200
5	1	70	25	33	99	>200
6	1	80	7	7	99	>200

[a] 0.025 M (±)-**1**, 244 mg CAL-B (70 mm CatCart); *t*-BuOMe, 0.1 mL min^{-1}.
[b] According to HPLC after a derivatisation with Ac_2O.
[c] According to HPLC.