Journal of Molecular Catalysis B: Enzymatic 114 (2015) 77–85

Contents lists available at ScienceDirect

Journal of Molecular Catalysis B: Enzymatic

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

# Substrate-engineering approach to the stereoselective chemo-multienzymatic cascade synthesis of *Nicotiana tabacum* lactone

Elisabetta Brenna [a], Francesco G. Gatti [a,*], Daniela Monti [b], Fabio Parmeggiani [a], Alessandro Sacchetti [a], Jessica Valoti [a]

[a] *Dipartimento di Chimica, Materiali e Ingegneria Chimica "G. Natta", Politecnico di Milano, Via Mancinelli 7, 20131 Milano, Italy*[1]
[b] *Istituto di Chimica del Riconoscimento Molecolare, C.N.R., Via Mario Bianco 9, 20131 Milano, Italy*

ARTICLE INFO

*Article history:*
Available online 31 December 2014

*Keywords:*
Multienzymatic cascade reaction
Ene-reductases
Alcohol dehydrogenases
Stereoselective
Lactones
Fragrances

ABSTRACT

A multistep stereoselective synthesis of each stereoisomer of *Nicotiana tabacum* lactone is reported. A two steps reduction of an $\alpha,\beta$-unsaturated ketoester gives the corresponding key intermediate ethyl 4-hydroxy-3-methylpentanoate. This one pot synthesis was catalyzed by a multienzymatic system comprising an ene-reductase (ER) and an alcohol dehydrogenase (ADH). This cascade process was highly chemoselective and stereoselective. In the last step, treatment of the hydroxyester with trifluoroacetic acid gives the $\gamma$-lactone in a very high overall yield (up to 78%) and with an excellent stereoselectivity (*de* > 94%, *ee* > 98%). The access to each stereoisomer was achieved by a substrate engineering approach and by selecting a Prelog or an *anti*-Prelog ADH. Furthermore, computational studies of the binding modes of the substrates into the catalytic site of ene-reductases have been carried out, giving an insight of the observed enantiodivergence.

© 2014 Elsevier B.V. All rights reserved.

## 1. Introduction

It is well established that the odor perception of chiral molecules is strictly related to their stereochemistry [1], this feature has an enormous impact in the field of fragrances, where quite often an enantiomer exhibits a completely different scent profile and/or odor threshold with respect to its antipode, and the same is true for odorous diastereoisomers [2]. Among all naturally occurring fragrances, $\gamma$-lactones are doubtlessly one of the most important classes of compounds, since they exhibit unique odoriferous properties [3]. For example, the 4,5-dimethyl substituted $\gamma$-lactone **1** is present into the sun-cured leaves of *Nicotiana tabacum* and it confers a typical and pleasant fruity character to the latter [4]. However, even in this case, either the odor profile and threshold of each stereoisomer are linked to the absolute configuration [5] (Fig. 1).

So far, several chemical methods for the stereoselective preparation of **1** have been reported in the literature (Scheme 1). A first approach was based on liquid chromatography (LC) separation of the four possible diastereoisomers of diester **2** (obtained from racemic **1** and (*R*)-2-phenylpropionyl chloride) [5]. Another strategy was based on the chiral pool, starting from (*S*)-glutamic acid **3**, and involving the Michael addition of lithium dimethylcuprate to an $\alpha,\beta$-unsaturated lactone intermediate [6]. A similar route was based on the addition of $Me_2CuLi$ to the chiral ester **4** [7]. Finally, an alternative synthesis relied on the iodolactonisation of **5** [8].

However, all these synthetic routes are characterized by a high number of steps (>5), low overall yields (<20%), modest up to good selectivity, complex purification processes, toxic or hazardous reagents and solvents, and impractical reaction conditions, which, altogether, make these syntheses neither "green" nor atom economic. In addition, none of them is feasible for the stereoselective preparation of each stereoisomer of **1**.

Anyway, a careful retrosynthetic analysis (Scheme 2) shows clearly that a shorter and more convenient route to **1** might be based on a stereospecific reduction of the C=C double bond of an $\alpha,\beta$-unsaturated ketoester such as **6a** or **6b**, followed by a stereoselective reduction of the carbonyl group of the corresponding saturated ketoester **7** to give access to the hydroxyester **8** (in principle the reversed order of the two steps could be equally possible); finally, the cyclization of **8** would afford the lactone.

It is clear that the two reductive steps are crucial for the definition of absolute configuration of **1**, while the ring closure of the key intermediate **8** should not give particular problems. However, only

* Corresponding author.
*E-mail address:* francesco.gatti@polimi.it (F.G. Gatti).
[1] Tel.: +39 02 2399 3070; fax: +39 02 2399 3180.

http://dx.doi.org/10.1016/j.molcatb.2014.12.011
1381-1177/© 2014 Elsevier B.V. All rights reserved.

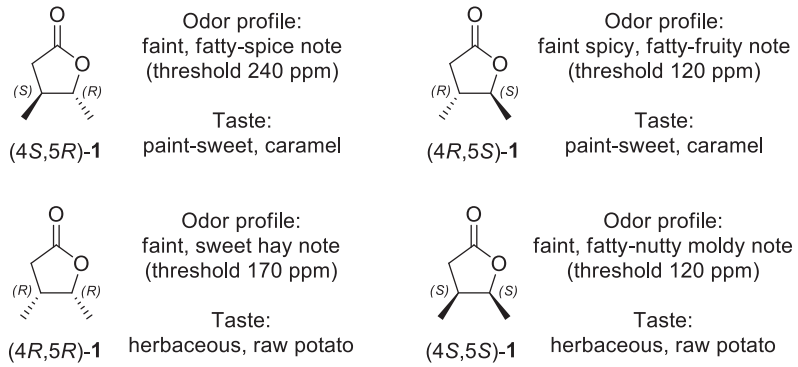
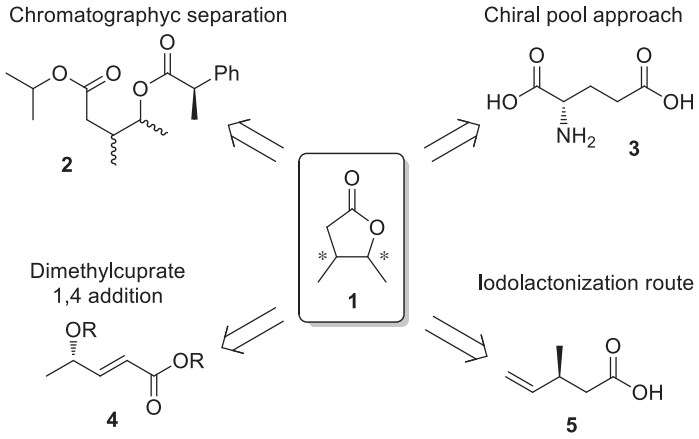



**Fig. 1.** Structure and sensorial properties of 4,5-dimethyl-$\gamma$-butyrolactones **1**.




**Scheme 1.** Synthetic approaches to lactone **1**.

whole-cell microorganisms [9] offer the unique feature to catalyze in a one-pot process the reduction of both the C=C double bond and the carbonyl group of unsaturated ketones, usually with a high stereoselectivity, but involving a troublesome workup. Specifically, the ene-reductase enzymes (ERs) catalyze the reduction of alkenes conjugated to electron-withdrawing groups (*e.g.* carbonyl groups of aldehydes and ketones or nitro groups) [10]. These biocatalysts are typically stereospecific, since *E* and *Z* isomers give the opposite enantiomers, however the stereoselectivity can be switched also by selecting regioisomers such as the olefin **10** (this approach is called "substrate engineering"). Whereas, the alcohol dehydrogenase enzymes (ADHs) reduce the carbonyl group of aldehydes or ketones [11], in this case the presence in nature of several enantiocomplementary ADHs allows an easier control of stereoselectivity.

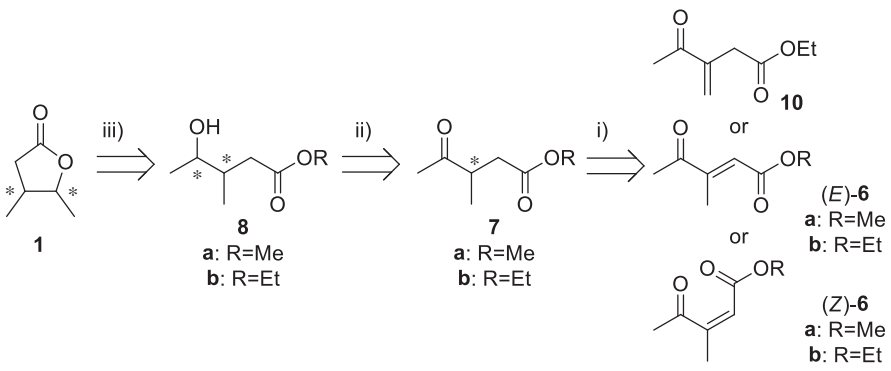
Crout et al. have tested the bioreduction of **6b** with several yeasts from different natural sources: even in the presence of a significant biodiversity, most of screened microorganisms gave always the same diastereoisomer of alcohol **8b**, *i.e.* (3*S*,4*S*)-**8b**, with a low up to good diastereoselectivity. The yields were low, because a significant portion of starting material was consumed by the ADH affording the corresponding allylic alcohol as side product [12]; therefore the ADHs of these microorganisms exhibit a low chemoselectivity.

However, concerning this problem and other typical drawbacks of whole-cell based transformations, it has been shown that the combination of an overexpressed ER with an ADH gives substantial improvements in terms of productivity, yield and in certain cases of stereoselectivity as well [13a–c]. Moreover, the availability of several pro-(*R*) or pro-(*S*) ADHs gives the possibility to prepare more stereoisomers, usually with a very high diastereoselectivity [13c,14].

Within our ongoing research program on the stereoselective synthesis of chiral fragrances by means of biocatalytic methods [15], we have been interested in the preparation of each stereoisomer of *N. tabacum* lactone **1** by coupling an ER with an ADH in a cascade system.

Indeed, the choice of the starting material among the alkenes (*E*)-**6** and (*Z*)-**6** could give access to the (*R*) or (*S*) enantiomer of the saturated ketoester **7**, whereas, in the second step, the choice of a pro-(*S*) or pro-(*R*) ADH would determine the absolute configuration of the second stereogenic center in **8**.

While our investigations were still in progress, the very same strategy was published by Pietruszka et al., in a very systematic and successful study [14b], with a one-pot three-step approach leading to **1**, thus proving the effectiveness of this strategy. As an update of their findings, in the following we report on: (i) the results we obtained by applying the same strategy with a different set of




**Scheme 2.** Retrosynthetic analysis of **1**: (i) substrate engineering approach for the enantioselective reduction of the C=C double bond; (ii) asymmetric reduction of the carbonyl group and (iii) ring closure.

Download English Version:

https://daneshyari.com/en/article/69669

Download Persian Version:

https://daneshyari.com/article/69669

Daneshyari.com