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Short and efficient chemoenzymatic synthesis of goniothalamin

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Abstract—A high-yielding three-step synthesis of goniothalamin involving an enzymatic kinetic resolution in the presence of vinyl acrylate followed by ring-closing metathesis is discussed.

Enzyme-catalyzed enantioselective acetylation of racemates in organic solvents is well recognized as a useful procedure for preparing chiral building blocks for organic synthesis.[1] Lipases (EC 3.1.1.3) are the most widely employed enzymes because they are cheap and readily available from many different sources, and in addition they possess high enantioselectivity for a broad range of substrates and high stability in organic solvents. One of the most popular lipases used in organic synthesis is lipase PS (*Pseudomonas cepacia*) from Amano Pharmaceutical Co. Ltd., and in particular the lipase immobilized on ceramic particles (PS-C Amano II).[2–6] The enzymatic kinetic resolution of alcohols is a well-studied reaction. However, such methods limit the yield of the pure enantiomer to 50%. The disadvantages of kinetic resolution can largely be avoided by employing a so-called dynamic kinetic resolution.[1,4–8]

A number of compounds possessing a 6-substituted 5,6-dihydro-α-pyrone ring system (Fig. 1) such as goniothalamin,[9] argentilactone,[10] goniodiol,[11] goniotriol,[12] callystatin,[13] fostriecin[14] have been isolated from plants and marine organisms. These natural products have been the targets of several syntheses due to their interesting biological activities.

Our group is interested in the stereoselective synthesis of oxygenated heterocyclic rings such as tetrahydrofurans, tetrahydropyrans, and lactones.[15] In this communication we report preliminary results on the chemoenzymatic synthesis of 6-substituted 5,6-dihydro-α-pyrone derivatives. In order to develop our approach we have chosen goniothalamin as the target compound. Goniothalamin shows antiprogestagenic and antiestrogenic effects[16] in vivo without toxic effects.[17] Moreover, the antitumor activity of goniothalamin has been evaluated in vitro showing antiproliferative effects, like tamoxifen, on both MCF-7 and T47-D cell lines.[16]

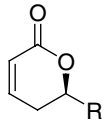

Figure 1.

As starting material we employed the racemic allylic alcohol **1** readily obtained from cinnamaldehyde and allylmagnesium bromide. As resolving agent for the transesterification reaction we chose vinyl acrylate. To the best of our knowledge vinyl acrylate has never been used as a resolving agent. In this way, following the empirical 'Kazlauskas rule',[1] we can directly obtain the ester **3** with the correct configuration. The resolution was carried out with PS-C Amano II (1 equiv w/w) (see Table 1).

In the first instance we performed the reaction with an excess of vinyl acrylate (5 equiv). The reactions gave nearly quantitative yields and good to high ee, particularly the reaction carried out in CH_2Cl_2. Moreover, good results were obtained with 3 or 1.5 equiv of vinyl acrylate. The control experiment without the enzyme proved that the nonenzymatic reaction was extremely

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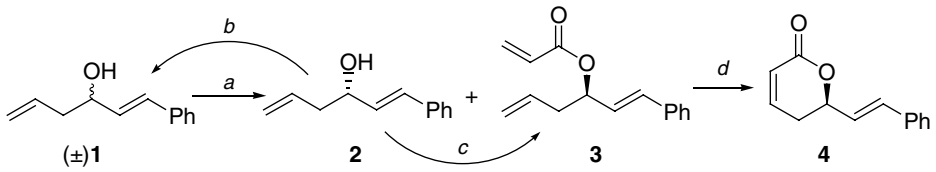
Table 1. Lipase-catalyzed transesterification of **1**[a]

Entry	Solvent	Vinyl acrylate (equiv)	Yield **2** (%)[b]	Ee **2** (%)	Yield **3** (%)[b]	Ee **3** (%)	E[c]
1	THF	5	50	92	49	96	162
2	CH_2Cl_2	5	48	>99	47	98	525
3	Toluene	5	49	>99	50	92	126
4	Toluene	3	48	>99	48	96	259
5	Toluene	1.5	50	92	49	94	106
6	CH_2Cl_2	1.5	48	98	41	94	149

[a] Reactions were carried out at 25 °C in 1 M solution for 24 h.
[b] Isolated yield.
[c] Calculated from $E = \ln\{[ee_P(1 - ee_S)]/(ee_P + ee_S)\}/\ln\{[ee_P(1 + ee_S)]/(ee_P + ee_S)\}$.



Scheme 1. Reagents and conditions: (a) PS-C Amano II, solvent, vinyl acrylate, 25 °C, 24 h; (b) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), diethyl ether, then CH_3OH, $NaBH_4$, rt; (c) PPh_3, DEAD, acrylic acid, toluene, 0 °C–rt 21%, 20% ee; (d) $(Pcy_3)_2Cl_2Ru{=}CHPh$, $Ti(OiPr)_4$, CH_2Cl_2, 18 h, reflux.

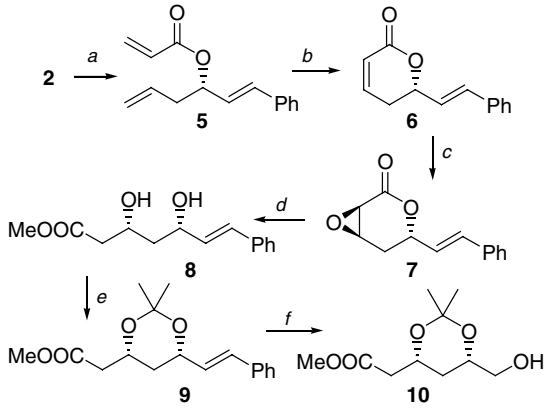
slow. The ee was determined by formation of the corresponding acetyl-(*R*)-mandelates and ^1H NMR analysis. Olefin metathesis of **3** with commercially available Grubbs' catalyst (10 mol%) in the presence of $Ti(OiPr)_4$ (0.3 equiv) in refluxing CH_2Cl_2 overnight gave goniothalamin **4** in 85% yield (Scheme 1).

In order to improve the yield of the resolution step, a dynamic kinetic resolution was carried out. Recently, (*p*-cymene)ruthenium(II) complexes have been successfully employed for dynamic kinetic resolution reactions of allylic alcohols in the presence of *p*-chlorophenyl acetate.[4] With our substrate the reaction was unsuccessful. Quantitative racemization of **2** was achieved in one pot by treatment with DDQ in diethyl ether, then adding methanol and $NaBH_4$.

Alcohol **2** was also treated under Mitsunobu reaction conditions using acrylic acid. However, both yield (21%) and ee (20%) of ester **3** were low.

Alcohol **2** was converted into *ent*-goniothalamin **6**, both in order to test its activity and because it is a convenient material for the synthesis of the interesting building block **10**. Moreover, the latter compound is the open form of the δ-lactone unit of mevinolin, a potent and selective HMG-CoA reductase inhibitor[18] and a key intermediate for the synthesis of several mevinolic acid analogs (Scheme 2).[19]

In conclusion a short synthesis of goniothalamin was realized starting from inexpensive cinnamaldehyde. The key steps were the kinetic resolution in the presence of vinyl acrylate followed by RCM. Enzymatic kinetic resolution of allylic alcohols with vinyl acrylate could be a useful shortcut for the synthesis of α,β-unsaturated δ-lactones.



Scheme 2. Reagents and conditions: (a) $CH_2{=}CHCOCl$, Et_3N, DMAP (cat.), 0 °C, 90%; (b) $(Pcy_3)_2Cl_2Ru{=}CHPh$, $Ti(OiPr)_4$, CH_2Cl_2, 18 h, reflux, 80%; (c) NaOH(aq), H_2O_2, MeOH, rt, 75%; (d) $(PhSe)_2$, $NaBH_4$, MeOH, rt, 88%; (e) CH_3COCH_3, PTSA, $CuSO_4$, rt, 85%; (f) O_3, MeOH, −78 °C, $NaBH_4$, rt, 75%.

Acknowledgements

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