A Chemoenzymatic Approach to C1-C6 Fragment of (–)-Putaminoxin

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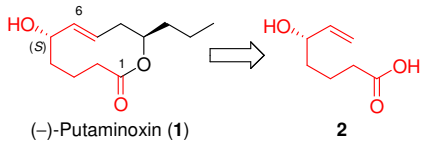
INTRODUCTION

(–)-Putaminoxin (**1**) is a decalactone isolated from the culture filtrates of the fungus *Phoma putaminum*, a leaf necrosis agent of the weed *Erigeron annuus*.[1,2] These and other structure related compounds showed significant phytotoxic activity against several plants.[1,3] Herein we describe our efforts to the synthesis of the C1-C6 fragment of the title compound [(*S*)-5-hydroxyhept-6-enoic acid (**2**)], using a kinetic enzymatic resolution approach as key step.



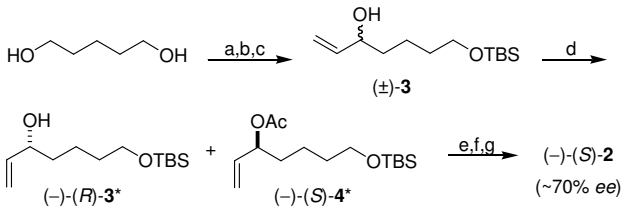
(–)-Putaminoxin (**1**) **2**

Figure 1. (–)-Putaminoxin (**1**).

RESULTS AND DISCUSSION

As previously described,[4] the racemic allylic alcohol (±)-**3** could be prepared in 3 steps from commercial available 1,5-pentanediol (Scheme 1).

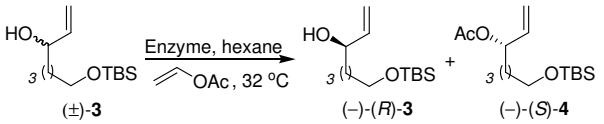
Scheme 1



Reagents e conditions: (a) *i:* NaH, THF, r.t., 45 min; *ii:* TBSCl, r.t., 45 min (70%); (b) 2.5 eq. IBX, *tert*-butanol, 80 °C, 1 h (72%); (c) *i:* CH_2=CHMgBr, THF, 0 °C, 80 min; *ii:* NH_4Cl aq. (72%); (d) CALB, vinyl acetate, hexanes, 32 °C, 15 h, (–)-(*R*)-**3** (*ee* = 98%) e (–)-(*S*)-**4** (*ee* = 94%) (best condition; see Table 1); (e) chromatographic separation of (–)-(*S*)-**4**; (f) TBAF, THF, r.t., 4 h; (g) 0.4 eq. 2-iodobenzoic acid, 2.6 eq Oxone®, MeCN/H_2O (2:1), r.t., 6 h (yield not optimized).*The absolute configuration of the products were giving based on the enantioselectivity of the enzyme, but it is under investigation.

The kinetic enzymatic resolution of (±)-**3** was performed using the lipases CALB, *P. cepacia* [immobilized on ceramic (Amano PS-CII) and diatomite (Amano PS-DI)] or *P. fluorescens* (Amano AK) as biocatalysts (Table 1). The time of the KR is a critical point to obtain the products with good *ee*, probably because the ratio of the reaction is similar to the two enantiomers of **3**.

Table 1. Kinetic Resolution (KR) of (±)-**3**.



(±)-**3** (–)-(*R*)-**3** (–)-(*S*)-**4**

Entry	Lipase	Time	(–)-(*R*)-3 (% *ee*)*	(–)-(*S*)-4 (% *ee*)*
1[4]	CALB	24 h	99	91
2		15 h	98	94
3	*P. cepacia* Amano PS CII	20 h	97	65
4		15 h	97	78
5	*P. cepacia* Amano PS-DI	20 h	>99	71
6		15 h	99	79
7	*P. cepacia* Amano AK	20 h	22	27

**ee* determined by chiral GC: β-cyclodextrin colunn, oven: 100-180 °C, rate: 2°C/min.

From the results showed in Table 1 is noteworthy that lower reactional times led to high *ee* of (–)-**4.** Reaction of (±)-**3** with CALB using dimethylcarbonate (DMC), DMC/hexanes and MeCN as solvents led, in all cases, to recovery of starting material. The acetate (–)-**4** was deprotected by TBAF and the alcohol thus obtained was oxidated by catalytic IBX affording the acid (–)-**2** in 70% *ee*.

CONCLUSION

The C1-C6 fragment of the (–)-**1** could be prepared from commercial available starting materials using a chemoenzymatic approach. The use of new lipases and DKR (*dynamic kinetic resolution*) are under investigation by us, as well as the ring closing metathesis key step to the construction of the ten-membered ring of (–)-**1**.

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FAPESP, CNPq, CAPES

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