Tetrahedron Letters 50 (2009) 5190–5193

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A lipase catalyzed condensation reaction with a tricyclic diketone: yet another example of biocatalytic promiscuity

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ARTICLE INFO

Article history:
Received 28 May 2009
Revised 18 June 2009
Accepted 24 June 2009
Available online 27 June 2009

Keywords:
Aldol condensation
Candida antarctica lipase B
Non-aqueous media
Tricyclic 1,3-diketone
Vinyl acetate

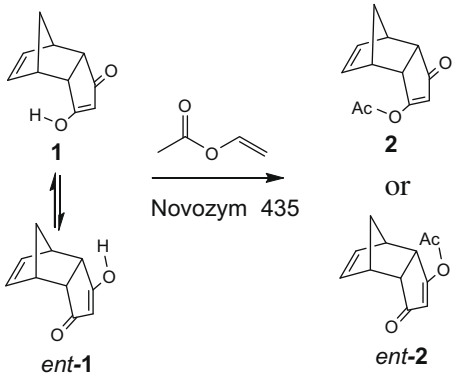
ABSTRACT

Novozym 435 (a commercially available immobilized form of *Candida antarctica* lipase B) was found to catalyze a condensation reaction of 5-hydroxy-endo-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one with acetaldehyde (enzymatically produced from vinyl acetate in situ) under low water conditions, in presence of 10% organic co-solvent (*N*,*N*-dimethyl formamide or pyridine), to form a bis-adduct. Even though the condensation reaction occurred with pyridine (acting as a base catalyst) in the presence of acetaldehyde and in the absence of enzyme, the reaction was very slow as compared to the enzymatic process. Thus, while the non-enzymatic process took 4 days to achieve 100% conversion; in presence of enzyme it was possible within 4 h.

1. Introduction

In 1997, Sheldon stated that the fine chemical industry, in contrast to bulk chemicals manufacturing, is reluctant to apply catalytic technologies.[1] In the last decade, there have been vigorous efforts to leverage biotechnological toolbox to evolve green chemical approaches.[2] As Jaeger had put it more picturesquely, enzyme-catalyzed processes are slowly replacing 'fire and sword' chemistry.[3] The key to strengthen this approach is to use usual enzymes in different ways by exploiting their biological potential. The use of nearly anhydrous media created an opportunity to use hydrolases for organic synthesis.[4] Among such applications, lipases top the list. One of the reasons (perhaps the most important one) is that lipases show tremendous versatility vis-à-vis the range of substrates and biotransformations they catalyze. Acylation and esterification have been carried out by lipases with numerous substrates.[5] Vinyl esters are often preferred as acyl donors as the resulting vinyl alcohol is rapidly converted to acetaldehyde thereby making the reaction faster and irreversible. Weber et al.[6] and Hogberg et al.[7] have shown that in organic solvents, vinyl acetate can produce acetaldehyde and can result in hemiacetal esters. In the present work, we describe for the first time a condensation reaction of acetaldehyde with a tricyclic diketone catalyzed by a frequently used commercial lipase (Novozym 435) under low water conditions.

5-Hydroxy-*endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one (**1** or *ent*-**1**, Scheme 1) is an interesting tricyclic 1,3-diketone which exists in the enol form exhibiting pseudo meso character and a very important synthon for the synthesis of large variety of naturally occurring cyclopentanoids,[8] cubane-type polycyclic compounds,[9] and other pharmaceutically important compounds.[10] The fast tautomerization of the cyclic diketone such as **1**, makes it exist as a racemic mixture of the two enol forms **1** and *ent*-**1** (Scheme 1) and thus opens up the possibility of a dynamic kinetic resolution.



Scheme 1. The fast enantiomerization of the cyclic diketone **1** (enol forms **1** and *ent*-**1**) and its aimed desymmetrization via enzymatic transacetylation.

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doi:10.1016/j.tetlet.2009.06.108

Toward that aim, Novozym 435 and vinyl acetate were chosen to enantioselectively transacetylate **1** (Scheme 1). Instead, we observed the novel condensation product between the diketone and acetaldehyde.

2. Results and discussion

An excess of vinyl ester with a co-solvent, DMF or pyridine, in minimum amount required to dissolve **1** in vinyl ester was employed to maintain a nearly solvent-free condition and to accelerate desymmetrization as compared to racemization which is a key requirement to achieve an efficient dynamic kinetic resolution.[11]

The progress of the reaction was initially monitored by thin layer chromatography (TLC) which indicated a gradual disappearance of the starting material and the appearance of a new spot. The reaction reached completion in 4 h, which was further confirmed by HPLC analysis (Fig. 1). A control without enzyme failed to achieve this reaction even after 5 days (Table 1, entries 2 and 4).

Surprisingly, this enzymatic product appeared more polar (R_f = 0.6 in ethyl acetate, hexane, and methanol = 4:2:1) than the expected acetyl derivative **2** (or *ent*-**2**), Scheme 1, (R_f >0.9 in the same solvent) of the alcohol which, for this purpose, was synthesized using standard procedure.[10] Interestingly, when vinyl propionate was used instead of vinyl acetate (Table 1, entries 5 and 6) the reaction produced the same product exhibiting identical R_f value in TLC and the same retention time in HPLC. However, the only difference was that the reaction with vinyl propionate was found to proceed three times slower than that with vinyl acetate and under the same conditions, took 12 h for the completion (Table 1, entries 1 and 5). This indicated that, it was the vinyl moiety and not the acyl group that is participating in the reaction.

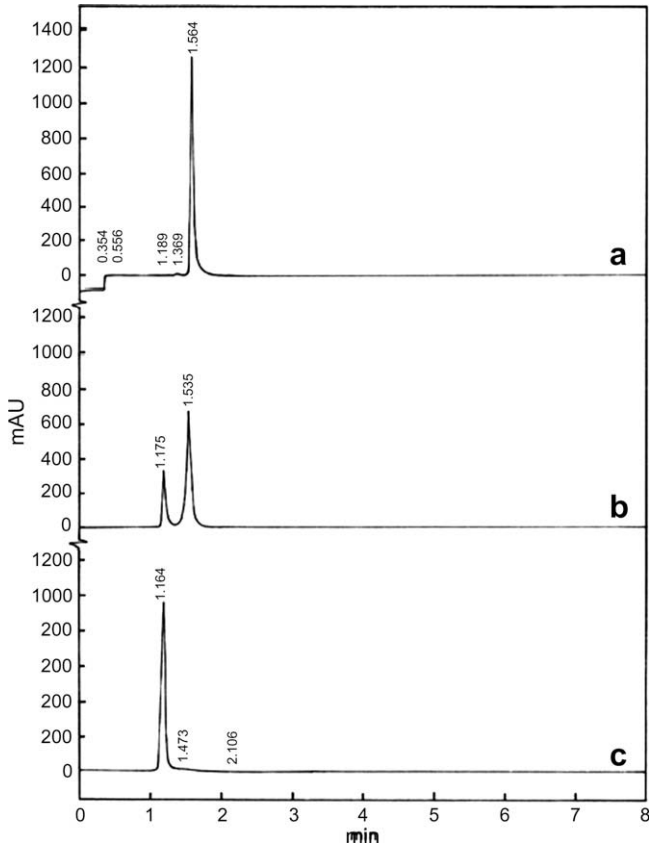
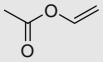
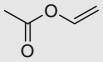
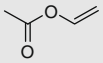
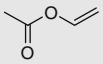
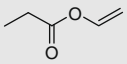
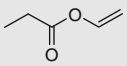
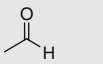
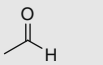


Figure 1. HPLC analysis of the enzymatic reaction: (a) at the start of the reaction, time t = 0 h showing only the starting material, the enol **1** (Scheme 2); (b) at time t = 0.5 h showing 30% conversion; (c) at t = 4 h showing complete disappearance of the enol **1** to the product **3** (Scheme 2).

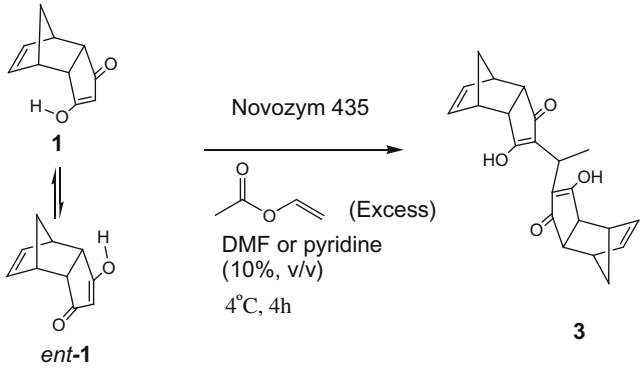
Table 1
Novozym 435 (Novo 435) catalyzed condensation reaction of 1 (or *ent*-1, Scheme 1) with vinyl esters and with acetaldehyde in nearly anhydrous conditions and in solvent-free media

Entry no.	Reactant **2** (excess)	Enzyme (10%, w/w)	Co-solvent (10%, v/v)	Time	*C* (%)*	Yield** (%)
1		Novo 435	DMF	4 h	100	95
2		—	DMF	5 days	0	—
3		Novo 435	Pyridine	4 h	100	97
4		—	Pyridine	5 days	0	—
5		Novo 435	Pyridine	12 h	100	98
6		—	Pyridine	5 days	0	—
7		Novo 435	Pyridine	4 h	100	94
8		—	Pyridine	4 days	100	95

* *C* corresponds to the conversion value obtained by HPLC.
** This corresponds to the product yield after work-up. The variations between three sets of experimental results were within 2%.

After the purification of the enzymatic product by column chromatography the ^{1}H NMR spectral data of the product revealed that it was not the expected acetyl derivative, **2** (or *ent*-**2**). Upon further analysis (with ^{13}C NMR, DEPT, and high resolution mass spectral data; details given as Supplementary data) the product was identified to be the bis-adduct of **1** or *ent*-**1** (**3**, Scheme 2).

Lipases have been reported to give abnormal reactions with vinyl acetate due to its hydrolysis to acetaldehyde.[6,7] To confirm that acetaldehyde produced was involved in the reaction, the reaction of 1 with an excess of acetaldehyde in presence of Novozym 435 and pyridine (10% v/v) was tried. This reaction led to the formation of the same product **3** (Table 1, entry 7). Evidently, here the



Scheme 2. The formation of an unusual bis-adduct **3**.