ELSEVIER

Journal of Molecular Catalysis B: Enzymatic 5 (1998) 219–221

JOURNAL OF MOLECULAR CATALYSIS B: ENZYMATIC

A new microorganism for highly stereospecific Baeyer–Villiger oxidation of prochiral cyclobutanones

Véronique Alphand, Claudio Mazzini, Jacques Lebreton, Roland Furstoss *

Groupe Biocatalyse et Chimie Fine, ERS CNRS 157, Université de la Méditerranée, Faculté des Sciences de Luminy, Case 901, 13288 Marseille Cedex 9, France

Received 17 October 1997; accepted 29 November 1997

Abstract

Baeyer–Villiger biooxidation of prochiral 3-substituted cyclobutanones were carried out using the fungus *Cunninghamella echinulata*. β-substituted γ-butyrolactones were thus obtained in high ees (ee ≥ 98%). These results were compared with those obtained using two *Acinetobacter* strains. © 1998 Elsevier Science B.V. All rights reserved.

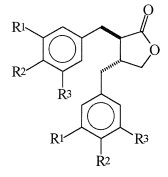
Keywords: Baeyer–Villiger oxidation; Prochiral cyclobutanone; *Cunninghamella echinulata*

1. Introduction

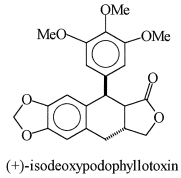
Chiral β-substituted γ-butyrolactones constitute an important class of compounds. These subunits are found in a variety of natural products [1] and serve as valuable building blocks for the synthesis of biologically important substances—i.e., lignans, known for their anti-leukemic and anti-cancerous activities [2].

We showed previously that the microbiological Baeyer–Villiger oxidation of prochiral 3-substituted cyclobutanones is a very efficient way to synthesise enantiomerically enriched γ-butyrolactones [3]. However, the ees and/or absolute configuration of the products obtained using the biocatalysts presently available are not always those desired. In this context, a screening led us to discover that the fungus *Cunninghamella echinulata* NRRL 3655 [4,5] was also able to perform these reactions. Thus, we could achieve the synthesis of enantiopure (*R*) and (*S*)-β-proline [6] and (*R*)-Baclofen® [7].

We describe here the potentialities of this fungus on an extended serie of prochiral 3-sustituted cyclobutanones **1a–8a** and we compare these results with those obtained using two



R_1 = -OH R_2 = R_3 = H (-)-enterolactone
R_1 = R_2 = -OCH_2O- R_3 = H (-)-hinokinin
R_1 = R_2 = OMe R_3 = H (-)-arctigenin

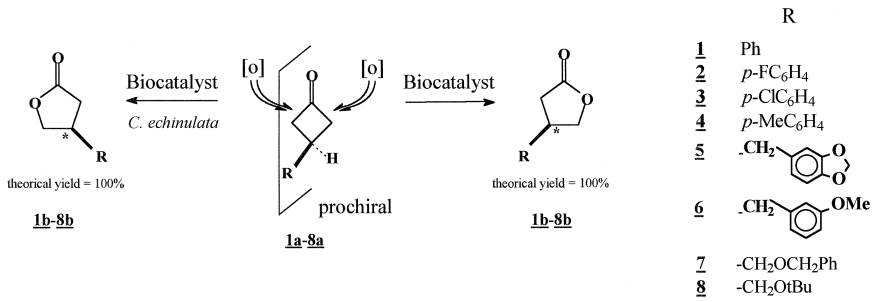


(+)-isodeoxypodophyllotoxin

Scheme 1.

* Corresponding author. Fax: +33-4-91-82-91-55;
E-mail: furstoss@gulliver.fr

PII: S1381-1177(98)00038-1



Scheme 2.

well-known *Acinetobacter* strains Schemes 1 and 2.

2. Results and discussion

Preliminary results indicated an excellent stereoselectivity in many cases but disappointing yields (< 30%). In order to improve them, we studied the influence of the culture media and the culture time on the lactone **1b** formation. Biotransformations were carried out with resting cells of *C. echinulata* (pH 7 phosphate buffer) and the lactone yield was determined after 24 h reaction and continuous extraction with dichloromethane. Best results were ob-

Table 1
Biotransformation of a series of 3-substituted cyclobutanones using whole cells of different microorganisms

Ketone	Microorganism	Yield (%)	Lactones **b** ee (o.p.)[a] (%)	Optical rotation and abs. conf.[b]
1a	*C. echinulata*	65	98	(−)-(*R*)
	A. calcoaceticus	70	43	(−)-(*R*)
	Acinetobacter TD63	84	47	(−)-(*R*)
2a	*C. echinulata*	80	> 98	nd
	A. calcoaceticus	89	19	nd
	Acinetobacter TD63	92	5	nd
3a	*C. echinulata*	30[c]	> 98	(−)-(*R*)
	A. calcoaceticus	88	85	(+)-(*S*)
	Acinetobacter TD63	15	89	(+)-(*S*)
4a	*C. echinulata*	4[c]	nd	nd
	A. calcoaceticus	73	91	(+)-(*S*)
	Acinetobacter TD63	61	93	(+)-(*S*)
5a	*C. echinulata*	68	(91)	(−)-(*S*)
	A. calcoaceticus	70	(100)	(−)-(*S*)
	Acinetobacter TD63	64	nd	nd
6a	*C. echinulata*	68	(77)	(−)-(*S*)
	A. calcoaceticus	83	(96)	(−)-(*S*)
	Acinetobacter TD63	94	(94)	(−)-(*S*)
7a	*C. echinulata*	74	98	(−)-(*R*)
	A. calcoaceticus	89	55	(+)-(*S*)
	Acinetobacter TD63	90	25	(−)-(*R*)
8a	*C. echinulata*	25[c]	> 98	nd
	A. calcoaceticus	43	89	nd
	Acinetobacter TD63	15	88	nd

[a] Ees were determined by g.c. on a chiral column [Octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin] except for lactones **5b** and **6b** (optical purity) and lactones **7b** and **8b** (Lipodex E g.c. column-Macherey–Nagel).
[b] Absolute configurations were determined by comparison of the sign of the optical rotation with literature values.
[c] This biotransformation has not yet been carried out under optimized conditions.
nd = Not determined.

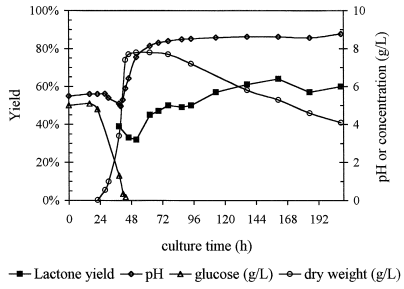


Fig. 1. Various culture parameters and lactone yields obtained after 24 h biotransformations carried out with differently aged mycelium of *C. echinulata*.

tained using cells grown during 6–8 days on a medium composed of tryptone, malt extract, yeast extract and glucose (cf. Fig. 1).

Using these experimental conditions, most prochiral cyclobutanones (except **5a** and **6a**) tested with *C. echinulata* led to enantiopure γ-butyrolactones (ee ≥ 98%) in good yields (> 60%). These results are presented Table 1. It is interesting to note that the obtained lactones exhibited the same «spatial» configuration (although there are switches—compounds **5b** and **6b**—in the labelling of the absolute configuration due to the Prelog's priority rules).

A comparative study achieved with both *Acinetobacteria* strains, *A. calcoaceticus* NCIMB 9871 and *Acinetobacter* TD63, indicated that the lactone yields were generally higher than with the fungus and the ees ranged from low to excellent (cf. Table 1). Their absolute configuration depends on the substituent. Thus, in the case of *para*-substituted phenyl butyrolactones, the (*R*)-enantiomer was formed in a smaller proportion as the substituent size increased: 43% ee, (*R*)-enantiomer major for lactone **1b** until 91% ee, (*S*)-enantiomer major for lactone **4b**.

Interestingly, lactones **5b** and **6b** were obtained in higher ees (100% and 96%) with *Acinetobacter* strains than with *C. echinulata*.

References

[1] S.S.C. Koch, A.R. Chamberlin, J. Org. Chem. 58 (1993) 2725.
[2] T. Honda, N. Kimura, S. Sato, D. Kato, H. Tominaga, J. Chem. Soc., Perkin Trans. 1 (1994) 1043 and references herein.
[3] R. Gagnon, G. Grognan, E. Groussain, S. Pedragosa-Moreau, P.F. Richardson, S.M. Roberts, A.J. Willetts, V. Alphand, J. Lebreton, R. Furstoss, J. Chem. Soc., Perkin Trans. 1 (1995) 2527.
[4] J. Lebreton, V. Alphand, R. Furstoss, Tetrahedron 53 (1997) 45.
[5] L. Andrau, J. Lebreton, P. Viazzo, V. Alphand, R. Furstoss, Tetrahedron Lett. 38 (1997) 825.
[6] C. Mazzini, J. Lebreton, V. Alphand, R. Furstoss, J. Org. Chem. 62 (1997) 5215.
[7] C. Mazzini, J. Lebreton, V. Alphand, R. Furstoss, Tetrahedron Lett. 38 (1997) 1195.