Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 5, pp. 1067-1068, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00126-3

Resolution of Racemic Linalool Oxide-Pyranoid by Microbial Esterification

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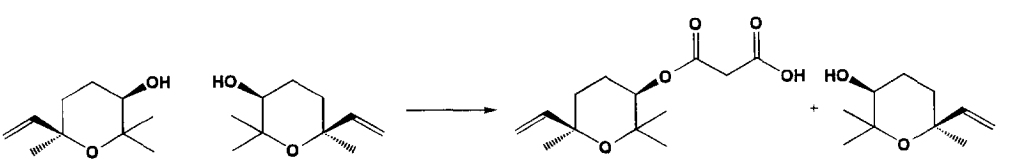
Abstract -Resolution of racemic *cis* and *trans*-linalool oxide-pyranoid via esterification with malonic acid by *Glomerella cingulata*, is described. The enantiomerically pure alcohols and malonic esters can be obtained.

Recent reviews have highlighted the need for selective methods to elaborate substituted tetrahydropyrans of high enantiomeric purity. [1, 2] Indeed, these compounds may constitute valuable chiral synthons for further synthesis of biologically active natural products. They are important structural fragments of numerous oxygenated natural products and have also been found as constituents of fruit aromas such as in Carica papaya fruit.[3, 4] In order to obtain the enantiomerically pure alcohol we have utilized the esterification with *Glomerella cingulata* [5] that has given exellent results in the resolution of linalool oxide-pyranoid. The results are summarized in the following Table.

Table. Resolution of the racemic secondary alcohols **1** and **3** by *Glomerella cingulata*.

alcohol	time (hr)	ester (%)	ee (abs conf)	alcohol (%)	ee (abs conf)
1	24	**2** (50)	100 (3*R*, 6*R*)	**1** (50)	100 (3*S*, 6*S*)
3	24	**4** (33)	100 (3*R*, 6*S*)	**3** (67)	75 (3*S*, 6*R*)
3	36	**4** (50)	100 (3*R*, 6*S*)	**3** (50)	100 (3*S*, 6*R*)

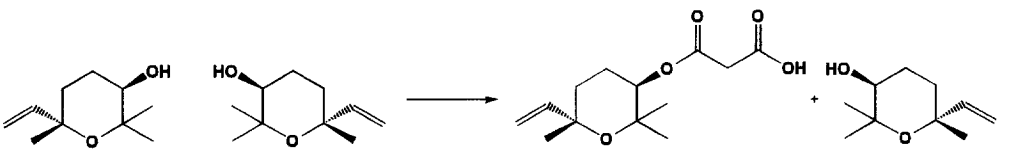
Racemic *cis*-linalool oxide-pyranoid (**1**), dissolved in DMSO, was added to a culture of *Glomerella cingulata* and esterified to give after 24 h (3*R*, 6*R*)-*cis*-linalool oxide-pyranoid-3-yl-malonate **2** in 50% yield (ee 100%) (Scheme 1, Table).



(rac)-**1** (3*R*, 6*R*)-**2** (3*S*, 6*S*)-**1**

Scheme 1

The recovered alcohol showed an ee of 100% of the (3*S*, 6*S*)-enantiomer. Practically the same results were obtained in the microbial esterification of the racemic *trans*-linalool oxide-pyranoid (**3**) but the reaction was slower (Scheme 2). The malonic acid was not added to the culture of *Glomerella cingulata* in the study. But the compounds **1** and **3** was converted to 3-yl-malonate **2** and **4** respectively. It is assumed that this esterification between the alcohols, and malonic acid which this fungus produce with the growth proceeded in the microbial transformation by *Glomerella cingulata*.



(rac)-**3** (3*R*, 6*S*)-**4** (3*S*, 6*R*)-**3**

Scheme 2

Experimental

Esterification on analytical scale. A nutrient broth was prepare by dissolving sucrose (15g), glucose (15g), polypeptone (5g), KCl (0.5g), $MgSO_4$ (0.5g), K_2PO_4 (1g), $FeSO_4 \cdot 7\ H_2O$ (0.01g) in 1L of distilled water. A sterilized nutrient broth (50ml) was inoculated with *Glomerella cingulata*. The mixture was incubated for 2 days at 28 °C on a reciprocatory shaker. Mycelia were transplanted on to the culture medium (15ml in a Petri dish) and incubated for 36-48 h, until mycelia occupied 100% of the surface area of culture medium. To the resulting mycelia the racemic alcohol **1** (60mg) and **3** (60mg) in DMSO (0.1 ml) were added, corresponding to 30mg of substrate per Petri dish. Aliquots were withdrawing periodically (see table) and monitored by GLC on a chiral column : CHROMPACK WCOAT Fused silica Cp-Cyclodextrin-B-2, 3, 6-M-19 (50 m X 0.25 mm, N_2 flow rate 1ml min^{-1}). The enantiomer separetions of the alcohols were achieved after alkaline hydrolysis of malonic esters.

Esterification on preparetive scale. To the resulting mycelia of grown cell **1** (1.0g) and **3** (1.0 g) in DMSO (1.0 ml) were added same as analytical scale. After 2 days, the reaction mixtures were extracted with dichrolomethane with a continuous liquid-liquid extractor, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The products were purified by column chromatography (silica gel, hexane / dimethyl ether ratio) to give the malonic ester and the unreacted alcohols. The yields, the absolute configurations and the enantiomeric excesses are listed in the Table. The absolute configurations of compounds **1** and **3** were assigned on the basis of the specific rotations in the literature.[6] The absolute configuration of the 3-yl-malonic ester **2** and **4** were assigned from literature data[6] of the alcohol obtained from alkaline hydrolysis of the malonic ester. Optical rotations were measured on a Japan Spectroscopic CO. LTD DIP-140 in $CHCl_3$: (3*S*, 6*S*)-**1**, [α]$_D$=-2.8 (*c*=1.1), (3*R*, 6*R*)-**2**, [α]$_D$=-25.6 (*c*=1.1), (3*S*, 6*R*)-**3**, [α]$_D$=+10.6 (*c*=0.9), (3*R*, 6*S*)-**4**, [α]$_D$=-24.6 (*c*=0.8). The enantiomeric exesses are determined by GLC on chiral column [retention time (min) of alcohols: (3*S*, 6*S*)-**1**, 31.8, (3*R*, 6*R*)-**1**, 32.1, (3*S*, 6*R*)-**3**, 31.3, (3*R*, 6*S*)-**3**, 31.5].

References and Notes

1. Boivin, T. L. B. *Tetrahedron* **1987**, 43, 3309.
2. Cardillo, G., Orena, M. *Tetrahedron* **1990**, 46, 3321.
3. Fiath, R. A., Forrey, R. R. J. *Agric. Food Chem.* **1977**, 25, 10.
4. Winterhalter, P., Katzenberger, D., Schreier, P. *Phytochemistry* **1986**, 25, 1347.
5. The strain stored in Gifu University (Japan) was used in this study.
6. Okazaki, Tomomi, Ohsuka, Akio, Kotake, Munio *Nippon Kagaku Kaishi* **1973**, 2, 359. [Chem. Abs. (**1973**) 78 136423h]

(*Received in Japan* 23 *March* 1995)