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A new resolution of (1α,2β,3α,4β)-2,3-dibromocyclohex-5-en-1,4-diol by lipase from *Mucor miehei*

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Abstract

An efficient resolution of 2,3-dibromocyclohex-5-en-1,4-diol has been carried out, using *Mucor miehei* lipase operating in an organic solvent. The enantioforms obtained may find application in the preparation of chiral conduritols.

Conduritols, 1,2,3,4-tetrahydroxycylohexenes,[1] represent an important class of cyclitols due to their biological properties and synthetic role as starting material in the preparation of bioactive molecules, such as glycosidase inhibitors.[2] Ten different stereoforms of conduritol are possible, from which conduritols A and D are *meso* forms, while B, C, E and F exist as pairs of enantiomers. Considering the crucial role that stereoselectivity plays in the chemical recognition regulation of the biological process, to have access to these cyclitols in enantiopure forms is particularly attractive and of synthetic interest. In the context of our research programme regarding the preparation of cyclitols in enantiopure forms by biocatalytic procedures, we have focused our attention on (1α,2β,3α,4β)-2,3-dibromocyclohex-5-en-1,4-diol, (±)-**1**, having C_2 symmetry, easily prepared by bromination/reduction of commercially available *p*-benzoquinone,[3] and which is known to be a starting material for access to six chiral conduritols, (+)- and (−)-conduritols B, C and E.[4]

Resolution of (±)-**1** has already been achieved by enantioselective hydrolysis of ester (±)-**2** in the presence of *Pseudomonas cepacia* lipase.[5] However, the concomitant spontaneous hydrolysis occurring in water has a detrimental effect on the enantiomeric purity of the products, making this unsuitable for preparative purposes. We thought this disadvantage could be avoided by the use of biocatalytic procedures, alcoholysis and esterification, operating in an organic solvent, and thus provide an efficient way of accessing enantiopure dialcohol **1**.

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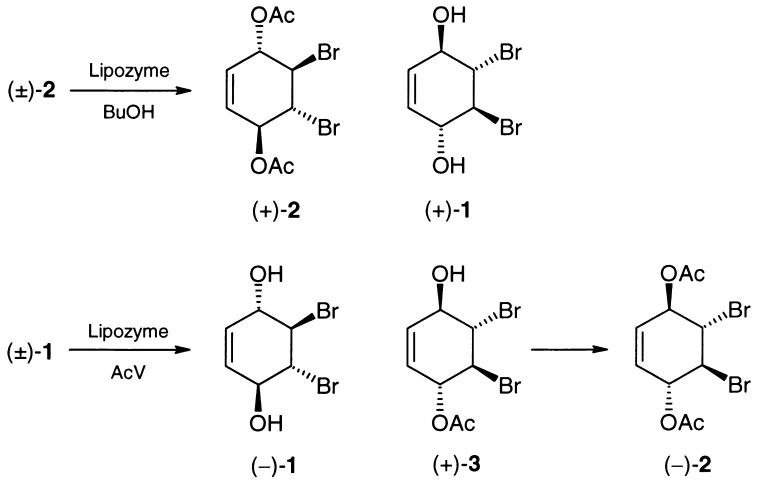
In this context, we first tried alcoholysis of (±)-**2** in *tert*-butyl methyl ether (TBME), using four different lipases whose effectiveness was proven in previous resolutions of cyclitols (Scheme 1).[6] Of these, after 24 h reaction, only *Mucor miehei* lipase on polymeric resin (Lipozyme®, Novo Nordisk) showed satisfactory activity in terms of the reaction rate and it was thus selected for further investigation.



Scheme 1. Substrate 10 mg/ml, lipase 20 mg/ml, *n*-BuOH or AcV 5 equiv., TBME, 45°C, 300 rpm

The alcoholysis of (±)-**2** in the presence of Lipozyme occurs with the recognition of the 1*R* enantiomer giving, at first, monoester (+)-**3**, the concentration of which, nevertheless, does not exceed 15% because it is itself quickly transformed into dialcohol (+)-**1**. The enantiopure nature of monoester and, consequently, of diol (+)-**1**, determined by chiral GC analysis, established the high enantioselectivity ($E > 200$) for *M. miehei* lipase. Under the reaction conditions adopted no spontaneous hydrolysis of the products occurs so that after 72 h the alcoholysis reached 50% conversion and allowed enantiopure (+)-**2** ($[\alpha]_D^{25}$ +12.0, *c* 0.4, CH_2Cl_2; lit.[5] $[\alpha]_D$ +11.7) and (+)-**1** ($[\alpha]_D^{25}$ +42.0, *c* 2.0, acetone; lit.[5] $[\alpha]_D$ +45.8) to be obtained.

When we tried the resolution of (±)-**1** by direct esterification with vinyl acetate in TBME using Lipozyme as the catalyst, the sequential esterification of the hydroxyl groups in the recognised enantiomer occurred with different rates. Thus, fast formation of monoester (+)-**3** in enantiopure form was observed, whose concentration rose to 40% in 4 h, followed by a further slow esterification step to give diester (−)-**2**. Following this procedure, on a preparative scale, 2 g of (±)-**1** in 6 h (50% conv.) furnished 0.96 g of (−)-**1** (yield 48%, ee >98%), 0.85 g of (+)-**3** (yield 37%, ee >98%) and 0.26 g of (−)-**2** (yield 10%, ee >98). Hydrolysis with NH_4OH:MeOH, 1:9, of these esters afforded the homochiral dialcohol (+)-**1** in a 42% overall yield.[7]

In conclusion, the enzymatic method described here offers a convenient route to gain access to bromoconduritols, (+)- and (−)-**1**, of synthetic interest in excellent ee and good yield.

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6. The following lipases have been investigated: from *Candida cylindracea*, *C. antarctica*, *Pseudomonas cepacia* and *Mucor miehei*. Sanfilippo, C.; Patti, A.; Nicolosi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 3273–3276. Sanfilippo, C.; Patti, A.; Piattelli, M.; Nicolosi, G. *Tetrahedron: Asymmetry* **1998**, *9*, 2809–2817. Sanfilippo, C.; Patti, A.; Piattelli, M.; Nicolosi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 1569–1573. Ling, L.; Ozaki, S. *Tetrahedron Lett.* **1993**, *34*, 2501–2504. Ling, L.; Watanabe, Y.; Akiyama, T.; Ozaki, S. *Tetrahedron Lett.* **1992**, *33*, 1911–1914.
7. The enantiomeric excesses of **1** and **2** were determined by chiral GC analysis on Megadex DMP β-dimethylpentyl βCDX OV1701 capillary column. For (+)-**3**, (+)-(1*R*,2*S*,3*S*,4*R*)-1-acetyloxy-2,3-dibromo-4-hydroxycyclohex-5-ene: white crystals, (from EtOAc/hexane), mp 147–148°C; ee >98% (determined by chiral GC analysis after exhaustive chemical acetylation); $[\alpha]_D^{25}$ +25.0 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$/TMS, 250.13 MHz): δ (ppm) 2.15 (s, 3H), 2.83 (d, $J=4.5$ Hz, 1H), 4.26 (m, 2H), 4.56 (m, 1H), 5.67–5.75 (m, 2H), 5.92 (ddd, $J=2.2$, 4.5, 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 62.9 MHz): δ (ppm) 20.9, 52.9, 59.9, 73.1, 74.2, 126.8, 130.9, 169.0.