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Unprecedented biocatalytic desymmetrization of hexitols

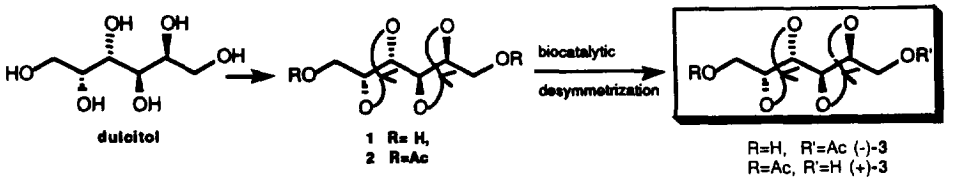
Carlo Bonini,* Rocco Racioppi and Licia Viggiani
Dipartimento di Chimica, Università della Basilicata, Via N. Sauro 85, 85100 Potenza, Italy

Abstract: An unprecedented biocatalytic desymmetrization of a dulcitol derivative leads to optically active hexitols. The best results have been obtained with PFL or Lipase PS, with ees superior to 98% and chemical yields of 75–86%. The absolute configurations of the title chiral compounds have been determined by transformation into known bromo derivatives, already utilized for the preparation of optically active tetrahydrofurans. © 1997 Elsevier Science Ltd. All rights reserved.

Biocatalytic transformation of prochiral or meso compounds into optically active synthons represents one of the most useful tools for the preparation of chiral products for organic synthesis.[1] Among them chiral polyols have attracted much attention because of the contemporary presence of multifunctional groups which can be manipulated for further synthesis. Many cyclic and alycyclic polyols have shown to be good substrates for different common enzymes (mainly lipases or esterases), both for kinetic resolution or desymmetrization[2] of meso compounds. Also sugar derivatives have shown to be good substrates: among them pentitols,[3] xilitols[4] and *myo*-inositol[5] derivatives have been successfully desymmetrized, both by hydrolysis of transesterification reactions. Nonetheless the use of enzymes needs to be more explored: to this end we decided to investigate meso hexitols, which, to our knowledge, have never been tested before. The choice fell on dulcitol, a naturally occurring hexitol which is an inexpensive commercially available compound. In order to protect secondary hydroxyl groups we thought, on the basis of our results on heptanediols cyclic derivatives,[6] that a rigid conformation of the molecule would be helpful for the enzymes ability to discriminate between enantiotopic hydroxyl groups.

Therefore dulcitol was transformed (see Scheme 1) into the diacetonide **1**, already prepared by other authors.[7] Compound **1** and its diacetyl derivative **2** were then subjected to different enzymes in order to obtain optically active compound **3**, by biocatalytic transesterification (in ether and vinyl acetate) or hydrolysis (phosphate buffer at pH 7). The best results, which are summarised in Table 1, show that *Pseudomonas fluorescens* L. or Lipase PS[8] are the enzymes of choice to effect the optimum desymmetrization in order to obtain enantiomerically pure[9] (−)- or (+)-**3**.

In order to determine the absolute configuration the title compound (+)-**3** was transformed (see Scheme 2) into the bromo derivative **4** and then, by deprotection of the isopropylidene groups and complete acetylation, into the enantiomer of known compound **5**, already utilized for the synthesis of

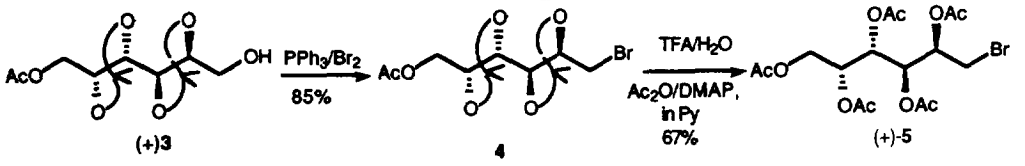


Scheme 1.

* Corresponding author. Email: bonini@unibas.it

Table 1. Desymmetrization of dulcitol derivative to give 3

Compound	Enzyme	time	chemical yield (%)	(ee%)	$[\alpha]_D$ (conc., $CHCl_3$)
1	*Pseudomonas fluorescens*	18 h	86	98	-11 (2.2)
1	*Candida cylindracea*	48 h	60	70	-9 (1.7)
1	Lipase PS	22 h	20	98	-12 (2.1)
2	Lipase PS	44 h	75	98	+12.5 (1.2)



Scheme 2.

optically active tetrahydrofurans.[10] The value and the sign of the specific rotation ($[\alpha]_D$=8.9, c.1.2, $CHCl_3$) of (+)-**5** allows the assignment of the compound (+)-**3** as 2R, 3S, 4R, 5S.

The described biocatalytic reaction allows an easy preparation of a highly functionalized complex molecule in enantiomerically pure form, which can be utilized for further transformations in organic synthesis.

Acknowledgements

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8. Lipase PS was given, as generous gift, by Amano Pharmaceutical Co.
9. The ee for compound **3** was determined by ^{1}H-NMR ($CDCl_3$) analysis with (−)-Eu(hfc)$_3$ at a different concentration, which shows clear differentiation of the CH_3 signals of the isopropylidene ring. Compound **3**, ^{1}H-NMR ($CDCl_3$): 1.35 (s, 3H), 1.4 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 1.8 (bs, 1H), 2.13 (s, 3H), 3.65 (dd, J=3.81 Hz, 1H), 3.78–3.85 (m, 2H), 4.02–4.12 (m, 3H), 4.33 (m, 1H), 5.10 ppm (m, 1H). ^{13}C-NMR ($CDCl_3$): 170.6, 110.5, 109.9, 81.2, 78.8, 78.2, 64.4, 62.5, 26.3, 20.8.10 ppm.
10. Lundt, I.; Frank, H. *Tetrahedron*, **1994**, *50*, 13285. The ^{1}H and ^{13}C-NMR data for compound **5** are in perfect agreement with those reported in this report. The $[\alpha]_D$ value for compound (−)-**5**, derived from natural D-galactonic acid, was reported to be −10.1 (c. 1.0, $CHCl_3$).

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