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Biocatalytic Desymmetrizations of Pentitol Derivatives

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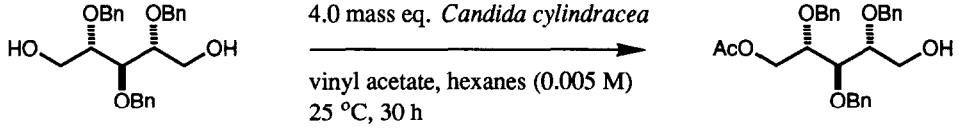
Key Words: acylation; catalysis; *Candida cylindracea* lipase; kinetic amplification of diastereomeric excess

Abstract: Several acylations of pentitol derivatives mediated by *Candida cylindracea* have been shown to be enantio-, or diastereo-, group selective; a pattern emerges from the selectivities of these reactions which may have some predictive value.

In studies directed towards syntheses of amino sugar derivatives, chirons derived from *meso* or otherwise symmetrical pentitols were required. This paper describes the methodology used to obtain these compounds: biocatalytic monoacylations of diols wherein the symmetry of the product is reduced with respect to the starting material. Some of these transformations are highly stereoselective, giving products of excellent stereoisomeric purity; a typical result is depicted below.

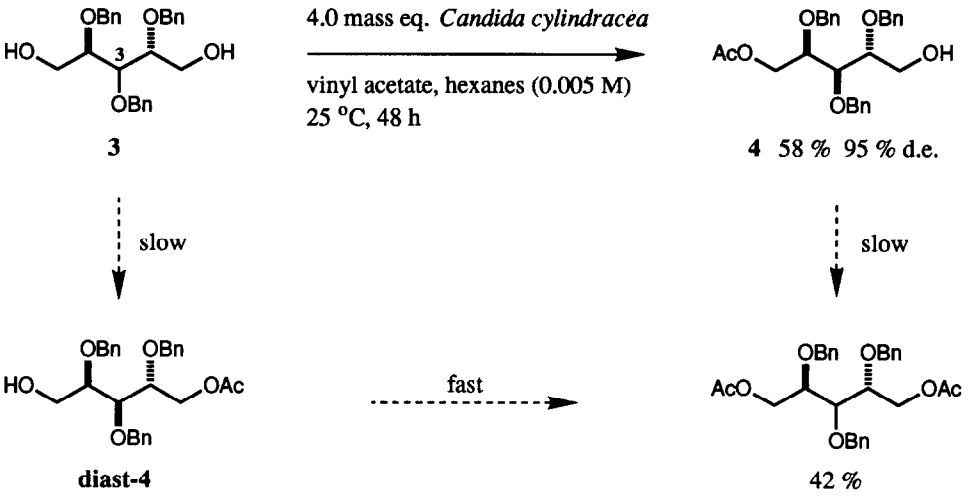


1 **2** 70 % >95 % e.e.

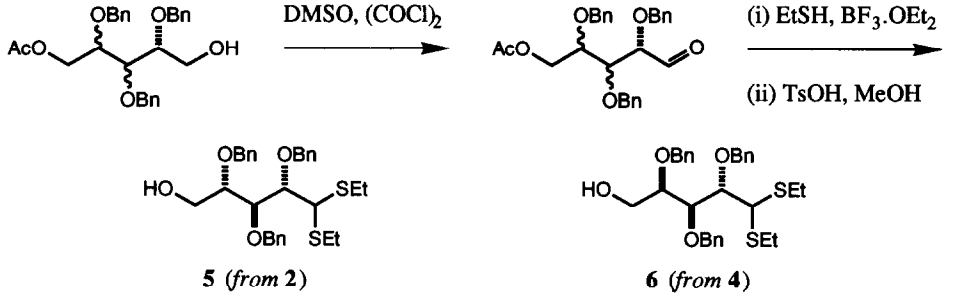
Diol **1** is conveniently prepared from adonitol via a three step sequence (tritylation, benzylation, detritylation). When 0.005 M hexane solutions of this material are treated with excess vinyl acetate in the presence of a crude preparation of the lipase *Candida cylindracea* gives monoacetate **2** and the corresponding diacetate. Kinetic amplification of enantiomeric excess[1-4] is operative, *ie* the optical purity of alcohol **2** is enhanced via relatively rapid removal of the minor enantiomer in a second acylation step. Consequently, the enantiomeric purity of **2** increases as the reaction proceeds, at the expense of chemical yield. In practice, good optical *and* chemical yields are obtained if the reaction is stopped when diol **1** has disappeared (TLC). Diacetate formed in this transformation can be hydrolyzed and recycled.[5] Enantiogroup selective, enzyme-mediated reactions are common,[6] but examples in which three synthetically useful asymmetric centers are generated are relatively rare.[7]

Diastereogroup selective acylation of the D-arabinitol derivative **3** is also mediated by *Candida cylindracea*. This reaction transforms the stereochemically silent C^3 carbon of the diol into a defined chiral

center. Presumably, *kinetic amplification of diastereomeric excess* is operative in this reaction, as illustrated below.

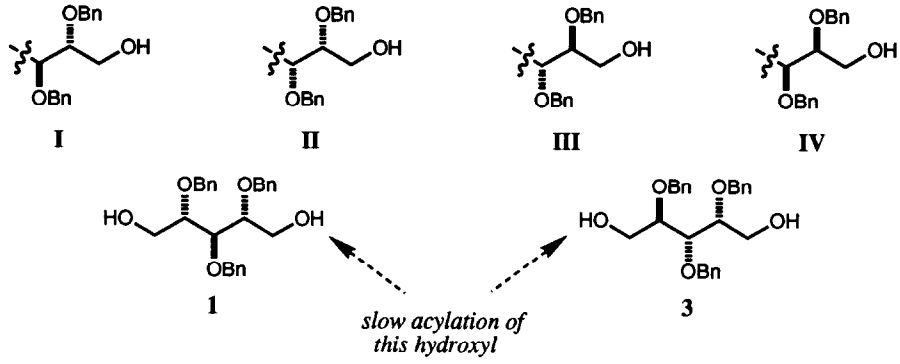


Absolute configurations of the product alcohols **2** and **4** were established by converting them to the dithioacetals **5** and **6**, respectively; the latter compounds (or their enantiomers) have been prepared in optically active form from pentoses.[8]

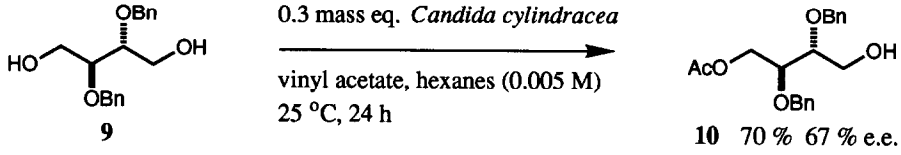


Group-selective acylations were also attempted using diols **7** and **8**, derived from L-arabitol and xylitol, respectively. However, acyl transfers to these substrates mediated by *Candida cylindracea* occurred in a stereorandom fashion.

It appears from these results that the stereochemical arrangement **I** is processed slowly by *Candida cylindracea*, whereas hydroxyl groups of entities **II** - **IV** are acylated relatively quickly. This accounts for the observed stereoselectivities for acylations of diols **1** and **3**, and the lack of selectivities for substrates **7** and **8** (neither of which contain fragment **I**).



In related work the *meso* diol **9**, an erythritol derivative, was acylated with appreciable enantiogroup selectivity. The absolute configuration of the predominant enantiomer of **10** was not established because the selectivity is not sufficient for practical appliactions; however, on the basis of the preceding discussion it seems likely to be that indicated below.[9]



Chemical and optical yield information for all the acylations presented in this paper are summaraized in the following Table.

Table. Optical and chemical yield information

compound	mass equivalents of *Candida cylindracea*	time (h)[a]	monoacetate opt. purity (%)	monoacetate yield (%)[d]	diacetate yield (%)[d]
1	4.0	48.5	>95[c] (d.e.)	58	42
3	4.0	30.0	>95[b]	70	28
7	4.0	24.5	12[c]	59	22
8	3.0	54.0	~0[b]	84	6
9	0.3	24.0	67[b]	70	17

[a] See the text for a representative experimental. [b] The enantiomeric excess was determined by ^{1}H NMR using (+)-Eu(hfc)$_3$. [c] The diastereomeric excess was determined by HPLC. [d] Isolated yields after flash chromatography.

Crude samples of *Candida cylindracea* are available for under $1 per gram (Sigma). Stereoselective acylations mediated by this enzyme proceed at a convenient rate when comparable masses of substrate and enzyme preparation are used; consequently, the experiments outlined in this paper are cheap and experimentally simple.[5] Moreover, some of these reactions have been performed using over 10 g of substrate, and significant scale-up should be possible. Such facile preparations of chirons are of obvious importance for contemporary asymmetric syntheses. Experiments are in progress to investigate biocatalytic desymmetrizations of other substrates; it will be interesting to determine whether or not the stereochemical bias observed for these acylations is exhibited in similar transformations mediated by *Candida cylindracea*.

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References and Notes

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5. Preparation of (2S, 3R, 4R)-1-O-Acetyl-2,3,4-tri-O-benzyladonitol (2): Hexane (232 mL) followed by 1.96 g (4 mass eq.) of the crude lipase obtained from *Candida cylindracea* (Sigma, EC 3.1.1.3) was added to a solution of 0.490 g (1.16 mmol, 1.00 eq.) of 7 in 2.14 mL (23.2 mmol, 20.0 eq.) of vinyl acetate. The resulting suspension was stirred at 25 oC for 30 h. The reaction was filtered through celite (washing with Et2O). The volatiles were removed in vacuo to give an oil which was purified via by flash chromatography (10-20% EtOAc in hexane). The monoacetate 2 (0.38 g, 70%) is a yellow oil: Rf 0.3 (20% EtOAc in hexane); [a]25D -9.0o (c 3.40, CHCl3); >95% ee (from 1H NMR using (+)-Eu(hfc)3); 1H NMR d 7.26-7.41 (m, 15 H), 4.71 (s, 2 H), 4.62 (m, 4 H), 4.42 (dd, J = 2.8 & 12.2 Hz, 1 H), 4.19 (dd, J = 5.7 & 12.2 Hz, 1 H), 3.86 (m, 2 H), 3.74 (br s, 2 H), 3.70 (m, 1 H), 2.00 (s, 3 H); 13C NMR d 170.0 (C), 137.9 (C), 137.8 (C), 128.5 (CH/CH3), 128.4 (CH/CH3), 128.2 (CH/CH3), 128.1 (CH/CH3), 128.0 (CH/CH3), 127.9 (CH/CH3), 78.6 (CH/CH3), 78.5 (CH/CH3), 77.0 (CH/CH3), 74.0 (CH2), 72.2 (CH2), 72.1 (CH2), 63.6 (CH2), 61.2 (CH2), 21.0 (CH/CH3); IR (neat) 1740 (st). Anal. Calcd for C28H32O6: C, 72.39; H, 6.94. Found: C, 72.20; H, 7.03. 1,5-Di-O-acetyl-2,3,4-tri-O-benzyladonitol (0.16 g, 28%) was also obtained as a yellow oil.
6. For recent examples see: Wang, Y.; Wong, C. *J. Org. Chem.* **1988**, *53*, 3127; Wang, Y.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C. *J. Am. Chem. Soc.* **1988**, *110*, 7200; Santaniello, E.; Ferraboschi, P.; Grisenti, P. *Tetrahedron Lett.* **1990**, *31*, 5657; Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 2697; Lam, L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047; Ader, U.; Breitgoff, D.; Klein, P.; Laumen, K. E.; Schneider, M. P. *Tetrahedron Lett.* **1989**, *30*, 1793.
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9. For a recent report of biocatalytic resolutions of other tetratol derivatives, see: Bestmann, H. J.; Philipp, U. C. *Angew. Chem. Int. Ed. Eng.* **1991**, *30*, 86.

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