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AN ENANTIODIVERGENT APPROACH TO D- AND L-ERYTHROSE VIA MICROBIAL OXIDATION OF CHLOROBENZENE

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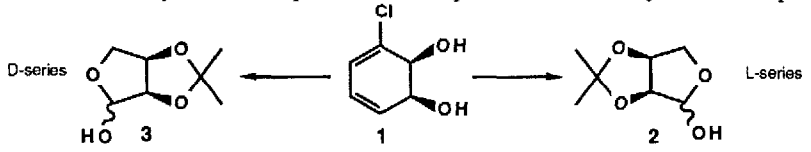
Abstract: D- and L-erythrose derivatives have been synthesized from chlorobenzene, *providing for the conversion of undesired pollutants to synthetically useful chiral intermediates.* The overall yields of the title compounds are compared to known preparation from arabinoses.

Use of microorganisms for the construction of chiral synthons has become increasingly common in organic synthesis.[2] Nearly twenty years ago, Gibson and coworkers reported the controlled microbial oxidation of several benzene derivatives to cyclohexadiendiols employing genetically manipulated strains of *Pseudomonas putida*.[3] Despite the operational simplicity and complete stereospecificity of the reaction, little use of this transformation has been made in organic synthesis, save for recent reports by Ley[4] and by us.[5] The reaction proceeds under exceedingly mild conditions and tolerates a variety of functional groups attached to the benzene ring,while providing for the introduction of two chiral centers as in the cis-diol **1**. Recently, we have reported a four step enantioselective synthesis of a prostaglandin

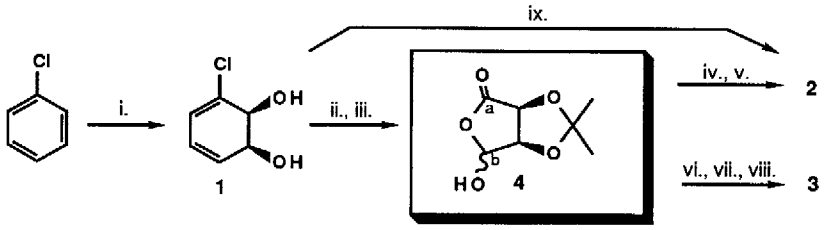


intermediate in the shortest route to $PGE_{2\alpha}$, which was obtained by combination of the microbially derived chiral pool reagents with Johnson's procedure for the attachment of prostaglandin side chains.[6] Synthons derived in this fashion have also been used in our group in the synthesis of the pyrrolizidine alkaloids (+)- and (-)-trihydroxyheliotridane.[7] Herein, we report an efficient and enantiodivergent approach to both enantiomers of 2,3-O-isopropylidene D- and L-erythrose **2** and **3** from chlorobenzene.

Chlorobenzene was oxidized using the procedure adapted from toluene diol preparation.[5] Diol **1** was protected as its acetonide and ozonized to hydroxylactone **4**.[8] Divergence into both enantiomeric series of erythrose was made possible at this point by controlling the site of reduction at either carbon **a** or **b** in the hydroxylactone **4**, Scheme 1. Reduction of **4** with $NaBH_4$ at the aldehyde site (carbon **b**) led to erythrose derivative **2** through subsequent reduction of the intermediate lactone. The enantiomer of **2** was prepared by subjecting the hydroxylactone to Wittig olefination, followed by reduction of the acid at carbon **a** to an alcohol which cyclized spontaneously to lactol **3** upon ozonolysis of the olefin. Authentic samples of both lactols were prepared from D- and L-arabinose and proved identical in all respects with those prepared from chlorobenzene.[9]

The two erythroses were prepared for two reasons: first, as a check of enantiomeric integrity of the reaction sequences, and second, in order to show that optically active sugars are accessible from arenes via the tandem microbial oxidation/chemical synthesis. As the erythroses are frequently used as chiral

synthons in the synthesis of complex natural products,[10] it should be pointed out that any operation, usualy involving addition of nucleophiles, that is performed on either **2** or **3** can be performed on **4** with identical enantiodivergency. Thus a realistic estimate of yield is the preparation of **4** from chlorobenzene (50% overall), since the actual conversion to **2** and **3** is unnecessary in real applications.[11]



Reagents: i. *Pseudomonas putida* 39-D; ii. DMP, p-TsOH; iii. O_3, EtOAc; then DMS; iv. $NaBH_4$, MeOH; v. DIBAL, CH_2Cl_2; vi. Ph_3PBrCH_3, BuLi, CH_2Cl_2; vii. LAH, Et_2O; viii. O_3, CH_2Cl_2; then DMS; ix. O_3, EtOAc; then $NaBH_4$

Scheme 1

In summary, a short enantiodivergent approach to both enantiomers of erythrose derivatives **2** and **3** has been accomplished, employing as the key step the microbial oxidation of chlorobenzene. Significantly, the carbohydrate manifold has been reached starting from an achiral aromatic source. This bodes well for the preparation of both enantiomeric series of more complex carbohydrates from arenes by appropriate oxidations of chlorodiol **1**. These endeavors will be reported in due course.

Acknowledgments

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10. (a) For a review of carbohydrates in organic synthesis see: Hanessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach* ; Pergamon Press: Oxford, 1983. (b) For the use of lactol **2** in organic synthesis see: Williams, D. R.; Klinger, F. D. *J. Org. Chem.* **1988**, *53*, 2134.
11. A realistic cost estimate for lactols **2** and **3** is $2.40/g from arabinoses, and $1.40/g for the unoptimized conversions listed here. These estimates exclude the cost of labor which is comparable for the two processes. The overall yield of lactol **2** from chlorobenzene was 45% . This compares with a yield of 39% from arabinose.

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