

Enzymatic hydroxylation of arene and symmetry considerations in efficient synthetic design of oxygenated natural products

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Abstract: Microbial oxidation of substituted aromatic compounds with mutant strains of *Pseudomonas putida* (39D) yields the corresponding arene cis-diols in efficient quantities and >99% ee. The use of these synthons in the practical preparation of oxygenated natural products is described with emphasis on the importance of symmetry considerations during synthetic planning in order to achieve enantiodivergent preparations of target compounds. The applications are highlighted by discussion of the syntheses of the following compounds from chlorobenzene: (+)- and (-)- erythrose, (+)- and (-)- ribonolactone, (+) - and (-)-trihydroxyheliotridane, (+)- and (-)-pinitol, kifunensine, lycoricidine and a model study for a short synthesis of (-)-morphine. The conclusion of the lecture places in perspective the use of halogenated aromatics in the chiral pool supply with the potential of efficiently replacing sugars. Brevity and efficiency of the synthetic sequences are emphasized.

INTRODUCTION

The challenge facing the synthetic chemists today is not so much the ability to prepare any given organic compound but rather to do so well, that is efficiently and with an element of esthetics. The field of biocatalysis has emerged in recent years as an important tool in the synthesis of optically pure organic compounds. The combination of organic synthesis, chemoenzymatic transformations, and clever synthetic design provides for a powerful protocol for a quick assembly of complex molecules. In the years to come, more emphasis will be placed on efficiency and practicality of the synthetic procedures. Various environmental and regulatory factors will dictate that waste materials and solvents be recycled or converted to useful end products. This presentation therefore focuses on an advanced mode of biocatalysis: the preparation of either or both enantiomers of a given target from achiral halogenated arenes. The synthesis of several carbohydrates, alkaloids, and cyclitols will highlight the discussion.

Arene cis-diols as carbohydrate synthons The synthesis of sugars has traditionally been accomplished by modifications of existing simple carbohydrates which also served as efficient chiral pool synthons.^{1,2} Indeed, many synthetic schemes in the seventies and eighties featured sugars as starting materials. The recognition that benzene is a triply reduced and triply dehydrated cyclohexanehexol (Fig. 1) allows for design of oxygenated compounds and sugars themselves directly from aromatic compounds. The pioneering work of Gibson³ on the dioxygenase mediated degradation of arenes more than 20 years ago provided the excellent synthon such as **2** for use in synthesis.

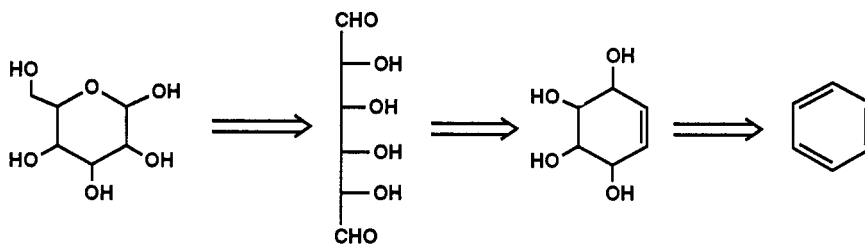


Fig. 1 Approach to Carbohydrates from Arenes

It took almost twenty years for the synthetic community to recognize the enormous potential of synthons such as **2**. Many research groups had utilized arene cis-diols in their synthetic efforts.⁴ As shown in Fig. 2, the intermediate cis-diol **2** is amenable to conversion to a variety of natural products. There are some unique elements connected with **2** that require a brief mention.

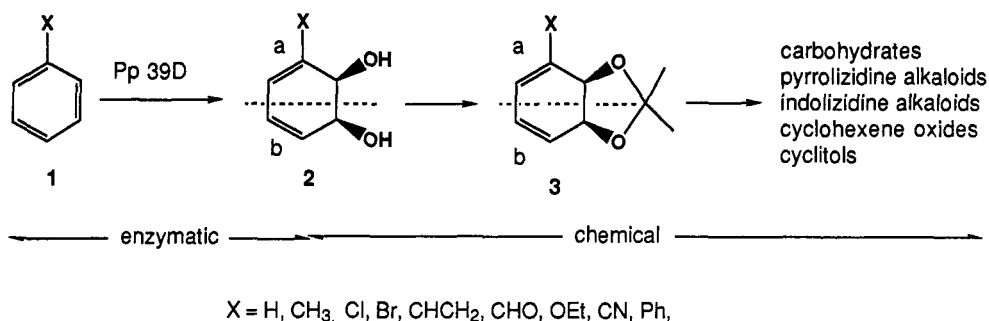


Fig. 2 Biocatalysis Approach to Synthesis via Arene Oxidation by *Pseudomonas putida* 39D

First, the diols contain a proenantiotopic plane of symmetry (dotted line, Fig 3) which enables their functionalization in an enantiodivergent manner to yield both enantiomers of a given target. The quadrants *a* and *d* vs quadrants *b* and *c* thus constitute the proenantiotopic space in

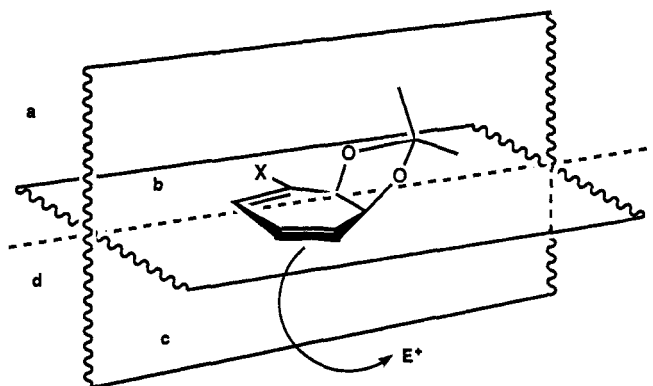


Fig. 3 Stereoelectronic Disposition of Arene cis-Diol Acetonides

which the subsequent transformations occur. Second, diastereoselectivity can be controlled by intramolecular delivery (quadrants *a* and *b*, syn relationship) or intermolecular delivery to a suitably hindered derivative, such as an acetonide (quadrant *c* and *d*, anti relationship). Third, the polarization of the halodiene allows for the expectation of fully regioselective C-C or C-hetero bond formation at C-4, the carbon possessing the most charge density. With this rationale, published recently in the context of an exhaustive synthesis of cyclitols,^{4b} we can expect to design an efficient synthesis of any isomer of simple monosaccharides and their hetero-substituted derivatives.

Synthetic applications The above rationale of synthetic design can best be exemplified on the enantiodivergent synthesis of D- and L- erythrose, Fig. 4.

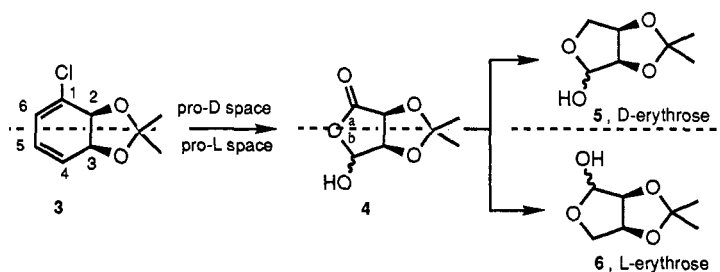


Fig. 4. Synthesis of D- and L-Erythroses from Chlorobenzene

The protected diol is ozonized to yield lactone - lactol **4** which contains a latent plane of symmetry similar to that of the diol. This selective reduction (BH_4^-) of the lactol gives L-erythrose while the selective reduction of the open-form acid (BH_3) gives the D-isomer. These reductive operations may be combined with the ozonolysis work-up to provide for a rapid preparation of the protected sugar derivatives. If free sugars are desired, the ozonolysis of the free diol **3** combined with the reduction can yield either isomer of erythrose in just two steps from chlorobenzene!

Lactone **4** is a unique compound. It is a chiral functional derivative of meso tartaric acid and, through careful design and symmetry considerations, can be used to provide both enantiomers of ribonolactones and trihydroxyheliotridanes as shown in Fig. 5.

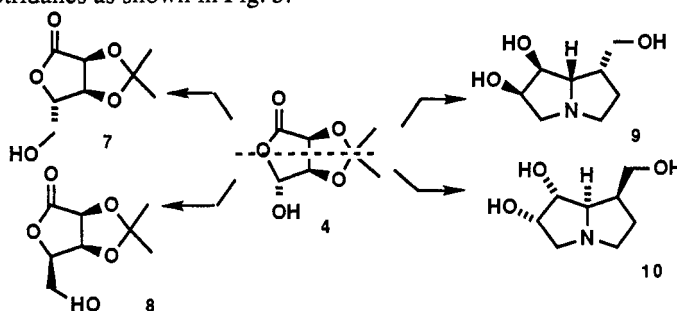


Fig. 5 Enantiovergent Synthesis of Ribonolactones and Pyrrolizidine Alkaloids

The true utility of lactone **4** can be appreciated from the following argument. Its oxidation would yield the anhydride of meso tartaric acid, which could be subjected to an enzymatic esterification to yield either enantiomer of mono acids convertible by selective reductions to the two erythroses. The generation of **4** directly and with differentiated functionalities allows for enantiodivergence without the necessity of using further enantiospecific reagents. Thus the consideration of symmetry can be viewed as a dimension in the overall synthetic sequence. Both enantiomers of a target should therefore be accessible via routes that are equivalent chemically and differ only in the symmetry space. This can be accomplished by switching the order in which various functionalizations take place as demonstrated on the synthesis of (+)- and (-)-pinitol, Fig. 6.

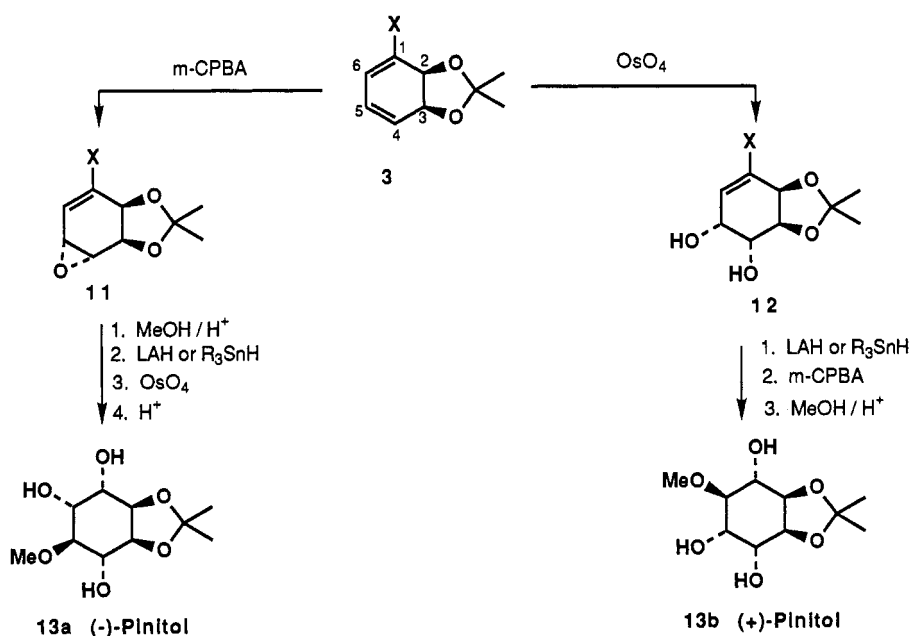


Fig. 6. Total Syntheses of (+) and (-) Pinitol

To extend the utility of arene cis-diols to the preparation of hexoses, and six-membered aza sugars of the nojirimycin type, we studied the oxidative cleavage of the vinylaldehyde with concomitant closure of the resulting carboxylate and a peripheral hetero-atom functionality, Fig. 7. The stereoselective functionalization of chlorobenzene diol **3** to the anti-diol **14** and azidohydrin **15** has been reported.^{4b}

Ozonolysis of the olefin and careful reductive work-up results in lactonization (or lactolization, if additional reduction is allowed to

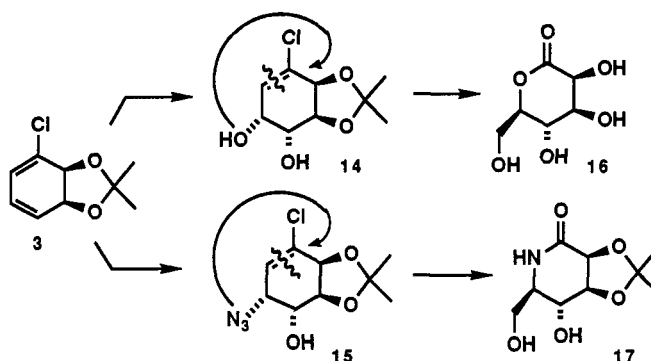
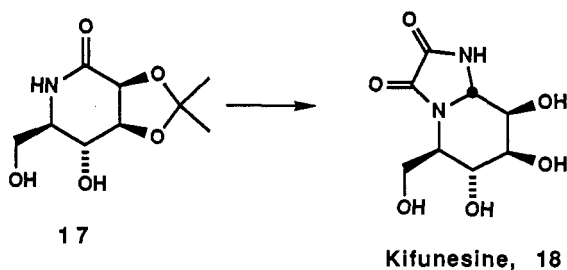


Fig. 7. D-mannose and Epinorjirimycin Synthesis

take place prior to work up). D-mannose, D-mannosolactone and deoxymannose are thus accessible. The azidoalcohol is smoothly converted to lactam **17** upon the reduction of the ozonide and azide groups. This compound is currently being converted to kifunesine **18**, a potent glycosidase inhibitor.



The diene in cyclohexadienes diols is a marvelously reactive entity. Its cycloadditions with acrylnitroso compounds yield regio and stereoselectively the bicyclic oxazines which can be further reduced and manipulated to aminocyclitols. The synthesis of conduramine A underscores the efficiency of this approach, Fig. 8.

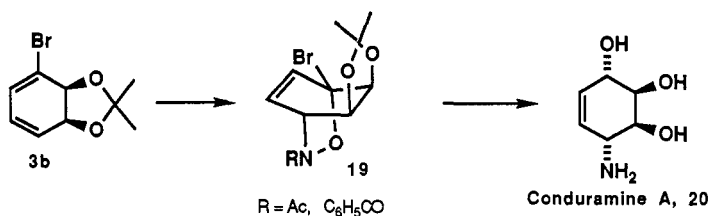
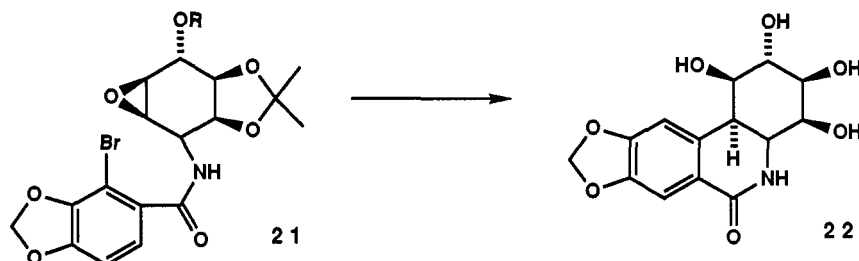


Fig. 8. Conduramine A Synthesis

Lycoricidine **22** is currently being synthesized from adduct of type **19** by intramolecular opening (metallation or radical generation) of the epoxide **21** generated in 3 steps from diol **36**!



In the final example, the model study aimed at the practical synthesis of (-)-morphine was undertaken to determine the fate of all chiral centers in the lower half of morphine. Toluene diol was used for this

purpose and alkylated with hexadienyl bromide. The Diels-Alder adduct obtained was transformed via Cope arrangement to ketone **25**. The unique feature of this synthesis is the fact that both modes of

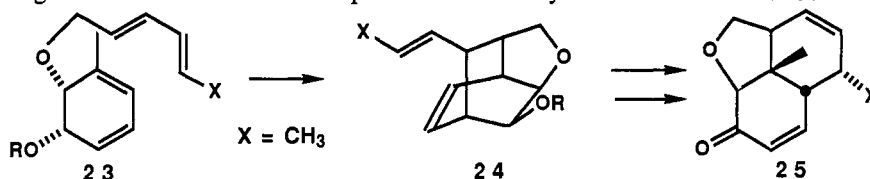


Fig. 9. Morphine model study

Diels-Alder possibilities in **23** can lead to **25**, either through the tandem cope rearrangement or the application of transition metal-accelerated [4+2] cycloaddition. This model bodes well for the actual efficient synthesis of (-)-morphine in the near future.

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CONCLUSION

In closing, it should be reiterated that the synthetic effort exemplified in this presentation complies with the requirements set forth in the introduction: the syntheses are extremely brief, efficient, and enantio-divergent. It is not for the authors to judge whether they also possess the elements of beauty—that judgement is left to the beholder. They are, however, practical and amenable to scale up processes.

Finally, an issue that will come to bear in the near future is that of regulation and environmental concern connected with chemicals. The overall philosophy of this research therefore should be viewed in the context of conversion of undesired (i.e. halogenated) aromatic compounds to useful (i.e. marketable) end products such as chiral synthons, simple sugars, or oxygenated natural products of interest, as shown in Fig. 10. At the same time that field of synthesis which relies on sugars or building blocks

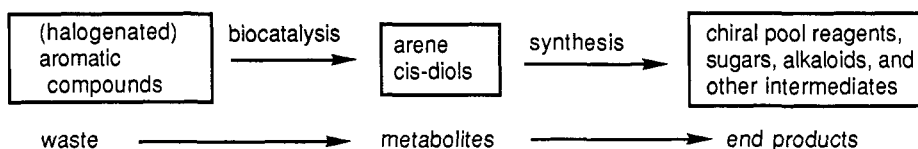


Fig. 10. Two-tier Conversion of Aromatics into Useful Compounds

can be challenged as it is unnecessary to either make sugars by tedious manipulations of other sugars or to use them as starting materials—that any particular combination of oxygenation can be assessed directly from arene diols is self evident. The diols are now commercially available in crystalline form and this should promote their use in synthesis⁵.

The field of biocatalysis is maturing quickly and is replacing the strictly traditional methods of organic synthesis. It is, as it should be, following the laws of evolution and improvement.

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