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Applications of enzymes in the synthesis of bioactive polyols

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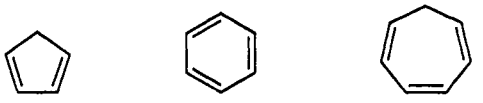
Abstract: Cyclopentadiene, benzene and cycloheptatriene were transformed to functionalized meso-diols. The resulting meso-diols or their corresponding meso-diacetates were subjected to enzymatic asymmetrizations using enzymes, particularly lipases, in organic or aqueous media. Examples of the use of the resulting aracemic products in the synthesis of a variety of polyols of biological interest are reviewed.

We are engaged in a program of synthesis of bioactive molecules by routes involving the following features: Readily available cyclic starting materials are subjected to stereospecific oxidation reactions which serve to set relative ring stereochemistry and produce compounds of the stereochemical class meso. These meso compounds are asymmetrized by use of enzymes to set absolute stereochemistry about the ring. Further manipulation then provides useful new chiral pool intermediates which are carried on to target molecules. In many instances, regioselective ring cleavage reactions are used to unveil acyclic compounds with fixed absolute stereochemistry.

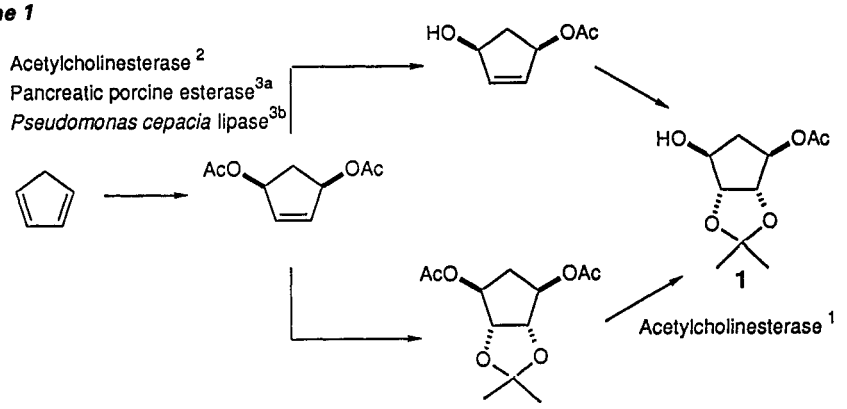
In this overview of recent efforts from our laboratory we will provide a synopsis of chemoenzymatic approaches to various bioactive targets utilizing the following as starting materials:



CHEMISTRY BASED ON CYCLOPENTADIENE

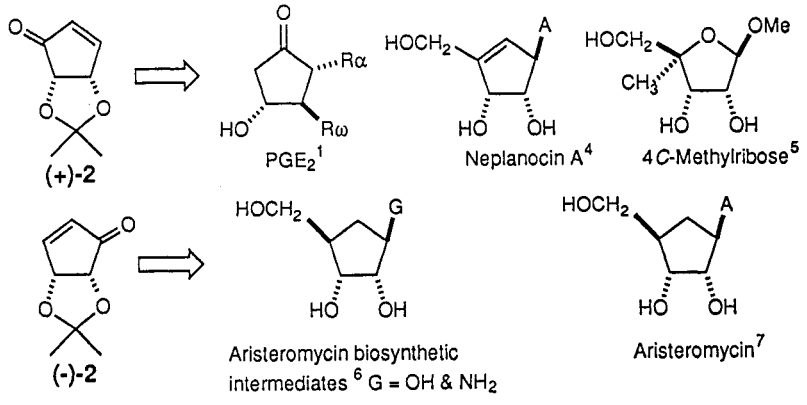
Our chemistry in the five-membered ring series begins with the addition of singlet oxygen to cyclopentadiene. This cycloaddition reaction, which is recurrent in our program, has the advantage of cleanly setting oxygen functionality cis at the termini of cyclic dienes. A variety of enzymes have been found useful in the production of chiral cyclopentanol **1** (Scheme 1).[1]

Scheme 1



The key chiral intermediate, the enone **2**, can be prepared in either enantiomeric series from **1**. Direct oxidation of **1** leads to (+)-**2** whereas protective group manipulations and oxidation at the former acetoxy bearing carbon of **1** leads to the enantiomer (-)-**2**. This ability to enter in either enantiomeric series in a straightforward fashion regardless of the enantiomeric outcome of the enzymatic asymmetrization is a consistent advantage of working with cyclic meso diol derivatives as substrates. Scheme 2 illustrates target molecules which we have prepared from the enones (+)- and (-)-**2**.

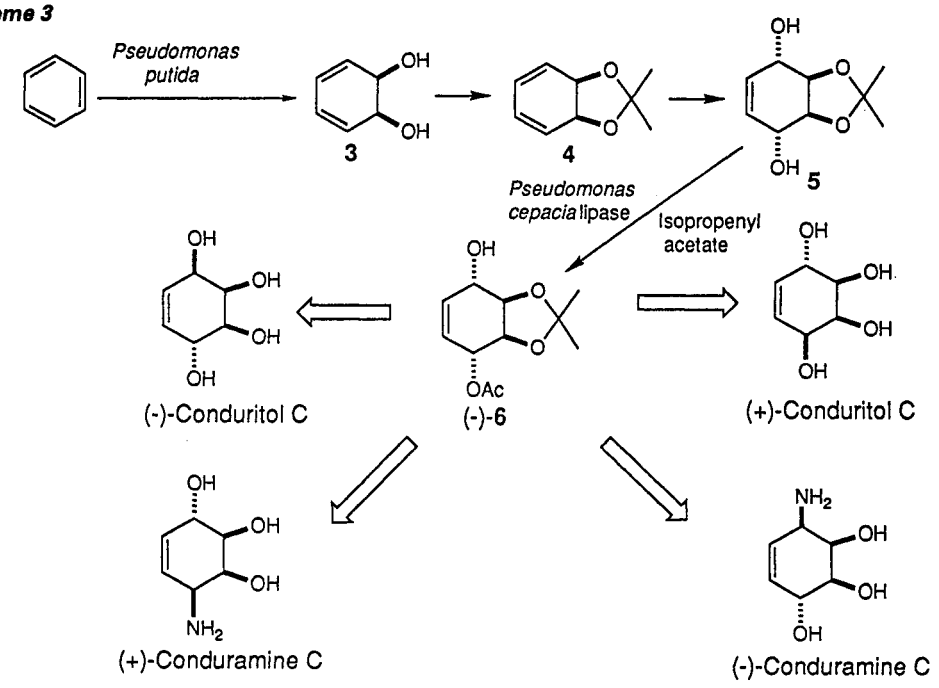
Scheme 2



CHEMISTRY BASED ON BENZENE

It appeared to us that *meso*-3,5-cyclohexadiene-1,2-diol (**3**), available by oxidation of benzene by mutants of *Pseudomonas putida*,[8] would provide an ideal starting material for the development of enantioselective syntheses of various cyclitols and related materials which are currently of interest as glycosidases inhibitors.[9] The diol **3** was protected as its acetonide **4** and the latter converted to the meso-2,3-diprotected conduritol A (**5**) by addition of singlet oxygen and thiourea reduction. The meso diol **5** was treated with crude lipase from *Pseudomonas cepacia* (Amano P-30 lipase) (*ca.* 1:1 substrate to crude lipase) in isopropenyl acetate[10] at 55 °C for 2 days to yield monoacetate **6** (90% yield, >95% ee). Variants on Mitsunobo chemistry were found to be very successful for the inversion of oxygenated centers and the introduction of amino substituents (Scheme 3).[11,12]

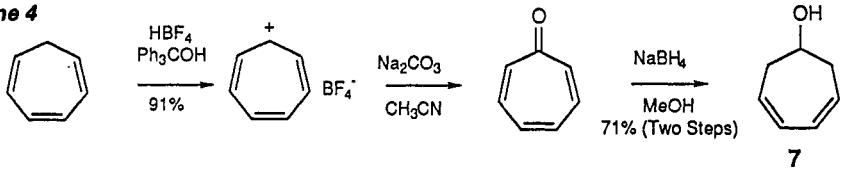
Scheme 3



CHEMISTRY BASED ON CYCLOHEPTATRIENE

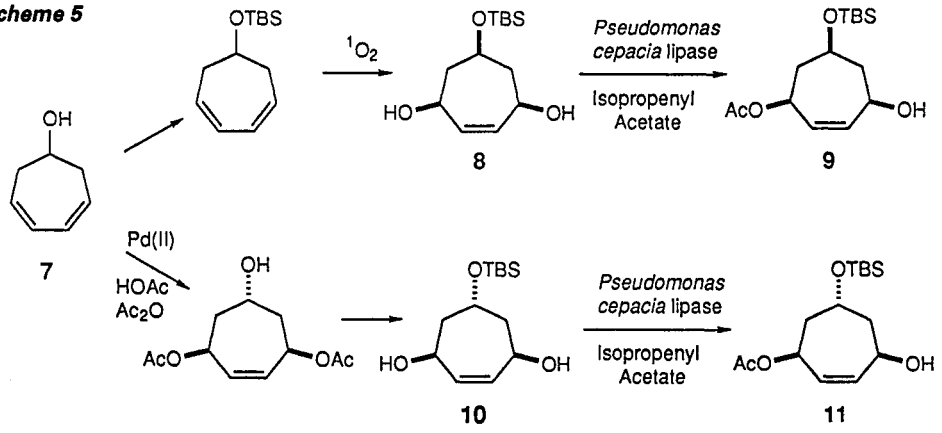
Cycloheptatriene can be transformed to tropone by a number of processes. We favor a variant based on the procedure of Reingold;[13] when tropylium ion is treated with carbonate a disproportionation ensues to provide tropone and cycloheptatriene. Tropone undergoes a reduction to 3,5-cycloheptadienol (**7**) with sodium borohydride in methanol (Scheme 4). The meso-diol **8** and

Scheme 4



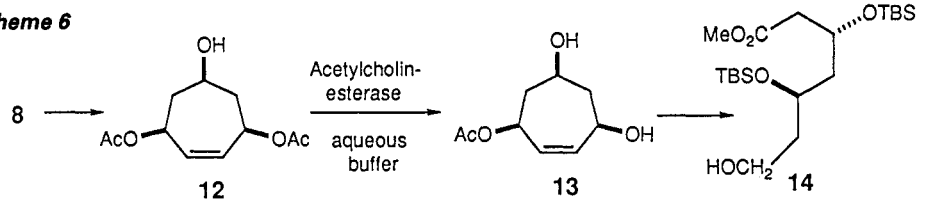
its diastereomer **10** were prepared utilizing singlet oxygen chemistry and Bäckvall Pd(II) chemistry, respectively. These diols are cleanly asymmetrized using *Pseudomonas cepacia* lipase in isopropenyl acetate to provide optically pure **9** and **11**, respectively (Scheme 5).[14]

Scheme 5



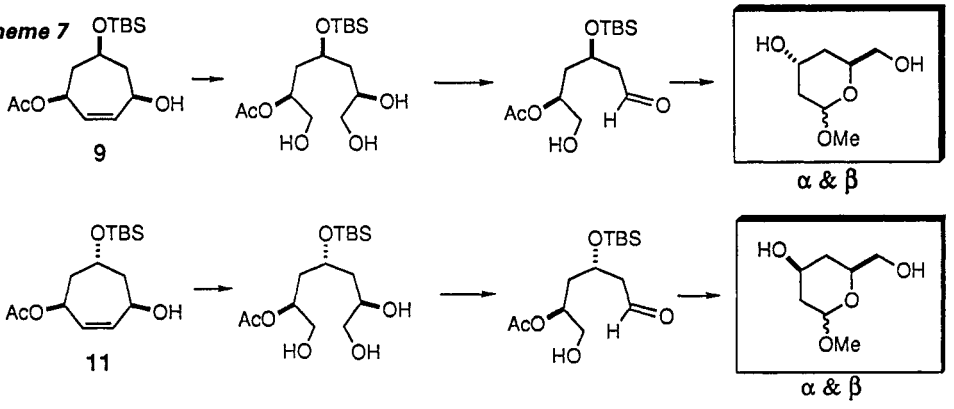
The preparation of **9** nicely illustrates that utilization of enzymes in organic media[15] often provides significant advantages in a synthetic sequence. In the aqueous-based sequence the diacetate was formed from compound **8**, the *t*-butyldimethylsilyl protecting group was removed to increase water solubility and the meso-diacetate **12** was asymmetrized using acetylcholinesterase in aqueous phosphate buffer to provide diol (+)-**13**. The manipulation of (+)-**13** to the important compactin analogue intermediate **14** required the differentiation of the allylic and non-allylic free hydroxyl groups as well as the replacement of the silyl-protecting group (Scheme 6).[16] By switching to enzyme chemistry in organic media three steps (the conversion to the diacetate and the removal and replacement of the *t*-butyldimethylsilyl) can be eliminated in the overall conversion of **8** to **14**.

Scheme 6



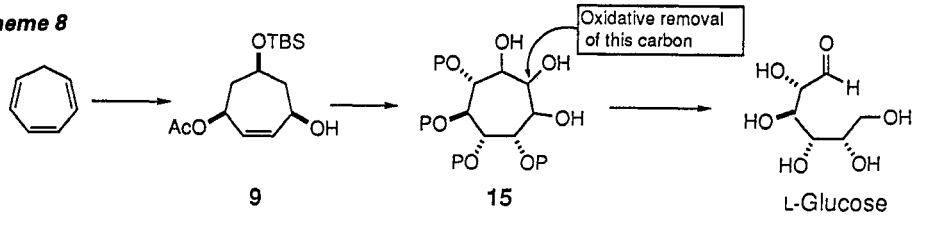
We have found these cycloheptatriene-derived aracemic intermediates to be useful in the synthesis of a variety of carbohydrate derivatives. All eight optically pure methyl glycosides of the 2,4-dideoxyhexoses have been prepared from **9** and **11**, four of which illustrated in Scheme 7.[17]

Scheme 7



Procedures which stereoselectively increased the oxidation level of **9** to that of intermediate **15** have allowed us to complete the transformation of cycloheptatriene to L-glucose (Scheme 8).[18]

Scheme 8



The stereochemical outcome of the above *Pseudomonas cepacia* lipase reactions, as well as others, *e.g.*, Scheme 9, suggest that the simple presence of some substituent Z (Figure 1)[14] is more

important than the stereochemical orientation of that substituent. Presumably this provides for superior differentiation of the ring sectors flanking the carbon bearing the oxygen which is being acylated or deacylated by the lipase. Figure 1 illustrates a simple working model of a cyclic alcohol in the lipase active site,[19] whereas Scheme 9 illustrates the enantio-complementary outcome of enzymatic reactions in aqueous and organic media.[20]

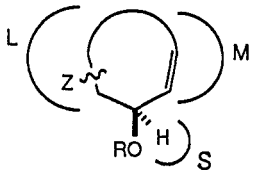
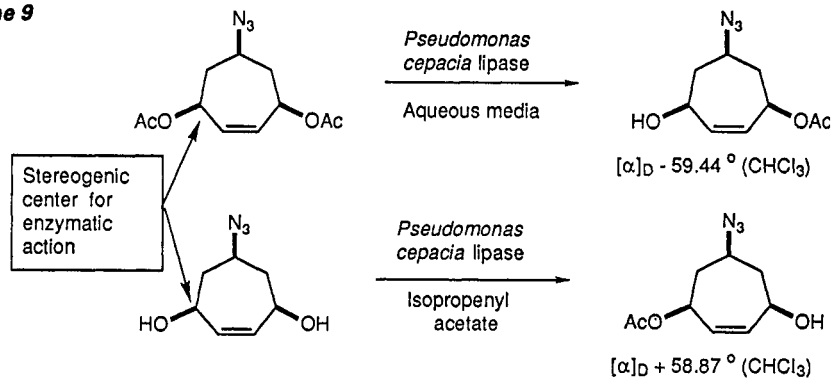


Figure 1.
Model of alcohol in *Pseudomonas cepacia* active site.

It is hoped that this short review serve to convince the reader of the remarkable advantages that can accrue by the incorporation of enzymatic steps into a synthetic design. The advantages of enantioselectivity of enzymatic reactions can be enhanced by use of meso compounds and the range of useful substrates can be extended by use of enzymes in organic media.

Scheme 9



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