Enantioselective synthesis of alkaloids and carbohydrates via chemoenzymatic methods

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ABSTRACT: Homochiral diene diols of type 1, derived biocatalytically by microbial dioxygenation of halogenated aromatic compounds, have served as precursors to a number of oxygenated natural products. Specifically, D-chiro-inositol (9), D-erythronolactone (10), (+)-lycoricidine (14), (+)-kifunensine (19), and L-threo-sphingosine (25) have all been synthesized from 1.

Prokaryotic dioxygenation of aromatics proceeds via homochiral cyclohexane-cis-diols of type 1. Large scale accumulation of these products can be accomplished by the use of various mutants of Pseudomonas organisms, namely Pseudomonas putida 39D (Pp39D). Synthons such as 1 have found widespread use in enantioselective synthesis of complex natural products as evidenced by a number of reviews in this area.

Fig. 1. Exhaustive design of carbohydrates
With better understanding of the chemistry of diene diols 1 we have progressed to more complex targets as well as to more general and exhaustive applications in the carbohydrate field. The results have been pleasing, and we are moving toward a fully general design of carbohydrate derivatives attainable in any stereo- or enantio-configuration from a single source, as shown in Fig. 1. Furthermore, the methods of further functionalization are tailored to be short, efficient, and environmentally benign. The following examples of syntheses illustrate the power of biocatalytic technology in the efficient synthesis of target molecules.

D-chiro-Inositol (9) was attained in a few steps as outlined in Fig. 2 by a unique oxidation of the acetonide derived from 1 with KMnO4. The unusual chloro epoxy diol 7 was reduced with (TMS)$_3$SiH and hydrolytically transformed to the final inositol in an overall yield of ~50%.

\[
\begin{align*}
\text{D-chiro-Inositol} & \rightarrow 1 \xrightarrow{(i) DMP/H^+/KMnO_4/MgSO_4/H_2O/acetone} 7 \xrightarrow{(ii) (TMS)$_3$SiH, AIBN} 8 \xrightarrow{(iii) H_2O/\Delta} 9 \\
& \text{(i) DMP/H$^+$/KMnO$_4$/MgSO$_4$/H$_2$O/acetone; (ii) (TMS)$_3$SiH, AIBN; (iii) H$_2$O/\Delta}
\end{align*}
\]

Fig. 2. Synthesis of D-chiro-inositol

D-Erythruronolactone was attained in one operation from chloro epoxy diol 7 by cleavage with aqueous periodate as shown in Fig. 3. This important compound has served as a starting material in several syntheses of oxygenated pyrrolizidine alkaloids.

\[
\begin{align*}
\text{D-Erythruronolactone} & \rightarrow 1 \xrightarrow{i} 7 \xrightarrow{ii} 8 \xrightarrow{iii} 9 \\
& \text{1. DMP/H$^+$/KMnO$_4$/MgSO$_4$/H$_2$O/acetone; 2. H$_2$O/\Delta}
\end{align*}
\]

Fig. 3. Synthesis of (+)-erythruronolactone

(+)-Lycoricidine was synthesized via an acyl nitroso [4+2] cycloaddition to the acetonide 9 and attained in an excellent overall yield (Fig. 4).

\[
\begin{align*}
(+)-Lycoricidine & \rightarrow 1 \xrightarrow{i} 12 \xrightarrow{1. Bu$_4$NIO$_4$} 13 \xrightarrow{5 \text{ steps}} 14 \\
X &= \text{Cl, Br}
\end{align*}
\]

Fig. 4. Synthesis of (+)-lycoricidine

(+)-Kifunensine was approached first via functionalization of mannojirimycin derivative 17, then by intersection of Hashimoto's synthesis as described in Fig. 5. This synthesis demonstrated that aza sugars are readily attainable as projected in Fig. 1.
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L-threo-sphingosine synthesis was accomplished as shown in Fig. 6. The strategy of this approach relied on the control in generating any of the four possible configurations of azido alcohols. Oxidative cleavage of azido mannose gave azido erythrose, which yields the title compound via Wittig reaction and reduction. The preparation of other sphingosines and ceramides is currently in progress.

The synthesis of aminosugars such as mannosamine relies on the cyclization mode C2–C6 as shown in Fig. 7. The preparation of pancreaticid and carbocyclic sugars or inositol conjugates relies on the successful nucleophilic opening of epoxides such as 20 or aziridines of type 28 with carbon nucleophiles as indicated in Fig. 7. This is a new field, and we have already made some progress in this area. Finally, we are working on an approach to the morphine alkaloids via [4+2] Diels–Alder reaction.
In conclusion, the power and efficiency of enantioselective synthesis of the diene diols has been demonstrated on a few selected syntheses presented herein. New applications to more complex natural products, execution of general carbohydrate design, and investigation of new metabolites form the current research focus of our program.

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REFERENCES


