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Enantioselective synthesis of alkaloids and carbohydrates via chemoenzymatic methods

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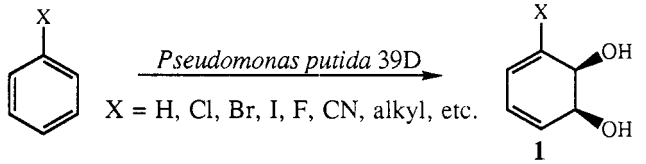
ABSTRACT: Homochiral diene diols of type **1**, derived biocatalytically by microbial dioxygenation of halogenated aromatic compounds, have served as precursors to a number of oxygenated natural products. Specifically, D-*chiro*-inositol (**9**), D-erythuronolactone (**10**), (+)-lycoricidine (**14**),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



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Prokaryotic dioxygenation of aromatics proceeds via homochiral cyclohexane-*cis*-diols of type **1**.[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.[2]

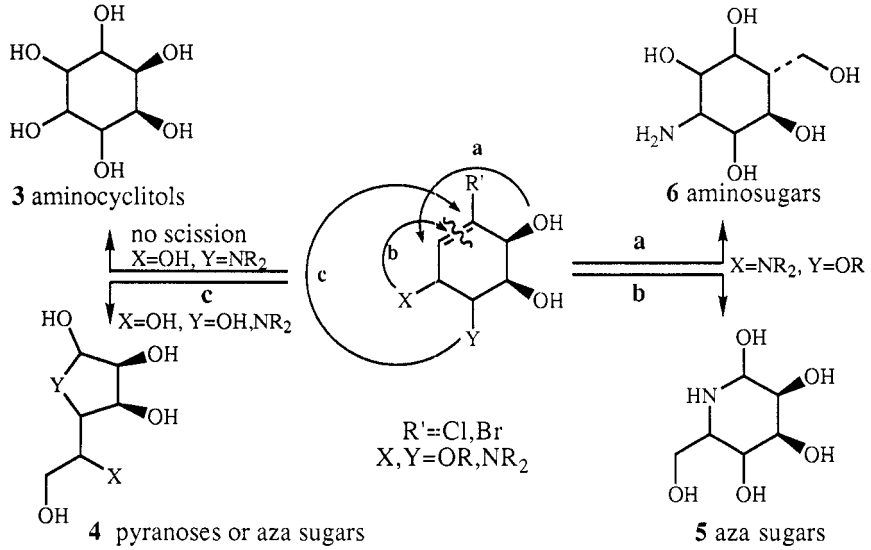
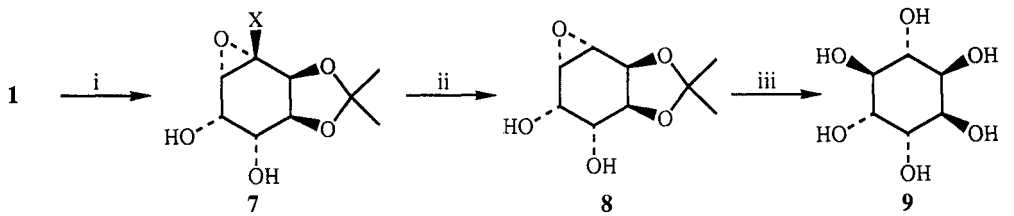


Fig. 1. Exhaustive design of carbohydrates

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 $KMnO_4$. The unusual chloro epoxy diol **7** was reduced with $(TMS)_3SiH$ and hydrolytically transformed to the final inositol in an overall yield of ~50%.[3]



(i) DMP/H^+/$KMnO_4$/$MgSO_4$/H_2O/acetone; (ii) $(TMS)_3SiH$, AIBN; (iii) H_2O/Δ

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.[4] This important compound has served as a starting material in several syntheses of oxygenated pyrrolizidine alkaloids.[5]

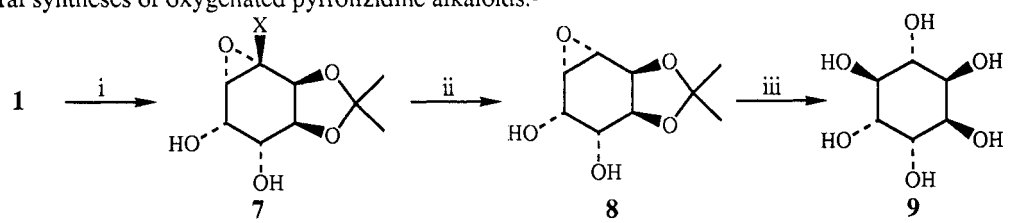


Fig. 3. Synthesis of (+)-erythruronolactone

(+)-Lycoricidine was synthesized via an acyl nitroso [4+2] cycloaddition to the acetonide **9** and attained in an excellent overall yield (Fig. 4).[6]

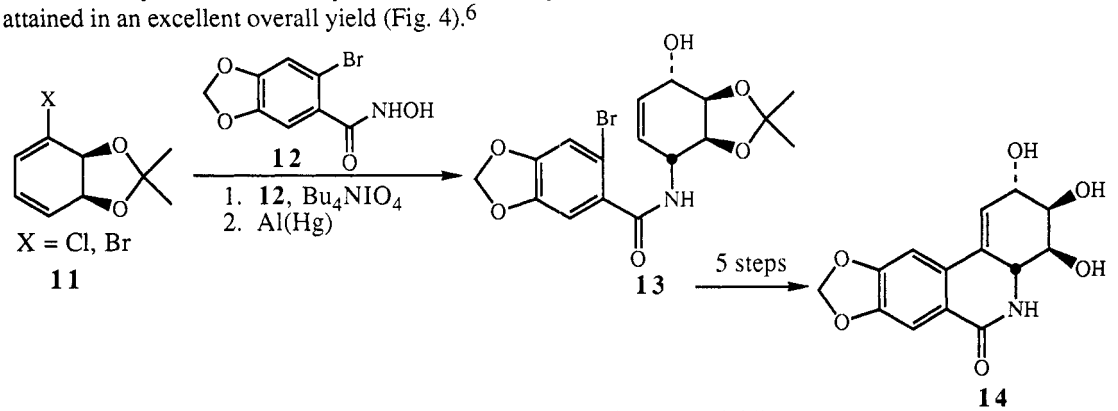


Fig. 4. Synthesis of (+)-lycoricidine

(+)-Kifunensine was approached first via functionalization of mannojirimycin derivative **17**, then by intersection of Hashimoto's synthesis as described in Fig. 5.[7] This synthesis demonstrated that aza sugars are readily attainable as projected in Fig. 1.[8]

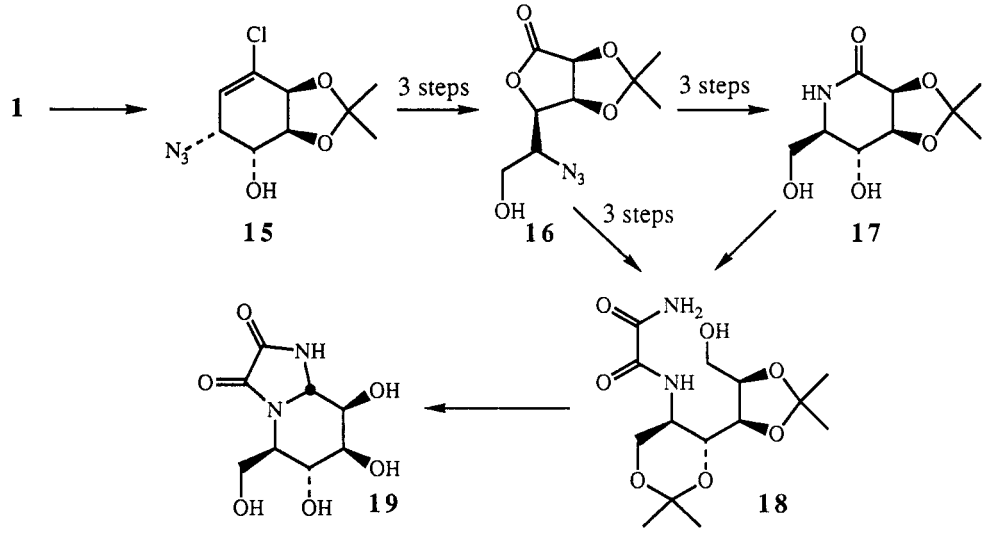


Fig. 5. Synthesis of (+)-kifunensine

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 **21**. Oxidative cleavage of azido mannose **22** gave azido erythrose **23**, which yields the title compound via Wittig reaction and reduction. The preparation of other sphingosines and ceramides is currently in progress.[9]

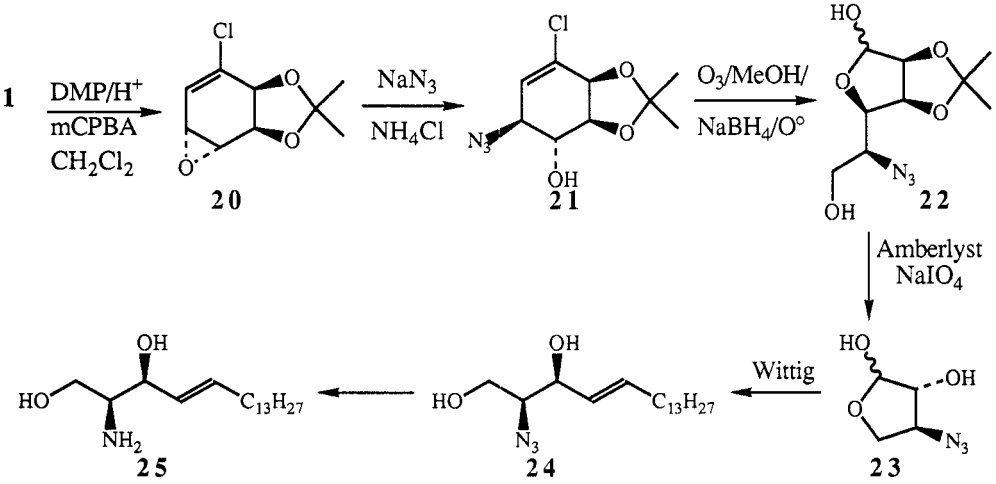


Fig. 6. Synthesis of L-*threo*-sphingosine

The synthesis of aminosugars such as mannosamine **26** relies on the cyclization mode C2–C6 as shown in Fig. 7. The preparation of pancratistatin 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.[10]

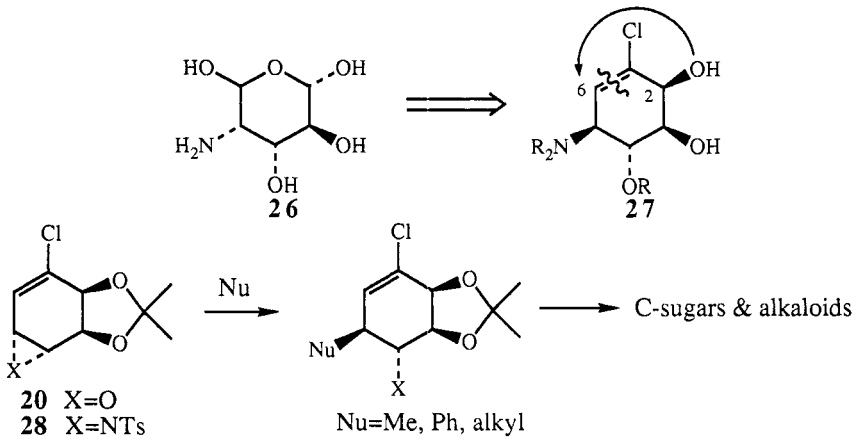


Fig. 7. Synthesis of aminosugars and pseudo-sugars

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.

ACKNOWLEDGMENTS. I am indebted to my many collaborators, students, and postdoctoral associates whose names are listed in the citations. Financial support from TDC Research, Inc., Genencor International, Mallinckrodt, NIH, and Jeffress Trust Fund is appreciated.

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