

Current status and future perspectives of cyclohexadiene-*cis*-diols in organic synthesis: versatile intermediates in the concise design of natural products

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The cyclohexadiene-*cis*-diols are a group of chiral synthons valuable in the synthesis of a diverse range of natural products and molecules of biological interest as well as in the development of concise and fully general methodologies for entire groups of organic molecules. Below, the authors briefly summarize the history of these synthons and project future trends in the field. At a time when brevity, enantiocontrol, efficiency and environmental concerns are of prime importance in an ever demanding discipline, the enzymatically produced *cis*-diols offer the organic chemist one possible method of realizing these goals.

Introduction

The enantioselective synthesis of natural products and therapeutic agents is an exciting and challenging area of organic synthesis. A successful organic chemist is always aware of the continually evolving need for efficient methods of assembling target molecules by means of succinct routes. There is currently an overwhelming array of techniques available for introducing chirality—the use of chiral pool synthons, chiral catalysts, and chemoenzymatic approaches, as well as classical resolution techniques. Unfortunately, a field such as biocatalysis, whose aim is the development of concise, practical routes to organic molecules, has yet to attract interest equal to that witnessed in the field of asymmetric catalysts and chiral auxiliaries—as much as the latter techniques, enzymes represent a valuable source of asymmetric catalysts. The ability of enzymes to recognize prochiral groups in a symmetric molecule, to resolve racemic molecules efficiently and to promote carbon–carbon bond formation is well documented.¹ Enzymes are powerful agents that remain an under-used resource despite immense developments in this field over the past two decades.

One of the more remarkable enzyme-catalysed transformations is the toluene-dioxygenase-mediated *cis*-hydroxylation of aromatics to cyclohexadiene-*cis*-diols, first reported by Gibson's group in 1968.² Following studies in pseudomonads on the degradation of benzene to muconic acid and other intermediates in the tricarboxylic acid cycle, Gibson isolated a mutant strain of *Pseudomonas putida* that lacked the enzyme catechol dehydrogenase, which further metabolizes diols of type 2; these compounds therefore accumulated in the fermentation broth (Fig. 1). This mutant strain, *P. putida* 39/D, was also found to oxidize toluene to its corresponding dihydrodiol with high enantiomeric excess.^{2a} Later the genes encoding the four components of the enzyme vital to dihydrodiol formation were isolated from *P. putida* and cloned into *Escherichia coli*.^{2c} The resultant recombinant microorganism, *E. coli* JM109

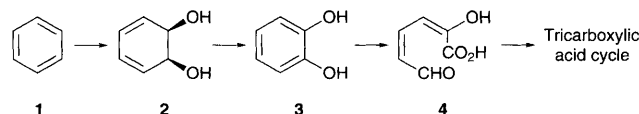


Fig. 1 Conversion of benzene to muconates by *Pseudomonas putida*

(pDTG601), has provided the desired diols in excellent space-time yields (that is, grams per litre per hour). Thus, Gibson's seminal research has provided the technology to furnish large amounts of *cis*-diol metabolites. Since then similar enzymes have been isolated, including naphthalene and biphenyl dioxygenases. Over two hundred metabolites produced by dioxygenase-mediated conversion of aromatics have been reported;³ some examples of these diverse metabolites are shown in Fig. 2.

For nearly twenty years, from the time of Gibson's first report, this unprecedented conversion aroused virtually no interest in the synthetic community until Ley's synthesis of pinitol in 1987.⁴ Since then several groups have utilized this biotransformation in the synthesis of a variety of compounds. In addition to the effort of Ley,^{4,5} whose pioneering disclosure opened up the field, the work of Roberts,⁶ Johnson,⁷ Boyd,⁸ Banwell⁹ and Carless¹⁰ deserve special credit. Notably active in further isolation of new metabolites have been the groups of Gibson, Boyd,⁸ Dalton,¹¹ Crout,¹² the group at the EPA laboratories in Gulf Breeze (Chapman and Eaton),¹³ the group of Ribbons¹⁴ and the group at the University of Minnesota (Wackett and Selifonov).¹⁵ Research into the structural features of arene dioxygenase continues through the efforts of Mason,^{16,17,18} Gibson, Whited (Genencor International) and the Turner group (University College, London). Our own group has pursued active research in the area of synthetic applications for almost ten years. Isolation of new metabolites remains high on the list of investigations as a source of new synthons for new targets. As an ongoing challenge, the development of short enantioselective synthetic routes to molecules of biological significance is of utmost importance, and the utilization of cyclohexadiene-*cis*-diols in practical total synthesis has been particularly instrumental in this regard.

As in any field of scientific endeavour one must pay close attention to the versatility of the methods and at the same time avoid overly committing any one particular method or technique to a broad range of problems. So it must be with the

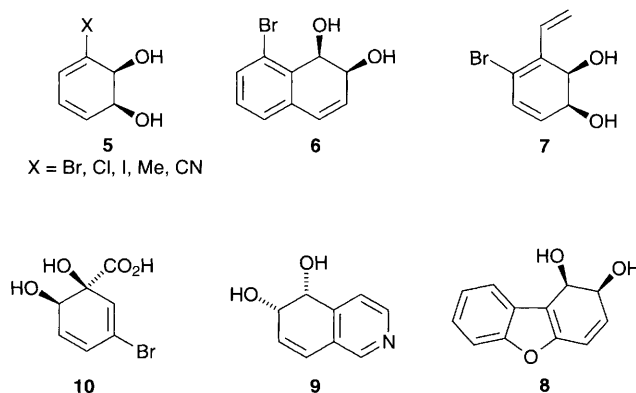


Fig. 2 Examples of arene metabolites formed from the *P. putida* 39/D or JM109 (DTG601) naphthalene dioxygenase-catalysed degradation of aromatics

exploitation in enantioselective synthesis of the metabolites derived from biooxidation of aromatics. The field is now at the point where the foundations have been laid for basic applications and indications of general utility in more sophisticated developments are emerging. Table 1 summarizes the accomplishments in the field over the last decade and some projections of likely future research. The first generation includes those general activities that have been accomplished by us and others during the first five years following Ley's disclosure of pinitol. The subsequent generations indicate activities of higher complexity or more sophisticated development of a previously researched field. (Bold text indicates those activities that have already been researched successfully as of this writing.) The third and fourth generations indicate the likely trends that this field is beginning to enter or will pursue in the future. It is safe to say that the field will continue to expand for some time.

Much has been written about the use of diol metabolites in several reviews. For the most part, the reviews summarize accomplishments according to the type of targets. In several recent essays^{19a,b} we have attempted not only to describe the generally accepted use of diols in synthesis but also to examine

the many different perspectives from which to view this methodology.

First is efficiency, the most obvious advantage of the use of cyclohexadiene-*cis*-diols in synthesis. For example, no approach to the total synthesis of inositol to date competes successfully with the brevity of those originating in arene *cis*-diols.²⁰

Second, brevity and efficiency are vital components of the now popular trend in 'environmentally benign' or 'green' chemical technology.^{19b} The diol-derived technology leads to short, concise routes that do not consume massive amounts of reagents or toxic, metal-derived components. A classic example is the three-step synthesis of *D-chiro*-inositol, which is amenable to further optimization on an industrial scale.^{20a}

Third, the diol metabolites exhibit diverse reactivity, which is inherent in their functional disposition and their unique symmetry elements (described previously, with several applications).^{19a,b,21b} They lend themselves to application in the design of fully general and exhaustive methods of synthesis for entire classes of compounds, such as carbohydrates,^{19a,b,c,22} examples from each of the major groups of which have been synthesized.²²

All of the past work has been accomplished with diols derived from monocyclic arenes, most of the work with the diols derived from bromo- or chloro-benzene. Now is the time to look ahead not only towards the exploitation of the remainder of the two hundred or so metabolites, but also towards the discovery of new strategies and proper matching of substrate and target. As portrayed in Table 1, the applications of this technology will gain in complexity in the next decade. Production technology is now firmly established, and several of the *cis*-diol synthons are commercially available. For all the advances in the technology, biocatalytic synthetic methods are not recognized in the United States to the extent they are in Europe—only two groups, our own and that of Carl Johnson, are actively pursuing the application of arene diols to synthesis as of this writing.

Some examples of the successful commercial application of cyclohexadiene-*cis*-diols are shown in Fig. 3. The first one is the synthesis of polyphenylene by the polymerization of benzene-*meso*-diol reported by ICI.²³ The second is an artful example of the power of biocatalysis, Genencor's process for indigo from glucose;²⁴ the naphthalene dioxygenase oxidation of indole constitutes the penultimate step in a plasmid-

Table 1 Evolution of the use of cyclohexadiene-*cis*-diols in synthesis

1st Generation	1987–1992	<ul style="list-style-type: none"> ● Single-ring metabolites ● Conduritol/inositol synthesis ● Monosaccharide synthesis ● Alkaloid synthesis ● Terpene synthesis
2nd Generation	1990–1995	<ul style="list-style-type: none"> ● Higher order metabolites ● Alkaloid synthesis ● Design of general methods for sugar synthesis ● Industrial applications
3rd Generation	1994–	<ul style="list-style-type: none"> ● Higher order substrates ● Higher complexity of targets ● Synthesis of glycoconjugates ● General methodology applications
4th Generation	1996–	<ul style="list-style-type: none"> ● Combinatorial chemistry ● Oligosaccharide synthesis ● Substrate/target matching ● Expression of enzymes

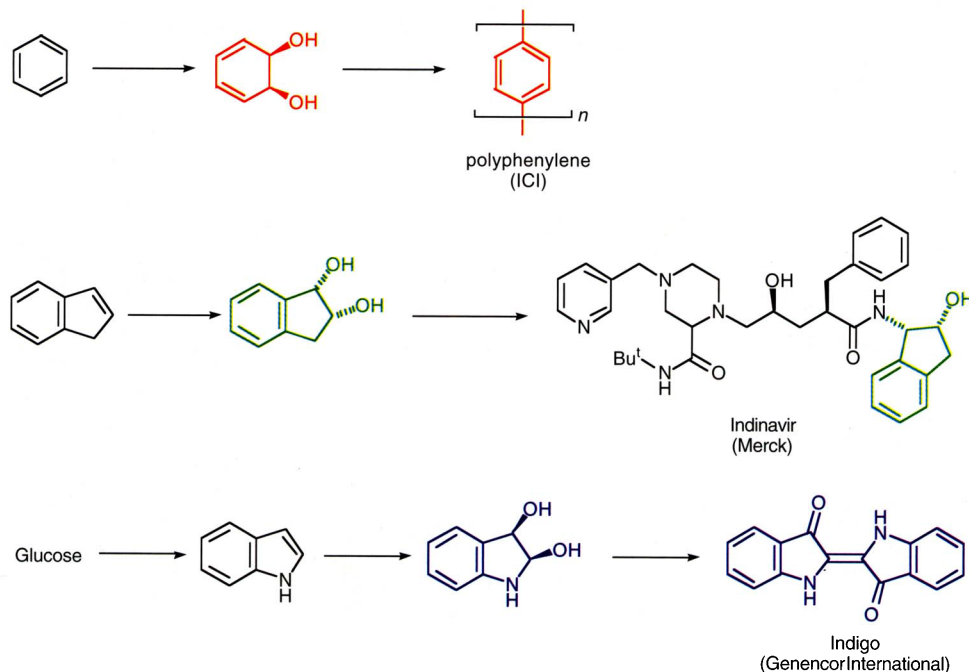


Fig. 3 Commercial applications of arene-*cis*-diols

engineered pathway. Finally, the Merck process for the anti-HIV drug Indinavir, projected for manufacturing on a scale of one million kilograms per year, uses the Ritter reaction to generate the crucial amino indanol from the biocatalytically derived indene-diol.²⁵ These applications illustrate the practical aspects of synthetic ventures utilizing diol metabolites. Major milestones and indications of some potential future directions of this exciting field are described in the next section.

The use of arene-*cis*-diols in organic synthesis

As the chemistry of arene-*cis*-diols has been extensively reviewed, the remainder of this article highlights research from our own group. For the excellent work of our colleagues in this area the reader is encouraged to consult several recent reviews.¹⁹

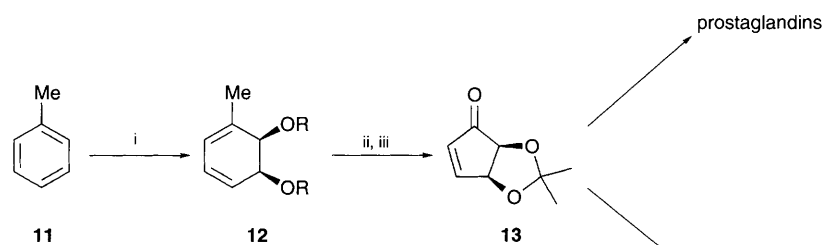
Of particular importance is the versatility of cyclohexadiene-*cis*-diols in enantiocontrolled synthesis. Our first entry into the field of cyclohexadiene-*cis*-diols culminated in the successful synthesis, through the exhaustive oxidation of the free diol and subsequent aldol condensation, of cyclopentenone **13**, an important intermediate in the preparation of prostaglandins and carbocyclic nucleosides (Scheme 1).^{20c,26}

Over the past decade we have developed synthetic routes from diene-diacetates to a diverse range of compounds. Such molecules include azasugars,^{22b,c} inositols,²⁰ glycosidase inhibitors²⁷ and alkaloids.²⁸ Several examples of naturally occurring compounds synthesized by the Hudlicky group from arenes

are shown in Fig. 4, where the coloured carbons indicate those originating from the biologically generated metabolite. Looking at the variety of compounds synthesized, one can see that arene-*cis*-diols represent an important branch point in the synthesis of structurally diverse molecules. The metabolites are readily available in high optical purity and possess a rich functionalization that can be further exploited in total synthesis of diverse targets.

The late 1980's and early 1990's saw an explosive growth in the chemistry of cyclohexadiene-*cis*-diols. Our own early efforts focused on an enantiodivergent synthesis of (+)- and (-)-pinitol (Scheme 2), which took advantage of the presence of the proenantiotopic plane in both the starting diene acetone **23** and the two enantiomers, **16a** and **16b**. Thus, through rational choice of the order of transformations, either enantiomer of pinitol is accessible from *achiral* chlorobenzene via a single enantiomer of the metabolite.²¹

The unprecedented conversion of diol **5a** to the protected glycol-chloroepoxide **24** was discovered upon the oxidation of the diene with potassium permanganate,^{20,32} Scheme 3. The halogenoepoxy diol can be prepared in large quantities by means of a one-pot protection and oxidation by non-toxic potassium permanganate under acidic conditions. (The by-product of this reaction is manganese dioxide, a common mineral in nature.) The unusually stable halogenoepoxide is a useful intermediate in the synthesis of a multitude of versatile synthons accessible by further reductive or hydrolytic transformations. For example, reduction and hydrolysis of **24** led to



Scheme 1 Reagents: i, *P. putida* 39/D; ii, O₃, DMS; iii, Al₂O₃

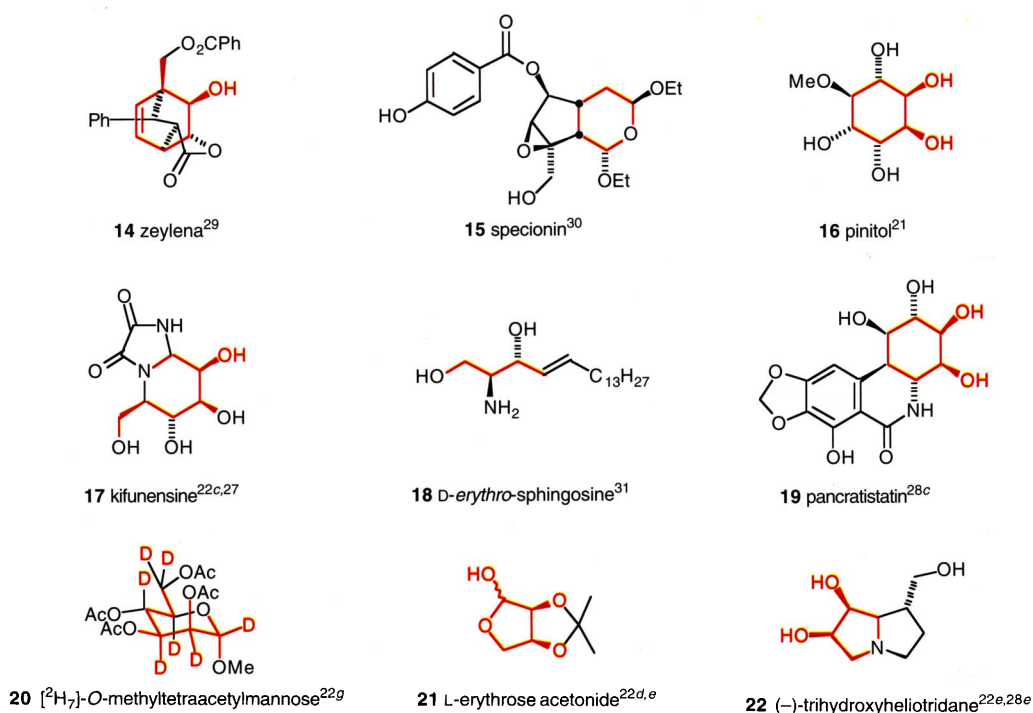


Fig. 4 Examples of naturally occurring compounds synthesized by the Hudlicky group, 1986-1996

a concise synthesis of *D-chiro*-inositol **16c**, the free alcohol of (+)-pinitol **16b**.²⁰

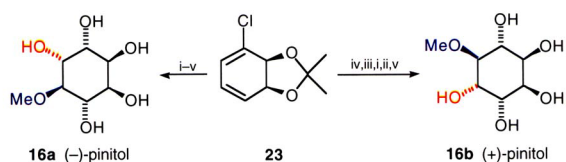
Diol derivatives such as **28** (Scheme 4) possess latent oxidation states that become accessible upon oxidative cleavage. Depending on the nature of the heteroatom functionalization at C4 or C5, entry into azasugars, monosaccharides, and amino and fluoro deoxysaccharides is possible. The type of sugar depends on several factors: which bond of the cyclohexane is cleaved (C1–C6 bond in **28** is cleaved to generate **29**), which of the peripheral substituents cyclizes onto the electrophilic centre generated by the cleavage (*i.e.* path **a** vs. **b**) and the nature of the peripheral substituents (*i.e.* OH, NH₂, SH). Details of this analysis, complete with examples, have recently been published.^{19a,b} For example, treatment of the protected azido alcohol **32** (Scheme 5) with ozone in methanol led to the methylhydroperoxide **33**, which was reduced with sodium

borohydride in the presence of cerium trichloride to give lactone **34**, which was further transformed to yield mannojirimycin **36**.^{22b,c}

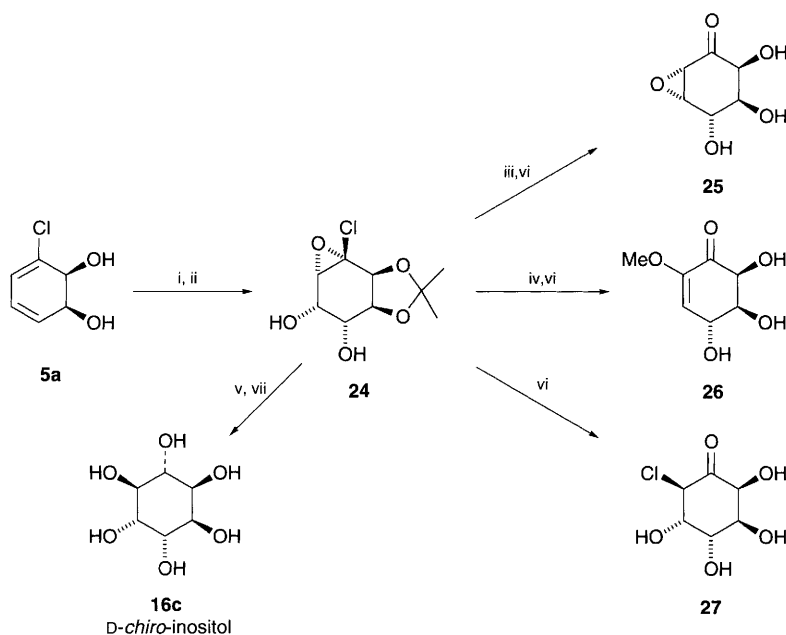
The lactone **34** also played a role in the enantioselective synthesis of the potent glycosidase inhibitor (+)-kifunensine **17** (Scheme 6).^{22c,27} Treatment of the lactone with 2,2-dimethoxypropane and camphorsulfonic acid gave a diacetonide, which was reduced with lithium aluminum hydride to give amine **37**. The introduction of the oxalate unit followed by treatment with methanolic ammonia gave the known alcohol **38**, which was cyclized to furnish (+)-kifunensine in three steps: oxidation of the alcohol to the aldehyde, cyclization in methanolic ammonia and removal of the acetonide groups with TFA.

Recently a new method for the synthesis of amino sugars from chlorocyclohexadiene-*cis*-diols was developed.^{22a} Ozonolysis of the alkene in **39** (Scheme 7) gave, after acetylation, the protected form of 4-deoxy-4-aminomannose **40**. The judicious choice of the placement of the nitrogenous substituent, the selection of the appropriate bond of the cyclohexane for oxidative cleavage, and the mode of recyclization, described above in Scheme 4, led also to the corresponding 2-amino and 3-amino isomers.^{22a}

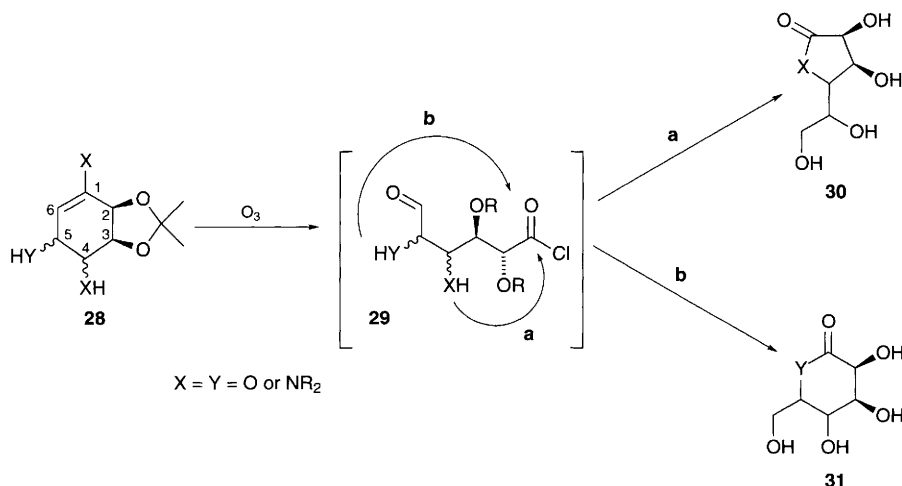
Apart from ventures concerned with the general synthetic methodology for the design of carbohydrates, the diol metabolites are exceedingly well suited for the preparation of



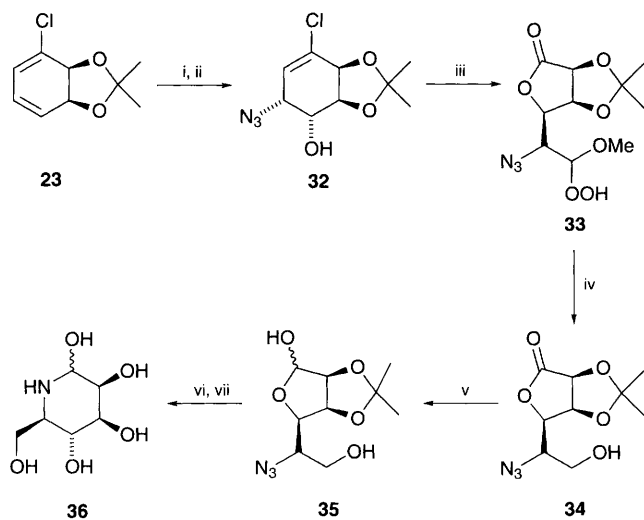
Scheme 2 Reagents: i, MCPBA; ii, MeOH; iii, Bu₃SnH; iv, OsO₄; v, HCl, MeOH



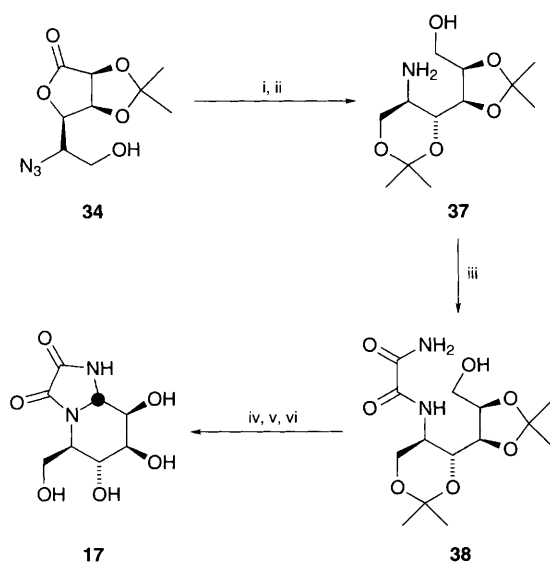
Scheme 3 Reagents: i, 2,2-DMP, TsOH; ii, KMnO₄, H₂SO₄; iii, Sml₂; iv, Zn, MeOH; v, TTMSS, AIBN; vi, H₃O⁺; vii, H₂O–PhCO₂Na, cat.



Scheme 4



Scheme 5 Reagents: i, MCPBA, CH_2Cl_2 ; ii, LiCl, ethyl acetoacetate; NaN_3 ; iii, O_3 , $\text{MeOH-H}_2\text{O}$, NaHCO_3 ; iv, NaBH_3CN , pH 3; v, DIBAL-H, -78°C ; vi, PMe_3 , $\text{THF-H}_2\text{O}$; vii, $\text{CF}_3\text{CO}_2\text{H-H}_2\text{O}$

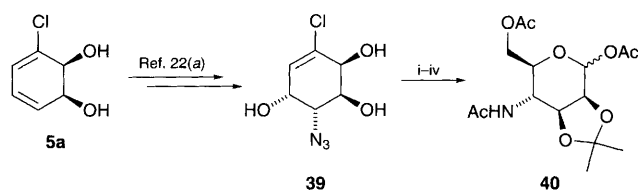


Scheme 6 Reagents: i, DMP, DCE, CSA; ii, LiAlH_4 ; iii, $(\text{MeO}_2\text{C})_2$, then NH_3 ; iv, $\text{CrO}_3 \cdot 2\text{py}$; v, NH_3 , MeOH ; vi, $\text{CF}_3\text{CO}_2\text{H-H}_2\text{O}$

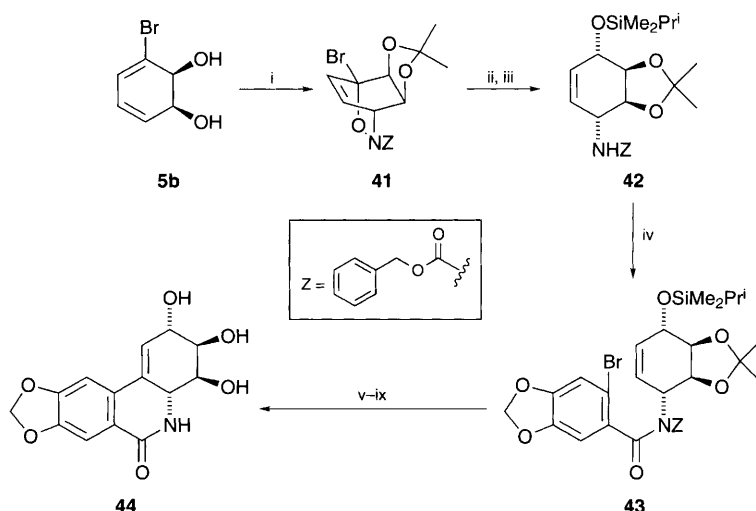
oxygenated alkaloids,²⁸ for example, the narcissus alkaloids lycoricidine and pancratistatin, which have been investigated as antitumor agents.³³ In 1992 Hudlicky and Olivo reported a short synthesis of lycoricidine **44** from bromo diol **5b**, as shown in Scheme 8. This approach featured the cycloaddition of the diene and the acyl-nitroso compound generated *in situ* from the hydroxamic acid to give the oxazine **41**.^{28a} Treatment of this molecule with sodium amalgam resulted in the reduction of the nitrogen–oxygen bond as well as reduction of the bromine–carbon bond. Following installation of the required 2-bromopiperonyl moiety, a modified Heck-type closure completed the B-ring. Treatment of the lactam with palladium and cyclohexene and removal of the alcohol protecting groups gave (+)-lycoricidine **44**.^{28b} A racemic synthesis of this alkaloid has also been accomplished by Martin from *meso*-diol derived from benzene.³⁴

The total synthesis of pancratistatin **19** was inspired by the challenge of securing a short route to this antimetabolic agent (Scheme 9). Subjecting the bromo diene **45** to Jacobsen–Evans's aziridination protocol gave the tosyl aziridine,^{28d} which underwent coupling with the cuprate derived from the ortho-metallation of amide **47**. Conversion of the secondary amine **48** to the Boc derivative **49** was accomplished through the removal of the tosyl group, reduction of the amide under controlled conditions, exchange of the phenolic protecting groups, and epoxidation on the *syn*-face of the free diol. Quite surprisingly, treatment of the triol **49** with sodium benzoate in water led to direct isolation of pancratistatin, in thirteen steps overall.^{28c} This technique has also been adapted to a short synthesis of 7-deoxypancratistatin.^{28f}

The diol derived from chlorobenzene served as a starting point for the synthesis of each of the four isomers of sphingosine.³¹ This general method relied upon functionalization of the C4–C5 double bond early in the synthesis. The approach to *D-ethyro*-sphingosine is highlighted in Scheme 10. Azido alcohol **50** was prepared from the epoxide *via* the corresponding bromohydrin. Ozonolysis of the alkene with reductive work-up gave the lactol **51**, which was treated with



Scheme 7 Reagents: i, O_3 , MeOH ; ii, NaBH_4 ; iii, Ac_2O , pyridine, DMAP, CH_2Cl_2 ; iv, H_2 , Pd/C (10%), EtOH



Scheme 8 Reagents: i, $\text{PhCH}_2\text{CO}_2\text{NHOH}$, Bu_4NIO_4 , CH_2Cl_2 ; ii, Al(Hg) , THF ; iii, $\text{ClSiMe}_2\text{Pr}^i$, imidazole, CH_2Cl_2 ; iv, BuLi , THF then 2-bromopiperonyl chloride; v, Pd(OAc)₂, Tl(OAc), DIPHOS, anisole; vi, Pd(C), cyclohexene, EtOH ; vii, $\text{CF}_3\text{CO}_2\text{H}$

acid and the resultant glycol converted into the labile azido erythrose **52** upon treatment with periodate. The completion of the syntheses of *D*-erythro-sphingosine **18** was realized by Wittig olefination and photo-isomerization of the predominant *cis*-isomer to the *trans*-isomer. The four possible combinations of hydroxy and azido groups in **50** at C4 and C5 are directly expressed in the four isomers of sphingosine.

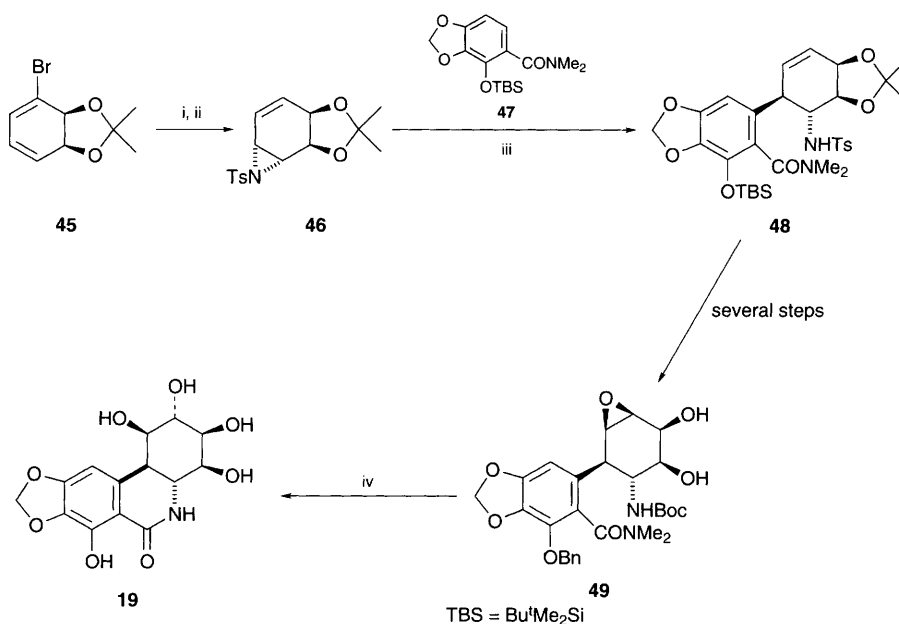
Quite recently we have developed an iterative procedure for the synthesis of cyclitol conjugates.³⁵ This methodology has provided a powerful means of producing such compounds with a diverse array of functionalization and stereochemistry. Our initial venture into this area culminated in the synthesis of the *L*-chiro-inositol-*gala*-quercitol conjugate **55** (Scheme 11) where the Lewis acid catalysed coupling between the epoxide and the alcohol, both easily accessible from bromo diol **5b**, established the necessary conjugate substructure, which was further functionalized to give the adduct **56**.^{35a}

Since then we have synthesized an amino derivative **58**^{35b} in a similar fashion exploiting the chemistry of the vinylaziridines used in the pancratistatin project assembly (Scheme 12). The aziridine was regio- and stereo-selectively opened with the hydroxy nucleophile in **57**, providing the amino inositol-norpseudo-hexose conjugate **58**, which was shown to have excellent calcium-chelating ability and a tendency for a tubular structure. The powerful metal-chelating ability of the amino-cyclitol dimer is evident in the striking X-ray analysis of its calcium chelate.^{35b,c}

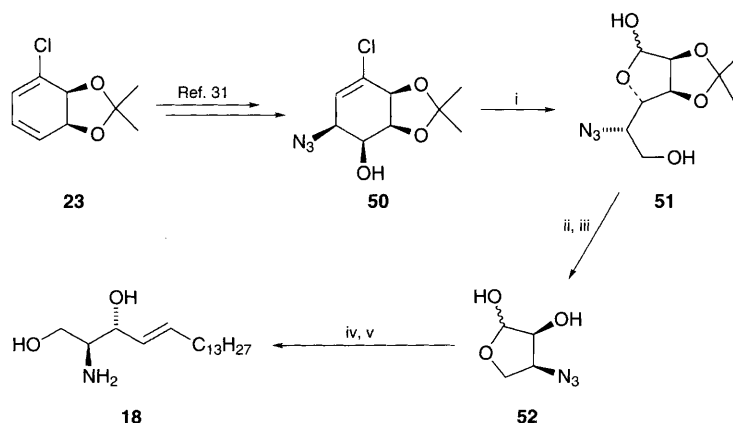
The relative ease of assembling molecules such as these permits the iterative coupling through which higher oligomers are accessible.^{35b,c} We are currently exploring the molecular and biological properties of these molecules and developing methods of securing access to yet higher oligomers, such as the tetramer **59** (Fig. 5), which suggests a β -turn normally found in a polypeptide backbone.^{35b} The advantage of our methodology is the ease of assembly of such molecules and the ability to perform the reactions in multigram quantities of intermediates. The latest development under consideration in our laboratory is the solid-state combinatorial approach to the preparation of libraries of oligomers and other conjugates for rapid screening. It is a new and exciting field in which interesting molecular and biological properties of these conjugates are to be discovered.

Future Developments

The accomplishments summarized here indicate the tremendous potential of this technology in the future of enantioselective synthesis. Well-developed and powerful synthetic methods such as the classic condensation reactions, the Diels–Alder reaction, the Wittig reaction, and others, all show one common quality: versatility and general use in many reactive systems. The demonstration that a single enantiomer of diols of type **5** yields a vast variety of structurally diverse products is complete. Higher order strategies delineated in the projections in Table 1 will soon begin to materialize through our efforts and those of



Scheme 9 Reagents: i, PhI=NTs, Cu(acac)₂, CH₃CN; ii, Bu₃SnH, AIBN, THF; iii, Bu^tLi, TMEDA, THF, then CuCN, then **46**; iv, aq. sodium benzoate

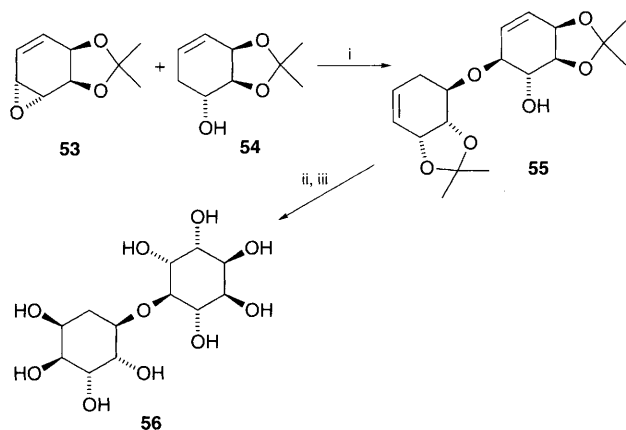


Scheme 10 Reagents: i, O₃, MeOH, NaBH₄; ii, Amberlyst 15 (wet); iii, NaIO₄, H₂O; iv, tetradecylphosphonium bromide, BuLi, THF; v, ref. 31(b)

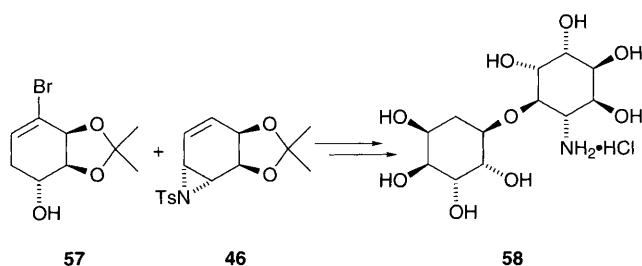
other workers in this field. The almost limitless variety of structures available by microbial dioxygenation of achiral aromatic molecules bodes well for future diversity in biocatalytic ventures. Fig. 6 portrays the long-term two-tier strategy of effective conversion of aromatic compounds to valuable end products by biocatalytic means. The field has a bright future indeed, especially in the effective preparation of chiral pool synthons for use by pharmaceutical industry and others.

Acknowledgements

None of the research completed by the group would have been possible without the effort of a dedicated group of some 200 undergraduate and graduate students and postdoctoral research associates who have been a part of the group over the years. The



Scheme 11 Reagents: i, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 ; ii, OsO_4 , NMO, Bu^tOH , H_2O , acetone; iii, HCl , MeOH



Scheme 12

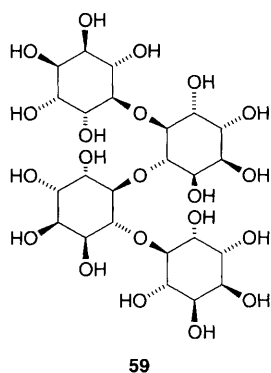


Fig. 5 L-chiro-inositol tetramer (1,2-trans-conjugate)

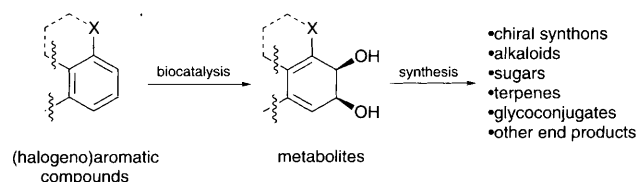


Fig. 6 A two-tier strategy for biocatalytic conversion of (halogenated) aromatic compounds to value-added end products

names of these people are contained in the citations; we graciously thank all of them for their contributions. The Jeffress Trust Fund, Genecor International, American Cyanamid, NSF, TDC Research Foundation and TDC Research, Inc., are duly thanked for the financial support for these and other projects.

We have been fortunate to enjoy a close collaboration with several people who have provided valuable advice in the area of cyclohexadiene-*cis*-diols. We would particularly like to acknowledge the assistance of Larry Kwart, to whom we owe our entry into this field, Gregg Whited (Genecor), Joel Bolonick (NZYM) and David Gibson (University of Iowa), all of whom have provided excellent support and intellectual guidance throughout the course of this research. Dr J. W. Reed is thanked for her help in the preparation of this manuscript.

We wish to thank the two institutions where our research has been carried out, the University of Florida and Virginia Tech.

Tomas Hudlicky was born in Prague, Czechoslovakia, in 1949, and he received elementary and middle school education there. After several years of work as process chemist apprentice and in other odd jobs in pharmaceutical chemistry, it became apparent that higher education opportunities were closed to him. In 1968 he emigrated to the US with his parents and sister. Hudlicky's educational experience continued at Blacksburg High School, from which he dropped out in the spring of 1969. Accepted as a probational student at Virginia Tech the following autumn, he received his B.S. in chemistry in 1973 and went on to pursue graduate studies at Rice University under the direction of Professor Ernest Wenkert in the field of indole alkaloid total synthesis, earning his Ph.D. in 1977. He then spent a year at the University of Geneva working under the late Professor Wolfgang Oppolzer on the synthesis of isocoumarin. In 1978 he joined the faculty at Illinois Institute of Technology as Assistant Professor and began the first phase of his research career in the field of general methods of synthesis for triquinane terpenes and other natural products containing five-membered rings by [4+1] cyclopentene, pyrroline and dihydrofuran methodologies. He returned to his alma mater Virginia Tech in 1982 and rose to the rank of Professor there in 1988. One year later, at the 20 year class reunion of the Blacksburg High School Class of 1969, he received his high school diploma. The next phase of his research involved the investigation of cyclohexadiene *cis*-diols in enantioselective synthesis that is summarized in this review.

In 1995 he moved to his present position at the University of Florida in Gainesville. His current research interests include the development of enantioselective synthetic methods, bacterial dioxygenase-mediated degradation of aromatics, design and synthesis of fluorinated inhalation anesthetic agents, synthesis of morphine and Amaryllidaceae alkaloids, and design of unnatural oligosaccharide conjugates with new molecular properties. His hobbies include skiing, martial arts and music.

Andrew Thorpe was born in Bolton, England, on December 3, 1968. He attended University College London, University of London, from where he received a B.Sc. (Hons) in Medicinal Chemistry in 1990. He then joined Professor Stanley Robert's group as a postgraduate at the University of Exeter, where he conducted Ph.D. research concerned with the synthesis of carbocyclic nucleosides. After receiving his Ph.D. in 1993 he joined Tomas Hudlicky's group where he developed novel methods of assembling disaccharide mimics. He is now a postdoctoral fellow with Eli Lilly and Company in Indianapolis, USA.

Footnote

† The authors are greatly indebted to the late Wolfgang Oppolzer. Professor Oppolzer's untimely passing on 15 March 1996 has left a serious void in the

synthetic community, cutting short his energetic career and his contribution to the art and craft of organic synthesis. His intellectual capacity and his style of problem solving served as an example and inspiration to many of us.

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