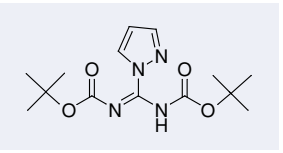
Aldrichimica Acta

Volume 32, Number 2, 1999

Enzymatic Dihydroxylation of Aromatics in Enantioselective Synthesis: Expanding Asymmetric Methodology

New Products

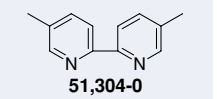
Both the solution- and solid-phase synthesis of guanidines have been accomplished with this reagent.[1-3]



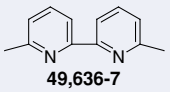
(1) Wu, Y. et al. *Synth. Commun*. **1993**, *23*, 3055. (2) An, H. et al. *Tetrahedron* **1998**, *54*, 3999. (3) Robinson, S.; Roskamp, E.J. *ibid*. **1997**, *53*, 6697.

43,416-7 ***N,N′*-Bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine**, 98%

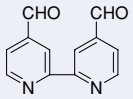
A variety of highly functional bipyridines, useful as organometallic ligands, have been prepared from these compounds. The methyl groups can be easily oxidized to the acid[1] or converted to the bromomethyl derivatives.[2,3] A number of alkenyl-substituted bipyridines have been prepared from the dicarboxaldehyde.[4,5]



51,304-0



49,636-7



47,466-5

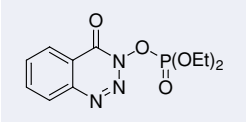
(1) Odobel, F. et al. *Tetrahedron Lett*. **1998**, *39*, 3689. (2) Schubert, U.S. et al. *ibid*. **1998**, *39*, 8643. (3) Ebmeyer, F.; Voegtle, F *Chem. Ber*. **1989**, *122*, 1725. (4) Kocian, O. et al. *Tetrahedron Lett*. **1990**, *31*, 5069. (5) Della, C. et al. *J. Heterocycl. Chem*. **1990**, *27*, 163.

51,304-0 **5,5′-Dimethyl-2,2′-dipyridyl**, 98%

49,636-7 **6,6′-Dimethyl-2,2′-dipyridyl**, 98%

47,466-5 **2,2′-Bipyridine-4,4′-dicarboxaldehyde**, 95%

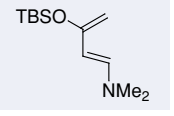
This peptide coupling agent is a stable crystalline solid, and is suitable for both solution- and solid-phase synthesis. No additives are needed to prevent racemization when using this reagent.



Fan, C-X. et al. *Synth. Commun*. **1996**, *26*, 1455.

49,596-4 **3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one**, 98%

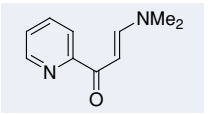
This diene has been reported to be significantly more reactive than Danishefsky's diene (1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene).



Kozmin, S.A.; Rawal, V.H. *J. Org. Chem*. **1997**, *62*, 5252.

49,595-6 ***trans*-3-(*tert*-Butyldimethylsilyloxy)-*N,N*-dimethyl-1,3-butadien-1-amine**, 90%

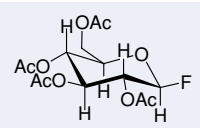
A variety of 2,2':6',2"-terpyridines can be prepared from this reagent.



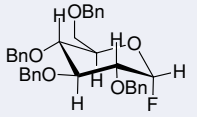
Jameson, D. L.; Guise, L. E. *Tetrahedron Lett*. **1991**, *32*, 1999.

51,167-6 **3-(Dimethylamino)-1-(2-pyridyl)-2-propen-1-one**, 95%

Glycosyl fluorides are widely utilized intermediates for C-, O-, N-, or S-glycosylations.[1,2]



51,054-8



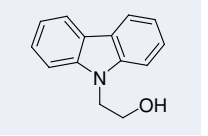
51,172-2

(1) Drew, K. N.; Gross, P. H. *J. Org. Chem*. **1991**, *56*, 509. (2) Jegou, A. et al. *Tetrahedron* **1998**, *54*, 14779.

51,054-8 **β-D-Glucopyranosyl fluoride tetraacetate**, 97%

51,172-2 **2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl fluoride**, 97%, predominantly α

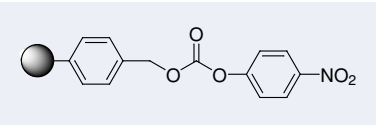
Monomers for the synthesis of azo-aromatic photoconductive polymers have been prepared from this compound.[1-3]



(1) Ho, M.S. et al. *Macromolecules* **1996**, *29*, 4613. (2) Toru, Y.; Tokuji, M. *J. Phys. Chem*. **1995**, *99*, 16047. (3) Zhao, C. et al. *Chem. Mater*. **1995**, *7*, 1237.

47,974-8 **9*H*-Carbazole-9-ethanol**, 97%

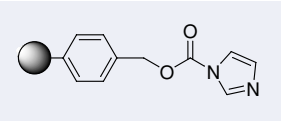
This carbonate resin is used to bind amines or amino acids as urethanes. Dipeptides and hydantoins have been prepared from these polymer-bound urethanes.[1-3]



(1) Dixit, D.M.; Leznoff, C.C. *J. Chem. Soc., Chem. Commun*. **1977**, 798. (2) Dressman, B.A. et al. *Tetrahedron Lett*. **1996**, *37*, 937. (3) Gouilleux, L. et al. *ibid*. **1996**, *37*, 7031.

49,483-6 **4-Nitrophenyl carbonate, polymer-bound**

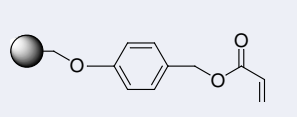
Solid-phase synthesis of peptides and peptidomimetics has been accomplished using polymer-bound carbonylimidazole. Carbamates are formed by reaction with unprotected amines. The carbamates are cleaved using trifluoroacetic acid.[1,2]



(1) Hauske, J.R.; Dorff, P. *Tetrahedron Lett*. **1995**, *36*, 1589. (2) Rotella, D.P. *J. Am. Chem. Soc*. **1996**, *118*, 12246.

49,823-8 **Carbonylimidazole, polymer-bound**

Solid-phase synthesis of β-peptoids using the Wang acrylate resin has been accomplished through Michael addition of amines. The peptoids are formed by further reaction of the resulting β-amine with acryloyl chloride followed by Michael addition of another amine. The peptoid is cleaved from the resin with trifluoroacetic acid.



Hamper, B.C. et al. *J. Org. Chem*. **1998**, *63*, 708.

51,017-3 **Wang acrylate resin**

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About Our Cover

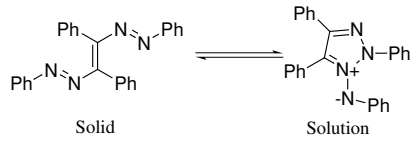
Alexander the Great Threatened by His Father (oil on canvas, 51in. x 37⅛in.) was painted by the Italian artist Donato Creti probably between 1700 and 1705. It represents a famous confrontation between Alexander and his father, King Philip of Macedon, as recorded by the ancient Greek historian Plutarch. Alexander was angered by his father's philandering and divorce from his mother, Olympia. Feelings came to a head at the banquet Philip hosted to celebrate his marriage to Cleopatra, a maiden much younger than he. Her uncle Attalus called upon the people present to pray that a legitimate heir to the Macedonian throne might be born from this union. Alexander flew into a rage, hurled his cup at Attalus, and shouted, "What about me?" Philip rose angrily and drew his sword as if to strike his son, but stumbled drunkenly and fell.

The artist chose to depict the most dramatic moment of this story, when the wedding guests are reacting to Philip's brash action. The cup Alexander has thrown lies on the step to the right. The frightened young woman wearing a diadem at the left is Cleopatra, and the astounded old man beneath the protagonists' outstreched hands is Attalus. The drama of the event is expressed not only through the emotion-charged gestures and expressions, but also by the sharply foreshortened view of the servant who has been knocked down on the left, the fluttering drapery at the upper right, the fantastic palace opening behind the banquet scene, and even the low vantage point from which we witness the action. A dynamic use of light also pervades the painting, accentuating the main actors, revealing the luxurious materials and rich colors, and illuminating distant chambers glimpsed through grand colonnades and courtyards.

This painting is part of the Samuel H. Kress Collection at the National Gallery of Art, Washington, D.C.

"Please Bother Us."

by Jai Nagarkatti, President



Professor Richard N. Butler of the National University of Ireland, Galway, kindly suggested that we make 1,2-bis(phenylazo)stilbene. This compound functions as an azolium 1,3-dipole and is useful for the preparation of triazolium salts. These salts can be easily converted to triazines, oxatriazines, or thiatriazines.

Butler, R. N.; O'Shea, D. F. *Heterocycles* **1994**, *37*, 571.

51,578-7 **α,β-Bis(phenylazo)stilbene**, mixture of isomers

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Lab Notes

Safe Transfer of Air- and Moisture-Sensitive Reagents in the Laboratory

Advances in organometallic chemistry in the last few decades have brought pyrophoric and moisture-sensitive reagents, especially those of organolithium and aluminum, into common usage in organic chemistry laboratories. The commercial availability and high selectivity of these reagents have made them indispensable in the modern chemistry laboratory, despite their highly reactive nature and the risks associated with their handling. In laboratory settings, these reagents are most conveniently transferred from commercial containers to reaction vessels by using either a syringe–needle combination or cannulation techniques,[1,2] without resorting to the use of a glove box or the Schlenk line of dedicated glassware.[3,4]

However, it is almost inevitable that small amounts of the pyrophoric liquid being transferred, e.g., *t*-BuLi solutions and Me_3Al, are exposed to the atmosphere on the tip of the needle or cannula, often causing sparks or small fires. While in most cases the fire is localized and burns out quickly, it always makes one apprehensive, considering the possibility that the sparks or fire may spread to other flammable materials abundant in organic chemistry laboratories. A simple device and a procedure to minimize such risks are described here.

A piece of glass tubing of approximately 6 mm ID and 4 cm in length is capped with rubber septa at both ends and the septa secured with copper wires. This tube is purged with inert gas and serves to protect the needle tip from being exposed to air. When withdrawing air-sensitive reagents, the needle is allowed to protrude through both septa and into the reservoir (**Figure 1**). Once the desired amount of reagent is removed, the tip of the needle or cannula is withdrawn from the reservoir and slid into the glass tubing filled with inert atmosphere, while the lower septum is kept in close contact with the cap of the reservoir to minimize exposure by the needle tip to the air during the process. The syringe or cannula is then safely transported (**Figure 2**) to the reaction flask and the sequence reversed to dispense the reagent (**Figure 3**). After the transfer is finished, the same procedure is followed to withdraw inert solvent to rinse the residual reagent from the syringe needle or cannula or to effect final quenching and cleaning. This simple device has virtually eliminated sparks associated with the transfer of pyrophoric reagents in the author's laboratory.

References: (1) Kramer, G. W.; Levy, A. B.; Midland, M. M. In *Organic Syntheses via Boranes*; Brown, H.C., Ed.; Wiley–Interscience: New York, NY, 1975. (2) Lane, C. F.; Kramer, G. W. *Aldrichimica Acta* **1977**, *10*, 11. (3) Capka, M. *Chem. Listy* **1973**, *67*, 1104. (4) Shriver, D. F. *The Manipulation of Air-Sensitive Compounds*; McGraw–Hill: New York, NY, 1969.

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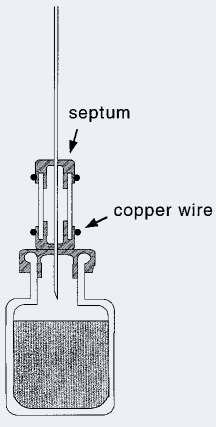

Figure 1

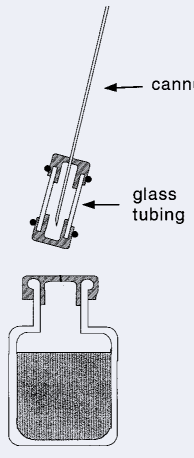

Figure 2

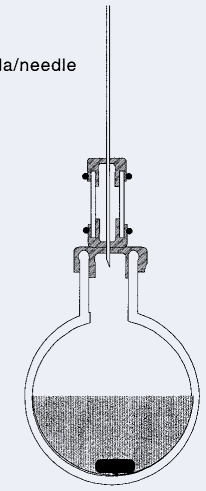
Figure 3

Maintaining a Constant Water Level in an Open, Warm-Water Bath

In our laboratories, we are required, for safety reasons, to use a steam bath to heat large-scale reactions (22-L or 50-L flask size) that contain flammable solvents (bp ≤ 80 °C, e.g., ethanol). This is accomplished by heating a water bath with steam coils that are immersed in the water. Extended periods of heating result in significant evaporation of the water, and lead to a reduction of the water level in the bath.

To maintain a constant water level in the bath during extended periods of heating, we cover the entire surface of the water with mineral oil (Aldrich cat. no. **33,077-9**). This greatly reduces the evaporation of the water, and little, if any, decomposition of the mineral oil occurs during a 72-hour period. For example, we have heated in this way a 12-L flask—in which an aldehyde deprotection step was carried out in acetone for 72 h—and observed no reduction of the water level in the bath. However, heating for more than 72 hours tends to accelerate decomposition of the oil. If longer heating times are required, the mineral oil can simply be decanted and replaced with a fresh batch.

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Enzymatic Dihydroxylation of Aromatics in Enantioselective Synthesis: Expanding Asymmetric Methodology†

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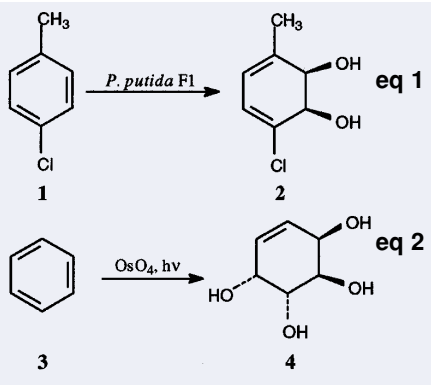
1. Introduction

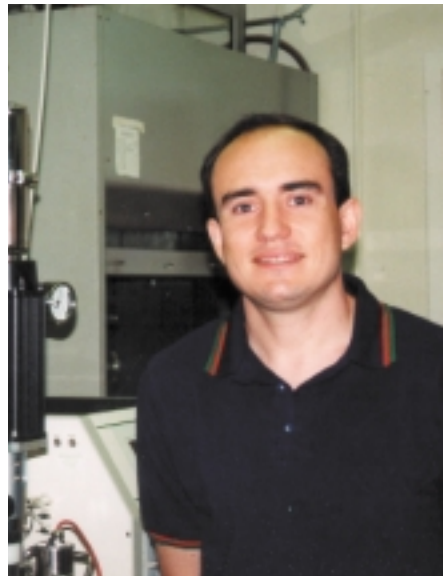
Studies of the microbial oxidation of aromatic hydrocarbons by soil bacteria led, in 1968, to the isolation of the first stable *cis*-cyclohexadienediol, **2** (**eq 1**).[1] Twenty-seven years later, Motherwell and Williams[2] reported the chemical equivalent of this reaction in their synthesis of racemic conduritol E (**4**) (**eq 2**).

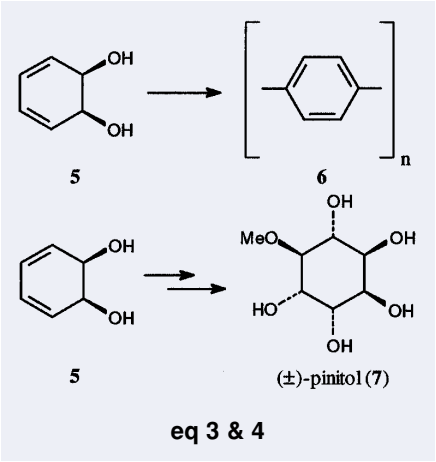


Prior to 1983, the *cis*-cyclohexadienediols produced by bacteria elicited little interest from synthetic chemists in industry and academia. In that year, however, chemists from Imperial Chemical Industries in England reported the use of the biocatalytically generated *meso-cis*-diol **5**—derived from benzene—as a monomer for the synthesis of polyphenylene (**6**) on an industrial scale (**eq 3**).[3,4]

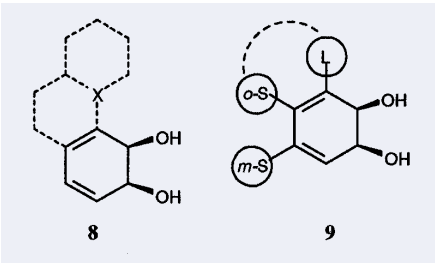
In the late eighties, an expansion of the use of these diols in synthetic ventures took place, and the *meso-cis*-diol **5** served as the starting material for many of the early syntheses. The first academic disclosure was Ley´s synthesis of racemic pinitol (**7**) in 1987 (**eq 4**),[5] and this milestone was followed by many applications reported by several groups worldwide.[6]

The synthetic achievements in this area have been reviewed previously on several occasions.[7-18] This review will focus on selected synthetic applications and the categories of reactions that can be used to exploit the array of functionalities available in the general structure **8**. The drawing represents the three major classes of aromatics: single-ring, fused, and biphenyls. For all such substrates, there have evolved the corresponding enzymes of slightly different topologies: toluene, naphthalene, and biphenyl dioxygenases. A recently published review[18] lists most of the diols for which accurate characterization data ($[\alpha]_D$, ee) are available. In this review, Boyd advances the idea of directing effects for the oxidation, as depicted in **9**, to explain the remarkable regio- and enantioselectivity of the dioxygenases.



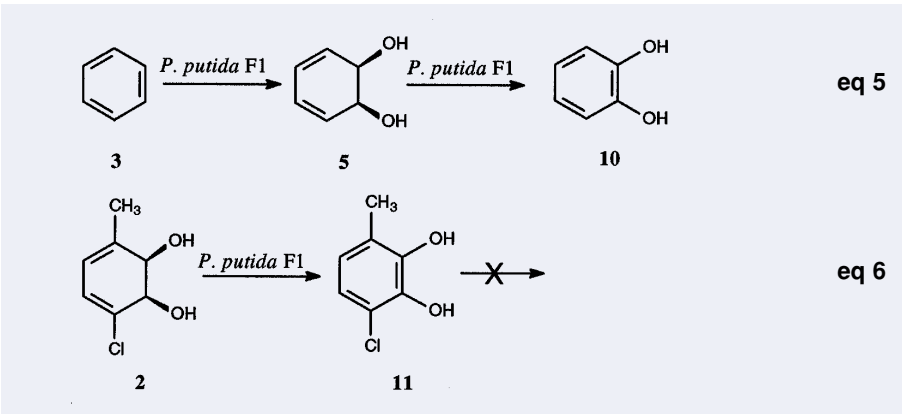


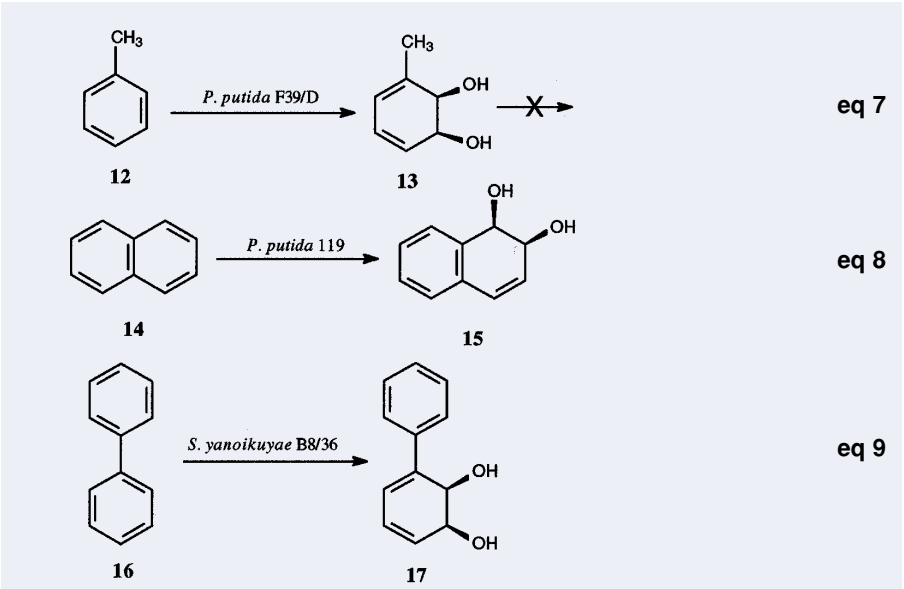
eq 3 & 4



Some of the reactive modes that are possible with these diols have already been reduced to practice, some are self-evident from the analysis of the reactive manifolds, and some undoubtedly await discovery. Most of the synthetic accomplishments originate in the use of only a few of the hundreds of diol metabolites isolated to date, and we include, at the end of this review, the full listing of diol metabolites known as of this writing (see Tables 1-5).

Such a list of actual structures before the eyes of a synthetic chemist should stimulate new thinking and the development of more complex strategies for advanced synthetic applications. Thus, this particular treatise contains, in addition to a historical overview, three areas of focus: production of metabolites, rationale for synthetic design, and applications according to the reaction type. The authors hope that this area will continue to expand, and that new and imaginative synthetic ventures from existing, as well as newly discovered, metabolites will be forthcoming.





2. Historical Perspective

In 1968, a strain of *Pseudomonas putida* (now designated as strain Fl), which grew with ethylbenzene as the sole source of carbon and energy, was isolated.[19] The organism also grew on benzene and toluene, and initial oxidation studies were conducted with toluene-grown cells. Oxygen uptake experiments showed that *P. putida* Fl rapidly oxidized benzene (**3**), *cis*-l,2-dihydroxycyclohexa-3,5-diene (*cis*-dihydrobenzenediol) (**5**), and catechol (**10**).[19] *trans*-Dihydrobenzenediol, the product of oxidative metabolism in mammalian systems,[20] was not oxidized. Toluene-grown cells did not accumulate detectable amounts of *cis*-dihydrobenzenediol, and evidence for its formation from benzene was provided by isotope experiments with cell extracts. The same cell extracts oxidized synthetic *cis*-dihydrobenzenediol to catechol (**10**) when NAD^+ was provided as an electron acceptor (**eq 5**).

The oxidation of fluorobenzene, chlorobenzene, bromobenzene, and iodobenzene by toluene-grown cells led to the formation of their respective 3-halogenated catechols which were resistant to further oxidation. The major product formed from *p*-chlorotoluene (**1**) was identified as 4-chloro-2,3-dihydroxy-l-methylbenzene (**11**), and extraction of 25 liters of a culture filtrate yielded 38 mg of (+)-*cis*-4-chloro-2,3-dihydroxy-1-methylcyclohexa-4,6-diene (**2**), the first stable *cis*-cyclohexadienediol.[1] A *cis*-diol dehydrogenase in the cell extracts oxidized **2** to **11** (**eq 6**).[1]

Subsequent studies led to the isolation of a mutant strain of *P. putida* Fl (strain 39/D, now designated F39/D) that was devoid of *cis*-diol dehydrogenase activity. Benzene-induced cells of strain F39/D oxidized benzene to *cis*-dihydrobenzenediol. Experiments with $^{18}O_2$ showed that both oxygen atoms in the dihydrodiol were derived from dioxygen,[21] stimulating initial thoughts that the intermediate in the transformation might be a dioxetane. Such an intermediate is unlikely to be formed from triplet oxygen species, however.

P. putida F39/D oxidized toluene (**12**) to enantiomerically pure *cis*-(1*S*,2*R*)-dihydroxy-3-methylcyclohexa-3,5-diene (**13**) (**eq 7**).[22,23] Other substrates oxidized to *cis*-dihydrodiols by strain F39/D were ethylbenzene,[24,25] *p*-fluorotoluene,[25] *p*-chlorotoluene,[25] *p*-bromotoluene,[25] chlorobenzene,[25] *p*-xylene,[26] and 3-methylcyclohexene.[27]

The identification of *cis*-dihydrodiols as intermediates in the degradation of benzene, toluene, and ethylbenzene led to studies of the reactions used by bacteria to initiate the degradation of aromatic hydrocarbons containing fused aromatic rings. Prior to 1971, it was generally believed that bacteria oxidize

naphthalene to *trans*-1,2-dihydroxy-1,2-dihydronaphthalene (*trans*-dihydronaphthalenediol).[28] However, the techniques used at that time did not differentiate between cis and trans isomers and a mutant strain of *Pseudomonas putida* (strain 119) was isolated that oxidized naphthalene (**14**) to *cis*-(1*R*,2*S*)-dihydroxy-1,2-dihydronaphthalene (**15**) (*cis*-dihydronaphthalenediol) (**eq 8**).[29,30] Both oxygen atoms in the *cis*-dihydrodiol were derived from a single molecule of dioxygen.[30]

Interest in the biodegradation of polychlorinated biphenyls led to the isolation of a *Beijerinckia* species strain B1[31] (now named *Sphingomonas yanoikuyae* strain B1)[32] that would grow with biphenyl (**16**) as the sole source of carbon. A mutant strain of this organism (strain B8/36) oxidized biphenyl to *cis*-(1*S*,2*R*)-dihydroxy-3-phenylcyclohexa-3,5-diene (**17**) (*cis*-dihydrobiphenyldiol) (**eq 9**).[31] Strain B8/36 oxidized anthracene and phenanthrene to *cis*-(1*R*,2*S*)-dihydroxy-1,2-dihydroanthracene and *cis*-(3*S*,4*R*)-dihydroxy-3,4-dihydrophenanthrene, respectively.[33,34] The major products formed from benzo[*a*]pyrene [BP] and benzo[*a*]anthracene [BA] were *cis*-9,10-dihydroxy-9,10-dihydro-BP and *cis*-1,2-dihydroxy-1,2-dihydro-BA, respectively.[35] In subsequent experiments, it was shown that *S. yanoikuyae* B8/36 oxidizes BA to *cis*-1,2-, *cis*-5,6-, *cis*-8,9-, and *cis*-10,11-dihydrodiols. With the exception of the 5,6-dihydrodiol, which was formed in trace quantities, the *cis*-dihydrodiols have an *R* absolute configuration at the hydroxylated benzylic centers. More recently, *S. yanoikuyae* B8/36 has been reported to oxidize chrysene to *cis*-(3*S*,4*R*)-dihydroxy-3,4-dihydrochrysene.[36]

Although *cis*-cyclohexadienediols are common intermediates in the bacterial oxidation of aromatic hydrocarbons, they are not formed exclusively from this class of compounds. In 1971, Reiner and Hegeman isolated a mutant strain of *Alcaligenes eutrophus* (strain B9) that oxidized benzoic acid (**18**) to (–)-*cis*-cyclohexadiene-l,2-diol-1-carboxylic acid (**19**) (**eq 10**).[37]

Subsequent studies by Reineke and colleagues showed that *A. eutrophus* strain B9 and *Pseudomonas sp*. strain B13 oxidize a variety of halogenated and methyl-substituted benzoic acids to *cis*-diol carboxylic acids.[38,39] In contrast to "ipso" dioxygenation, other *Pseudomonas* strains oxidize substituted benzoates to dihydrodiols, as Ribbons has shown in the case of the oxidation of cumic acid (**20**) to 2,3-dihydroxy-4-isopropylcyclohexa-4,6-dienoic acid (**21**) (**eq 11**).[40,41] (Note that the stereochemistry of the diol is the opposite of that in **2** with respect to the alkyl substituent.) Recently, the absolute stereochemistry and the reactive tendencies of the *cis*-diol **21** have been reported.[42]

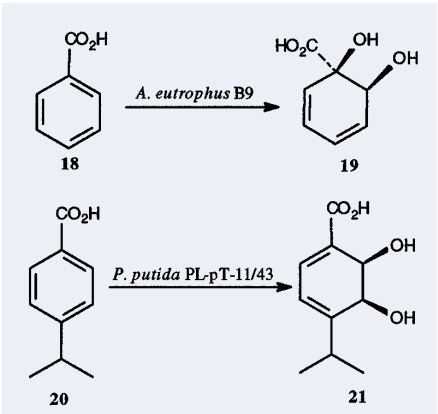
It is evident from the tables at the end of this review that some element of predictability exists with respect to the regio- and stereochemical outcome of the enzymatic dioxygenation of aromatic compounds. It should be noted that the trends in oxidation patterns (specificities) are unique and sometimes complementary for individual oxygenases.[43] These aspects, combined with the description of experimental needs in the next section, allow the nonspecialist access to this technology in order to enhance the art of asymmetric synthesis.

3. Whole-Cell Oxidation of Aromatics—Diol Formation

Several reviews are available in the area of microbial degradation of aromatic compounds[44-46] and these should be consulted by the nonspecialist before he/she begins preparative biotransformations.

Most of our current knowledge of the products formed by toluene (TDO), naphthalene (NDO), and biphenyl (BPDO) dioxygenases has been obtained with mutants that do not express their respective *cis*-dihydrodiol dehydrogenases. A laboratory procedure for the oxidation of chlorobenzene to 1-chloro-(2*S*,3*S*)-dihydroxycyclohexa-4,6-diene by *P. putida* F39/D has been described.[47] In practice, this procedure can be used for other volatile substrates. Solid substrates such as naphthalene and biphenyl can be added directly to the culture flask. Under these conditions, the aromatic hydrocarbons induce the synthesis of their respective dioxygenases. The induced cells can be harvested, resuspended in a mineral salts medium or buffer, and examined for their ability to oxidize different substrates. In such cases, pyruvate is usually added to provide the NADH necessary for the dioxygenase reaction. Constitutive mutants, such as *P. putida* UV4,[3] do not require an inducer, since the dioxygenase is present under all growth conditions.

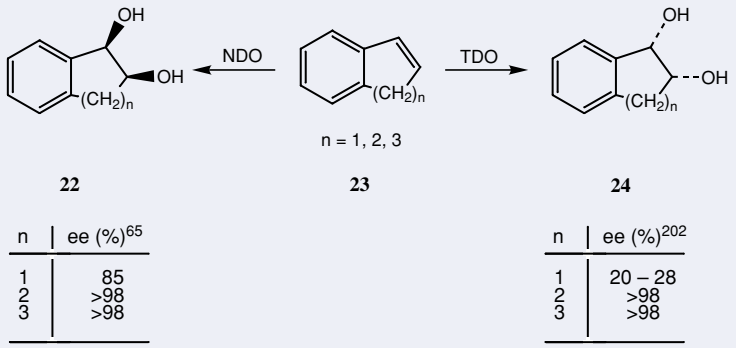
Inducers are not always the substrates used for the isolation of the wild type strains. For example, salicylate and anthranilate induce the synthesis of NDO in *Pseudomonas sp*. NCIB 9816,[48] and *m*-xylene induces BPDO in *Sphingomonas yanoikuyae* B8/36.[49] Care must be taken in the interpretation of results provided by blocked mutants, since other enzymes may be present that can affect the final distribution and stereochemistry of the isolated products.[50,51] In addition, it is advisable to examine each mutant for reversion to the wild type strain. For example, *P. putida* 119, the strain first used to isolate *cis*-dihydronaphthalenediol,[29] produced revertants when the cells reached the stationary growth phase. This was accompanied by the rapid disappearance of *cis*-dihydronaphthalenediol from the culture medium.[52] The subsequent use of the stable dihydrodiol dehydrogenase mutant *Pseudomonas sp*. 9816/11 alleviated this problem.[53]



eq 10 & 11

The genes encoding TDO,[54] NDO,[55] and BPDO[56] have been cloned and expressed in *Escherichia coli*. There are several advantages to using recombinant strains for the production of *cis*-dihydrodiols. These include the control of dioxygenase synthesis by the isopropyl-β-D-thiogalactoside (IPTG)-inducible promoters, the use of multicopy plasmids for the synthesis of increased amounts of enzyme, and the use of vector controls to identify host background activity. A major drawback often encountered in the synthesis of large amounts of proteins by recombinant strains is the production of the desired enzyme in the form of inactive inclusion bodies. One way to minimize the formation of inclusion bodies is to lower the temperature of the culture at the start of dioxygenase synthesis.

TDO, NDO, and BPDO are related multicomponent enzyme systems with overlapping substrate specificities. Each system uses a short electron transport chain to transfer electrons from NAD(P)H to their oxygenase components that consist of dissimilar (αβ) subunits.[57] The dioxygenation reaction is believed to occur at a mononuclear iron site in the α subunit. This is supported by recent X-ray structural data on the NDO oxygenase component;[58] however, the precise mechanism of dioxygenation, which involves the highly endothermic disruption of aromaticity, is unknown. The components of the TDO, NDO, and BPDO oxygenase systems have been purified and used in substrate specificity studies. Although such experiments are time-consuming and labor-intensive, they provide unequivocal evidence for the identification of the initial oxidation products formed from specific substrates. They have been particularly useful in demonstrating that NDO can catalyze monohydroxylation, desaturation (dehydrogenation), O- and N-dealkylation, and sulfoxidation reactions.[43]



n	ee (%)[65]
1	85
2	>98
3	>98

n	ee (%)[202]
1	20 – 28
2	>98
3	>98

Figure 1. Antipodal specificity of toluene and naphthalene dioxygenases.

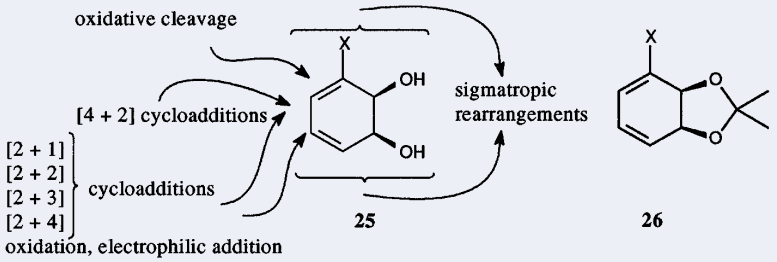


Figure 2. Local bond-forming sites in the *cis*-dienediols.

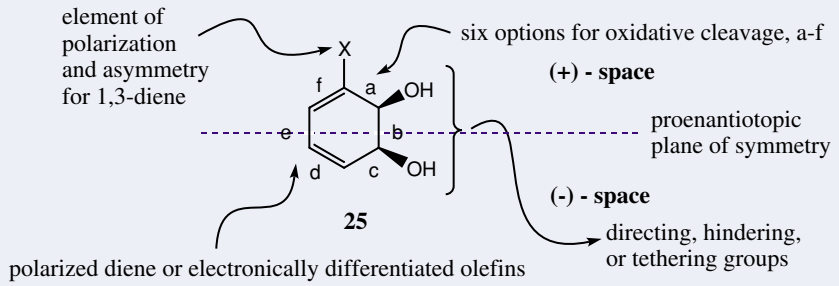
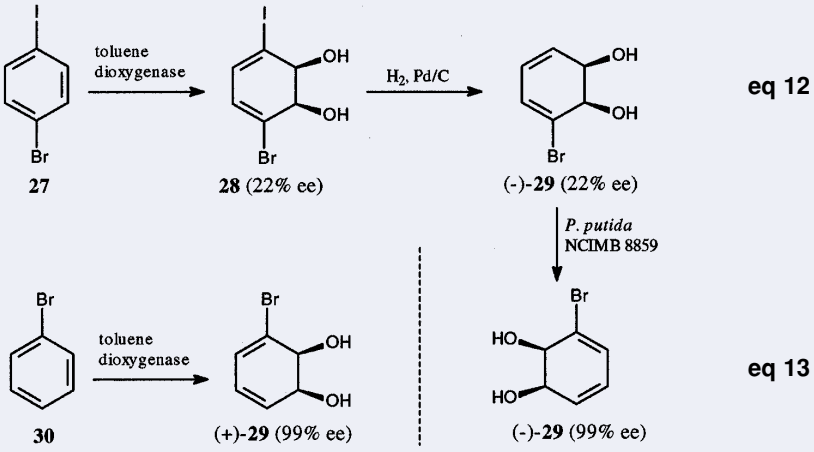


Figure 3. Global elements for stereomanipulation and enantiodivergence in the *cis*-dienediols [(+) and (–) space are assigned arbitrarily].



The discovery of the enzymatic asymmetric dihydroxylation of aromatic compounds by toluene, naphthalene, and biphenyl dioxygenases, and the availability of mutant and recombinant bacterial strains that express these enzymes, provided the community of organic chemists with the opportunity to use these biocatalysts in the preparation of useful synthetic intermediates. The following discussion aids the chemist not yet acquainted with these powerful tools.

There are generally two types of bacteria that are used to oxidize aromatic compounds to *cis*-cyclohexadienediols. From the point of view of a nonspecialist, the following narrative reiterates the principles mentioned above and should serve as a guide to those wishing to learn the technique. The organisms most commonly used are mutants of the wild type strain that have lost the ability to dehydrogenate *cis*-diols and recombinant strains of *Escherichia coli* that contain the cloned dioxygenase genes. Consequently, there are two procedures to be followed in terms of utilizing these organisms to produce *cis*-cyclohexadienediols. Both procedures can be easily performed with minimal skills in microbiology.

The first procedure involves the use of blocked mutants in which the enzyme synthesis must be induced by a known aromatic inducer (for *P. putida* F39/D this might be toluene, chlorobenzene, bromobenzene, or several other monocyclic aromatic compounds). If the inducer is also the substrate to be converted to a *cis*-cyclohexadienediol, the procedure is simple. The mutant is grown in a mineral salts medium, which provides the requisite inorganic elements (N, P, Mg, Fe, etc.), and an organic substrate that does not repress the synthesis of the dioxygenase (usually pyruvate or glucose). The aromatic compound can usually be added at the start of the growth. The accumulation of *cis*-cyclohexadienediol is monitored spectrophotometrically until the biotransformation ceases. Variations of this procedure are used when the substrate does not induce dioxygenase synthesis. The mutant is grown in a mineral salts medium with pyruvate or glucose in the presence of an inducing substrate as described above. Following the induction period, a new substrate is added, which, if recognized by the enzyme, is oxidized to the corresponding diol. The final fermentation broth contains the metabolites derived from the inducer and the substrate; thus, such a process necessitates a separation. Alternatively, the cells may be separated from the broth after induction and resuspended in a fresh medium before addition of the second substrate. The bacterial cells are then removed and the clear supernatant extracted with acid-free ethyl acetate.

The second procedure is slightly more complex to execute, but leads to potentially higher cell and product yields, and is ideal for testing new compounds as substrates for oxidation. It relies on the use of a recombinant organism in which transcription of the genes encoding the dioxygenase is initiated by exposure to a known nonaromatic inducer, in most cases isopropyl-β-D-thiogalactoside (IPTG). The cells are allowed to grow and synthesize the dioxygenase before the introduction of the substrate to be oxidized. Separation problems are avoided, but the procedure requires the use of a fermentor with carefully regulated oxygen levels, temperature, pH, CO_2 release, and nutrient/substrate feeds. Quite recently, an attempt has been made to transfer the genes encoding TDO from *E. coli* JM109 (pDTG601) to yeast cells[59] by a procedure successfully implemented by Stewart for cyclohexanone monooxygenase from *Acinetobacter*.[60] This particular enzyme has been successfully used in both isolated and whole-cell fermentations, with applications in organic synthesis by Furstoss,[61] Taschner,[62] and Stewart.[60] If the genetic information for the biosynthesis of the more complex dioxygenase enzyme systems can be transferred to yeast also, it will no doubt greatly enhance the attractiveness of this methodology to the traditionally trained synthetic practitioner.

The diols produced from aromatic substrates vary in stability and are usually isolated by extraction. They are then crystallized and stored at low temperature. They are more stable as free diols than in the protected forms (see section on cycloadditions). For shipping or long-term storage, it is best to store them as frozen suspensions in pH 8.5 phosphate buffer. So far, with very few exceptions, they are produced with the absolute stereochemistry as shown, and, in most cases, absolute enantiomeric purity— except for the diol derived from fluorobenzene,[63] the *meso*-diols originating from symmetrical substrates, and diols from several more highly substituted aromatic rings. As noted earlier, the enantiomeric specificities of individual dioxygenases are often unique and in some cases complementary; thus, both enantiomers of certain oxidation products can be accessed through the use of different oxygenase systems.[43] For example, naphthalene dioxygenase and toluene dioxygenase oxidize some hydrocarbons related to indene to the antipodal *cis*-diols, albeit in diverse enantiopurities (**Figure 1**). However, recent studies have identified organisms capable of generating several enantiopure *cis*-diols of opposite chirality to that of previously identified metabolites. It has been shown that a carbazole-utilizing strain oxidizes biphenyl, biphenylene, and 9-fluorenone to previously unobserved *cis*-diol enantiomers.[64] Thus, both enantiomers of several *cis*-diols can be generated through either subsequent chemical conversion of the diols,[65] enantioselective enzymatic resolution,[66] symmetry-driven design,[67,68] or the use of strains expressing dioxygenases with different specificities as mentioned above.

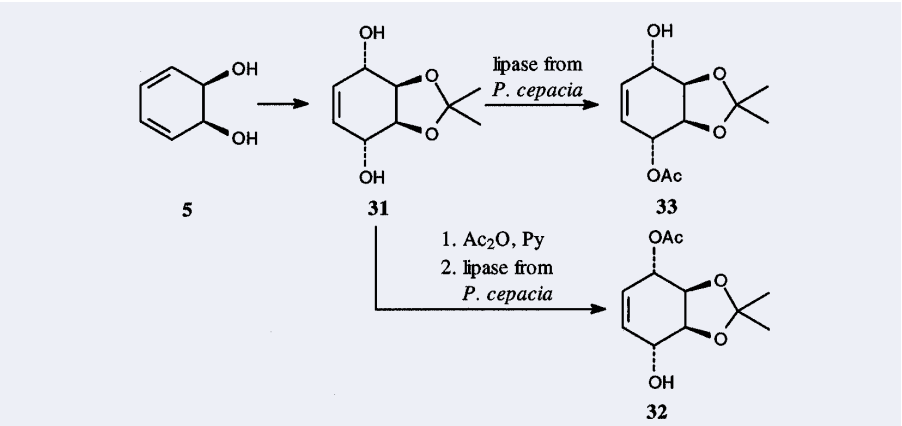


Figure 4. Enantiodivergence by lipase resolution.

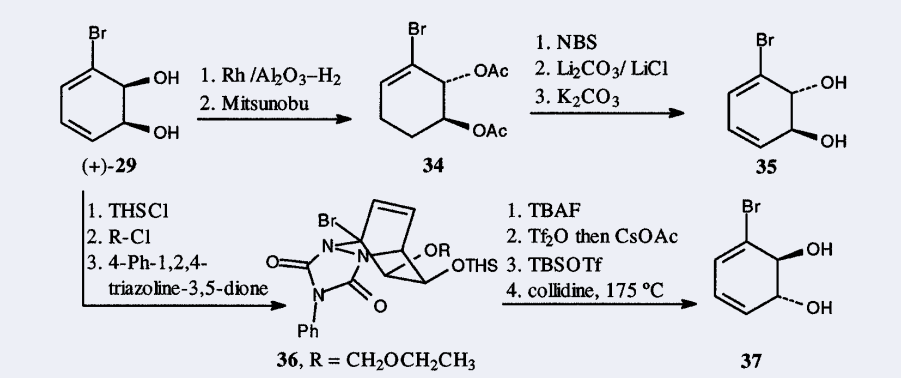


Figure 5. Two approaches to the "diastereomeric switch" of diols.

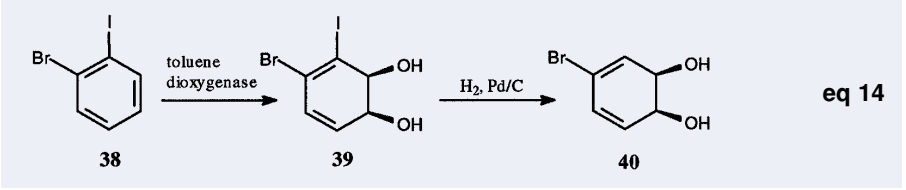
4. Synthetic Design Rationale

cis-Dihydroarenediols of the general structure **25**, and their acetonides **26** contain an amazing combination of mutually intertwined functionalities and, therefore, many possibilities for further use. The intellectual analysis of these possibilities can be summarized in two separate ways: first, various "local" bond-forming reactions as divided by class and shown in **Figure 2**; second, the "global" implications that address the enantio-, stereo-, and regioselectivities that can be expected from the manipulation of these compounds (**Figure 3**).

The issues of enantioselectivity are addressed by manipulating the *order* of reactions to a given target in such a manner as to elaborate specifically only one terminus (or apex) of the cyclohexadienediol, with the crucial enantiodifferentiation step performed in either "D" or "L" space in relation to the final absolute stereochemistry of the target (note: +/- and D/L are arbitrarily assigned). The appropriate "switch" is made following the removal of the differentiating group X. These strategies have already been elucidated and described in several disclosures and need not be discussed here.[10,11,13-17,67,68]

Another means by which enantiodivergence is achieved was reported by Boyd.[65] It relies first on the directing effect of the larger C-1 substituent in the enzymatic oxidation step of **27**, and, then, on the greater reactivity of the iodine in the Pd/C hydrogenolysis of **28** as shown in **eq 12**. In this way, the enantiomeric pair of diols **29** is obtained (**eq 13**).

The efficiency of this method relies on the ability of the enzyme to completely differentiate between the iodine and bromine atoms in the aromatic substrate. Unfortunately, **28** is obtained in very low optical purity, and this is translated into optically impure **29**. Boyd overcame this problem by exposing the scalemic mixture of **29** to a second fermentation step using a nonblocked strain of *Pseudomonas*, which is able to completely metabolize the undesired enantiomer (in this case the (2*S*,3*S*)-(+)-enantiomer)



eq 14

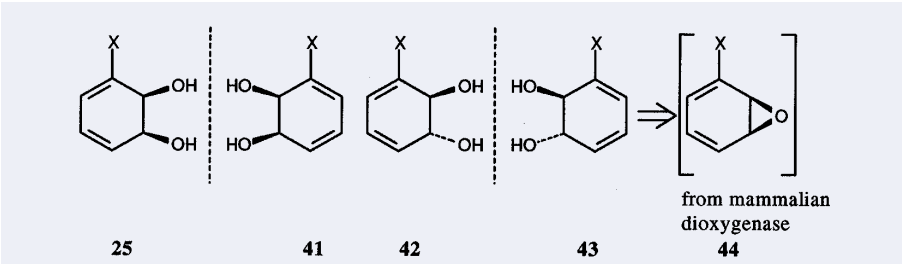


Figure 6. Enantio- and diastereodifferentiation strategy.

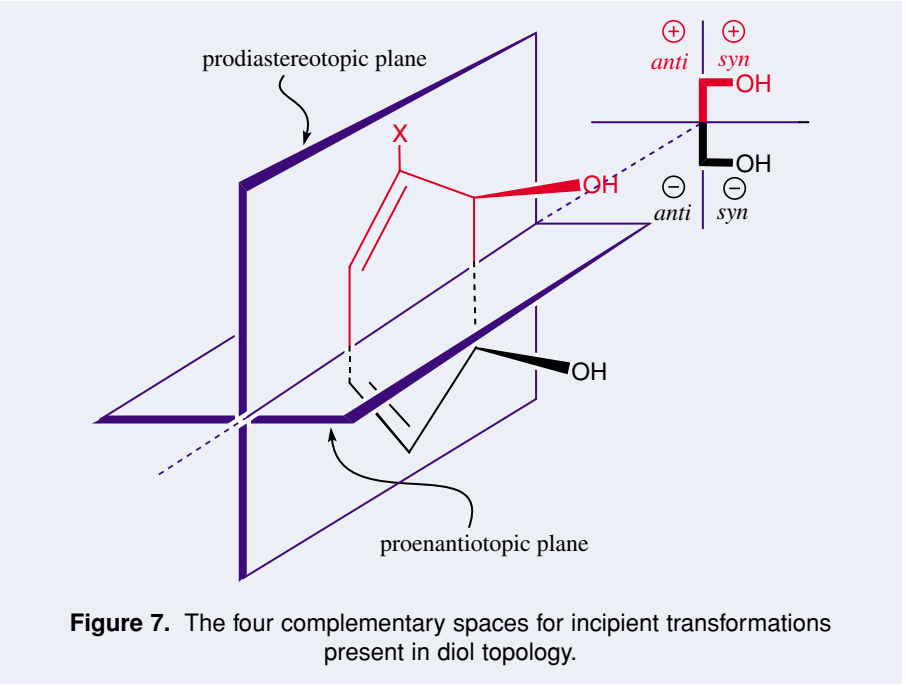


Figure 7. The four complementary spaces for incipient transformations present in diol topology.

leaving (–)-**29** to accumulate. This approach has the obvious disadvantage that a considerable amount of valuable (+)-**29** has to be created and then destroyed to attain the target.

A completely different approach to enantiodifferentiation of the dienediol residue was developed by Johnson.[66] The *meso*-diol **5** was functionalized to the conduritol derivative **31**, which was enzymatically resolved into either of the enantiomers **32** or **33**, as shown in **Figure 4**, to allow for the enantiodifferentiation of the projected targets.

The issue of enantiodivergence is crucial to the credibility of chemoenzymatic synthesis: too frequently the traditionalists in the synthetic organic community criticize the use of enzymatic reactions, and justify the rather inefficient chiral-auxiliary approach to asymmetric synthesis by pointing out that *ent*-enzymes are unavailable. The above result and the symmetry-based approach[13,14,67] clearly rebuff such criticism.

Boyd[69] has also addressed the "diastereomeric switch" between the cis diols and their trans isomers. Boyd's method for the conversion of cis diols to the trans isomers is accomplished as shown in **Figure 5**. In this process, the reactive diene needs to be reduced to the alkene to avoid aromatization during the Mitsunobu inversion of the proximal hydroxyl group. The diene is restored later by a bromination–elimination process to furnish **35**. Independently, an alternative procedure for the preparation of trans diols was reported (also shown in Figure 5).[70] In this case, the diene system was "protected" by a reversible Diels–Alder reaction with the active dienophile, 4-phenyl-1,2,4-triazoline-3,5-dione, and the inversion performed with **36** to ultimately yield **37**. Interestingly, these two approaches become complementary, since they do not involve the inversion of the same stereocenter.

In addition, Boyd's method has also been successfully applied to the synthesis of 3,4-diols such as **40** from *o*-iodobromobenzene (**eq 14**). All combinations of enantio- and diastereomeric ventures are now possible from diol pairs **25**/**41** and **42**/**43** (**Figure 6**). The latter pair corresponds to diols that would be formed by the hydrolytic opening of arene oxides of type **44**, which are produced by the action of more highly evolved eukaryotic enzymes on aromatics.[20,33] Thus, the issues concerning the availability of metabolites in both enantiomeric constitutions and the approach to targets in both absolute configurations are addressed.

The summary of all design principles based on symmetry[11,13,14,67,68] is offered by the drawing in **Figure 7**. Diastereoselectivity issues are controlled by either directing or hindering effects of the biochemically installed diol, whereas the regioselectivity of the first functionalization is controlled by the polarization of the diene system. This regioselectivity also determines the commitment to a specific enantiomeric space, here arbitrarily assigned as "+" for the "upper domain" and "–" for the "lower domain". There are four possibilities for the configuration of the next chiral center to be constructed: syn or anti to the diol in either "+" or "–" space as configured in the enantiomer of the final product (see projection in Figure 7). These operations are relatively easy to control and lead to a fully exhaustive design of a particular class of compounds.[11,13,14,67,68]

There are a number of bond-forming reactions possible from the multiple functionalities of these types of compounds. The diene undergoes a variety of regioselective [4+2] cycloadditions, including its intramolecular variants. Separate cycloaddition chemistry can be initiated singly at the disubstituted olefin. The presence of a polarized diene unit allows for controlled interaction with electrophilic reagents. The allylic alcohol functionalities are amenable for use in Claisen-type rearrangements, as was proposed in the very first publication from our laboratory in 1988[71] and reduced to practice in 1997.[72] Since every carbon atom in these molecules is either unsaturated or oxygenated, the preparation of polyoxygenated compounds, such as cyclitols and carbohydrates, starting from *cis*-dihydroarenediols, is convenient. The logic of this design flows from these considerations and is discussed in the following sections. The oxidation of the periphery of the dienediol and subsequent cleavage of any one

of the six bonds provide access to acyclic chains with defined stereochemistry, as in the case of carbohydrates. Their carbon content is addressed by the controlled oxidative loss of either 0, 1, or 2 carbon atoms from the dienediol unit. The following section briefly outlines the diversity of chemical operations possible with *cis*-dihydroarenediols, and provides examples of specific synthetic applications.

5. Applications to Synthesis

Peripheral oxidative functionalization of dienediols yields the first level of synthons with increased complexity, here shown as "primary synthons" in **Figure 8**. The materials are then further functionalized to "secondary synthons" (**Figure 9**) before a decision is made with regard to the cleavage of the cyclohexane ring. The oxidative functionalization of acetonides **26**, derived from **25**, yields *anti*-epoxides **45**, diols **46**, or aziridines **47**. The unusual production of chloroepoxide **48** seems to be the consequence of 1,4-addition of $KMnO_4$ across the polarized diene. Singlet oxygen and acylnitroso compounds yield cyclic peroxides **49** and oxazines **50**, the latter regiospecifically, and both with the expected anti stereochemistry. Boronate esters[73] and acetals derived from benzaldehyde[74] and other aldehydes[75] have been reported as protecting and directing groups, although the most common protective group remains the acetonide. The functionalization of free diols has been limited to monoprotection as in **51**. In most instances (except for epoxidation in the case of **52**), the stereoselectivity in the transformations of free diols is poor. The details of these reactions can be found in several reviews.[7-11]

These primary synthons can be manipulated further into the secondary synthons shown in Figure 9. The most common transformations involve the removal of the halogen that directed the primary functionalization to the more electron-rich olefin and functioned to preserve the asymmetry. Both primary and secondary synthons (some of which are now commercially available) have been used primarily in cyclitol and sugar syntheses (see the corresponding sections for examples).

The reactivity of the dienediols (free or protected) has been exploited in cycloadditions, leading to C–C, C–O, or C–N bond formation; peripheral oxidation; and further functionalization, as well as partial or full oxidative cleavage. The latter two aspects find use in the general design of carbohydrates.

Interesting applications emerged from Stephenson's group.[76,77] A derivative of the iron complex **55** (**Figure 9**) undergoes nucleophilic addition with sodium malonate, leading to stereospecific C–C bond formation.[77] The epoxyaziridine **64** results from a rearrangement of oxazines of type **50**.[78]

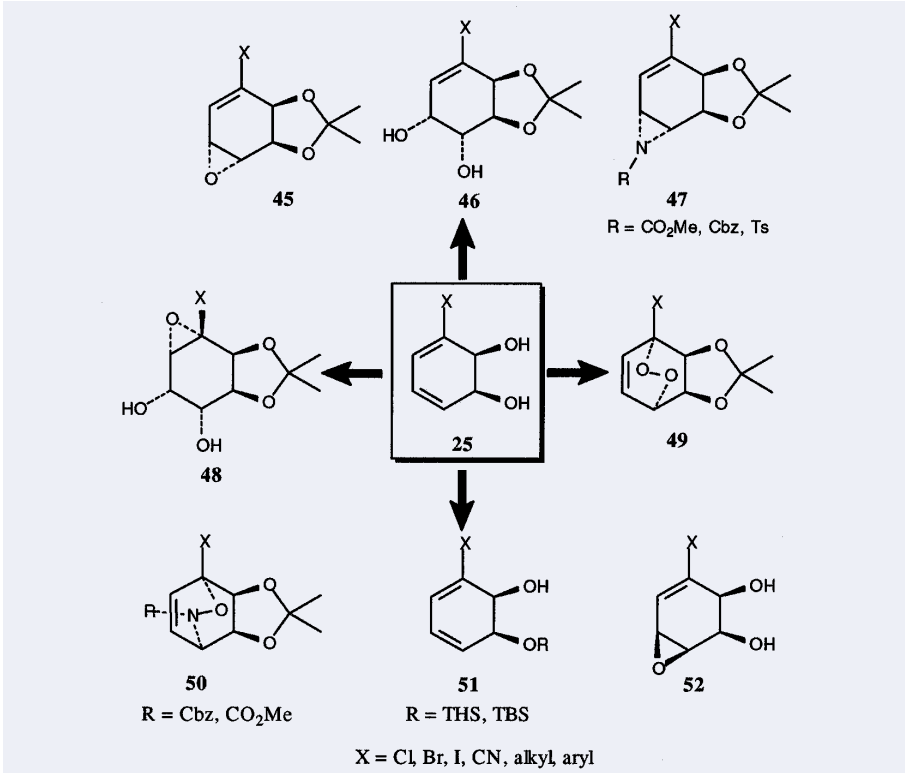


Figure 8. Examples of primary synthons.

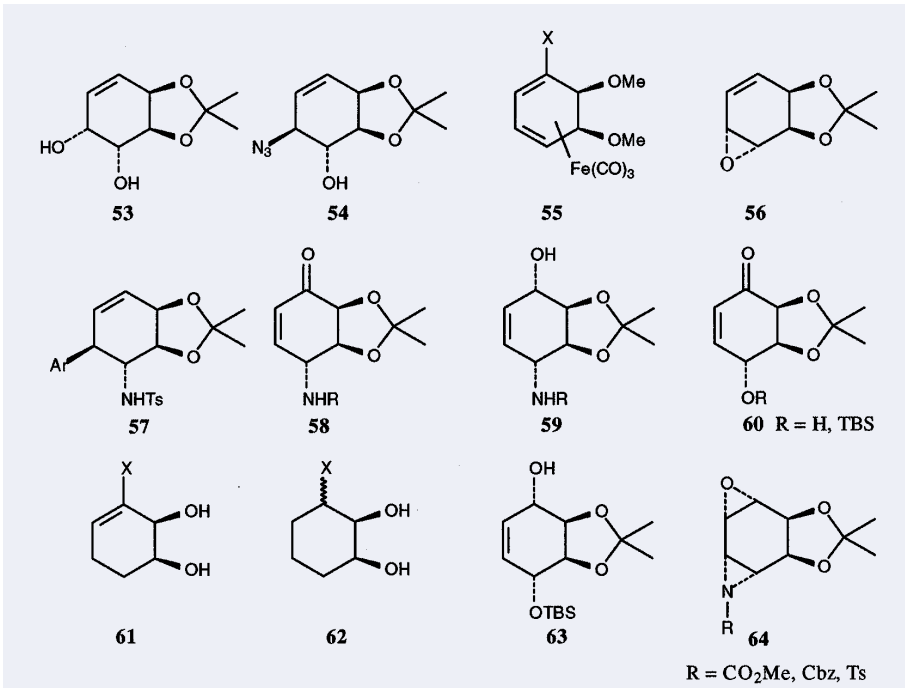


Figure 9. Examples of secondary synthons.

5.1. Cycloadditions

cis-Cyclohexadienediols derived from monocyclic aromatics are reactive towards cycloadditions; the halodienes (X = Cl, Br, I, F), where the diene functionality is quite polarized, are especially reactive. In fact, acetonides **26** dimerize readily, even at (or below) room temperature,[79-81] although the free diols are reasonably stable in the crystalline state. The acetonide of dihydrostyrenediol, **66**, dimerizes to three different Diels–Alder products[82] with spectacular regio- and stereoselectivity, as shown in **Figure 10**.

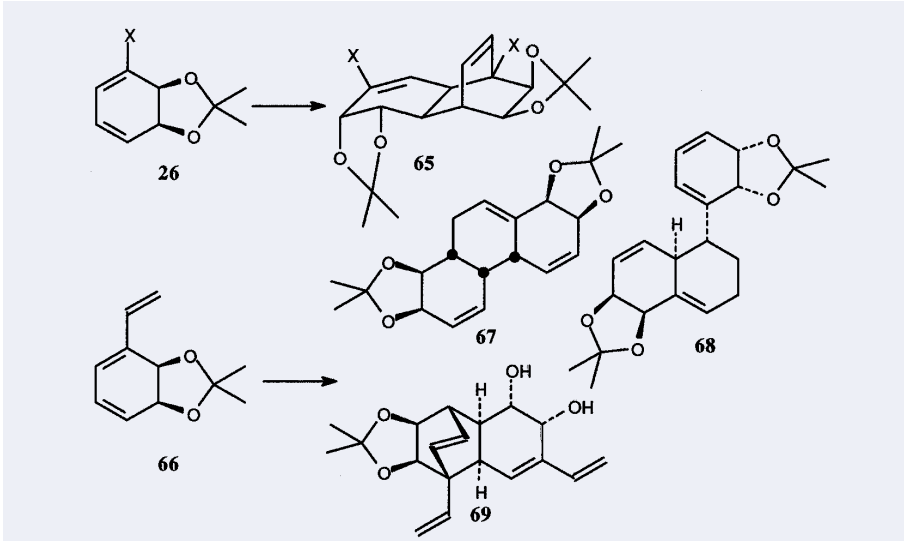


Figure 10. Diels–Alder adducts of some dienediol acetonides.

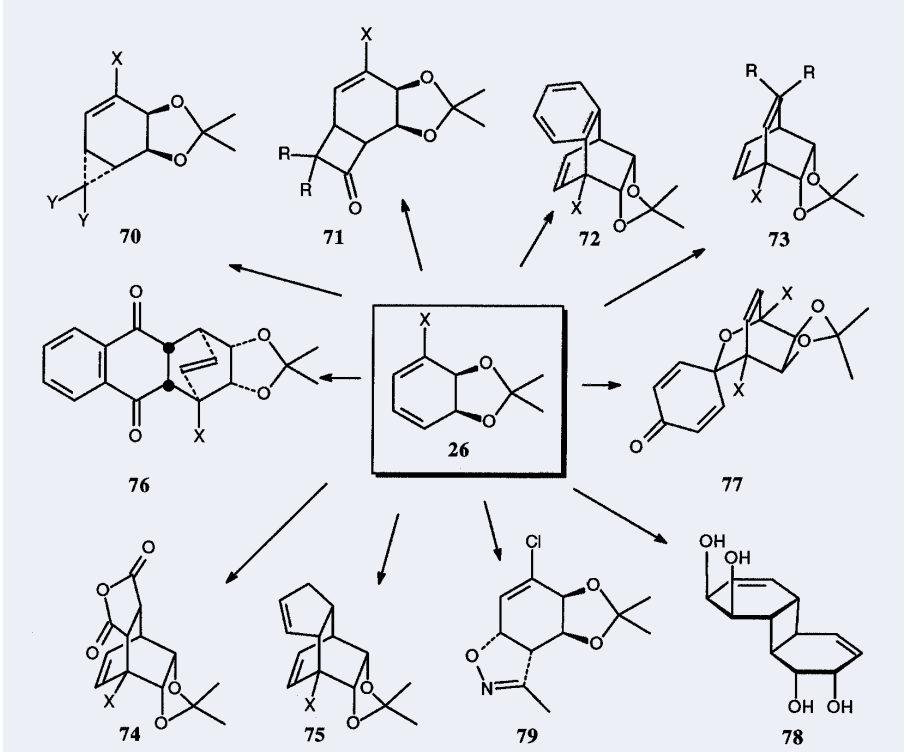


Figure 11. Cycloadditions of some dienediols and their acetonides.

The electronic parameters of *cis*-cyclohexadienediols have been investigated both experimentally[79-87] and by calculations.[83,87] Complete regioselectivity is expected for cycloadditions with polarized dienophiles, such as acylnitroso compounds. Other types of cycloadditions also exhibit preference for the more electron-rich olefin. These parameters have been exploited in many cycloadditions, as indicated in **Figure 11**. The selectivity of cycloadditions of dienediols and their derivatives, where X is not a halogen, is, as expected, much lower. Cyclopropanation;[88-92] ketene addition;[93] benzyne cycloaddition;[84-85] benzo- and naphthoquinone additions ([4+2] and photo [2+2]);[85] a variety of acrylate,[87] propiolate,[87] and maleic anhydride[85] Diels–Alder additions; singlet-oxygen,[68,71,83,94] and acylnitroso cycloadditions[68,78,83,87,95,96] have all been exploited. The *cis*-diol derived from benzene undergoes a photosensitized [2+2] cycloaddition to produce dimer **78** (**Figure 11**).[97] The singlet-oxygen and acylnitroso cycloadditions have found applications in the synthesis of conduritols and conduramines (see examples in the next section and in recent reviews).[8,10,11,13,18,98,99]

Advanced intermediates with applications in natural product synthesis have been obtained by means of simple cycloaddition processes. For example, the lower portion of morphine, with all five contiguous stereogenic centers, has been synthesized by the intramolecular Diels–Alder reaction from dihydrotoluene- and β-azidoethyldihydrobenzenediols, respectively. In the first model study, the diene was partially reduced; this allowed the remaining olefin to function as a dienophile and lead to **82** (**Figure 12**). The more advanced intermediate, **85**, was similarly synthesized from **83**. With diene **86**, the initial cycloaddition produced **87**, which underwent a Cope rearrangement to furnish **88**, possessing the same skeleton as **82**, albeit with a different stereochemistry.[100] Adduct **82** was originally reported with the wrong stereochemistry;[100] the correct stereochemical assignment[101] was made in 1998 by X-ray analysis when discrepancies were noted in the spectra of **82** and **85**. The stereochemistry of **88** was obtained as shown by a Diels–Alder/Cope sequence, but the correlation of the two routes was not chemically confirmed.[100] Banwell has also applied the tandem Diels–Alder/Cope sequence to the synthesis of octalins **91**,[86] and later to intermediates such as **92**, that are used in taxane synthesis.[74]

5.2. Cyclitols, Conduritols, Conduramines, Inositols, and Derivatives

Conduritols A–F, as well as some of the inositols—all shown in **Figure 13**—have been synthesized from either epoxide **45** or **52**,[102] diol **46**, or the singlet-oxygen adduct **49**. Because the details of their syntheses have been reviewed in several instances,[11,15,98,99] only the generalized approaches are shown here.

The *cis*-dihydroarenediols, as well as the primary synthons shown in Figure 8, are ideally suited for the synthesis of this simple class of cyclitols (**Figure 14**).[68,103] Conduramines become available by cleaving the nitrosyl Diels–Alder adducts **50** to ketoamines **58** and hydroxyamines **59**, or by opening epoxides with nitrogen nucleophiles to **54**. Lipase desymmetrization of meso conduramines has been used by Johnson in enantiodivergent syntheses of conduramine A-1.[104] All of the sequences leading to cyclitols begin with the protected cis diol **26** (X = Cl, Br), except the conduritol C synthesis by Carless, which employed the syn epoxide **52**.[102] Inositol synthesis becomes possible by careful peripheral oxidation of the dienediols.

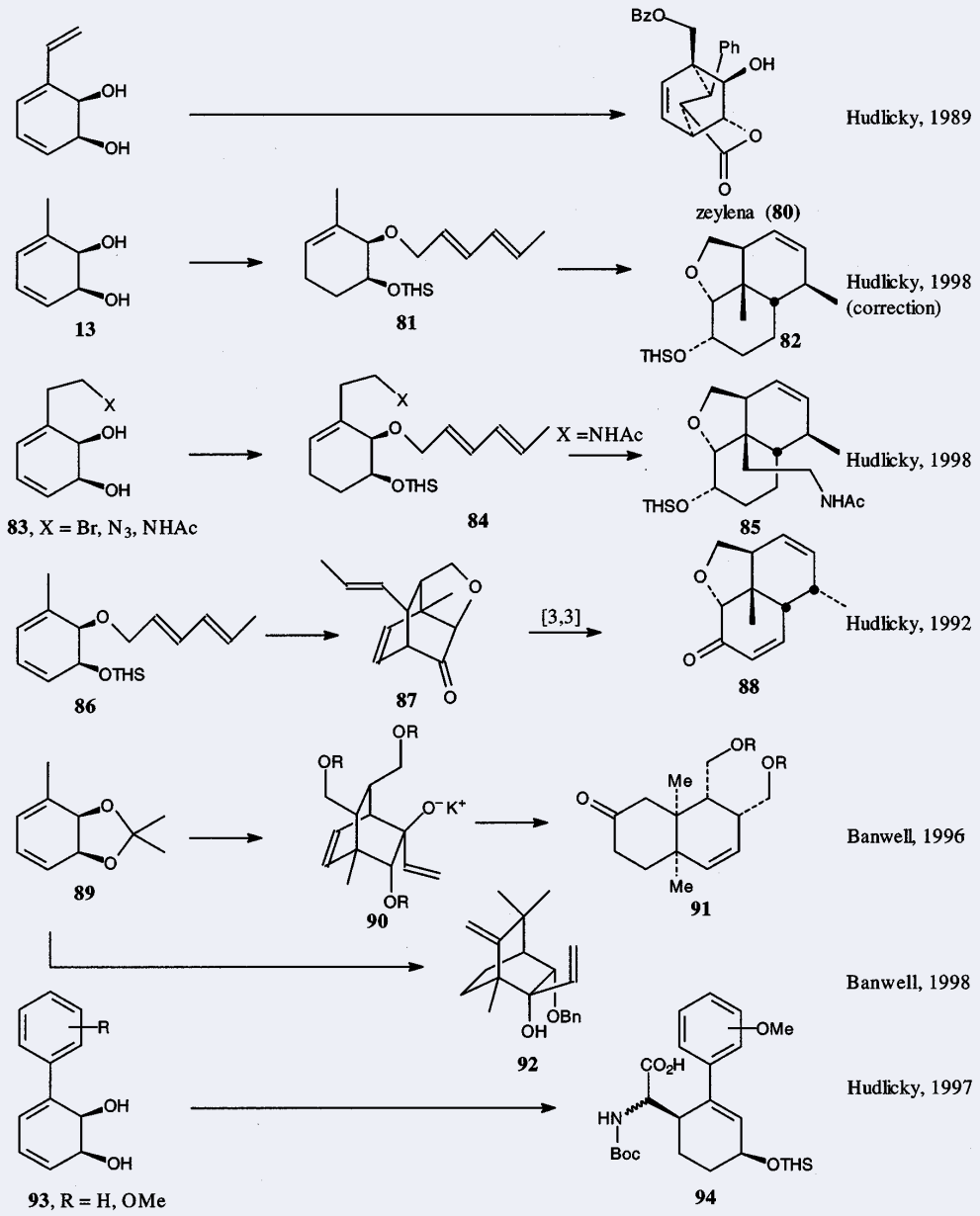


Figure 12. Examples of cycloadditions and sigmatropic processes aimed at natural product synthesis.

Following Ley's pioneering preparation of racemic **7**,[5] a resolution using (–)-menthoxyacetyl chloride[105] produced both enantiomers, as shown in Figure 15. Hudlicky's group accomplished the enantiodivergent preparation of both pinitols (**Figure 15**) by employing the symmetry principles discussed in the previous section.[67,68]

In 1990, we reported two enantiodivergent syntheses of (+)- and (–)-pinitol from optically pure, protected diol **26** (**Figure 15**). The concept of "proenantiotopic symmetry" was first reported in connection with this synthesis, whereby identical sets of reagents were used in a different order to attain enantiodivergence.[67,68]

Of the nine isomeric inositols portrayed in Figure 13, D-*chiro*-, L-*chiro*-, *allo*-, *neo*-, and *muco*-inositols have been synthesized from bromobenzene. D-*chiro*- and *allo*-inositols have also been prepared from the unique chloroepoxide **48**.[106,107] Recently, the preparation of some of these inositols has been optimized to medium scale.[108,109] A recently published handbook compiles structures and includes references to the synthesis of major cyclitols and derivatives.[110]

Amino inositols, fluorodeoxyinositols, and fluorodeoxyamino inositols have also been synthesized, as shown in **Figure 16**. In all of these preparations, careful planning with respect to the placement of the electrophilic epoxides (the recipients of F^-, N_3^-, NHR, OH, etc.) is the key to efficient synthesis. Recently, 3-deoxy-3-fluoro-L-*chiro*-inositol (**117**) has been made, via fluorohydrin **116**, by the selective opening of vinyloxirane **45** with fluoride.[111] Fortamine (**118**) was prepared by Vandewalle from the meso diol derived from benzene.[112] The fluoroamino inositol **119**, along with its enantiomer, were synthesized recently in our laboratories because of its structural resemblance to the antibiotic L-*myo* inosamine.[113] Conduritol analogs such as **120**[114] and **121**[115] led to investigations of "unnatural" derivatives that contain the cyclitol or conduramine motifs.

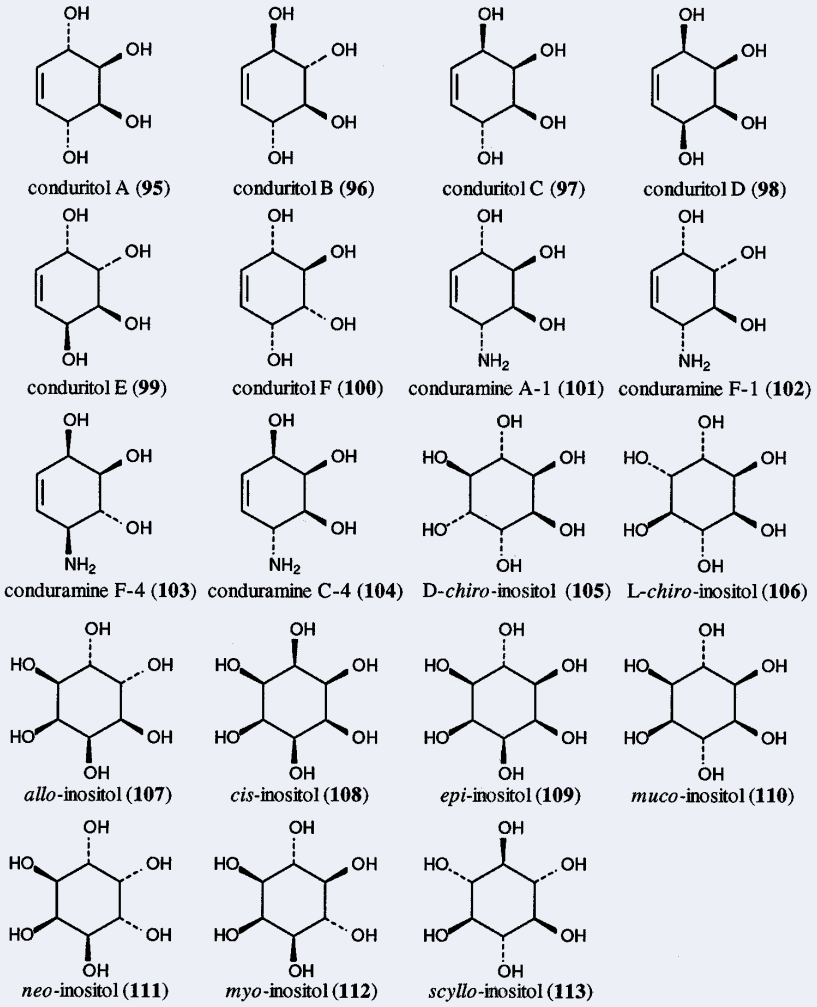


Figure 13. All conduritols, conduramines, and inositols.

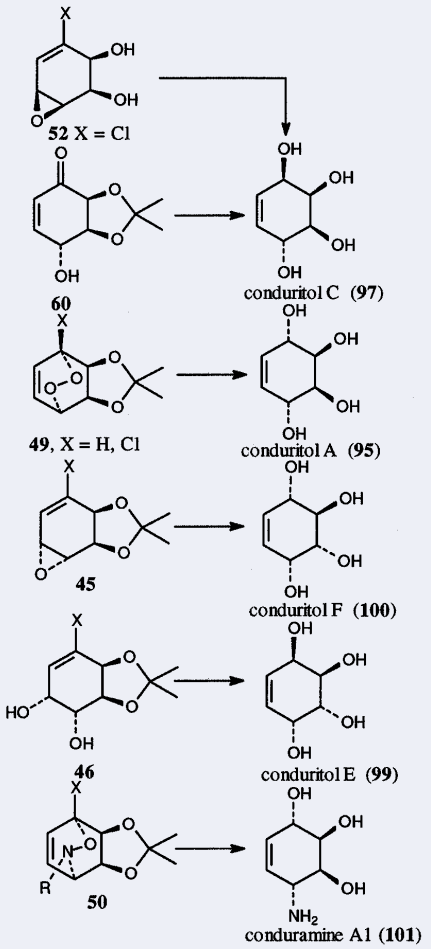


Figure 14. Conduritol and conduramine synthesis.

As the field of inositol and cyclitol synthesis matured, more complex structures were targeted. Dihydronaphthalenediol-derived analogs such as **123** were synthesized from the epoxydiol **122**, and were shown to have interesting molecular and biological properties.[116] Dimeric ethers and amines of type **124** (**Figure 17**) were also recently prepared via *cis*-dihydronaphthalenediol, and were shown to have interesting solid-state properties.[117,118]

The oligomers of L-*chiro*-inositols such as **127** are made by iterative coupling of primary synthons **125** with vinyl oxiranes **45**. Compound **127** possesses a natural β-turn in its secondary structure.[119,120] The amino cyclitol dimeric ether **128**, prepared similarly, chelates calcium ions and forms helical assemblies in the solid state (**Figure 17**).[120] The chemistry of the higher inositol conjugates (an octamer has recently been synthesized) and their derivatives is likely to have a major impact on medicinal and materials chemistry in the near future.

5.3. Carbohydrates

To execute a general and exhaustive design of carbohydrates, it is necessary that the cyclohexene ring be cleaved at a selected location and the resulting compound reductively cyclized in a premeditated fashion. The placement of heteroatoms other than oxygen onto the periphery of the dienediol also provides access to heterosugars. By simple oxidation of the periphery of the dienediol, followed by selective reductive cyclizations, many permutations of hexoses become possible, as shown in **Figure 18**. Notice that, even though there are two options for 6- and 5-membered-ring closures, the resulting sugars will be diastereomeric, depending on the definition of peripheral stereochemistry prior to cleavage and recyclization. Thus, all 16 isomers of single hexoses are available from a single precursor as a function of detailed planning, usually from primary synthons such as epoxides or diols.

A detailed analysis of this strategy has been published,[11,13-17] and most examples have been reduced to practice. The first application involved the two-carbon oxidative scission of **26** to provide protected erythruronolactone **135** in 51% yield in just 3 steps from bromo- or chlorobenzene.[121,122] A periodate cleavage of chloroepoxide diol **48** gave lactone **135**, a synthon with a proenantiotopic plane of symmetry, in 38% overall yield (**Figure 19**).[123]

Both enantiomers of erythrose (**136**), as well as L-ribonolactone (**137**), have been made from **135**. Because of its symmetry, the latter compound was found to be a useful synthon for pyrrolizidine alkaloid synthesis (see Figure 24).

Azasugars were synthesized from azido alcohols of type **138** (all four diastereomers of this synthon were prepared[124]) by oxidative cleavage of C6–C1 followed by recyclization of the reduced nitrogenous function, as in the synthesis of mannojirimycin (**139**) (**Figure 20**).[125]

Reductive cyclization employing different hydroxyl groups results in the selective

syntheses of 2-, 3-, or 4-aminosugars, the latter made from the isomeric azidohydrin **140**. Glucosamine (**141**) and deoxyaminomannose **142** are prepared in this fashion.[126] Sphingosines **143** (all four isomers) have been prepared via azidoerythroses **144** by successive cleavage of C6–C1 and C2–C3 in intermediates **138** and **140**, after the stereochemistry of the alcohol and azido groups had been defined (**Figure 20**).[124,127] Deuteromannose derivative **145** was prepared from pentadeuterobromobenzene by this strategy.[128]

Following the principal strategy of first precisely defining the peripheral substitution and then applying oxidative cleavage/reductive cyclization, deoxyfluorosugars also become available, as exemplified by the glucose and mannose derivatives **147** and **148**, respectively.[129]

Deoxysugars such as *pseudo*-β-D-altropyranose (**149**)[130] and a pseudosugar-inositol conjugate, **150**,[131] were prepared as shown in **Figure 21**. These examples demonstrate the enormous power of the reductive cyclization technology as a fully exhaustive method of synthesis for *any* carbohydrate derivative. The technique relies on the definition of stereochemistry on the cyclic precursor prior to oxidative cleavage. Its various iterations have since been used by Banwell to construct sugars such as nonulosonic acid derivative **152** from chlorobenzene,[132] and by Johnson in the synthesis of azasugars and analogs.[133,134] The rationale for the exhaustive strategy for carbohydrate synthesis has been delineated in detail on several occasions.[11,14,15,17]

Cleavage and reductive cyclization of conduramines, such as **59**, obtained by lipase-mediated resolution, led to 1-deoxygalactonojirimycin (**153**), as reported by Johnson (**Figure 22**).[133]

A combination of Suzuki-type coupling with oxidoreductive recyclization strategy has been exploited by Johnson in the preparation of various glycomimetics, e.g., aza-*C*-disaccharides (**Figure 22**).[134] It is expected that applications such as these will grow as the complexity of the targets that are attained increases.

5.4. Alkaloid Synthesis

Certain oxygenated alkaloids lend themselves quite naturally to considerations involving the incorporation of *cis*-dihydroarenediols into their design. In addition, the enantiodivergent design that furnished both enantiomers of pinitol has also been found to be applicable to erythruronolactone, which possesses the same proenantiotopic plane of symmetry.

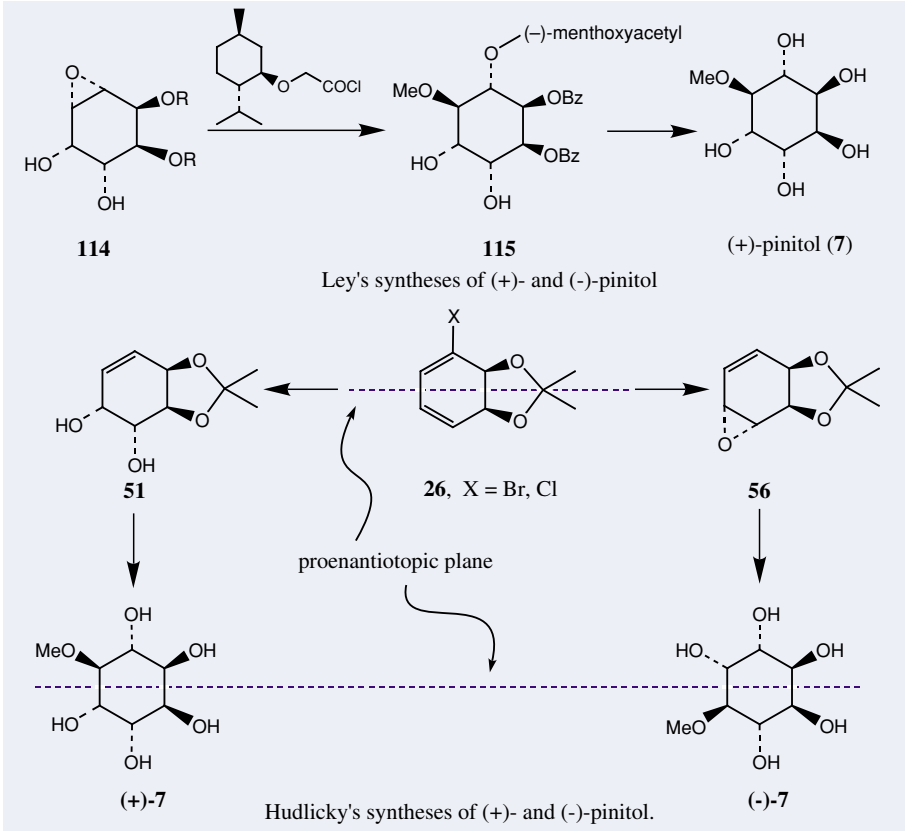


Figure 15. Enantiodivergent syntheses of pinitols.

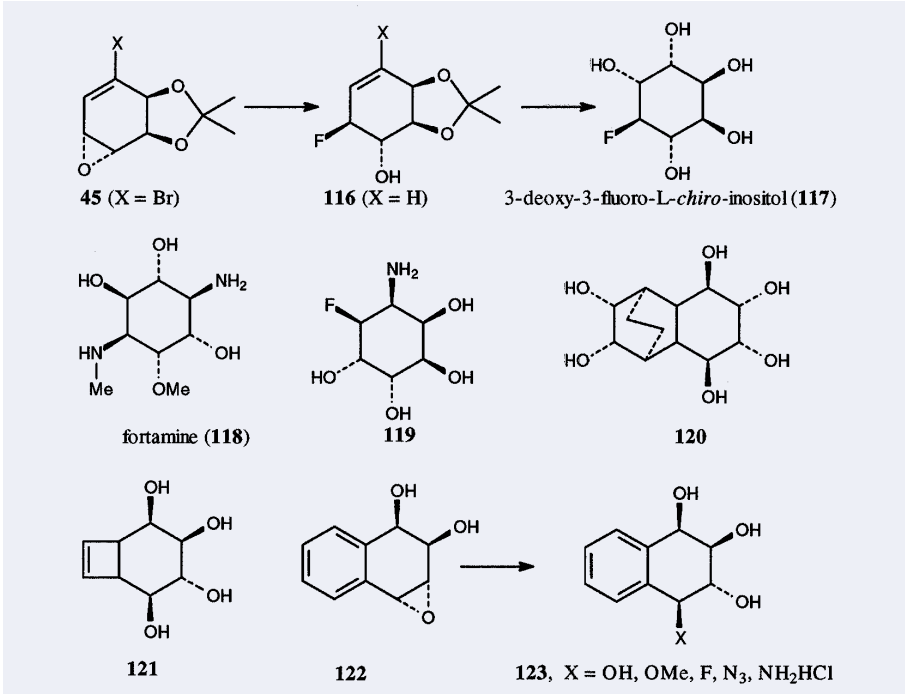


Figure 16. Analogs of conduritols, conduramines, and inositols.

Thus, either conduramine **58**, cyclitol **60**, or erythruronolactone **135** can be manipulated directly into both enantiomers of a target compound by principles of the commutative law of algebra (**Figure 23**). This law states that the summation of a set of numbers is independent

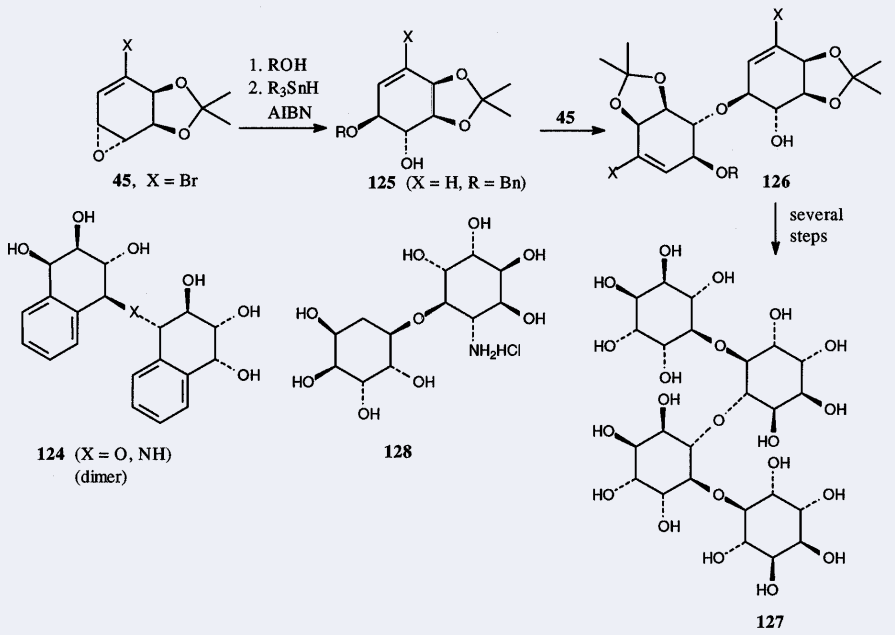


Figure 17. Inositol oligomers synthesized via iterative coupling.

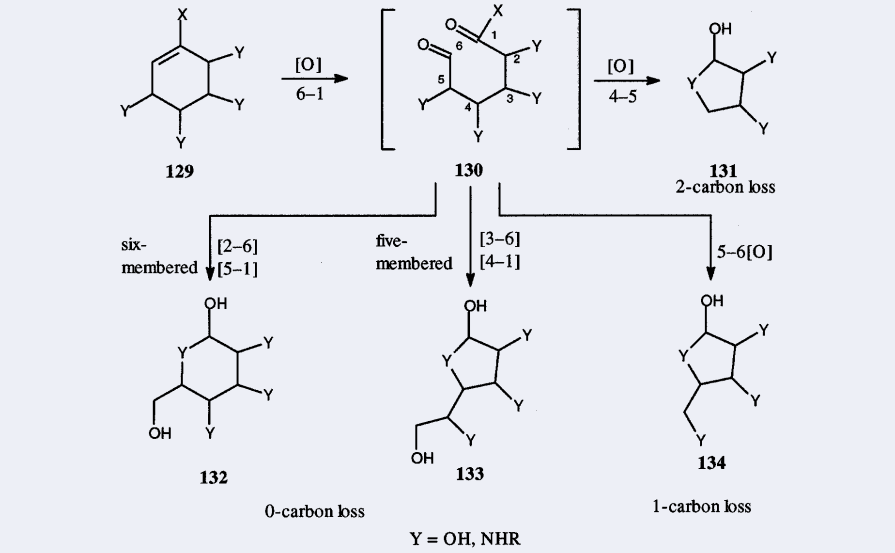
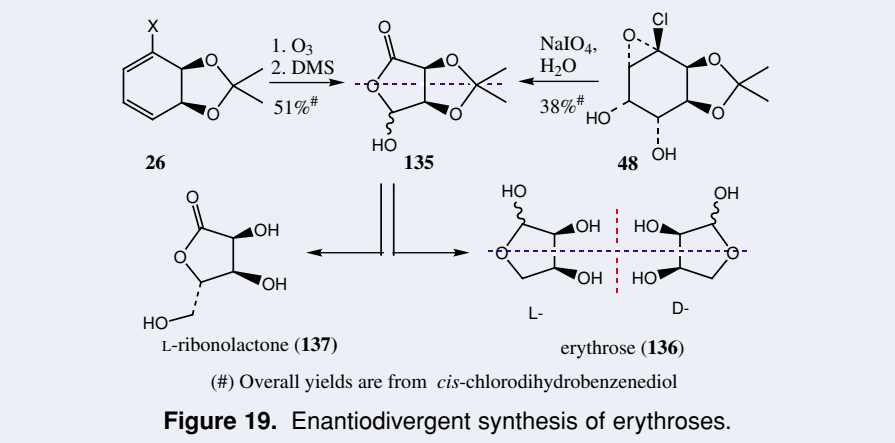


Figure 18. Examples of permutations in oxidoreductive cyclizations for carbohydrates.



(#) Overall yields are from *cis*-chlorodihydrobenzenediol

Figure 19. Enantiodivergent synthesis of erythroses.

of the order of addition of individual numbers. Thus, it is the precise ordering of chemical events (otherwise identical in the pathways to each enantiomer) that determines the symmetry of the product.

Figure 24 displays another application of this principle to the synthesis of trihydroxyheliotridanes.[122,135] Erythruronolactone (**135**) was converted to D- and L-erythroses by taking advantage of different rates of reaction at the carboxylate vs. aldehyde termini.[121,122] Wittig synthesis of the diene, followed by conversion of the remaining alcohol to the azide, allowed the formation of vinylaziridines **158** in both enantiomeric series. In both series, these were formed as diastereoisomeric pairs from *E/Z* dienes in a 5:1 ratio. Thermolysis generated the pyrrolizidines in an overall [4+1] intramolecular pyrrolizine annulation,[136] whose development and history have been reviewed.[110] Pyrrolizidine alkaloids synthesized by this method in our laboratory in the racemic series included platynecine, hastanecine, turneforcidine, dihydroxyheliotridane, supinidine, isoretronecanol, and trachelanthimidine, validating the [4+1] pyrrolizine annulation as a fully general method of synthesis.[135,136] Because of the endo mode of cyclization of the intermediate ylide, **160**, that is generated by thermolysis, the diastereomers of vinylaziridines converged stereoselectively to single isomers of pyrrolizidines in each series.

In 1992, taking advantage of the rapid generation of conduramines by the acylnitroso Diels–Alder reaction, we synthesized lycoricidine from bromobenzene in nine steps (**Figure 25**).[87,95] Oxazine **50** was reduced and acylated to the functionalized conduramine derivative **161**. The abnormal Heck cyclization followed by deprotection yielded (+)-lycoricidine **162**. The racemate of the natural product was also synthesized by Martin along a similar pathway from *cis*-dihydrobenzenediol.[137]

Kifunensine (**165**), an unusual indolizidine alkaloid, which also classifies as a hydroxylated piperidine (or azasugar), has been obtained in conjunction with our projects in carbohydrate chemistry involving oxidative cleavage of the functionalized cyclohexene **163** and its appropriate reductive cyclization (**Figure 26**).[138,139] Azido alcohol **163** was selectively transformed first to the azamannosolactone or mannojirimycin intermediate **139**, whose cyclization with oxalylamide did not yield kifunensine; however, the furanose form of azidomannose **164** was successfully transformed to kifunensine[138,139] by a known literature procedure.[140]

Our interest in amaryllidaceae alkaloids led us to the first asymmetric synthesis of pancratistatin (**169**), attained in 13 steps from bromobenzene via the addition of arylcuprate

166 to vinylaziridine **47** (**Figure 27**). In this first-generation synthesis,[141] the robust aryl amide and tosyl amide moieties had to be manipulated to intermediate **168**, whose treatment in refluxing water under pH controlled conditions (catalytic amount of sodium benzoate) furnished the target alkaloid in a remarkable sequence of five consecutive reactions.[141-143]

In the second-generation attempt,[142] aimed at 7-deoxypancratistatin (**173**), some major improvements were realized by taking advantage of the potential electrophilicity of the carbamate group in aziridines **171** in order to avoid using the robust benzamide moiety. The modified Bischler–Napieralski cyclization of **172** under the conditions reported by Banwell[144] gave the cyclic amide and eventually led to an 11-step synthesis of 7-deoxypancratistatin (**Figure 27**).[142,143] The enantiomers of both alkaloids can be prepared from 4-substituted iododiols **26** by the application of the "racemic switch" method of Boyd.[65] *ent*-7-Deoxypancratistatin has recently been synthesized from **26** via an additional lipase-catalyzed enrichment procedure.[145]

The recognition that amaryllidaceae alkaloids as well as morphine alkaloids may be viewed as oxygenated biphenyls (**Figure 28**) led us to consider a design in which synthons such as **177** would be made by either direct enzymatic oxidation of the corresponding biphenyls, or by a Suzuki-type coupling of *cis*-halodihydrobenzenediols with the appropriate aryl fragment. Such thinking led us to design the synthesis of narciclasine (**Figure 29**).[146]

The synthesis took advantage of the unique symmetry found in **178**—the metabolite obtained by biooxidation of *m*-dibromobenzene—and its subsequent cycloaddition with acylnitroso carbamate to oxazine **179**. Suzuki coupling of **179** with arylboronic acid followed by reductive cleavage of **180** did not generate the expected hydroxycarbamate. Instead, the unsaturated ketone **181** was formed and then transformed into the anti alcohol by means of directed hydride reduction, or standard reduction followed by Mitsunobu inversion (**Figure 29**). Finally, closure of the B ring was made through the Bischler–Napieralski-type reaction as in the case of 7-deoxypancratistatin synthesis.[142,146]

The enzymatic dioxygenation of biphenyls was pursued, and a number of metabolites have been identified, among them the desired diol **182** that is derived from 2,3-dimethoxybiphenyl.[147] An approach to morphine was envisioned, where the stereochemistry of the C–14 and C–9 centers would be controlled by the outcome of a sigmatropic process, which would transfer the configuration of one of the OH groups to a carbon center. Ideally suited

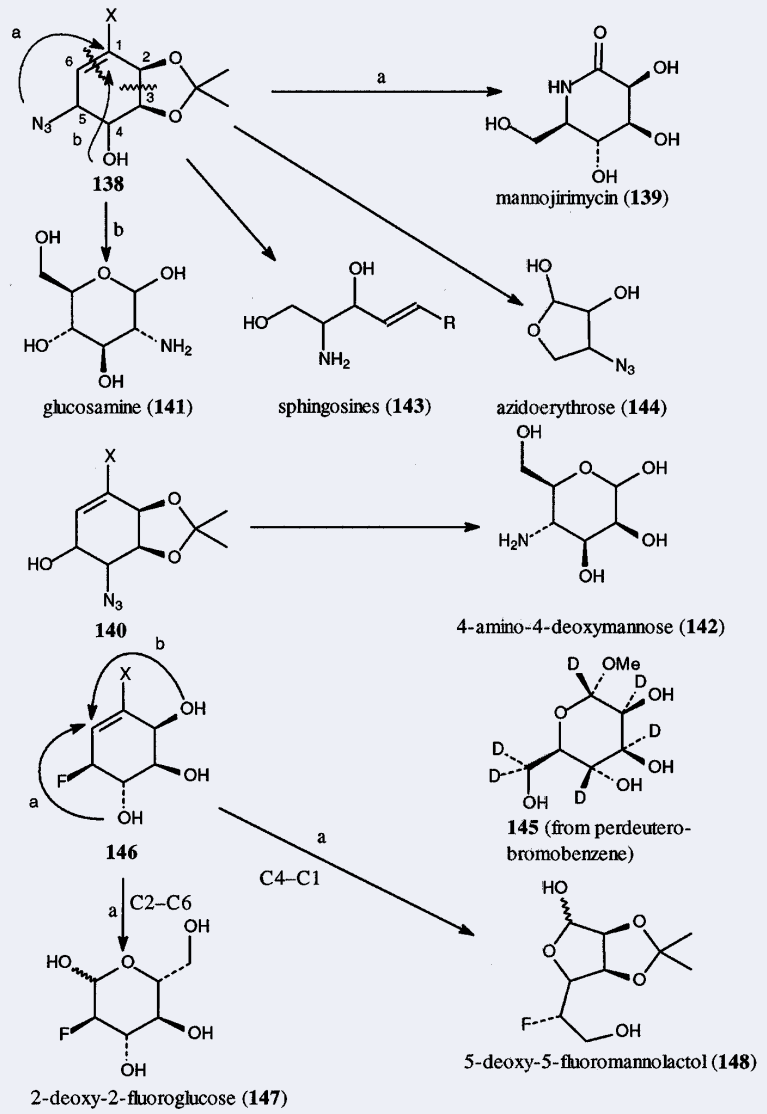


Figure 20. Design of aza-, amino-, fluorodeoxy-, and perdeuterosugars by oxidative cleavage–reductive cyclization strategy.

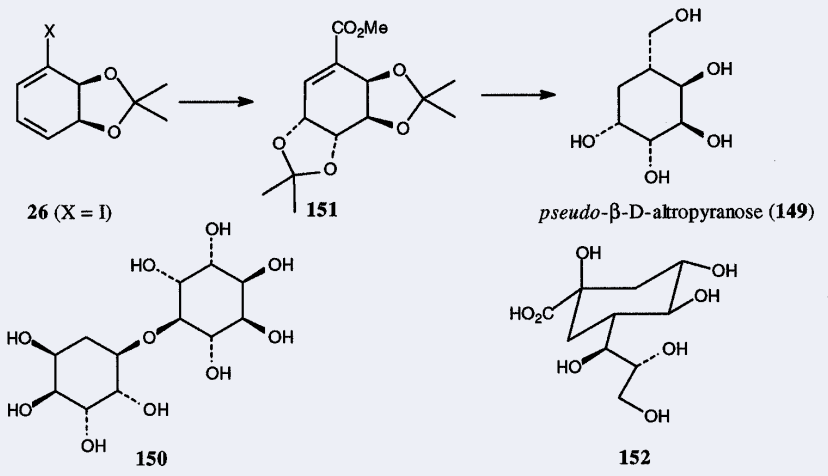


Figure 21. Synthesis of deoxysugar analogs.

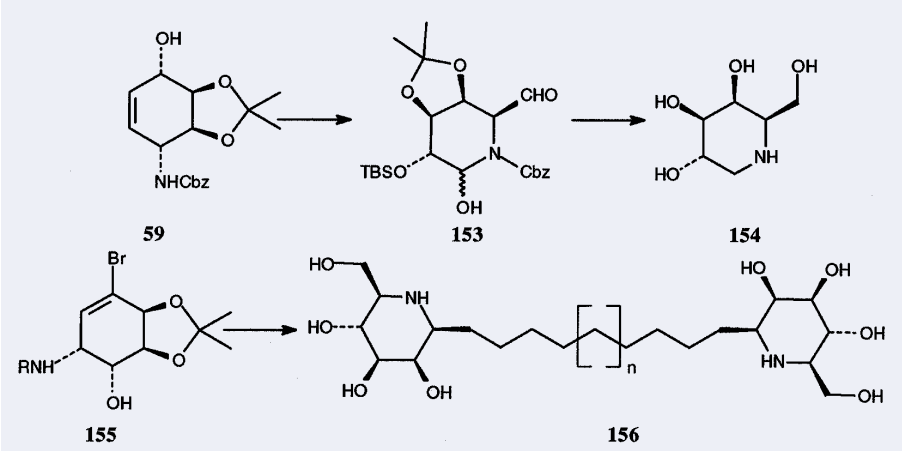


Figure 22. Syntheses of nojirimycin analogs and carbon-tethered glycomimetics.

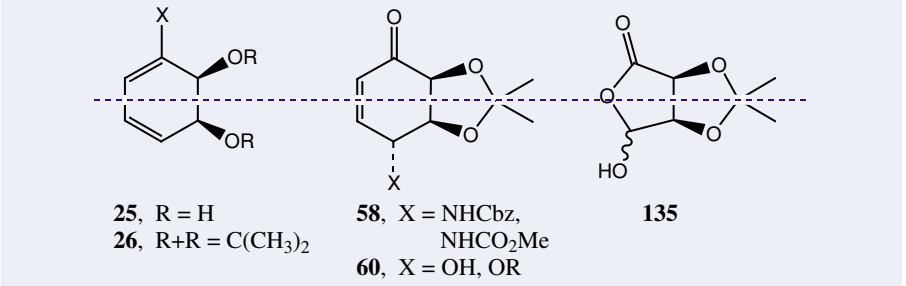


Figure 23. Synthons containing a proenantiotopic plane.

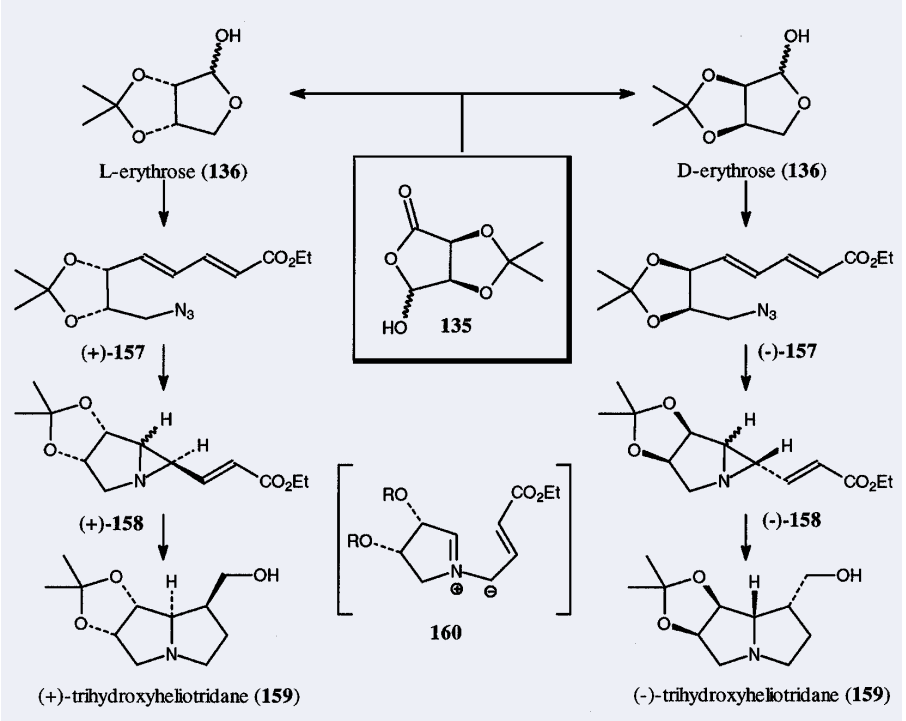


Figure 24. Enantiodivergent synthesis of oxygenated pyrrolizidine alkaloids.

for this purpose is the Kazmaier modification[148] of the Claisen rearrangement of the corresponding glycine enolates, and we have applied it to glycinate **183** (**Figure 30**).[72] Amino acid esters generally fail to rearrange under standard Ireland conditions, but react successfully in the presence of a Lewis acid, such as $ZnCl_2$ or $SnCl_4$. To fully control the relative stereochemistry of C–9 and C–14, **184**, which was generated as a 4:1 mixture of stereoisomers, was transformed into lactone **185** in which the bulky NHBoc group would be epimerized to the exo surface of the bicyclic ring system.

Diols **186**, derived from β-bromoethyl and *o*-bromo-β-bromoethylbenzene, comprised the starting point for a tandem radical cyclization approach to morphine in the former case and a stepwise cyclization in the latter (**Figure 31**). In the tandem as well as the stepwise approach, the bromocatechol unit required for the aromatic ring of morphine was made enzymatically from bromobenzene with an organism that also expressed the second enzyme in the pathway, namely, the diol dehydrogenase.[149,150]

The tandem process, modeled after Parker's approach,[151] provided low yields of the pentacyclic precursor **188**, with the epi configuration at C–14 (**Figure 31**).[149,150] When *o*-bromo-β-bromoethylbenzene was first converted to the isoquinoline derivative **189**, through a single radical cyclization followed by attachment of the bromocatechol (in an ent configuration), *ent*-morphinan (**190**) was attained.[150] The isoquinoline formation was nonstereospecific with respect to C–9 (morphine numbering) and resulted in a 2:1 mixture of isomers (α/β). However, the isoquinoline in the correct enantiomeric series was obtained selectively via acid-catalyzed cyclization of the acyliminium salt **191**.[152] Dibenzoate **191** yields **192** stereospecifically, and the trans isomer of **191** gives accordingly the α-isomer of **192**, thus providing for a fully enantiodivergent approach to morphine. The mechanistic details of the acid-catalyzed cyclization of **191** and its trans isomer have recently been published.[153] Further refinements in this multigeneration process are ongoing and include the generation of precursors for **191** by electrochemical oxidations.[152] Additional routes to morphine are being pursued via Diels–Alder cycloadditions of compounds related to **85** and **88**, but containing the required elements of the aromatic ring of morphine.

5.5. Miscellaneous Natural Products

The incorporation of certain *cis*-dihydroarenediols into synthetic sequences results almost always in a significant shortening of the routes to the desired targets. We recognized such advantages in our pursuit of the total syntheses of natural products, even during the very first project that we undertook in this area.[71] The protected dihydroxylated

cyclopentenone **194** has been used by Johnson in a triply convergent synthesis of prostaglandin $PGE_2\alpha$ (**195**) (**Figure 32**).[154,155] The starting enone itself is available in several steps from arabinose by published methods,[156-158] only two of which employ the diols derived from either chlorobenzene[158] or toluene.[71,158] Ozonolysis of the diol derived from toluene provides ketoaldehyde **193**, which is dehydrated with alumina to provide the important enone, **194**, in just three operations from toluene.[71] An alternative to this process (sometimes not easily reproduced because of the nature of the aluminum oxide catalyst) has been developed by using the diol derived from chlorobenzene and its high-yielding ozonolysis to erythruronolactone (**135**); intermediate **135** was converted to **194** by the method of Borchardt (**Figure 32**).[156]

The bicyclic enone, **194**, is a very useful five-carbon synthon (every carbon is differentially functionalized), and we have used it in a synthesis of specionin (**200**), an antifeedant for the spruce budworm.[159] This particular approach relied on the [2+3] intermolecular cyclopentene annulation developed in our laboratories,[160] and provided specionin via vinylcyclopropane **197** and its rearrangement (thermal or fluoride ion-catalyzed)[160] products, cyclopentenes **198** or **199** (**Figure 33**). Noteworthy in this synthesis is the fact that the initial biochemically installed asymmetry is propagated through the synthesis and is later destroyed in the final elaboration to the bisacetal ring in **200**.

The unusual natural product zeylena (**80**), containing a *trans*-diol unit, has been investigated in connection with the antitumor properties of related cyclohexene oxides. We approached its synthesis from the diol derived from styrene by "protecting" the reactive triene unit via its Diels–Alder reaction with diethyl azodicarboxylate (DEAD) (**Figure 34**).

Following the Mitsunobu inversion of the distal hydroxyl with cinnamic acid, the triene was liberated; intramolecular Diels–Alder reaction with cinnamate set the required bicyclo[2.2.2]octane framework. Further oxidative adjustments of the styrene double bond led to the synthesis of zeylena.[161]

Methyl shikimate (**206**) was synthesized by Johnson[104,162] from the meso diol of benzene via lipase resolution (**Figure 35**).

Both enantiomers have been obtained by transforming the resolved conduritol A derivative, **204**, into the iodoenone **207**. Vandewalle[163] reported a synthesis of shikimate as portrayed in Figure 35. In this synthesis, the protected conduritol **209** was transformed via Mitsunobu elimination and subsequent epoxide opening to dithiane **210** and further to methyl shikimate (**206**).

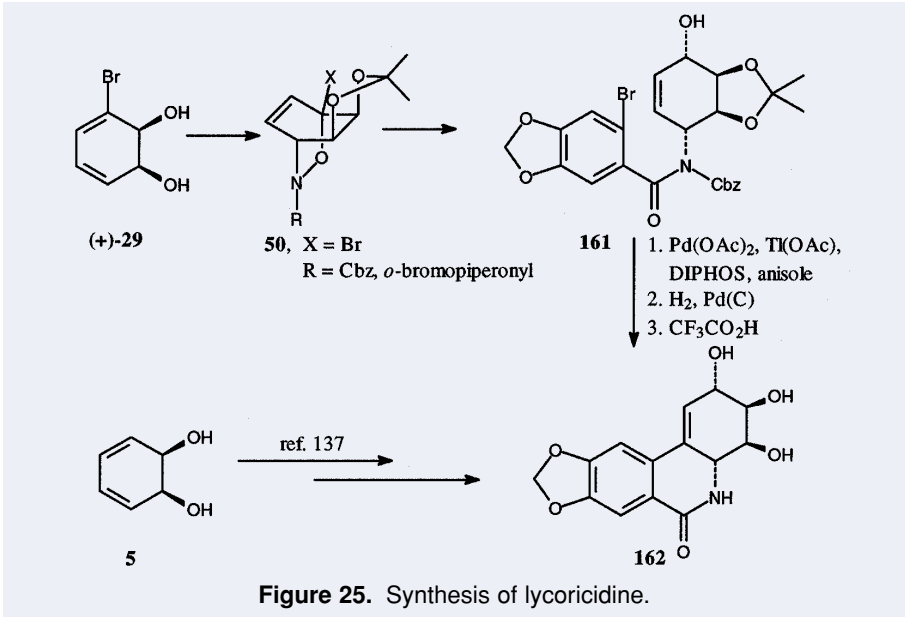


Figure 25. Synthesis of lycoricidine.

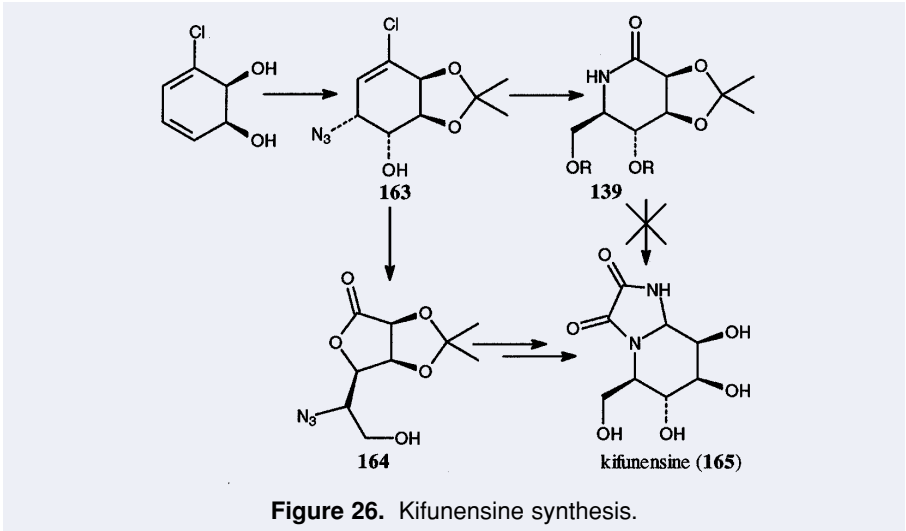


Figure 26. Kifunensine synthesis.

Coupling of synthons derived from **25** to C_2-symmetric derivatives and preparation of phenanthrene-type ring systems has been reported recently.[164]

Banwell synthesized tropolones from dihydrobenzene- or dihydrotoluenediols[88] by taking advantage of the cyclopropanation of the double bonds in the dienediol (**Figure 36**).

The *meso*-diol **25** (X = H) was cyclopropanated, the diol unit deprotected, oxidized, and rearranged with Lewis acid to tropolone **213**. In the case of dihydrotoluenediol, the selectivity of the cyclopropanation favored the more electron-rich (i.e., methyl-bearing) olefin; this was also the case with bromodihydrobenzenediol (**214**). This particular application, followed by the two-carbon oxidative-scission strategy outlined earlier, gave a differentially functionalized cyclopropane suitable for elaboration into chrysanthemates or other pyrethroids, such as deltamethrin (**219**).[89]

Banwell applied the anion-accelerated oxy-Cope rearrangement of bicyclo[2.2.2]-octanes, derived from *cis*-dihydrotoluene-diol, to the synthesis of the taxane AB ring system (**Figure 37**). The required bicyclo[2.2.2]octane framework was generated by iminoketene addition to yield **220**. The Cope rearrangement generated the oxygenated core of the AB ring system of taxol, **222**. In a more advanced study, the initial adduct, **224**, was subjected to transannular cyclization to provide the tricyclic skeleton **225**, the fragmentation of which, modeled after Holton's taxane synthesis, furnished the ring A allylic alcohol, **226**.[74]

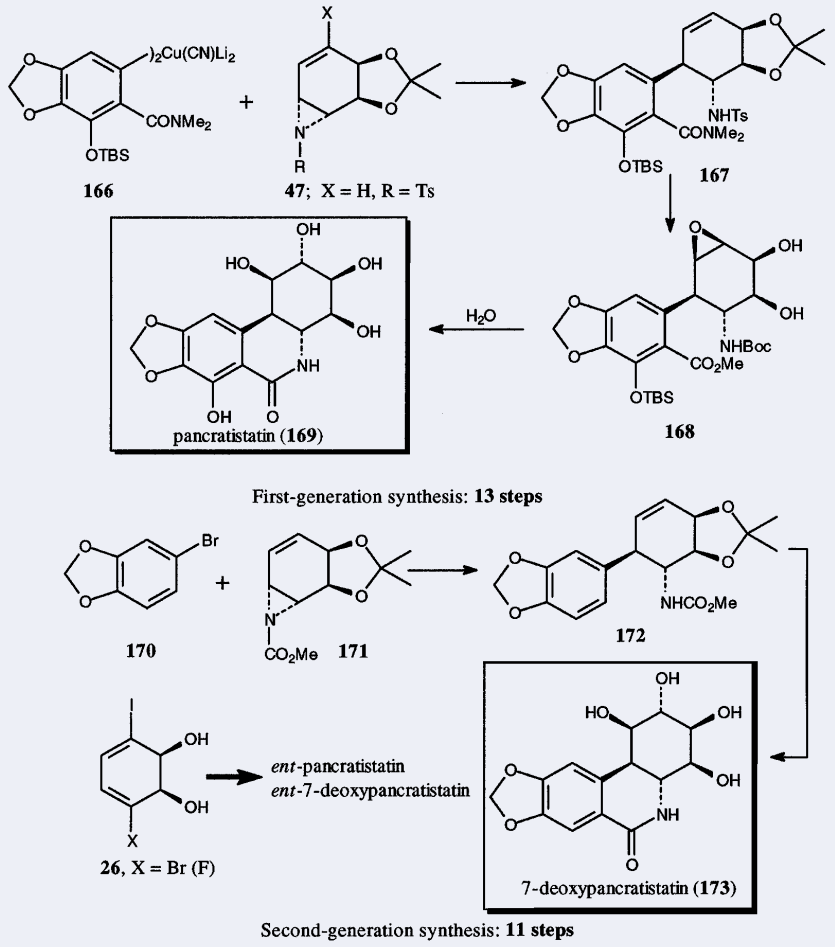


Figure 27. First asymmetric synthesis of pancratistatin and second-generation synthesis of (+)- and (–)-7-deoxypancratistatin

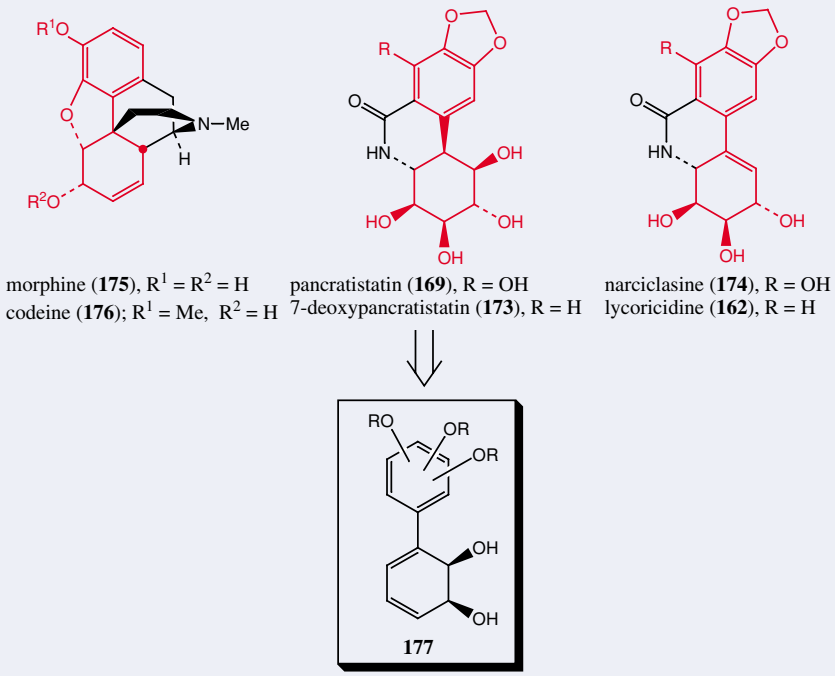


Figure 28. Disconnection of morphine and amaryllidaceae alkaloids to oxygenated biphenyls.

5.6. Recent Applications of Commercial Significance

Several applications of commercial value of the *cis*-cyclohexadienediols have already been reduced to practice. In addition to the pioneering work of ICI (now Zeneca) on the commercial synthesis of polyphenylene[3,4] from benzene via the corresponding meso diol, and the medium-scale preparation of several inositols (D-*chiro*-, L-*chiro*-, *allo*-, *muco*-, and *neo*-) published by our group, there are other examples as shown in **Figure 38**.

Merck considered the biocatalytic production of dihydroindenediol for incorporation into the AIDS drug indinavir.[165] Genencor manufactures indigo by a combination of metabolic engineering of the aromatic amino acid pathway and naphthalene dioxygenase-mediated oxidation of indole to *cis*-dihydroindolediol, which dehydrates to indoxyl, the precursor of indigo.[166,167] The preparation of D-*chiro*-inositol and other inositols has been performed on a medium scale (50–100 g) and can be considered easily scalable to multikilogram quantities.[108] It is expected that other targets of commercial significance will soon employ some of the metabolites discussed in this review in their synthetic sequences.

Quite recently, both chloro- and bromodihydrobenzenediols have been used in reactions on polymer supports.[168] Ketalization was accomplished on polystyrene resin via benzyl ether linkers, as depicted in Figure 38. Many diverse structures have been generated by these methods and freed from the resin by CF_3CO_2H. The yields reported are comparable to those from the solution-phase synthesis of similar compounds.

6. Conclusion and Outlook

It is evident that a tremendous amount of work has been accomplished in the utilization of metabolites derived from aromatics. The pioneering work of Gibson, Ribbons, and the EPA group in Pensacola (associated with the University of Minnesota) made it possible to lay the groundwork for the synthetic community to take full advantage of the rich potential of these compounds. Yet, the expansion of chemoenzymatic methods in general, and the use of *cis*-dihydroarenediols in particular, has hardly begun, as evidenced by the relatively few groups worldwide involved in this area.[6,14] The applications to synthesis have so far originated in only a few of the diols listed in the tables. More complex strategies, as well as the use of tandem reaction sequences and an expanded reservoir of polyfunctional metabolites, should support further growth of this discipline. Without a single exception, all

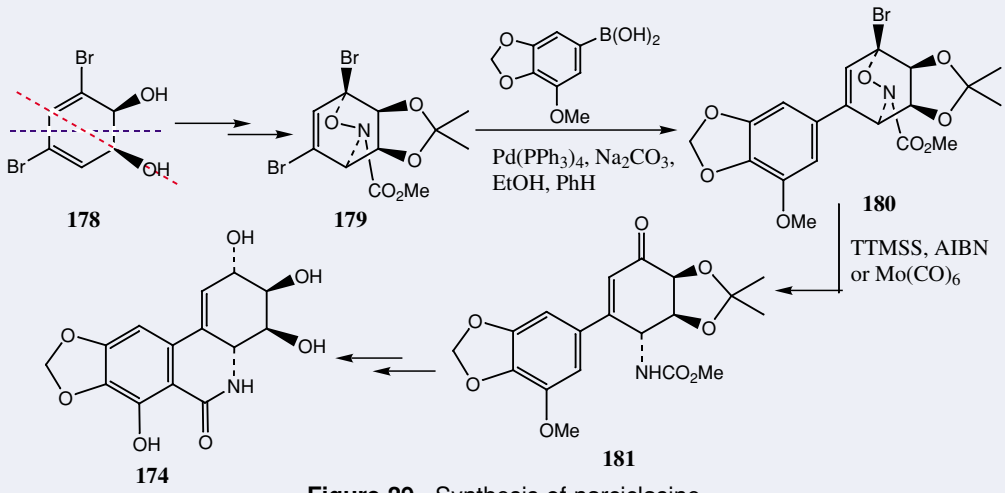


Figure 29. Synthesis of narciclasine.

total syntheses (certainly those from our laboratory) that incorporate a *cis*-diol in the sequence toward the target molecule are considerably shorter than the traditional approaches in the literature. This trend will no doubt continue with new applications. The readers are invited to view the collection of structures in the tables and apply them in their own innovative designs.

7. Acknowledgments

The authors are grateful to the many coworkers who participated in the ventures described in this review during the period 1988–1998, and whose names are listed in the citations. The generous financial support for this work came from NSF (CHE-9315684, CHE-9521489 and CHE-9615112), EPA R82613, Genencor International, Mallinckrodt Specialty Chemicals, Jeffress Trust Fund, TDC Research, Inc., TDC Research Foundation, and NIH (support of Gibson's work only). Several outside postdoctoral fellowships (Michel Desjardins, Kurt Konigsberger, and Jacques Rouden) are also acknowledged. Logistical help from Dr. Gregg Whited, from Genencor International, Inc., is greatly appreciated. The authors are also in debt to Prof. Gustavo Seoane (Universidad de la República, Montevideo, Uruguay) for his initial input. Careful proofreading and many suggestions for the final draft were provided by Dr. Josie Reed, Prof. Douglas Ribbons, and Dr. Sol Resnick. To all these individuals go our heartfelt thanks. Last, but not least, one of us (TH) is indebted to Dr. Larry Kwart, whose convincing arguments and practical advice led to the establishment of microbial oxidation technology in the group. Without his initial input, none of the work described in this review would have ever come to fruition.

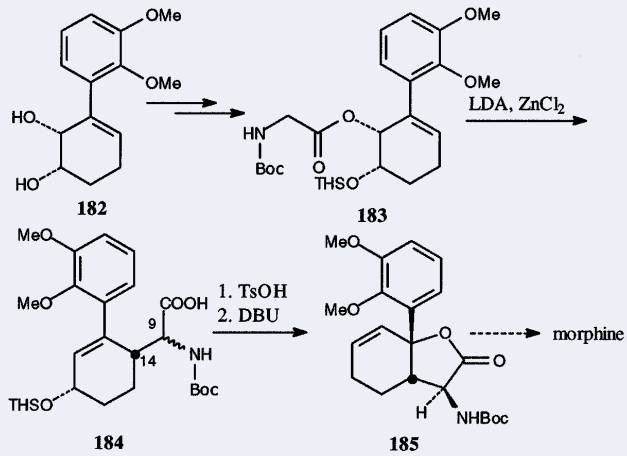


Figure 30. Claisen rearrangement approach to morphine.

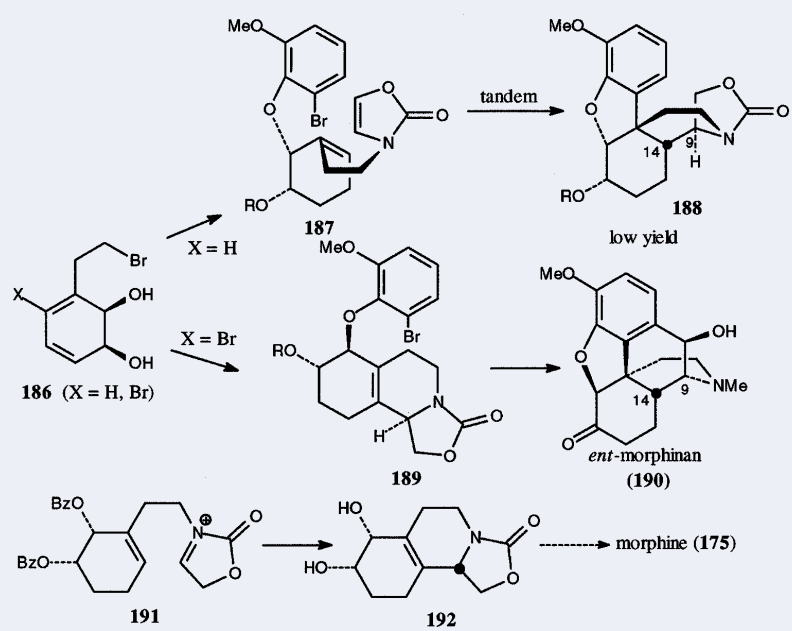


Figure 31. Tandem vs. stepwise radical cyclization approach to morphine.

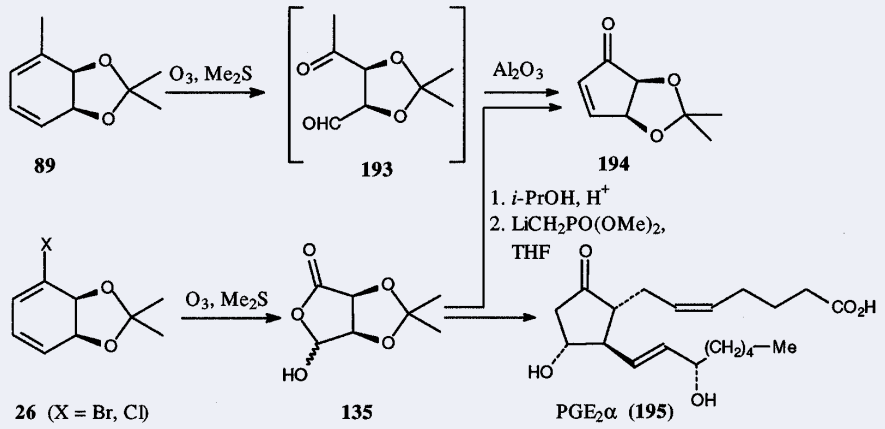


Figure 32. Two approaches to a prostaglandin intermediate.

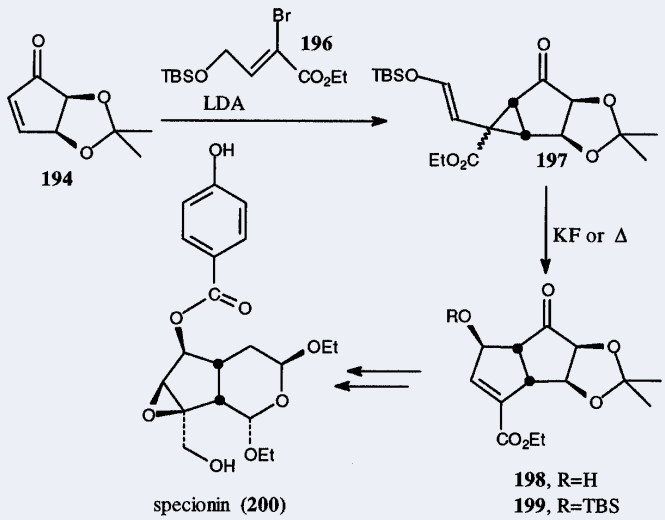


Figure 33. Synthesis of specionin.

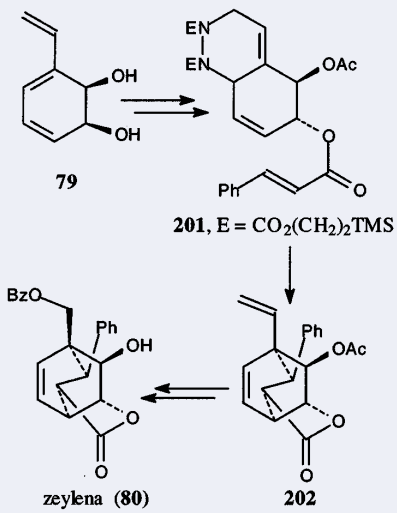


Figure 34. Synthesis of zeylena.

8. References and Notes

(†) In Tables 1–5, compounds are pictured exactly as reported in the literature. In some cases, the absolute stereochemistry is inferred but not necessarily proven beyond doubt. Compounds in brackets imply that the actual diol has not been isolated. Compounds in color are those that have been exploited in synthetic ventures.

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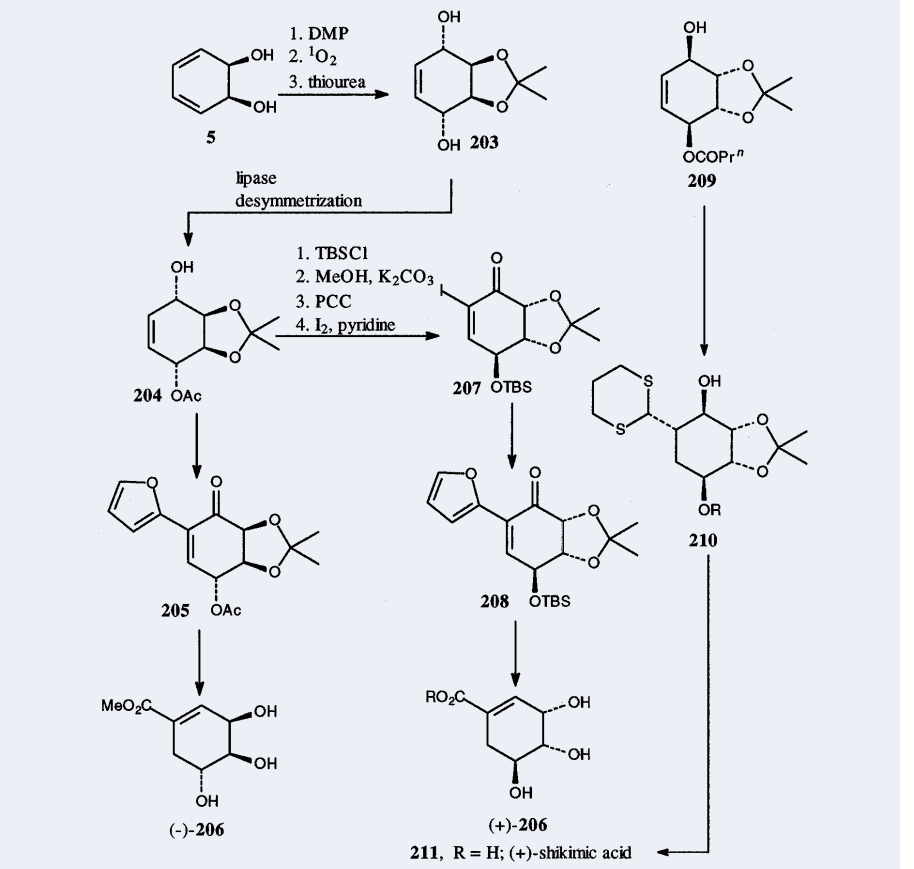

Figure 35. Synthesis of methyl shikimate and shikimic acid.

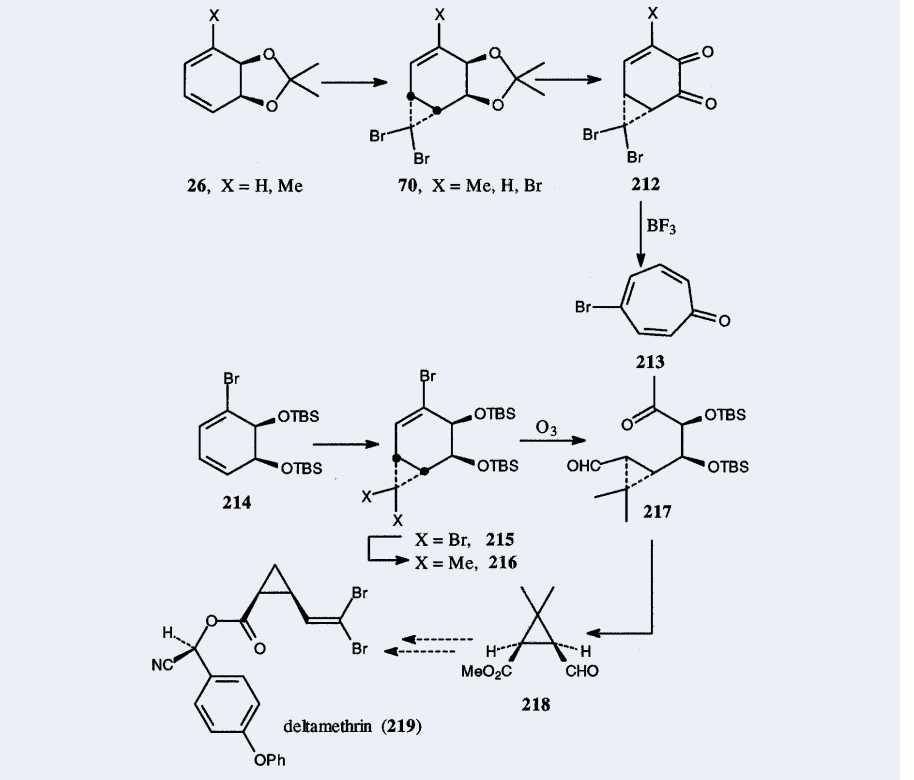

Figure 36. Synthesis of tropolones and synthons for chrysanthemates.

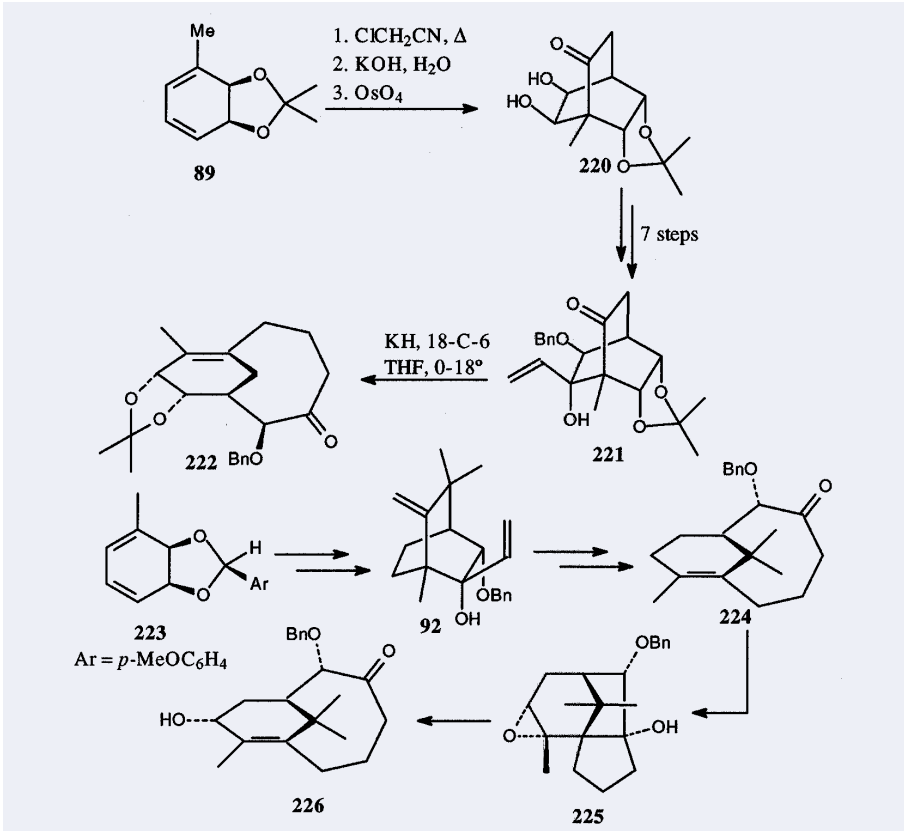

Figure 37. Approaches to taxanes.

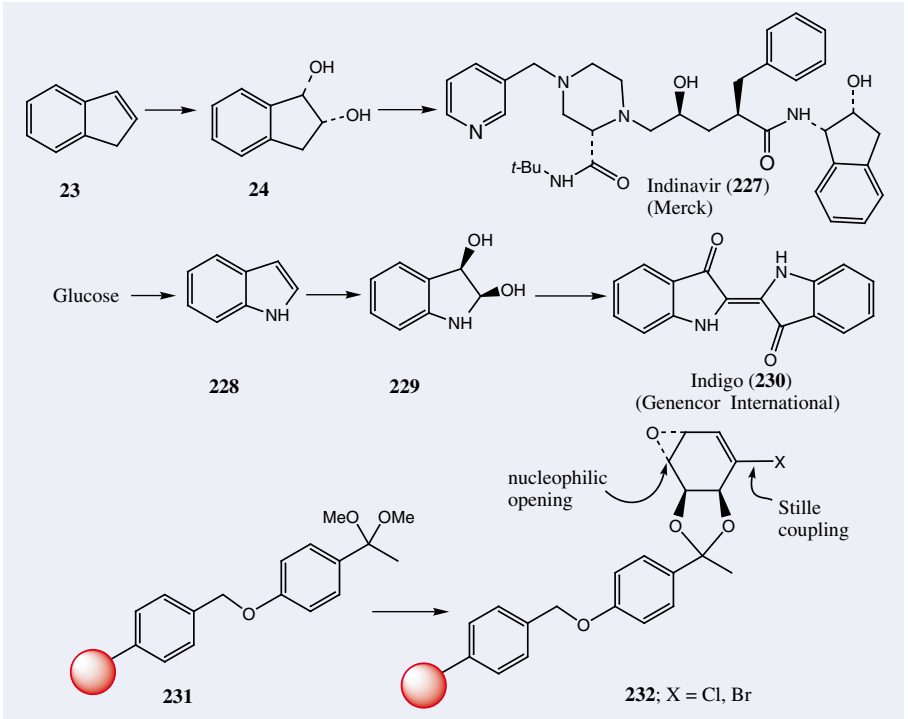

Figure 38. Potential commercial applications of *cis*-dihydroarenediols.

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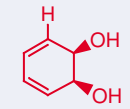
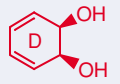
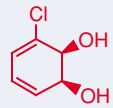
Table 1. Diols Derived from Monocyclic Aromatics



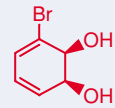
P. putida 39/D,
(ref. 19,21)



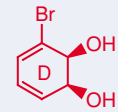
E. coli JM109(pDTG601A)
(ref. 218)



P. putida 39/D
P. putida UV4
(ref. 25,63,184)



P. putida UV4
E. coli JM109 (pDTG601A)
(ref. 63,184)



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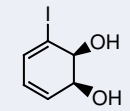
(ref. 126,170)



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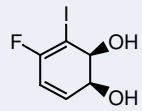

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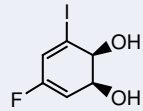
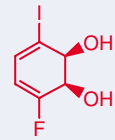
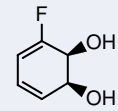


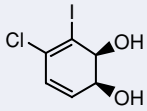
P. putida UV4
(ref. 170)



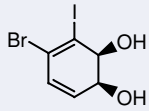
P. putida UV4
E. coli JM109 (pDTG601A)
(ref. 145,170)



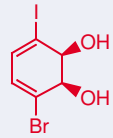
P. putida UV4
(ref. 63,184)



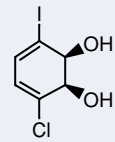
P. putida UV4
(ref. 170)



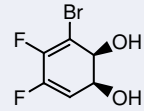
P. putida UV4
(ref. 170)



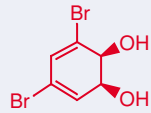
P. putida UV4
E. coli JM109(pDTG601A)
(ref. 145,169)



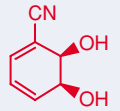
P. putida UV4
(ref. 169)



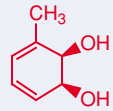
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 219)



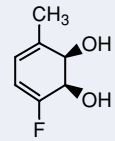
E. coli JM109(pDTG601A)
(ref. 146)



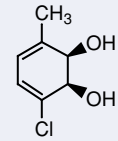
P. putida 39/D
P. putida UV4
(ref. 161,184)



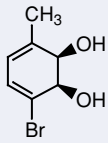
P. putida 39/D
P. putida UV4
(ref. 22,63,180)



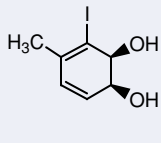
P. putida 39/D
P. putida UV4
(ref. 25,169)



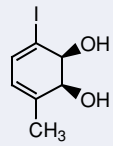
P. putida 39/D
(ref. 1,25)



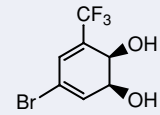
P. putida
(ref. 25,39)



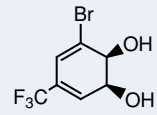
P. putida UV4
E. coli JM109(pDTG601A)
(ref. 170)



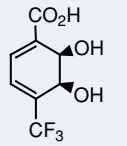
P. putida UV4
E. coli JM109(pDTG601A)
(ref. 169, 170)



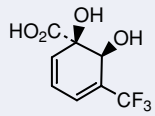
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 219)



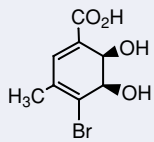
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 219)



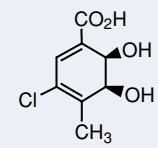
P. putida JT107
(ref. 177)



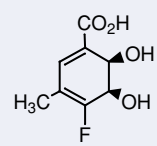
P. putida mt-2 +
A. eutrophus B9
(ref. 183)



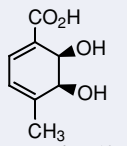
P. putida JT107
(ref.40)



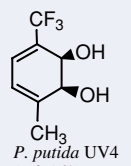
P. putida JT107
(ref. 40)



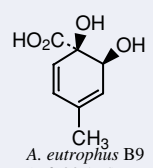
P. putida JT107
(ref. 40)



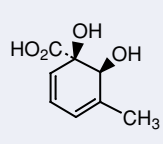
P. putida JT107
(ref. 40)



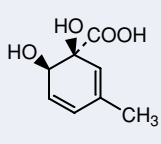
P. putida UV4
(ref. 169)



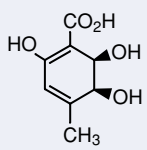
A. eutrophus B9
(ref. 38,175)



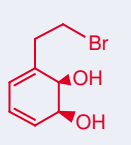
A. eutrophus B9
Pseudomonas sp. B13
(ref. 38,39,175)



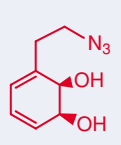
Pseudomonas sp. B13
(ref. 39,175)



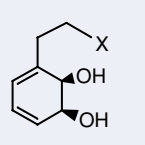
P. putida JT107
(ref. 40)



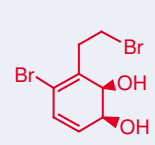
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 192)



E. coli JM109(pDTG601A)
(ref. 242)

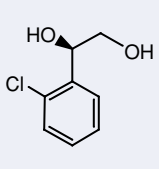


X = CN, SCN, NCS, OAc, OH
E. coli JM109(pDTG601A)
(ref. 242)

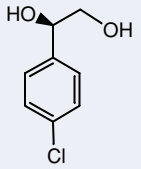


P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 193)

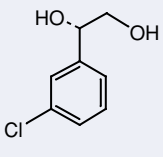
Table 1. Diols Derived from Monocyclic Aromatics (cont.)



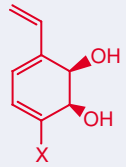
P. putida 39/D
(ref. 186,187)



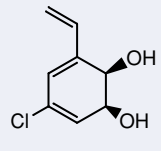
P. putida 39/D
(ref. 187)



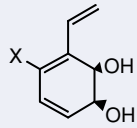
P. putida 39/D
(ref. 187)



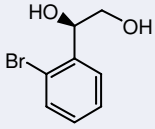
X = H, Cl
P. putida 39/D
(ref. 71,135,187)



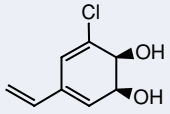
P. putida 39/D
(ref. 187)



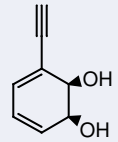
X = Cl, Br
P. putida 39/D
(ref. 187-189)



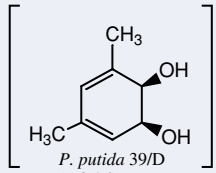
P. putida 39/D
(ref. 189)



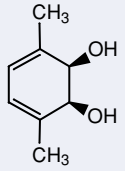
P. putida 39/D
(ref.187)



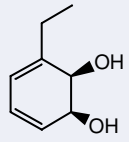
P. putida 39/D
(ref. 71,192)



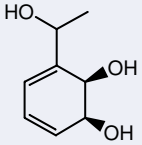
P. putida 39/D
(ref. 26)



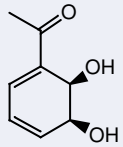
P. putida 39/D
(ref. 26)



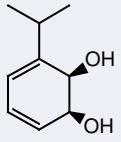
P. putida 39/D
(ref. 24)



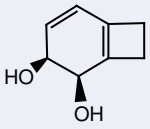
P. putida 39/D
(ref. 24)



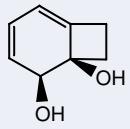
P. putida 39/D
(ref. 24)



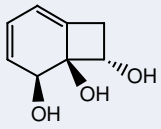
P. desmolytica
P.convexa
(ref. 175,196)



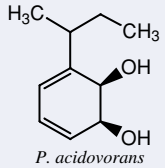
P. putida UV4
(ref. 191,231)



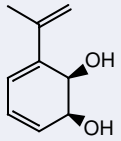
P. putida UV4
(ref. 191,231)



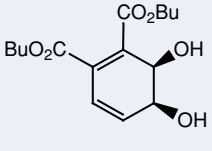
P. putida UV4
(ref. 231)



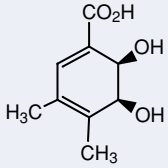
P. acidovorans
(ref. 203)



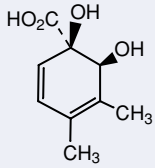
P. putida
(ref. 194, 196)



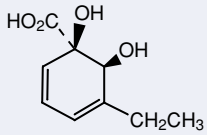
Micrococcus sp. 12B
(ref. 186)



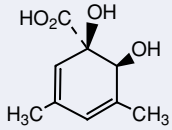
P. putida JT107
(ref. 40)



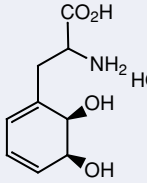
P. putida
(ref. 181)



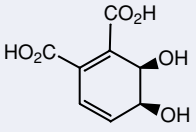
P. putida
(ref. 181)



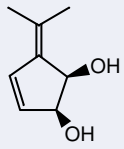
Pseudomonas sp. B1
(ref. 175)



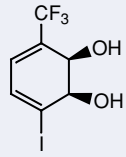
unidentified strain
(ref. 195)



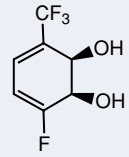
Micrococcus sp. 12B
(ref. 186)



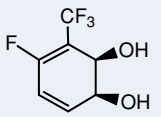
P. putida RE213
(ref. 232)



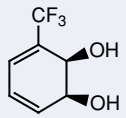
P. putida UV4
(ref. 169)



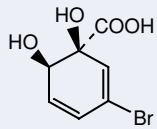
P. putida NCIB12190
(ref. 174)



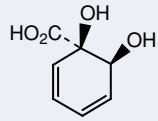
P. putida NCIB12190
(ref. 174)



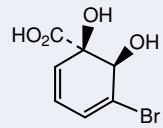
P. putida UV4
P. putida 39/D
(ref. 63,174,229)



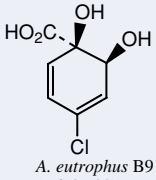
A. eutrophus B9
(ref. 38,39)



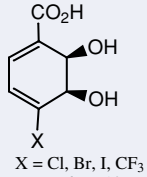
P. putida,
A. eutrophus B9
(ref. 37-39,175,181)



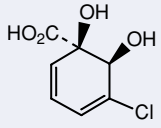
A. eutrophus B9
Pseudomonas sp. B13
(ref. 38,39)



A. eutrophus B9
(ref. 37,38)

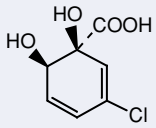


X = Cl, Br, I, CF_3
P. putida JT107
(ref. 40,177)

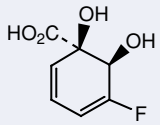


P. fluorescens
A. eutrophus B9
(ref. 37,38,175,178)

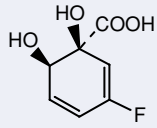
Table 1. Diols Derived from Monocyclic Aromatics (cont.)



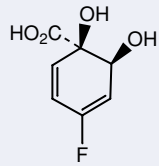
Pseudomonas sp. WR91
A. eutrophus B9
(ref. 37,179)



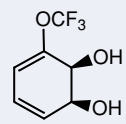
A. eutrophus B9
(ref. 37,38,39)



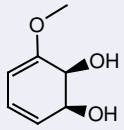
A. eutrophus B9
(ref. 37,38)



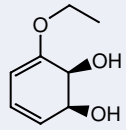
A. eutrophus B9
(ref. 38)



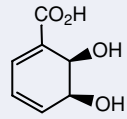
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 227)



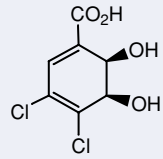
P. putida UV4
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 63,184,228)



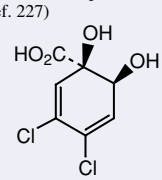
P. putida 39/D
E. coli JM109(pDTG601A)
P. putida UV4
(ref. 184,220,228)



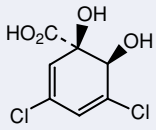
P. putida JT107
(ref. 40)



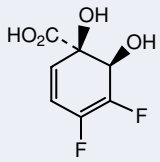
P. putida JT107
(ref. 40)



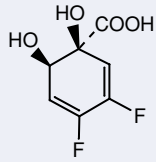
Pseudomonas sp. B13
(ref. 175)



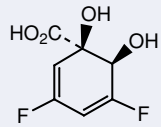
A. eutrophus B9
(ref. 38,175)



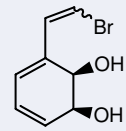
P. putida JT103
(ref. 176)



P. putida JT103
(ref. 176)

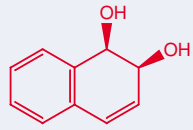


P. putida JT103
(ref. 173,176)

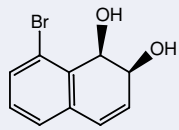


E. coli JM109(pDTG601A)
(ref. 241)

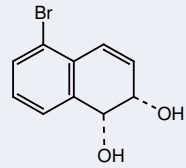
Table 2. Diols Derived from Fused Aromatic Systems



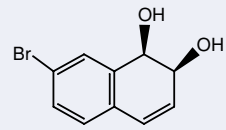
P.putida UV4, *P. putida* 119
P. putida NCIB 9816/11
A. quadruplicatum
E. coli JM109(pDTG601A)
(ref. 29,30,117,198,199,200,234)



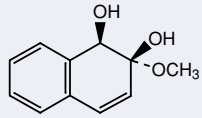
P. putida NCIB 9816/11
(ref. 197)



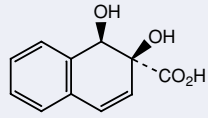
P. putida NCIB 9816/11
(ref.197)



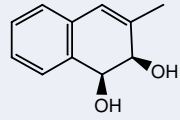
P. putida NCIB 9816/11
(ref. 197)



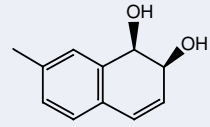
P. testosteroni
(ref. 201)



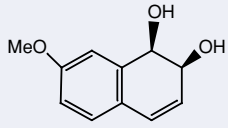
P. testosteroni
(ref. 201)



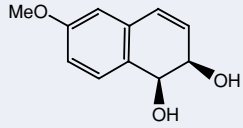
P. putida NCIB 9816/11
(ref. 222)



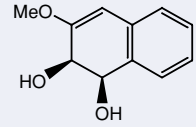
P. putida NCIB 9816/11
(ref. 222)



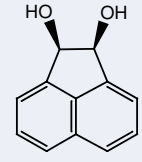
P. putida 39/D
P. putida NCIB 9816/11
E. coli JM109 (pDTG601A)
E. coli JM109 (pDTG141)
S. yanoikuyae B8/36
(ref. 223)



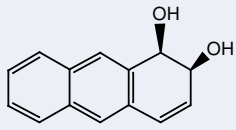
P. putida 39/D
P. putida NCIB 9816/11
E. coli JM109 (pDTG601A)
E. coli JM109 (pDTG141)
S. yanoikuyae B8/36
(ref. 223)



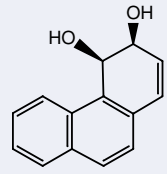
P. putida 39/D
E. coli JM109 (pDTG601A)
(ref. 223)



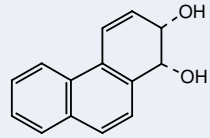
Beijerinckia sp.
(ref. 205)



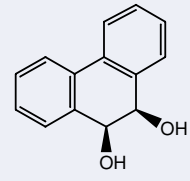
P. putida 119
S. yanoikuyae B8/36
(ref. 33,212)



P. putida 119
S. yanoikuyae B8/36
(ref. 34,212)

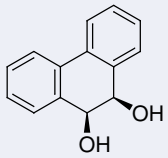


P. putida 119
S. yanoikuyae B8/36
(ref. 34,212)

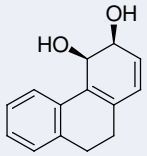


A. quadruplicatum PR/6
(ref. 213)

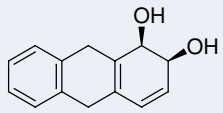
Table 2. Diols Derived from Fused Aromatic Systems (cont.)



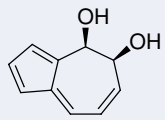
P. putida NCIB 9816/11
E. coli JM109(pDTG141)
(ref. 235)



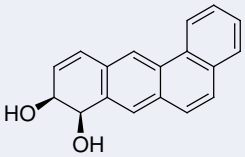
P. putida NCIB 9816/11
E. coli JM109(pDTG141)
(ref. 235)



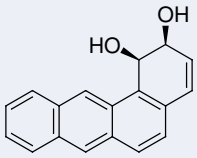
P. putida NCIB 9816/11
E. coli JM109(pDTG141)
(ref. 235)



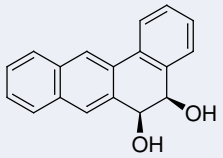
P. putida UV4
(ref. 238)



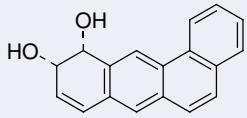
S. yanoikuyae B8/36
(ref. 35,214)



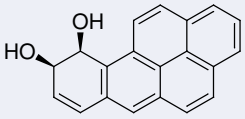
S. yanoikuyae B8/36
(ref. 35,214)



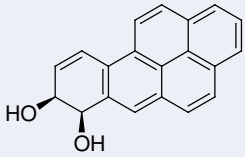
S. yanoikuyae B8/36
(ref. 35,214)



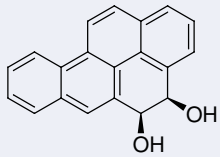
S. yanoikuyae B8/36
(ref. 35,214)



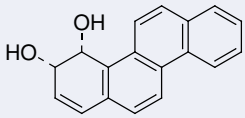
S. yanoikuyae B8/36
(ref. 35,214)



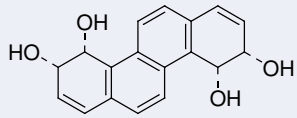
S. yanoikuyae B8/36
S. capricornicum (green algae)
(ref. 35,214,216)



S. yanoikuyae B8/36
S. capricornicum (green algae)
(ref. 35,214,216)



S. yanoikuyae B8/36
(ref. 243)



S. yanoikuyae B8/36
(ref. 243, 244)

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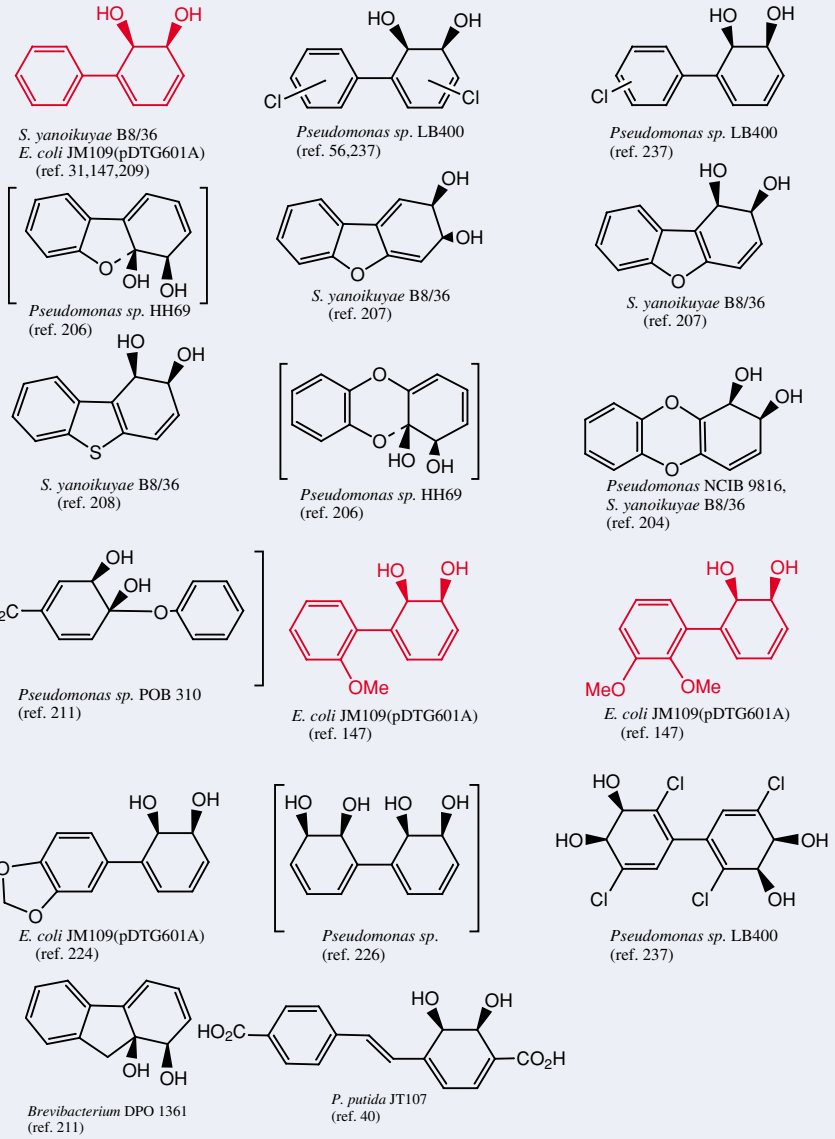
Table 3. Diols Derived from Linked Aromatic Systems



S. yanoikuyae B8/36
E. coli JM109(pDTG601A)
(ref. 31,147,209)

Pseudomonas sp. LB400
(ref. 56,237)

Pseudomonas sp. LB400
(ref. 237)

Pseudomonas sp. HH69
(ref. 206)

S. yanoikuyae B8/36
(ref. 207)

S. yanoikuyae B8/36
(ref. 207)

S. yanoikuyae B8/36
(ref. 208)

Pseudomonas sp. HH69
(ref. 206)

Pseudomonas NCIB 9816,
S. yanoikuyae B8/36
(ref. 204)

Pseudomonas sp. POB 310
(ref. 211)

E. coli JM109(pDTG601A)
(ref. 147)

E. coli JM109(pDTG601A)
(ref. 147)

E. coli JM109(pDTG601A)
(ref. 224)

Pseudomonas sp.
(ref. 226)

Pseudomonas sp. LB400
(ref. 237)

Brevibacterium DPO 1361
(ref. 211)

P. putida JT107
(ref. 40)

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Table 4. Diols Derived from Aromatic Heterocycles

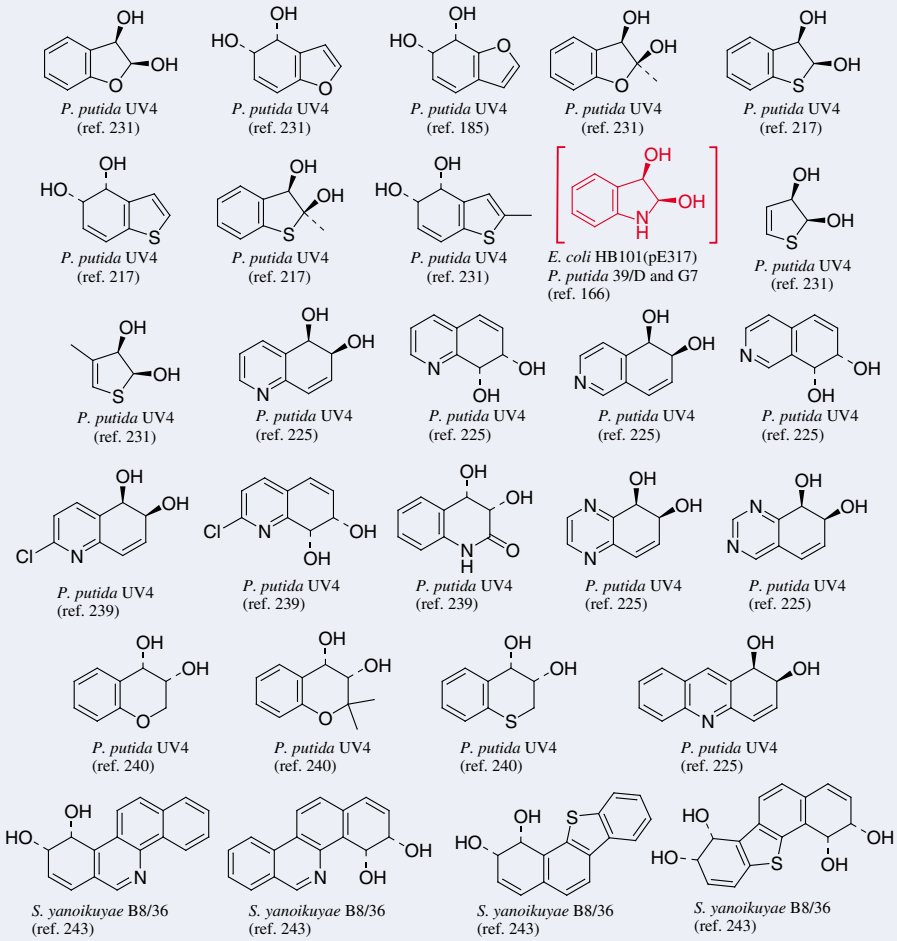

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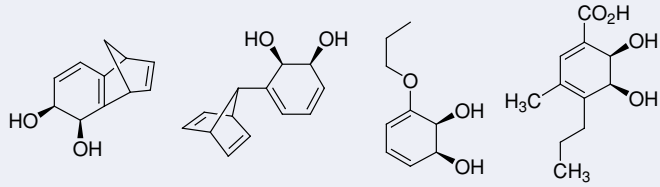
Table 5. Miscellaneous Diols



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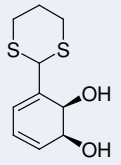
P. putida BM2 (ref. 182)

P. putida 39/D (ref. 135)

P. putida JT107 (ref. 40)



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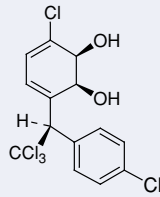

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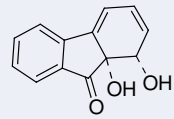
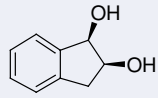
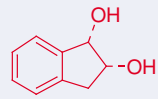


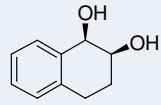
Pseudomonas sp. F274 (ref. 210)



P. putida NCIB 9816/11
P. putida NCIMB 8859
(ref. 50,65)



P. putida UV4
P. putida 39/D
(ref. 65,202,236)



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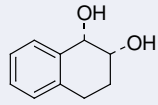
P. putida NCIMB 8859
S. yanoikuyae B8/36
(ref. 65,171,215)



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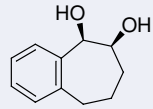
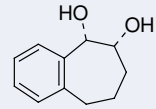


P. putida NCIB 9816/11
P. putida NCIMB 8859
S. yanoikuyae B8/36
(ref. 50,65,233)



P. putida UV4
P. putida 39/D
(ref. 65,202,230,233)

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Note Added in Proof

Total Syntheses

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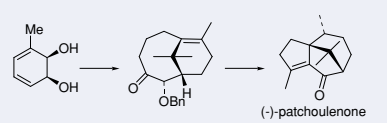

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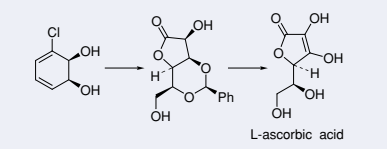

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About the Authors

Tomas Hudlicky was born in 1949 in Prague, Czechoslovakia, where he received his elementary and middle school education. After several years of working as a 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 U.S. 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 isocomene. In 1978, he joined the faculty at the Illinois Institute of Technology as an 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 annulation methodologies. He returned to his alma mater, Virginia Tech, in 1982, and rose to the rank of Professor 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 *cis*-cyclohexadienediols in enantioselective synthesis, as 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, hockey, martial arts, and music.

David Gonzalez was born in Montevideo, Uruguay in 1965. He attended elementary and middle school at Instituto Crandon, and received his undergraduate education at the School of Chemistry of the Uruguayan public University (Universidad de la República). He performed undergraduate research in the Natural Products laboratory of Professor Patrick Moyna, where he later worked as a lab technician. In 1994, with the aid of a grant from SAREC and a master's fellowship from CONICYT, he obtained his master's degree in the area of bioactive marine natural products under the orientation of Professor Eduardo Manta. He was later accepted as a graduate student at the University of Florida, where he completed his doctoral degree in Professor Tomas Hudlicky's group. His current research interests involve the use of microbial biotransformations as a tool in organic synthesis. The results of his research have been presented at several meetings and have led to seven publications.

Dr. David T. Gibson was born in Wakefield, Yorkshire, England. He received a B.Sc. degree (First Class Honors) in Biochemistry in 1961 from the University of Leeds, England. He obtained his Ph.D. in 1964 in the same department under the guidance of the late Stanley Dagley. His dissertation research played a major role in the elucidation of the meta ring-fission pathway used by bacteria to degrade aromatic compounds. Dr. Gibson's initial postdoctoral studies were conducted in the laboratory of Dr. Charles J. Sih in the College of Pharmacy at the University of Wisconsin, where he worked on the microbial degradation of the steroid A ring. He then began studies on the bacterial oxidation of hydrocarbons with the late Dr. Reino E. Kallio in the Department of Microbiology at the University of Illinois. In 1967, he joined the faculty of the Department of Microbiology at the University of Texas at Austin as an assistant professor. The following year, he worked as a Research Biochemist in the Pharmaceuticals Division of Imperial Chemical Industries at Alderly Edge, Cheshire, England. In 1969, he returned to the Department of Microbiology at the University of Texas, rising through the ranks to Professor of Microbiology in 1975, and Director of the Center for Applied Microbiology in 1981. During this period, he studied the chemistry and enzymology of the reactions used by bacteria, fungi, and algae to initiate the degradation of aromatic hydrocarbons. In 1988, he was appointed to his current position as Foundation Professor in Microbiology and Biocatalysis at the University of Iowa. Dr. Gibson's current interests focus on the structure and function of bacterial enzymes that catalyze the asymmetric dihydroxylation of aromatic hydrocarbons. He is the author of more than 150 publications and the mentor of 22 graduate students. He has served on the editorial boards of the Journal of Biological Chemistry, the Journal of Bacteriology, and Biodegradation. From 1981–1988, he was a member of the Scientific Advisory Board of AMGEN. In 1997, he received the Proctor and Gamble Award in Applied and Environmental Microbiology from the American Society for Microbiology.

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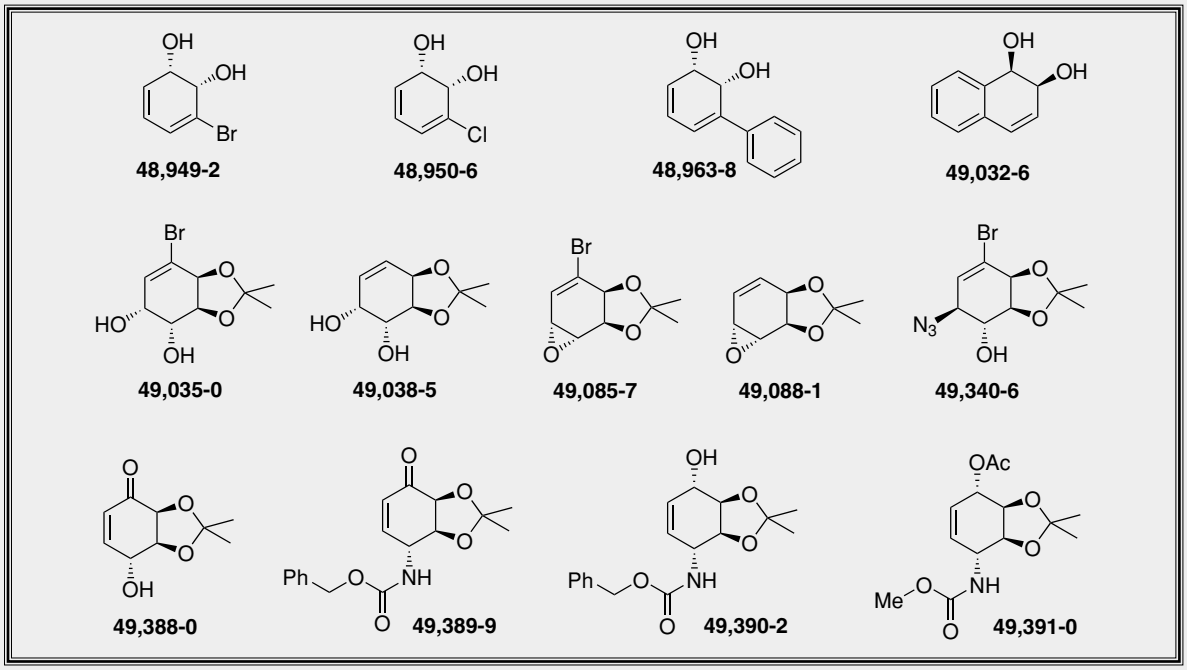

48,949-2 **(1*S-cis*)-3-Bromo-3,5-cyclohexadiene-1,2-diol**, 96%

48,950-6* **(1*S-cis*)-3-Chloro-3,5-cyclohexadiene-1,2-diol**, 98%

48,963-8* **(1*S-cis*)-3-Phenyl-3,5-cyclohexadiene-1,2-diol**, 98%

49,032-6* **(1*R-cis*)-1,2-Dihydro-1,2-naphthalenediol**, 98%

49,035-0 **[3a*S*-(3aα,4α,5α,7aα)]-7-Bromo-3a,4,5,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxole-4,5-diol**, 99%

49,038-5 **[3a*S*-(3aα,4α,5α,7aα)]-3a,4,5,7a-Tetrahydro-2,2-dimethyl-1,3-benzodioxole-4,5-diol**, 98%

49,085-7 **[3a*S*-(3aα,5aβ,6aβ,6bα)]-4-Bromo-3a,5a,6a,6b-tetrahydro-2,2-dimethyloxireno[*e*]-1,3-benzodioxole**, 98%

49,088-1 **[3a*R*-(3aα,5aβ,6aβ,6bα)]-3a,5a,6a,6b-Tetrahydro-2,2-dimethyloxireno[*e*]-1,3-benzodioxole**, 96%

49,340-6 **[3a*S*-(3aα,4α,5β,7aα)]-5-Azido-7-bromo-3a,4,5,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-4-ol**, 99%

49,388-0 **(3a*S*,7*R*,7a*S*)-7,7a-Dihydro-7-hydroxy-2,2-dimethyl-1,3-benzodioxol-4(3a*H*)-one**, 98%

49,389-9 **(3a*S*,7*R*,7a*S*)-7-(Carbobenzyloxyamino)-7,7a-dihydro-2,2-dimethyl-1,3-benzodioxol-4(3a*H*)-one**, 98%

49,390-2 **(3a*R*,4*S*,7*R*,7a*S*)-7-(Carbobenzyloxyamino)-3a,4,7,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-4-ol**, 98%

49,391-0 **(3a*R*,4*S*,7*R*,7a*S*)-3a,4,7,7a-Tetrahydro-7-(methoxycarbonylamino)-2,2-dimethyl-1,3-benzodioxol-4-ol 4-acetate**, 98%

* All these products are offered as a suspension in phosphate buffer. The unit size corresponds to the actual amount of product and not the total volume. The label provides simple instructions on how to extract the product from the suspension prior to use. The chemical purity of each product was determined on the pure crystals prior to suspending them in the phosphate buffer.

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49,751-7	**Benzylzinc bromide**
52,165-5	**3-Bromobenzylzinc bromide**
49,946-3	**4-Bromobenzylzinc bromide**
49,766-5	**5-Bromo-2-thienylzinc bromide**
49,775-4	***tert*-Butylzinc bromide**
49,776-2	**4-Chlorobenzylzinc chloride**
49,777-0	**4-Chlorobutylzinc bromide**
49,779-7	**6-Chlorohexylzinc bromide**
49,781-9	**5-Chloropentylzinc bromide**
49,783-5	**4-Chlorophenylzinc iodide**
49,789-4	**4-Cyanobutylzinc bromide**
49,790-8	**2-Cyanoethylzinc bromide**
49,796-7	**3-Cyanopropylzinc bromide**
49,803-3	**Cyclohexylzinc bromide**
49,804-1	**Cyclopentylzinc bromide**
49,807-6	**3,5-Dichlorophenylzinc iodide**
49,842-4	**3,5-Dimethylphenylzinc iodide**
49,944-7	**2-Ethoxybenzylzinc chloride**
49,945-5	**4-Ethoxybenzylzinc chloride**
49,846-7	**3-(Ethoxycarbonyl)phenylzinc iodide**
49,847-5	**4-(Ethoxycarbonyl)phenylzinc iodide**
49,849-1	**4-Ethoxy-4-oxobutylzinc bromide**
49,850-5	**6-Ethoxy-6-oxohexylzinc bromide**
49,851-3	**5-Ethoxy-5-oxopentylzinc bromide**
49,852-1	**3-Ethoxy-3-oxopropylzinc bromide**
49,855-6	**2-Ethylhexylzinc bromide**
49,857-2	**4-Ethylphenylzinc iodide**
49,860-2	**4-Fluorobenzylzinc chloride**
49,896-3	**Isobutylzinc bromide**
49,878-5	**2-Methoxybenzylzinc chloride**
49,883-1	**3-Methoxyphenylzinc iodide**
49,885-8	**4-Methoxyphenylzinc iodide**
49,905-6	***exo*-2-Norbornylzinc bromide**
49,907-2	**4-Pentenylzinc bromide**
49,928-5	**Pentylzinc bromide**
49,933-1	**Phenylzinc iodide**
49,937-4	**Propylzinc bromide**

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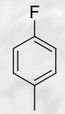
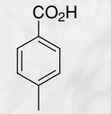
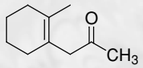
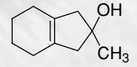
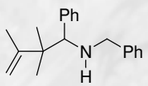
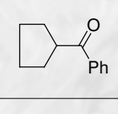
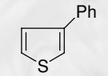
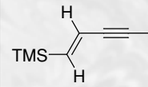
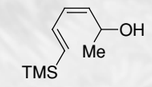
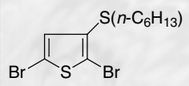
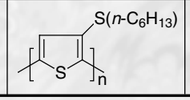
Uses of Mg*

Reactant	Product	Ref.
		13
		10
		10
		14

Uses of Zn*

Reactant	Product	Ref.
		13
		9
		12
		11

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49,955-2 **Zinc, highly reactive Rieke® metal** (5g Zn* in 100mL tetrahydrofuran)

References: (1) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press, Inc.: Boca Raton, FL, 1996; Aldrich Catalog Number Z28,012-7. (2) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925. (3) Hanson, M. V.; Brown, J. D.; Rieke, R. D.; Niu, Q.J. *Tetrahedron Lett.* **1994**, *35*, 7205. (4) Cintas, P. *Activated Metals in Organic Synthesis*; CRC Press, Inc.: Boca Raton, FL, 1993; Aldrich Catalog Number Z24,607-7. (5) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 7275. (6) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (7) Negishi, E.; King, A. O.; Okukado, N. *ibid.* **1977**, *42*, 1821. (8) Velarde-Ortiz, R.; Guijarro, A.; Rieke, R. D. *Tetrahedron Lett.* **1998**, *39*, 9157. (9) Rieke, R.D.; Kim, S-H.; Wu, X. *J. Org. Chem.* **1997**, *62*, 6921. (10) Rieke, R.D.; Sell, M.S.; Xiong, H. *J. Am. Chem. Soc.* **1995**, *117*, 5429. (11) Wu, X.; Chen, T-A.; Rieke, R.D. *Macromolecules* **1995**, *28*, 2101. (12) Chou, W-N.; Clark, D.L.; White, J.B. *Tetrahedron Lett.* **1991**, *32*, 299. (13) Rieke, R.D.; Hanson, M.V. *Tetrahedron* **1997**, *53*, 1925; and references cited therein. (14) Sell, M.S.; Klein, W.R.; Rieke, R.D. *J. Org. Chem.* **1995**, *60*, 1077.

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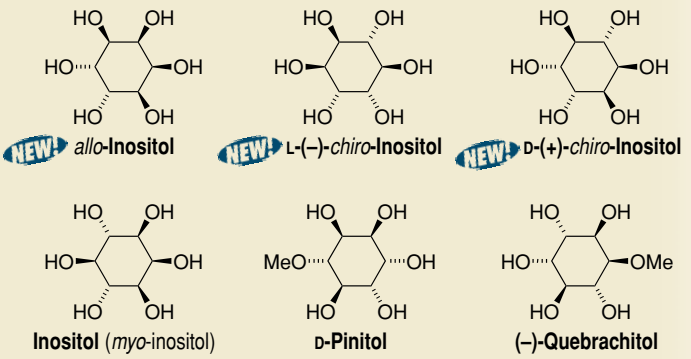
References: (1) Potter, B.V.L. *Nat. Prod. Rep.* **1990**, *7*, 1. (2) Bellington, D.C. *Chem. Soc. Rev.* **1989**, *18*, 83. (3) Berridge, M.J.; Irvine, R.F. *Nature* **1989**, *341*, 197. (4) Hudlicky, T.; Cebulak, M. *Cyclitols and Their Derivatives. A Handbook of Physical, Spectral, and Synthetic Data*; VCH: New York, 1993. (5) Hudlicky, T. et al. *Chem. Rev.* **1996**, *96*, 1195. (6) Hudlicky, T. et al. *Synthesis* **1996**, 897.



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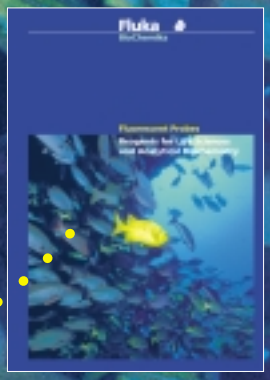

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30,697-5	***tert*-Butyl methyl ether,** 99.8%	**30 ppm**
28,911-6	**Carbon tetrachloride,** 99.5+%	**20 ppm**
28,830-6	**Chloroform,** 99+%	**10 ppm**
27,099-7	**Dichloromethane,** 99.8%	**10 ppm**
29,630-9	**1,4-Dioxane,** 99.8%	**30 ppm**
45,984-4	**Ethyl alcohol,** 99.5%, non-denatured (TAX-PAID)	**30 ppm**
27,764-9	**Ethyl alcohol,** reagent, denatured	**30 ppm**
25,952-7	**Ethylene glycol dimethyl ether,** 99.5%	**30 ppm**
24,665-4	**Heptane**, 99%	**10 ppm**
22,706-4	**Hexanes**	**20 ppm**
29,699-6	**Methyl acetate,** 99.5%	**30 ppm**
32,241-5	**Methyl alcohol,** 99.8%	**20 ppm**
27,438-0	**Methyl sulfide,** 99+%	**30 ppm**
31,032-8	**Propylene carbonate,** 99.7%	**30 ppm**
27,097-0	**Pyridine,** 99.8%	**30 ppm**
18,656-2	**Tetrahydrofuran,** 99.9%	**30 ppm**
24,451-1	**Toluene,** 99.8%	**20 ppm**

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218th National Meeting, New Orleans, LA
August 22–25, 1999

Organizer: Professor P. V. Ramachandran – Purdue University

Sunday, August 22, 1999

INORGANIC DIVISION SYMPOSIUM
(ORGN, CO-SPONSOR)

AM Session Chair: L. Barton

9:00 AM
S. Strauss
Selective Fluorination of B–H Bonds

9:30 AM
R. Grimes
Small Metallacarboranes in Synthesis: Beyond Metallocenes

10:00 AM
F. Hawthorne
Synthetic Challenges and Structural Victories in Polyhedral Borane Chemistry

10:30 AM
L. Sneddon
Metal-Catalyzed Syntheses of New Polyborane Monomers and Polymers

11:00 AM
T. Fehlner
Utilization of Monoboranes in the Syntheses of Metallaboranes of Groups 5–9

11:30 AM
K. Wade
Recent Studies of Icosahedral Carboranes

PM Session Chair: S. Krishnamurthy

1:30 PM
H. C. Brown
Organoboranes for Organic Syntheses: Recent Advances in the Syntheses of Amines

2:00 PM
P. Knochel
Stereoselective Rearrangement of Organoboranes: A New Method of Cyclic and Acyclic Stereocontrol of Adjacent Carbon Centers

2:30 PM
A. Suzuki
Cross-Coupling Reactions of Organoboron Compounds with Organic Electrophiles

3:00 PM
D. Matteson
A Mystery Story of Ligand Transfer on Boron

3:30 PM
K. Smith
Selective Polymeric Organoborohydride Agents—Synthesis and Applications

4:00 PM
P. K. Jadhav
Enantioselective Allylboration Reaction with Diisopinocampheylborane Reagents

4:30 PM
M. Zaidlewicz
Organoborane Dienophiles as 1-Alkene Equivalents, Terpenylboranes and Catalytic Hydroboration of Dienes and Enynes

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Monday, August 23, 1999

INORGANIC DIVISION SYMPOSIUM
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AM Session Chair: K. Wade

8:30 AM
S. Shore
Cyclic Organohydroborate Metallocene Complexes

9:00 AM
H. Noth
N- and *B*-Metalated Borazines: Will There Be a Renaissance in Borazine Chemistry?

9:30 AM
R. Contreras
Boron in Optically Active Heterocycles

10:00 AM
L. Barton
Reactions of Metallaboranes: From Cluster Degradation to the Formation of Linked Clusters

10:30 AM
N. Hosmane
Organometallics Derived from Carboranes and Boranes

11:00 AM
W. Siebert
Hydroboration and Diboration of Unsaturated Compounds

11:30 AM
R. B. King
Analogies Between the Chemical Bonding in Deltahedral Boranes and Planar Aromatic Hydrobcarbons

PM Session Chair: C. Recatto

1:30 PM
M. Cook
Borane Chemistries through Sodium Borohydride

2:00 PM
J. Bruening
Borane Reagents for the Pharmaceutical Industry: CalSelect™ Reducing Agents

2:30 PM
C. Goralski
Lithium Aminoborohydrides: Reagents with Multiple Personalities

3:00 PM
M. Srebnik
The Chemistry and Applications of C-1 Bridged Phosphorus Boronates

3:30 PM
M. Periasamy
New Organic Synthetic Methods Using Sodium Borohydride/Iodine System

4:00 PM
J. S. Cha
Alkylboranes as Selective Reducing and Hydroborating Agents

4:30 PM
N. N. Joshi
Oxazaborolidine-Catalyzed Reduction of Functionalized Ketones

Wednesday, August 25, 1999

ORGANIC DIVISION SYMPOSIUM
(INOR, CO-SPONSOR)

AM Session Chair: P. V. Ramachandran

8:30 AM
A. Pelter
Some Alkene Syntheses via Organoboranes

9:00 AM
N. Miyaura
Rhodium-Catalyzed Addition of Organoboronic Acids to Aldehydes and Enones

9:30 AM
H. Yamamoto
Designer Lewis Acid Catalysts of Boron

10:00 AM
I. Paterson
Stereocontrolled Synthesis of Concanamycin F Using Chiral Boron Enolates

10:30 AM
R. Hoffmann
Synthesis of Heterocyclic Compounds by Domino-Hydroformylation-Allylboration-Hydroformylation Reactions

11:00 AM
E. I. Negishi
Hydrometalation and Carbometalation of Alkynyl- and Alkenylboranes and Hydroboration of Alkynyl- and Alkenylmetals

11:30 AM
A. Soloway
Boranes in Developing of Tumor Targeting Agents for Boron Neutron Capture Therapy

PM Session Chair: D. Matteson

1:00 PM
N. Petasis
Synthesis of Amine Derivatives from Organoboronic Acids

1:30 PM
G. Kabalka
Solventless Suzuki Coupling Reactions on Alumina

2:00 PM
J. Soderquist
New Asymmetric Organoborane Conversions with 10-TMS-9-BBD Systems

2:30 PM
K. K. Wang
Synthesis of Conjugated Dienes, Diene-allenes, Ene-diynes, Enyne-allenes, and Related Compounds via Organoboranes

3:00 PM
Y. Yamamoto
Tris(pentafluorophenyl)boron-Catalyzed Reduction of Alcohols and Ethers with Hydrosilanes

3:30 PM
T. Cho
Catalytic Asymmetric Reduction of α-Functionalized Ketones

4:00 PM
P. V. Ramachandran
Organoboranes for Fluoro-Organic Synthesis: Transition Metal Catalyzed Hydroboration of Perfluoroalkyl(aryl)ethylenes

4:30 PM
N. M. Yoon
Borohydride Exchange Resin–Nickel Boride, A Versatile Reagent for Organic Synthesis

5:00 PM **Concluding Remarks**

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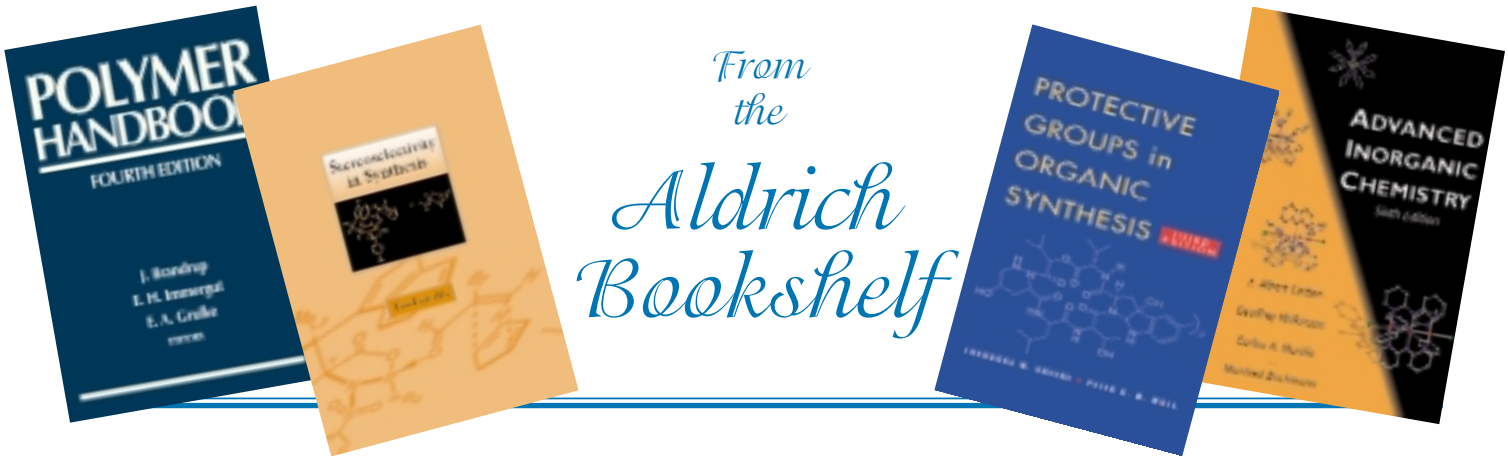
48,516-0	**Acetonitrile-***1*-^{13}C, 99 atom % ^{13}C
48,517-9	**Acetonitrile-***1*-^{13}C-^{15}N, 99 atom % ^{13}C, 99 atom % ^{15}N
48,521-7	**Acetonitrile-**$^{13}C_2$, 99 atom % ^{13}C
49,167-5	**Acetonitrile-**$^{13}C_2$-^{15}N, 99 atom % ^{13}C, 99 atom % ^{15}N
49,168-3	**Acetonitrile-***2*-^{13}C-^{15}N, 99 atom % ^{13}C, 99 atom % ^{15}N
48,533-0	**Benzene-**d_5, 99 atom % D
48,563-2	**Benzene-**^{13}C, 99 atom % ^{13}C
48,540-3	**Chloroform-**^{13}C, 99 atom % ^{13}C
49,218-3	**Dichloromethane-**^{13}C, 99 atom % ^{13}C
49,219-1	**Dichloromethane-***d*, 95 atom % D
48,551-9	**Methyl-**^{13}C **sulfoxide**, 99 atom % ^{13}C
48,618-3	**Pyridine-**^{15}N, 99 atom % ^{15}N
48,621-3	**Toluene-***2,3,4,5,6*-d_5, 98 atom % D
48,707-4	**Toluene-**α,α,α-d_3, 99 atom % D
48,708-2	**Toluene-**α-^{13}C, 99 atom % ^{13}C



From the Aldrich Bookshelf

Protective Groups in Organic Synthesis

3rd ed., T.W. Greene and P.M. Wuts, John Wiley & Sons, New York, NY, 784pp. Hardcover. Details the use of protecting groups in synthetic organic chemistry. Expanded by more than 50%, provides readers with a compendium of 1,050 of the most useful protective groups as well as 5,350 references to original publications.

Z41,242-2

Stereoselectivity in Synthesis

T. Ho, John Wiley & Sons, New York, NY, 1999. Hardcover. Shows how to choose the best method for a given synthesis. Provides readers with a thorough understanding of stereoselectivity in organic and medicinal chemistry as well as the pharmaceutical, agricultural, and food industries.

Z41,243-0

Organic Coatings: Science and Technology

2nd ed., Z.W. Wicks, F.N. Jones, and S.P. Pappas, John Wiley & Sons, New York, NY, 1999, 630pp. Hardcover. Combines a presentation of contemporary scientific knowledge in the field of organic coatings with a summary of its applied technology. This new self-contained volume is more accessible and contains new developments in the field since the publication of the first edition.

Z41,244-9

Flavourings

E. Ziegler and H. Ziegler, Eds., Wiley-VCH, Weinheim, Germany, 1998, 710pp. Hardcover. Provides a comprehensive insight into the production, processing, and applications of various food flavourings. Focuses on the conventional and new analytical methods employed in the field. Covers food legislation as well as quality control.

Z41,253-8

Kirk-Othmer Encyclopedia of Chemical Technology

4th ed., Concise, M. Grayson and D. Eckroth, Eds., John Wiley & Sons, New York, NY, 1999. Hardcover. This abridged version of a 28-volume set contains information about 1,100 topics of interest to chemists.

Z41,246-5

Polymer Handbook

4th ed., J. Brandrup, E. Immergut and E.A. Grulk, Eds., John Wiley & Sons, Somerset, NJ, 1999, 2336pp. Hardcover. Contains information pertaining to polymerization, depolymerization, and characterization in solution or in the solid state. Explores developments in the field since 1989, such as new PVT relationships and new copolymer reactivity parameters.

Z41,247-3

Measure for Measure

R. Young and T. Glover, Blue Willow, Inc., Littleton, CO, 1996, 864pp. Softbound. A comprehesive conversion factor reference that contains over 39,000 conversions for over 5100 different units. Designed specifically for engineers, scientists, students, and teachers. Comes in a convenient size (4in. W x 6in. H x 1in. D) with a durable white Lexotone® cover.

Z41,248-1

Advanced Inorganic Chemistry

6th ed., F.A. Cotton and G. Wilkinson, John Wiley & Sons, New York, NY, 1999. Hardcover. Incorporates many new chemical developments, particularly recent theoretical advances in the interpretation of bonding and reactivity in inorganic compounds. As in previous editions, the chapters devoted to the elements form the core and are covered in periodic table sequence.

Z41,245-7

Chemistry of Advanced Materials: An Overview

L.V. Interrante and M.J. Hampden-Smith, Eds., Wiley-VCH, New York, NY, 1998, 580pp. Hardcover. Advanced materials are substances such as composites (tennis rackets are graphite composites), super alloys (used in the aerospace industry), and advanced ceramics (used in semi-conductors, superconductors in the levitating bullet train, and tiles in the space shuttle). This is the first volume in a new series, Chemistry of Advanced Materials, devoted to providing a broad perspective about materials chemistry and helping scientists and engineers understand the importance of chemistry in materials science and engineering.

Z40,863-8

The Systematic Identification of Organic Compounds

7th ed., R.L. Shriner, C.F. Hermann, T.C. Morrill, D.Y. Curtin, and R.C. Fuson, John Wiley & Sons, New York, NY, 1997, 669pp. Hardcover. Updated edition explores the fundamentals of organic qualitative analysis. Provides protocols for both wet and spectroscopic methods of analysis. Includes one chapter of identification exercises.

Z40,642-2

Fragrances: Beneficial and Adverse Effects

P.J. Frosch, J.D. Johansen, and I.R. White, Eds., Springer-Verlag, New York, NY, 1998, 234pp. Hardcover. Presents numerous aspects of fragrance use and safety in a comprehensive form. Provides detailed information about recent neuropharmacological and psychosocial findings, chemistry and identification of sensitizers by various assays, skin absorption studies, and environmental issues. International guidelines for manufacturers are provided and commented upon.

Z40,866-2

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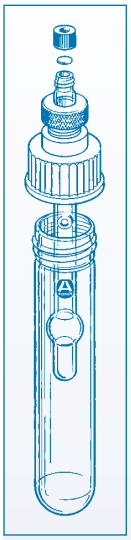


MNNG (1-methyl-3-nitro-1-nitrosoguanidine; cat. no. **12,994-1**) is probably the most convenient precursor to diazomethane, because it is stable and crystalline, and generates diazomethane upon treatment with aqueous alkali.

This newly designed apparatus incorporates System 45 technology that eliminates glass joints, clamps, and grease and permits the preparation of diazomethane without the need for codistillation with ether (see below). Request Technical Information Bulletin No. AL-180.

The screw thread closure and PTFE adapter provide an efficient, gas-tight connection between the inner tube and the outer body section. For storage, simply remove the inner tube assembly from the threaded outer section and screw on the PTFE lined screw cap. Access to the material is made through the open-top septum cap with a syringe. Supplied complete with threaded body, threaded inner tube, PTFE adapter, 32mm cap, O-ring, lock nut, septum, and 8mm open-top cap.

Typical Generator Setup

- 1mmol (133mg) or less of MNNG reagent is placed in the inside tube through the 8mm open-top screw cap along with 0.5mL of water to dissipate any heat generated.
- Ether (~3mL) is placed in the outside tube and the two parts are assembled and held together by tightening the 32mm screw cap.
- Immerse the lower part in an ice bath and inject (dropwise, very slowly to prevent frothing or possible buildup of back pressure) about 0.6mL of 5*N* sodium hydroxide through the PTFE-faced silicone septum via a syringe with a narrow gauge needle (No. 22) to prevent diazomethane leakage around the shank. (See below for syringe ordering information.)
- Diazomethane collects in the ether ready for use.

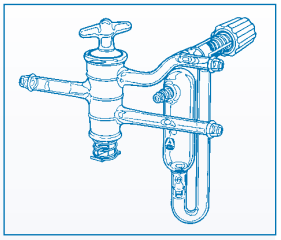
Diazoethane, despite its lower volatility, can be generated similarly from ENNG (1-ethyl-3-nitro-1-nitrosoguanidine; cat. no. **E4,160-5**). This apparatus is also useful for the generation of radioactive or deuterated diazomethane because it is a closed system.

WARNING: MNNG is mutagenic and exposure may cause skin sensitivity. While MNNG is more convenient for the generation of small quantities of diazomethane, Diazald is the preferred reagent for large-scale production of diazomethane. However, it has recently been reported that Diazald can be used in place of MNNG in the above apparatus. See: F. Ngan and M. Toofan *Journal of Chromatographic Science* **1991**, *29*, 8. Diazomethane has been reported to be explosive, particularly on contact with ground-glass joints during distillation.

Description	Cat. No.
MNNG diazomethane generator	**Z41,173-6**
Replacement parts	
O-ring seal	**Z41,174-4**
PTFE-faced silicone septum, 32mm	**Z41,175-2**
PTFE-faced silicone septum, 8mm	**Z41,176-0**
Screw cap with hole, 8mm	**Z41,177-9**
Disposable syringes	
All PE/PP, 1mL (order needles below)	**Z23,072-3**
Disposable needles, 22 gauge, 1in. L	**Z11,806-0**

ALDRICH SAFE-PURGE VALVES

For the safe and efficient purging of reaction vessels with inert or process gases. Vessel, vacuum, and purge gas lines connect to 10mm o.d. valve inlets.



- Built-in check valve prevents oil and air from being pulled into system
- Rear hose connector vents toxic gases from bubbler to fume hood
- Sturdy, high-performance construction

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Z22,532-0

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Z22,533-9

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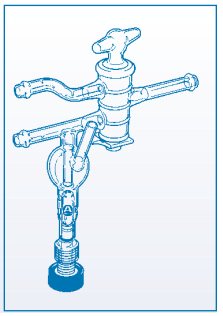
Z10,361-6



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