CHEMICAL REVIEWS

REVIEW

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Chemoenzymatic Synthesis of Inositols, Conduritols, and Cyclitol Analogues

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CONTENTS

1. INTRODUCTION

Cyclitols are defined as cycloalkanes containing one hydroxyl group on each of three or more ring atoms; that is, they are cycloalkane polyols, excluding diols.[1] The term inositol is used generically for one subclass of cyclitols, namely, the isomers of 1,2,3,4,5,6-cyclohexanehexols. The term conduritol is a trivial name for the isomers of cyclo(hex)-5-ene-1,2,3,4-tetrols. It has been applied to other ring structures, including polycyclic ones. Thus, according to the definition above, conduritols are not cyclitols (they are cycloalkenes, not cycloalkanes), although in the literature, the term cyclitol is often used vaguely and simply refers to a polyhydroxylated cyclic compound.

The 64 possible structures of hexahydroxycyclohexanes or inositols reduce by symmetry principles to just nine compounds, one D,L pair and seven meso isomers, as shown in Figure 1.

With appropriate differentiation of the hydroxyl groups by other functionalities (esters or phosphates, for example), the number of possible stereoisomers again approaches the theoretical limit. Thus, it is possible to prepare all 64 isomers as long as the synthesis begins with an optically pure material and all of the incipient hydroxyl groups are installed in a protected form so that no intermediates pass through the meso space. The principles of such design have been discussed on several occasions[2] and also have been reduced to practice; examples of these syntheses are shown in section 3 of this review.

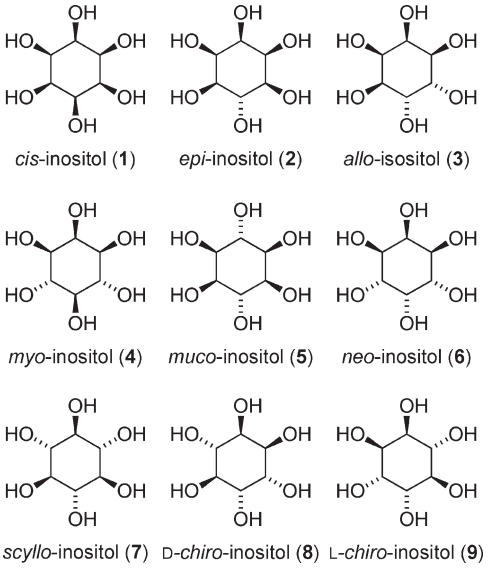

Figure 1. The nine inositols.

Examples of some cyclitols and/or conduritols are shown in Figure 2. Narciclasine (**10**), an Amaryllidaceae constituent, is a potent antineoplastic agent and has been the subject of numerous biological and synthetic studies.[3] Phosphatidylinositol (**11**) is a component of mammalian cell membranes. Phosphorylated derivatives of **11** (phosphoinositides) play a fundamental role in a multitude of cellular processes.[4] Quinic acid (**12**), a constituent of cinchona bark, is a versatile chiral building block for organic synthesis and has been used as a convenient starting material, most notably in the Gilead synthesis of oseltamivir.[5]

Bicyclitol **13** and amino inositol **14** are examples of nonnatural cyclitol derivatives. Bicyclitol **13** was prepared in several steps from 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and

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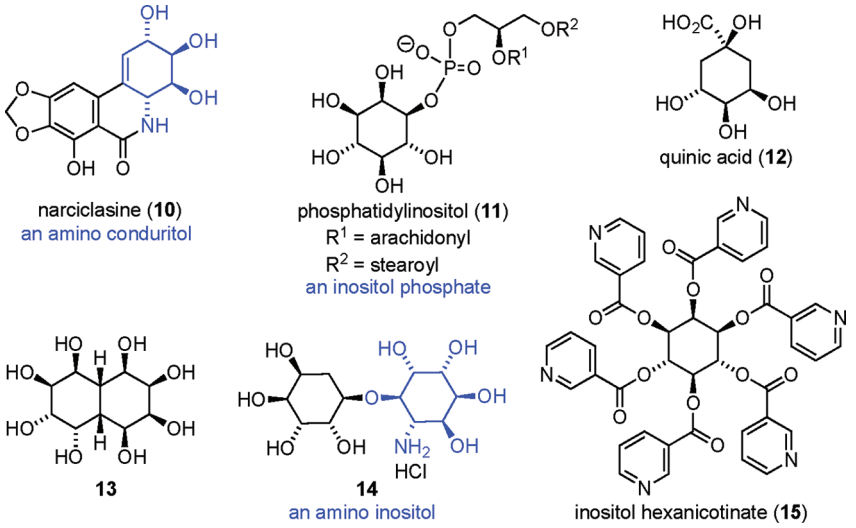

Figure 2. Examples of some cyclitols and conduritols.

p-benzoquinone and displayed a strong inhibitory activity of α-glucosidase from yeast.[6] Amino inositol **14**, one of the inositol oligomers studied in the Hudlicky group, was prepared chemoenzymatically from bromobenzene and formed an extended secondary helical structure when crystallized from an aqueous solution of calcium chloride, with calcium ions bridging the amino residues.[7] Inositol hexanicotinate (**15**) is an example of a commercial product. It is a source of nicotinic acid (niacin, vitamin B_3) in food supplements. Approximately 70% of the orally ingested dose is absorbed into the bloodstream, where it is slowly hydrolyzed to nicotinic acid and *myo*-inositol.

The chemistry of these compounds has a long history from the perspectives of both their syntheses and the biological activities that some of these compounds and their derivatives exhibit.[8] *myo*-Inositol is the most ubiquitous in nature, and most of the inositols are commercially available. The syntheses of cyclitols (inositols as well as conduritols) traditionally rely on sequences starting from either carbohydrates or manipulations of *myo*-inositol, and such protocols contain many protective and deprotective operations.[9] In 1996, Hudlicky and co-workers published a review that covered some of the chemoenzymatic approaches to various cyclitols, mainly those originating in cyclohexadiene-*cis*-1,2-diols obtained by enzymatic oxidation of aromatic compounds.[10] This article offers a comparison between the syntheses of cyclitols achieved from cyclohexadiene-*cis*-1,2-diols and those based on various methods of enzymatic resolution of racemic mixtures and desymmetrization of meso compounds. Some examples of syntheses using enzymatic C−C bond-forming reactions are discussed in section 6.

2. BRIEF HISTORY OF INOSITOL CHEMISTRY

In his publication from 1850 titled "Ueber eine neue, aus dem Muskelfleische gewonnene Zuckerart" (About the new form of sugar isolated from the muscular tissue), Scherer[11] described for the first time the isolation of inositol from the meat extract (*inos* in Greek = muscle). Although he reported the correct elemental analysis, the structure of the new compound was not elucidated at that time because of limited quantities available. There was, however, an interesting remark about its nature: "Der Geschmack dieses interessanten Stoffes ist deutlich und schnell süfs." ("The taste of this interesting compound is distinctly sweet.")

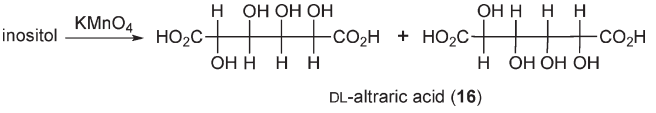

Figure 3. Cleavage of the unknown inositol with potassium permanganate.

In the 1880s, Maquenne[12] isolated inositol from the leaves of the walnut tree in sufficient quantities to confirm the elemental composition and to identify the compound as cyclohexanehexol. Maquenne also first speculated about the biosynthesis of inositol and proposed D-glucose or D-mannitol as its most probable precursor.

It took another 50 years to establish the correct configuration, mainly because of the lack of reactivity of the inositol under both acidic and basic conditions and failed attempts at its derivatization. In 1929, Posternak[13] cleaved the sturdy inositol with potassium permanganate to an optically inactive acid, which he identified five years later as DL-altraric acid[14] (Figure 3). Of the seven optically inactive inositols only four, namely, allo, myo, epi, and neo, can furnish this acid upon treatment with potassium permanganate. One of them, *allo*-inositol, could be disregarded based on the observation of Anderson, who, in 1914, first isolated optically inactive inositol monophosphate from wheat bran (all monophosphates derived from *allo*-inositol must be, by definition, optically active).[15]

The final structural proof was independently reported in 1942 by Posternak[16] and by Dangschat and Fischer.[17] (Of interest to the reader might be the fact that this is Hermann O. L. Fischer, the son of Nobel Prize winner Emil Fischer!) Posternak oxidized inosose (**17**) (Scheme 1) with potassium permanganate and isolated DL-idaric acid (**18**), which can be obtained only from *myo*-inositol and not from *epi*- or *neo*-inositol. Dangschat and Fischer prepared the acetonide **19**, which they also converted to DL-idaric acid in several steps. Thus, the compound that was isolated for the first time more than 90 years ago was elucidated as *myo*-inositol.

Wieland and Wishart[18] achieved the first synthesis of inositol in 1914, as shown in Figure 4. Benzenehexol (**20**) was prepared in several steps from diacetylhydroquinone by the procedure

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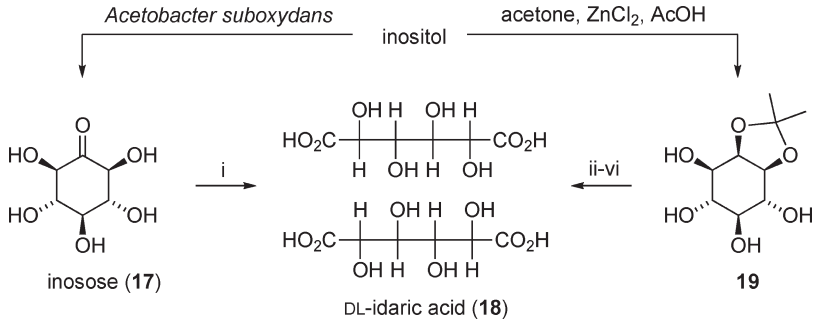
Scheme 1[a]



[a] Reagents: (i) $KMnO_4$, Na_2CO_3, 0 °C; (ii) acetic anhydride (Ac_2O), pyridine (py); (iii) HCl, acetone; (iv) lead tetraacetate [$Pb(OAc)_4$], benzene; (v) CH_3CO_3H; (vi) hydrolysis.

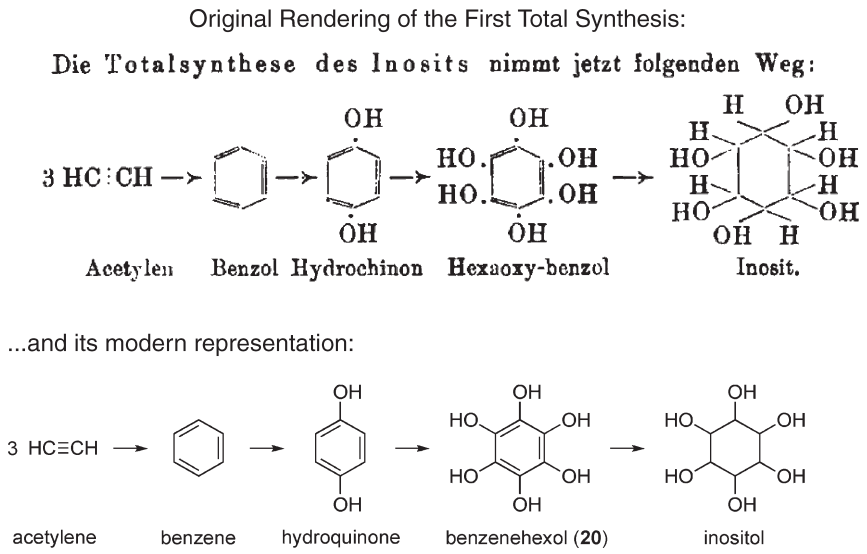
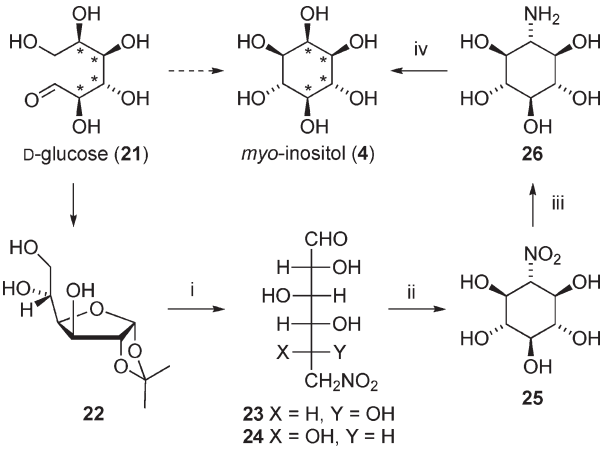


Figure 4. Two representations of the first total synthesis of an inositol. The original scheme was reprinted from ref 18. Copyright 1914 Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

established by Nietzki and Benckiser.[19] As shown in the original rendering in Figure 4, hydroquinone was obtained by oxidation of benzene, itself prepared from acetylene. In this context, it is interesting to note that the "total synthesis" of benzene was accomplished by cyclotrimerization of acetylene—a reaction discovered 20 years earlier by Berthelot in 1864 during his classic experiment (heating condensed acetylene in a closed steel pipe to several hundred degrees).[20] The major product of subsequent catalytic hydrogenation of **20** with palladium black was an inositol, identical to that isolated by Scherer and Maquenne. The high purity of **20** was critical for the success of the hydrogenation. The authors noted that the synthesis might have been shortened considerably if benzenehexol could have been prepared by the known reaction between carbon monoxide and molten potassium.[21]

It was the insight of Fischer who realized the relationship between the four stereocenters in D-glucose and the corresponding ones in *myo*-inositol, marked with asterisks in Scheme 2. This observation provided the foundation for the first synthesis conducted in a nonracemic fashion. Monoacetone glucose (**22**) was subjected to treatment with lead tetraacetate, followed by condensation with nitromethane and deprotection of the acetonide to

Scheme 2[a]



[a] Reagents: (i) (a) $Pb(OAc)_4$, benzene, 80%; (b) nitromethane ($MeNO_2$), sodium methoxide (MeONa), 95% aqueous EtOH; (c) 0.1 N H_2SO_4, 75−80 °C, 75 min, then neutralization with $Ba(OH)_2$; (ii) (a) **23**, 0.12 N $Ba(OH)_2$, H_2O; (b) H_2SO_4, 2 N acetic acid (AcOH); (iii) catalytic hydrogenation; (iv) $NaNO_2$, AcOH, 8−12% from **26**.

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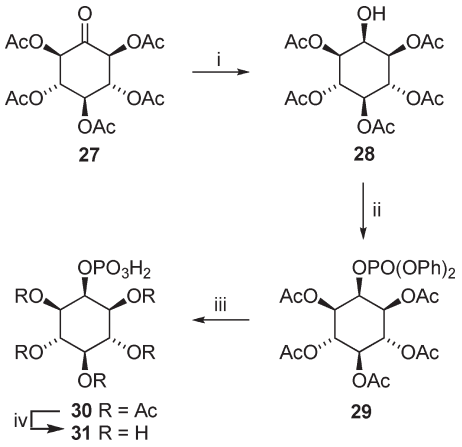
Scheme 3[a]



[a] Reagents: (i) H_2, PtO_2, methanol (MeOH); (ii) diphenylchlorophosphonate, 80 °C, 64%; (iii) H_2, PtO_2, 80%; (iv) MeONa, MeOH, quantitative.

obtain 6-nitro-6-deoxy-D-glucose (**23**) and 6-nitro-6-deoxy-L-idose (**24**).[22] Treatment of **23** with aqueous barium hydroxide initiated the cyclization to a mixture of nitrodeoxyinositols (among them nitrodeoxyscyllitol **25**), which were reduced to the corresponding amino compounds by catalytic hydrogenation.[23] One of them, aminodeoxyscyllitol **26**, was then transformed to *myo*-inositol by deamination with nitrous acid in 8−12% yield.[24] Higher yields were obtained if the penta-*O*-acetate of **26** was used in the final deamination with nitrous acid. This transformation of D-glucose to *myo*-inositol again stirred up the question as to whether such a process might have an analogy in nature. Subsequent biosynthetic studies confirmed the hypothesis.[25]

The first synthesis of a specific inositol phosphate was that of *myo*-inositol-2-phosphate (**31**), Scheme 3.[26] It began with the peracetylated inosose **27**, available in two steps from *myo*-inositol by selective oxidation with *Acetobacter suboxydans*[27] (see Scheme 1) and acetylation. The selective oxidation at (C-2) served as "protection" of the hydroxy group at that position. Reduction of the keto group ("deprotection") then led to 1,3,4,5,6-pentaacetyl *myo*-inositol (**28**). As a rule, such a change in oxidation states—oxidation and reduction (or vice versa) of the same group—in order to prevent side reactions are better avoided in a synthetic plan, but in this case, it greatly facilitated the synthesis. Phosphorylation of **28** with diphenylchlorophosphonate at 80 °C afforded ester **29**, which was subjected to hydrogenation in presence of platinum oxide to get the pentaacetate **30**. Deacetylation under Zemplen conditions afforded *myo*-inositol-2-phosphate **31** in 51% yield from **28**. The synthetic monophosphate **31** had the same melting point as the monophosphate first isolated by Anderson in 1914[15] and was later found to be identical.[28]

Current research is still aimed at efficient syntheses of natural cyclitols, especially inositol phosphates, but an increasing number of reports also describe analogues with novel architectures. For example, several bicyclic trans-fused inositols, such as **32** or **33**, prepared from 1,4-dihydrotetraline, (Figure 5), are locked in rigid conformations with five hydroxy groups axially and one equatorially oriented (5a/1e).[29] These compounds are analogues of *myo*-inositol (**4**) that adopt higher-energy conformations than those of the parent inositol with one axial and five equatorial

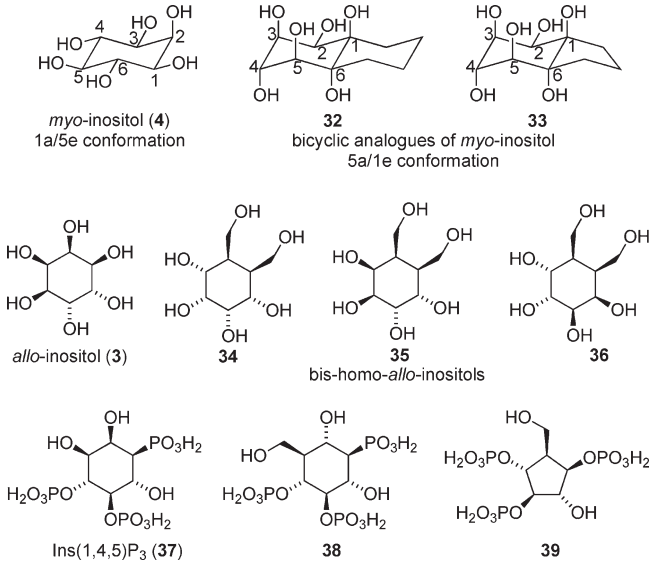
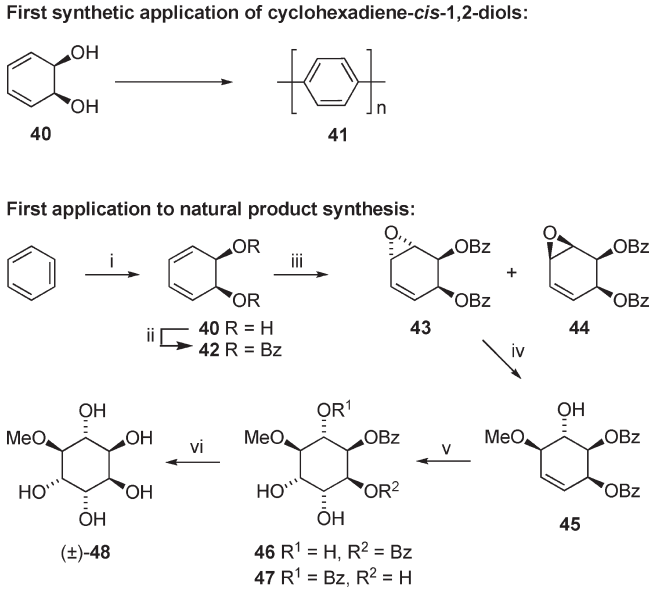


Figure 5. Inositols and their analogues.

Scheme 4[a]



[a] Reagents: (i) *P. putida*; (ii) benzyl chloride (BzCl), py, 4-(dimethylamino)-pyridine (DMAP), 0 → 25 °C, 84%; (iii) *meta*-chloroperoxybenzoic acid (*m*-CPBA), 1,2-dichloroethane, pH 8 phosphate buffer, 73% of **43**, 14% of **44**; (iv) MeOH, camphorsulfonic acid (CSA), 88%; (v) OsO_4, *N*-methylmorpholine *N*-oxide (NMO), *tert*-butyl alcohol (*t*-BuOH), tetrahydrofuran (THF), H_2O, 65%; (vi) triethylamine (Et_3N), MeOH, H_2O, quantitative.

hydroxyl groups (1a/5e). If phosphorylated, they are expected to have an altered biological profile compared to their naturally occurring counterparts. Various bis-homoinositol analogues, among them allo derivatives **34**−**36** were recently reported as potential inhibitors of α-glycosidases.[30]

A molecule that continues to attract attention is D-*myo*-inositol 1,4,5-tris(phosphate) [Ins(1,4,5)P_3, **37**], an intracellular secondary messenger.[31] There is ongoing interest in the syntheses of its

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analogues and their structure−activity relationship. Racemic analogue 6-deoxy-6-hydroxymethyl *scyllo*-inositol 1,2,4-triphosphate (**38**) was prepared from *myo*-inositol and is a potent agonist at the platelet D-*myo*-inositol 1,4,5-tris(phosphate) receptor.[32] Effective Ins(1,4,5)P_3 agonists do not necessarily have to contain a six-membered ring, as demonstrated by the pentacyclic mimic **39**.[33]

3. SYNTHESIS OF INOSITOLS AND CONDURITOLS FROM CYCLOHEXADIENE-*CIS*-1,2-DIOLS

3.1. Synthesis of Inositols

Many of the syntheses of cyclitols reported after 1987 start from cyclohexadiene-*cis*-1,2-diols. Although the first report of an optically active 1,2-dihydronaphthalene-1,2-diol derived by bacterial dioxygenation dates back to 1953,[34] it was not until the seminal contributions of Gibson et al.[35] in 1968 that these compounds were identified and their stereochemistry assigned. The discovery of enzymatic dihydroxylation of aromatic compounds went unnoticed by organic chemists until 1983, when the Imperial Chemical Industries (ICI) group reported the synthesis of polyphenylene **41**[36] from the biochemically generated *cis*-cyclohexa-3,5-diene-1,2-diol **40** derived from benzene (Scheme 4).

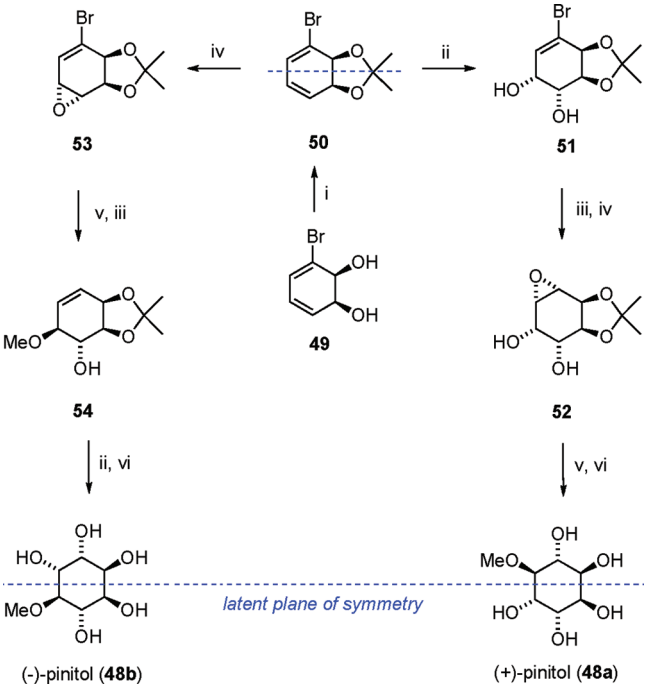
The pioneering work in the use of cyclohexadiene-*cis*-1,2-diols in the synthesis of natural products was the preparation of (±)-pinitol from benzene by Ley and co-workers.[37] The key step was the microbial oxidation of benzene by *Pseudomonas putida*, according to the procedure by the ICI group. Yields of 40−50 g/L of *meso*-diol **40**, obtained by fermentation, were claimed for the ICI process[38] (Scheme 4). The hydroxy groups in **40** were protected as benzoates in **42**, and subsequent treatment with *meta*-chloroperoxybenzoic acid (*m*-CPBA) led to vinyl epoxides **43** and **44**. Regioselective opening of the oxirane ring in **43** with MeOH provided **45**, whose dihydroxylation with catalytic OsO_4 and hydrolysis afforded (±)-pinitol **48** in 35% overall yield from **40**. Ley continued work toward inositol phosphates with subsequent chemoenzymatic syntheses of various phosphorylated *myo*-inositols and derivatives thereof.[39]

The events described above combined with Gibson et al.'s development in the mid-1980s of recombinant organisms that overexpressed toluene (and other, related) dioxygenase enzymes led to an explosion of applications to synthesis by several groups worldwide. Following Hudlicky's synthesis of prostaglandin $E_2\alpha$ ($PGE_2\alpha$) in six steps from toluene in 1988,[40] reports of syntheses of conduritols and inositols started to appear in the literature.

It was recognized that these diols offer several advantages over other potential starting materials for the synthesis of cyclitols: (a) they are readily available by the microbial oxidation of aromatic substrates in high yields and enantiomeric purities;[41] (b) they provide the six-carbon framework of the target cyclitol; (c) the two double bonds are easily oxygenated by dihydroxylation or epoxidation; and (d) the syntheses are often enantiodivergent, as was demonstrated on the synthesis of both enantiomers of pinitol by the Hudlicky group in 1990 (Scheme 5).[42]

A six-step synthesis of pinitols **48a** and **48b** started from the free diol **49**, derived from bromobenzene by fermentation with *Escherichia coli* JM109(pDTG601a). The enantiodivergent design was based on the concepts of latent symmetry and proenantiotopic functionality.[43] The latent plane of symmetry exhibited by the two enantiomers of pinitol, as shown in Scheme 5, allows for the preparation of either enantiomer by the use of identical transformations but with changes in the order of their application

Scheme 5[a]



[a] Reagents: (i) 2,2-dimethoxypropane (DMP), *p*-toluenesulfonic acid (*p*-TsOH), quantitative; (ii) OsO_4, NMO, H_2O, acetone, 85%; (iii) $LiAlH_4$, THF, 85%; (iv) *m*-CPBA, CH_2Cl_2, 86%; (v) MeOH, Al_2O_3, 90%; (vi) HCl, H_2O, acetone.

in the particular synthesis. Applications of these principles allow for the synthesis of both enantiomers of a product from a single enantiomer of a starting material, as demonstrated on many subsequent syntheses of carbohydrates, cyclitols, and alkaloids having similar latent planes of symmetry.[44]

The issues of diastereoselectivity were achieved by either osmylation (leading to **48a** through **51**) or epoxidation (leading to **48b** through **53**) of the acetonide **50** to initiate the divergent pathways. Thus, the vinyl halide in **51** was reduced and then converted to epoxide **52**, whose opening with methanol and deprotection gave (+)-pinitol **48a**. Conversely, methanolysis of epoxide **53** and reduction of the vinyl halide provided olefin **54**, which was subsequently dihydroxylated and deprotected to yield (−)-pinitol **48b**.

In 1993, Carless and co-workers[45] reported the syntheses of *muco*-, *allo*-, and *epi*-inositols from the *meso*-diol **40**, derived from benzene, and the first total synthesis of (±)-quebrachitol (2-*O*-methyl-*chiro*-inositol) (Scheme 6). The syntheses were achieved from common intermediates obtained from the photooxidation of diol **40** with singlet oxygen and subsequent reduction of the diastereomeric endocyclic peroxides **55** with thiourea in MeOH to provide conduritol A (**56**) and conduritol D (**57**). Dihydroxylation of conduritol A (**56**) with osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) provided access to *muco*-inositol (**5**, 82% yield). Epoxidation of conduritol A (**57**) and opening of epoxide **58** with aqueous acid at elevated temperature yielded a racemic mixture of *chiro*-inositols (**8**) and (**9**). Alternatively, complete acetylation of conduritol D (**57**), dihydroxylation, and deprotection provided access to *allo*-inositol (**3**), whereas syn epoxidation with peracetic acid, opening of epoxide **59** with aqueous acid, and hydrolysis afforded *epi*-inositol (**2**).

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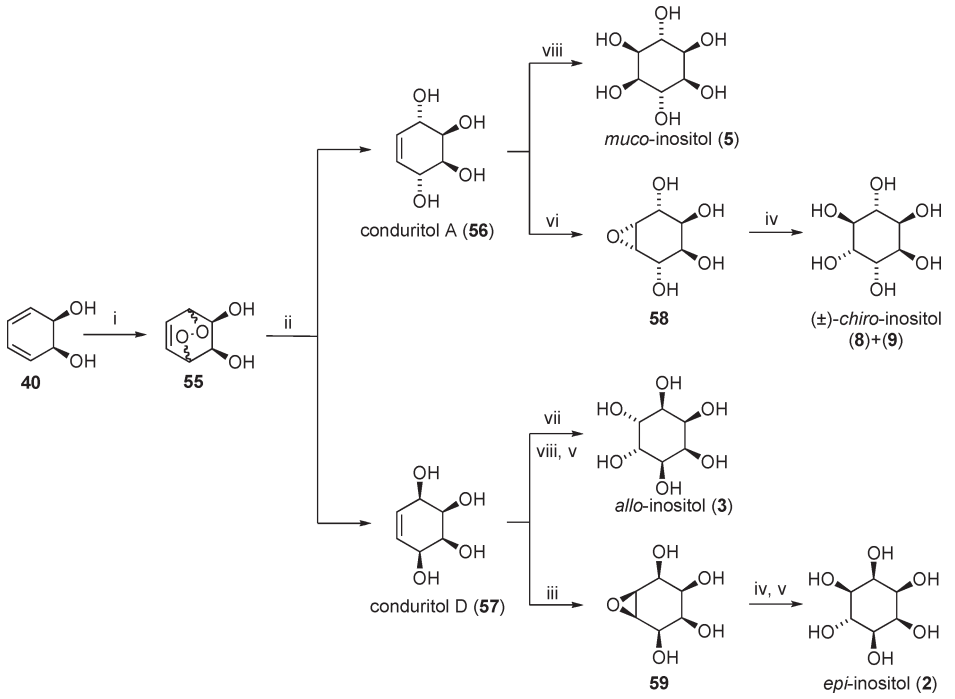
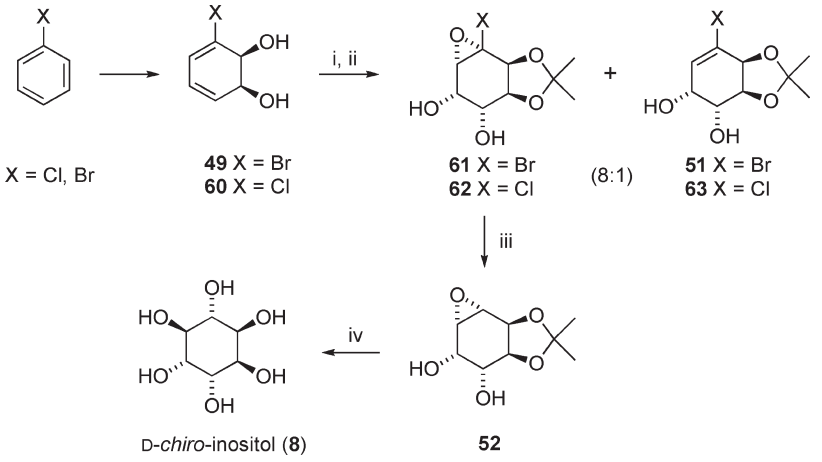
Scheme 6[a]



[a] Reagents: (i) $^1O_2$, −70 °C; (ii) thiourea, MeOH, 95−100%; (iii) CH_3CO_3H, AcOH; (iv) H_3O^+, 80 °C, 90−100%; (v) K_2CO_3, MeOH; (vi) *m*-CPBA, CH_2Cl_2/MeOH (3:1 v/v), 63%; (vii) Ac_2O, py, 79%; (viii) OsO_4, NMO, acetone/H_2O (4:1 v/v), 65−82%.

Scheme 7[a]



[a] Reagents: (i) 2,2-dimethoxypropane, acetone, *p*-TsOH; (ii) $KMnO_4$, $MgSO_4$, H_2O, acetone, 22% for **61** from **49**, 32% for **62** from **60**; (iii) tris(trimethylsilyl)silane, 2,2-azobis(isobutyronitrile) (AIBN), toluene, 48% from **61**, 42% from **62**; (iv) sodium benzoate, H_2O, 77%.

Epoxide **58** was also converted to (±)-quebrachitol in four additional steps (not shown). The versatility of the oxidation/reduction strategy using diene diol **40** to produce conduritols A and D provides rapid and selective access to three inositols (and racemic *chiro*-inositol) from benzene.

In 1993, Hudlicky and co-workers[46] reported the first chemoenzymatic synthesis of D-*chiro*-inositol (**8**) from both bromo- and chlorobenzene, as shown in Scheme 7. A one-pot protection/oxidation sequence from *cis*-diols **49** or **60**, derived by fermentation, provided halo epoxides **61** and **62** as 8:1 mixtures with diols **51** and **63**. After recrystallization, halo epoxides **61** and **62** were isolated in 22% and 32% yields, respectively. The mechanism of the formation of halo epoxides by permanganate oxidation was discussed in a subsequent publication.[47] The known epoxide **52** was prepared in 42% yield by reduction of **61** or **62** with tris(trimethylsilyl)silane and 2,2-azobis(isobutyronitrile) (AIBN) in toluene. The selective opening of epoxy diol **52** was extensively studied and led to the formation of mixtures of both D-*chiro*-inositol (**8**) and *neo*-inositol (**6**). The solution to this obstacle was realized by the treatment of **52** with a catalytic amount of sodium benzoate in water at reflux. The opening with water under nearly neutral conditions proceeded in almost quantitative yield

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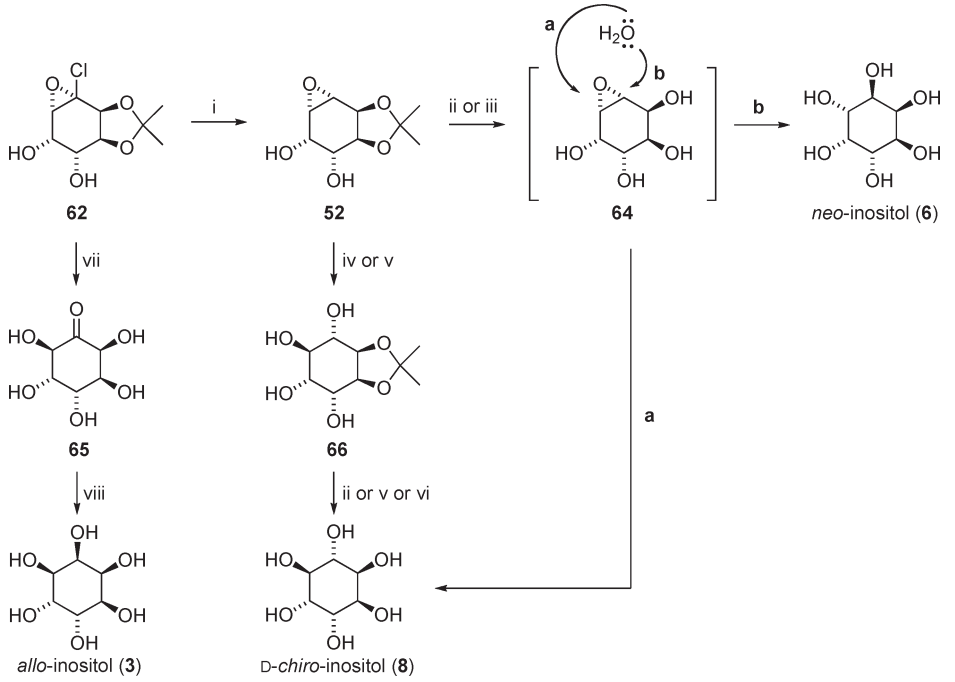
Scheme 8[a]



[a] Reagents: (i) tris(trimethylsilyl)silane, AIBN, toluene, 110 °C; (ii) H_2O, Amberlite IR 118 (H^+ form), 100 °C; (iii) H_2O, 100 °C; (iv) Amberlyst A21 and Amberlite IRA 904 (1:1), 100 °C, 85%; (v) sodium benzoate, H_2O, 98%; (vi) H_2O, Amberlyst 15, 25 °C; (vii) H_2O, Al_2O_3, 80 °C, 85%; (viii) H_2, Raney nickel (RaNi), MeOH, 90%.

(>95% of D-*chiro*-inositol) and, after a single recrystallization, gave pure D-*chiro*-inositol (**8**) in 77% yield (8% overall from **49**, 10% overall from **60**). On a preparative scale, the synthesis was performed without chromatography and without isolation of epoxide **52** in an overall yield of 13%.

A follow-up communication expanded the divergent pathways to *neo*-, D-*chiro*-, and *allo*-inositols from the previously established halo epoxy intermediates **61** and **62**, Scheme 8 (shown only for **62**).[48] The preparation of these three inositol isomers was attained by careful optimization of the oxirane ring-opening in **62** and **52**. Inosose **65** was obtained in 85% yield from **62** upon treatment with alumina in water. Raney nickel hydrogenation of **65** gave *allo*-inositol (**3**) in >90% yield whereas hydride reduction of **65** provided poor selectivity and a 3:1 mixture of *allo*- and D-*chiro*-inositols. Hydrolysis of **52**, Scheme 8, under basic conditions (Amberlite IRA 904 and Amberlyst A21 1:1) at elevated temperature afforded acetonide **66** in 85% yield. The subsequent acid treatment of **66** provided D-*chiro*-inositol (**8**). Acid hydrolysis of **52** using Amberlite IR 118 (H^+ form) in boiling H_2O for one hour gave a 7:3 mixture of D-*chiro*-inositol (**8**) and *neo*-inositol (**6**) through the intermediate epoxy tetrol **64**. Competition between the opening of the oxirane ring and the hydrolysis of the acetonide in **52**, followed by a series of Payne rearrangements, was invoked to explain the observed lack of selectivity. The low solubility of *neo*-inositol in water−alcohol mixtures allowed for its separation from **8** by recrystallization.

A practical and scalable synthesis of *allo*-inositol was published by the Hudlicky group in 1997 and consisted of five chemical steps from the acetonide-protected diene diol **50**[49] (Scheme 9). The sequence started with the dihydroxylation of the more electron-rich double bond of **50**, followed by dehalogenation under radical conditions [tributyltin hydride (Bu_3SnH), AIBN] to provide olefin **67** in 90% yield. Protection of the free diol in **67** followed by dihydroxylation with $RuCl_3/NaIO_4$ gave bis-acetonide **68** in 70% yield after recrystallization. The dihydroxylation did not occur on unprotected **67**. Final treatment of bis-acetonide **68** with aqueous HCl in ethanol led to crystalline *allo*-inositol (**3**) in overall yield of 51% from diol **49**.

Another multipronged approach from Hudlicky and co-workers led to the synthesis of both L-*chiro*-inositol and *muco*-inositol through the microbial oxidation of bromobenzene.[50] The syntheses diverged from allylic epoxide **53** (Scheme 10). The route to L-*chiro*-inositol (**9**) started with Lewis-acid-mediated epoxide opening with benzyl alcohol, followed by reduction of the vinyl halide to give **69** in 66% yield over the two steps. The double bond of **69** was dihydroxylated, the acetonide was hydrolyzed with HCl/EtOH to pentol **70**, and the benzyl group removed by catalytic hydrogenation to yield L-*chiro*-inositol (**9**) in 32% yield from allylic epoxide **53** (seven steps and 22% overall yield from diol **49**). The synthesis of *muco*-inositol (**5**) started with the ring-opening of epoxide **53** with aqueous hydroxide and reduction to get diol **71**, which was oxidized with *m*-CPBA to obtain the α-epoxide **72** and the *β*-epoxide **73** in a 1:1.8 ratio and in 71% yield. The allylic hydroxyl-directed syn epoxidation predominated and gave the *β*-epoxide as a major product despite the steric encumbrance of the acetonide moiety. The hydrolysis of the diastereomers **72** and **73** is chemically redundant[51] on the basis of trans-diaxial attack of a nucleophile and produces a single isomer of the corresponding *trans*-diol. Treatment of a mixture of epoxides **72** and **73** with 10% aqueous sulfuric acid yielded a mixture of *muco*- and *myo*-inositol in a 16:1 ratio and 75% yield. *muco*-Inositol (**5**) was isolated by recrystallization from isopropanol/water (70:30).

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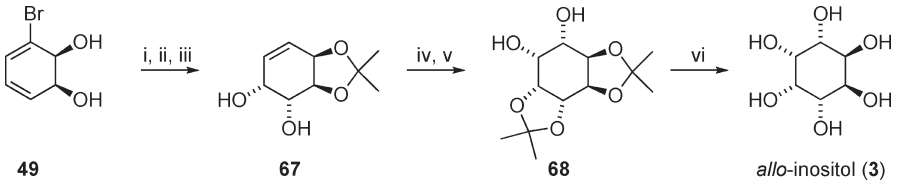
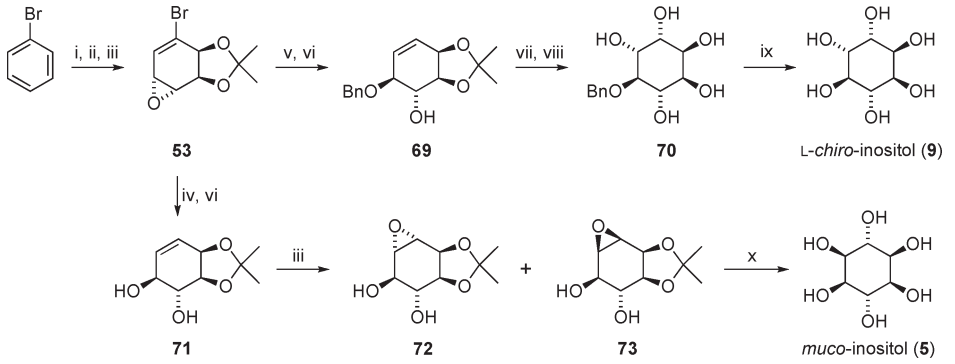
Scheme 9[a]



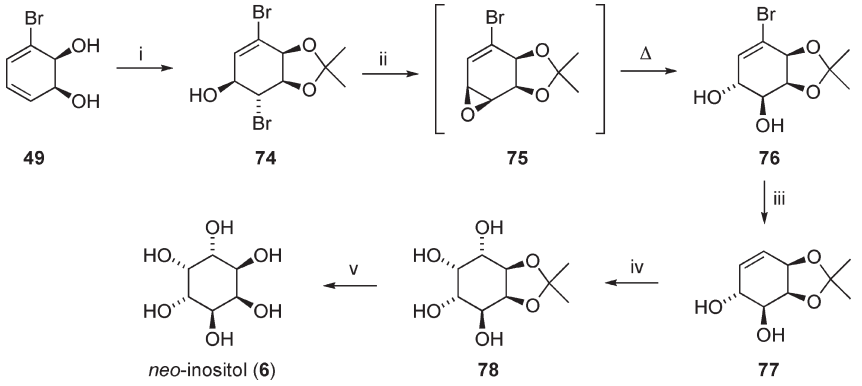
[a] Reagents: (i) 2,2-dimethoxypropane, acetone, *p*-TsOH; (ii) OsO_4, NMO, acetone, H_2O, 85% from **49**; (iii) tributyltin hydride (Bu_3SnH), AIBN, THF, reflux, 90% from **50**; (iv) 2,2-dimethoxypropane, acetone, *p*-TsOH, 98%; (v) $RuCl_3$, $NaIO_4$, acetonitrile (MeCN), H_2O, 0 °C, 71%; (vi) HCl, EtOH, 96%.

Scheme 10[a]



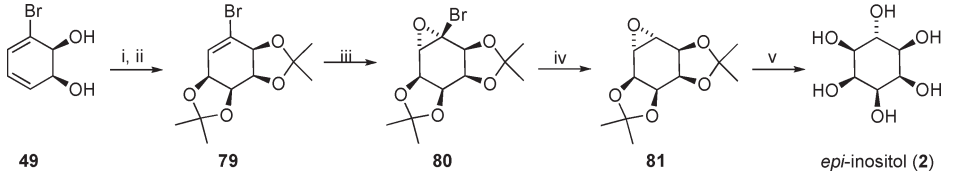
[a] Reagents: (i) *E. coli* JM109 (pDTG601); (ii) 2,2-dimethoxypropane, acetone, *p*-TsOH, 95%; (iii) *m*-CPBA, CH_2Cl_2, 71% combined yield of **72**/**73** 1:1.8; (iv) 10% aqueous KOH, H_2O, 1,2-dimethoxyethane (DME), 87%; (v) benzyl alcohol (BnOH), boron trifluoride etherate ($BF_3 \cdot OEt_2$), −10 °C, 85%; (vi) Bu_3SnH, AIBN, THF, reflux, 78% for **69**, 90% for **71**; (vii) OsO_4, NMO, acetone/H_2O, 75%; (viii) HCl, EtOH, 25 °C, 79%; (ix) 10% Pd/C, H_2, H_2O, 81%; (x) **72**/**73** 1:1.8, 10% aqueous H_2SO_4, 75% combined yield of **5**/**4** 16:1.

Scheme 11[a]



[a] Reagents: (i) 2,2-dimethoxypropane, acetone, *p*-TsOH, then 1,3-dibromo-5,5-dimethylhydantoin, H_2O, acetone, 61%; (ii) 10% aqueous KOH, DME, 25 °C, then reflux; (iii) Bu_3SnH, AIBN, benzene, reflux; (iv) OsO_4, NMO, *t*-BuOH, H_2O, acetone; (v) HCl, MeOH, 14% from **74**.

Scheme 12[a]



[a] Reagents: (i) OsO_4, NMO, CH_2Cl_2; (ii) 2,2-dimethoxypropane, *p*-TsOH, (75% for two steps); (iii) *m*-CPBA, CH_2Cl_2, $CHCl_3$, 50 °C, 70%; (iv) Bu_3SnH, $(PhCO_2)_2$, THF, 67 °C, 85%; (v) Dowex 1X8−200 (H^+ form), H_2O, reflux, 90%.

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A stereoselective synthesis of *neo*-inositol (**6**) was completed by Hudlicky and co-workers in 2000 (Scheme 11).[52] Treatment of bromohydrin **74** under basic conditions in boiling 1,2-dimethoxyethane (DME) led to the formation of *trans*-diol **76** through epoxide **75**. Reduction of the vinyl bromide furnished olefin **77**, which was dihydroxylated in presence of OsO_4 to afford tetrol **78**. Hydrolysis in methanolic HCl provided *neo*-inositol (**6**) in 9% overall yield from diene-*cis*-diol **49**, without the need for chromatographic purification of any of the intermediates.

A recent synthesis from the Gonzalez group detailed a five-step (chemical steps) sequence to *epi*-inositol and alluded to the stereodivergent possibility toward *cis*-inositol (Scheme 12).[53] A brief study was conducted on the directing effects of osmylation of diol **49** and pertained to the steric-electronic competition of the dihydroxylation. The use of a nonpolar solvent (toluene, dichloromethane) allowed for a favorable ratio (80:20 *cis*/*trans*) of *syn*-tetrol protected as the bis acetonide **79** in 75% yield from **49**. The vinyl bromide **79** was epoxidized and dehalogenated to provide epoxide **81**. Epoxide **81** proved to have a very crowded β face and was resistant to epoxide opening without acetonide hydrolysis. No reactivity was observed upon treatment of **81** with 20% KOH in water−methanol mixtures at room temperature or at reflux. However, when **81** was boiled in water in the presence of acidic resin it was readily deprotected to form the intermediate tetrol epoxide, which was subsequently opened to furnish *epi*-inositol (**2**).

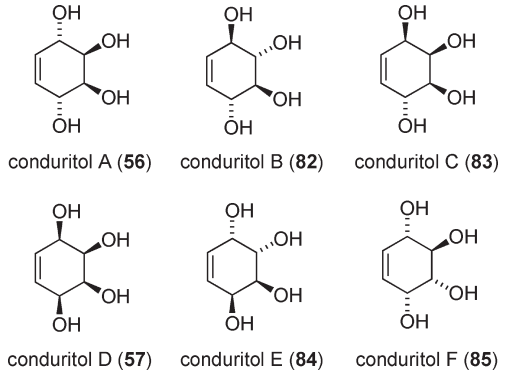


Figure 6. The six conduritols.

3.2. Synthesis of Conduritols

The structures of the six conduritols are shown in Figure 6. Of these, two are meso, and four are as D,L pairs. Their syntheses from cyclohexadiene-*cis*-1,2-diols have been accomplished in both racemic and enantioselective manner.

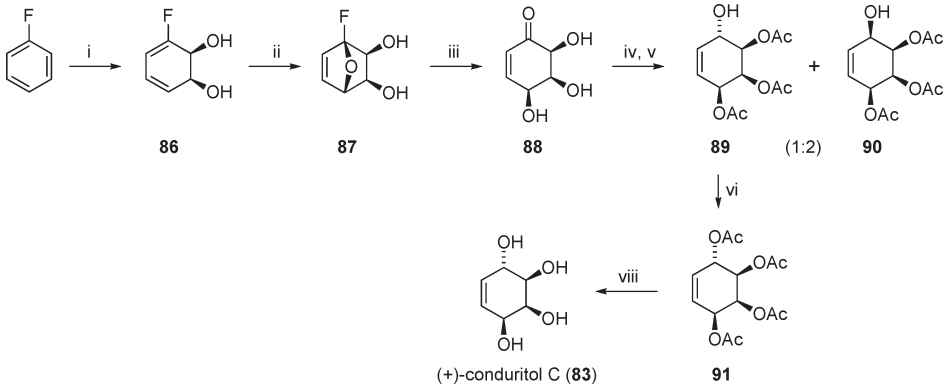
Carless and co-workers were the first to apply the microbial oxidation of benzene to conduritol synthesis in 1989.[54] This approach utilized a methylene-blue-sensitized photo-oxidation of *meso*-diol **40** (Scheme 6), which provided a mixture of endoperoxides **55** (anti/syn = 2.8:1) that were separable by chromatography. Reduction of the individual endoperoxide isomers with thiourea or sodium borohydride provided conduritols A (**56**) and D (**57**).

A follow-up communication reported the synthesis of (+)-conduritol C from diol **86** (Scheme 13), available from fluorobenzene by microbial oxidation in 60% *ee* and crystallized to complete enantiomeric purity.[55] The diene moiety in **86** was oxidized with *m*-CPBA to form the cyclic ether **87** in 20% yield.[56] Treatment of **87** with trifluoroacetic acid in aqueous acetone provided the hydroxy enone **88** in 50% yield. Acylation and Luche reduction provided an inseparable mixture of triacetates **89** and **90**. Acetylation of **89** and **90**, separation, and deprotection of **91** afforded (+)-conduritol C (**83**) in 88% yield. Comparison of optical purity was made against the (−)-enantiomer to ascertain the fact that the scalemic diol derived from fluorobenzene was indeed crystallized to optical purity {$[\alpha]_D$ = +213 (*c* 0.4, H_2O); lit.[57] $[\alpha]_D^{25}$ = −209 (*c* 2, H_2O)}.

Johnson and co-workers published the enantioselective syntheses of (+)- and (−)-conduritol C from benzene.[58] Their strategy, similar to that used for the first time by Balci and co-workers in their synthesis of conduritol A,[59] was based on a singlet-oxygen photo-oxidation/reduction sequence followed by a lipase resolution and a series of protection−deprotection steps to establish the required divergence from intermediate **94** (Scheme 14). Protection of **94** at C-1 followed by Mitsunobu inversion at C-4 furnished **95**, which was converted to (+)-conduritol C (**83**). Conversely, Mitsunobu inversion at C-1 of **94** gave benzoate **96**, which provided the (−)-enantiomer upon deprotection.

The enantiocontrolled synthesis of conduritols (+)-E and (−)-F from bromobenzene was reported in 1991 by the Hudlicky group (Scheme 15).[60] Acetonide **50**, derived from the biochemically generated diol **49**, allowed for stereoselective

Scheme 13[a]



[a] Reagents: (i) *P. putida*; (ii) *m*-CPBA, Na_2CO_3, CH_2Cl_2, 20%; (iii) H_2O/acetone (1:100 v/v), trifluoroacetic acid (TFA), 50%; (iv) Ac_2O, py, 0 °C, 80%; (v) $NaBH_4$, $CeCl_3$, MeOH, 98%; (vi) Ac_2O, py; (viii) K_2CO_3, MeOH, 88%.

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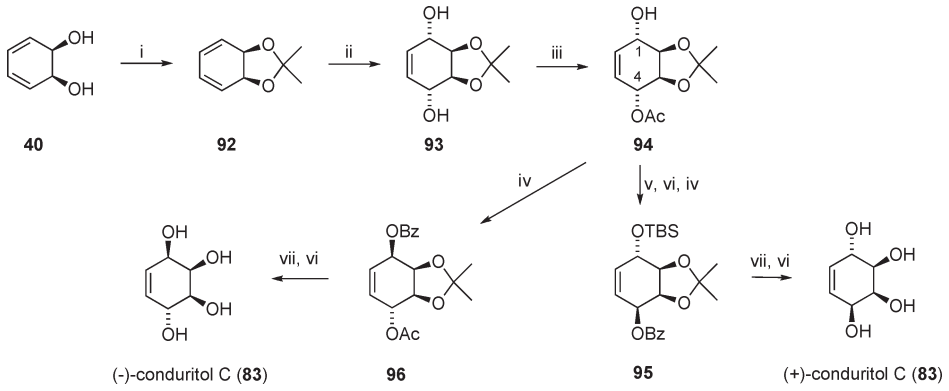
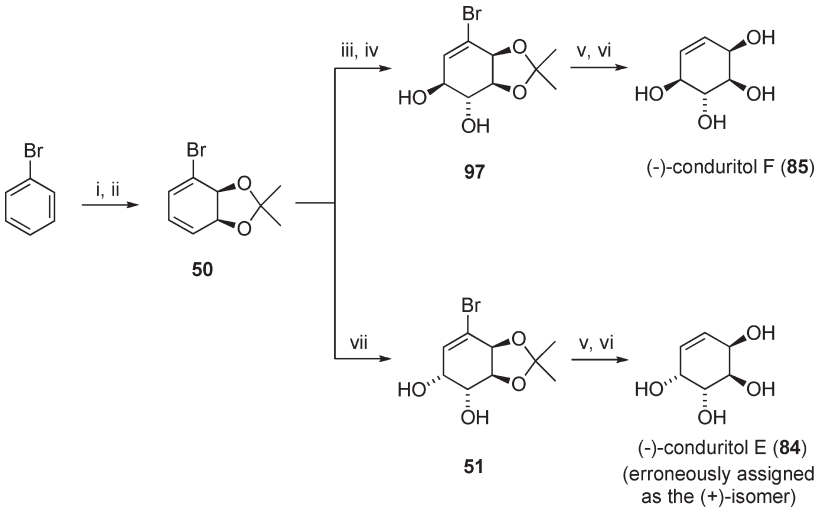
Scheme 14[a]



[a] Reagents: (i) 2,2-dimethoxypropane, CH_2Cl_2, *p*-TsOH, 82%; (ii) $^1O_2$, *meso*-tetraphenyporphyrine, CH_2Cl_2, MeOH, 0 °C, then thiourea, 65%; (iii) Amano P-30 lipase, isopropenyl acetate, 55 °C, 90%; (iv) benzoic acid ($PhCO_2H$), diethyl azodicarboxylate (DEAD), triphenylphosphane (Ph_3P), THF, 0 °C, quantitative for **96**, 89% for **95**; (v) *tert*-butyldimethylsilyl chloride (TBSCl), imidazole, *N*,*N*-dimethylformamide (DMF); (vi) K_2CO_3, MeOH; (vii) *p*-TsOH, MeOH, 84% from **96** for (−)-**83**; 66% from **95** for (+)-**83**.

Scheme 15[a]



[a] Reagents: (i) *P. putida*; (ii) 2,2-dimethoxypropane, acetone, *p*-TsOH; (iii) *m*-CPBA, CH_2Cl_2, 80%; (iv) aqueous KOH, dimethyl sulfoxide (DMSO), 63%; (v) Bu_3SnH, toluene, 85% for **84**, 79% for **85**; (vi) HCl, H_2O, or AcOH, H_2O, THF, quantitative; (vii) OsO_4, H_2O, acetone, 85%.

introduction of either *cis*- or *trans*-diols at the distal olefin by osmylation (to **51**) or epoxidation/hydrolysis (to **97**), respectively. Dehalogenation and deprotection of **51** and **97** then furnished conduritol E (**84**), erroneously assigned in the 1991 report as the (+)-E isomer ($[\alpha]_D^{20}$ = +330, *c* 4.5, H_2O) and conduritol F (**85**), respectively.

In his 1992 synthesis of conduritol E epoxide **99**, Carless[61] applied a similar sequence of chemical transformations to reach conduritol E from chlorobenzene, through dihydroxylation of acetonide derived from **60**, removal of the halogen, and hydrolysis, as shown in Scheme 16. Carless reported optical rotation for (−)-conduritol E as $[\alpha]_D^{25}$ = −320 (*c* 0.5, H_2O) and pointed out the erroneous assignment in the Hudlicky synthesis. Clearly, the diols derived from chloro- and bromobenzene have the same absolute stereochemistry; hence, the conduritols obtained from them must be the same. Later that year, a four-step enantioselective synthesis of (−)-conduritol C from chlorobenzene was also reported (Scheme 16).[62] The latter synthesis featured the hydroxyl-directed *syn*-epoxidation, opening of the β-epoxide in **100** with water, and subsequent dehalogenation of **101** to yield (−)-conduritol C (**83**, 38% overall yield) without the use of protecting groups.

In a 2006 report on new metabolites from the microbial oxidation of dihalobenzenes, the Hudlicky group provided a five-step synthesis of (−)-conduritol E as means of confirmation of the absolute stereochemistry for diol **102** (Scheme 17).[63] The fermentation of *o*-dibromobenzene with *E. coli* JM109 (pDTG601a) gave **102**, which was protected as its acetonide and converted to *cis*-diol **103** by dihydroxylation of the more electron-rich double bond. Reduction of the dibromide **103** with Bu_3SnH/AIBN gave diol **67**, whose deprotection with methanolic HCl furnished (−)-conduritol E, thereby establishing the absolute stereochemistry of the metabolite.

It is clear from the examples discussed so far that the cyclohexadiene-*cis*-1,2-diols serve as ideal starting materials for the synthesis of inositols, conduritols, and other highly

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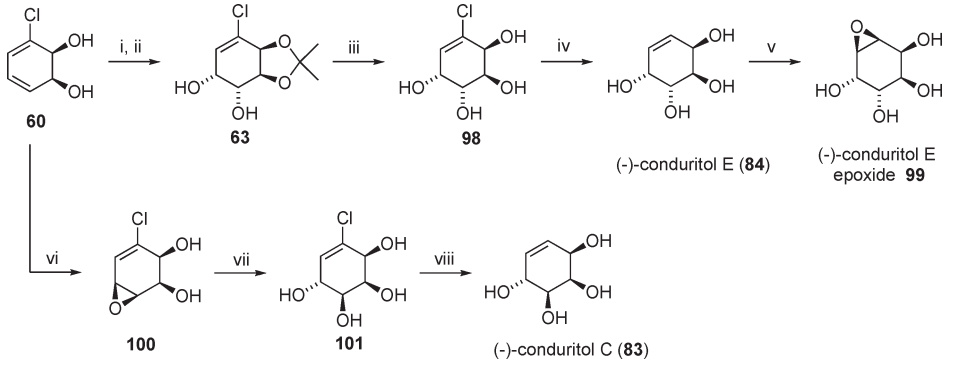
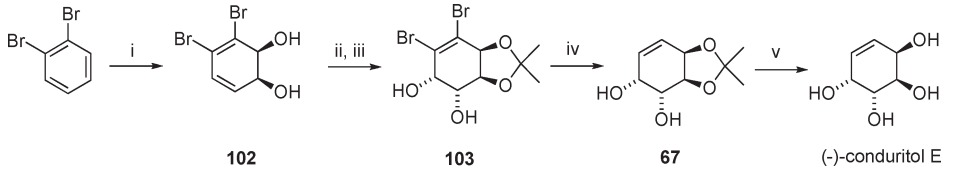
Scheme 16[a]



[a] Reagents: (i) 2,2-dimethoxypropane, *p*-TsOH, acetone, 97%; (ii) OsO_4, NMO, H_2O, acetone, 65%; (iii) aqueous AcOH, 85 °C, quantitative; (iv) Na/NH_3, THF, 60%; (v) *m*-CPBA, aqueous AcOH, 68%; (vi) *m*-CPBA, acetone, 61%; (vii) H_2O, CF_3CO_2H, 90%; (viii) Na/NH_3, 70%.

Scheme 17[a]



[a] Reagents: (i) *E. coli* JM109 (pDTG601); (ii) 2,2-dimethoxypropane, *p*-TsOH, 95%; (iii) OsO_4, NMO, H_2O, acetone, 71%; (iv) Bu_3SnH, AIBN, THF, 64%; (v) 3% HCl, MeOH, 81%.

oxygenated natural products. Of special significance is the symmetry-based strategy that provides both enantiomers of a product from a single enantiomer of the starting diol, as has been demonstrated in the synthesis of (+)- and (−)-pinitol and many other natural products.[41a,b,43] Synthetic organic chemists often voice a criticism of enzymatic strategies by claiming that only one enantiomer can result from enzyme-mediated transformations. The symmetry-based approach addresses this criticism well.

In the field of cyclohexadiene-*cis*-1,2-diols, a partial chemical solution to enantiodivergence issues was provided by Boyd and was based on his proposed model explaining the regio- and stereoselectivity of the enzymatic dihydroxylation, as shown in Figure 7.

Boyd, Dalton, and co-workers[64] demonstrated that some 1, 4-disubstituted iodoarenes such as **104a**−**d** (Scheme 18) afford mixtures of both enantiomers of the corresponding diols when subjected to whole-cell fermentation with *P. putida* UV4. In all of the cases studied, the *ent*-isomer of the diol was the major, albeit not exclusive, product, in agreement with the proposed model where the larger group directs the dihydroxylation and the directing effect of the iodine atom is stronger than that of the group in the *p*-position (F, Cl, Br, or Me).[65] The enantiomeric excess of *ent*-**105a**−**d** ranged from good [88% *ee* for X = F; 80% *ee* for X = Me (methyl, CH_3)] to low (15% *ee* for X = Cl; 22% *ee* for X = Br). Catalytic hydrogenation of the scalemic mixtures of **105** and *ent*-**105** afforded the corresponding scalemic mixtures of diols **49**, **60**, **86**, and **106**, respectively. Kinetic resolution of the scalemic mixtures was achieved by subjecting the mixture to growing cultures of the wild-type strain of *P. putida* NCIMB 8859. This process led to the enrichment of the ent products and provided the *ent*-diols **49**, **60**, **86**, and **106**, not attainable from the corresponding monosubstituted arenes, in >98% *ee*'s with ca. 30% recovered yields. A similar enrichment is also possible with

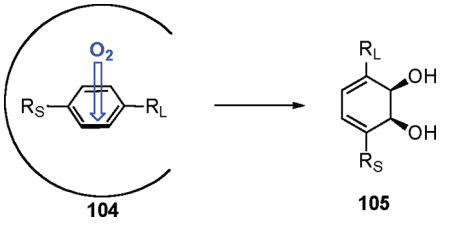


Figure 7. Boyd's model to account for stereoselectivity of the enzymatic dihydroxylation.

acylation of scalemic mixtures of **105** followed by lipase resolution[66] to furnish enantiomericaly enriched *ent*-cyclohexadiene-*cis*-1,2-diols and their derivatives.[67] Recently, Lewis and co-workers[68] reported a tricarbonyliron(0)-promoted diene rearrangement of a protected *ipso*-diol derived from microbial dihydroxylation of benzoic acid as a new method of attaining *ent*-diols derived from benzoate esters.

4. SYNTHESIS OF FUNCTIONAL AND STRUCTURAL ANALOGUES OF INOSITOLS AND CONDURITOLS FROM CYCLOHEXADIENE-*CIS*-1,2-DIOLS

4.1. Synthesis of Conduramines

The homochiral *cis*-diols derived from aromatic compounds are ideal for the synthesis of both functional and structural derivatives of cyclitols. For example, substitution of any of the hydroxyls in cyclitols with an amino group leads to conduramines as well as amino inositols. Figure 8 shows the structures of some of the conduramines that have been synthesized.

The aminocyclitol motif is found in several natural products, most notably in aminoglycoside antibiotics and Amaryllidaceae

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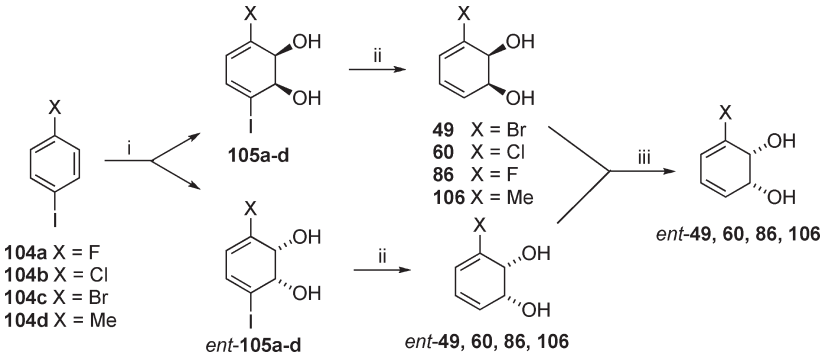
Scheme 18[a]



[a] Reagents: (i) *P. putida* UV4; (ii) H_2, Pd/C; (iii) *P. putida* NCIMB 8859.

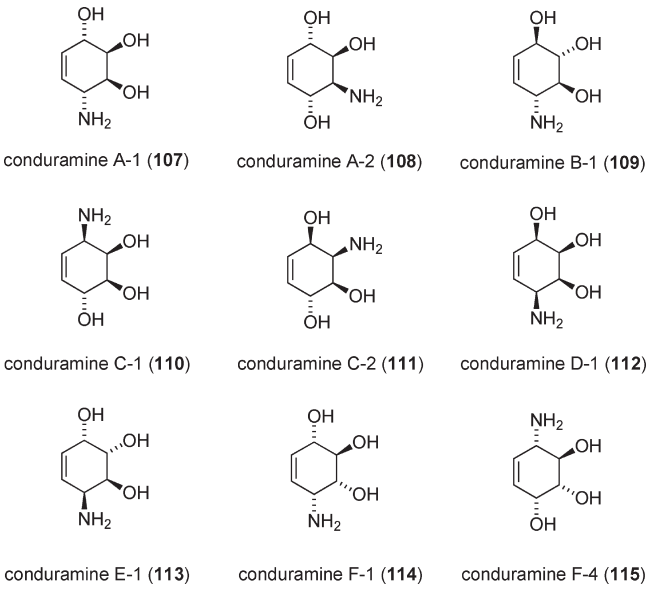


Figure 8. Structures of some conduramines.

alkaloids. The former are conjugates of an aminocyclitol and one or more carbohydrate units (often aminosugars). They display antimicrobial activity against both gram-positive and gram-negative bacteria, against mycobacteria, and against protozoa. Several agents of this class are currently in clinical use. For example, streptomycin (**120**), Figure 9, is prescribed for the treatment of tuberculosis.[69]

Many members of the Amaryllidaceae group of alkaloids (**10**, **116**−**118**, Figure 9) exhibit potent biological activities as both antitumor agents and inhibitors of various natural glycosidases because their structures mimic several biologically important carbohydrates. Related to this group is oseltamivir (**119**) (its phosphate salt is Tamiflu), designed to mimic the transition state of glycolysis. Strictly speaking, according to the definition cited above, it is not a cyclitol: however, it can be regarded as a "dideoxy diamino analogue" of one.

There are natural products that contain the cyclitol motif with additional carbo- or heterofunctionality, such as (−)-laminitol **121**, (−)-gabosine **122**, shikimic acid **123**, and quinic acid **12**, all shown in Figure 10. Some conduramines are active as glycosidase inhibitors, and there are numerous reports on the synthesis of conduramines and their analogues. As an extensive review on

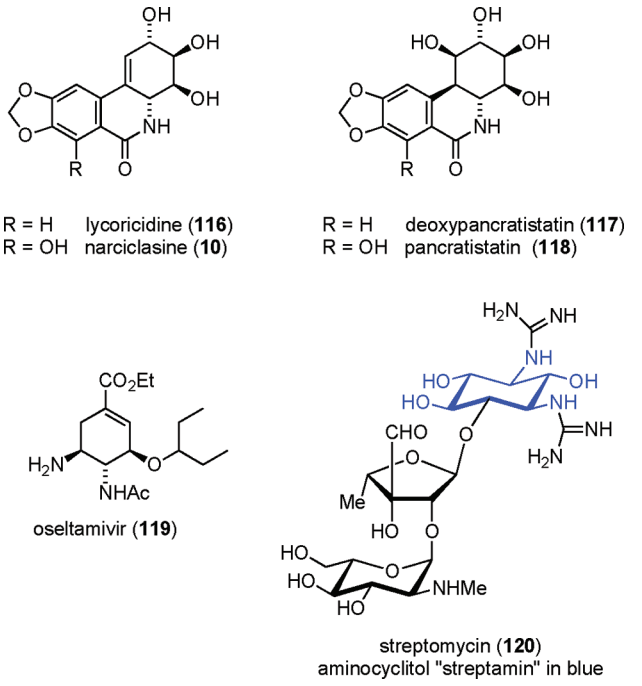


Figure 9. Examples of natural (and nonnatural) products containing the aminocyclitol or analogous motifs.

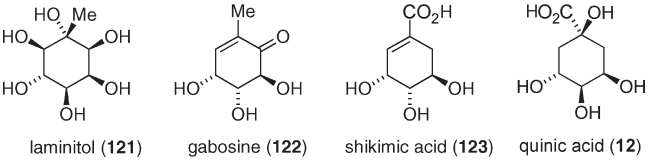


Figure 10. Functional analogues of cyclitols.

amino- and diaminoconduritols was published recently,[9c] these compounds are discussed here in an abbreviated fashion.

The hetero-Diels−Alder reaction between protected cyclohexadiene-*cis*-1,2-diols, derived from microbial oxidation, and nitroso dienophiles gives rapid access to derivatives of conduramine A-1. *meso*-Diacetate **124** (Scheme 19) was reacted with a chiral nitroso dienophile derived from D-mannofuranose **125** to form dihydrooxazine **126** in 89% yield (94% *ee*).[70] Cleavage of

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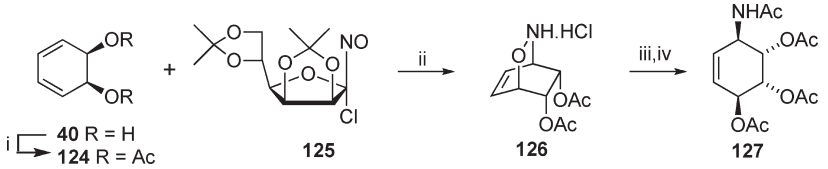
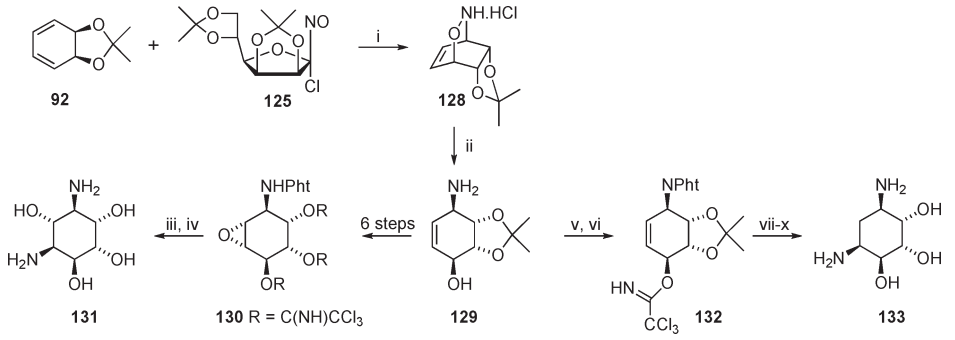
Scheme 19[a]



[a] Reagents: (i) Ac_2O, py, 96%; (ii) $CHCl_3$, EtOH, −70 °C, then −40 °C, 4 days, 89% (94% *ee*) (iii) Zn, HCl, H_2O, 5 °C; (iv) Ac_2O, py, 82% two steps.

Scheme 20[a]



[a] Reagents: (i) Et_2O, EtOH, −30 °C, 7 days, 82%; (ii) Al/Hg, aqueous THF, 0 °C, 2 days, 94%; (iii) (a) triethylaluminum (Et_3Al), DME, 0 °C, 3 h; (b) EtOH, 30 min; (c) Ac_2O, py, 80%; (iv) (a) 1 M HCl, acetone, MeOH; (b) N_2H_4, EtOH, $CHCl_3$, 80 °C, 79%; (v) *N*-ethoxycarbonylphthalimide, Na_2CO_3, $CaSO_4$, acetone, 90%; (vi) CCl_3CN, NaH, 91%; (vii) *N*-iodosuccinimide, CH_2Cl_2, 66% (viii) HCl, CH_2Cl_2, MeOH, then Ac_2O, py, 95%; (ix) Bu_3SnH, AIBN, 92%; (x) N_2H_4, $CHCl_3$, EtOH, 80 °C, 72%.

the N−O bond with Zn/HCl afforded conduramine A-1 tetraacetate (**127**) in 82% yield.

An analogous hetero-Diels−Alder reaction of the diene in acetonide **92** and nitroso dienophile **125** (Scheme 20) was reported by Piepersberg and co-workers[71] in their synthesis of diaminocyclitols **131** and **133** through conduramine A-1 derivative **129**.

The Diels−Alder adduct **128** was reduced with aluminum amalgam in wet tetrahydrofuran (THF) to the protected conduramine **129**, which was then converted to epoxide **130** in six steps. The intramolecular opening of the epoxide by the vicinal trichloacetimidato group and deprotection provided the diamino cyclitol **131**. Alternatively, conversion of **129** to the trichloacetimidate derivative **132** furnished the diamino cyclitol **133** in three subsequent steps.

Hudlicky and Olivo[72] reported a different approach, one that exploited the hetero-Diels−Alder reaction between chiral bromo- and chloro-cyclohexadiene acetonides **134** and **50** and nitrosyl dienophiles generated in situ from acetohydroxamic acid or benzyl-*N*-hydroxycarbamate (Scheme 21).

The addition of the nitrosyl dienophiles occurred anti to the acetonide moiety of **134** or **50** with complete regioselectivity, affording oxazines **135**−**137** as single enantiomers. The reductive cleavage of the N−O bond with Al/Hg was accompanied by dehalogenation, and the oxazines **135** and **136** afforded the same product **138**, whereas reduction of the acetyl protected oxazine **137** afforded acetamide **139**. Treatment of **138** under acidic conditions gave **140**, which was hydrogenated to dihydroconduramine A-1 (**143**). Acid treatment of acetamide **139** gave **141**, whose peracetylation gave conduramine A-1 tetraacetate **142**. An analogous approach to protected enantiomers of conduramine A-1 was reported by Johnson and co-workers,[73] who used an enzymatic resolution of a racemic derivative of type **139** (containing a benzoyl group instead of an acetyl).

A concise and stereospecific synthesis of conduramine F-4 (**115**) and conduritol F (**85**), published by Balci and co-workers[74] in 1994, was achieved through a common allylic epoxide intermediate **146** (Scheme 22). Acetonide **92**, obtained by protection of *meso*-diol **40** derived from benzene, was subjected to photooxygenation in carbon tetrachloride, with tetraphenylporphyrin as a sensitizer, to give only the anti isomer of the *endo*-peroxide **145** in high yield (95%). Triethyl phosphite was used for the deoxygenation of **145** to yield allylic epoxide **146** in moderate yield (55%). Opening of epoxide **146** with water provided conduritol F (**85**) in quantitative yield, whereas treatment with ammonia in methanol gave amino alcohol **147**, whose deprotection furnished conduramine F-4 (**115**).

A synthesis of (−)-conduramine C-4 (**152**) by Gonzalez and co-workers[75] started from bromobenzene, which was first converted to acetonide **50** in two steps (Scheme 23). Reaction of **50** with *N*-bromosuccinimide gave a mixture of bromohydrins **74** and **148**,[76] which were transformed to epoxides **75** and **53**, respectively, upon treatment with sodium hydroxide. The two epoxides were isolated in 50% yield and in a ratio of 7:1 after chromatography. Regioselective opening of the oxirane ring of **75** with sodium azide afforded azido alcohol **149** in 98% yield. Its reduction with triphenyl phosphine provided **150**, whose radical debromination gave amino alcohol **151** in 56% yield over the two steps. Direct conversion of **149** to **151** was achieved by reaction with $LiAlH_4$ in THF, albeit in a low 31% yield. Deprotection of **151** under acidic conditions afforded (−)-conduramine C-4 (**152**).

4.2. Synthesis of Natural Products

Highly oxygenated natural products became obvious targets for syntheses beginning with optically pure cyclohexadiene-*cis*-1, 2-diols. Several chemoenzymatic syntheses of Amaryllidaceae alkaloids, compounds containing an aminocyclitol or conduramine

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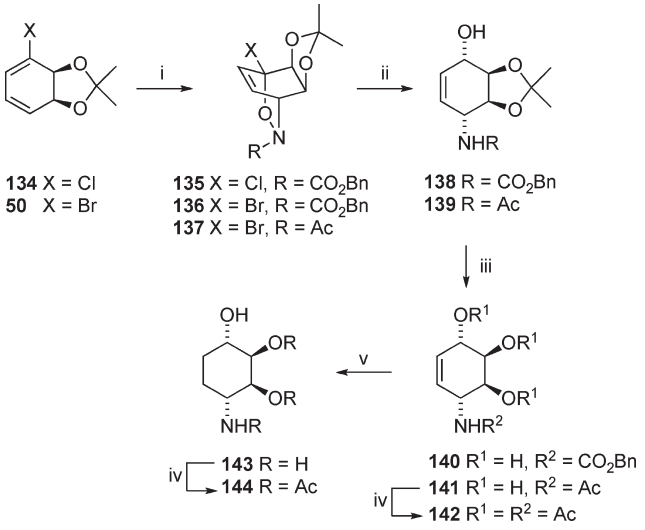
moiety and shown in Figure 9, were reported by the groups of Hudlicky and Banwell. Abbreviated descriptions of these syntheses highlight only the key steps and overall strategy. For more detailed discussions, the reader should refer to the corresponding primary literature, as well as reviews.[3b,77]

A short synthesis of lycoricidine (**116**, Figure 11) was based on an acylation of a protected conduramine A-1 derivative **153** with 6-bromopiperonic acid chloride **154** to amide **155**. Transformation to the alkaloid was achieved by an intramolecular Heck reaction followed by deprotection.[78]

The first asymmetric synthesis of pancratistatin (**118**) utilized opening of the aziridine ring in **157** by the lithium cyanocuprate species generated from **158** to furnish **159**, which yielded pancratistatin after several additional steps.[79] Ring-opening of the aziridine **157** with methyl indole-3-carboxylate was later used in the synthesis of β-carboline-1-one mimics of pancratistatin.[80]

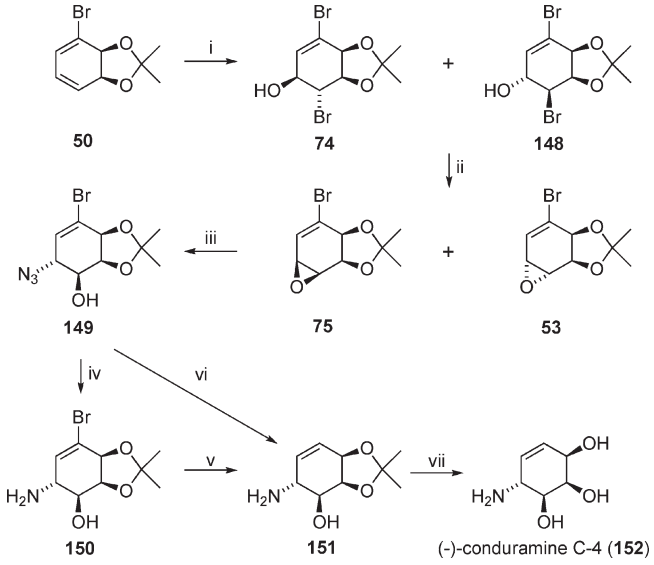
An analogous approach through aziridine opening was also used in the synthesis of *ent*-deoxypancratistatin (*ent*-**117**), from the antipodal diol *ent*-**49**. This material was prepared by enzymatic dihydroxylation of *p*-iodobromobenzene according to the method developed by Boyd (see Scheme 18). Because the fermentation produced scalemic mixture of diol **49**, additional enrichment through enzymatic acylation/hydrolysis was employed to produce optically pure *ent*-**49**. The key step involved the opening of the aziridine ring of **160** by a metalated species generated from **161** to provide **162**, which was transformed to *ent*-deoxypancratistatin (*ent*-**117**).[67] Interestingly, *ent*-**117** displayed 10-fold lower

Scheme 21[a]



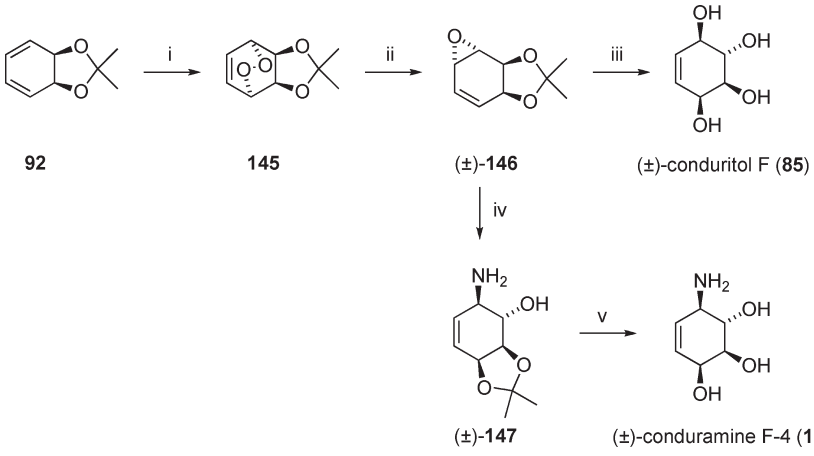
[a] Reagents: (i) tetrabutylammonium periodate (*n*-Bu_4NIO_4) and benzyl-*N*-hydroxycarbamate or acetohydroxamic acid, 54% of **135**, 52% of **136**, 51% of **137**; (ii) Al/Hg, THF, H_2O, 91% of **138**, 77% of **139**; (iii) AcOH, THF, H_2O, 99% of **140**, 99% of **141**; (iv) Ac_2O, py, 63% of **142**, 97% of **144**; (v) **140**, H_2, Pd/C, MeOH, 54% of **143**.

Scheme 23[a]



[a] Reagents: (i) *N*-bromosuccinimide (NBS), THF, H_2O; (ii) NaOH, tetrabutylammonium hydrogensulfate (Bu_4NHSO_4), CH_2Cl_2, 44% of **75**, 6% of **53**; (iii) **75**, NaN_3, NH_4Cl, THF, EtOH, H_2O, 98%; (iv) PPh_3, THF, AcOH, then H_2O, 74%; (v) Bu_3SnH, 1,1′-azobis(cyclohexanecarbonitrile), THF, 75%; (vi) $LiAlH_4$, THF, 31%; (vii) (a) Dowex (H^+ form); (b) 2 M NH_4OH.

Scheme 22[a]



[a] Reagents: (i) $^1O_2$, tetraphenylporphyrin, CCl_4, 95%; (ii) $CHCl_3$, triethyl phosphite [$P(OEt)_3$], 55%; (iii) H_2SO_4, H_2O, $BaCO_3$, quantitative; (iv) MeOH, NH_3; (v) H_2SO_4, H_2O, $BaCO_3$.

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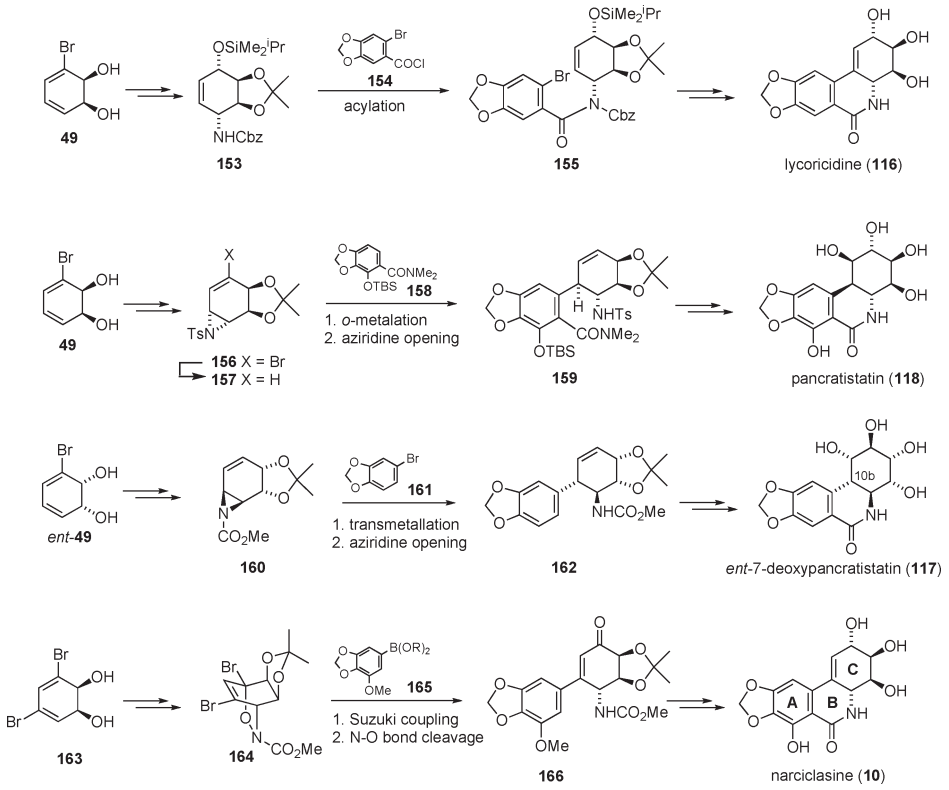

Figure 11. Chemoenzymatic syntheses of Amaryllidaceae constituents (Hudlicky group).

biological activity against human cancer cell lines than the natural enantiomer. The *cis*-fused 10β-epimer of 7-deoxypancratistatin was also prepared from diol **49** through a short synthesis involving the aza-Payne rearrangement.[81] Quite unexpectedly, this compound was shown to be completely inactive against the same cancer cell lines, indicative of the importance of the trans fusion of rings B and C in these alkaloids.[82]

A short synthesis of narciclasine (**10**, Figure 11) started from 1,3-dibromobenzene, which was subjected to enzymatic dihydroxylation to diol **163** and produced as a single isomer as a result of the symmetry present in the starting arene. A hetero-Diels–Alder reaction was employed to produce oxazine **164**. Suzuki–Miyaura coupling between oxazine **164** and boronic acid **165** followed by the reductive cleavage of the N–O bond afforded advanced intermediate enone **166**, which was transformed to narciclasine (**10**) in four additional steps.[83]

Suzuki–Miyaura coupling was also used by Banwell and coworkers as a key step for connecting the B- and C-rings of the skeleton of Amaryllidaceae alkaloids, namely, in their synthesis of *ent*-lycoricidine (**116**), 3-epi-*ent*-lycoricidine (**169**), and 4-deoxy-3-epi-*ent*-lycoricidine (**170**)[84] and in the synthesis of *ent*-narciclasine (**10**)[85] (Figure 12).

A synthesis of pancratistatin analogue **176** (Figure 13), bearing no oxygen atoms in the A-ring, featured a cobalt-catalyzed cyclotrimerization between the functionalized amino quercitol derivative **174** and bis(trimethylsilyl)acetylene as a key step. The tetracyclic tosyl amide **175** was obtained in 83% yield and was converted to the silicon analogue of 7-deoxypancratistatin **176** in several more steps.[86]

A multigenerational approach to the Amaryllidaceae constituents recently provided a concise synthesis of 7-deoxypancratistatin (**117**) that employed the intramolecular opening of an aziridine ring (Figure 13). The new strategy used the epoxy aziridine **177**, available from diol **49** in several steps. Opening of the oxirane ring of **177** with the aluminum acetylide derived from **178** followed by the reduction of the triple bond by catalytic hydrogenation using Lindlar catalyst or by hydroboration provided *cis*-olefin **179**. This material was adsorbed on silica gel and heated to 120 °C to furnish the key phenanthrene intermediate **180**. Phenanthrene-to-phenanthridone oxidative cleavage and recyclization strategy was used to subsequently transform this compound to 7-deoxypancrastatin (**117**), *trans*-dihydrolycoricidine (**181**), and various C-1 analogues of **117**.[87] The latter group of compounds yielded several C-1 analogues with potent activities against several human cancer cell lines.[87b]

Microbial oxidation of toluene by *P. putida* provided cyclohexadiene-*cis*-1,2-diol **106** (Scheme 24) and was exploited by Carless and Oak in their synthesis of (−)-laminitol (**121**),[88] a natural product inhibiting the growth of *Neurospora crassa*. Laminitol exhibits the stereochemistry of *myo*-inositol but bears a methyl group at C-4. The protection of hydroxy groups of diol **106** furnished acetonide **182**, whose epoxidation with *m*-CPBA occurred regioselectively at the trisubstituted double bond and stereoselectively anti to the isopropylidene group to afford allylic epoxide **183**. Hydrolysis of the epoxide provided **184** and, upon longer treatment (6 days) with aqueous acid, furnished the tetrol **185**, a methyl derivative of conduritol F. Epoxidation of **185**, directed by the allylic hydroxy groups, afforded **186**. Opening of the oxirane ring in **186** was nonselective and afforded a 1:1 mixture of cyclitol **187** (with a muco configuration) and (−)-laminitol (**121**). Peracetylation, chromatography, and deacetylation provided pure **187** and **121** with 70% recovery.

Another natural product, (−)-gabosine (**122**) (Scheme 25) was prepared from diol **188**, derived enzymatically from

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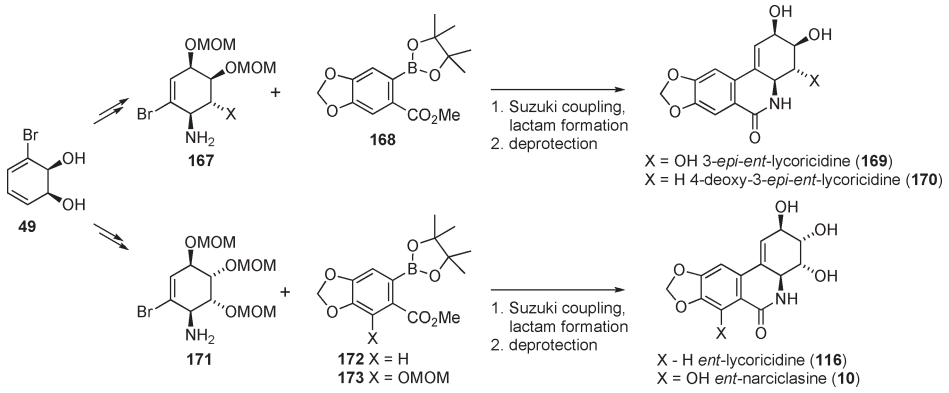

Figure 12. Chemoenzymatic syntheses of Amaryllidaceae constituents (Banwell group).

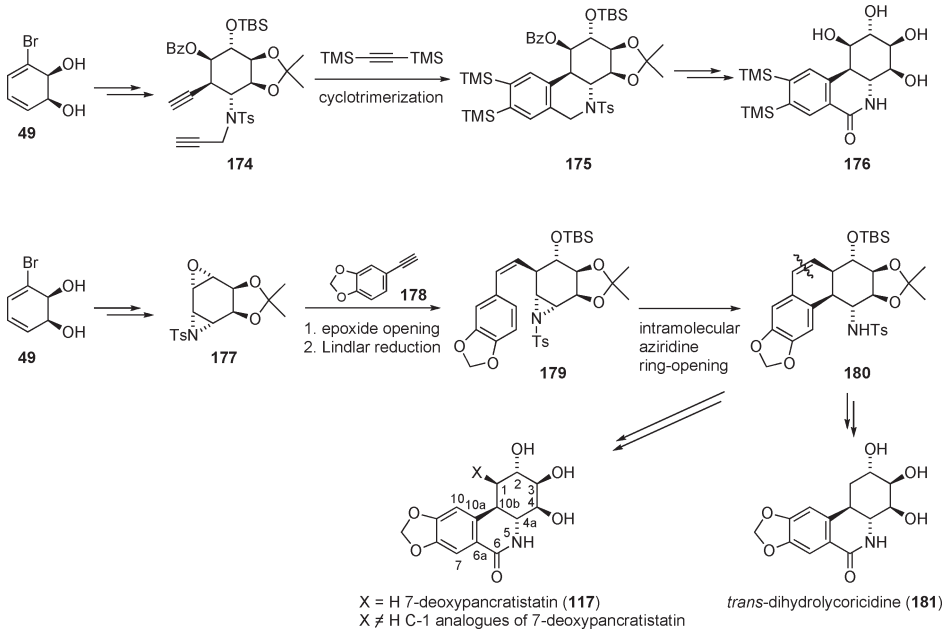

Figure 13. Recent synthesis of 7-deoxypancratistatin and nonnatural derivatives (Hudlicky group).

iodobenzene.[89] Protection of the distal hydroxy group gave **189**, which was dihydroxylated with catalytic osmium tetroxide to triol **190**. Protection of the vicinal diol as isopropylidene ketal **191**, Swern oxidation to iodo enone **192**, and iron(III)-catalyzed coupling of the vinyl iodide in **192** with methylmagnesium chloride at 0 °C provided **193**, whose deprotection afforded (−)-gabosine (**122**).

Pericosines, examples of which are shown in Figure 14, are metabolites isolated from the fungus *Periconia byssoides*. These compounds have attracted attention because of the variety of biological activities they display: antitumor activity against some human cancer cell lines, inhibitory activity against P388 leukemia cells in mice, and inhibitory activity against EGFR (epidermal growth factor receptor) and topoisomerase II.[90] Donohoe and co-workers[91] reported the first synthesis of a pericosine. Their synthesis of pericosine B (**195**) (Figure 14) started from diol **49**, which was converted to the target compound in seven steps and in 10% overall yield. The synthesis also established the absolute configuration of **195**, unknown at the time. Recently, Boyd and co-workers[92] reported chemoenzymatic syntheses of pericosines A−C. For example, pericosine A (**196**, Figure 14) was prepared from methyl ester diol **194** in four steps and 41% overall yield.

4.3. Synthesis of Other Analogues

The preceding sections outlined the majority of syntheses of cyclitol derivatives as well as some of the natural products containing cyclitol and their derivatives. The cyclohexadiene-*cis*-1,2-diols have been shown to be ideal starting materials for such purposes. Following the preparation of natural cyclitols and aminocylitols, more advanced applications have been reported, including the synthesis of oligoinositol conjugates and inositol-containing polymers (see section 7). The preparation of some nonnatural derivatives of cyclitols is covered in this section.

Cyclohexadiene-*cis*-1,2-diols are convenient starting materials for the synthesis of pseudosugars (carbasugars),[93] compounds that have been investigated for their activities as glycosidase inhibitors[94] and have usually been synthesized by traditional methods.[95] Structures of some pseudosugars that have been prepared from cyclohexadiene-*cis*-1,2-diols are shown in Figure 15.

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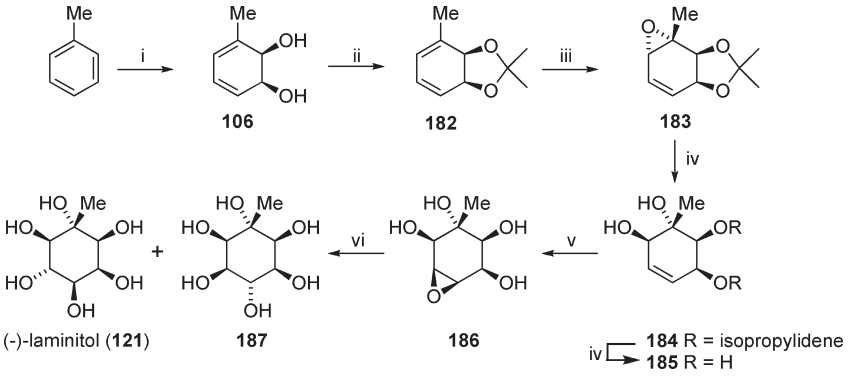
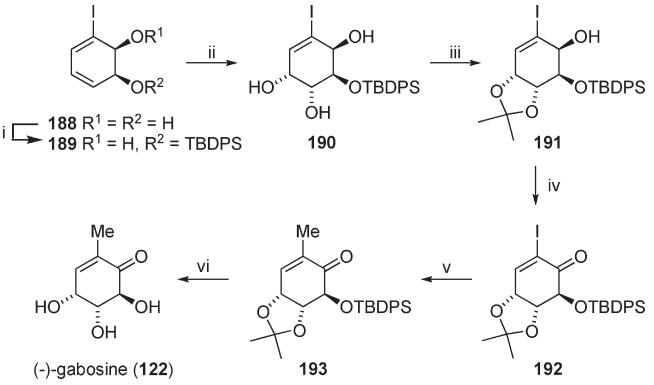
Scheme 24[a]



[a] Reagents: (i) *P. putida*; (ii) 2,2-dimethoxypropane, *p*-TsOH, 65%; (iii) *m*-CPBA, CH_2Cl_2, Na_2CO_3, 0 °C, 47%; (iv) H_2O/THF (1:5), *p*-TsOH, 6 days, 78% of **185** from **183**; (v) *m*-CPBA, CH_2Cl_2, 10 days, 73%; (vi) H_2O, TFA, reflux, 4 h, 95% combined yield of a 1:1 mixture of **121** and **187**.

Scheme 25[a]



[a] Reagents: (i) *tert*-butyl diphenylchlorosilane (TBDPSCl), imidazole, CH_2Cl_2; (ii) OsO_4, NMO, acetone, H_2O, 4 °C, 30 h; (iii) 2,2-dimethoxypropane, *p*-TsOH, 3 h, then Et_3N, 78% from **188**; (iv) $(COCl)_2$, DMSO, −78 °C, 1 h, then Et_3N, −78 to −10 °C, 30 min, 85%; (v) methylmagnesium bromide (MeMgBr), $FeCl_3$, *N*-methylpyrrolidinone, THF, 0 °C, 30 min, 94%; (vi) HCl, MeOH, 96 h, then tris(dimethylamino)sulfonium difluorotrimethyl siliconate $[(Me_2N)_3S^+F_2SiMe_3^-]$, THF, 30 min, 85%.

Examples of some syntheses of carbasugars are shown in Scheme 26. Boyd used the diol **188**, derived from iodobenzene by fermentation, whose protection, followed by diastereoselective osmium tetroxide-catalyzed dihydroxylation, furnished **203**.[93c] This material was transformed to methyl ester **204** by carbonylation with palladium acetate under an atmosphere of carbon monoxide. Catalytic hydrogenation of the double bond of **204** afforded a mixture of **205** and **207**, separated following acylation as the corresponding dibenzoyl esters **206** (56%) and **208** (28%). Reduction of **205** with $LiAlH_4$ afforded **209**, which was treated with trifluoroacetic acid (TFA) in wet THF to obtain pseudo-α-L-galactopyranose (**200**).

Hudlicky's group used diol **194**, derived chemoenzymatically from methyl benzoate, in the synthesis of pseudo-α-L-galactopyranose (**200**) and its isomer **199**, as outlined in Scheme 26.[93d] The choice of methyl benzoate-derived diol **194** avoided the carbonylation step that would normally have to be performed with diols derived from iodo- or bromobenzene. Dihydroxylation of the acetonide prepared from **194** followed by acetylation and

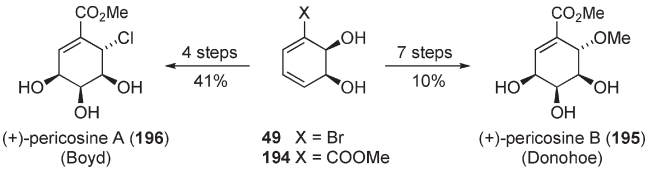


Figure 14. Chemoenzymatic syntheses of pericosines (principal authors in parentheses).

hydrogenation afforded a 4:1 mixture of diastereomeric esters **210** and **211**. Reduction of **210** provided the acetonide-protected derivative of pseudo-α-L-galactopyranose, whose physical and spectral properties were matched with those of Boyd's intermediate **209**, completing a formal synthesis of pseudo-α-L-galactopyranose. The deprotection to **200** was not performed.

Enzymatic dihydroxylation of benzonitrile (Scheme 27) with *P. putida* affords diol **212**, which gives rapid access to cyclitols with a skeleton resembling that of shikimic acid (**123** in Figure 10), an important biogenic precursor of aromatic amino acids in plants.[96] Protection of the diol in **212** with 2,2-dimethoxypropane and acetone in the presence of trifluoroacetic acid provided acetonide **213**. Dihydroxylation or epoxidation of **213** occurred regio- and stereoselectively anti to the isopropylidene group, leading to diol **214** or epoxide **215**, respectively. Diol **214** was elaborated to (6*R*)-6-hydroxyshikimic acid **216**. Epoxide **215** was converted to cyanocyclitol **217**. Alternatively, selective epoxidation directed by the hydroxy groups of unprotected diol **212** gave exclusively the *syn*-epoxide **218**, which was converted to cyanocyclitol **219** in several steps.

A fluorine atom is often introduced into molecules to improve the physiochemical properties of target compounds. An enantiodivergent approach to 1,2-dideoxy-2-amino-1-fluoro-*allo*-inositol (**220**) is shown in Scheme 28.[97] The approach employs the same strategy that led to the synthesis of both enantiomers of pinitol (Scheme 5) and takes advantage of the latent plane of symmetry in the starting acetonide **50**. By establishing either the syn or anti dihydroxylation in **67** or **53**, respectively, and by changing the order of application of the reagents, full enantiodivergence is attained. Selective dihydroxylation of **50** followed by reduction with tributyltin hydride initiated with AIBN gave diol **67**. The facial selectivity of epoxidation of **67** to **221** is controlled by the directing effect of the free hydroxy groups and by the steric

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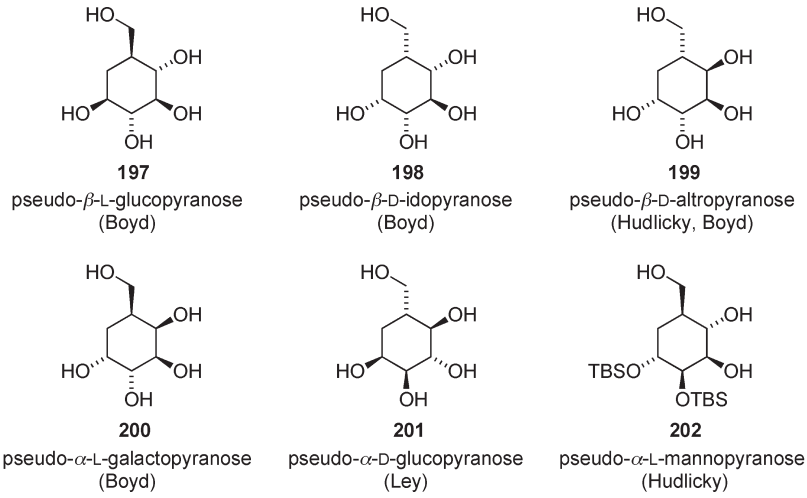
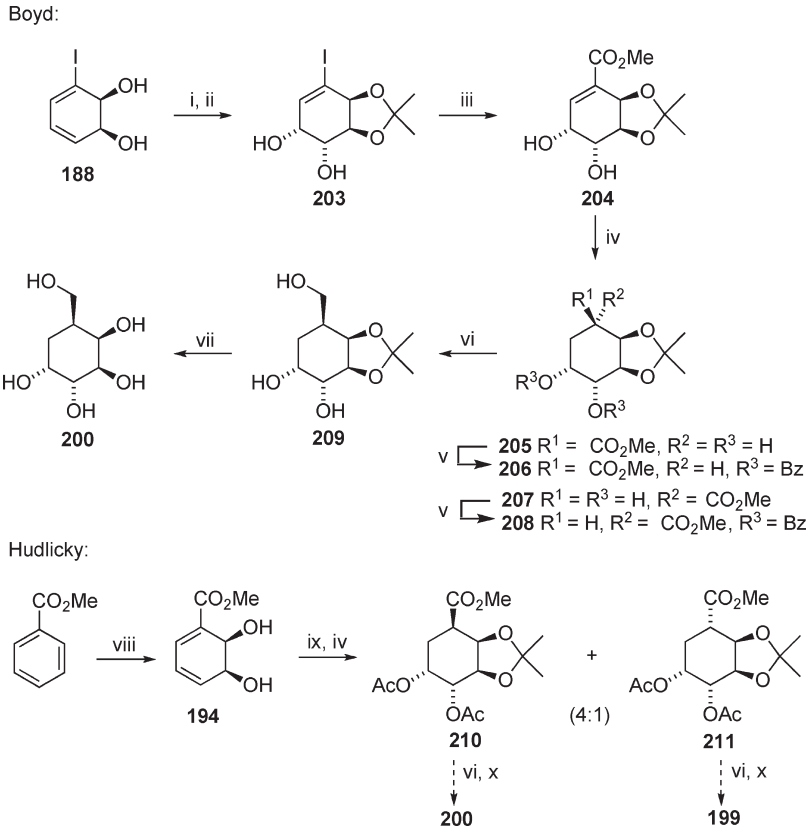


Figure 15. Structures of some pseudosugars that have been synthesized from cyclohexadiene-*cis*-1,2-diols (principal authors in parentheses).

Scheme 26[a]



[a] Reagents: (i) 2,2-dimethoxypropane, acetone, *p*-TsOH, 98%; (ii) OsO_4, NMO, acetone, H_2O, 87%; (iii) CO, palladium(II) acetate [$Pd(OAc)_2$], sodium acetate trihydrate ($AcONa \cdot 3H_2O$), MeOH; 81%; (iv) H_2, Rh/Al_2O_3, EtOH; (v) BzCl, py, 56% of **206**, 28% of **208** (yields from **204**); (vi) **206**, $LiAlH_4$, THF, reflux, 76%; **210**, $LiAlH_4$, THF, reflux, 76% (vii) TFA, THF, H_2O, 50 °C, 81%; (viii) *E. coli* JM109 (pDTG601a); (ix) (a) 2, 2-dimethoxypropane, acetone, *p*-TsOH; (b) OsO_4, NMO, acetone, H_2O; (c) Ac_2O, py; (x) H_3O^+ (not performed).

imposition of the acetonide moiety. Regioselective opening of the oxirane ring in **221** with tetrabutylphosphonium fluoride dihydrofluoride (TBPF-DF) as the fluoride source, and protection of the *cis*-diol produced **222**, in which the free hydroxyl was converted, through its triflate, to the corresponding azide. Reduction and complete deprotection then yielded (+)-**220**.

The synthesis of enantiomer (−)-**220** started by selective epoxidation of **50** to epoxide **53**, which was opened with TBPF-DF to afford alcohol **223**. Debromination, performed with tributyltin hydride/AIBN, followed by substitution of the hydroxy group (as its triflate) with azide produced **224** and ultimately led to the enantiomer (−)-**220**. Similar protocols were also

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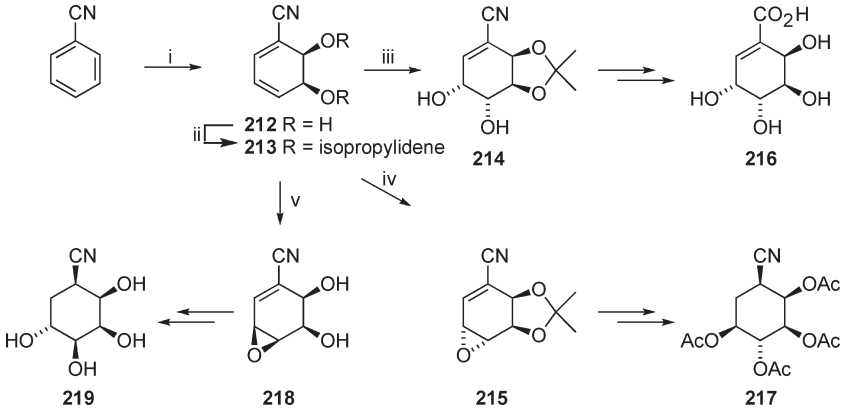
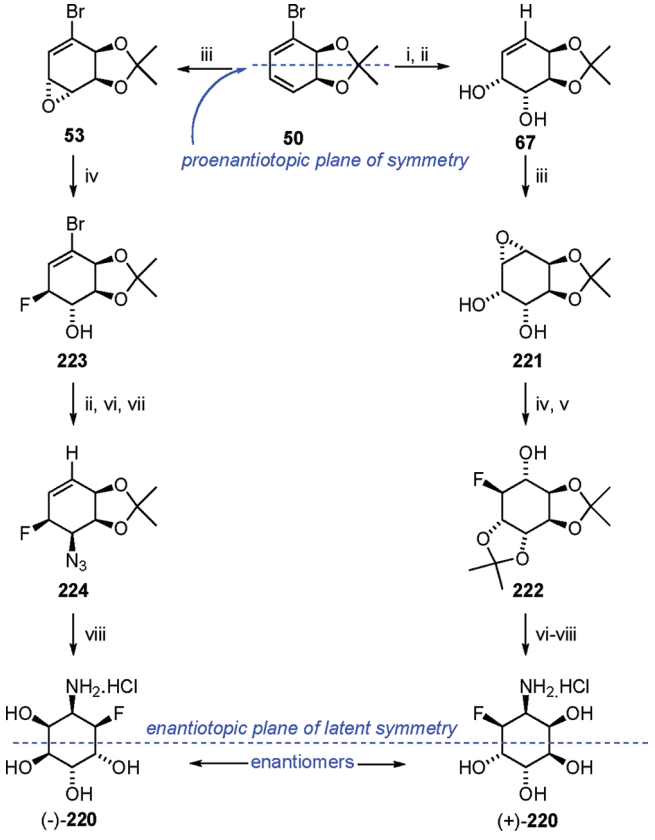
Scheme 27[a]



[a] Reagents: (i) *P. putida*; (ii) 2,2-dimethoxypropane, acetone, TFA, 90%; (iii) **213**, OsO_4, NMO, acetone, H_2O, 4 days, 55%; (iv) **213**, *m*-CPBA, CH_2Cl_2, 43%; (v) **212**, *m*-CPBA, CH_2Cl_2, 71%.

Scheme 28[a]



[a] Reagents: (i) OsO_4, NMO, H_2O, *t*-BuOH, 84%; (ii) Bu_3SnH, AIBN, benzene, reflux, 90% for **67**, 95% for **224**; (iii) *m*-CPBA, CH_2Cl_2, reflux, 80%; (iv) tetrabutylphosphonium fluoride dihydrofluoride (TBPF-DF), 70% for **222**, 75% for **223**; (v) 2,2-dimethoxypropane, acetone, *p*-TsOH; 85%; (vi) trifluoromethanesulfonic anhydride (Tf_2O), py, CH_2Cl_2, 90%; (vii) NaN_3, DMF, 80%; (viii) H_2, Pd/C, MeOH, HCl, 80%.

employed for the synthesis of 5-deoxy-5-fluoro-*myo*-inositol, 2-dideoxy-2-amino-1-fluoro-*allo*-inositol, and 3-deoxy-3-fluoro-L-*chiro*-inositol[98] and found application as well in the synthesis of fluorocarbohydrates.[99]

Analogues of (−)-conduritol F containing a hydrophobic aromatic moiety became readily available from (1*R*,2*S*)-1,2-dihydronaphthalene-1,2-diol **225** (Scheme 29), obtained by fermentation of naphthalene with recombinant *E. coli* strain expressing naphthalene dioxygenase.[100] This material was converted to epoxide **226**, whose opening with various nucleophiles under neutral or basic conditions afforded several functionalized hydrins **227** as single stereoisomers. These compounds were deprotected to **228** by acid-catalyzed hydrolysis.

Amino-bridged conduramine dimer **229** was prepared by opening of the oxirane ring of **226** by conduramine **227** (X = NH_2) in *tert*-butanol at 120 °C in a sealed tube. Deprotection furnished the fully hydroxylated dimer **230**. Structurally related polyhydroxylated tetrahydronaphthalene ethers were prepared by Hudlicky and co-workers from dihydronaphthalene diol **225**.[101]

New heteroanalogues of conduritols and inositols were reported by Gonzalez and co-workers. An approach to various conduritol C (i.e., **237**) and F (i.e., **233**, **236**) analogues and other cyclitols derived from them is shown in Scheme 30. Epoxide **231** was opened regioselectively with ammonium thiocyanate, and the product **232** was deprotected to produce 4-deoxy-4-thiocyano-conduritol F **233**.[102] The double bond of conduritols allows for further oxygenation, as demonstrated by dihydroxylation of acetonide **232**, which, after deprotection, furnished deoxythiocyanoinositol **234**. In an analogous fashion, phenylselenyl derivative **235** was prepared from **231** by reaction with diphenyldiselenide in the presence of sodium borohydride.[103] Deprotection of **235** under acidic conditions afforded 6-deoxy-6-phenylselenylconduritol F **236**. Attempted dihydroxylation of the double bond in **235** with $RuCl_3/NaIO_4$ triggered an unexpected 2,3-sigmatropic rearrangement to afford a conduritol C derivative **237** as the main product. Opening of epoxide **53** with thiophenol in the presence of $Yb(OTf)_3$ followed by debromination gave **238**, which was deprotected to 6-deoxy-6-phenylthioconduritol F **239**.[104] Attempt at dihydroxylation of the double bond of **239** with $RuCl_3/NaIO_4$ led primarily to the oxidation of the sulfide to sulfone **240** (56%), whereas dihydroxylated sulfone **241** was isolated in a lower yield of 29%. Opening of the oxirane ring of **53** with azide ion (Scheme 30) followed by palladium-catalyzed cross-coupling reaction either with aryl- or alkynyltrifluoroborates gave **242**[105] or **243**,[106] respectively. The azido group can be reduced to give access to new aminocyclitols, or it can undergo [3 + 2] dipolar cycloaddition with alkynes to form cyclitols of type **244**.[107]

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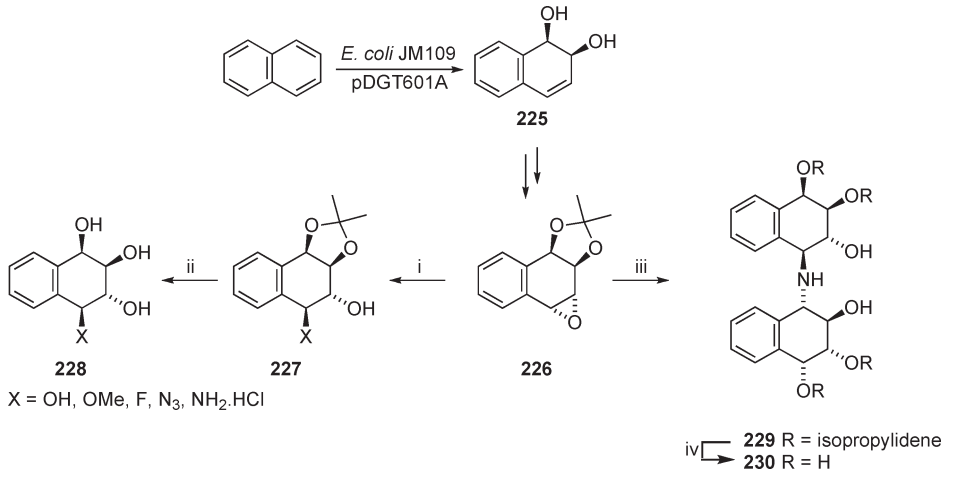
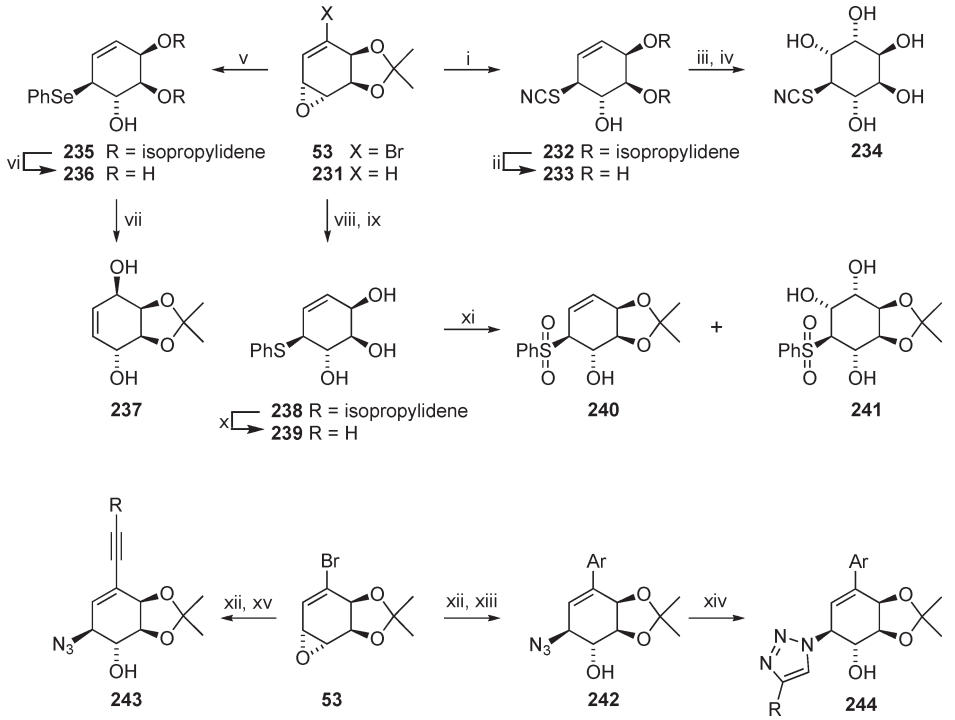
Scheme 29[a]



[a] Reagents: (i) nucleophile, basic or neutral conditions; (ii) TFA, H_2O, THF, 70−90%; (iii) **226**, **227** (X = NH_2), *t*-BuOH, 120 °C, sealed tube, 50%; (iv) TFA, H_2O, THF, 90%.

Scheme 30[a]



[a] Reagents: (i) **231**, NH_4SCN, MeCN, 1 h, 85%; (ii) Dowex 50 (H^+ form), MeOH, H_2O, 24 h, 90%; (iii) **232**, $RuCl_3$, $NaIO_4$, ethyl acetate (AcOEt), MeCN, H_2O, 15 min, 82%; (iv) Dowex 50 (H^+ form), MeOH, H_2O, 1 h, 93%; (v) **231**, diphenyldiselenide, $NaBH_4$, DME, 2 h, 72%; (vi) Dowex (H^+ form), MeOH, H_2O, 72 h, 77%; (vii) **235**, $RuCl_3$, $NaIO_4$, AcOEt, MeCN, H_2O, 0 °C, 2 h, 30%; (viii) **53**, benzenethiol (PhSH), $Yb(OTf)_3$, toluene, 1 h, 78%; (ix) Bu_3SnH, AIBN, THF, reflux, 4 h, 75%; (x) Dowex 50 (H^+ form), MeOH, H_2O, 1 h, 90%; (xi) $RuCl_3$, $NaIO_4$, 0 °C, 30 min, 56% of **240**, 29% of **241**; (xii) NaN_3, NH_4Cl, THF, EtOH, H_2O, reflux, 1 h, 98%; (xiii) potassium aryltrifluoroborate ($ArBF_3K$), tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$], Cs_2CO_3, toluene, H_2O, 43−71%; (xiv) alkyne, $CuSO_4$, sodium ascorbate, toluene, H_2O, 62−88%; (xv) potassium alkynyltrifluoroborate, $Pd(PPh_3)_4$, Cs_2CO_3, toluene, H_2O, 90 °C, 47−74%.

In a subsequent report, Bellomo and Gonzalez further expanded their work on sulfur analogues of cyclitols.[108] Acetonide **50** (Scheme 31) was converted to diastereomeric epoxides **53** and **75**. Depending on the reaction conditions, these epoxides were transformed either to thiocyanoconduritol derivatives **245** and **246** or directly to episulfides **247** and **248**. These sulfur derivatives (**245**−**248**) serve as building blocks for the synthesis of new thioconduritols and thioinositols.

Analogues of fagopyritols, conjugates of cyclitols and carbohydrates, are studied in relation to their potential role in etiology of

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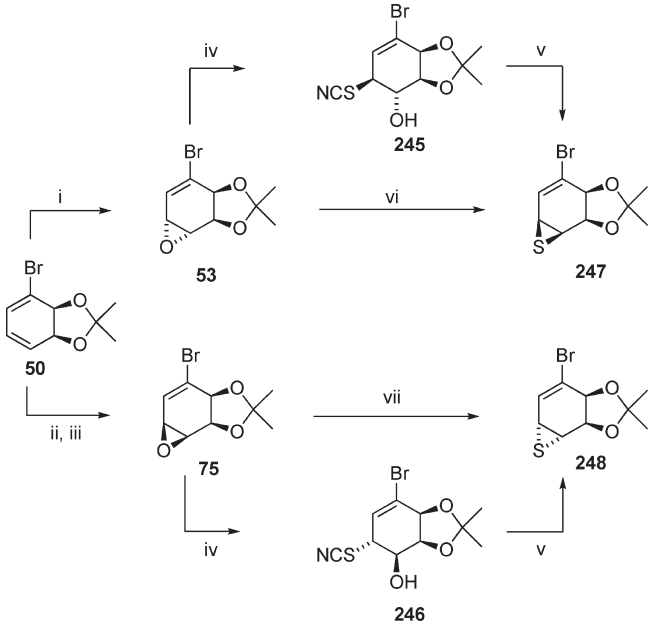
type II diabetes. The first chemoenzymatic synthesis of a potential insulin mimic starting from benzene was reported by Ley and Yeung[109] in 1992. More recently, the Gonzalez group employed the easily accessible azidoconduritiol **249** (Scheme 32). Azidoconduritol **249** was coupled with trichloroacetimidate **250** to form β-glycoside **251** in 92% yield and was further converted to β-D-galactopyranosyl-(1′,1)-conduramine F-4 **252** in 80% yield by Staudinger reaction followed by global deprotection.[110] Alternatively, dihydroxylation of **251** with $RuCl_3/NaIO_4$ gave **253** in 91% yield, and this material was converted, after reduction of the azido group and deprotection, to β-D-galactopyranosyl-(1′,3)-4-amino-4-deoxy-L-*chiro*-inositol **254**.

Scheme 31[a]



[a] Reagents: (i) *m*-CPBA, CH_2Cl_2, 85%; (ii) NBS, THF, H_2O; (iii) NaOH, Bu_4NHSO_4, CH_2Cl_2, reflux, 50% two steps; (iv) NH_4SCN or KSCN, MeCN, 85% for **245**, 68% for **246**; (v) K_2CO_3, 18-crown-6, CH_2Cl_2, 75% for **247**, 55% for **248**; (vi) KSCN, 18-crown-6, MeCN, pH 8, 24 h, 50%; (vii) KSCN, 18-crown-6, MeCN, pH 10, 36 h, 48%.

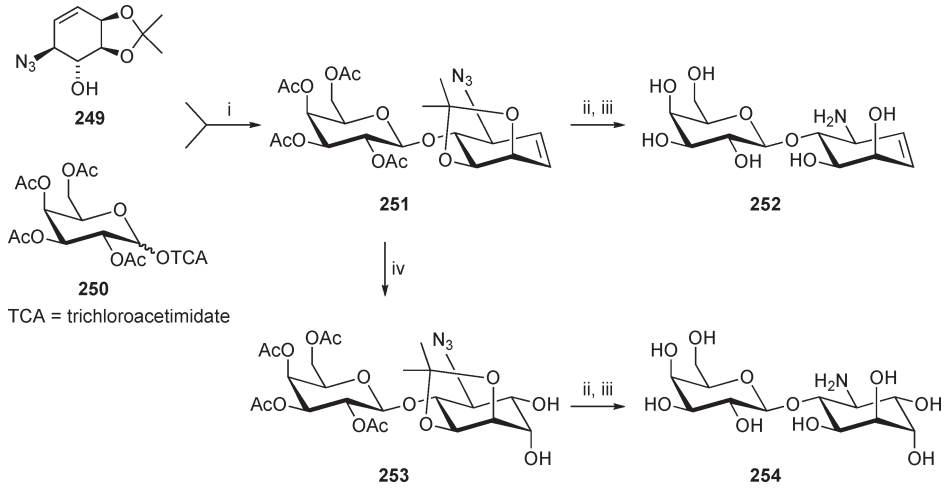
Oseltamivir (**119**, Figure 16) is, as its phosphate, an orally available agent for the treatment and prevention of influenza viruses and has attracted a great deal of attention, particularly in connection with the spread of H5N1 influenza, a subtype of the avian influenza, and its transmission to humans. Of the numerous syntheses reported, four have started with optically pure cyclohexadiene-*cis*-1,2-diols derived from microbial oxidation of arenes. These syntheses are discussed here in an abbreviated fashion. Although oseltamivir itself is not a cyclitol according to the definition mentioned at the outset of this review, it can be regarded as a dideoxy diamino analogue, and in fact, the syntheses discussed proceed through conduramines as key intermediates.

Fang and co-workers[111] reported a synthesis of oseltamivir starting from bromo diol **49** (Figure 16), which was transformed in several steps to aziridine **255**. Opening of the aziridine ring in **255** with 3-pentanol followed by deprotection gave conduramine C-3 derivative **256**, which was transformed in several steps to **257**. The incorporation of the ethyl ester group by treatment of **257** with $[Ni(CO)_2(PPh_3)_2]$ in the presence of ethanol and reduction of the azido group afforded **119**. The synthesis was also performed azide-free through intermediate **258**, which was transformed to **119** by substitution of bromine for iodine, palladium-catalyzed ethoxycarbonylation, and deprotection.

Banwell and co-workers[112] reported a formal synthesis of **119** also starting from bromo diol **49** (Figure 16). They first transformed the diol **49** to *N*-tosyloxycarbamate **259**. Treatment of **259** with catalytic amount of $Cu(MeCN)_4PF_6$ in the presence of 3-pentanol triggered an intramolecular aziridination, followed by opening of the strained *N*-acylaziridine ring by 3-pentanol to afford cyclic carbamate **260**, which was transformed in three additional steps [hydrolysis of the carbamate, *N*-acylation, and removal of the *p*-methoxybenzyl (PMB) group] into Fang's intermediate **256**.

Hudlicky's group reported two syntheses[113] of oseltamivir starting from ethyl benzoate (Figure 16), which is oxidized by *E. coli* JM109 (pDTG601A) to diol **261**. This step reliably delivers ca. 1 g/L of **261** on 15-L fermentor scale. The starting material provides nine of the 17 carbon atoms that are present in

Scheme 32[a]



[a] Reagents: (i): trimethylsilyl trifluoromethanesulfonate (TMSOTf), CH_2Cl_2, −15 °C, 30 min, 92%; (ii) PPh_3, THF, 24 h, then H_2O, 4 h; (iii) Dowex (H^+ form), MeOH, then 2 M aqueous NH_3, 80% from **251** to **252**, 51% from **253** to **254**; (iv) $RuCl_3$, $NaIO_4$, AcOEt, MeCN, H_2O, 0 °C, 91%.

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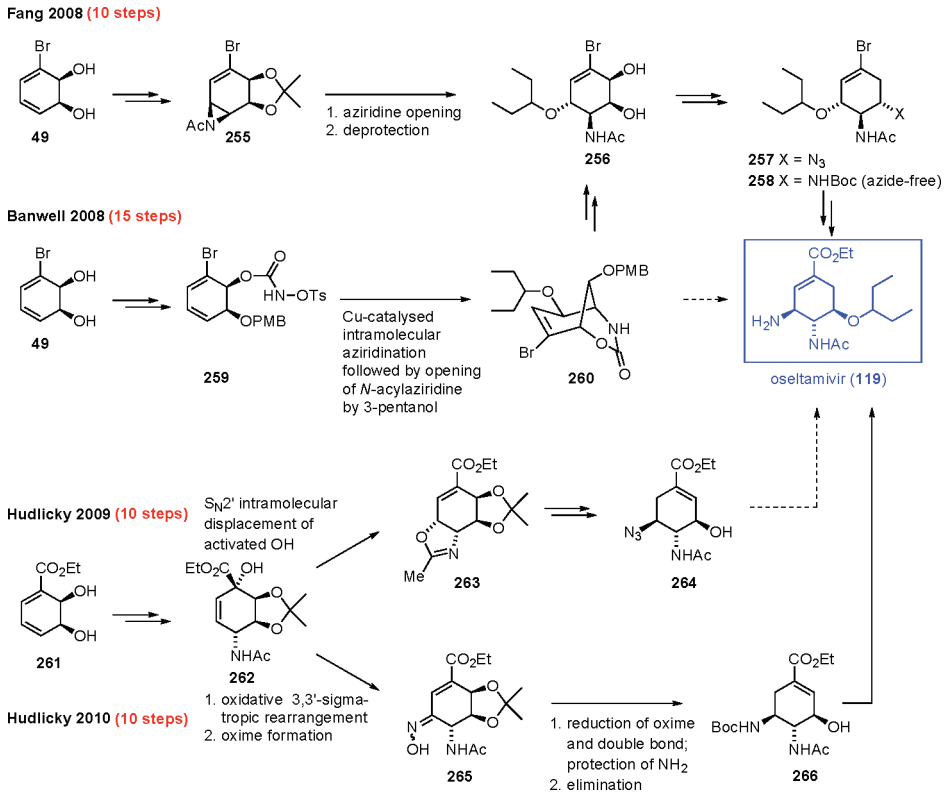

Figure 16. Chemoenzymatic syntheses of oseltamivir.

the final product. Diol **261** was transformed to conduramine A-1 derivative **262** by a hetero-Diels–Alder cycloaddition followed by the reduction of the intermediate oxazine. The first-generation synthesis continued with an intramolecular S_N2' displacement of activated hydroxyl group to produce oxazoline **263**, which then provided azido alcohol **264**, an intermediate that was earlier transformed to **119** by Fang.[114]

The key step of the second-generation approach was the Dauben–Michno oxidative transposition of allylic alcohol in **262**, followed by in situ oxime formation to **265**. Reduction of the oxime and the double bond, protection of the amino group, and elimination of the C-2 ether moiety then provided the allylic alcohol **266**. The introduction of the pentan-3-yl moiety led to **119** and was achieved using the procedures of either Shibasaki[115] or Corey.[116] This second-generation procedure provided the penultimate intermediate **266** in 10 chemical steps reduced to just five operations without the use of chromatography and with a 52% overall yield of **266** from diol **261**.

5. SYNTHESIS VIA ENZYMATIC RESOLUTION OF RACEMIC MIXTURES AND DESYMMETRIZATION OF MESO COMPOUNDS

An interesting early example of a chemoenzymatic synthesis related to cyclitols was shown at the beginning of this review. The oxidation of *myo*-inositol (**4**) with *A. suboxydans* (Schemes 1 and 3) afforded *myo*-inosose-2 (**17**), a meso compound that was used in the synthesis of monophosphate **31**.[26] The regioselective oxidation provides for the controlled introduction of the phosphate group at the later stage of the synthesis and can also be regarded as a protection at that position. Some other cyclitols, however, when oxidized with *A. suboxydans*, provide optically active products, and such cases are examples of oxidative desymmetrization. For example, *epi*-inositol (**2**) is oxidized to an optically active (−)-*epi*-inosose-2. Optically active D- and L-*chiro*-inositols are oxidized to C_2 symmetrical diketones.[117] Indeed, desymmetrization of meso compounds and kinetic resolution of racemic mixtures provide viable alternatives to microbial dihydroxylation of arenes in approaches to optically pure cyclitols.[118]

In the context of the synthesis of cyclitols, desymmetrization and resolution often blend. The syntheses from *myo*-inositol (meso compound), for example, often start with regioselective protection that produces racemic mixtures, which are subsequently resolved.[119] Lipases, a subclass of hydrolyses, are the most frequently used enzymes to achieve either resolution or desymmetrization. They catalyze the resolution of both esters (by hydrolysis) and of alcohols (by acylation). Typically, they are used early in the synthetic sequence to provide enantiomericaly enriched starting materials. Many lipases are commercially available; they do not require additional cofactors; and, if desirable, the reaction can be carried out in organic solvents.[120] Unlike fermentation, which requires special equipment, lipase-catalyzed reactions are easily carried out in conventional glassware. This aspect alone makes their use attractive to synthetic organic chemists.

Ohno and co-workers[121] reported the first enantioselective synthesis of fortamine (**274**), a 1,4-diaminocyclictol moiety of antibiotics fortimicin A and B, using a desymmetrization of *meso*-**267** by pig liver esterase (PLE) to prepare optically pure acid (+)-**268** (>96% *ee*) (Scheme 33). The necessity of the double bond in *meso*-**267** was mentioned as a requirement to reach high optical purity, as the corresponding saturated substrate provided only 75% *ee* when subjected to PLE.[122] The optically pure carboxylic acid **268** was protected and transformed to carbamate **269** by Curtius rearrangement as the key step. Hydrolysis of

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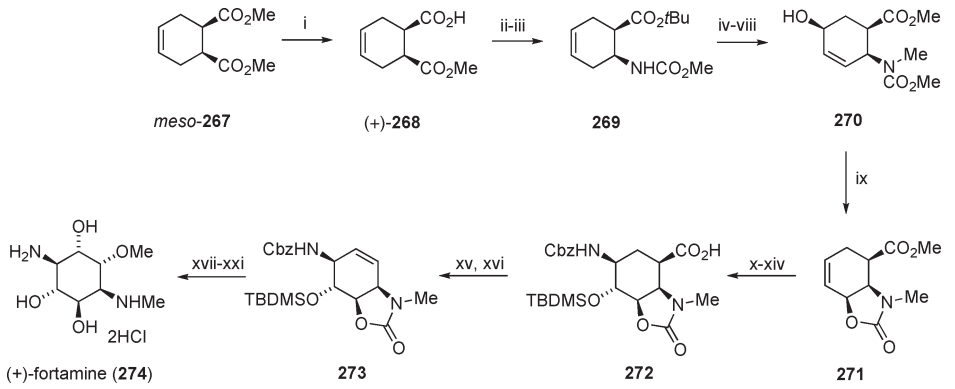
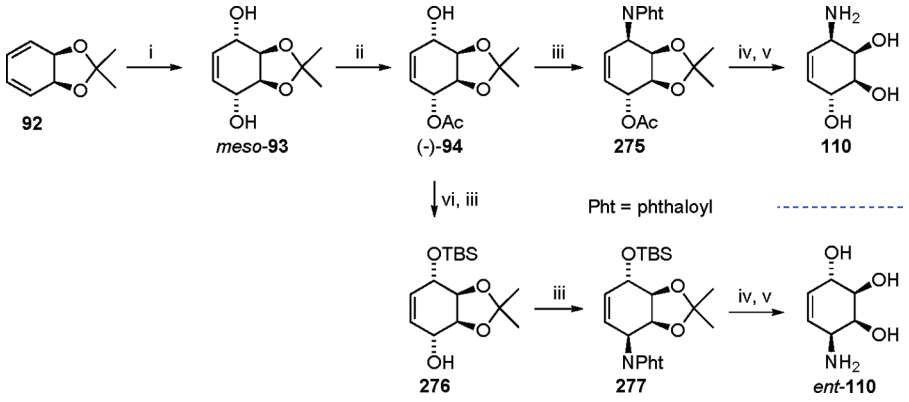
Scheme 33[a]



[a] Reagents: (i) pig liver esterase, 98% (96% *ee*); (ii) isobutylene; NaOH, 85%; (iii) ethyl chloroformate, Et_3N; NaN_3, heat; MeOH, *p*-TsOH, 92%; (iv) TFA, 0 °C, quantitative; (v) I_2, KI, $NaHCO_3$, H_2O, CH_2Cl_2, 98%; (vi) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), benzene, heat, 94%; (vii) MeI, Ag_2O, 95%; (viii) MeONa, MeOH, 0 °C, 99%; (ix) Ms_2O, Et_3N, 1,2-dichloroethane (DCE), 0 °C → 25 °C, 96%; (x) *m*-CPBA, CH_2Cl_2, 92%; (xi) $TMSN_3$, $ZnCl_2$, CH_2Cl_2, reflux; HCl/MeOH, 99%; (xii) H_2, Pd/C, MeOH; benzyl chloroformate (CbzCl), $NaHCO_3$, dioxane, H_2O, 89%; (xiii) TBSCl, imidazole, DMF, 92%; (xiv) NaOH, MeOH, H_2O, quantitative; (xv) Barton's reagent (1-oxa-2-oxo-3-thiaindolizinium chloride), DMAP, CCl_3Br, benzene, THF, reflux, 71%; (xvi) DBU, toluene, reflux, 72%; (xvii) NaH, benzyl bromide (BnBr), DMF, 0 °C, 96%; (xviii) OsO_4, trimethylamine *N*-oxide, *t*-BuOH, H_2O, 50 °C, quantitative; (xix) NaH, DMF, 0 °C; then MeI, DMF, 0 °C, 95%; (xx) tetra-*n*-butylammonium fluoride (*n*-Bu_4NF), THF, quantitative; (xxi) 6 M HCl, reflux; H_2, Pd/C, MeOH, 98%.

Scheme 34[a]



[a] Reagents: (i) (a) $^1O_2$; (b) thiourea; (ii) *P. cepacia* lipase (Amano P-30), isopropenyl acetate, 55 °C; (iii) phthalimide, DEAD, PPh_3, toluene, 0 °C, 1 h, 61% from **94** to **275**, 67% for **277**; (iv) *p*-TsOH, MeOH, reflux; (v) 40% aqueous methylamine ($MeNH_2$), 80% from **275** to **110**, quantitative from **277** to *ent*-**110**; (vi) TBSCl, imidazole, DMF, 98%.

the *t*-butyl ester group in **269** followed by iodolactonization and further manipulations provided allylic alcohol **270**. Mesylation of **270** triggered an intramolecular S_N2' displacement to form the cyclic carbamate **271**, which was transformed in several steps to acid **272**. Decarboxylation of **272** using Barton's reagent (1-oxa-2-oxo-3-thiaindolizinium chloride) followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in boiling toluene afforded **273**. Diastereoselective dihydroxylation of **273** followed by methylation and global deprotection gave (+)-fortamine hydrochloride **274**. Liu and Vandewalle[123] reported a synthesis of (+)-fortamine based on a lipase-catalyzed desymmetrization of 2-cyclohexene-*cis*-1,4-diol as one of the key steps. The same group also exploited such desymmetrization in the enantioselective syntheses of several conduritols,[124] nonnatural methyl shikimate,[125] and pseudosugars.[126] Another example of desymmetrization in the synthesis of natural products was the formal synthesis of quinic acid (**12**) by Sakai and co-workers,[127] who used desymmetrization of *meso*-1,3-*cis*, 3,5-*cis*-1,3-diacetoxy-5-benzyloxycyclohexane as the key step.

Johnson and co-workers used acetonide **92** (Scheme 34) for the synthesis of both enantiomers of conduramine C-1 **110** and *ent*-**110**.[73] Reaction of **92** with singlet oxygen followed by reduction with thiourea gave *meso*-2,3-di-*O*-isopropylidene conduritol A (**93**), which was subjected to desymmetrization with *Pseudomonas cepacia* lipase (Amano P-30) in the presence of isopropenyl acetate to furnish the monoacateate (−)-**94**, previously used by Johnson for the synthesis of both enantiomers of conduritol C (see Scheme 14). Reaction of **94** with phthalimide under Mitsunobu conditions afforded **275**, which was fully deprotected to provide (−)-conduramine C-1 (**110**). Its enantiomer was prepared by protection of **94** by silylation of the hydroxy group, deacetylation to **276**, and the analogous amination protocol to furnish (+)-conduramine C-1 (*ent*-**110**).

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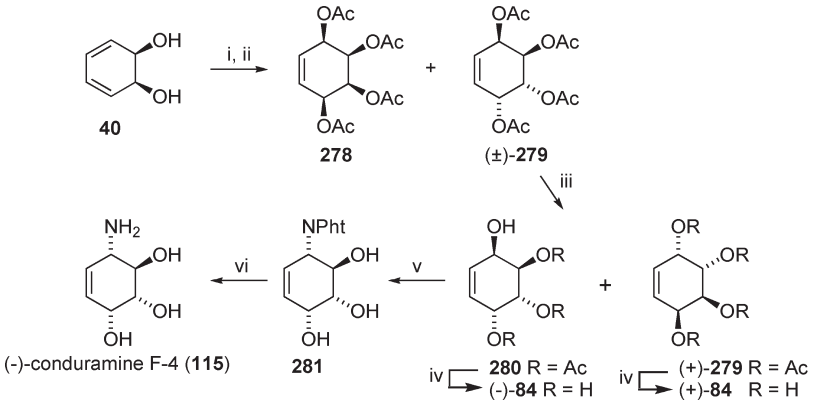
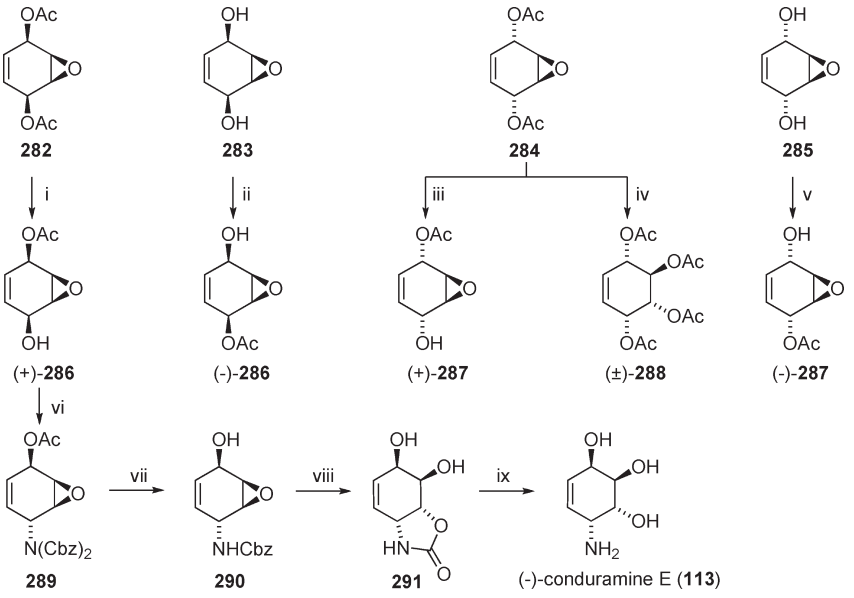
Scheme 35[a]



[a] Reagents: (i) OsO_4, NMO, CH_2Cl_2, 0 °C; (ii) Ac_2O, py; (iii) Lypozyme IM, *n*-BuOH, methyl *tert*-butyl ether; (iv) aqueous NH_3; (v) phthalimide, DEAD, PPh_3; (vi) aqueous $MeNH_2$.

Scheme 36[a]



[a] Reagents: (i) *n*-hexane, 0.2 M phosphate buffer (pH 7), lipase SP 523 (4% w/w), 80−90%, (94% *ee*); (ii) vinylacetate, Lipozyme IM (5% w/w), methyl *tert*-butyl ether, 60% (>95% *ee*); (iii) *n*-hexane, phosphate buffer (pH 7), Amano lipase AY30 (10% w/w), 5 h, 90% (60% *ee*); (iv) phosphate buffer (pH 7), 3 days; then Ac_2O, Et_3N, DMAP, 70%; (v) vinylacetate, Amano lipase AY30 (10% w/w), methyl *tert*-butyl ether, 13 days, 35% (63% *ee*); (vi) NH_3, PPh_3, DEAD, THF, 80−92%; (vii) NH_3, MeOH (quantitative); (viii) AcOH, H_2O, 110 °C, 92%; (ix) $Ba(OH)_2$, 50 °C, 86%.

Nicolosi and co-workers[128] reported the synthesis of several cyclitols from *meso*-diol **40** (Scheme 35). Dihydroxylation of **40** catalyzed by OsO_4 in the presence of *N*-methylmorpholine-*N*-oxide followed by acetylation afforded a mixture of conduritol D tetraacetate (**278**) and racemic conduritol E tetraacetate (**279**). The racemic **279** was subjected to alcoholysis with *n*-butanol catalyzed by an immobilized lipase from *Mucor miehei* (Lypozyme IM) to obtain alcohol **280** and unreacted tetraacetate (+)-**279**. After 5 h, the conversion reached 22%, and upon longer incubation, the concentration of **280** did not increase, and products of further deacetylation were formed. After 48 h, the conversion reached 50%, and purification of the reaction mixture afforded tetraacetate (+)-**279** in 48% yield (>95% *ee*), which was hydrolyzed to (+)-conduritol E (+)-**84**. The polar residues were hydrolyzed to furnish (−)-conduritol E (−)-**84**. The alcohol **280** was also converted to (−)-conduramine F-4 (−)-**115** by amination under Mitsunobu conditions followed by deprotection.

Prinzbach and co-workers[129] reported desymmetrization of meso-configured epoxy cyclohexene diols **282**−**285** and demonstrated their utility with the synthesis of (−)-conduramine E **113** (Scheme 36). Optically pure monoacetate (+)-**286**, obtained by enzymatic resolution of diacetate **282**, was subjected to Mitsunobu conditions to install the bis-protected amine in the allylic position, providing **289**. The acetate and a single carbobenzyloxy (Cbz) group were hydrolyzed to yield the 1,4-allylic amino alcohol **290**, which was subsequently treated under aqueous acidic conditions to effect the epoxide opening and formation of urethane **291**. Treatment of **291** under mild hydrolytic conditions provided (−)-conduramine E (**113**).

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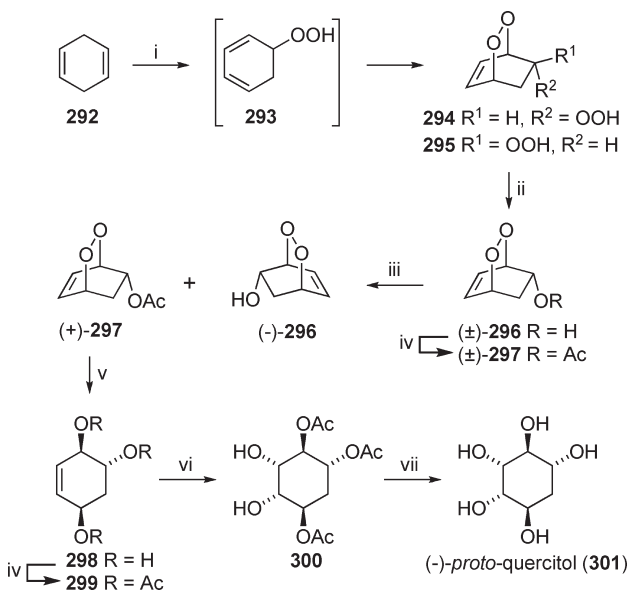
A synthesis of both enantiomers of *proto*-quercitol utilizing a remarkable lipase resolution of a hydroxyl group in the presence of an endoperoxide functionality was reported by Balci and co-workers (Scheme 37).[130] Tetraphenylporphyrin-sensitized photooxygenation of cyclohexa-1,4-diene **292** afforded a mixture of bicyclic peroxides (±)-**294** (63%) and (±)-**295** (7%) through the intermediate ene reaction product **293**. The reduction of the hydroperoxide group of (±)-**294** with dimethyl sulfide in the presence Ti(IV) catalyst afforded (±)-**296**, which was resolved to (+)-**297** and (−)-**296** by enzymatic esterification with vinyl acetate, catalyzed by commercially available *Candida cylindracea* lipase. The alternative resolution, namely, a hydrolysis of ester (±)-**297** at pH 7, led to either decomposition (with *C. cylindracea* lipase and pig liver esterase), likely a consequence of the presence of the sensitive endoperoxide group, or no reaction (with porcine pancreatic lipase and horse liver esterase). Cleavage of the endoperoxide bridge of (+)-**297** with thiourea followed by acetylation afforded the triacetate **299**. Dihydroxylation of the double bond in **299** with osmium tetroxide provided **300**, which was then deprotected to (−)-*proto*-quercitol (**301**). In the same fashion, (−)-**296** was converted to (+)-*proto*-quercitol (not depicted).

Scheme 37[a]

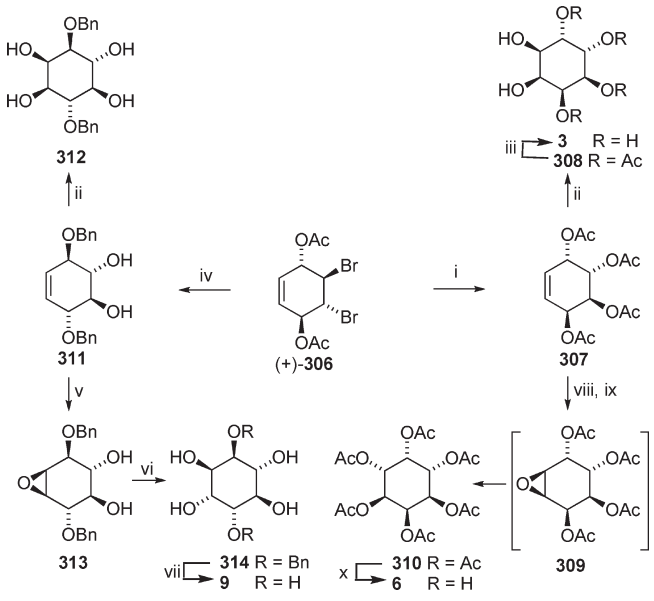


[a] Reagents: (i) $^1O_2$, tetraphenylporphyrine, CH_2Cl_2, 25 °C, 48 h, 63% of **294**, 7% of **295**; (ii) **294**, dimethyl sulfide (Me_2S), $Ti(O^iPr)_4$, CH_2Cl_2, 5 °C, 95% of (±)-**296**; (iii) vinyl acetate, *C. cylindracea* lipase, 20 °C, 38 h, 47% of (−)-**299** (91% *ee*), 42% of (+)-**298** (72% *ee*); (iv) AcCl; (v) thiourea; (vi) **299**, OsO_4, NMO; (vii) NH_3, MeOH.

Enantiopure C_2-symmetric dibromocyclohexenediol **305** and its diacetate **306** served as starting materials for the synthesis of numerous cyclitols, as outlined in Scheme 38. These versatile intermediates are readily available by enzymatic resolution of racemic diacetate **304**, prepared in several steps from benzoquinone, with pig pancreatic lipase in a phosphate buffer. The diol (+)-**305** and diacetate (+)-**306** are easily separated from each other, owing to their different solubilities in dichloromethane.[131]

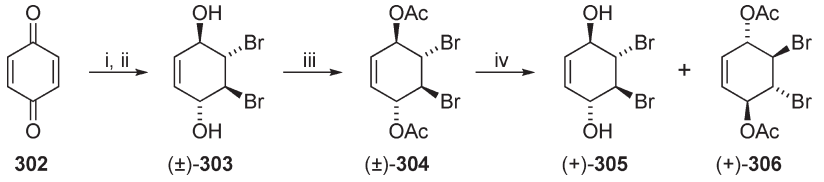
Further utilization of the C_2-symmetric diacetate (+)-**306** is shown in Scheme 39.[132] Substitution of bromides in (+)-**306** by sodium acetate led to conduritol E tetraacetate (+)-**307**. Dihydroxylation of (+)-**307** with ruthenium trichloride and sodium periodate led to (+)-**308** regardless of the direction of attack of the dihydroxylating agent. Deacetylation of **308** then gave *allo*-inositol **3**. If the tetraacetate (+)-**307** was treated with trifluoroperacetic acid, epoxide (+)-**309** was formed, which was hydrolyzed in situ and then acetylated to obtain **310**, whose hydrolysis afforded *neo*-inositol (**6**). The starting dibromide (+)-**306** was also converted to protected conduritol B (−)-**311** by a reaction with sodium benzylate in anhydrous THF. The reaction

Scheme 39[a]



[a] Reagents: (i) AcONa, AcOH, 10 days, 125 °C, 95%; (ii) $RuCl_3$, $NaIO_4$, MeCN, 82−90%; (iii) MeONa, MeOH, 83%; (iv) sodium benzoate (BnONa), BnOH, THF, 80%; (v) $(CF_3CO)_2O$, H_2O_2, CH_2Cl_2, Na_2CO_3, 71%; (vi) H_2SO_4, dioxane, H_2O, 80%; (vii) H_2, Pd/C, EtOH, H_2O, 99%; (viii) $(CF_3CO)_2O$, H_2O_2, CH_2Cl_2, $NaHCO_3$, 71%; (ix) Ac_2O, py, 83%; (x) MeONa, MeOH, then NaOH, H_2O, 99%.

Scheme 38[a]



[a] Reagents: (i) Br_2, $CHCl_3$, 0 °C, 98%; (ii) $NaBH_4$, Et_2O, −20 to 25 °C, 88%; (iii) Ac_2O, py, 68%; (iv) porcine pancreatic lipase, phosphate buffer (pH 7), 4 days, 38% of (+)-**305**, 38% of (+)-**306**.

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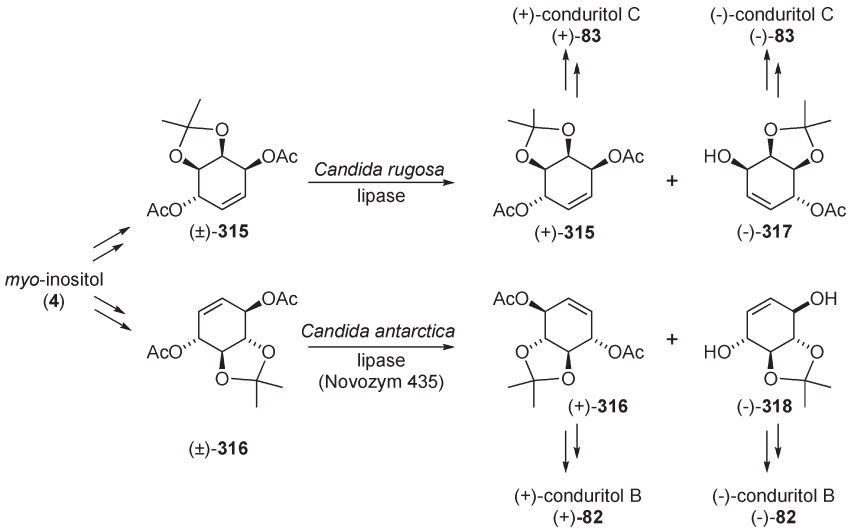
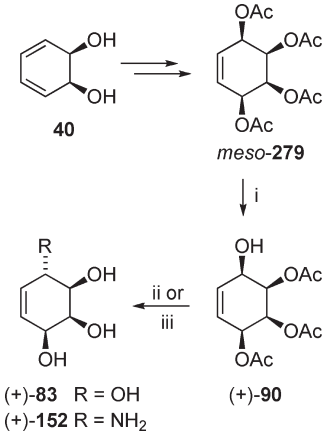


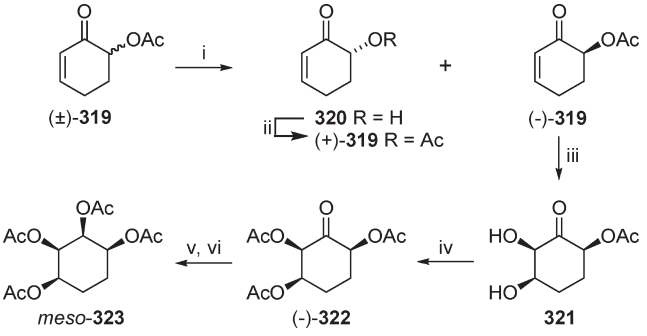
Figure 17. Resolution of racemic conduritol derivatives.

Scheme 40[a]



[a] Reagents: (i) porcine pancreatic lipase, *n*-BuOH, methyl *t*-butyl ether 40 °C, 60 h, 73% of **90** (>95% *ee*), 27% of **279**; (ii) (a) DEAD, PPh_3, BzOH, toluene; (b) K_2CO_3, MeOH, 75%, for two steps to **83**; (iii) (a) DEAD, PPh_3, phthalimide, toluene, then 40% aqueous $MeNH_2$, 80% of (+)-**152**.

Scheme 41[a]



[a] Reagents: (i) pig liver esterase, phosphate buffer (pH 7) 49% of (−)-**319** (97% *ee*), crude **320** was subjected to acetylation; (ii) AcCl, py, 44% of (+)-**319** from *rac*-**319** (92% *ee*); (iii) OsO_4, NMO, acetone, H_2O, −5 °C; (iv) AcCl, py, 85% from (−)-**319**; (v) $NaBH_4$, $CeCl_3.7\ H_2O$, MeOH, 82%; (vi) AcCl, py, 84%.

proceeds through intermediate epoxides that are opened by the alkoxides at the allylic positions. Dihydroxylation of **311** led to a protected inositol **312**, exhibiting the myo configuration. Epoxidation of (−)-**311** furnished (−)-**313** and the trans-diaxial opening of the epoxide in (−)-**313** gave (−)-**314**, which was fully deprotected to L-*chiro*-inositol (**9**). It should be noted that, for the synthesis of meso compounds such as **3** and **6**, one does not need enantiomericaly pure starting material, as racemates would give the same product. However, inositols such as **3** and **6** are usually not the synthetic targets on their own. More important are derivatives such as phosphates. These are often chiral; the optically pure intermediates, such as those shown in Schemes 38 and 39, are valuable building blocks for their synthesis. Such was the intention of Altenbach and co-workers, which they demonstrated on the synthesis of various *myo*-inositol phosphates through conduritol B derivatives, such as (−)-**311**.[133] The dibromides **305** and **306** were also used in the synthesis of several azido/amino and diazido/diamino-*myo*-inositols and their phosphates.[134]

All diastereoisomers of conduritols (**56**, **57**, **82**−**85**) and several stereoisomers of inositol (**2**−**7**, **9**) were prepared from *myo*-inositol through the racemic conduritol derivatives **315** and **316** (Figure 17).[135] Synthesis of conduritols B and C is shown in Figure 17. The resolution of **315** with *Candida rugosa* lipase afforded diacetate (+)-**315** in 49% yield (95% *ee*) and monoacetate (−)-**317** in 48% yield (95% *ee*). Deprotection of (+)-**315** and (−)-**317** afforded (+)- and (−)-conduritol C (**83**), respectively. In a similar fashion, (±)-**316** was resolved with immobilized lipase from *Candida antarctica* (Novozym 435) to diacetate (+)-**316** and diol (−)-**317** and then converted to conduritol B (**82**). The resolved (+)-**315** and (+)-**316** were also utilized as starting materials in a divergent synthesis of all optically active regioisomers of *myo*-inositol mono- and biphosphates.[136]

Another example of a conduritol being used as a synthetic intermediate is shown in Scheme 40. Desymmetrization of conduritol D tetraacetate **279** with porcine pancreatic lipase afforded triacetate (+)-**90** in 73% (>95% *ee*), which was

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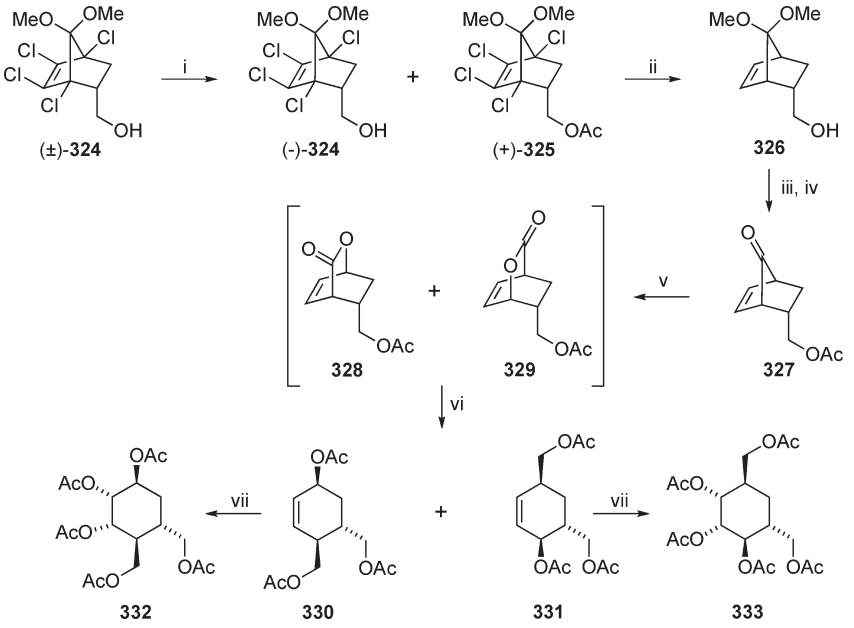
Scheme 42[a]



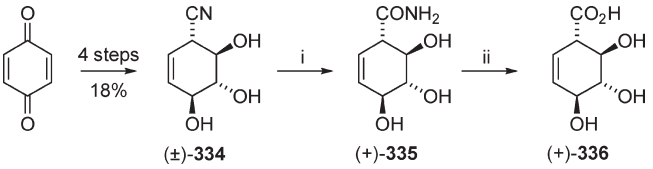
[a] Reagents: (i) *C. rugosa* lipase, vinyl acetate, 25 °C, 44% of (+)-**325** (94% *ee*), 54% of (−)-**324** (68% *ee*); (ii) (+)-**325**, Na/NH_3, −33 °C, 79%; (iii) Amberlyst-15, acetone, H_2O, 99%; (iv) AcCl, py, CH_2Cl_2, 98%; (v) *m*-CPBA, Na_2CO_3, CH_2Cl_2, 75% combined yield of **328** and **329**; (vi) (a) $LiAlH_4$, THF; (b) AcCl, py, CH_2Cl_2, 36% of **330**, 45% of **331**; (vii) (a) OsO_4, NMO; (b) Ac_2O, py, 70% of **332**, 65% of **333**.

converted to (+)-conduritol C (**83**) and (+)-conduramine C-4 (**152**) by Mitsunobu reaction and hydrolysis.[137]

The resolution of racemic α-acetoxy cyclohexenone **319** (Scheme 41) with pig liver esterase was the key step in the stereoselective synthesis of cyclitol derivative (−)-**322** and its enantiomer.[138] The resolution afforded (*R*)-6-hydroxy-2-cyclohexene-2-one (**320**), which was immediately acetylated to provide (+)-**319** in 44% (92% *ee*) and (*S*)-acetoxy-2-cyclohexene-1-one (−)-**319** in 49% (97% *ee*). The continuation of the synthesis is shown for only one enantiomer. Dihydroxylation of (−)-**319** occurred diastereoselectively, syn to the acetoxy group, to furnish **321**, which was acetylated in situ to triacetoxy derivative (−)-**322** in 42% overall yield from racemic **319**. Luche reduction of **322** and acetylation afforded *meso*-**323**.

Bicyclic adduct **324** (Scheme 42) was used as a convenient starting material in the synthesis of cyclitol derivatives **332** and **333**.[139] Racemic **324** is readily available by the Diels−Alder reaction between 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and allyl alcohol. Resolution of (±)-**324** was accomplished by treatment with *Candida rugosa* lipase in the presence of vinyl acetate, affording (+)-**325** in a yield of 44% (94% *ee*) and unreacted (−)-**324** in 54% yield (68% *ee*; reaction interrupted after 40% conversion). Lower levels of enantiomeric excess were observed using porcine pancreatic lipase or Novozyme 435. Reduction of (+)-**325** with sodium in liquid ammonia accompanied by deacetylation gave **326** in 79% yield. Treatment of **326** under acidic conditions afforded norbornene-7-one **327**, which was subjected to Baeyer−Villiger oxidation, providing a mixture of lactones **328** and **329**, which was not separated. The mixture of the lactones was reduced with $LiAlH_4$ and acetylated to furnish **330** and **331**, respectively. After separation, dihydroxylation, and acetylation, these compounds yielded **332** [14% overall from (+)-**325**] and **333** [17% overall from (+)-**325**], respectively.

Scheme 43[a]



[a] Reagents: (i) *R. erythropolis* A4 (nitrile hydratase), tris-(hydroxymethyl)aminomethane hydrochloride (Tris-HCl) buffer (pH 8), 35 °C; (ii) *R. erythropolis* A4 (amidase), Tris-HCl buffer (pH 8), 35 °C.

Most chemoenzymatic syntheses begin with a biotransformation step. An example of the use of enzymatic transformations at the end of a synthetic sequence is shown in Scheme 43. Racemic cyano-cyclitol (±)-**334** was first prepared in four steps from *p*-benzoquinone. The nitrile group was then hydrolyzed by whole cells of *Rhodococcus erythropolis* A4, an organism expressing a nitrile hydratase/amidase bienzymatic system.[140] After 24 h, when the biotransformation was complete, the reaction mixture consisted of ca. 40% of nitrile **334**, 20% of amide **335**, and 40% of acid **336**. Based on the maximum observed value of 40% *ee* of the recovered starting nitrile, the enantioselectivity of the hydrolysis of nitrile **334** to amide **335** was low. The second step, hydrolysis of the amide **335** to acid **336**, displayed much better selectivity with *ee* values of **335** and **336** in the range of 70−90%, depending on the reaction time.

Resolution of readily available *myo*-inositol derivatives affords important building blocks, particularly for the synthesis of inositol phosphates.[141] Two examples are shown in Figure 18. Racemic **337** was resolved by acetylation with acetic anhydride catalyzed by Lipase CES from *Pseudomonas* sp. to give (+)-**338** in 49% yield (98% *ee*) and (+)-**337** in 49% yield (100% *ee*).[141c]

dx.doi.org/10.1021/cr1004138 |*Chem. Rev.* 2011, 111, 4223–4258

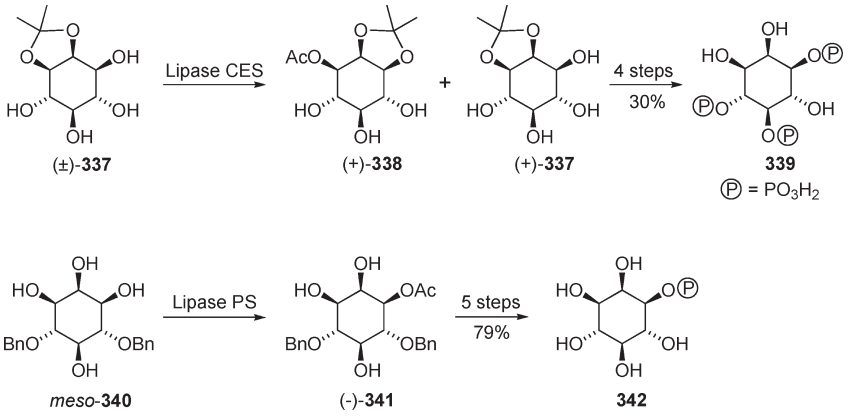
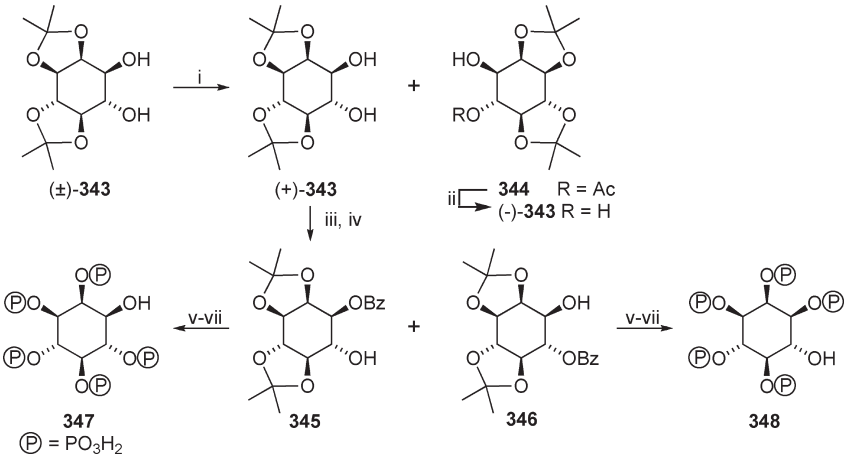


Figure 18. Resolution and desymmetrization of *myo*-inositol derivatives.

Scheme 44[a]



[a] Reagents: (i) *C. rugosa* lipase, Ac_2O, Et_2O, 25 °C, 46% of (+)-**343** (87% *ee*), 48% of (−)-**343**, (84% *ee*); (ii) LiOH, H_2O, MeOH, 0 °C; (iii) BzCl, py, 82% combined, **345**/**346** = 91:9; (iv) py, H_2O, 100 °C, **345**/**346** = 64:36; (v) 80% aqueous AcOH, 100 °C, 1 h; (vi) (a) $(EtO)_2P-Cl$, $^iPr_2NEt$, DMF; (b) H_2O_2, 50%; (vii) (a) TMSBr, CH_2Cl_2; (b) 1 M LiOH, 80 °C, 3 h; (c) Dowex (H^+ form) (d) NaOH, pH 10, quantitative.

The tetraol **337** was converted to D-*myo*-inositol 1,4,5-phosphate in four more steps and in an overall yield of 30% from (+)-**337** (13% from *myo*-inositol).

Benzyl-protected meso derivative **340** (Figure 18) was used in a multigram-scale preparation of D-*myo*-inositol-1-phosphate **342**.[141d] Desymmetrization of **340** with lipase PS from *Pseudomonas* sp. gave optically pure acetate (−)-**341** in 89% yield after recrystallization. The enzyme was recovered by filtration. The target phosphate **342** was obtained in five high-yielding steps in 79% yield from (−)-**341**.

Chung and co-workers reported a divergent synthesis of inositol phosphates. Racemic diol **343** (Scheme 44) was first prepared from *myo*-inositol and then resolved by acetylation catalyzed by *Candida rugosa* lipase to obtain unreacted diol (+)-**343** in 46% yield (87% *ee*) and the monoacetylated product **344** in 48% yield (87% *ee*). Hydrolysis of the acetate with lithium hydroxide in aqueous methanol afforded (−)-**343**. The optical purity of diols (+)-**343** and (−)-**343** was increased to 98% *ee* by recrystallization from hexane/chloroform with approximately 70% recovery. The diols (+)-**343** and (−)-**343** were the starting materials for the synthesis of all 32 optically active regioisomers of *myo*-inositol tris-, tetrakis-,[142] and pentakis-phosphates.[143]

The synthesis of the pentakis-phosphates is also shown in Scheme 44. The diol (+)-**343** was benzoylated to give **345** and **346** in a 91:9 ratio and in 82% combined yield. Pyridine-mediated acyl migration shifted the **345**/**346** ratio to 64:36. Deprotection of the isopropylidene groups, treatment with diethyl chlorophosphite and Hünig's base in DMF, oxidation with hydrogen peroxide, and global deprotection gave **347** and **348**. Enantiomers of **347** and **348** were prepared in the same way from (−)-**343**.

In the context of the synthesis of inositol phosphates, it is appropriate to mention the way nature incorporates phosphate groups into molecules with multiple reaction sites such as inositols. The enzymes are kinases for selective phosphorylations and phosphatases for selective dephosphorylations. In contrast to the efficiency of these enzymes in vivo is the fact that these enzymes are rarely used in laboratory practice. The reason might be that, in nature, several specific enzymes are required to synthesize the target inositol phosphate. Mimicking such an approach in the laboratory would require the knowledge of reactivity of many kinases/hydrolases, and these enzymes would also have to be commercially available. None of these conditions are yet fully met. Currently, a combination of

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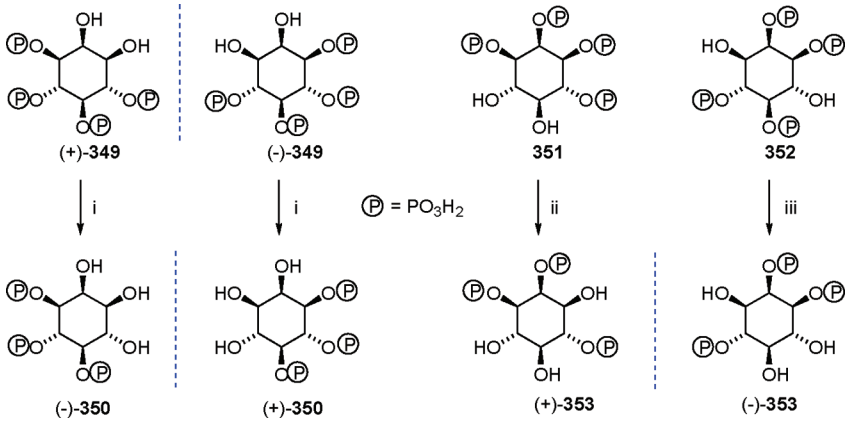
Scheme 45[a]



[a] Reagents: (i) InsP5/InsP4-phosphohydrolase from *D. discoideum*, 1.5 h, 25 °C, 70−80% in both cases; (ii) phytase from *D. discoideum*, pH = 5.1, 45%; (iii) 5-phosphatase from *D. discoideum*, pH 7, 95%.

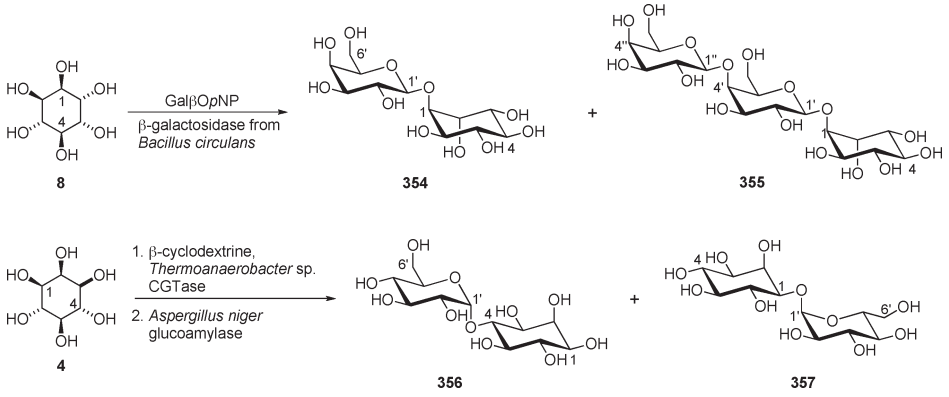


Figure 19. Synthesis of glycosylated inositols.

traditional synthesis and enzymatic techniques seems to be the best option for the synthesis of inositol phosphates.

An example of exploitation of the high selectivity of hydrolyses was reported by Vogel and co-workers. In the course of their investigation of inositol phosphates, they isolated several hydrolases from *Dictyostelium discoideum* converting inositol tetra- and pentaphosphates into triphosphates. InsP5-/InsP4-phosphohydrolase exhibits high regioselectivity and low stereoselectivity; that is, it converts the enantiomericaly pure substrates at nearly equal rates. Conversion of enantiomeric tetraphosphates (+)-**349** and (−)-**349** (Scheme 45) afforded enantiomeric triphoshates (−)-**350** and (+)-**350**, respectively.[131b]

A different situation is the hydrolysis of regioisomers **351** and **352**. Hydrolysis of tetraphosphate **352** with enzyme from Ins-(1,4,5)P_3 5-phosphatase family from *D. discoideum* led to (−)-**353**, whereas its enantiomer (+)-**353** was isolated upon hydrolysis of **351** with phytase-type enzyme from the same organism.[144] Although these examples illustrate the power of this approach, they also show its current limitation. First, to arrive, for example, at triphosphate (−)-**350**, one first needs to prepare stereoselectively tetraphosphate (+)-**349**. Second, one needs a specific hydrolase to effect the transformation of (+)-**349** to (−)-**350**. Short, divergent, and selective synthesis of inositol phosphates remains a challenging task.

Glycosylated inositols have been proposed as putative mediators of insulin that are released in response to insulin-receptor binding, and their deficiency might thus play role in the etiology of type II diabetes. Rapid access to this class of compounds was demonstrated with glycosyl transfer from cellobiose or lactose to *myo*-inositol with enzyme extracts or growing cultures of *Sporobolomyces singularis*.[145] More recently, a regioselective galactosylation of D-*chiro*-inositol (**8**) and D-pinitol (**48**), catalyzed by *β*-galactosidase from *Bacillus circulans*, was reported.[146] For example, galactosylation of **8** (Figure 19) with *p*-nitrophenyl-*β*-D-galactopyranoside (Gal*β*O*p*NP) as the glycosyl donor in sodium acetate buffer (pH 5.0) at 50 °C afforded monogalactosylated **354** (43%) and digalactosylated **355** (9%). A detailed study on the galactosylation of D- and L-*chiro*-inositols, D-pinitol, and *myo*-inositol and their derivatives with *β*-galactosidase from *Thermoanaerobacter* sp. strain TP6-B1 was also reported.[147] In a search of compounds with potential anti-inflamatory activity, *myo*-inositol (**4**, Figure 19) was glucosylated with *β*-cyclodextrine by reaction catalyzed by cyclodextrine glucosyl transferase (CGTase) in a phosphate buffer at pH 6.[148] The resulting polyglucosylated products were selectively hydrolyzed with glucoamylase from *Aspergillus niger* to obtain 4-glucosylated inositol **356** and 1-glucosylated inositol **357** (separated by high-performance liquid chromatography) in a combined yield of 32% (**356**/**357** = 73:27).

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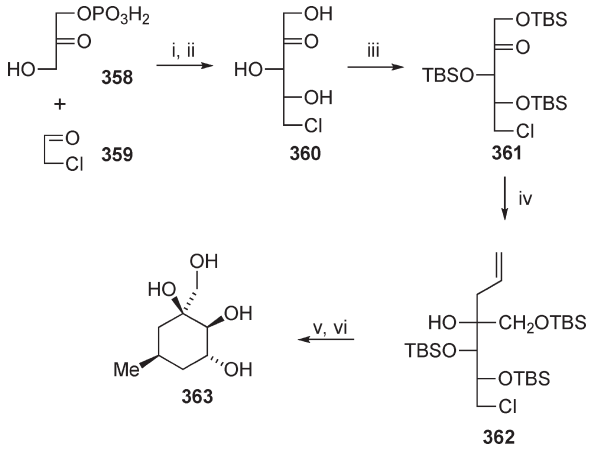
6. SYNTHESIS VIA ENZYME-CATALYZED CARBON−CARBON BOND FORMATION

Enzymes also catalyze carbon−carbon bond formation, and numerous examples of such processes have been documented. Squalene cyclase and various oxynitrilases, transketolases, and aldolases have all been exploited in biocatalytic syntheses of chiral building blocks.[149]

Schmid and Whitesides reported a chemoenzymatic approach to cyclitols using rabbit muscle aldolase (RAMA; EC 4.1.2.13), an enzyme that catalyzes aldol condensation between dihydroxyacetone phosphate (DHAP) and aldehydes and gives products with D-*threo* configuration (3*S*, 4*R* stereochemistry).[150] The reaction between dihydroxyacetonephosphate (**358**) and chloroacetaldehyde (**359**), catalyzed by RAMA, followed by in situ dephosphorylation with acid phosphatase (AP; EC 3.1.3.2) afforded exclusively 5-deoxy-5-chloro-*threo*-pentulose (**360**) (Scheme 46). Silylation of **360** led to **361**, which was treated with allylmagnesium bromide to afford alditol **362**, whose radical cyclization with Bu_3SnH/AIBN followed by deprotection gave cyclitol **363**.

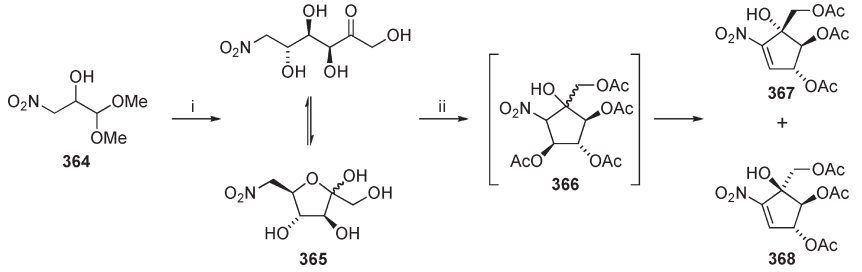
This approach was expanded by Wong and co-workers,[151] who reported tandem enzymatic-aldol and intramolecular nitroaldol reactions (Scheme 47). The dimethyl acetal **364**, product of a nitroaldol reaction between nitromethane and glyoxal dimethylacetal, was hydrolyzed under acidic conditions. The resulting crude aldehyde was subjected to aldolization with DHAP catalyzed by rabbit muscle fructose diphosphate (FDP) aldolase. After the conversion of DHAP reached >95%, the pH was adjusted to 4.8, and the mixture was treated with sweet potato acid phosphatase to obtain 6-nitrofructose **365** as the major product. Treatment of **365** with acetic anhydride (Ac_2O) in presence of boron trifluoride etherate ($BF_3 \cdot OEt_2$) triggered an intramolecular nitroaldol condensation to form **366**, which underwent elimination to produce a 1:1 mixture of nitrocyclitols **367** and **368** in 51% combined yield from **364**.

Scheme 46[a]



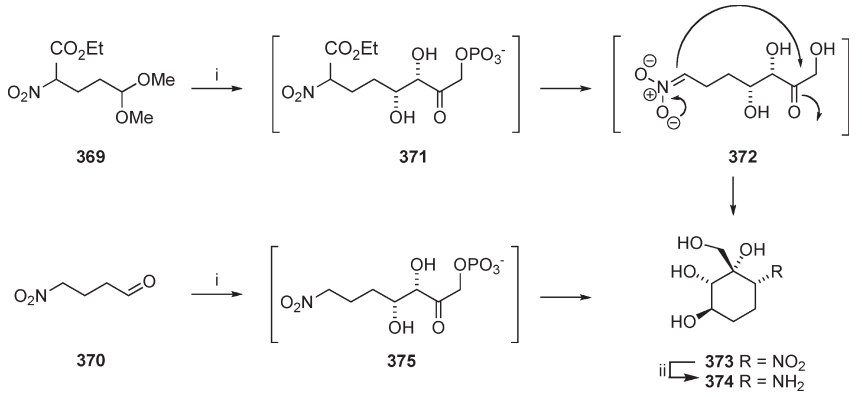
[a] Reagents: (i) rabbit muscle aldolase (RAMA; EC 4.1.2.13); (ii) acid phosphatase (AP; EC 3.1.3.2), 50%; (iii) TBSOTf, Et_3N, 67%; (iv) allylmagnesium bromide, Et_2O, 79%; (v) Bu_3SnH, AIBN, 75%; (vi) TBAF, 96%.

Scheme 47[a]



[a] Reagents: (i) (a) aqueous HCl, pH 1, 70 °C, 6 h; (b) dihydroxyacetone phosphate (DHAP), rabit muscle FDP aldolase, pH 5.5, 24 °C, 13 h; (c) sweet potato acid phosphatase, pH 4.7, 37 °C, 12 h; (ii) Ac_2O, $BF_3 \cdot OEt_2$, 51% combined yield of **367** and **368** (1:1).

Scheme 48[a]



[a] Reagents: (i) (a) DHAP, rabbit muscle aldolase, pH 7; (b) phytase, pH 3.9, 30 °C, 60% from **369**, 69% from **370**. (ii) H_2, PtO_2, MeOH, AcOH, 80%.

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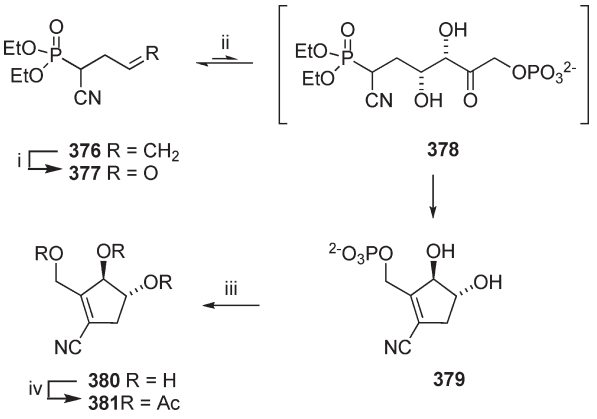
An analogous approach was used for the synthesis of nitrocyclitol **373** (Scheme 48).[152] Treating either **369** or **370** with dihydroxyacetone phosphate in the presence of rabbit muscle aldolase, followed by hydrolysis of the phosphate group by phytase, afforded **373** in 60% yield from **369** and in 69% yield from **370**. The reaction sequence from **369** likely involves a retro-Claisen-type step to generate the acy form of the nitro group in **372**, which then cyclizes to **373**. Reduction of the nitro group in **373** was effected by catalytic hydrogenation and provided aminocyclitol **374** in 80% yield.

Another modification was reported by Gijsen and Wong,[153] who synthesized triol **380** (Scheme 49) by tandem enzymatic-aldol and intramolecular Horner−Wadsworth−Emmons reactions as key steps. Although **380** is not a cyclitol according to the strict definition, the synthesis is shown to demonstrate the flexibility of this approach. The starting phosphonate **376**, readily available from allylbromide and diethyl cyanomethyl-phosphonate, was first subjected to ozonolysis followed by reductive workup to obtain aldehyde **377**. The crude **377** was treated in presence of rabbit muscle FDP aldolase and DHAP at pH 6.0−6.8, and after the DHAP had been consumed (20 h), the pH was adjusted to 4.8, and the mixture was treated with sweet potato acid phosphatase to cleave the phosphate group. The isolated crude triol **380** was acetylated to make the purification easier, and **381** was obtained in 71% yield from **376**. An NMR study showed that the intramolecular Horner−Wadsworth−Emmons reaction took place during the incubation with FDP aldolase and not during workup.

Scheme 49[a]



[a] Reagents: (i) (a) O_3, −78 °C; (b) Me_2S, −78 to 0 °C; (ii) dihydroxyacetone phosphate (DHAP), rabbit mucle FDP aldolase, pH 6.1−6.8, 23 °C, 20 h; (iii) sweet potato acid phosphatase, pH 4.8, 15 h; (iv) Ac_2O, py, 71% from **376**.

7. CONCLUSIONS AND FUTURE PROSPECTS

This review has provided a survey of the syntheses of cyclitols and their derivatives by methods that incorporate enzymatic transformations. The two major strategies involve either the use of enzymatically derived cyclohexadiene-*cis*-1,2-diols as starting materials for the synthesis of polyhydroxylated compounds or the use of enzymes to effect resolution, desymmetrization, and carbon−carbon bond formation.

As the field of cyclitol synthesis has been saturated by the implementation of one or the other method, it is not likely that major new advances for the synthesis of the known targets will materialize in the near future. More important than the preparation of specific targets, however, is the impact that biocatalytic methods of synthesis impart on further development of thought aimed at more sophisticated applications of either cyclitols themselves or the enzyme-based methods.

Two examples of extrapolation to larger projects are presented here as a conclusion to the overview. The first example evolved naturally from the general synthesis of inositols from cyclohexadiene-*cis*-1,2-diols. The D-*chiro*-inositol-based polymer **382** was prepared by Grubbs metathesis in several steps from diol **49** (Figure 20).[154] Similarly, the homogeneous tetramer **383**, having the L-*chiro*-inositol configuration, was prepared by iterative

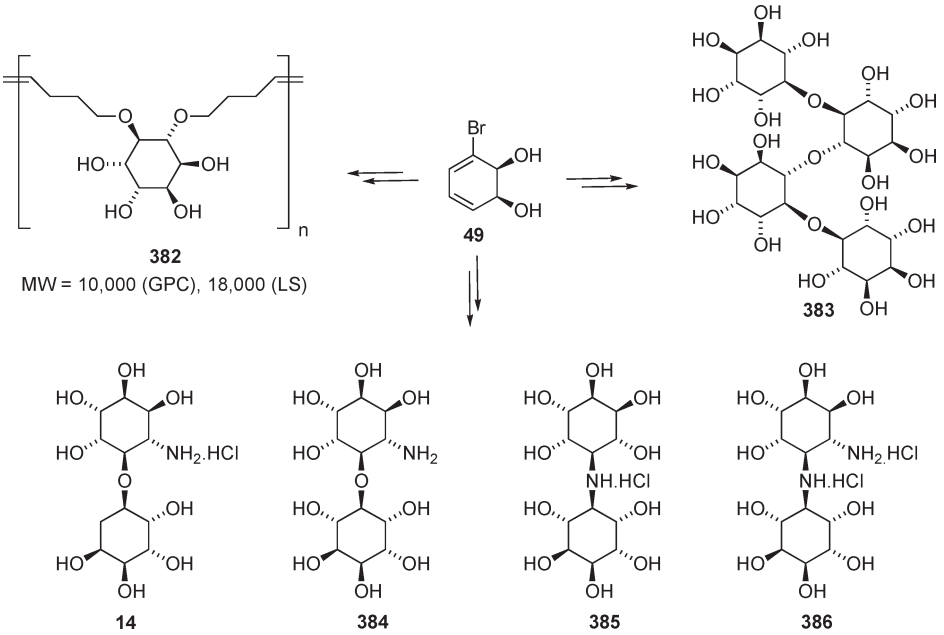


Figure 20. Synthesis of inositol-based conjugates, oligomers, and polymers.

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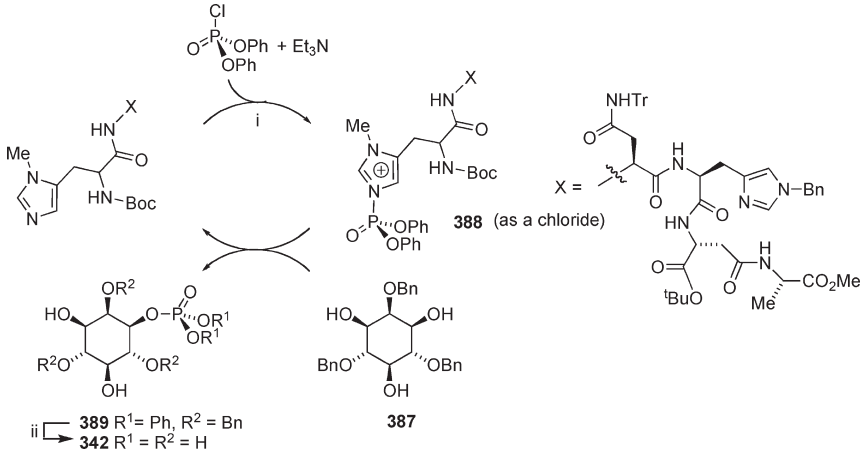
Scheme 50[a]



[a] Reagents: (i) **387**, **388** (0.02 equiv), diphenylchlorophosphate (1.6 equiv), Et_3N (1.7 equiv), toluene, 0 °C, 68%; (ii) Li, NH_3, THF, 96%.

coupling of intermediates derived from diol **49**.[7,155] Conjugates such as **14** and **384**−**386** have also been synthesized from **49**. The lower-molecular-weight conjugates have shown antiglycosidic properties, whereas the oligomers and polymers derived from the optically pure diols such as **49** might find applications in the design of templates for asymmetric synthesis and the production of materials for chiral separation, respectively.

These developments could not have materialized were it not for the simpler applications of cyclohexadiene-*cis*-1,2-diols to the synthesis of cyclitols, starting with the seminal contributions of the ICI and Ley groups in 1983 and 1987, respectively. More sophisticated applications stemming from the use of cyclohexadiene-*cis*-1,2-diols (now commercially available) will no doubt be reported in the near future.

The following example illustrates how biocatalysis can influence thinking about reaction mechanisms and applications to synthesis. It is not a chemoenzymatic synthesis such as the ones discussed above, but it demonstrates well how understanding of the action of enzymes might lead to exciting synthetic ventures.

Inspired by the mechanism of action of histidine kinases,[156] Sculimbrene and Miller developed a catalylic asymmetric phosphorylation using a low-molecular-weight peptide-based kinase mimic (Scheme 50).[157] Phosphorylation of **387** in the presence of diphenylchlorophosphate and triethylamine using 2 mol % of pentapeptide **388** as the catalyst led to **389** in 68% yield and >98% *ee*. Global deprotection with lithium in ammonia afforded *myo*-inositol-1-phosphate **342** in 98% yield. The synthesis reliably delivers >0.5 g of **342** starting from 1 g of *myo*-inositol.

The synthesis of inositol phosphate **342** by the method described above clearly demonstrates how the knowledge of enzyme mechanisms can lead to the development of artificial enzyme mimics. Similarly, the preparation of the inositol conjugates shown in Figure 20 would not have materialized without the many preceding projects in the cyclitol monomer synthesis. We hope that the material presented in this review will provide synthetic organic chemists with the motivation and inspiration not only to use biological methods but also to invent new and exciting applications based on cyclitols.[158]

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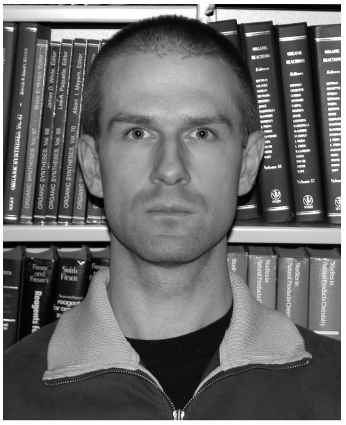
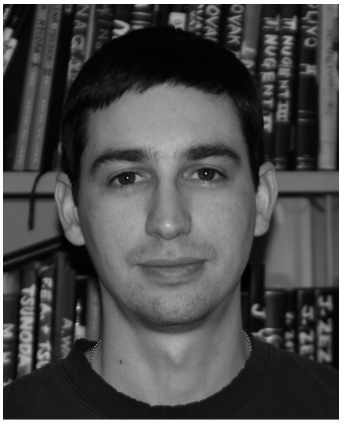
BIOGRAPHIES



Jan Duchek was born in Zlín, Czech Republic. He received an M.Sc. degree in 2003 from the Institute of Chemical Technology Prague working with Professor Oldřich Paleta and a Ph.D. degree in 2009 from ETH Zürich working under the direction of Professor Andrea Vasella. He then joined Professor Tomas Hudlicky at Brock University as a Swiss National Science Foundation postdoctoral fellow working on the synthesis of morphine alkaloids and microbial oxidation of arenes.



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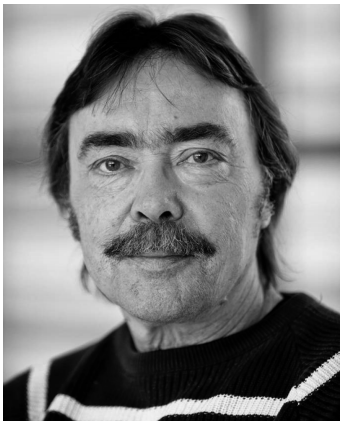
David R. Adams was born in 1979 in Albany, Georgia. After completing his B.Sc. (2006) in chemistry from the University of Florida in Gainesville, FL, he worked as a research scientist at Albany Molecular Research, Inc. In 2009, he began his Ph.D. study at Brock University in St. Catharines, Ontario, Canada, under the guidance of Professor Tomas Hudlicky in the field of alkaloid total synthesis.



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 the pharmaceutical industry it became apparent that higher education opportunities were closed to him. In 1968, he emigrated to the United States 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 cyclohexadiene-*cis*-1,2-diols in enantioselective synthesis. In 1995, he moved to the University of Florida in Gainesville, FL. In 2003, Dr. Hudlicky accepted an offer from Brock University, where he currently holds a position as Canada Research Chair Professor of Organic Synthesis and Biocatalysis. 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 nonnatural oligo-saccharide conjugates with new molecular properties. His hobbies are skiing, hockey, martial arts, and music.

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(158) Note added in proof: As this review went to press, two noteworthy publications appeared. Lewis and co-workers reported a chemoenzymatic synthesis of new inositol−amino acid hybrid structures: Pilgrim, S.; Kociok-Köhn, G.; Lloyd, M. D.; Lewis, S. E. *Chem. Commun.* **2011**, *47*, 4799. In addition, Gonzalez and co-workers reported a chemoenzymatic approach towards triazolic analogs of pancratistatin: de la Sovera, V.; Bellomo, A.; Gonzalez, D. *Tetrahedron Lett.* **2011**, *52*, 430.