Chiro-Inositols in Organic Synthesis

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Abstract: D- and L-chiro inositols are the enantiomeric pair of carbocyclic carbohydrates obtained from naturally occurring pinitol and quebrachitol. As apposed to well-known sugars that contain a ring oxygen, an anomeric carbon and a primary alcohol, these carbohydrates are comprised of only six secondary alcohols, no ring oxygen and hence no anomeric position. This leads to an inherent complexity and their use as synthetic precursors, chiral ligands and chiral auxiliaries have grown as methods to overcome this complex nature have been developed. Strategies for selective alcohol protection, synthetic transformations, their use in asymmetric synthesis and NMR spectroscopy are discussed in this mini-review.

Keywords: D-*chiro*-inositol, L-*chiro*-inositol, pinitol, quebrachitol, asymmetric synthesis.

INTRODUCTION

Inositols are part of the carbocyclic family of carbohydrates that are classified as carbohydrates, in the sense that they have the same formula of $C_6H_{12}O_6$, Fig. (**1**). However, the chemistry of inositols is very different due to the lack of a ring oxygen and the presence of only secondary hydroxyls. As a result, they are not subject to anomeric reactions nor do they exist in equilibrium with open chain forms. Of the nine inositol stereoisomers, D- and L-*chiro*-inositols exist as a pair of enantiomers, and hence serve as valuable scaffolds for asymmetric synthesis. Thus, the topic of this mini-review will focus on D- and L-*chiro*-inositols, which have been shown to be useful, but are still underutilized chiral-pool molecules. The conversion of L or D into other inositol isomers has been the subject of multiple reports and has been referenced [1]. Finally, the reader is referred to the following references for nomenclature and numbering of the cyclitols shown below [2, 3].

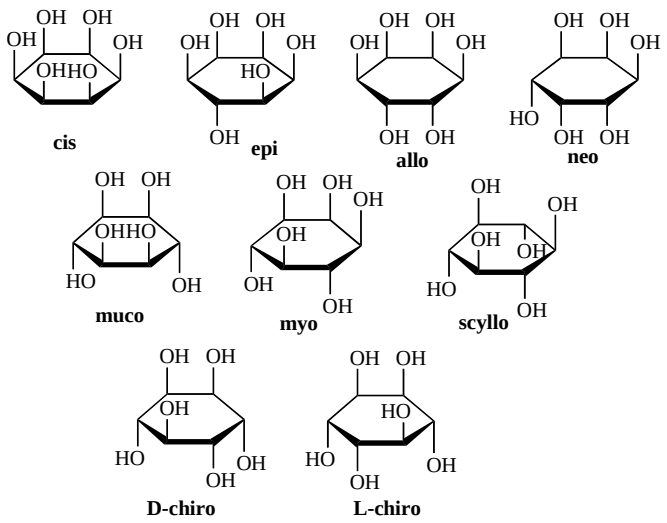
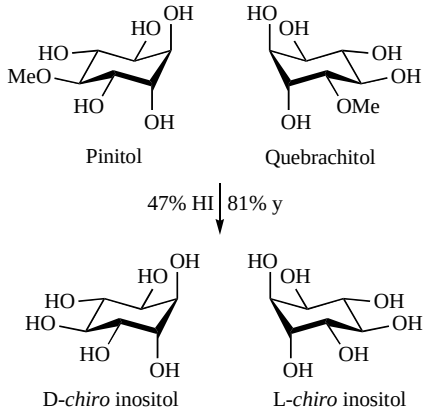


Fig. (1). The inositol family.

PREPARATION AND PROTECTION

D- and L-*chiro*-inositols are usually obtained from plants as their methyl ethers pinitol and quebrachitol, respectively. The occurrence of these ethers tends to be specific to the plant families with only very rare examples of both being found in one family. Thus, pinitol is commercially extracted from pine trees, while quebrachitol [4] is extracted from natural rubber serum, a waste product from rubber processing [5]. Demethylation [6, 7] of either is achieved without difficulty to give the corresponding cyclitols in a process easily performed on the 100g scale in good yields and requires only recrystallization to purify (Scheme **1**) [8]. Pinitol and quebrachitol can also be esterified as the pentaacetate and then demethylated with chromium trioxide in acetic acid, followed by saponification [9].



Scheme 1.

Alternatively, Hudlicky has synthesized numerous inositols from diol (Scheme **2**), which is obtained by employing bacterial oxidation of chlorobenzene as the key step [10]. For example, D-*chiro*-inositol was obtained via *syn*-diol **1** by acetonide protection, then oxidation and dehalogenation with tris(trimethylsilyl)silane/AIBN to give the epoxide. Base-catalyzed hydrolysis with concomitant acetonide deprotection gave the inositol.

Finally, with the widespread use of ring-closing metathesis in synthesis, its use in the synthesis of other inositol isomers would be expected and has indeed been reported for both D- and L-inositols [11-13]. Additional methods for the synthesis of D-inositol have been reported and include the Ferrier reaction of hex-5-enopyranosides [14, 15]. The epimerization of *myo*-inositol [16-19], and an aldol cyclization of a methyl-ß- D-galactopyranoside derivative with several subsequent functional group transformations [20].

A variety of protection schemes for the *chiro*-inositols have been established [21-23], however only a select few are routinely used, as these have proven to be very robust and reliable in both formation and removal. Perhaps the most common is protection of the *cis* diols as acetals (Scheme **3**). This involves formation of the triacetonide **2** with subsequent selective hydrolysis of *trans* acetonide [24]. This is a very robust and selective procedure and allows for isolation of large amounts of the di-*O*-isopropylidene **3**. Formation of the dicyclohexylidene analog of **3** also occurs readily in an overall 77% yield [25, 26]. We have also developed a procedure for the formation of the dimethylidene using diethoxymethane, 1,3,5-trioxane, sulfuric acid,

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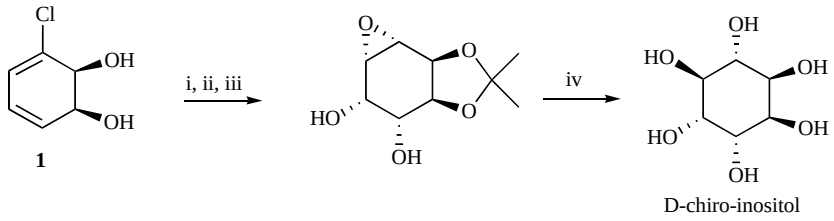
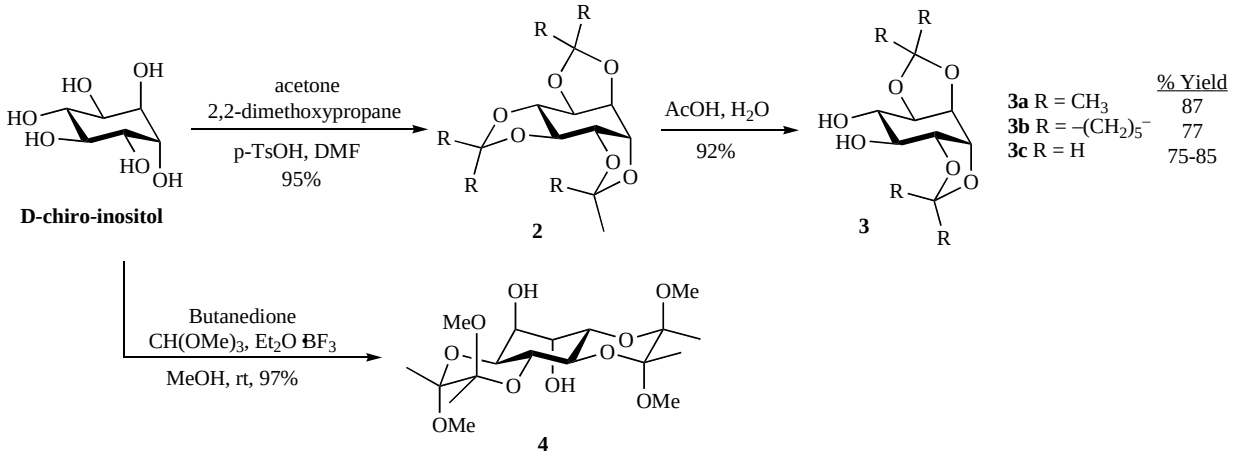


Reagents: (i) DMP, TsOH; (ii) $KMnO_4$, $MgSO_4$, H_2O, acetone; (iii) TTMS, AIBN, PhMe, 110 ^{0}C; (iv) NaOBz, H_2O, 100 ^{0}C

Scheme 2.



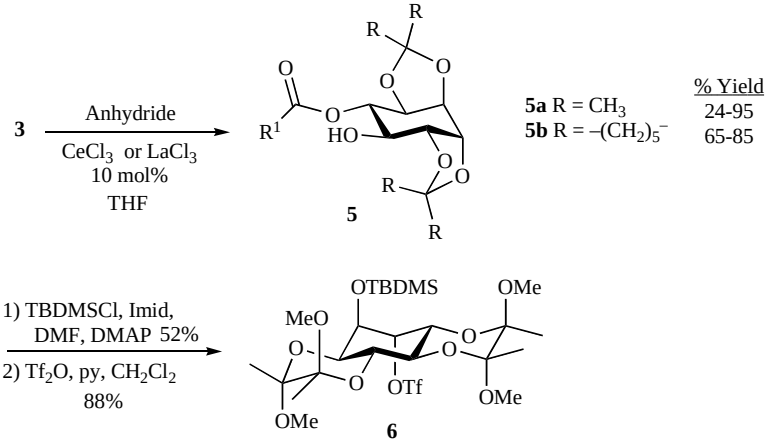
Scheme 3.

and trimethylorthoformate in a three-step process; although acceptable yields are obtained, this is an extremely finicky sequence of reactions that resist scale-up due to difficulties in driving the equilibrium toward the tri-protected material and an inability to remove the large amount of mineral acid that is required. Typically, 1-1.5ml of concentrated sulfuric acid per 1g of inositol is required. An alternative to **3** is formation of the *trans* diol **4**, in which the axial hydroxyl groups are left isolated allowing for their further elaboration [27].

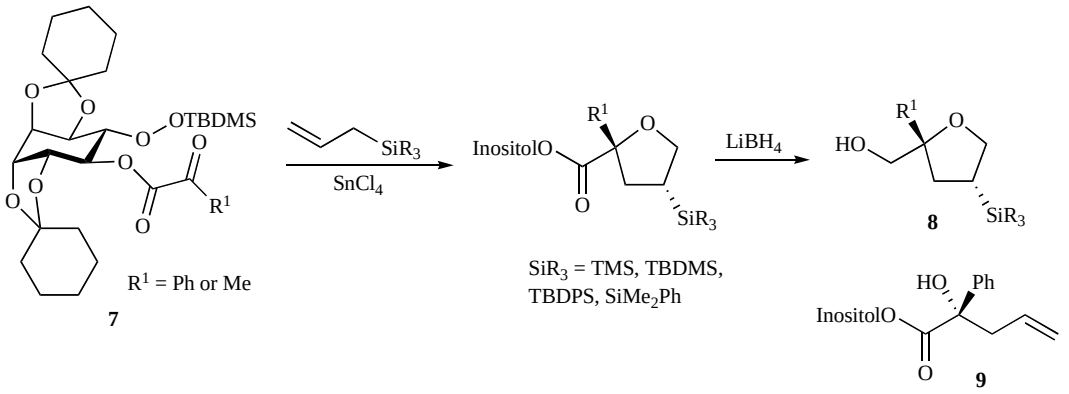
Further selective differentiation of the diol moieties in both **3** and **4** have been achieved. Examples include the selective esterification of both **3a** and **3b**, using a variety of anhydrides in the presence of catalytic lanthanide salts to give mono esterification product **5** as the sole product and in very good yields, Scheme **4** [24]. For example, the use of chloroacetic anhydride produced a 95% yield of the corresponding mono ester. Other mono protection strategies for the diols of **3** appear to be much more facile for **3b** rather than **3a**. For example, mono etherification of **3b** as a silyl, benzyl or methoxymethyl ether in yields of 77% to 89% has been reported [25], and appear to be assisted by the increased size of the cyclohexylidene sisted by the increased size of the cyclohexylidene protecting groups; alternatively these strategies fail to selectively mono protect **3a**. Bisacetal **4** is also amenable to mono protections. In our labs, we have successfully performed a mono silylation, which is easily transformed to triflate **6** in overall good yield. Martin-Lomas has also reported the mono glycosidation of **4**, using trichloro-acetimidates donors in good yields (40-63%) [23].

CHIRAL AUXILIARIES

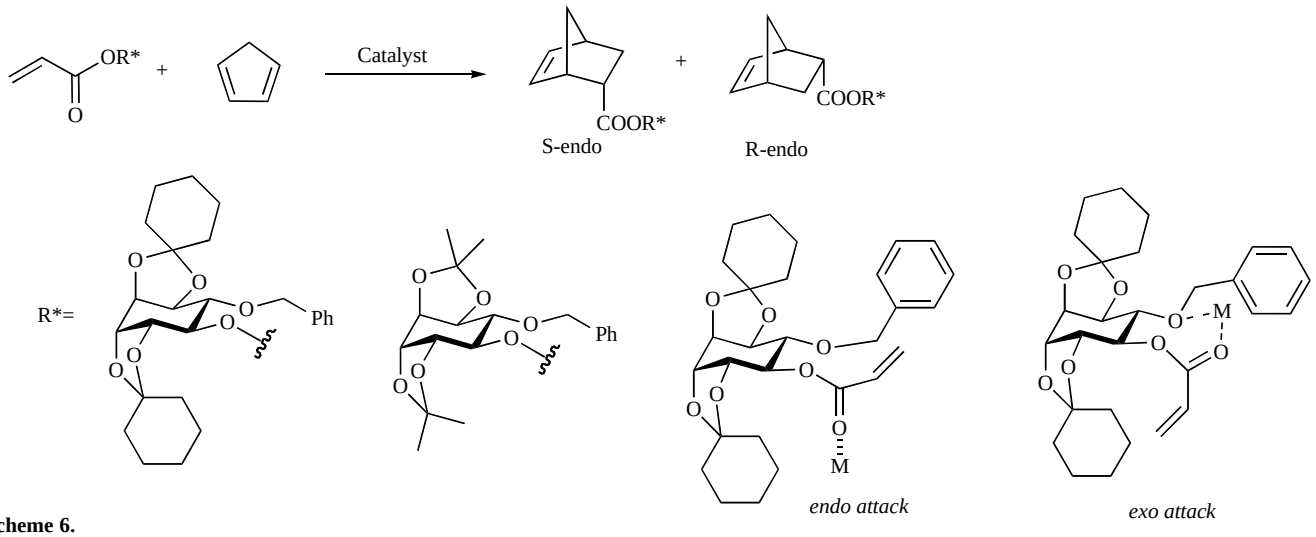
Ozaki and Akiyama reported numerous asymmetric transformations using inositols as auxiliaries in the 1990's [28]. For example, using silyl protected dicyclohexylidene **7**, [3+2] cycloadditions of allylsilanes gave high level of diastereoselectivities (>98%) of furan derivatives via 1,2-silyl migrations (Scheme **5**) [25]. Reduction with $LiBH_4$ gave the chiral tetrahydrofurans **8** in good overall yields and excellent ee's. A variety of large silanes were introduced at the diequatorial hydroxyls of the inositol, to function as a blocking moiety for the subsequent tin(IV) chloride mediated reaction. The yields of



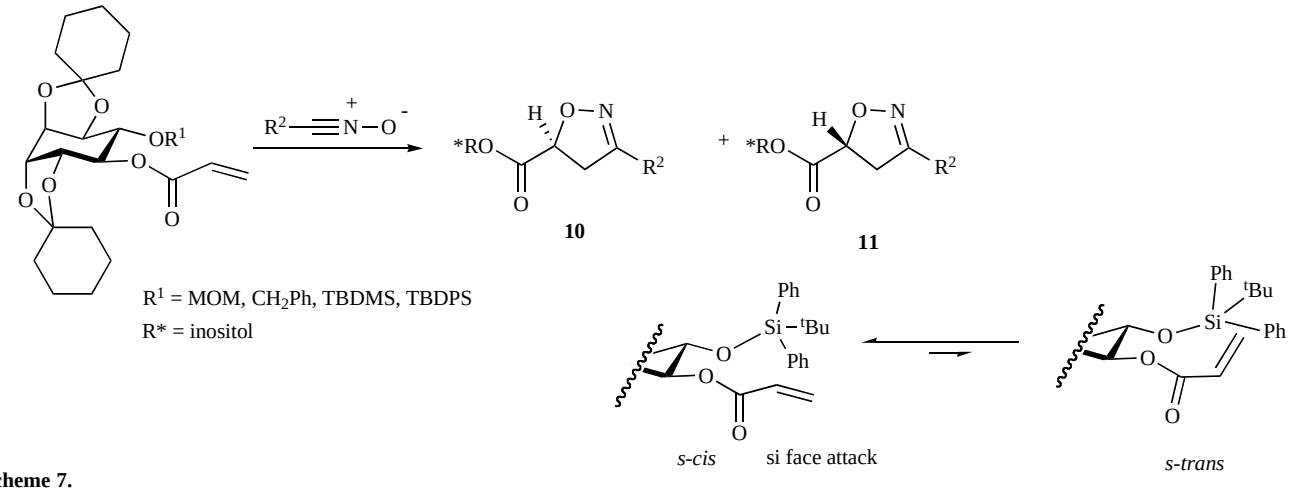
Scheme 4.



Scheme 5.



Scheme 6.

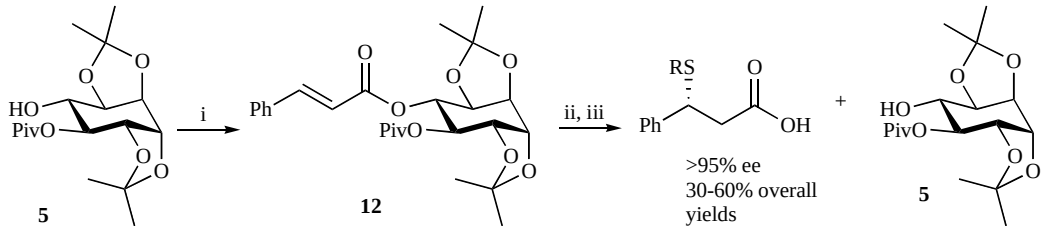


Scheme 7.

these reactions ranged from 48-85%, although in some cases when R^1 was a Ph, $SiMe_3$, and $SiPhMe_2$, the by-product **9** was formed in 21-22% yield. The ee's for this reaction were almost all greater than 95%.

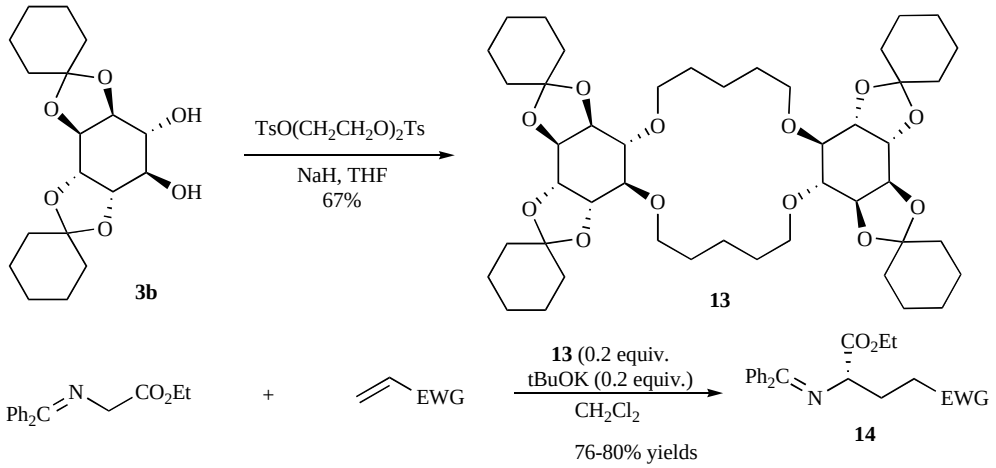
In another example, Akiyama used the same cyclohexylidene protected inositol, differently substituted at the equatorial hydroxyls, for asymmetric Diels-Alder reactions, catalyzed by Lewis acids (Scheme **6**) [29]. Yields ranged from 0-97% with *endo*:*exo* ratios as high as 99:1, in which $AlCl_3$ and Et_2AlCl gave preference to *endo* over *exo*. *Exo* diastereoselectivity could be obtained with $SnCl_4$, in which chelation of the lone pairs of the benzyl oxygen and the carbonyl oxygen forced the dienophile into a spatial orientation where *exo* attack was favored.

These types of systems have also been used for the reduction of α-keto esters [30] and the addition of nitrile oxides to chiral acryloyl esters [31]. This last example leads to the formation of optically active Δ^2 -isoxazolines, which are useful intermediates in the preparation of β-hydroxy carbonyl compounds. A range of auxiliaries were prepared and reacted with nitrile oxides (Scheme **7**). Yields varied from 81-89% and diastereoselectivities were from 1:1 (R^1 = Bn) to 95:5 (R^1 = TBDPS). The isoxazolines **10** and **11** were then cleaved from the auxiliary with L-selectride. The high selectivity in the case of TBDPS can be rationalized by the steric bulk of both the cyclohexylidene protecting groups and the TBDPS ether, leading to a more favorable s-*cis* conformation. *Si* facial attack, as shown, leads to the

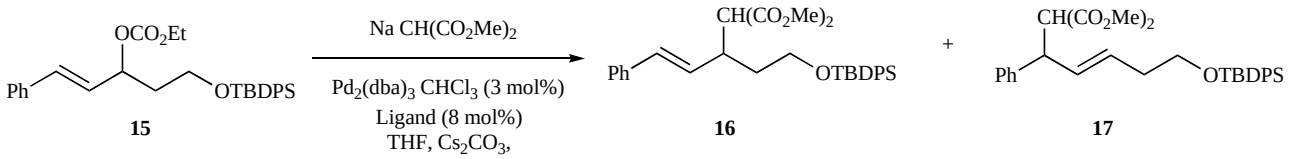


Reagents: (i) PhCH=CHCOCl, Py, DMAP, CH_2Cl_2, 89%; (ii) RSH, BuLi, THF; (iii) KOH(aq), MeOH workup.

Scheme 8.



Scheme 9.



Ligand	% Yield	Ratio 16 : 17
s-BINAP	93	2.1 : 1
s-TolBINAP	91	1.6 : 1
s,s-Trost	81	4.8 : 1

Scheme 10.

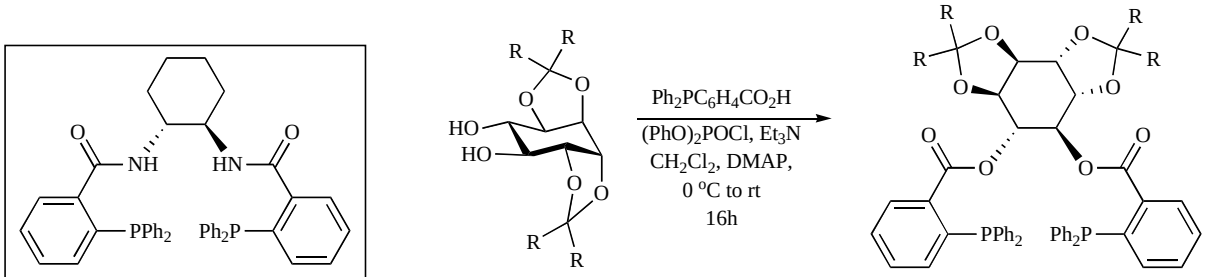
major product **10**. The minor products **11** are formed from the less favored s-*trans* conformation, where the alkene is negatively interacting with the silyl ether.

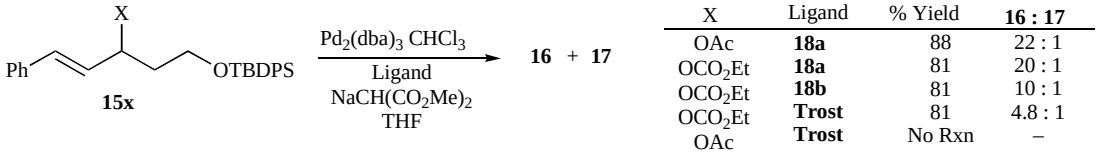
A final example of chiral inositols functioning as auxiliaries is their use in the Michael reaction. Noticing the excellent selectivities that Akiyama obtained, we constructed the acceptor **12** (Scheme **8**) using both D- and L-inositols and subjected these to addition with a variety of lithium thiolates [32]. Diastereoselectivities were all >99:1 when using aromatic thiols, but dropped noticeably (3:1) when using alkyl thiols. The yields of these reactions were acceptable i.e. 65-80%. Simplification of the overall procedure was also achieved by elimination of the final hydrolysis step. Workup, after addition of thiol, using aq. KOH/MeOH resulted in the addition and hydrolysis step in one pot. Separation was easily achieved by partitioning of the resulting chiral acid in water and auxiliary **5** in the dichloromethane layer. Filtering of **5** through a silica plug followed by re-esterification with cinnamoyl chloride gave **12**, in overall 85-91% yields.

CHIRAL LIGANDS

The number of reports on the use of inositols in catalysis are fewer in number. Akiyama has reported the synthesis of crown ether **13**, which was derived from L-*chiro*-inositol **3b**, in a one step reaction with diethyleneglycol di-*O*-tosylate (Scheme **9**) [33]. Several glycine imines and solvents were tested for yields and activity, and it was observed that dichloromethane and the ethyl ester imine shown, were optimal. Good yields and high ee's (80-96% ee) were obtained in the asymmetric Michael addition when the electron-withdrawing group was either an ester or ketone. Use of acrylonitrile gave only a 46% ee and 70% yield.

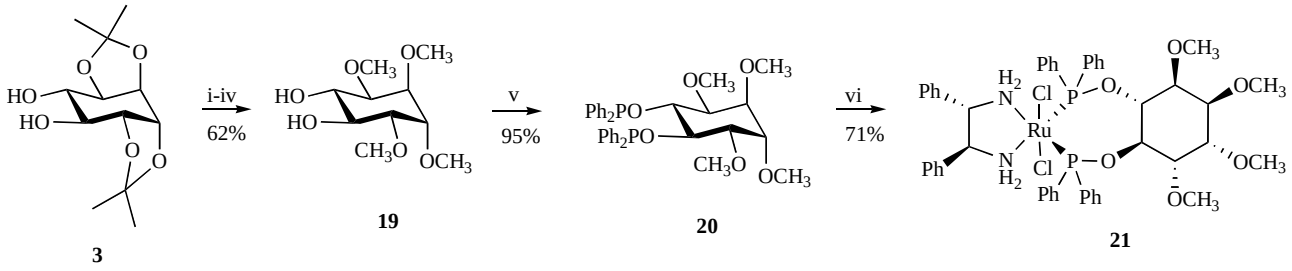
Recently, we developed an inositol-based phosphine ligand for metal-catalyzed reactions and have applied this to the asymmetric allylic alkylation reaction (AAA), in which regioselectivity is an issue. We previously discovered that with specific substrates the regioselectivity of the alkylation can be problematic, such as the situation depicted in Scheme **10**. In this reaction, we reported that carban-





X	Ligand	% Yield	Ratio of 16 : 17
OAc	**18a**	88	22 : 1
OCO_2Et	**18a**	81	20 : 1
OCO_2Et	**18b**	81	10 : 1
OCO_2Et	**Trost**	81	4.8 : 1
OAc	**Trost**	No Rxn	–

Scheme 11.



Reagents: (i) BnBr, NaH, DMF; (ii) TFA; (iii) MeI, NaH, DMF; (iv) Pd/C, H_2, EtOH; (v) Ph_2PCl, Py, THF; (vi) $RhCl_2(PPh_3)_3$, N,N-(–)-1,2-diphenylethylenediamine, PhMe.

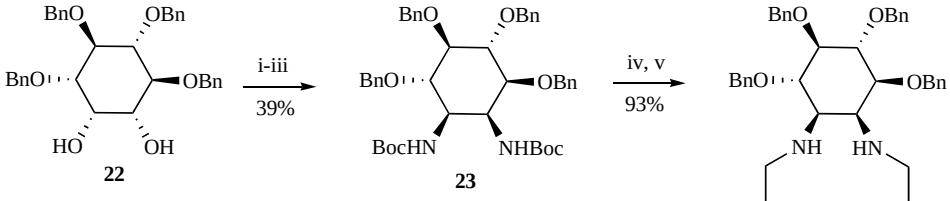
Scheme 12.

ions derived from dimethyl malonate showed very poor regioselectivity for substrate **15**, using a number of chiral ligands and conditions (only three results shown) [34]. Given that separation of **16** and **17** is impossible in a practical sense, we attempted to solve this poor regioselectivity by the use of inositols.

The Trost ligand has become the standard bearer for the AAA reaction, producing exceptional ee's and yields [35]. However as seen in Scheme **10**, it fails in inducing acceptable regioselectivity. Given that the chiral cyclohexyldiamine is the determinant for the stereoselective induction, we postulated that replacement with an inositol, as depicted in Scheme **11**, would solve this problem and provide increased regioselectivity due to the acetal protecting groups. Thus, reaction of two equivalents of 2-(diphenylphosphino)-benzoic acid with inositols **3a** and **3c** gave high yields of ligands **18** [36]. The use of these ligands in the AAA reaction of **15** as both the carbonate and acetate, were gratifyingly good. Excellent regioselectivity is observed with **18a**, in which a 22:1 ratio is observed with very good yields. The size of the inositol protecting group appears to be significant, as use of **18b** results in a lowering of the regioselectivity to 10:1. Finally, an increase in the reactivity of ligands **18** towards acetates has also been observed vs the Trost ligand, which was unreactive towards the acetate of **15** under these conditions.

Reaction of other allylic substrates with **18a**, as the ligand has also displayed equal or even more impressive regioselectivity, however it appears that the ee's with this ligand may be suspected. Poor ee's have been observed with two other substrates and this may be a result of the ester linkage in **18** versus the amide linkage in the Trost ligand, which has been reported to be critical. Future work in this system appears to necessitate the incorporation of a diamine inositol, which has been prepared and reported by Hudlicky [37]. *Chiro*-inositol based diphosphinite ligands have also been constructed for asymmetric hydrogenation reactions (Scheme **12**) [38]. The synthesis began with multiple protection/deprotection steps to generate **19**, which underwent facile conversion to **20** using chlorodiphenyl phosphine. This series of reactions illustrate an important aspect of acetonide **3**, in that the rigidity of **3** at times can limit the reactivity of the alcohol moieties. Thus, a more flexible substrate such as **19** is needed and requires reprotection of **3** for the eventual formation of **20**. Metal complexation of **20** was then achieved with a variety of ruthenium metals and co-ligands, one such example being **21**. The catalytic activity of the complexes towards asymmetric hydrogenation reactions was then carried out on the ketone acetophenone, a bulky amide 3-quinuclidinone, α-ketoester methyl benzoylformate and the alkene dimethyl itaconate, in which only acetophenone and 3-quinuclidinone were converted to their respective alcohols. However, the selectivities of these reductions were a disappointing 24-50%.

A final report on the synthesis of metal ligands incorporating an inositol is from the d'Alarcao labs [39]. Athough *myo*-inositol is used as the inositol, the synthetic strategies in theory could be applied to the *chiro*-inositols, and therefore it is presented in Scheme **13**. Conversion of diol **22** to a dimesylate, displacement with azide followed by hydrogenolysis in the presence of Boc_2O provided diamine **23**. Hydrogenolysis without Boc_2O was reported to be inconsistent, perhaps due to metal poisoning by the product, and thus the Boc-amine circumvented this issue. Removal of the protecting groups followed by imine formation proceeded in high yields to provide bis-pyridyl ligand **24**. The authors also reported *N*-Me analog in addition, but have not reported the use of **24** in any metal-catalyzed reactions.



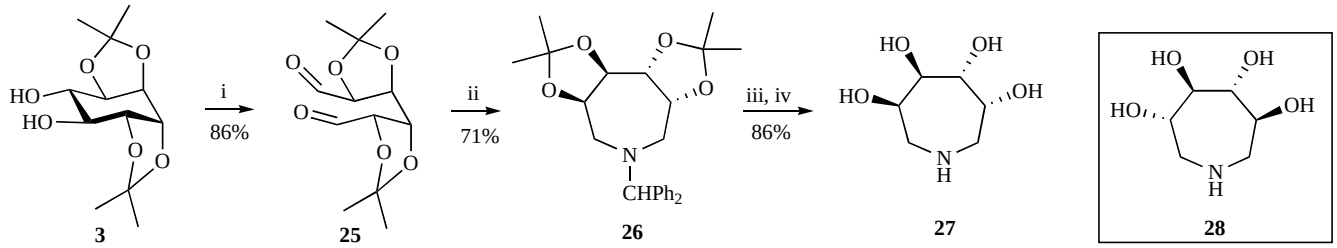
Reagents: (i) MsCl, Py; (ii) NaN_3, DMF, 85 °C; (iii) H_2, Boc_2O, $Pd/CaCO_3$, EtOH, THF; (iv) HCl, MeOH, H_2O; (v) 1. 2-pyridine carboxaldehyde, p-TSA, PhMe, 4A MS, 85 °C; 2. BH_3 THF, THF, 23 °C; 3. 6M HCl

Scheme 13.

CHIRAL MATERIALS AND BIOACTIVE MOLECULES

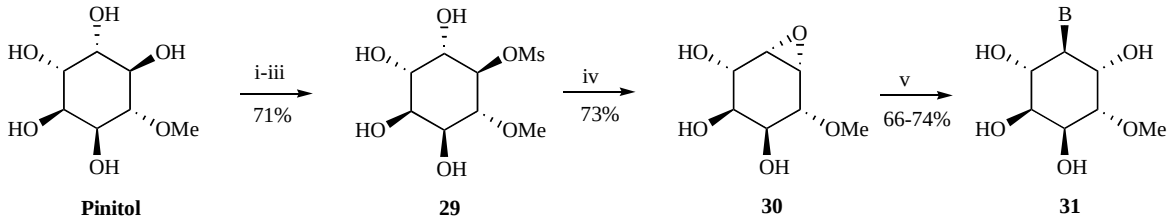
Given the availability of either enantiomer of the *chiro*-inositols, their use in the synthesis of enantiomerically pure and biologically active molecules other than glycosylinositols, would appear to be ideal. One such target that has been exploited is enzyme inhibition using amino sugars, specifically tetrahydroxyazepanes. Falshaw and Painter have published multiple manuscripts involving a facile method for the construction of these azepanes via an oxidative cleavage of the diequatorial diols of either D- or L-inositol **3** to give dialdehyde **25** (Scheme **14**) [40-42]. The key step in this overall sequence was found to be the double reductive amination of **25**. It was hypothesized that initial imine formation and subsequent reduction were fast compared to the cyclization step. Thus, slow addition of the benzhydrylamine at low temperature circumvented multiple intermolecular additions that led to acyclic, high-mass products and gave **26** in good overall yield. Multiple isomers of **27** have been prepared by this group via protecting group manipulations. For example, the L-*ido*-tetrahydroxyazepane (+)-**28** has also been synthesized. With these isomers and their enantiomers in hand, biological testing was performed and indicated that the D-*manno*-tetrahydroxyazepane [(–)-**27**] showed selective inhibition of α-L-fucosidase and ß-D-galactosidase, while the enantiomer [(+)-**27**] was a selective inhibitor of an α-D-galactosidase. In contrast, (+)-**28** was a broad spectrum hexosidase inhibitor, but showed none of the reported hexosaminidase inhibition, while its enantiomer was a poor hexosidase inhibitor [40].

In a related context, Zhan and Lou have used pinitol to construct nucleoside analogs via an epoxy inositol (Scheme **15**) [43]. The first three steps involved protection, mesylation and deprotection to give **29**, which underwent selective epoxide formation to produce **30** due to the adjacent methoxy ether. Reaction of **30** with triazole bases gave complete regioselectivity providing **31**, however mixtures of isomers were obtained with nitroindazoles. The compounds were evaluated for *in vitro* cytotoxicity and displayed limited activity to human lung and bladder cancer cell lines.



Reagents: (i) $NaIO_4$-activated silica, CH_2Cl_2; (ii) $NaCNBH_3$, $(Ph)_2CHNH_2$, AcOH (2 equiv.), 3 Å molecular sieves, MeOH, -78 °C to RT; (iii) conc. HCl, MeOH–CH_2Cl_2, reflux; (iv) $Pd(OH)_2/C$, H_2, MeOH

Scheme 14.



Reagents: (i) DMP, acetone, p-TsOH, rt, 16 h; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 24 h; (iii) 75% aq. TFA, 80 °C, 12 h; (iv) anhy. MeOH, K_2CO_3, rt, 6 h; (v) azole-bases, DBU, DMSO, 100 °C, 48 h.

Scheme 15.

Epoxides of inositols are perhaps one of the older classes of inositol compounds and depending on the protecting groups can be extremely stable [44]. For example, **32** Fig. (**2**) is extremely unreactive and can undergo acid deprotection of the isopropylidenes leaving the epoxide untouched [45]. Falshaw and co-workers have constructed epoxides from both D- and L-*chiro*-inositols for assessment of their

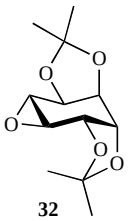


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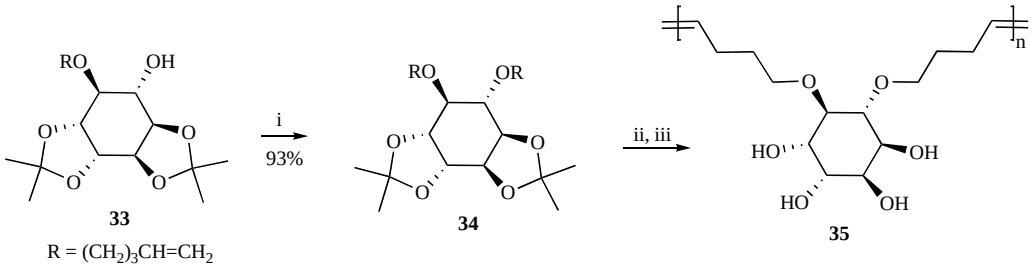
Fig. (2). A stable inositol epoxide.

Finally, chiral inositol polymers using acyclic diene metathesis have been prepared for use in chiral separation and catalyst/metal binding materials (Scheme **16**) [47]. Preparation of diene **34** from **33** followed by polymerization with Grubb's first-generation catalyst and deprotection gave polymer **35**. Tetrahydroxyl polymer **35** has a molecular weight estimated 10,000 by GPC analysis and light scattering analysis estimated the average molecular weight 18,000. D-*chiro*-inositol **33** was initially constructed via whole-cell fermentation from bromobenzene, as discussed previously in this review.



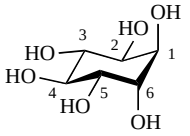
33 **34** **35**

R = $(CH_2)_3CH=CH_2$

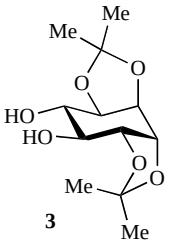
Reagents: (i) 5-bromopentene, NaH, DMF; (ii) Grubbs catalyst; (iii) THF–TFA–H_2O, 4:1:1.

Scheme 16.

Table 1. ^{1}H NMR Data of Selected Inositols



D-*chiro*-inositol



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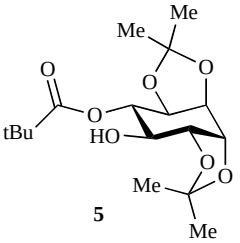

5

Assignment	Chemical Shift	Coupling in Hz
	Chiro-inositol (D_2O/DMSO)	(D_2O/DMSO)
1,6	4.03/3.65	$J_{1e,2a}$ = 2.7/2.4
2,5	3.77/3.42	$J_{1e,6e}$ = 3.4/3.8
3,4	3.60/4.36	$J_{2a,3a}$ = 9.9/9.5
		$J_{3a,4a}$ = 9.5/8.9
OH (1,6)	–/4.36	$J_{1,6\text{-OH}}$ = 4.1 (DMSO)
OH (2,5)	–/4.03	$J_{2,5\text{-OH}}$ = 5.6 (DMSO)
OH (3,4)	–/4.15	$J_{3,4\text{-OH}}$ = 3.8 (DMSO)
	3 ($CDCl_3$)	
1,6	4.33-4.36	m
2,5	4.14-4.23	m
3,4	3.52-3.60	m
OH	3.52-3.60	
CMe_2	1.51	s
CMe_2	1.36	s
	5 ($CDCl_3$)	
3	4.92	dd, J = 8.3, 11.5
1,6	4.46	m
2,5	4.23	m
4	3.60	dd, J = 8.3, 11.5
CMe_2	1.51	s
CMe_2	1.50	s
CMe_2	1.27	s
CMe_2	1.26	s
tBu	1.25	s

glycosidase inhibitory activities and found them to be very robust to chemical manipulations [46]. Thus, as a synthetic intermediate, they appear to be somewhat limited.

NMR OF SELECTED INOSITOLS

The twofold axis of symmetry in *chiro*-inositols, and symmetric derivatives, gives three pairs of equivalent protons, and hence the

assignment of the spectra is very straightforward. Abraham has published both the D_2O and DMSO-d_6 solution spectra along with detailed coupling constant information, which are listed in Table **1** [48]. As expected, the same chemical shift patterns exist for di-*O*-isopropylidene **3** [49], however upon monosubstitution, the symmetry is destroyed and individual protons are observed, as in inositol **5** [32].

SUMMARY

Chiro-inositols have been shown to provide excellent asymmetric induction in a wide variety of transformations. However, the use of these inositols has not been widely adopted, perhaps due to being undiscovered to main stream synthetic chemists. Although the majority of their use has been as chiral auxiliaries, further development as chiral ligands may bring enhanced use and recognition to this class of molecules. Their use in the synthesis of other chiral molecules has certainly been established and should continue to grow.

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Received: May 19, 2008 **Revised: August 05, 2008** **Accepted: August 11, 2008**