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Inositols as chiral templates: 1,4-conjugate addition to tethered cinnamic esters†

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The 1,4-addition of thio nucleophiles to *chiro*-inositols containing a cinnamyl Michael acceptor proceeded with excellent diastereochemical induction and good yields. Cleavage of the inositol auxiliary provides β-thio hydrocinnamic acids in >99% ee's.

Methodologies for the efficient asymmetric synthesis of natural products and other materials are of great importance in organic synthesis, and in the past decades enormous strides have occurred in the development of asymmetric synthesis.[1,2] A number of asymmetric catalysts or 'abiological' catalysts have now approached efficiency and selectivity levels comparable to those of enzymes, and can have the advantage of either enantiomer being available. In recent years, C_2-symmetric chiral molecules have received a great deal of attention in ligand–metal catalysis and as auxiliaries.[3,4] These systems have additional benefits in terms of flexibility in ligand design and convenient synthesis.

We recently initiated a program to develop inositols as C_2-symmetric molecules for use as auxiliaries in asymmetric synthesis. Inositols are a family of nine hydroxylated cyclohexanes that include the enantiomeric pair D- and L-*chiro*-inositol, Fig. 1. These are derived from the naturally occurring pinitol and quebrachitol, which are obtained from pine and rubber trees, respectively, by simple demethylation.[5] Although all four of these are commercially available, quebrachitol has received the majority of the attention in asymmetric synthesis.[6,7]

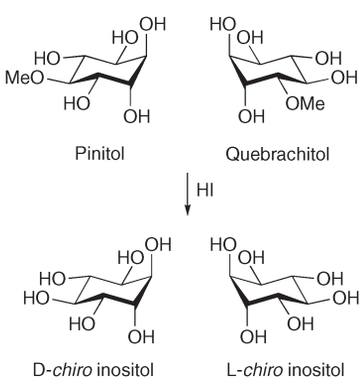
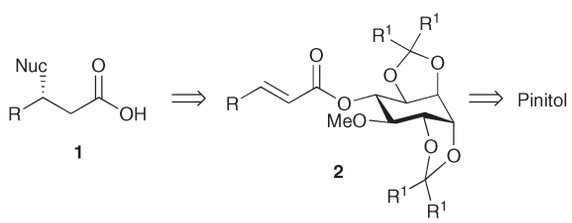


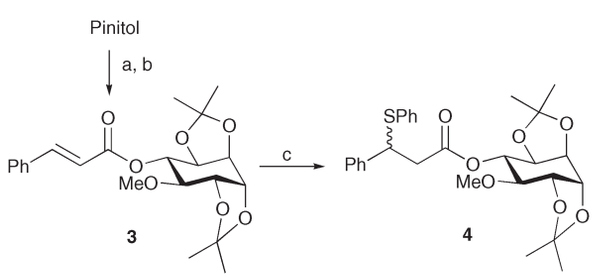
Fig. 1 Chiral inositols.

Our initial goal to develop the inositols further was to use the esters **2** as Michael acceptors, which could subsequently be hydrolyzed to provide chiral molecules such as acids **1**, Scheme 1. Formation of the required acceptor **2** would be accomplished by simple protection of the *cis*-diols of pinitol to give the di-acetals, followed by esterification of the remaining lone hydroxy moiety. As this involved a reasonably straightforward synthesis of an acceptor, we entertained the possibility that the methoxy group would provide a large enough steric bias to produce facial selectivity on the unsaturated moiety. This would involve shielding of the front (*Si*) face of the acceptor to give attack from the less-hindered *Re*-face (back side).[8]



Scheme 1 Retrosynthetic strategy for inositol auxiliaries.

We began our studies by protection of pinitol as the di-*O*-isopropylidene acetal, which produces a single isomer under literature procedure,[9] Scheme 2. Reaction with cinnamoyl chloride gave ester **3** in a very convenient 85% yield. Treatment of a thiophenol/THF solution with 10 mol% BuLi at 0 °C or room temperature followed by **3** gave a myriad of products. However, reaction at −10 °C gave the single addition adduct **4** in a reasonable 75% yield but a disappointing 1 : 1 diastereoselectivity. Obviously, the size of the methoxy moiety was unable to hinder approach from the front face and a larger group was required.



Scheme 2 *Reagents and conditions*: a) acetone, $(MeO)_2CMe_2$, TsOH, DMF, 84%; b) PhCH=CHCOCl, DMAP, Py, CH_2Cl_2, 85%; c) PhSH, BuLi, THF, 75%.

We therefore converted D-*chiro*-inositol to di-*O*-isopropylidene **5** in 93% yield, again according to literature procedure,[10] for subsequent de-symmerization of the C_2-symmetric diols. Using the procedure developed by Clarke *et al.*,[11,12] we recently disclosed a convenient method for the monoesterification of **5**,[10] enabling the placement of a larger protecting group at a single hydroxy moiety. Thus, treatment of **5** with pivaloyl anhydride in the presence of catalytic ytterbium chloride gave **6** as a single isomer in high yield, Scheme 3. This enabled subsequent esterification using cinnamoyl chloride to provide acceptor **7** with the methoxy group replaced by the pivoyl ester.

Gratifyingly, the initial reaction with thiophenol gave a good yield of the addition product and a single isomer as shown by ^{13}C NMR. A range of thiol nucleophiles were subsequently tested as

† Electronic supplementary information (ESI) available: experimental details for the preparation and analysis of compounds **3**, **4**, **6**, **7**, **8a–e**, **10a**, **10b**, **10e**, **11a–11d**, **13a**, **13b** and **13d**. See http://www.rsc.org/suppdata/ob/b4/b408467e/

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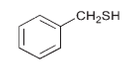
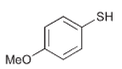
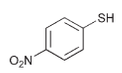
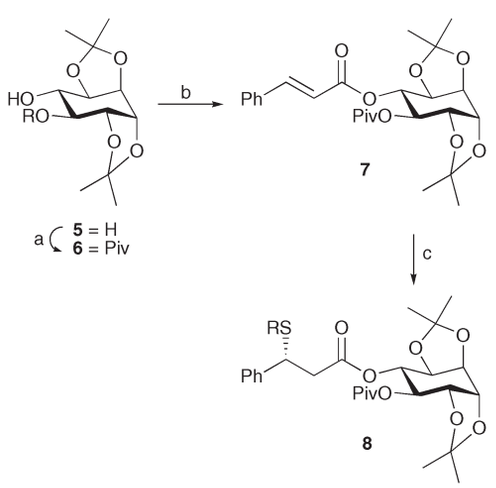
Table 1 Conjugate addition of thiols

Entry	Thiol	Product (% yield)[a] *ds*[b]	Product (% yield)[a] *ds*[b]
1		**8a** (79%) *>99 : 1*	**10a** (75%) *>99 : 1*
2		**8b** (74%) *>99 : 1*	**10b** (72%) *>99 : 1*
3		**8c** (68%) *>99 : 1*	—
4		**8d** (76%) *>99 : 1*	—
5		0	—
6		0	—
7		**8e** (71%) *3 : 1*	**10e** (31%) *2.5 : 1*

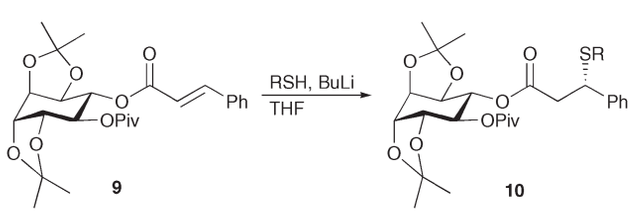
[a] Isolated yield. [b] Determined by ^{13}C NMR on crude mixtures.



Scheme 3 *Reagents and conditions*: a) $(Me_3CO)_2O$, 10% $YbCl_3{\cdot}6H_2O$, THF, 83%; b) PhCH=CHCOCl, DMAP, Py, CH_2Cl_2, 89%; c) RSH, BuLi, THF.

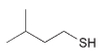
shown in Table 1. As seen, entries 1 and 2 gave good yields and selectivities with the D-*chiro*-inositol-derived acceptor. The use of electron donating substituents on the aromatic ring, entries 3 and 4, also gave excellent selectivities but the products proved to be unstable and began to decompose immediately. As seen in entries 5 and 6, aromatic thiols with electron withdrawing groups failed to react. Finally, the less hindered methylbutanethiol in entry 7 gave a comparable yield but disappointing selectivity.

To verify the usefulness of inositols in asymmetric synthesis, the L-isomer of acceptor **9** was synthesized in an analogous manner to that of **7** and also subjected to reaction with thiol nucleophiles, Scheme 4. Again, as seen in entries 1 and 2 of Table 1, excellent selectivities are observed, and as expected with comparable yields to the D-*chiro*-inositol. Given the lack of stability of the amino- and methoxy-benzenethiols and the lack of reactivity of nitro- and chloro-benzenethiols, reaction with these was not attempted.



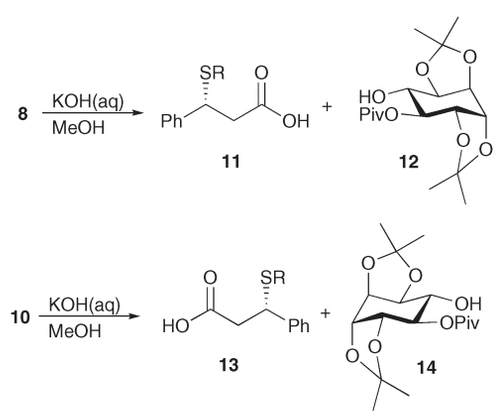
Scheme 4 L-*chiro*-Inositol.

Table 2 Hydrolysis of esters **8** and **10**

Entry	R	Product (% yield)[a] % *ee*[b]	Product (% yield)[a] % *ee*
1	Ph	**11a** (76%) *>95*	**13b** (74%) *>95*
2	Bn	**11b** (75%) *>95*	**13b** (72%) *>95*
3		**11c** (59%) *>95*	
4		**11d** (72%) *33*	**13d** (67%) *34*

[a] Isolated yield. [b] The stereochemistry was determined by comparison of the optical rotation to the known 3-benzylthio-3-phenylpropanol after $LiAlH_4$ reduction of **8a**; and comparison of **11a** to literature values (see ESI). All other compounds were established by comparison of NMR data to **8a** or **8c** and **10a** or **10c**.

The final step in verifying *chiro*-inositols as useful auxiliaries involved selective cleavage of the auxiliary to provide acids **11** and **13**, Scheme 5. Careful monitoring of the reaction by tlc enabled the selective cleavage of the thiol ester moiety without cleavage of the pivalate ester. Upon completion of the reaction, the mixtures were diluted with water and extracted with CH_2Cl_2 to provide inositols **12** and **14** in high yields. The crude inositols were filtered through a silica plug and re-esterified with cinnamoyl chloride to give **7** and **9** in overall 85–91% yields. Thus, an important aspect of a chiral auxiliary, namely the ability to be recycled, has been realized with this system.

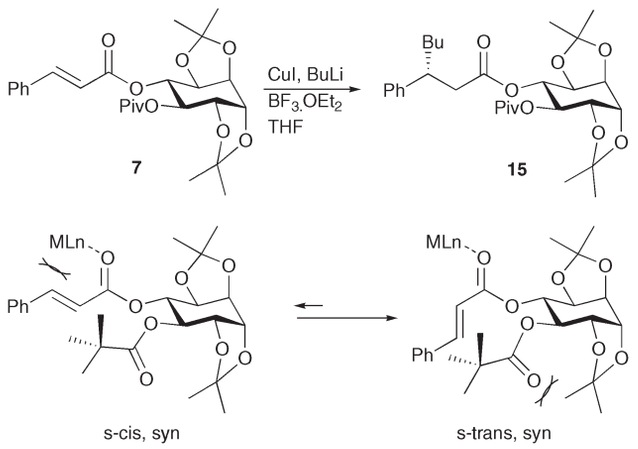


Scheme 5 Cleavage of the inositol auxiliary.

Isolation of the desired enantiomers **11** and **13** was achieved in typical fashion by acidification of the aqueous layer to give the acids in good yields as shown in Table 2. Chiral GC analysis of the acids showed that excellent ee's are achieved with this system.[13] In all cases, except for the aliphatic thiol, only one isomer was observed in reactions with both the D- and L-derivatives **7** and **9**. Simplification of the overall procedure has also been achieved by elimination of the final hydrolysis step. Workup after addition of the thiol, as in Schemes 3 and 4, can be modified by simply using aq. KOH/MeOH, thus achieving the addition and hydrolysis step in one pot.

Given the success with thiol nucleophiles, we next attempted the addition of an alkyl cuprate, Scheme 6. Although addition did occur, the yield was a disappointing 43%, and all attempts at modification of the conditions did not result in any improvements. A possible rationalization for this low yield is due to the conformation of the Michael acceptor.[8] Presumably, coordination of the metal with the cinnamoyl carbonyl, and pivoyl carbonyl, causes unfavorable interaction between the metal carbonyl and the carbon–carbon double bond in the *s-cis*, *syn* conformation. Typically, this unfavorable interaction leads to the *s-trans*, *syn* conformation, which then undergoes addition.[14,15] However, in our system, formation of the *s-trans*, *syn* conformation presumably leads to unfavorable interactions of the pivoyl group and a methyl group of the isopropylidene acetal.

This forces the molecule to adopt the usually unfavoured *s-cis*, *syn* conformation, which is supported by the stereochemical outcome of the addition reaction. If **7** was adopting the *s-trans*, *syn* conformation, stereochemistry opposite to that observed would be expected. We therefore used the methoxy-bearing inositol **3**, which as expected gave a 1 : 1 diastereomeric mixture of the butyl addition product.



Scheme 6 Organocopper addition.

In conclusion, *chiro*-inositols appear to be highly effective as chiral auxiliaries in conjugate 1,4-additions of aromatic thiols and contain all the requirements of an effective auxiliary, primarily high diastereoselectivity. Of equal importance is the short, facile, high-yielding, three-step synthesis and the demonstrated ease with which the inositol auxiliary can be recycled. Further development of these inositols in asymmetric synthesis, including the use of alternative nucleophiles for conjugate addition, is underway and will address the apparent drawback of the rigid, bulky acetal protecting groups. The use of alternative groups such as a methylene acetal is expected to alleviate the problems associated with the use of organocuprates.

Acknowledgements

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Notes and references

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