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The stereoselective syntheses of 1-aryl-1,6-dideoxyinositol derivatives

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ABSTRACT

This Letter describes the first report of a highly stereoselective synthesis of triethereal cyclohexanones via copper(I) mediated 1,4-addition of organometallic reagents to glucose-derived triethereal cyclohexenone. The cyclohexanones generated can be reduced with modest stereoselectivity to afford a variety of substituted inositol derivatives as potential pyranose sugar mimetics. The protocol generated a range of substituted cyclohexanones in good yield as single stereoisomers.

The stereoselective synthesis of C-glycosides has received increased attention in recent years as interest has grown in the development of selective inhibitors of glycoside transporter proteins for clinical application.[1] The inhibition of sodium dependent glucose cotransporter-2 (SGLT-2), a transporter protein located in the kidney responsible for the reabsorption of glucose in the kidney, has received particular consideration as potential treatment of type II diabetes mellitus and obesity. This interest has led to several C-glycoside compounds, such as Dapagliflozin **1** and Canagliflozin **2**, reaching advanced clinical trials to investigate this mechanism (Fig. 1).[2] During the investigation of the spirocyclic SGLT-2 inhibitor **3**, we became interested in the utility of inositol carbocyclic mimics of the pyranose sugar core as SGLT-2 inhibitors.[3]

The proposed targets in this series were to be biaryl substituted inositols such as **4** to emulate the activity of the pyranose system. The ideal approach would be to introduce the aryl group at the inositol C-1 position at a late stage of the route, followed by manipulation of the functionality at the inositol C-5 (Scheme 1). We believed that we could achieve our synthetic goal by entering the system via the known triethereal cyclohexenone **5** using 1,4-addition of organocuprate reagents.[4,5]

The ketone of cyclohexanone **6** would then offer ample scope to vary the functionality of the inositol C-5 position. The initial targets in this series would be the C-5 hydroxy compounds **4** that would require a stereoselective reduction of ketone **6**.

Currently, minimal literature precedent exists for the 1,4-addition to triethereal cyclohexenones, such as **5**, and no reports exist describing copper(I) mediated addition to this system.[6] The organocuprate addition to cyclic enones is an established approach to substituted cyclohexanones, however, the introduction of a β-oxygen function impacts the stability of the products due to elimination to cyclohexenones under basic conditions or aromatization to phenol **7**.[6b,7] The inclusion of an ether group adjacent to the ketone, will further increase the acidity of the ketone α-proton, enhancing the system's propensity to eliminate and aromatize to a phenol (Scheme 2).[6b] There is no literature precedent for copper mediated 1,4-additions to cyclohexenones with ethereal groups at

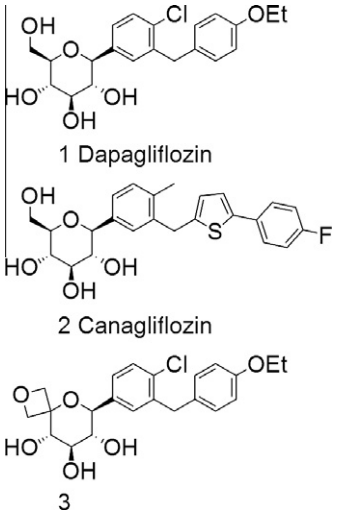

Figure 1. Recently published SGLT-2 inhibitor C-glycosides.

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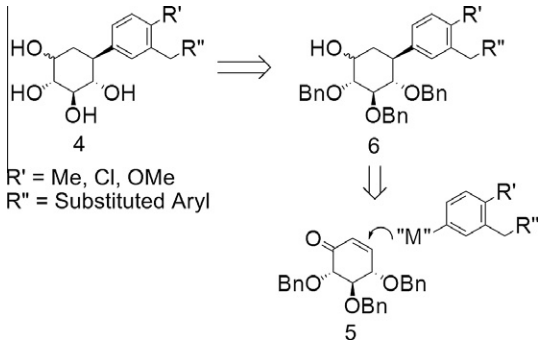
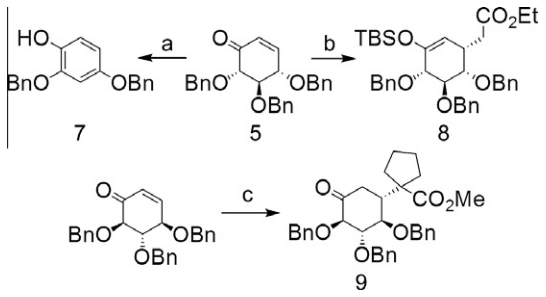


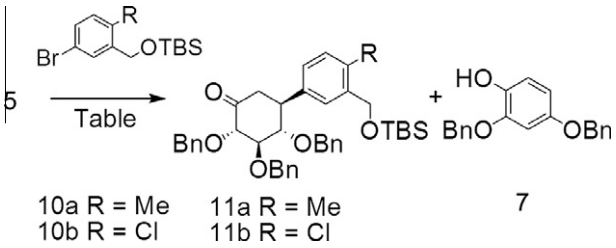
Scheme 1. Synthetic approach to aryl inositol targets.



Scheme 2. Literature precedent for 1,4-addition approach. Reagents and conditions: (a) Ref. 6b; dimethylmalonate, NaH or NaOEt, THF, rt, 45 min; (b) Ref. 6a; TBSOC(OEt)=CH_2, $LiClO_4$, Et_2O, rt, 48 h; (c) Ref. 6a; ethyl 1,3-dithiolane-2-carboxylate, *n*-BuLi, THF, −78 to −20 °C, 3 h.

both *alpha*- and *beta*-positions relative to the ketone. The stereochemical outcome of the addition was also unclear. Of the two reports detailing 1,4-addition to triethereal cyclohexenones such as **5**, one describes the *anti*-addition product **9** that would be anticipated from addition to γ-substituted enone,[6a] whereas the other report describes a lithium perchlorate mediated *syn*-addition of silyl enol ether to afford **8**.[6b]

The prototype experiments to add aryl groups **10**–**5** via the generation of an organocuprate without additives at a range of temperatures and stoichiometries afforded the phenol elimination



Scheme 3. Optimization of copper(I) mediated 1,4-addition.

Table 1
Summary of copper(I) mediated addition optimization

Aryl	*n*-BuLi (equiv)	CuI (equiv)	*T* (°C)	Add (equiv)	Products
10a	3	3	−20	None	**7**
10a	3	3	−20	TMS–Cl (**3**)	**5**
10a	3	1.5	−20	$BF_3{\cdot}Et_2O$ (1)	**7** (25%) **11a** (25%)
10b	5	2.5	−78	$BF_3{\cdot}Et_2O$ (**2**)	**11b** (75%)

product **7** (Scheme 3, Table 1). It is well established that certain additives alter the outcome of organocuprate reagents.[8] When trimethylsilyl chloride was included in the reaction, we were encouraged to find that the reaction returned starting material **5** rather than the phenol elimination product **7**, suggesting that the conditions could be effectively modulated to improve substrate stability during the addition reaction. Indeed, it was found that the addition of 1 equiv of boron(III) fluoride etherate complex to the mixture and performing the addition at −20 °C afforded 25% conversion to the desired cyclohexane **11a** as a single stereoisomer and 25% yield of phenol **7**.[8b,c] Further optimization found that performing the reaction at −78 °C with 2.5 equiv of aryl organocuprate in the presence of 2 equiv of boron(III) fluoride etherate afforded cyclohexane **11b** in 75% yield as a single stereoisomer (Table 1). We found that quenching the reaction by slow addition of 1 N HCl at −78 °C was key to preventing epimerization of the inositol C-4 ethereal carbon.[9]

The stereochemistry of the addition products were confirmed by NOE experiments and subsequently via the X-ray crystal structure of the 4-chlorophenyl adduct **12c** (Fig. 2).

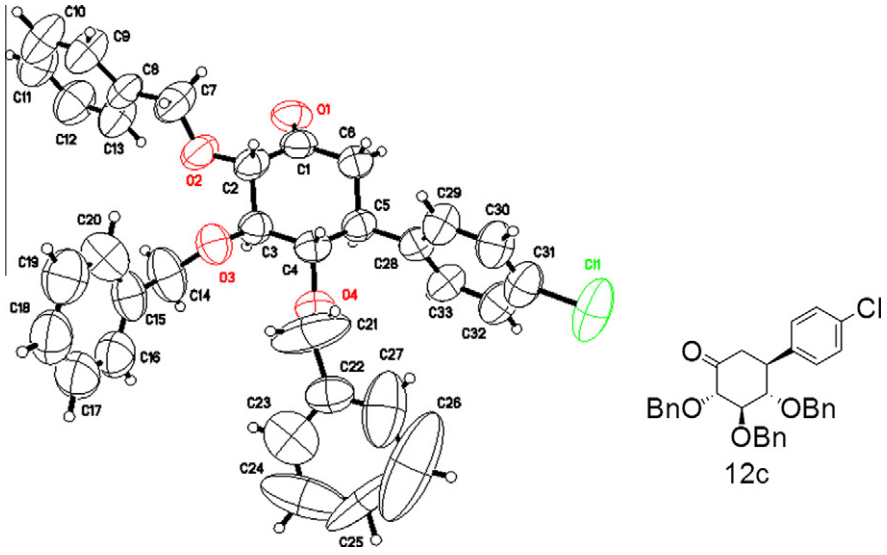


Figure 2. X-ray structure of 4-chlorophenyl adduct **12c**.

Having established conditions in hand to generate cyclohexanones such as **11** in good yield as single stereoisomers, we sought to investigate the scope of the reaction as a general method for generating triethereal substituted cyclohexanones via this novel methodology.

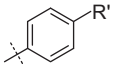
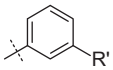
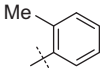
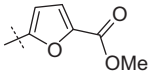
We were gratified to find that the reaction did indeed translate to a broader application and allowed a range of organocuprates to be added to cyclohexenone **5** ((Scheme 4), Table 2). A range of aryl rings, with a variety of steric and electronic characteristics could be added in good yield and as single stereoisomers **12a**–**12l**. Even the challenging *o*-tolyl cuprate successfully afforded product **12h** in 70% yield. Simple alkyl (methyl adduct **12i**), cyclic alkyl (cyclobutane adduct **12j**), and *t*-butyl adduct **12k** groups were added in 50–77% yield and as a single stereoisomer. The addition of furanyl ester (**12l**) suggested the potential to incorporate heterocycles using this methodology.

With a general method for the stereoselective generation of cyclohexanones **12a**–**12l** in hand, attention turned to the stereoselective reduction of the cyclohexanone and deprotection to complete the synthesis of 1-substituted-1,6-dideoxyinositols (Scheme 5). Our approach to exploring SAR required that we needed access to both inositol C-5 stereoisomers. The initial conditions attempted were the reduction of tolyl adduct **12d** with sodium borohydride at 0 °C to afford an inseparable 5:1 mixture of C-5 epimers (α:**13a** and β:**13b**) in 99% yield.[11a] The stereoselectivity of the reduction was improved to 8:1 α:β ratio by cooling to −10 °C. Testing a range of alternative reducing agents did not afford highly stereoselective conditions, a finding consistent with the results reported for related carbasugar systems.[11]

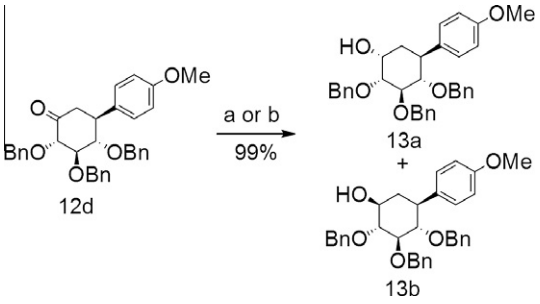
The stereochemical outcome of the reduction could be inverted by the addition of cerium(III) chloride heptahydrate which generated a 1:3 α:β C-5 epimer ratio in 90% yield. The addition of di-isobutylaluminium hydride at −78 °C and warming to 0 °C afforded a 1:4 α:β C-5 epimer ratio in 99% yield.[12] The ratio of diastereoisomers could be enhanced to a 1:12 α:β C-5 epimer mix by a single recrystallization from heptanes. It has been reported by Gomez that a hydroxyl group adjacent to the cyclohexanone carbonyl greatly enhances the stereoselectivity in the reduction step by affording anchimeric delivery of the borohydride reagent to the carbonyl.[11c] However, in this system removal of the benzyl protecting groups from **12d** resulted in epimerization of the hydroxyl group adjacent to the ketone during the hydrogenation, and subsequent sodium borohydride reduction afforded a complex mixture.

Scheme 4. Scope of copper(I) mediated addition.

Table 2
Conditions and results of copper(I) mediated additions

Entry	R	R'	Condition	Yield (%)
12a		H	A	75
12b		F	B	73
12c		Cl	A	83
12d		Me	A	76
12e		CO_2Et	C	82
12f		OMe	A	79
12g		F	A	72
12h		—	A	70
12i	Me	—	A	50
12j		—	A	61
12k	*t*-Bu	—	A	77
12l		—	D	65

Conditions: A—commercial Grignard reagent; B—lithium/halogen exchange at −78 °C for 1 h; C—magnesium/iodine exchange at −40 °C for 40 min (see Ref. 10); D—magnesium/bromine exchange at −15 °C for 40 min.



Scheme 5. Selective reduction of cyclohexanone adducts. Reagents and conditions: (a) $NaBH_4$, THF–MeOH, −10 °C; **13a**:**13b** = 8:1; (b) DIBALH, THF–toluene, −78 °C; **13a**:**13b** = 1:4 (1:12 recrystallized).

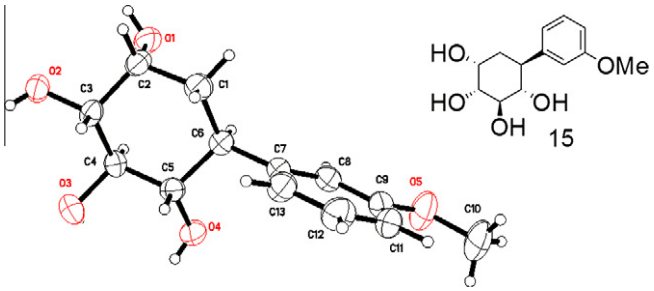


Figure 3. X-ray structure of 1-(3-methoxyphenyl)-1,6-dideoxyinositol **15**.

The route to the 1-substituted-1,6-dideoxyinositol targets was completed by hydrogenolysis of **13a** to deprotect the hydroxyl groups. Once the protecting groups had been removed, the diastereomeric aryl inositol products could be separated either by chromatography or crystallization. The *p*-tolyl adduct **12d** was converted into *p*-tolyl dideoxyinositol **14** as a single isomer in 53% overall yield. This chemistry was applied to *meta*-methoxy adduct **12f** to afford crystalline product **15** that confirmed the inositol C-5 stereochemical assignment by X-ray crystallography (Fig. 3).

In this Letter, we have demonstrated the stereoselective synthesis of 1-aryl-1,6-dideoxyinositols via the first reported organocuprate addition of aryl groups to a triethereal cyclohexenone derived from glucose. The highly substituted cyclohexanone provides a useful synthon for further elaboration into carbasugar systems. In this Letter, the novel cyclohexanone products were reduced with modest stereoselectivity and deprotected to afford either inositol C-5 hydroxyl stereoisomers.

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