JOC The Journal of Organic Chemistry

Article

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Synthesis of *allo*- and *epi*-Inositol via the NHC-Catalyzed Carbocyclization of Carbohydrate-Derived Dialdehydes

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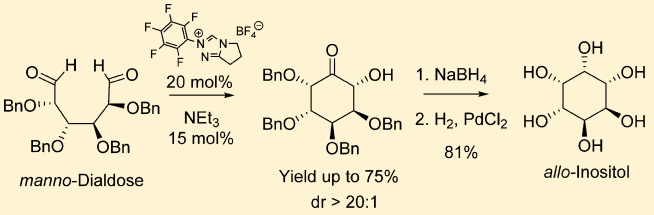
Supporting Information

ABSTRACT: A synthesis of carbocyclic sugars from carbohydrate-derived dialdehydes using organocatalysis has been developed. Sorbitol, mannitol, and galactitol were converted via 1,6-tritylation, perbenzylation or permethylation, detritylation, and Swern oxidation into 2,3,4,5-tetra-*O*-alkyldialdoses that were cyclized via the benzoin reaction promoted by a triazolium carbene. Manno- and galacto-configured dialdehydes gave predominantly single inosose stereoisomers in up to 75% yield if the mixture was acetylated prior to isolation while the gluco-dialdehyde afforded a mixture of three stereoisomers in 61% overall yield. The inososes were stereospecifically reduced using sodium borohydride and then deprotected to give *allo*- and *epi*-inositol in good yield that confirmed the structural and stereochemical assignments.



INTRODUCTION

The synthesis of natural products from inositols requires orthogonally protected derivatives that are difficult to access due to the numerous secondary alcohols of similar reactivity. An attractive route to these protected inositols is the cyclization of appropriately protected carbohydrates such as that developed by Ferrier, which when promoted by mercury(II) chloride or palladium(II) chloride generates cyclitols and deoxycyclitols from glycals and 6-deoxyglycals, respectively.[1,2] The Ferrier II reaction has found application in total synthesis, notably, the synthesis of (+)-galanthamine,[3] fumagillin analogue FR65814,[4] and both enantiomers of Calystegine B_2.[5] The demonstrated utility of the Ferrier II reaction has been a motivating factor in the development of alternative syntheses of inositols from sugars. Methods include the samarium diiodide mediated cyclizations combining a carbonyl and reactive partner,[6,7] radical cyclizations,[8] as well as nitroaldol cyclizations.[2,9] We envisaged that organocatalysis would furnish cyclic acyloins from carbohydrate-derived dialdehydes as an alternative to the Ferrier reaction or the samarium diiodide mediated reductive cyclization.

The use of *N*-heterocyclic carbenes (NHCs) as catalysts in organic synthesis is well established.[10−13] NHCs are able to catalyze a variety of transformations including transesterification,[14] Stetter reactions,[15,16] crossed benzoin condensations,[17−19] and Diels−Alder chemistry.[20] In particular, the triazolium carbenes developed by Rovis formed from precatalysts **1** and **2** by treatment with base show excellent stability and wide applicability (Figure 1).[21,22] In the case of the benzoin condensation, thiazolium and triazolium-type NHC catalysts show good reactivity with chiral catalysts able to promote stereoselective transformations. Intermolecular[17−19] and intramolecular[23−25] variants of the reaction have been

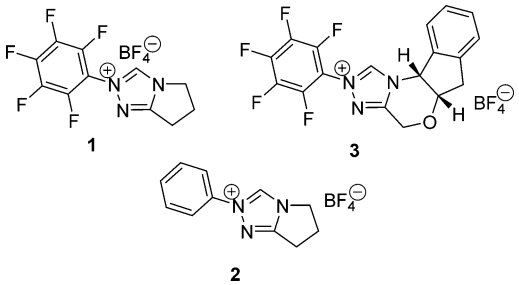


Figure 1. NHC precatalysts.

reported, usually using aromatic aldehydes that act as the Umpolung partner crossed with ketones or aldehydes. Enders et al. has reported intramolecular crossed benzoin reactions using a chiral triazolium catalyst using substochiometric quantities of base,[25] and more recently, Ema et al. reported the synthesis of chiral α-hydroxycyclohexanones by the cyclization of aliphatic keto-aldehydes using precatalysts **1** and **3**.[24] The application of organocatalysis to the cyclization of aliphatic dialdehydes is still relatively unexplored.

There have been some recent applications of organocatalysis in carbohydrate chemistry. The deoxygenation of hexoses and pentoses affording 2-deoxylactones can be affected using NHCs[26] and C-glycosylation can be achieved starting with 2-nitroglycals.[27] A 1995 patent claims the synthesis of D-*chiro*-inositol directly from glucodialdose using a thiazolium derived carbene in water; however, no information on yield, stereoselectivity, characterization data, or even the catalyst used was given.[28,29] There has been significant interest in the synthesis of

Received: March 19, 2014
Published: April 21, 2014

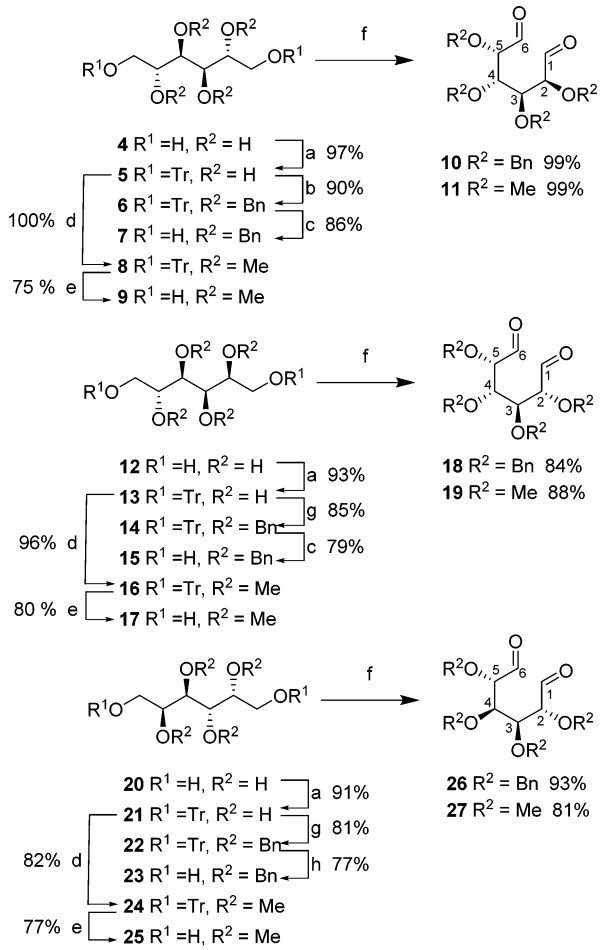
   dx.doi.org/10.1021/jo500645z | J. Org. Chem. 2014, 79, 5088−5096

inositols and their phosphorylated derivatives due to their function in the cell as intracellular messengers.[30] The preparation of partially protected inositols as described herein could lead to novel inositol phosphate isomers that may be of biological importance.

RESULTS AND DISCUSSION

Simple protocols have been established in the literature to generate suitably protected sugar-derived 1,6-dialdehyde substrates (Scheme 1).[7,31−34] Starting with mannitol (**4**), selective 1,6-bis-tritylation to give **5** followed by perbenzylation using sodium hydride/benzyl bromide afforded ether **6**.[35] Removal of the trityl groups under acid-catalyzed conditions afforded the 1,6-diol **7** that was then cleanly oxidized to the 1,6-dialdehyde **10** using Swern conditions.

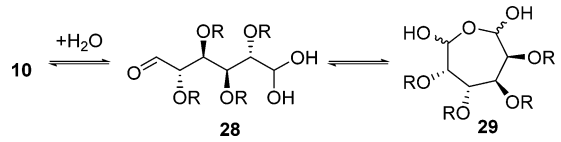
Scheme 1. Preparation of Carbohydrate-Derived 1,6-Dialdehydes



(a) TrCl, pyr., reflux, 1.5 h; (b) BnBr, NaH, Bu_4NI, THF 25 °C, 6 h, reflux, 19 h; (c) 2:1 DCM/MeOH, TFA, 18 h; (d) MeI, NaH, THF, 25 °C, 18 h; (e) 1:1 DCM/MeOH, TsOH, 18 h; (f) (i) $(COCl)_2$, DMSO, DCM, −78 °C, 25 min, (ii) Et_3N, −78 to 25 °C, 1.5 h; (g) BnBr, NaH, THF, 25 °C; (h) 3:1 toluene/MeOH, TFA, 65 °C, 16 h.

Although the synthesis of **10** is known,[34] the spectral data has not been reported. The dialdehyde **10** showed characteristic symmetry in the ^{1}H NMR spectrum with two aliphatic broad singlets and a single aldehyde resonance at δ 9.70 confirming the structure. Over 24 h, the resonances assigned to the dialdehyde disappeared and were replaced with a complex mixture of resonances tentatively assigned to products of hydration based upon a series of peaks in the ^{13}C NMR spectrum between δ 99.9 and 97.3 ppm (Scheme 2). The new

Scheme 2. Hydration of Dialdehyde 10



mixture that was in equilibrium with the dialdehyde as treatment with ethyl (triphenylphosphoranylidene)acetate afforded diethyl (2*E*,8*E*)-4,5,6,7-tetra(benzyloxy)decan-2,8-di-endioate as the sole product by NMR. The dialdehyde was not stable to silica gel chromatography and was stored at −15 °C after preparation.

As an alternative to benzyl protection on oxygen, the tetramethyl derivative **9** was also synthesized by permethylation of **5** using sodium hydride/methyl iodide and trityl removal. Swern oxidation afforded the dialdehyde **11**[31] as the sole product in 72% overall yield from mannitol.

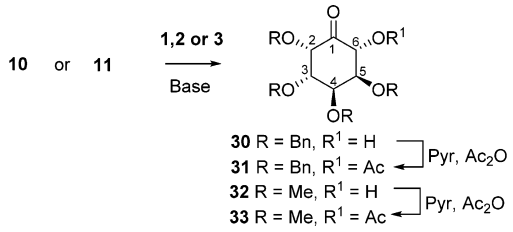
The dialdehydes **18** and **19**[36] and **26** and **27**[32] were similarly prepared from sorbitol (**12**) and galactitol (**20**), respectively. The aldehyde groups in both **18** and **19** are chemically nonequivalent while galactitol is *meso*-substituted, so **26** and **27** display symmetry in their NMR spectra. The symmetrical trityl ethers **6**, **21**, and **22** had reduced solubility; thus, crystallization without chromatography could be used for their purification.

Manno-dialdehydes **10** and **11** were chosen as initial substrates for carbocyclization due to their symmetry that simplifies the possibilities for cyclization, the results of which are shown in Table 1. The dialdehyde **10** was completely consumed within 24 h when stirred with **1**, **2**, or **3** and base, and a single inosose diastereomer was isolated from the reactions of **1** and **3** and assigned as inosose **30**. The relatively electron-rich precatalyst **2** yielded a complex mixture of products, and so, this catalyst was excluded from further study. Similar yields were obtained using methyl ether protected dial **11**, and the stereochemistry of the product was found to be the same. The choice of base played an important role in the reaction outcome for which there is ample literature precedence,[24,25] and triethylamine gave superior yields over DBU while early attempts utilizing potassium *tert*-butoxide gave complex mixtures. Analysis of the crude reaction mixtures by NMR suggested that yields should have been higher and that some material was decomposing during silica gel chromatography. Acetylation of the crude reaction mixture afforded an increased yield of cyclized material **31** that had greater stability during isolation (entry 6).

The assignment of the structure, conformation, and stereochemistry of the product was made on the basis of two-dimensional (2D) NMR experiments on **30** and its acetylated derivative **31**. Greater dispersion was seen in **31**, and so, its NMR and conformation are discussed (Figure 2). The assignment of protons around the ring in **31** was based on the COSY spectrum and began with the assignment of α proton H-6 that was shifted downfield to δ 5.62 ppm due to the attached acetate group. All protons showed crosspeaks to their neighbors. A 10.4 Hz $^3J_{H5-H6}$ coupling was observed that indicated a *trans*-diaxial relationship between these protons. The 3.2 Hz $^3J_{H5-H4}$ coupling indicated H-4 was gauche to the

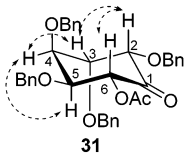
dx.doi.org/10.1021/jo500645z | J. Org. Chem. 2014, 79, 5088−5096

Table 1. NHC-Promoted Cyclization of 10 and 11



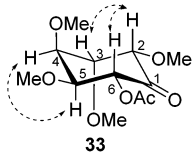
entry[a]	aldehyde	base (mol %)	precatalyst (mol %)	solvent	temp	time (h)	product	yield[b]
1	**10**	DBU (15)	**3** (20)	dioxane	100	24	**30**	22
2	**10**	DBU (15)	**1** (20)	dioxane	100	24	**30**	40−50
3[c]	**10**	NEt_3 (15)	**1** (20)	DCE	40	16	**30**	54
4	**10**	DBU (15)	**2** (20)	dioxane	25	24	–	–
5	**10**	NEt_3 (10)	**1** (15)	DCE	40	16	**30**	55
6[d]	**10**	NEt_3 (15)	**1** (20)	DCE	40	16	**31**	75
7	**11**	NEt_3 (15)	**1** (20)	DCE	40	16	**32**	62
8	**11**	NEt_3 (100)	**1** (20)	DCE	40	16	**32**	59

[a]Reactions were performed on 100−185 mg of dialdehyde using 50 mL/g solvent. [b]Isolated yield by flash chromatography. [c]Scale was 1.02 g of **10**. [d]The crude mixture was acetylated prior to chromatography.



31

$^3J_{H5\text{-}H6}$ 10.4 Hz $^3J_{H3\text{-}H4}$ 4.1 Hz
$^3J_{H4\text{-}H5}$ 3.2 Hz $^3J_{H2\text{-}H3}$ 3.2 Hz
$^4J_{H2\text{-}H6}$ 1.0 Hz



33

$^3J_{H5\text{-}H6}$ 10.6 Hz $^3J_{H3\text{-}H4}$ 4.1 Hz
$^3J_{H4\text{-}H5}$ 2.9 Hz $^3J_{H2\text{-}H3}$ 3.2 Hz
$^4J_{H2\text{-}H6}$ 0.9 Hz

Figure 2. Conformation, ROESY interactions (dashed arrows), and coupling constants of **31** and **33**.

axial H-5 and therefore H-4 was equatorial. The 2D ROESY NMR of **31** showed a through space interaction between H-2 and H-6 from which H-6 was assigned as *cis* to H-2 and axial. This made assignment of the stereochemistry of H-2 and H-3 possible due to the $^3J_{H2-H3}$ 3.2 Hz coupling and confirmed that no epimerization at other centers occurred. We also observed ^4J coupling between H-2 and H-6 across the carbonyl group in the COSY NMR. This coupling manifested as line broadening at H-2 and H-6 in the one-dimensional ^{1}H NMR at 600 MHz although a clear doublet of doublets was observed for H-2 at 300 MHz. Normally, ^4J couplings are observed along an M or W path where all elements are coplanar, but coplanarity is not required if the hydrogens are separated by an sp^2 hybridized center, and so, this coupling could not be used to assign stereochemistry.[37] The ^{13}C NMR spectra of **30** and **31** were assigned using the HSQC experiment, and products exhibited carbonyl resonances at δ 205 and 198 ppm, respectively. A carbonyl stretching frequency was observed in the infrared spectrum of **30** at 1732 cm^{-1} consistent with a cyclohexanone. Coupling around the ring for the methyl ether analogue **33** showed identical coupling patterns and similar ROESY interactions as depicted in Figure 2.

Sorbitol-derived dials **18** and **19** have no plane of symmetry, and so, four possible stereoisomers can arise from the cyclizations, the results of which are shown in Table 2. In the best case (entry 1), a 61% yield of cyclization products was isolated from the benzyl ether protected dialdehyde **18** using triethylamine with extensive chromatography required to separate all stereoisomers. Of the four expected stereoisomers from the reaction, two were produced with the other product resulting from epimerization of an α stereocenter. Surprisingly, one of the isomers **30** isolated from the reaction mixtures of **18** was identical to that isolated from the cyclization of manno-dialdehyde **10**. The stereochemistry of the starting materials differ at C-2, and epimerization must occur prior to or during the cyclization as the center is remote from the ketone moiety in the product. Cyclization was observed for the methyl ether analogue **19**; however, decomposition occurred on silica, and so, the diastereomers were not separated or characterized.

The reaction manifold for dialdehyde **18** is shown in Scheme 3. Isomer **30** results from epimerization at C-2 in the starting material **18** generating manno-dialdehyde **10** and then formation of the Breslow intermediate **43** at C-1 or C-6. Cyclization occurs through a possible transition state **44** that necessarily has two axial and two equatorial benzyl ethers and presumably an equatorial catalyst as this also allows for hydrogen bonding in the transition state. After proton transfer, the cyclization leads to the intermediate **45** that eliminates the catalyst affording observed **30**. The stereoisomer **34** can be derived directly from **18** by formation of the Breslow intermediate at C-1 to give **46** followed by cyclization of C-1 onto C-6 generating a new equatorial stereocenter via the possible transition state **47**. The cyclized intermediate **48** then eliminates the catalyst giving **34**. The pathway to isomer **35** involves formation of the regioisomeric Breslow intermediate **49** at C-6 and then cyclization of C-6 onto C-1 through a possible transition state **50** with three axial benzyl ethers and an equatorial catalyst (or its ring-flipped conformer) to afford **51** that eliminates the catalyst to give **35**. The observed conformation of **35** also has these three axial benzyl ethers, so it is reasonable to propose a transition state such as **50**. Isomer **35** was difficult to isolate analytically pure as the compound was prone to decomposition on silica gel and several columns were required to remove other isomers.

When **30**, **34**, and **35** were separately resubmitted to the reaction conditions, they were recovered unchanged indicating that the pathways to **30**, **34**, and **35** are under kinetic control. Higher temperatures improved the yield of products but did not greatly affect isomeric ratios.

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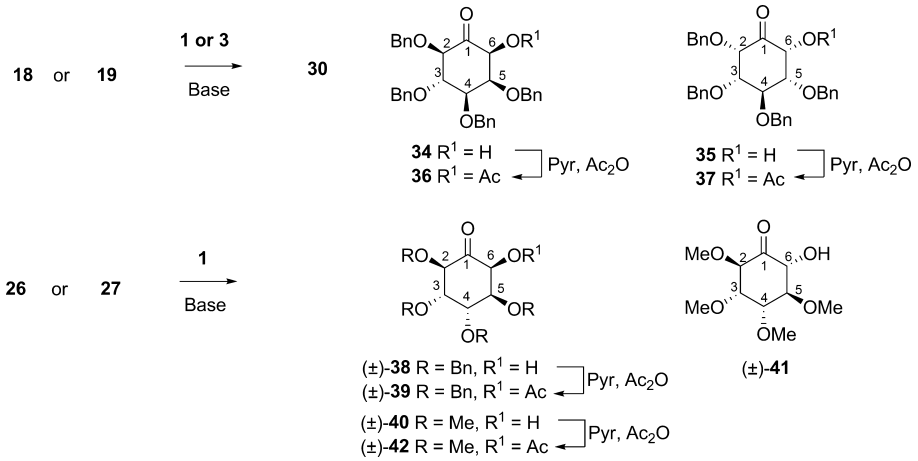
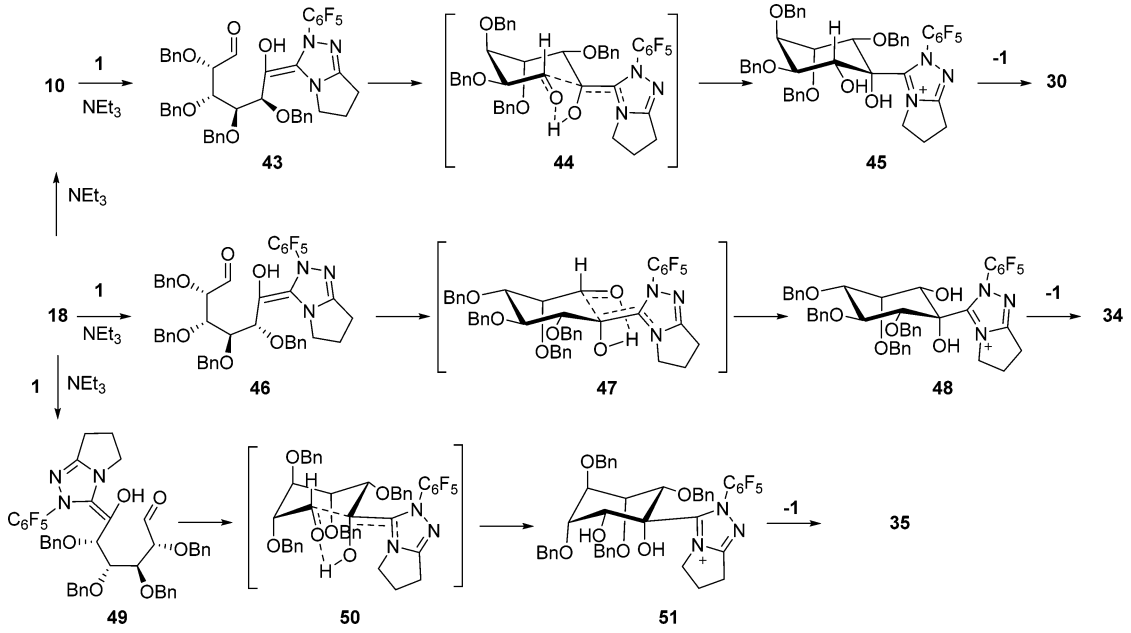
Table 2. Carbocyclizations of Gluco-dials 18 and 19 and Galacto-dials 26 and 27



entry[a]	aldehyde	base (mol %)	precatalyst (mol %)	solvent	temp	product	ratio[b]	yield
1[c]	**18**	NEt_3 (15)	**1** (20)	DCE	40	**30**:**34**:**35**	32:23:45	61
2	**18**	DBU (15)	**1** (20)	CH_3CN	40	**30**:**34**:**35**	ND[d]	25
3	**18**	DBU (15)	**1** (20)	dioxane	40	–	–	0
4[e]	**18**	DBU (15)	**1** (20)	DCE	25	**30**:**34**:**35**	42:19:39	35
5	**18**	NEt_3 (15)	**1** (20)	DCE	25	**30**:**34**:**35**	36:22:46	38
6	**18**	*i*-Pr_2NEt (100)	**1** (20)	DCE	40	**30**:**34**:**35**	ND[d]	33
7	**18**	imidazole	**1** (20)	DCE	40	**30**:**34**:**35**	ND[d]	38
8	**19**	NEt_3 (15)	**2** (20)	DCE	25	–	–[f]	0
9	**26**	NEt_3 (15)	**1** (20)	DCE	40	**38**	–	12
10	**26**	NEt_3 (100)	**1** (20)	DCE	40	**38**	–	12
11[g]	**26**	DBU (15)	**1** (20)	DCE	60	**38**	–	18
12	**27**	NEt_3 (15)	**1** (20)	DCE	60	**40**:**41**	92:8	65
13	**27**	NEt_3 (15)	**1** (20)	DCE	40	**40**:**41**	87:13	54

[a]Reactions were performed on 100−127 mg of dialdehyde in 50 mL/g solvent and left for 16 h and products isolated by flash chromatography. [b]Ratios determined from isolated products. [c]Scale was 1.7 g of **18**. [d]The mixture of isomers isolated from the first column was not further purified, and the ratio could not be accurately determined. [e]Reaction took 40 h to reach completion. [f]Decomposition occurred on silica gel. [g]Scale was 1.07 g of **11**.

Scheme 3. Reaction Manifold for Dialdehyde 18



The cyclization of benzyl ether protected galacto-dial **26** afforded a single stereoisomer **38** in low yield as well as , unidentified products (Table 2). Attempts to isolate the benzyl-protected **38** free from impurities were unsuccessful due to a

dx.doi.org/10.1021/jo500645z | J. Org. Chem. 2014, 79, 5088−5096

close running unidentified byproduct that lacked ketone resonances in the ^{13}C NMR, and so, the product was converted to the acetate derivative **39**. Due to the low yield of products, it was not clear if small amounts of other stereoisomers were produced in the reactions of **26**. Switching protecting groups to methyl ethers gave good yields for the cyclization reactions, and two isomers **40** and **41** were isolated from the reaction although the major isomer **40** was again isolated containing an impurity that was removed upon acetylation. On the basis of the stereochemistry of the products, it is clear that no epimerization occurs in the reactions of **26** and the stereoisomers are generated in the ring-closure step. As galacto-dials **26** and **27** are *meso*-substituted, the products of the cyclization are racemic, and we are yet to investigate enantioselective versions of the reaction for **26**.

The assignment of stereochemistry in the cyclization products **34**–**42** was based upon ROESY 2D NMR experiments and ^3J coupling constants predominantly using the acetate derivatives (Figure 3). The gluco-dial derived acetate

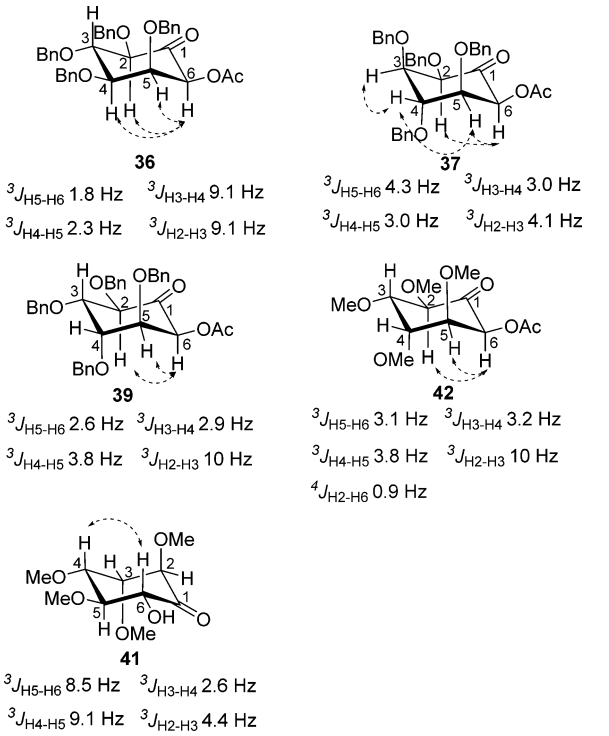


Figure 3. Conformation, selected ROESY interactions (dashed arrows), and coupling constants of **36**, **37**, **39**, **41**, and **42**.

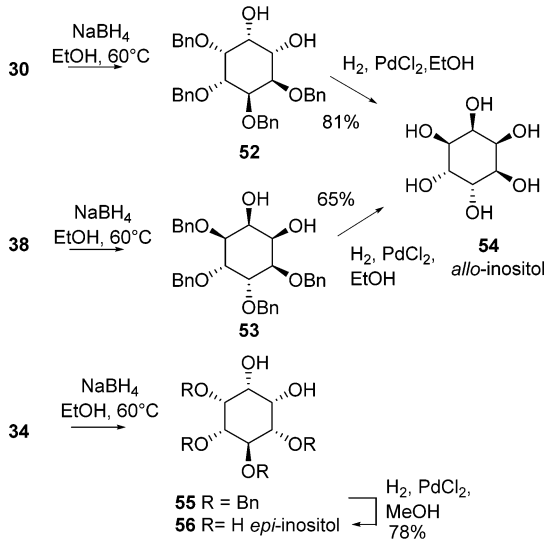
ester **36** exhibited 9.1 Hz *trans*-diaxial $^3J_{H2-H3}$ and $^3J_{H3-H4}$ couplings while the 2.3 Hz $^3J_{H4-H5}$ coupling indicated that H-4 also had an equatorial neighbor. The 2D ROESY NMR showed crosspeaks between H-2, H-4, and H-6 making H-6 axial and *cis* to the other axial hydrogens. Both **35** and its acetate derivative **37** lacked characteristic *trans*-diaxial couplings in their ^1H NMR spectra. Furthermore, it was difficult to isolate hydroxyketone **35** in an analytically pure state as it underwent some decomposition on silica. The ROESY spectrum of the acetate ester **37** showed a through-space interaction between H-2 and H-6 indicating that these atoms were *cis*- and axial. Coupling constants around the ring indicated all gauche couplings (2.9–4.7 Hz) assuming a chair structure, and H-3 and H-5 were therefore equatorial while the remaining center at H-4 was assigned on the basis of the stereochemistry of the starting material.

The major product from galacto-dials **26** and **27** were **38** and **40**, respectively, with both inososes having the same stereochemistry. In the acetate derivatives **39** and **42**, there is a single large *trans*-diaxial coupling between H-2 to H-3 with H-4 equatorial and *cis* to H-3. A ROESY interaction in the spectrum of **39** between H-2 and H-6 indicated an axial H-6 allowing for the assignment of the stereochemistry at C-6 and C-5 due to the J_{H5-H6} 2.6 Hz coupling.

The minor alcohol **41** is epimeric at the newly created hydroxyl center and ring-flipped relative to the major isomer **40** (and its acetate derivative **42**). Assignment of the stereochemistry in **41** was made on the basis of coupling constants supported by ROESY interactions between H-4 and H-6. The $^3J_{H5-H6}$ 8.5 Hz and $^3J_{H4-H5}$ 9.1 Hz couplings indicate that H-5 is axial and has two axial neighbors, and the small H-3 to H-4 coupling makes H-3 equatorial and *cis* to the axial H-4. The equatorial assignment of H-2 is supported by the lack of ROESY interactions seen with other axial protons and the stereochemistry of the starting material.

In order to demonstrate the utility of the cyclization process and to confirm the structure and stereochemistry assigned to these products, we investigated $NaBH_4$ reductions of hydroxyketones **30**, **34**, and **38** to generate protected inositols and ultimately inositols (Scheme 4).

Scheme 4. Synthesis of *allo*- and *epi*-Inositols from 30, 34, and 38



The reduction of hydroxyketone **30** gave a single product **52** in good yield; however, the diol **53** exhibited a broadened ^1H NMR spectrum from which it was difficult to assign resonances. Conformations were slowly exchanging at room temperature, and the spectrum at −100 °C gave only partially resolved signals. Removal of the benzyl groups using $PdCl_2/H_2$ gave an 81% yield of *allo*-inositol **54** for the two steps from which the stereochemistry of the reduction **30** was deduced. The *allo* stereochemistry of the diol explained the NMR as there is literature precedent for the slow conformational exchange of *allo*-inositol derivatives.[38] The reduction of the hydroxyketone **38** also yielded *allo*-inositol **54** as the final product in 65% overall yield after removal of the benzyl groups. The

dx.doi.org/10.1021/jo500645z | J. Org. Chem. 2014, 79, 5088–5096

intermediate diol **53** differed to diol **52** obtained from **30** in the position on the ring of the two hydroxyl groups; however, interpreting the NMR of the diol was again difficult due to coalescence near ambient temperature. The sodium borohydride reduction of the inosose **34** also afforded a single diol **55**. Hydrogenolysis of the benzyl groups yielded *epi*-inositol **56** from which the stereochemistry of the reduction could once more be deduced.

In all three reductions using sodium borohydride, the substrates have an axial 3-benzyloxy substituent hindering one face of the carbonyl that has been shown to control inosose reduction.[39] It is likely that the reactive conformations match the conformations determined by NMR as the alternative conformers have either three or four unfavorable axial benzyloxy groups. Furthermore, the alternative conformers would still have one axial 3-benzyloxy substituent and an axial 2-hydroxy substituent that would direct hydride to the opposite face to that observed.[40] According to the model developed by Cieplak[41] to explain reduction of cyclohexanones, the antibonding orbital ($\sigma_{\ddagger}^{*}$) of the incipient nucleophile is more stabilized by the C2−H axial bond than the C2−C3 bond, and so, the axial hydride approach is preferred. It is apparent that, in the reduction of **30**, **34**, and **38**, the stereoelectronic stabilization of the axial hydride approach cannot overcome the steric hindrance encountered on this face.

In conclusion, NHC catalysis provides a novel method for the synthesis of inosose derivatives in moderate to good yield from readily synthesized mannitol-, sorbitol-, and galactitol-derived 1,6-dialdehydes. While the reactions of manno- and galacto-dials yielded mainly single isomers from the cyclization, the reaction of gluco-dials yielded mixtures of hydroxyketone stereoisomers. Substitution of benzyl ethers by methyl groups dramatically improved the yield for the galacto-substituted dialdehyde indicating the sensitivity of the cyclization to stereochemistry and to steric effects. The inosose products of cyclization were converted to inositols by a stereoselective reduction using $NaBH_4$ and protecting group removal. The inositols were consistent with the assigned stereochemistry in the inosose products of cyclization. The synthesis of *allo*-inositol was achieved in an overall yield of 33% over six steps; however, *epi*-inositol was produced in low yield due to an unsatisfactory cyclization step. The chemistry of the inosose derivatives is currently being examined, and their use in synthesis will be reported in due course.

EXPERIMENTAL SECTION

General Experimental. Trityl chloride was recrystallized from acetyl chloride, NHC **1** was synthesized using a literature procedure,[22] and other catalysts were purchased from Strem Chemicals, Boston, MA, USA. Solvents were dried using literature procedures.[42] All other reagents are commercially available and were used as purchased. NMR performed in D_2O were referenced to internal 1,4-dioxane (^{1}H δ 3.75 ppm, ^{13}C δ 67.2 ppm), and spectra recorded in $CDCl_3$ were referenced to residual solvent. Melting points are uncorrected. HRMS were recorded in positive ESI V mode (source temperature, 80 °C; desolvation temperature, 150 °C; capillary, 2.5 kV). Ring protons in the ^{1}H NMR were assigned using COSY and ROESY spectra. Ring carbons were assigned in the ^{13}C NMR spectra using the HSQC experiment.

*General Procedure for Tritylation of **4**, **12**, and **20**.* To a solution of the alditol **4**, **12**, or **20** (1 equiv) in pyridine (5.5 mL/mmol) was added trityl chloride (2.2 equiv), and the mixture was heated under reflux for 1.5 h. The volatiles were removed under reduced pressure, and the residue was partitioned between DCM and saturated $NaHCO_3$. The aqueous phase was extracted with DCM until no product remained in the aqueous layer (TLC), and the combined organic extracts were washed with a further portion of saturated $NaHCO_3$ before drying (Na_2SO_4) and concentrating under reduced pressure. The residue was purified by flash chromatography (1:1 EtOAc/hexanes) to give the 1,6-di-*O*-tritylated alditols **5**[31] (7.10 g, 97%), **13**[36] (3.41 g, 93%), or **21**[32] (3.33 g, 91%). All products had ^{1}H and ^{13}C NMR spectra matching those previously reported.

*General Procedure for the Benzylation and Methylation of 1,6-Di-O-tritylated Alditols **5**, **13**, and **21**.* To a solution of 1,6-di-*O*-trityl alditol **5**, **13**, or **21** (1 equiv) in THF (6 mL/mmol) under N_2 was added either benzyl bromide (4.8 equiv) or methyl iodide (4.8 equiv). A 60% oil dispersion of NaH (4.8 equiv) was added gradually, and the mixture was stirred for 6 h and then heated under reflux overnight. If the reaction was incomplete (^{1}H NMR or TLC), Bu_4NI (0.15 equiv) was added, and the mixture was heated for a further hour before careful quenching with MeOH. The solvent was removed under reduced pressure, and the residue was partitioned between H_2O/DCM. The organic phase was collected and washed with a further portion of H_2O before being dried (Na_2SO_4) and concentrated under reduced pressure. Alditol **6**[35] (4.34 g, 90%) was recrystallized from DCM/MeOH. Alditol **14**[35] (1.70 g, 85%) was purified by flash chromatography using 9:1 hexanes/EtOAc, and **8**[31] (0.74 g, 100%), **16**[36] (1.25 g, 96%), and **24**[32] (0.90 g, 82%) were absorbed onto a bed of silica, washed with hexanes, and eluted with EtOAc. All products had ^{1}H and ^{13}C NMR matching those previously reported.

*General Procedure for Detritylation of Alditols **6**, **14**, and **22**.* To a solution of the protected alditol **6**, **14**, or **22** (1 equiv) in 2:1 MeOH/DCM (15 mL/mmol) was added TFA (1.0 mL/mmol), and the mixture was stirred overnight. The mixture was neutralized using saturated $NaHCO_3$ solution, and after ensuring no acid remained, the organic phase was collected, and the aqueous phase was extracted twice with DCM. The combined organic extracts were washed with a further portion of saturated $NaHCO_3$ before being dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (2:3 to 13:7 EtOAc/hexane) affording **7** (510 mg, 86%), **15** (1.40 g, 79%), or **23** (199 mg, 77%). All products had ^{1}H and ^{13}C NMR matching those previously reported.[33]

*General Procedure for Detritylation of Alditols **8**, **16**, and **24**.* To a solution of the protected sugar (1 equiv) in 1:1 DCM/MeOH (24 mL/mmol) was added *p*-TSA·H_2O (3.2 equiv), and the resulting mixture was stirred for 18 h. Solid Na_2CO_3 (3.3 equiv) was added, and the mixture was stirred for an additional 10 min before concentrating under reduced pressure. The residue was dissolved in DCM, and insolubles were removed by filtering through Celite. The volatiles were removed under reduced pressure, and the residue was purified by dry flash column chromatography (1:1 EtOAc/hexanes then 3:17 MeOH/EtOAc) to give **9**[31] (230 mg, 75%), **17**[36] (241 mg, 80%), or **25**[32] (594 mg, 77%). All products had ^{1}H and ^{13}C NMR matching those previously reported.

*General Procedure for the Swern Oxidation of 2,3,4,5-Tetra-O-alkyl Alditols **7**, **9**, **15**, **17**, **23**, and **25**.* To a solution of dry DMSO (4.8 equiv) in dry DCM (2.2 mL/mmol) at −78 °C under N_2 was added a solution of $(COCl)_2$ (2.4 equiv) in dry DCM (1.1 mL/mmol) slowly via syringe, care being taken that, during the addition, the temperature of the solution did not rise above −60 °C. The solution was stirred for 10 min before a solution of diol (1 equiv) in dry DCM (10.8 mL/mmol) was added slowly via syringe, again taking care that solution temperature did not rise above −60 °C, and the mixture was stirred for a further 20 min. Et_3N (5 equiv) was added, and the mixture was stirred at below −60 °C for 15 min before being allowed to come to room temperature (ca. 1.5 h). The solvent was removed under reduced pressure, and the residue was dissolved in diethyl ether and then filtered. The filtrate was concentrated under reduced pressure affording the crude dialdehydes **10**, **11**[31] (225 mg, 99%), **18**, **19**[36] (212 mg, 88%), **26**, or **27**[32] (0.80 g, 81%) that were used without further purification. Dialdehydes **11**, **19**, and **27** had ^{1}H and ^{13}C NMR matching those previously reported.

*2,3,4,5-Tetra-O-benzyl-D-manno-hexodialdose (**10**).* Pale yellow oil (0.99 g, 99%); $[\alpha]_D^{29}$ −2.3 (c 4.4, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (d, J = 1.3 Hz, 2H), 7.39−7.13 (m, 20H), 4.64 (d, J =

dx.doi.org/10.1021/jo500645z | J. Org. Chem. 2014, 79, 5088−5096

11.9 Hz, 2H), 4.60 (d, J = 11.4 Hz, 2H), 4.50 (d, J = 11.4 Hz, 2H), 4.42 (d, J = 11.9 Hz, 2H), 4.13 (br s, 2H), 4.05 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 136.6, 136.5, 127.7, 127.6, 127.3, 127.2, 127.2, 127.1, 82.6, 79.4, 72.9, 71.7; FT-IR (neat) 2858, 1721 cm^{-1}.

*2,3,4,5-Tetra-O-benzyl-D-gluco-hexodialdose (**18**).* Pale yellow oil (1.70, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 9.66 (d, J = 1.5 Hz, 1H), 7.37−7.14 (m, 20H), 4.82 (d, J = 11.7 Hz, 1H), 4.71 (br d, J = 11.7 Hz, 1H), 4.57−4.43 (m, 4H), 4.53 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.09−4.04 (m, 2H), 4.01−3.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 199.8, 137.1, 137.0, 137.0 (2C), 128.4, 128.3, 128.2, 128.2, 128.0, 127.9, 127.9, 127.7, 83.4, 81.6, 79.5, 78.7, 74, 73.6, 72.9, 72.6 (4 masked aryl C); FT-IR (neat) 3030, 2867, 1728 cm^{-1}.

*1,6-Di-O-trityl-2,3,4,5-tetrakis-O-benzyl-D-galactitol (**22**).* Prepared according to the general procedure and after quenching the reaction, water (20 mL) was added, and the precipitated solid was collected. The solid was washed with water (50 mL) and then triturated with methanol and dried to give a white crystalline solid (1.61 g, 81%); mp 211−215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.12 (m, 50H), 4.52 (d, J = 11.7 Hz, 2H), 4.47 (d, J = 12.3 Hz, 2H), 4.42 (d, J = 12.3 Hz, 2H), 4.36 (d, J = 11.7 Hz, 2H), 4.04−3.95 (m, 2H), 3.93−3.83 (m, 2H), 3.36 (dd, J = 10.0, 4.9 Hz, 2H), 3.30 (dd, J = 10.0, 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1. 138.92, 138.9, 128.7, 128.12, 128.1, 127.7, 127.6, 127.5, 127.2, 127.1, 126.9, 86.8, 79.0, 78.6, 73.5, 72.6, 63.9; FT-IR (neat) 3060, 2934, 2889, 1066 cm^{-1}; MS (ESI) 1049.5; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{72}H_{66}O_6Na$: 1049.4698; found 1049.4716.

*2,3,4,5-Tetrakis-O-benzyl-D-galactitol (**23**).*[33] To a solution of **22** (0.50 g, 0.48 mmol) in toluene (30 mL) at 100 °C was slowly added MeOH (10 mL) and then TFA (1.0 mL), and the mixture was heated under reflux for 6 h. The mixture was cooled to room temperature, poured onto a saturated solution of $NaHCO_3$ (20 mL), and stirred for 15 min. The organic phase was collected, and the aqueous phase was extracted again with toluene. The combined organic extracts were concentrated under reduced pressure, and the residue was purified by flash chromatography (2:3 to 1:1 EtOAc/hexane) affording **23** as a white powder (201 mg, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.17 (m, 20 H) 4.81−4.63 (m, 8 H) 4.03−3.96 (m, 2H) 3.92−3.74 (m, 6H), 2.54 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.4, 128.4, 128.4, 127.9, 127.9, 127.7, 80.3, 80.1, 74.3, 72.8, 66.5; (ESI-MS): m/z 565 [M + Na]$^+$.

*2,3,4,5-Tetra-O-benzyl-D-galacto-hexodialdose (**26**).* Pale yellow oil, (1.07 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 2H), 7.40−7.10 (m, 20H), 4.66 (br d, J = 11.8 Hz, 2H), 4.49 (d, J = 11.8 Hz, 2H), 4.47 (d, J = 11.4 Hz, 2H), 4.34 (br d, J = 11.4 Hz, 2H), 4.16−4.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 137.0 (2C), 128.3, 128.2, 128.1, 128.1, 127.8, 127.7, 83.3, 78.3, 73.6, 73.2; FT-IR (neat) 3027, 2907, 2872, 1731, 1026 cm^{-1}.

General Procedure for NHC-Mediated Carbocylizations of Dialdehydes. To a suspension of precatalyst **1** (0.20 equiv) in DCE (5 mL) under N_2 was added a solution of Et_3N in DCE (1.00 M, 0.15 equiv), and the mixture was stirred for 10 min. A solution of dialdehyde (1 equiv) in DCE (50 mL/g) was then added, and the mixture was maintained at 25−60 °C as specified in Tables 1 and 2 for 16−40 h. The solvent was removed under reduced pressure, and the residue was taken up in a minimal volume of DCM, filtered through a bed of silica, and washed through with 1:1 EtOAc/hexane (ca. 20 mL) for reactions of **10**, **18**, and **26** or neat EtOAc for **11**, **19**, and **27**. The products were further purified as specified.

*(2S,3S,4R,5R,6R)-2,3,4,5-Tetrakis(benzyloxy)-6-hydroxycyclohexanone (**30**).* Purified by column chromatography (3:7 EtOAc/hexanes) to give a light yellow syrup (550 mg, 54%); $[\alpha]_D^{30}$ −35.6 (c 5.9, DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−6.96 (m, 20H), 4.86 (d, J = 11.7 Hz, 1H), 4.85 (d, J = 12.3 Hz, 1H), 4.75 (d, J = 11.7 Hz, 1H), 4.68 (d, J = 12.3 Hz, 1H), 4.63−4.55 (m, 3H, H2 and H6), 4.48 (d, J = 11.7 Hz, 1H), 4.44 (d, J = 12.3 Hz, 1H), 4.40 (d, J = 12.3 Hz, 1H), 3.95 (dd, J = 3.8, 3.8 Hz, 1H, H3), 3.82−3.72 (m, 2H, H4 and H5), 3.53 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 138.5, 137.9, 137.8, 137.6, 128.6, 128.5, 128.45, 128.4, 128.38, 127.9, 127.89, 127.8, 127.7, 82.5, 80.5, 77.9, 76.6, 75.2, 73.8, 73.6, 73.5, 72.7 (3 masked aryl C); FT-IR (neat) 3469, 3030, 2872, 1732, 1104, 1027, 1026 cm^{-1}; MS (ESI) m/z 561 [M + Na]$^+$; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{34}H_{34}O_6Na$ 561.2253; found 561.2250.

Typical Procedure for the Acetylation of Hydroxyketones. To a solution of the hydroxyketone (0.10−0.20 mmol) in pyridine (1 mL) was added acetic anhydride (50 μL, 0.53 mmol), and the mixture was stirred overnight. The solvent was removed by azeotropic distillation with toluene, and the residue was purified by flash chromatography (1:3 to 3:7 EtOAc/hexanes for **31**, **36**, **37**, and **39**; 4:1 EtOAc/hexanes for **33** and **42**).

*(2S,3S,4S,5S,6R)-6-Acetoxy-2,3,4,5-tetrakis(benzyloxy)-cyclohexanone (**31**).* Colorless syrup (90 mg, 65%); $[\alpha]_D^{23}$ −24.2 (c 1.2, DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45−7.18 (m, 18H), 7.17−7.10 (m, 2H), 5.62 (dd, J = 10.4, 1.0 Hz, 1H, H6), 4.89 (d, J = 11.7 Hz, 1H), 4.74 (d, J = 12.9 Hz, 1H), 4.72 (d, J = 12.9 Hz, 1H), 4.64 (d, J = 12.3 Hz, 1H), 4.58 (d, J = 3.2, 1.0 Hz, 1H, H2), 4.52 (d, J = 12.1 Hz, 1H), 4.50 (d, J = 12.3 Hz, 1H), 4.41 (d, J = 12.3 Hz, 1H), 4.40 (d, J = 12.3 Hz, 1H), 4.04 (dd, J = 10.4, 3.2 Hz, 1H, H5), 3.94 (dd, J = 4.1, 3.2 Hz, 1H, H3), 3.81 (dd, J = 4.1, 3.2 Hz, 1H, H4), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5 (C1), 169.9 (CO_2), 137.9, 137.8, 137.7, 128.45, 128.4, 128.3, 127.9, 127.85, 127.8, 127.7, 81.0 (C2), 78.9 (C5), 77.7 (C3), 77.6 (C6), 75.0 (C4), 73.8, 73.7, 73.6, 72.8, 29.7 (6 masked aryl C); FT-IR (neat) 3030, 2871, 1742 (br) cm^{-1}; MS (ESI) m/z 581 [M + H]$^+$, 603.2 [M + Na]$^+$; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{36}H_{36}O_7Na$ 603.2359; found 603.2360.

*(2S,3S,4R,5R,6R)-6-Hydroxy-2,3,4,5-tetramethoxycyclohexanone (**32**).* Purified by column chromatography (9:1 EtOAc/hexanes) to give a colorless syrup (115 mg, 62%); $[\alpha]_D^{32}$ 30.0 (c 7.1, DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.44 (d, J = 9.7 Hz, 1H, H6), 4.30 (dd, J = 3.5, 1.5 Hz, 1H, H2), 4.00 (dd, J = 4.1, 3.5 Hz, 1H, H3), 3.89 (dd, J = 4.1, 2.9 Hz, 1H, H4), 3.60 (s, 3H), 3.56 (s, 3H), 3.50 (s, 3H), 3.46 (s, 3H), 3.41 (dd, J = 9.7, 2.9 Hz, 1H, H5); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.7 (C1), 84.4 (C5), 82.8 (C2), 79.3 (C3), 76.2 (C6), 75.8 (C4), 60.0, 59.9, 59.2, 58.9; FT-IR (neat) 3472, 2934, 2833, 1734 cm^{-1}; MS (ESI) m/z 257 ([M + Na]$^+$); HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{10}H_{18}O_6Na$ 257.1001; found 257.0995.

*(2S,3S,4S,5S,6R)-6-Acetoxy-2,3,4,5-tetramethoxycyclohexanone (**33**).* Crystalline solid (35 mg, 99%); mp 67−70 °C; $[\alpha]_D^{30}$ 6.1 (c 0.33, DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.46 (br d, J = 10.6 Hz, 1H, H6), 4.27 (dd, J = 3.2, 0.9 Hz, 1H, H2), 3.95 (dd, J = 4.1, 3.2 Hz, 1H, H3), 3.91 (dd, J = 4.1, 2.9 Hz, 1H, H4), 3.69 (dd, J = 10.6, 2.9 Hz, 1H, H5), 3.60 (s, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 3.45 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.2 (C1), 169.9 (CO_2), 83.1 (C2), 80.8 (C5), 79.1 (C3), 77.4 (C6), 75.9 (C4), 60.0, 59.9, 59.3, 59.0, 20.7 (CH_3); FT-IR (neat) 2922, 2838, 1750, 1728 cm^{-1}; MS (ESI) m/z 299 [M + Na]$^+$; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{12}H_{20}O_7Na$ 299.1107; found 299.1100.

*(2R,3S,4R,5R,6S)-2,3,4,5-Tetrakis(benzyloxy)-6-hydroxycyclohexanone (**34**).* Purified by column chromatography (3:7 EtOAc/hexane then 1:19 MeOH/toluene) to give a white solid (232 mg, 14%); mp 129−131 °C; $[\alpha]_D^{27}$ −6.7 (c 1.8, DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52−7.12 (m, 20H), 4.93 (d, J = 11.7 Hz, 1H), 4.90 (d, J = 10.6 Hz, 1H), 4.88 (d, J = 11.6 Hz, 1H), 4.86 (d, J = 10.6 Hz, 1H), 4.73 (d, J = 11.7 Hz, 1H), 4.73 (d, J = 11.7 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 11.7 Hz, 1H), 4.20−4.16 (m, 2H), 4.14 (dd, J = 2.3, 2.3 Hz, 1H), 4.12 (dd, J = 8.8, 1.2 Hz, 1H), 3.80 (dd, J = 9.4, 2.3 Hz, 1H), 3.41 (d, J = 6.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.2, 138.4, 138.0, 137.9, 137.3, 128.5, 128.4, 128.3, 128.2, 128.14, 128.1, 127.93, 127.9, 127.7 (2C), 127.69, 127.6, 83.6, 82.5, 79.8, 77.9, 76.1, 74.9, 74.7, 73.6, 73.2; FT-IR (neat) 3430, 3030, 2867, 1734 cm^{-1}; MS (ESI) m/z 561 [M + Na]$^+$, 577.2 [M + K]$^+$; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{34}H_{34}O_6Na$ 561.2253; found 561.2247.

*(2S,3S,4R,5S,6R)-2,3,4,5-Tetrakis(benzyloxy)-6-hydroxycyclohexanone (**35**).* Purified by column chromatography (3:7 EtOAc/hexane and 1:19 MeOH/toluene) to give a light yellow syrup (463 mg, 27%); $[\alpha]_D^{28}$ −40.4 (c 0.6, DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50−7.20 (m, 18H), 7.12−7.06 (m, 2H), 4.88 (d, J = 11.7 Hz, 1H), 4.73 (d, J = 12.3 Hz, 1H), 4.58−4.54 (m, 4H) 4.48−4.43 (m, 2H), 4.39 (d, J =

dx.doi.org/10.1021/jo500645z | J. Org. Chem. 2014, 79, 5088−5096

12.3 Hz, 1H), 4.36 (d, J = 12.3 Hz, 1H), 4.25−4.20 (m, 1H), 4.18−4.13 (m, 1H), 3.80 (dd, J = 2.8, 2.8 Hz, 1H), 3.36 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 138.0, 137.71, 137.7, 137.0, 128.5, 128.4, 128.3, 128.2, 128.0, 127.79, 127.75, 127.7, 127.6, 127.5, 82.2, 81.3, 80.3, 74.3, 73.6, 73.2, 73.0, 72.7, 72.3 (2 masked aryl C); FT-IR (neat) 3429, 3030, 2871, 1731, 1069, 1026 cm^{-1}; MS (ESI) m/z 561 [M + Na]$^+$; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{34}H_{34}O_6Na$ 561.2253; found 561.2261.

*(2R,3S,4S,5S,6S)-6-Acetoxy-2,3,4,5-tetrakis(benzyloxy)-cyclohexanone (**36**).* Colorless syrup (13 mg, 81%); $[\alpha]_D^{24}$ −15.0 (c 0.53, EtOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44−7.17 (m, 20H), 5.15 (d, J = 1.8 Hz, 1H, H6), 4.93 (d, J = 11.1 Hz, 1H), 4.90 (d, J = 10.5 Hz, 1 H), 4.84 (d, J = 10.5 Hz, 1H), 4.81 (d, J = 12.1 Hz, 1H), 4.78 (d, J = 12.1 Hz, 1H), 4.72 (d, J = 11.7 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 11.1 Hz, 1H), 4.20 (dd, J = 9.1, 9.1 Hz, 1H, H3), 4.12 (dd, J = 2.3, 1.8 Hz, 1H, H5), 4.11 (br d, J = 9.1 Hz, 1H, H2), 3.84 (dd, J = 9.1, 2.3 Hz, 1H, H4), 2.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.6 (C1), 169.8 (CO_2), 138.4, 137.8, 137.75, 137.5, 128.5, 128.4, 128.3, 128.2, 128.19, 128.1, 128.0, 127.9, 127.85, 127.7, 127.66, 127.6, 83.9 (C2), 82.1 (C3), 80.0 (C4), 76.1, 75.8 (C6), 75.2 (C5), 74.1, 73.7, 73.2, 20.6; FT-IR (neat) 3030, 2921, 2864, 1758, 1739, 1095, 1074, 1025 cm^{-1}; MS (ESI) m/z 581 [M + H]$^+$, 603.2; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{36}H_{36}O_7Na$ 603.2359; found 603.2341.

*(2S,3S,4S,5R,6R)-6-Acetoxy-2,3,4,5-tetrakis(benzyloxy)-cyclohexanone (**37**).* Yellow syrup (13 mg, 40%); $[\alpha]_D^{34}$ −25.0 (c 0.60, EtOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40−7.22 (m, 18H), 7.10−7.06 (m, 2H), 5.48 (d, J = 4.7 Hz, 1H, H6), 4.92 (d, J = 11.7 Hz, 1H), 4.75 (d, J = 12.3 Hz, 1H), 4.59 (d, J = 12.5 Hz, 1H), 4.54 (d, J = 12.3 Hz, 1H), 4.54 (d, J = 12.5 Hz, 1H), 4.48 (br d, J = 4.1 Hz, 1H, H2), 4.38 (d, J = 11.0 Hz, 1H), 4.35 (d, J = 11.0 Hz, 1H), 4.22−4.19 (m, 1H, H3), 4.18−4.15 (m, 1H, H5), 3.83 (dd, J = 2.9, 2.9 Hz, 1H, H4), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9 (C1), 170.0, 138.2, 137.8, 137.7,136.9, 128.6, 128.4, 128.24, 128.2, 127.9 (2 × C), 127.83, 127.8, 127.7, 127.6, 127.5, 80.9 (C3), 80.5 (C2), 80.2 (C5), 75.4 (C6), 73.5, 73.3 (C4), 73.0, 72.7, 72.5, 20.7 (1 masked aryl C); FT-IR (neat) 3030, 2925, 2869, 1761, 1740, 1065, 1026 cm^{-1}; MS (ESI) m/z 581 [M + H]$^+$, 603 [M + Na]$^+$; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{36}H_{36}O_7Na$ 603.2359; found 603.2369.

*(±)-(2R,3S,4R,5S,6S)-6-Acetoxy-2,3,4,5-tetrakis(benzyloxy)-cyclohexanone (**39**).* Colorless oil (14 mg, 17% from dialdehyde **26**); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45−7.41 (m, 2H), 7.34−7.22 (m, 16H), 7.11−7.06 (m, 2H), 5.61 (d, J = 2.6 Hz, 1H, H6), 4.92 (d, J = 11.3 Hz, 1H), 4.83 (d, J = 11.9 Hz, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 11.9 Hz, 1H), 4.58 (d, J = 10 Hz, 1H, H2), 4.57 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.34 (d, J = 11.9 Hz, 1H), 3.98 (dd, J = 10.0, 2.9 Hz, 1H, H3), 3.91 (dd, J = 3.8, 2.6 Hz, 1H, H5), 3.84 (dd, J = 3.8, 2.9 Hz, 1H, H4), 2.19 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.8 (C1), 169.8 (CO_2), 138.3, 137.9, 137.6, 137.3, 128.5, 128.4, 128.3, 128.29, 128.05, 128.0, 127.95, 127.92, 127.9, 127.71, 127.67, 127.66, 83.6 (C2), 80.4 (C3), 76.7 (C5), 75.9 (C6), 74.7 (C4), 74.2, 73.9, 73.8, 73.4, 20.7; FT-IR (neat) 3030, 2869, 1741 (br), 1227, 1103, 1043, 1026 cm^{-1}; MS (ESI) m/z 603 [M + Na]$^+$, 619 [M + K]$^+$; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{36}H_{36}O_7Na$ 603.2332; found 603.2337.

*(±)-(2R,3S,4S,5R,6S)-6-Hydroxy-2,3,4,5-tetramethoxycyclohexanone (**40**).* Purified by column chromatography (9:1 EtOAc/hexane) to give a colorless syrup (76 mg, 60%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.53 (dd, J = 3.9, 0.9 Hz, 1H, H6), 4.14 (dd, J = 9.7, 0.9 Hz, 1H, H2), 3.91 (dd, J = 3.9, 3.5 Hz, 1H, H5), 3.87 (dd, J = 3.5, 3.2 Hz, 1H, H4), 3.57 (s, 3H), 3.52 (dd, J = 9.7, 3.2 Hz, 1H, H3), 3.52 (s, 3H), 3.51 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.3 (C1), 85.0 (C2), 82.6 (C3), 79.6 (C5), 76.1 (C4), 74.3 (C6), 60.1, 59.7, 59.64, 59.6; FT-IR (neat) 3459, 2932, 2832, 1736, 1111, 1092, 1062 cm^{-1}; MS (ESI) 257 [M + Na]$^+$; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{10}H_{18}O_6Na$ 257.1001; found 257.0995.

*(±)−(2R,3S,4S,5R,6R)-6-Hydroxy-2,3,4,5-tetramethoxycyclohexanone (**41**).* Colorless syrup (5 mg, 5%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.44 (d, J = 8.5 Hz, 1H, H6), 3.84 (d, J = 4.4 Hz, 1H, H2), 3.82 (dd, J = 4.4, 2.6 Hz, 1H, H3), 3.77 (dd, J = 9.1, 2.6 Hz, 1H, H4), 3.63 (s, 3H), 3.54 (s, 3H), 3.43 (s, 3H), 3.42 (dd, J = 9.1, 8.5 Hz, 1H, H5), 3.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) 206.6 (C1), 84.7 (C5), 81.1 (C2), 80.3 (C4), 77.6 (C3), 76.1 (C6), 60.7, 59.0, 59.0, 58.2; FT-IR (DCM solution) 3492, 2941 2841, 1746, 1103 cm^{-1}; MS (ESI) 257 [M + Na]$^+$; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{10}H_{18}O_6Na$ 257.1001; found 257.0997.

*(±)-(2R,3S,4R,5S,6S)-6-Acetoxy-2,3,4,5-tetramethoxycyclohexanone (**42**).* Colorless syrup (33 mg, 56%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.53 (dd, J = 3.1, 0.9 Hz, 1H, H6), 4.14 (br d, J = 10.0 Hz, 1H, H2), 3.94 (dd, J = 3.8, 3.2 Hz, 1H, H5), 3.89 (dd, J = 3.8, 3.2 Hz, 1H, H4), 3.59 (s, 3H), 3.57 (dd, J = 10.0, 3.2 Hz, 1H, H3), 3.53 (s, 3H), 3.52 (s, 3H), 3.46 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.5 (C1), 169.8 (CO_2), 85.2 (C5), 82.1 (C3), 78.2 (C5), 76.3 (C4), 75.9 (C6), 59.8, 59.72, 59.7 (2 × C), 20.7; FT-IR (neat) 2935, 2834, 1741, 1229, 1113, 1089, 1070, 1052 cm^{-1}; MS (ESI) 299 [M + Na]$^+$; HRMS (ESI) m/z: calcd for $C_{12}H_{20}O_7Na$ [M + Na]$^+$: 299.1107; found 299.1105.

*allo-Inositol (**54**).*[43] To a solution of hydroxyketone **30** (50 mg, 93 μmol) in EtOH (2 mL) was added $NaBH_4$ (7 mg, 0.19 mmol), and the mixture was heated under reflux for 1 h. The solvent was removed under reduced pressure, and the residue was filtered through a plug of silica eluting with EtOAc. Following concentration, the residue was purified by column chromatography (50% EtOAc/hexanes), and the main fraction (R_f = 0.4) was collected. The purified diol was taken up in EtOH (2 mL), $PdCl_2$ (1 mg) was added, and the heterogeneous mixture was stirred under an atmosphere of H_2 for 16 h. The mixture was then filtered through Celite and washed through with a small portion of H_2O. Removal of solvents gave the title compound as a crystalline solid (13 mg, 81%); mp 280 °C (dec); lit.[44] 270−280 °C (dec); ^{1}H NMR (300 MHz, D_2O) δ 4.05−3.95 (m, 4H) 3.93−3.85 (m, 2H); FT-IR (neat) 3348 br, 2919 cm^{-1}; MS (ESI) 203 [M + Na]$^+$.

*epi-Inositol (**56**).*[45] A solution of hydroxyketone **34** (65 mg, 0.12 mmol) in EtOH (2 mL) was treated with $NaBH_4$ (8 mg, 0.21 mmol) as per **30** to yield a crystalline solid (17 mg, 78%); mp 280 °C (dec.) lit.[46] 305 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.06 (dd, J = 3.1, 2.8 Hz, 2H), 3.83 (t, J = 9.9 Hz, 1H), 3.72 (t, J = 3.1 Hz, 1H), 3.47 (dd, J = 9.9, 2.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.1, 72.4, 70.6, 67.4; FT-IR (neat) 3447, 3372, 3285, 3234, 2912 cm^{-1}; MS (ESI) 203 [M + Na]$^+$.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, and selected 2D NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

K.S. would like to thank the Australian Government for an APA award, and we thank the University of New England for an internal research grant.

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