Novel Synthesis of Enantiomerically Pure Natural Inositols and Their Diastereoisomers

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The various inositol polyphosphates have been found to trigger many important biological processes. Although the knowledge of this phosphoinositide signaling system has been discovered in the past 10 years, many factors remain unclear. For this reason, there is an increased demand for supplies of D-*myo*-inositol and particularly of novel analogues to investigate these biological mechanisms in more detail. Herein, we report the efficient syntheses of all diastereoisomers of inositol starting with 6-*O*-acetyl-5-enopyranosides. Conversion of 6-*O*-acetyl-5-enopyranosides into the corresponding substituted cyclohexanones (Ferrier-II rearrangement) was found to proceed efficiently with a catalytic amount of palladium dichloride. Stereoselective reduction of β-hydroxy ketones obtained provided the precursors to all inositol diastereoisomers in good to excellent yields and with high stereoselectivities. Good accessibility of these enantiomerically pure inositol diastereoisomers results in the efficient syntheses of D-*myo*-inositol 1,4,5-trisphosphate and D-*myo*-inositol 1,3,4,5-tetrakisphosphate.

Introduction

The inositols belong to an important class of biologically active compounds, the cyclitols.[1] The major study concerning inositols has been devoted to one of the isomers, *myo*-inositol. Of the nine possible stereoisomers, *myo*-inositol is generally the most abundant.[2] It is widespread in all higher organisms and most microorganisms and plays very important roles in cellular signal transduction.[3] In particular, D-*myo*-inositol 1,4,5-trisphosphate, Ins(1,4,5)P_3, acts as a second messenger by binding to specific receptors on the endoplasmic reticulum, thus stimulating the release of calcium ions from intracellular stores. The increased cytosolic Ca^{2+} concentration initiates a number of cell-type specific physiological responses[4] Ins(1,4,5)P_3 is metabolized by phosphorylation at position 3 to give D-*myo*-inositol 1,3,4,5-tetrakisphosphate, Ins(1,3,4,5)P_4. The biological functions of Ins(1,3,4,5)P_4 are less clear than that of Ins(1,4,5)P_3 but involve the regulation of calcium homeostasis through the stimulation of calcium entry into the cell and/or the modulation of various intracellular calcium pools.[5] Realization of the fundamental cellular role played by *myo*-inositol phosphates has led to increases in biological and chemical approaches to unravel the details of these complex pathways. Despite a large understanding of *myo*-inositol and its phosphates,[6] there is still no definite knowledge of the biological functions of the other eight stereoisomers:[7] *cis*-inositol, *epi*-inositol, *allo*-inositol, *muco*-inositol, *neo*-inositol, D-*chiro*-inositol, L-*chiro*-inositol, *scyllo*-inositol. Four stereoisomers (*neo*-inositol, D-*chiro*-inositol, L-*chiro*-inositol, *scyllo*-inositol) are recognized to be in nature, yet the other four isomers (*cis*-inositol, *epi*-inositol, *allo*-inositol, *muco*-inositol) are the unnatural synthetic products. As to *cis*-inositol, it is known that it readily forms the strong complexes with metal cations and with anions.[8] Furthermore, the isolation of inositol polyphosphates receptors[9] has led to an understanding of the structure recognition parameters. Subsequently, the application of analogues of inositols to the identifica-

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tion of specific binding subunits has also been reported.[10] To investigate how receptor to receptor−inositol interactions, the synthesis of a series of inositol isomers and their phosphorylated derivatives would be desiable. For these reasons, we wished to prepare inositol diastereoisomers, which should be good tools for the chemical and biological research. Herein, we report the novel and practical syntheses of all nine stereoisomers of inositol as enantiomerically pure forms starting from 6-*O*-acetyl-5-enopyranosides. We further describe the total syntheses of D-*myo*-inositol 1,4,5-trisphosphate and D-*myo*-inositol 1,3,4,5-tetrakisphosphate utilizing this method. Furthermore, the present procedure provides the synthetic possibility for all isomers of the inositol polyphosphates.

Results and Discussion

General Strategy. Our approach relies on the Ferrier-II carbocyclization, which is well-established for the conversion of 6-deoxyhex-5-enopyranosides into the corresponding chiral-substituted cyclohexanones.[11] This reaction has been conveniently used for the syntheses of natural products and carbocyclic analogues of carbohydrates.[12] There have been several reports concerning the improvement of the reaction conditions of this rearrangement. Lukacs[12a] and Ogawa[12b] have independently developed the use of a catalytic amount of Hg(II) salts as effective promoters. Recently, we revealed that the effective use of a catalytic amount (5 mol %) of $PdCl_2$[13] promoted the conversion of a variety of 6-deoxyhex-5-enopyranosides into cyclohexanones and found that the reaction proceeded stereoselectively in good yields.[14,15] Independently, the Bender and Prestwich groups have shown that the terminally substituted enol esters also undergo the Ferrier-II carbocyclization in the presence of a stoichiometric amount of Hg(II) salts. Utilizing this rearrangement, they developed a novel route to enantiomerically pure *myo*-inositol derivatives.[16] These observations prompted us to examine the $PdCl_2$-catalyzed reaction of 6-*O*-acetyl-5-enopyranosides with of Hg(II) salts as promoters. We further envisioned that penta-oxygenated cyclohexanones prepared from 6-*O*-acetyl-5-enopyranosides might be precursors to all of the inositol diastereoisomers. Although there are many reports on the synthesis of each inositol diastereoisomer,[17] few attempts have so far been made at a systematic approach to all inositol diastereoisomers. [17p]

As outlined retrosynthetically in Scheme 1, 6-*O*-acetyl-5-enopyranosides prepared from methyl glucoside, methyl galactoside, and methyl mannoside will be converted into cyclohexanones through Ferrier-II carbocyclization. Stereoselective reduction of the cyclohexanones will provide a series of diastereoisomers of inositol in the protected forms. According to this route, we initially investigated the carbocyclization mediated by $PdCl_2$.

Carbocyclization of 6-*O*-Acetyl-5-enopyranosides Mediated by $PdCl_2$.[18] The substrates, enol acetates, were prepared from known pyranosides[19] as shown in Scheme 2.

Oxidation of methyl 2,3,4-tri-*O*-benzylglycosides **1**−**3** by Moffat's procedure[20] provided the corresponding unstable aldehydes, which were immediately treated with acetic anhydride in the presence of appropriate bases to afford the desired enol acetates (**4**−**6**). In all cases, the *Z*-isomers were predominantly obtained, and each isomer could be isolated through column separation. Thus, we examined initially the reactivities of the *Z*- and *E*-isomers of **4**−**6** (**4a** and **4b**, **5a** and **5b**, **6a** and **6b**, respectively) to clarify the catalytic activity of $PdCl_2$ (Table 1).

Treatment of glucoside Z-isomer **4a** with 5 mol % of $PdCl_2$ in aqueous dioxane at 60 °C for 3 h afforded the penta-oxygenated cyclohexanone in 81% yield as a 49:24:17:10 (**7a**, **7b**, **7c**, and **7d**) diastereoisomeric mixture

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Scheme 1

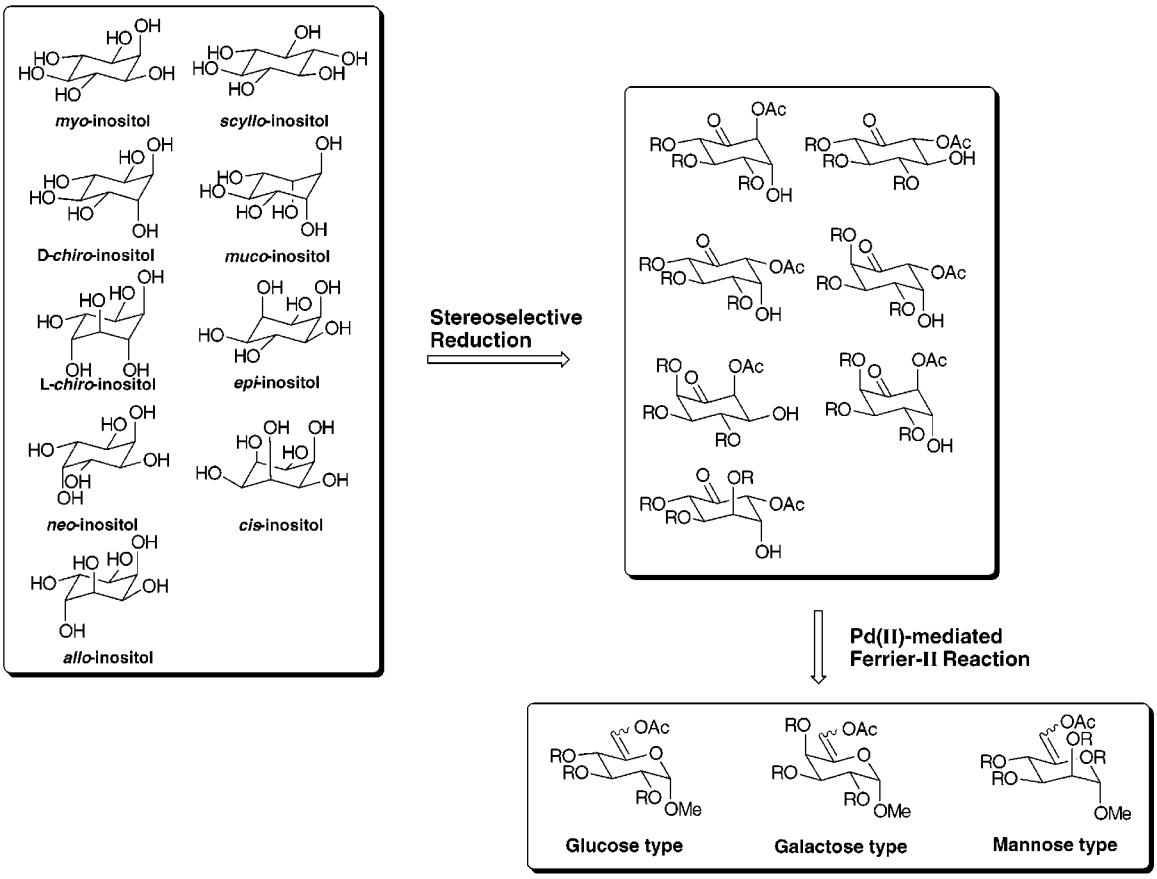
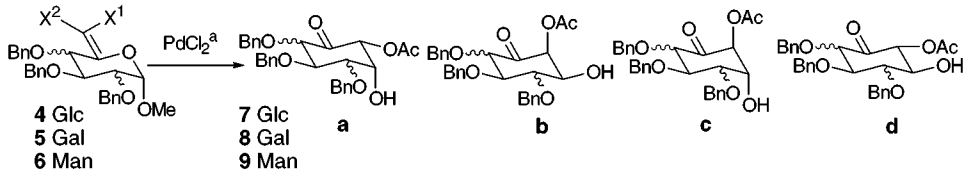


Table 1. $PdCl_2$-Mediated Ferrier-II Reaction of 6-*O*-Acetyl-5-enopyranosides

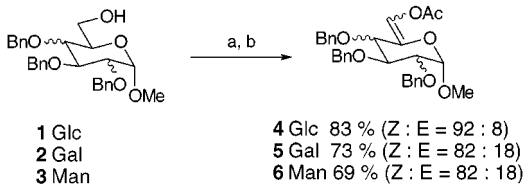


entry	substrates			$PdCl_2$ (eq)	solvent	yield (%)	a : b : c : d[b]
1	Glc	**4a**	X^1=OAc X^2=H	0.05	dioxane - H_2O (4:1)	81	49 : 24 : 17 : 10
2		**4b**	X^1=H, X^2=OAc	0.05	dioxane - H_2O (2:1)	N.R.	———
3				0.10	dioxane - H_2O (2:1)	75	50 : 23 : 15 : 11
4	Gal	**5a**	X^1=OAc X^2=H	0.05	dioxane - H_2O (2:1)	88	40 : 11 : 42 : 7
5		**5b**	X^1=H, X^2=OAc	0.05	dioxane - H_2O (2:1)	15	44 : 12 : 37 : 7
6	Man	**6a**	X^1=OAc X^2=H	0.05	dioxane - H_2O (2:1)	76	100
7		**6b**	X^1=H, X^2=OAc	0.05	dioxane - H_2O (2:1)	58	100

(entry 1). In marked contrast, the *E*-isomer **4b** was scarcely transformed into the corresponding cyclohexanone within 3 h (entry 2). Interestingly, increasing the amount of palladium chloride to 10 mol % promoted the reaction of **4b** (entry 3). In the case of galactoside, the reaction of *Z*-isomer **5a** also proceeded smoothly to give cyclohexanone in 88% yield as a 40:11:42:7 (**8a**, **8b**, **8c**, and **8d**) mixture.[21] The reaction of **5b** under the same conditions afforded the cyclohexanone as a diastereoisomeric mixture in a similar ratio but in poor yield. As for mannoside, *Z*-isomer **6a** and *E*-isomer **6b** yielded only

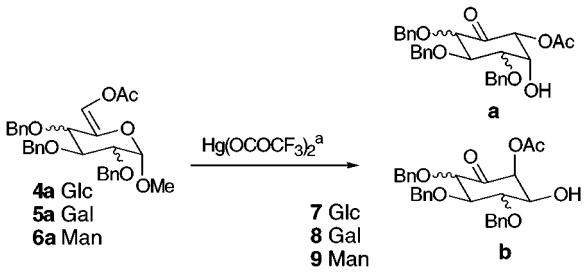
(21) Carbocyclization of **5a** was reported to give **8a**, **8b**, **8c**, and **8d** (11:40:42:7).[18] Further evidence indicated that major products were **8a** and **8c** as reported in this paper.

Scheme 2[a]



[a] Key: (a) DCC, DMSO, pyridine, TFA, benzene, rt, 12 h; (b) Ac_2O, Et_3N, DMAP, $ClCH_2CH_2Cl$, 100 °C, 2 h.

Table 2. $Hg(OCOCF_3)_2$-Mediated Ferrier-II Reaction of 6-*O*-Acetyl-5-enopyranosides



entry	substrates	solvent	yield (%)	a : b [b]
1	Glc **4a**	acetone - H_2O (4:1)	20	80 : 20
2	Gal **5a**	dioxane - H_2O (2:1)	75	48 : 52
3	Man **6a**	dioxane - H_2O (2:1)	19	100

[a] Conditions: 60 °C, 3 h, 0.05 equiv of $Hg(OCOCF_3)_2$ was employed. [b] The assignment of the ratio was based on the ^1H NMR (400 MHz) analysis of the diastereoisomeric mixtures.

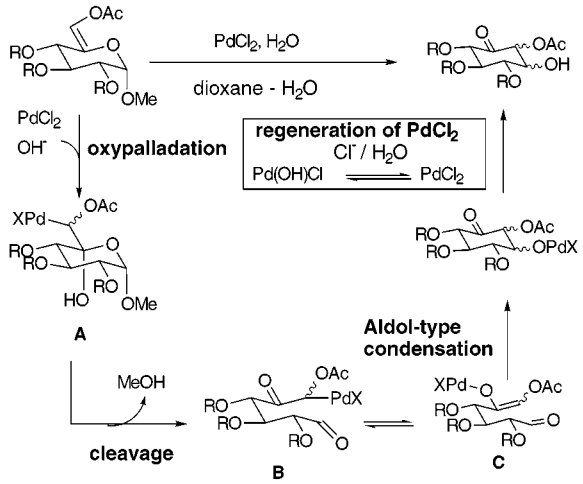
9a as a single product, respectively. It is noteworthy that the geometry of the enol acetates did not affect the stereochemical outcome of the reaction (entries 1 and 3, 4 and 5, 6 and 7). This observation suggests that the stereochemical integrity at the C-6 position of the substrates must be lost during or prior to the subsequent cyclization. Similar stereochemical scrambling at the C-6 of enopyranosides with a Hg(II) salt promoter has been reported by Bender[16a] and Kakinuma independently,[22] and this fact would support our speculation.

We next examined the catalytic activity of Hg(II) salt for a comparison with that of $PdCl_2$ (Table 2).

The glucoside *Z*-isomer **4a** was treated with 5 mol % of $Hg(OCOCF_3)_2$ under the similar conditions mentioned above to afford the penta-oxygenated cyclohexanone in 20% yield as a 80:20 (**7a** and **7b**) diastereoisomeric mixture (entry 1). In this case, the other two diastereoisomers were not detected spectroscopically. Similarly, **5a** gave only **8a** and **8b** in 75% with a ratio of 48:52 (entry 2). In the case of mannoside **6a**, the formation of **9a** was observed as a single isomer but in low yield (entry 3).

These results showed that the use of a palladium catalyst was essential to carry out this transformation at a practical reaction rate (compare Tables 1 and 2). The higher efficacy of palladium chloride compared with $Hg(OCOCF_3)_2$ as a catalyst might be attributed to the coordination effect of the palladium salt to a C−C double bond in the initial oxypalladation step of the reaction. A more interesting observation was that the ratio of the diastereomixtures of the products obtained was dependent on the choice of a promoter. With glucoside **4a** and galactoside **5a**, although the $Hg(OCOCF_3)_2$-catalyzed process provided only two diastereoisomers, the four isomers which are essential for the preparation of all of the inositol diastereoisomers could only be obtained at once using $PdCl_2$ as the promoter (compare Table 1, entries 1 and 4, and Table 2, entries 1 and 2). In our previous study on the Ferrier-II carbocyclization of terminally unsubstituted enopyranosides by palladium chloride and mercury salt, no remarkable difference in diastereoisomeric ratio was observed. However, dependent on the choice of a promoter, the enol acetates of glucose and galactose were converted into the corresponding carbocycles in a distinct diastereoisomer distribution, which could be easily separable over silica gel chromatography. This method enables the independent synthesis of all nine inositol diastereomers.

Scheme 3



Mechanistic Consideration

Judging from these results, the Pd(II) salt- and Hg(II) salt-catalyzed Ferrier-II carbocyclization of enol acetates may proceed via different reaction courses.

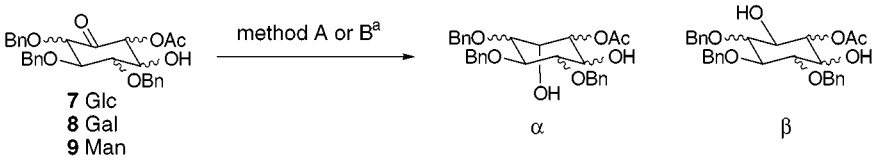
With respect to $PdCl_2$, in the course of the reaction (Scheme 3), oxypalladation to the enol acetate component of 6-*O*-acetyl-5-enopyranoside occurs to give the unstable hemiacetal **A**. Subsequently, hemiacetal **A** loses methanol to afford the dicarbonyl intermediate **B**, which is the precursor of the enolate **C**. This then takes part in an aldol-like intramolecular cyclization to give the cyclohexanone. Although the formation of palladium enolate **C** is not clear at present, it might be a crucial step for this carbocyclization.

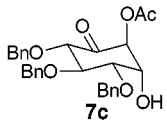
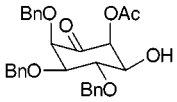
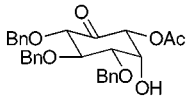
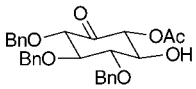
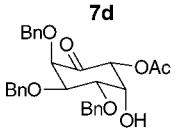
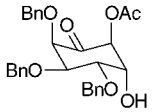
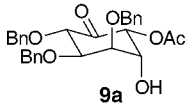
Stereoselective Reduction.[23] Encouraged by these results, we then focused on the stereoselective reduction of these β-hydroxycyclohexanones, which would satisfy the stereochemical requirements of all of the naturally occurring inositols and their unnatural diastereoisomers. Among the several reducing agents, $Me_4NBH(OAc)_3$, which reduces usually β-hydroxyl ketones to their cor-

(22) Yamauchi, N.; Terachi, T.; Eguchi, T.; Kakinuma, K. *Tetrahedron* **1994**, *50*, 4125−4136.

(23) Takahashi, H.; Kittaka, H.; Ikegami, S. *Tetrahedron Lett.* **1998**, *39*, 9707−9710.

Table 3. Stereoselective Reduction of the β-Hydroxycyclohexanes



entry	substrate	method	conditions	yield	α : β [b]	
1	 **7c**	A	0 °C, 3 h	91 %	<1 : 99	→ **D-*chiro*-inositol**[c]
2		B	0 °C, 0.5 h	84 %	87 : 13	→ **muco-inositol**[c]
3	 **8b**	A	r.t., 24 h	46 %	70 : 30	
4		B	-78 °C, 0.5 h	90 %	<1 : 99	→ **epi-Inositol**[c]
5	 **7a**	A	r.t., 3 h	94 %	<1 : 99	
6		B	0 °C, 0.5 h	97 %	>99 : 1	→ **myo-inositol**[c]
7	 **7d**	A	r.t., 24 h	37 %	78 : 22	
8		B	0 °C, 0.5 h	86 %	22 : 78	→ **scyllo-inositol**[c]
9	 **8a**	A	0 °C, 3 h	93 %	<1 : 99	→ **neo-inositol**[c]
10		B	-78 °C, 0.5 h	88 %	98 : 2	
11	 **8c**	A	r.t., 48 h	N.R.	– : –	
12		B	0 °C, 0.5 h	96 %	<1 : 99	→ **allo-inositol**[c]
13	 **9a**	A	0 °C, 3 h	92 %	<1 : 99	→ **L-*chiro*-inositol**[c]
14		B	-40 °C, 0.5 h	92 %	98 : 2	

[a] Method A: $Me_4NBH(OAc)_3$ (5.0 Equiv), $CH_3CN-AcOH$. Method B: $NaBH_4$ (1.5 Equiv), MeOH. [b] The assignment of the ratio was based on the ^1H NMR (400 MHz) analysis of the diastereomixtures. [c] All the products were deacetylated (NaOH, MeOH) and successively debenzylated ($Pd(OH)_2/C$, H_2).

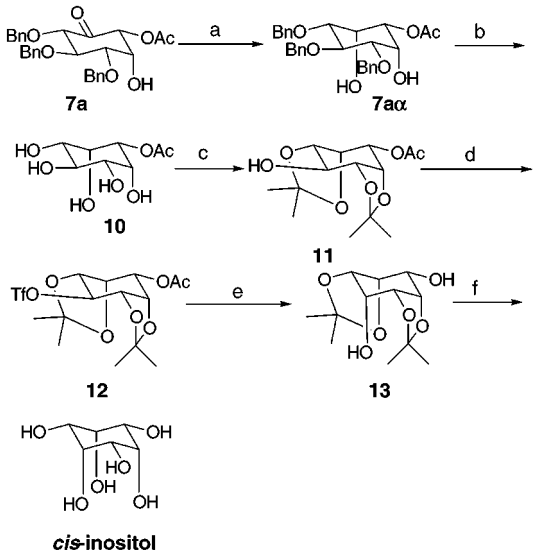
responding anti diols with high diastereoselectivity, and $NaBH_4$ were examined as comparative reducing agents (Table 3).

As shown in Table 3,[24] the reduction of β-hydroxyketones **7c**, **7a**, **8a**, and **9a** with $Me_4NBH(OAc)_3$ (method A)[25] provided anti diols in good yields with excellent diastereoselectivities (entries 1, 5, 9, and 13). The intramolecular delivery of a hydride directed by the β-hydroxyl group, as proposed by Evans, may account for high diastereoselectivity. Unfortunately, β-hydroxyketones **8b**, **7d**, and **8c** were not reduced or were in diminished yields, and moreover, low diastereoselectivities were observed in this method. Comparison of the NMR spectra of these substrates suggests that the conformations of **8b**, **7d**, and **8c** differ significantly from those of **7c**, **7a**, **8a**, and **9a**. These conformational changes may prevent the chelation of a hydroxyl group with the reducing reagent. Reduction with $NaBH_4$ (method B) was also performed for comparison. As shown in Table 3, high diastereoselectivities were attained for all substrates tested. It should be pointed out that the stereochemical course of $NaBH_4$ reduction was complementary to that of $Me_4NBH(OAc)_3$ reduction. We speculate that a hydride complex attacked from the less hindered site of ketones because $NaBH_4$ could not coordinate to the hydroxyl group. Overall, the set of reductions presented in Table 3 provided the eight stereoisomers (D-*chiro*-, *muco*-, *epi*-, *myo*-, *scyllo*-, *neo*-, *allo*-, L-*chiro*-) of the inositols in protected form (see Table 3). The only isomer, i.e., *cis*-inositol, that was not provided in Table 3 was easily derived from **7a** (vide infra).

(24) The reduction of **8b** with $Me_4NB(OAc)_3$ was reported to provide **8ba** in excellent yield.[22] Further evidence indicated that **8ba** and **8bb** were obtained as mixtures (70:30) shown in Table 3.

(25) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

Scheme 4[a]



[a] Key: (a) $NaBH_4$, MeOH, 0 °C, 30 min, 97%; (b) H_2, $Pd(OH)_2$/C, MeOH, rt, 12 h, quant; (c) concd H_2SO_4, acetone, 0 °C, 1 h, 83%; (d) Tf_2O, pyridine, CH_2Cl_2, rt, 1 h, 89%; (e) (i) CF_3COOCs, 18-crown-6, toluene, DMF, 80 °C, 1.5 h, (ii) satd $NaHCO_3$, rt, 1 h, 78% from **11**; (f) TFA, MeOH, 60 °C, 3 h.

Reduction of the β-hydroxyketone **7a** with $NaBH_4$ furnished **7a**α in 97% yield as a single diastereoisomer (Scheme 4). Removal of the benzyl groups from **7a**α with H_2 in the presence of $Pd(OH)_2$ on carbon was accomplished furnishing the pentaol **10** in quantitative yield. Next, we examined the regioselective protection of the pentaol and found that the reaction with acetone under acidic conditions provided **11** in 83% yield as a single product. The inversion of the hydroxyl group of **11** was successfully proceeded by the reaction of the corresponding triflate **12** with CF_3COOCs and 18-crown-6[26] followed by saponification with $NaHCO_3$, to afford **13**. **13** was deprotected under acidic conditions to afford *cis*-inositol in 78% yield.

Synthesis of the Nine Diastereoisomers of Inositol. For conversion to the other free inositols, **7c**β was deacetylated (NaOH, MeOH) and successively debenzylated ($Pd(OH)_2$/C, H_2) to afford D-*chiro*-inositol in quantitative yield. Similarly, **7c**α and **8b**α were independently converted into *muco*-inositol, **8b**β and **7a**α into *epi*-inositol, **7a**β and **7d**α into *myo*-inositol, **7d**β into *scyllo*-inositol, **8a**β into *neo*-inositol, **8a**α, **8c**β, and **9a**α into *allo*-inositol, and **9a**β into L-*chiro*-inositol. Thus, all nine inositol diastereoisomers obtained, the spectra of which were fully consistent with reported data.[27]

Synthesis of D-*myo*-Inositol-1,4,5-trisphosphate. Scheme 5 shows our synthetic route.

The synthesis of D-*myo*-inositol 1,4,5-trisphosphate started from **14** (Scheme 5). After protection of the primary alcohol as a TBDMS ether, the secondary alcohol was protected as a benzyl ether. Treatment of **16** with TBAF in THF afforded **17** in 95% yield. Moffat oxidation gave aldehyde, which was, without further purification, transformed into the enol acetate **18** by the reaction of Et_3N, DMAP, and Ac_2O. Ferrier-II carbocyclization of **18** in the presence of a catalytic amount of $PdCl_2$ furnished the β-hydroxyketone **19** in 53% isolated yield. Stereoselective reduction with $Me_4NBH(OAc)_3$ provided the anti diol **20** in good yield. BOM groups were readily introduced to diols **21** in 78% yield with BOMCl and diisopropylethylamine. Sequential deacetylation by basic methanolysis and deprotection of the MPM groups with DDQ in wet CH_2Cl_2 afforded the triol **23**. Treatment of the triol **23** with bis(benzyloxy)(*N*,*N*-diisopropylamino)-phosphine in the presence of tetrazole and the oxidation gave the fully protected Ins(1,4,5)P_3 derivative **24**. Finally, hydrogenolysis of the benzyl groups and BOM groups provided the optically active D-*myo*-inositol 1,4,5-trisphosphate **25** in 99% yield, identical with an authentic sample in all respects.[28]

Synthesis of D-*myo*-Inositol-1,3,4,5-tetrakisphosphate. Having established the synthesis of D-*myo*-inositol-3,4,5-trisphosphate, the synthesis of D-*myo*-inositol-1,3,4,5-tetrakisphosphate was the next challenging target (Scheme 6).

The 4,6-*O*-methoxybenzylidene group of **26** was regioselectively removed to afford **27** in 64% yield. Moffat oxidation and successive transformation into the enol acetate gave **28**. Ferrier-II carbocyclization of **28** in the presence of a catalytic amount of $PdCl_2$ furnished the β-hydroxyketone **29** with the desired stereoselectivity in 29% isolated yield. Stereoselective reduction with $Me_4NBH(OAc)_3$ provided the anti diol **30** in 96% yield. The BOM groups were readily introduced to the diols **31** in 86% yield with BOMCl and diisopropylethylamine. Sequential deacetylation by basic methanolysis and deprotection of the MPM groups with DDQ in wet CH_2Cl_2 afforded the tetrol **33**. Treatment of the tetrol **33** with bis(benzyloxy)(*N*,*N*-diisopropylamino)phosphine in the presence of tetrazole and the oxidation gave the fully protected Ins(1,3,4,5)P_4 derivative **34**. Finally, hydrogenolysis of the benzyl groups and the BOM groups provided D-*myo*-inositol 1,3,4,5-tetrakisphosphate, Ins(1,3,4,5)P_4, **35**, in an optically pure form, identical with an authentic sample in all respects.[29]

Conclusions

We have demonstrated that all of the inositol diastereoisomers can be prepared from methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside, methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside, and methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside utilizing Ferrier-II carbocyclization mediated by $PdCl_2$. Our synthetic approach offers the following attributes: (i) the starting materials are readily available in low cost; (ii) $PdCl_2$-catalyzed Ferrier-II carbocyclization of methyl 6-*O*-acetyl glycopyranosides efficiently provides adequate precursors of all inositol diastereoisomers; (iii) stereoselective reduction of the pentaoxygenated cyclohexanones is controlled by $Me_4NB(OAc)_3$ and $NaBH_4$ in a complementary manner. Overall, we have described a novel strategy to synthesize a series of inositol diastereoiso-

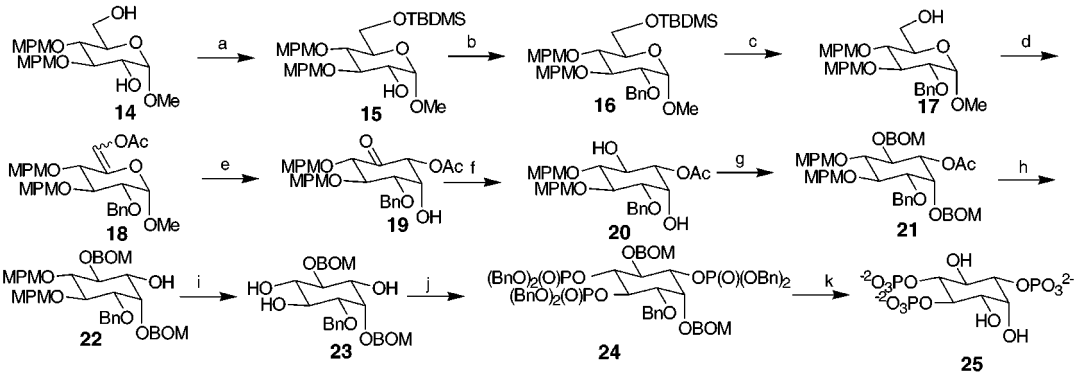
(26) (a) Sato, K.; Yoshitomo, A.; Takai, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 885−890. (b) Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, 1555−1556.

(27) For characterization, see: (a)Angyal, S. J.; Ordier, L. *Carbohydr. Res.* **1982**, *100*, 43−54. (b) Sasaki, K.; Hicks, K. B.; Nagahashi, G. *Carbohydr. Res.* **1988**, *183*, 1−9.

(28) For NMR spectroscopy, see: Lindon, J. C.; Baker, D. J.; Farrant, R. D.; Williams, J. M.*Biochem. J.* **1986**, *233*, 275−277.

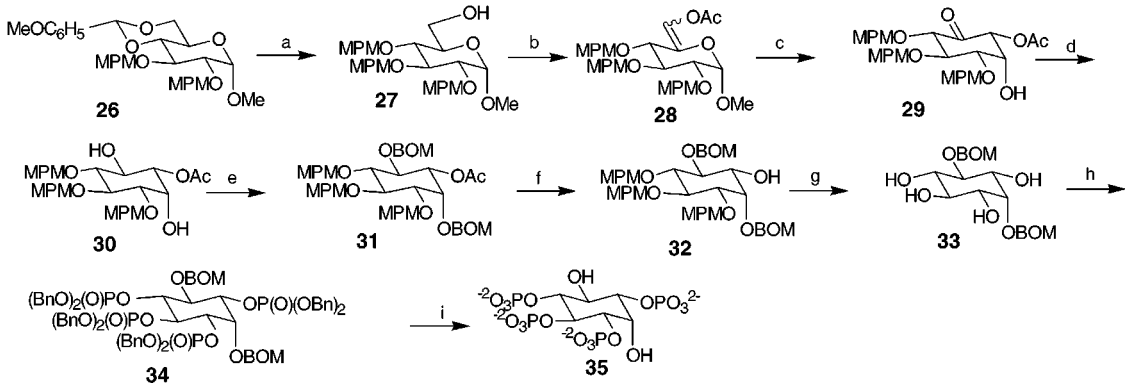
(29) For NMR spectroscopy, see: (a) Lindon, J. C.; Baker, D. J.; Williams, J. M.; Irvine, R. F. *Biochem. J.* **1987**, *244*, 591−595. (b) Cerdan, S.; Hansen, C. A.; Johanson, R.; Inubushi, T.; Williams, J. R. *J. Biol. Chem.* **1986**, *261*, 14676−14680.

Scheme 5[a]



[a] Key: (a) TBDMSCl, imidazole, DMF, 0 °C, 30 min, 94%; (b) NaH, BnBr, DMF−THF, rt, 30 min, 82%; (c) TBAF, THF, rt, 1 h, 95%; (d) (i) DCC, DMSO, TFA, PhH, rt, 12 h, (ii) Ac_2O, Et_3N, DMAP, $ClCH_2-CH_2Cl$, reflux, 5 h, 80%; (e) $PdCl_2$, dioxane−H_2O, 60 °C, 8 h, 53%; (f) $Me_4NBH(OAc)_3$, AcOH−CH_3CN, rt, 3 h, 81%; (g) BOMCl, *i*-Pr_2NEt, $ClCH_2CH_2Cl$, reflux, 5 h, 78%; (h) NaOH, MeOH, 60 °C, rt, 10 min, 81%; (i) DDQ, CH_2Cl_2−H_2O, rt, 1 h, 80%; (j) (i) $(BnO)_2P(i\text{-}Pr_2N)$, tetrazole, CH_2Cl_2, rt, 12 h, (ii) *m*-CPBA, Na_2HPO_4, rt, 1 h, 89%; (k) H_2, $Pd(OH)_2$/C, MeOH, rt, 12 h, 99%.

Scheme 6[a]



[a] Key: (a) TMSCl, $NaBH_3CN$, −20 °C 30 min, 64%; (b) (i) DCC, DMSO, TFA, PhH, rt, 12 h, (ii) Ac_2O, Et_3N, DMAP, $ClCH_2CH_2Cl$, reflux, 5 h, 63%; (c) $PdCl_2$, dioxane−H_2O, 60 °C, 4 h, 29%; (d) $Me_4NBH(OAc)_3$, AcOH−CH_3CN, rt, 3 h, 96%; (e) BOMCl, *i*-Pr_2NEt, $ClCH_2CH_2Cl$, reflux, 3 h, 86%; (f) NaOH, MeOH−THF, rt, 2 h, 94%; (g) DDQ, CH_2Cl_2−H_2O, rt, 3 h, 98%; (h) (i) $(BnO)_2P(i\text{-}Pr_2N)$, tetrazole, CH_2Cl_2, rt, 24 h, (ii) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, rt, 2 h, 76%; (i) H_2, $Pd(OH)_2$/C, MeOH, rt, 48 h, 98%.

mers. Furthermore, we applied this methodology to the syntheses of D-*myo*-inositol 1,4,5-trisphosphate and D-*myo*-inositol 1,3,4,5-tetrakisphosphate efficiently. As we have presented, this approach will be widely applicable to the synthesis of all natural and unnatural analogues of phosphoinositols. The biological uses of these derivatives will be reported in due course.

Experimental Section

General Procedures. Melting points are uncorrected. IR spectra were measured with an FT/IR spectrometer. Mass spectra were measured by EI-MS, FAB-MS and High Resolution (HR)-FAB-MS. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, D_2O, and CD_3OH at 400 MHz (^1H NMR) pulse Fourier transform NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm downfield from TMS. Optical rotations were measured in a 1 dm cell. Analytical and preparative TLC was conducted on precoated TLC plates (silica gel 60 F_{254}, Merck). Column chromatography was performed using Merck silica gel 60N (100−210 μm). All anhydrous solvents were purified according to standard methods.

(*E*)-Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-*gluco*-hex-5-enopyranoside (4*E*) and (*Z*)-Methyl 6-*O*-Acetyl-tri-2,3,4-*O*-benzyl-α-D-*gluco*-hex-5-enopyranoside (4*Z*). To a solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (5.00 g, 10.78 mmol) in dimethyl sulfoxide−benzene (100.0 mL, 1:1) were added anhydrous pyridine (0.86 mL, 10.78 mmol), trifluoroacetic acid (0.42 mL, 5.39 mmol), and finally, *N*,*N*-dicyclohexylcarbodiimide (6.67 g, 32.34 mmol). The mixture was stirred for 1 day at room temperature. After the addition of pentane (50.0 mL), the *N*,*N*-dicyclohexylurea was removed by filtration. The filtrate was poured into brine and diluted with benzene. The solution was dried over Na_2SO_4 and evaporated in vacuo. The crude methyl 2,3,4-tri-*O*-benzyl-α-D-*gluco*-hexodialdo-1,5-pyranoside (4.30 g) thus obtained, without further purification, was treated with triethylamine (6.01 mL, 43.12 mmol), acetic anhydride (4.07 mL, 43.12 mmol), and 4-(dimethylamino)pyridine (131.7 mg, 1.08 mmol) in 1,2-dichloroethane (100.0 mL) at reflux temperature for 3 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Chromatography (EtOAc/hexane 1:2) of the residue gave **4*E*** and **4*Z*** as diastereomixtures (4.50 g, 8.93 mmol, 82.8%, **4*E***/**4*Z*** 8:92) as a syrup. **4*E***: TLC R_f 0.68 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 504 (M^+); HRMS (EI) calcd for $C_{30}H_{32}O_7$ 504.2148, found 504.2149; IR (neat) 1755.4 cm^{-1}; $[\alpha]^{24}_D$ +25.0 (EtOH, *c* = 1.025). **4*Z***: TLC R_f 0.65 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 504 (M^+); HRMS (EI) calcd for $C_{30}H_{32}O_7$ 504.2148, found 504.2152; IR (neat) 1755.4 cm^{-1}; $[\alpha]^{24}_D$ −29.6 (EtOH, *c* = 1.005)

(*E*)-Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-*galacto*-hex-5-enopyranoside (5*E*) and (*Z*)-Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-*galacto*-hex-5-enopyranoside (5*Z*). Compound **5*E*** and **5*Z*** were prepared from methyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (1.28 g, 2.76 mmol) as de-

scribed for the preparation of **4*E*** and **4*Z***. Chromatography (EtOAc/hexane 1:3) gave **5*E*** and **5*Z*** as diastereomixtures (1.01 g, 2.00 mmol, 72.6%, 5*E*/5*Z* 18:82) as a syrup. **5*E***: TLC R_f 0.41 (EtOAc/hexane 1:2); MS (EI) *m*/*z* 504 (M^+); HRMS (EI) calcd for $C_{30}H_{32}O_7$ 504.2148, found 504.2141; IR (neat) 1757.4 cm^{-1}, $[\alpha]^{24}_D$ +11.6 (EtOH, *c* = 1.060). **5*Z*** (733.0 mg, 1.454 mmol, 52.7%): TLC R_f 0.39 (EtOAc/hexane 1:2); MS (EI) *m*/*z* 504 (M^+); HRMS (EI) calcd for $C_{30}H_{32}O_7$ 504.2148, found 504.2145; IR (neat) 1759.3 cm^{-1}; $[\alpha]^{24}_D$ +9.0 (EtOH, *c* = 1.085).

(*E*)-Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-*manno*-hex-5-enopyranoside (6E) and (*Z*)-Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-*manno*-hex-5-enopyranoside (6Z). Compounds **6*E*** and **6*Z*** were prepared from methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (973.0 mg, 2.10 mmol) as described for the preparation of **4*E*** and **4*Z***. Chromatography (EtOAc/hexane 1:3) gave **6*E*** and **6*Z*** as diastereomixtures (730.0 mg, 1.45 mmol, 69.1%, 6*E*/6*Z* 18:82) as a syrup. **6*E***: TLC R_f 0.43 (EtOAc/hexane 1:2); MS (EI) *m*/*z* 504 (M^+); HRMS (EI) calcd for $C_{30}H_{32}O_7$ 504.2148, found 504.2134; IR (neat) 1759.3 cm^{-1}; $[\alpha]^{24}_D$ +75.1 (EtOH, *c* = 1.125). **6*Z***: TLC R_f 0.40 (EtOAc/hexane 1:2); MS (EI) *m*/*z* 504 (M^+); HRMS (EI) calcd for $C_{30}H_{32}O_7$ 504.2148, found 504.2131; IR (neat) 1755.4 cm^{-1}; $[\alpha]^{24}_D$ −11.5 (EtOH, *c* = 1.140).

(1*R*,2*R*,3*S*,4*R*,5*S*)-3,4,5-Tribenzyloxy-2-hydroxy-6-oxocyclohexyl Acetate (7a), (1*S*,2*S*,3*S*,4*R*,5*S*)-3,4,5-Tribenzyloxy-2-hydroxy-6-oxocyclohexylAcetate(7b),(1*S*,2*R*,3*S*,4*R*,5*S*)-3,4,5-Tribenzyloxy-2-hydroxy-6-oxocyclohexyl Acetate (7c), and (1*R*,2*S*,3*S*,4*R*,5*S*)-3,4,5-Tribenzoyloxy-2-hydroxy-6-oxocyclohexyl Acetate (7d). A mixture of **4** (11.4 g, 22.62 mmol) and $PdCl_2$ (200.5 mg, 1.13 mmol) in dioxane−water (240 mL, 2:1) was stirred at 60 °C for 3 h. After the reaction was finished, water was added and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Chromatography using (EtOAc/hexane 1:2) gave the four diastereoisomers **7a**,**7b**,**7c**,**7d** as mixtures (8.22 g, 16.78 mmol, 74.2%, **7a**/**7b**/**7c**/**7d** 49:24:17:10). **7a**: TLC R_f 0.26 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 490 (M^+); HRMS (EI) calcd for $C_{29}H_{30}O_7$ 490.1992, found 490.1988; IR (KBr) 1759.3, 1726.5 cm^{-1}; mp 51.7°; $[\alpha]^{24}_D$ −43.6 ($CHCl_3$, *c* = 0.910). Anal. Calcd for $C_{29}H_{30}O_7$: C, 71.00; H, 6.16. Found: C, 71.047; H, 6.252. **7b**: HT568D TLC R_f 0.11 (EtOAc/hexane 1:2); MS (EI) *m*/*z* 490 (M^+); HRMS (EI) calcd for $C_{29}H_{30}O_7$ 490.1992, found 490.1992; IR (neat) 3426.0, 1743.9 cm^{-1}; $[\alpha]^{D}_{24}$ −22.4 ($CHCl_3$, *c* = 0.140). **7c**: TLC R_f 0.48 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 490 (M^+); HRMS (EI) calcd for $C_{29}H_{30}O_7$ 490.1992, found 490.1978; IR (neat) 1749.7 cm^{-1}; $[\alpha]_D{}^{24}$ −30.4 ($CHCl_3$, *c* = 1.155). **7d**: TLC R_f 0.45 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 490 (M^+); HRMS (EI) calcd for $C_{29}H_{30}O_7$ 490.1992, found 490.1994; IR (neat) 1747.7 cm^{-1}; $[\alpha]^{24}_D$ −9.2 ($CHCl_3$, *c* = 0.970).

(1*R*,2*R*,3*S*,4*R*,5*R*)-3,4,5-Tri(benzyloxy)-2-hydroxy-6-oxocyclohexyl Acetate (8a), (1*S*,2*S*,3*S*,4*R*,5*R*)-3,4,5-Tri(benzyloxy)-2-hydroxy-6-oxocyclohexylAcetate(8b),(1*S*,2*R*,3*S*,4*R*,5*R*)-3,4,5-Tri(benzoyloxy)-2-hydroxy-6-oxocyclohexyl Acetate (8c), and (1*R*,2*S*,3*S*,4*R*,5*R*)-3,4,5-Tri(benzyloxy)-2-hydroxy-6-oxocyclohexyl Acetate (8d). Compounds **8a**, **8b**, **8c**, and **8d** were prepared from methyl 2,3,4-*O*-benzyl-α-D-galactopyranoside (6.10 g, 12.10 mmol) as described for the preparation of **7a**, **7b**, **7c**, and **7d**, yielding **8a**, **8b**, **8c**, and **8d** (5.13 g, 10.47 mmol, 86.5%, **8a**/**8b**/**8c**/**8d** 40:11:42:7). **8a**: TLC R_f 0.52 (CH_2Cl_2/MeOH 60:1); MS (EI) *m*/*z* 490 (M^+); HRMS (EI) calcd for $C_{29}H_{30}O_7$ 490.1991, found 490.1991, IR (neat) 1745.8, 1715.0 cm^{-1}; $[\alpha]^{24}_D$ +33.1 ($CHCl_3$, *c* = 0.710). **8b**: TLC R_f 0.54 (CH_2Cl_2/MeOH 60:1); MS (EI) *m*/*z* 490 (M^+); HRMS (EI) calcd for $C_{29}H_{30}O_7$ 490.1991, found 490.1989; IR (KBr) 1747.7, 1736.2 cm^{-1}; mp 51 °C; $[\alpha]^{24}_D$ +59.3 ($CHCl_3$, *c* = 0.650). Anal. Calcd for $C_{29}H_{30}O_7$: C, 71.00; H, 6.16. Found: C, 71.04; H, 6.34. **8c**: TLC R_f 0.50 (CH_2Cl_2/MeOH 60:1); MS (EI) *m*/*z* 490 (M^+); HRMS (EI) calcd for $C_{29}H_{30}O_7$ 490.1991, found 490.1993; IR (KBr) 1749.7, 1732.3 cm^{-1}; mp 107.5 °C; $[\alpha]^{24}_D$ +61.3 ($CHCl_3$, *c* = 1.120). Anal. Calcd for $C_{29}H_{30}O_7$: C, 71.00; H, 6.16. Found: C, 71.14; H, 6.11. **8d**: TLC R_f 0.28 (Et_2O: benzene/hexane 2:1:1); MS (EI) *m*/*z* 490 (M^+); HRMS (EI) calcd for $C_{29}H_{30}O_7$ 490.1991, found 490.2009; IR (KBr) 1747.7 cm^{-1}; $[\alpha]^{24}_D$ +44.1 ($CHCl_3$, *c* = 0.153).

(1*R*,2*R*,3*R*,4*R*,5*S*)-3,4,5-Tri(benzyloxy)-2-hydroxy-6-oxocyclohexyl acetate (9a) Compound **9a** was prepared from **6** (2.00 g, 3.968 mmol) as described for the preparation of **7a**, **7b**, **7c**, **7d.** Chromatography (EtOAc: hexane 1:4) gave **9a** (1.48 g, 3.020 mmol, 76.1%) as a solid: TLC R_f 0.52 (EtOAc: hexane 1:1); MS (EI) *m*/*z* 490 (M^+); HRMS (EI) calcd for $C_{29}H_{30}O_7$ 490.1992, found 490.1990; IR (KBr) 1753.5, 1738.1 cm^{-1}; mp 65.3 °C; $[\alpha]^{24}_D$ −28.5 ($CHCl_3$, *c* = 1.000).

D-1-*O*-Acetyl-3,4,5-tri-*O*-benzyl-*myo*-inositol (7aβ). $Me_4NBH(OAc)_3$ (69.7 mg, 0.265 mmol) was dissolved in CH_3CN−AcOH (0.6 mL 1:1) and cooled to −20 °C. At this temperature, **7a** (26.2 mg, 0.053 mmol) in CH_3CN (0.3 mL) was added, and the mixture was allowed to warm to room temperature and stirred for 3 h. Then saturated aqueous Rochelle salt (1.00 mL) was added and stirred for an additional 30 min. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Chromatography (EtOAc: hexane, 1:1) of the residue gave **7a**β (24.6 mg, 0.050 mmol, 94.3%) as a solid: TLC R_f 0.36 (EtOAc: hexane 1:1); MS (EI) *m*/*z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}0_7$ 492.2148, found 492.2149; IR (KBr) 1740.0 cm^{-1}; mp 124.8 °C; $[\alpha]^{24}_D$ −2.2 ($CHCl_3$, *c* = 0.330).

D-1-*O*-Acetyl-3,4,5-tri-*O*-benzyl-*chiro*-inositol (7cβ). $Me_4NBH(OAc)_3$ (65.8 mg, 0.250 mmol) was dissolved in CH_3CN−AcOH (0.6 mL 1:1) and cooled to −20 °C. At this temperature, **7c** (24.6 mg, 0.050 mmol) in CH_3CN (0.3 mL) was added, and the mixture was allowed to warm to 0 °C and stirred for 3 h. Then saturated aqueous Rochelle salt (1.00 mL) was added and stirred for an additional 30 min. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Chromatography (EtOAc: hexane, 1:1) of the residue gave **7c**β (22.3 mg, 0.045 mmol, 90.0%) as a syrup: TLC R_f 0.52 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2149, found 492.2148; IR (neat) 1747.7 cm^{-1}; $[\alpha]^{24}_D$ +10.5 ($CHCl_3$, *c* = 0.985).

D-3-*O*-Acetyl-1,5,6-tri-*O*-benzyl-*myo*-inositol (7dα). $Me_4NBH(OAc)_3$ (65.8 mg, 0.250 mmol) was dissolved in CH_3CN−AcOH (0.6 mL 1:1) and cooled to −40 °C. At this temperature, **7d** (20.0 mg, 0.041 mmol) in CH_3CN (0.3 mL) was added, and the mixture was allowed to warm to room temperature and stirred for 1 day. Then saturated aqueous Rochelle salt (1.00 mL) was added and the mixture stirred for an additional 30 min. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Chromatography (EtOAc: hexane, 1:1) of the residue gave **7d**α and **7d**β as diastereomixtures (7.4 mg, 0.015 mmol, 36.6% **7d**α/**7d**β 78:22) as a syrup. **7d**α: TLC R_f 0.24 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2145; IR (KBr) 1741.9 cm^{-1}; mp 67.0 °C; $[\alpha]^{24}_D$ +6.0 ($CHCl_3$, *c* = 0.490).

D-1-*O*-Acetyl-3,4,5-*O*-tribenzyl-*neo*-inositol (8aβ). **8a**β was prepared from **8a** (28.9 mg, 0.059 mmol) as described for the preparation of **7a**β, yielding **8a**β as a syrup (27.1 mg, 0.055 mmol, 93.3%): TLC R_f 0.38 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2150; IR (neat) 1732.3 cm^{-1}; $[\alpha]^{24}_D$ −13.4 ($CHCl_3$, *c* = 0.290).

D-2-*O*-Acetyl-4,5,6-tri-*O*-benzyl-*muco*-inositol (8bα). **8b**α was prepared from **8b** (24.3 mg, 0.050 mmol) as described for the preparation of **7a**β, yielding **8b**α and **8b**β as diastereomixtures (11.2 mg, 0.023 mmol, 45.5%, **8b**α/**8b**β 70:30) as a syrup. **8b**α: TLC R_f 0.27 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2143; IR (neat) 1732.3 cm^{-1}; $[\alpha]^{24}_D$ +24.6 ($CHCl_3$, *c* = 0.265).

L-2-*O*-Acetyl-4,5,6-tri-*O*-benzyl-*chiro*-inositol (9aβ). **9a**β was prepared from **9a** (25.1 mg, 0.051 mmol) as described for the preparation of **7a**β, yielding **9a**β (23.1 mg, 0.047 mmol, 92.2%) as a syrup: TLC R_f 0.33 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2138; IR (KBr) 1730.4 cm^{-1}; $[\alpha]^{24}_D$ −4.7 ($CHCl_3$, *c* = 0.270).

D-3-*O*-Acetyl-1,5,6-tri-*O*-benzyl-*epi*-inositol (7aα). A mixture of **7a** (44.8 mg, 0.091 mmol) and $NaBH_4$ (5.2 mg, 0.137 mmol) in MeOH (1 mL) was stirred at 0 °C for 30 min, and then saturated aqueous $NaHCO_3$ was added to the reaction mixture. The mixture was diluted with CH_2Cl_2, dried over Na_2-

SO_4, filtered, and concentrated. The residue was purified by column chromatography (EtOAC/hexane, 2:1) to give **7a**α (43.4 mg, 0.08 mmol, 96.7%) as a solid: TLC R_f 0.32 (EtOAc/hexane 1:1); MS (EI) *m/z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2152; IR (KBr) 1714.9 cm^{-1}; mp 105.0 °C.

D-3-*O*-Acetyl-1,5,6-tribenzyl-*muco*-inositol (7cα**).** **7c**α was prepared from **7c** (22.1 mg, 0.045 mmol) as described for the preparation of **7a**α. Chromatography (EtOAC/hexane, 1:1) gave **7c**α and **7c**β (18.6 mg, 0.038 mmol, 92.2%, **7c**α/**7c**β 87:13) as diastereomixtures. **7c**α: TLC R_f 0.52 (EtOAc/hexane 1:1); MS (EI) *m/z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2149.

D-1-*O*-Acetyl-3,4,5-tri-*O*-benzyl-*scyllo*-inositol (7dβ**).** **7d**β was prepared from **7d** (20.0 mg, 0.041 mmol) as described for the preparation of **7a**α. Chromatography (EtOAc/hexane, 1:1) gave **7d**β and **7d**α (17.4 mg, 0.035 mmol, 85.4%, **7d**β/**7d**α 78:22) as diastereomixtures. **7d**β: TLC R_f 0.48 (EtOAc/hexane 1:1); MS (EI) *m/z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2138; IR (KBr) 1718.8 cm^{-1}; mp 62.7 °C.

D-2-*O*-Acetyl-4,5,6-tri-*O*-benzyl-*allo*-inositol (8aα**).** A mixture of **8a** (37.0 mg, 0.076 mmol) and $NaBH_4$ (4.3 mg, 0.113 mmol) in MeOH (2 mL) was stirred at −78 °C for 30 min, and then saturated NH_4Cl was added to the reaction mixture. The mixture was diluted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (EtOAc/hexane, 1:1) to give **8a**α and **8a**β (33.1 mg, 0.067 mmol, 88.2%, **8a**α/**8a**β 98:2) as diastereomixtures. **8a**α: R_f 0.46 (EtOAc/hexane 1:1); MS (EI) *m/z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2143; IR (neat) 1740.0 cm^{-1}; $[\alpha]^{24}_D$ +14.0 ($CHCl_3$, $c = 0.380$).

D-2-*O*-Acetyl-tri-4,5,6-*O*-benzyl-*epi*-inositol (8bβ**).** **8b**β was prepared from **8b** (19.7 mg, 0.041 mmol) as described for the preparation of **8a**α. Chromatography (EtOAC/hexane, 1:1) gave **8b**β (18.1 mg, 0.037 mmol, 89.5%,) as a solid: TLC R_f 0.24 (EtOAc/hexane 1:1); MS (EI) *m/z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2142; IR (KBr) 1718.8 cm^{-1}; mp 141 °C; $[\alpha]^{24}_D$ +3.4 ($CHCl_3$, $c = 0.160$).

D-1-*O*-Acetyl-3,4,5-tri-*O*-benzyl-*allo*-inositol (8cβ**).** **8c**β was prepared from **8c** (40.3 mg, 0.082 mmol) as described for the preparation of **7a**α, yielding **8c**β (38.7 mg, 0.079 mmol, 96.3%) as a solid: TLC R_f 0.32 (EtOAc/hexane 1:1); MS (EI) *m/z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2141; IR (KBr) 1720.7 cm^{-1}; mp 61.8 °C; $[\alpha]_D^{24}$ −0.4 ($CHCl_3$, $c = 1.270$).

D-3-*O*-Acetyl-1,5,6-tri-*O*-benzyl-*allo*-inositol (9aα**)**. A mixture of **9a** (98.2 mg, 0.200 mmol) and $NaBH_4$ (11.4 mg, 0.300 mmol) in MeOH (5 mL) was stirred at −40 ° C for 30 min, and then saturated NH_4Cl was added to the reaction mixture. The mixture was diluted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (EtOAc/hexane, 1:1) to give **9a**α and **9a**β (90.7 mg, 0.184 mmol, 92.0%, **9a**α/**9a**β 98:2) as diastereomixtures: TLC R_f 0.41 (EtOAc/hexane 1:1); MS (EI) *m/z* 492 (M^+); HRMS (EI) calcd for $C_{29}H_{32}O_7$ 492.2148, found 492.2149; IR (neat) 1738.1 cm^{-1}; $[\alpha]^{24}_D$ −17.1 ($CHCl_3$, $c = 0.380$).

D-3-*O*-Acetyl-*epi*-inositol (10). To a solution of **7a**α (200.0 mg, 0.407 mmol) in MeOH (5.00 mL) was added 20% $Pd(OH)_2$ on carbon (40.0 mg) at r.t., the mixture was hydrogenolyzed at r.t. for 2 days. The solution was filtered and the filtrate was concentrated to give **10** in quantum yield as a solid: FABMS (FAB-NBA + NaI) *m/z* 245 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_8H_{14}O_7Na$ 245.0637, found 245.0632; IR (KBr) 1730.4 cm^{-1}; mp 60.7 °C. Anal. Calcd for $C_8H_{14}O_7$: C, 43.24; H, 6.35. Found: C, 43.32; H, 6.48.

D-3-*O*-Acetyl-1,2,4,5-di-*O*-isopropylidene-*epi*-inositol (11). To a mixture of **10** (89.8 mg, 0.405 mmol) in acetone (10 mL) was added concentrated H_2SO_4 (0.40 mL) at 0 °C. The reaction mixture was stirred for 1 h and then neutralized with saturated $NaHCO_3$ aqueous, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was evaporated. Chromatography (EtOAc/hexane 1:1) to give **11** (101.3 mg, 0.335 mmol, 82.7%) as a solid: TLC R_f 0.42 (EtOAc/hexane 1:1); MS (EI) *m/z* 302 (M^+); HRMS (EI) calcd for $C_{14}H_{22}O_7$ 302.1366, found 302.1380; IR (KBr) 1749.7 cm^{-1}; mp 173.7 °C. Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.33. Found: C, 55.75; H, 7.52.

D-1,2,4,5-Di-*O*-isopropylidene-*cis*-inositol (13). To a mixture of **11** (38.8 mg, 0.128 mmol), pyridine (1.80 mL), and CH_2Cl_2 (0.30 mL) was added Tf_2O 65 μL (0.384 mmol) at −20 °C. The solution was allowed to stir at room temperature for 1 h. The mixture was quenched with saturated $NaHCO_3$ aqueous, extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The solvent was evaporated to give **12**, the crude **12** (38.6 mg, 0.089 mmol), without further purification, was treated with cesium trifluoroacetate 65.7 mg (0.267 mmol), and 18-crown-6 (235.2 mg, 0.890 mmol) in a mixed solvent of toluene−DMF (3/1, 10 mL) was heated at 80 °C for 90 min, neutralized with pyridine at room temperature, and evaporated to give a residue. To a methanolic solution of the residue a saturatred aqueous $NaHCO_3$ was added and stirred at room temperature for 1 h. The reaction mixture was filtered to remove the precipitates, neutralized with acetic acid, and evaporated. The remaining residue was purified on a column of silicagel (EtOAc/hexane 1:3) to give **13** (20.4 mg, 0.078 mmol, 78.3% from **11**) as a solid: TLC R_f 0.45 (EtOAc/hexane 1:1); MS (EI) *m/z* 242 ($M^+ - H_2O$); mp 164 °C.

D-*chiro*-Inositol. To a solution of **7c**β (50.3 mg, 0.102 mmol) in MeOH (4 mL) was added 10 N NaOH (1 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for 12 h. The mixture was poured into water and diluted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (EtOAC: hexane, 3:1) to give deacetylated compound (37.1 mg, 0.082 mmol, 80.4%) as a syrup, which was dissolved in MeOH (1 mL). To this solution was added 20% $Pd(OH)_2$ on carbon (7.4 mg) at rt, and the mixture was hydrogenolyzed at rt for 1 day. The solution was filtered, and the filtrate was concentrated to give d-*chiro*-inositol (12.6 mg, 0.070 mmol, 68.6%) as a solid: ^1H NMR (400 MHz, D_2O) δ 3.88 (2H, brs), 3.60 (2H, m), 3.44 (2H, m); ^{13}C NMR (100.58 MHz, D_2O) δ 73.80, 72.70, 71.50; FABMS *m/z* 179 (M − H); $[\alpha]^{24}_D$ +85.5 (H_2O, $c = 0.100$).

***muco*-Inositol. *muco*-Inositol** was prepared from **7c**α (74.0 mg, 0.15 mmol) as described for the preparation of **D-*chiro*-inositol**, yielding ***muco*-inositol**. (11.7 mg, 0.065 mmol, 43.3%) as a solid. **8b**α (8.6 mg, 0.017 mmol) also provided ***muco*-inositol** (3.1 mg, 0.017 mmol, quant) as a solid: ^1H NMR (400 MHz, D_2O) δ 3.88 (2H, t, $J = 5.9$ Hz), 3.75 (4H, d, $J = 5.9$ Hz); ^{13}C NMR (100.58 MHz, D_2O) δ 73.14, 71.00; FABMS *m/z* 179 (M − H).

***epi*-Inositol. *epi*-Inositol** was prepared from **8b**β (40.4 mg, 0.082 mmol) as described for the preparation of **D-*chiro*-inositol**, yielding ***epi*-inositol** (14.8 mg, 0.082 mmol, quant) as a solid. ***epi*-Inositol** was also prepared from **7a**α (53.1 mg, 0.108 mmol) as described for the preparation of **D-*chiro*-inositol**, yielding ***epi*-inositol** (14.2 mg, 0.079 mmol, 73.0%) as a solid: ^1H NMR (400 MHz, D_2O) δ 3.93 (2H, brs), 3.71 (1H, t, $J = 9.9$ Hz), 3.60 (1H, brs), 3.35 (2H, d, $J = 9.9$ Hz); ^{13}C NMR (100.58 MHz, D_2O) δ 75.41, 72.70, 70.98, 67.77.

***myo*-Inositol. *myo*-Inositol** was prepared from **7a**β (50.2 mg, 0.102 mmol) as described for the preparation of **D-*chiro*-inositol**, yielding ***myo*-inositol** (15.2 mg, 0.132 mmol, 82.4%) as a solid. ***myo*-Inositol** was also prepared from **7d**α (64.8 mg, 0.132 mmol) as described for the preparation of **D-*chiro*-inositol**, yielding ***myo*-inositol** (18.2 mg, 0.101 mmol, 76.5%) as a solid: ^1H NMR (400 MHz, D_2O): δ 3.90 (1H, t, $J = 2.9$ Hz), 3.46 (2H, t, $J = 9.5$ Hz), 3.37 (2H, dd, $J = 9.5$, 2.9 Hz), 3.11 (1H, t, $J = 9.5$ Hz); ^{13}C NMR (100.58 MHz, D_2O): δ 75.32, 73.37, 73.15, 72.10.

***scyllo*-Inositol. *scyllo*-Inositol** was prepared from **7d**β (50.2 mg, 0.102 mmol) as described for the preparation of **D-*chiro*-inositol**, yielding ***scyllo*-inositol** (18.4 mg, 0.102 mmol, quant) as a solid: ^1H NMR (400 MHz, D_2O) δ 3.95 (brs); ^{13}C NMR (100.58 MHz, D_2O) δ 74.42.

***neo*-Inositol. *neo*-Inositol** was prepared from **8a**β (156.5 mg, 0.595 mmol) as described for the preparation of **D-*chiro*-inositol**, yielding ***neo*-inositol** (8.2 mg, 0.046 mmol, 7.7%) as a solid: ^1H NMR (400 MHz, D_2O) δ 3.92 (2H, brs), 3.64 (4H, brs); ^{13}C NMR (100.58 MHz, D_2O) δ 72.55, 70.30.

***allo*-Inositol. *allo*-Inositol** was prepared from **8a**α (34.6 mg, 0.070 mmol) as described for the preparation of **D-*chiro*-inositol**, yielding ***allo*-inositol** (8.9 mg, 0.049 mmol, 70.0%)

as a solid. ***allo*-Inositol** was also prepared from **8c**β (44.0 mg, 0.089 mmol) as described for the preparation of **D-*chiro*-inositol**, yielding ***allo*-inositol** (12.4 mg, 0.069 mmol, 76.7%) as a solid: ^{1}H NMR (400 MHz, D_2O) mesured at 90 °C δ 4.35 (2H, s), 4.08 (4H, s); ^{13}C NMR (100.58 MHz, D_2O) δ 72.68, 71.08, 70.50.

L-*chiro*-Inositol. L-*chiro*-Inositol was prepared from **9a**β (44.7 mg, 0.091 mmol) as described for the preparation of **D-*chiro*-inositol**, yielding **L-*chiro*-inositol** (14.2 mg, 0.079 mmol, 86.8%) as a solid: ^{1}H NMR (400 MHz, D_2O) δ 3.88 (2H, brs), 3.60 (2H, m), 3.44 (2H, m); ^{13}C NMR (100.58 MHz, D_2O) δ 73.80, 72.70, 71.50; $[\alpha]^{24}_D$ −56.3 (H_2O_3, c = 0.200).

***cis*-Inositol.** To a solution of **13** (16.1 mg, 0.06 mmol) in MeOH (2 mL) was added TFA (0.1 mL) at 0 °C. The reaction mixture was allowed to stir at 60 °C for 3 h. The solvent was evaporated to give ***cis*-inositol** as a solid: ^{1}H NMR (400 MHz, D_2O) mesured at +2 °C δ 3.73 (2H, s), 3.50 (4H, s); ^{13}C NMR (100.58 MHz, D_2O) δ 77.60, 69.20.

Methyl 3,4-*O*-Dimethoxybenzyl-α-D-glucopyranoside (14). To a mixture of methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside (211.6 mg, 0.526 mmol), MPM trichloroacetimidate (1.49 g, 5.260 mmol), and Et_2O (5.00 mL) was added a catalytic amount of TfOH at 0 °C. The solution was allowed to stir at room temperature for 1 h. The mixture was quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O, and dried over Na_2SO_4. The solvent was evaporated. The crude methyl 2,6-di-*O*-benzoyl-3,4-*O*-dimethoxybenzyl-α-D-*gluco*-pyranoside thus obtained, without further purification, was treated with 5 N NaOH aqueous (1.00 mL) at 0 °C and then allowed to stir at room temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, dried over Na_2SO_4. The solvent was evaporated. The remaining residue was purified on a column of silicagel (EtOAc/hexane 1:2) to give **14** (155.7 mg, 0.359 mmol, 68.3%) as a solid: TLC R_f 0.24 (EtOAc/hexane 1:1); MS (EI) m/z 313 (M^+ − MPM); FABMS (FAB-NBA + NaI) m/z 457 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{23}H_{30}O_8Na$ 457.1838, found 457.1843; mp 80.7 °C; $[\alpha]^{24}_D$ +35.6 (EtOH, c = 1.045).

Methyl 6-*O*-*tert*-Butyldimethylsilyl-3,4-di-*O*-dimethoxybenzyl-α-D-glucopyranoside (15). To a solution of **14** (203.0 mg, 0.468 mmol) in *N*,*N*-dimethylformamide (5.00 mL) were added imidazole (47,8 mg, 0.702 mmol) and *tert*-butyldimethylchlorosilane (105.8 mg, 0.702 mmol) at 0 °C. The solution was allowed to stir at room temperature for 30 min. The mixture was quenched with water, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was evaporated, and the remaining residue was purified on a column of silicagel (EtOAc/hexane 1:2) to give **15** (241.3 mg, 0.44 mmol, 94.0%) as a syrup: TLC R_f 0.38 (EtOAc/hexane 1:2); MS (EI) m/z 427 (M^+ − MPM); FABMS (FAB-NBA + NaI) m/z 571 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{29}H_{44}O_8SiNa$ 571.2704, found 571.2689; $[\alpha]^{24}_D$ +48.5 (EtOH, c = 1.090).

Methyl 6-*O*-*tert*-Butyldimethylsilyl-2-*O*-benzyl-3,4-di-*O*-methoxybenzyl-α-D-glucopyranoside (16). **15** was dissolved in *N*,*N*-dimethylformamide−THF (4.8 mL 5:1) and cooled to 0 °C. At this temperature, sodium hydride (54.8 mg, 1.370 mmol) and benzyl bromide (0.15 mL, 1.284 mmol) were added and the mixture stirred for 30 min. Then the reaction was quenched with ice−water. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Chromatography (EtOAc/hexane, 1:5) of the residue gave **16** (221.8 mg, 0.347 mmol, 81.1%) as a syrup: TLC R_f 0.75 (EtOAc/hexane 1:2); FABMS (FAB-NBA + NaI) m/z 661 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{36}H_{50}O_8$-SiNa 661.3172 found 661.3187; $[\alpha]^{24}_D$ +34.6 (EtOH, c = 1.200).

Methyl 2-*O*-Benzyl-3,4-di-*O*-methoxybenzyl-α-D-glucopyranoside (17). To a solution of **16** (210.5 mg, 0.330 mmol) in THF (3.00 mL) was added tetrabutylammonium fluoride in THF (99 μL, 0.990 mmol) at room temperature. The solution was stirred for 1 h. The reaction mixture was evaporated, and the remaining residue was purified on a column of silicagel (EtOAc/hexane 1:2) to give **17** (163.6 mg, 0.312 mmol, 94.5%) as a syrup: TLC R_f 0.21 (EtOAc/hexane 1:1); MS (EI) m/z 403 (M^+ − MPM); FABMS (FAB-NBA + NaI) m/z 547 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{30}H_{36}O_8Na$ 547.2308, found 547.2314; $[\alpha]^{24}_D$ +16.3 (EtOH, c = 1.015).

(*E*)-Methyl 6-*O*-Acetyl-2-*O*-benzyl-di-3,4-*O*-methoxybenzyl-α-D-*gluco*-hex-5-enopyranoside (18*E*) and (*Z*)-Methyl 6-*O*-Acetyl-2-*O*-benzyl-3,4-*O*-dimethoxybenzyl-α-D-*gluco*-hex-5-enopyranoside (18*Z*). To a solution of 17 (552.0 mg, 1.053 mmol) in dimethyl sulfoxide−benzene (10.0 mL 1:1) were added anhydrous pyridine (85 μL, 1.053 mmol), trifluoroacetic acid (41 μL, 0.527 mmol), and finally, *N*,*N*-dicyclohexylcarbodiimide (652.0 mg, 3.160 mmol). The mixture was stirred for 1 day at room temperature. After the addition of pentane (10.0 mL), the *N*,*N*-dicyclohexylurea was removed by filtration. The filtrate was poured into brine and diluted with benzene. The solution was dried over Na_2SO_4 and evaporated in vacuo. The crude methyl 2-*O*-benzyl-3,4-tri-*O*-benzyl-α-D-*gluco*-hexodialdo-1,5-pyranoside thus obtained, without further purification, was treated with triethylamine (0.59 mL, 4.212 mmol), acetic anhydride (0.40 mL, 4.212 mmol), and 4-(dimethylamino)pyridine (12.8 mg, 0.105 mmol) in 1,2-dichloroethane (120.0 mL) at reflux temperature for 5 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Chromatography (hexane/EtOAc 3:1) of the residue gave 18*E* and 18*Z* (434.6 mg, 0.771 mmol, 73.2%, 18*E*/18*Z* 5:95) as diastereomixtures. 18*E*: TLC R_f 0.50 (EtOAc/hexane 1:1); MS (EI) m/z 564 (M^+); HRMS (EI) calcd for $C_{32}H_{36}O_9$ 564.2359, found 564.2362; IR (neat) 1753.5 cm^{-1}; $[\alpha]^{24}_D$ −33.5 ($CHCl_3$, c = 1.125). 18*Z*: TLC R_f 0.48 (EtOAc/hexane 1:1); MS (EI) m/z 564 (M^+); HRMS (EI) calcd for $C_{30}H_{36}O_8$ 564.2359, found 564.2366; IR (neat) 1755.4 cm^{-1}; $[\alpha]^{24}_D$ −69.3 ($CHCl_3$, c = 1.065).

(1*R*,2*R*,3*S*,4*R*,5*S*)-3-Benzyloxy-2-hydroxy-4,5-bis(4-methoxybenzyloxy)-6-oxocyclohexyl Acetate (19). A mixture of **18** (96.5 mg, 0.171 mmol) and $PdCl_2$ (3.00 mg, 0.017 mmol) in dioxane−water (3.30 mL, 2:1) was stirred at 60 °C for 8 h. After the reaction was finished, water was added and the mixture extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Chromatography using (EtOAc/hexane 1:2) gave **19** (49.9 mg, 0.091 mmol, 53.0%): TLC R_f 0.33 (EtOAc/hexane 1:1) as a solid; MS (EI) m/z 550 (M^+); HRMS (EI) calcd for $C_{31}H_{34}O_9$ 550.2203, found 550.2197; IR (KBr) 1740.0 cm^{-1}; mp 141.0 °C; $[\alpha]^{24}_D$ −45.9 ($CHCl_3$, c = 1.115).

D-1-*O*-Acetyl-3-*O*-benzyl-4,5-*O*-dimethoxybenzyl-*myo*-inositol (20). $Me_4NBH(OAc)_3$ (353.9 mg, 1.345 mmol) was dissolved in CH_3CN−AcOH (3.0 mL 1:1) and cooled to −40 °C. At this temperature, **19** (148.0 mg, 0.269 mmol) in CH_3-CN (1.0 mL) was added, and the mixture was allowed to warm to room temperature and stirred for 3 h. Then saturated aqueous Rochelle salt (3.00 mL) was added and the mixture stirred for an additional 30 min. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Chromatography (EtOAc/hexane, 1:2) of the residue gave **20** (124.3 mg, 0.225 mmol, 83.6%) as a solid: TLC R_f 0.23 (EtOAc/hexane 1:1) MS (FAB-NBA + NaI) m/z 575 (M^++Na); HRMS (FAB-NBA + NaI) calcd for $C_{31}H_{36}O_9Na$ 575.2257, found575.2255; IR (KBr) 1738.1 cm^{-1}; mp 102.3 °C; $[\alpha]^{24}_D$ −3.4 ($CHCl_3$, c = 0.390). Anal. Calcd for $C_{31}H_{36}O_9$: C, 67.38; H, 6.57. Found: C, 67.38; H, 6.67.

D-1-*O*-Acetyl-3-*O*-benzyl-2,6-di-*O*-benzyloxymethyl-4,5-di-*O*-methoxybenzyl-*myo*-inositol (21). To a solution of **20** (155.4 mg, 0.282 mmol) in 1,2-dichloroethane (6.00 mL) were added diisopropylethylamine (0.39 mL, 2.256 mmol) and benzylchloromethyl ether (0.35 mL, 2.256 mmol). The reaction mixture was stirred at refluxed temperature for 5 h. After the reaction was finished, water was added and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Cromatography using (EtOAc/hexane 1:3) gave **21** (173.5 mg, 0.219 mmol, 77.7%) as a syrup: R_f 0.79 (EtOAc/hexane 1:1); FABMS (FAB-NBA + NaI) m/z 816 (M^+ + Na) FABHRMS (FAB-NBA + NaI) calcd for $C_{47}H_{52}O_{11}Na$ 815.3408, found 815.3427; IR (neat) 1740.0 cm^{-1}; $[\alpha]^{24}_D$ −61.1 ($CHCl_3$, c = 0.550).

D-3-*O*-Benzyl-2,6-di-*O*-benzyloxymethyl-4,5-di-*O*-methoxybenzyl-*myo*-inositol (22). To a solution of **21** (12.7 mg,

0.016 mmol) in MeOH (2.00 mL) was added 10 N NaOH (0.5 mL) at 0 °C. The solution was allowed to stir at room temperature for 10 min. The mixture was quenched with water, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was evaporated, and the remaining residue was purified on a column of silicagel (EtOAc/hexane 1:3) to give **22** (9.8 mg, 0.013 mmol, 81.3%) as a solid: TLC R_f 0.72 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 629 (M^+ − MPM); FABMS (FAB-NBA + NaI) *m*/*z* 773 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{45}H_{50}O_{10}Na$ 773.3301, found 773.3307; mp 77.7 °C; $[\alpha]^{24}_D$ −53.7 ($CHCl_3$, c = 0.73).

D-3-*O*-Benzyl-2,6-di-*O*-benzyloxymethyl-*myo*-inositol (23). To a solution of **22** (43.1 mg, 0.058 mmol) in CH_2Cl_2−water (1.9 mL 18:1) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (39.2 mg, 0.174 mmol) at 0 °C. The solution was allowed to stir at room temperature for 1 h. The mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was evaporated. The remaining residue was purified on a column of silicagel (EtOAc/hexane 1:1) to give **23** (23.3 mg, 0.046 mmol, 79.3%) as a solid: TLC R_f 0.34 (EtOAc/hexane 2:1); FABMS (FAB-NBA + NaI) *m*/*z* 533 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{29}H_{34}O_8Na$ 533.2151, found 533.2164; mp 112.0 °C; $[\alpha]^{24}_D$ +26.8 ($CHCl_3$, c = 0.450).

D-3-*O*-Benzyl-2,6-*O*-dibenzyloxymethyl-1,4,5-*O*-tris-(dibenzylphosphono)-*myo*-inositol (24). To a solution of **23** (36.0 mg, 0.071 mmol) in CH_2Cl_2 (2.0 mL) were added 1*H*-tetrazole (39.8 mg, 0.568 mmol) and dibenzyldiisopropylphosphoramidite (0.14 mL, 0.426 mmol) at room temperature and the mixture stirred. The solution was cooled (0 °C), and NaH_2PO_4 (100.8 mg, 0.710 mmol) and *m*-CPBA (140.0 mg, 0.568 mmol) were added. The reaction mixture was allowed to stir at room temperature for 1 h. The mixture was quenched with saturated aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and washed with 1 N HCl. The organic phase was neutralized with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated. The remaining residue was purified on a column of silica gel (EtOAc/hexane 1:1) to give **24** (81.3 mg, 0.063 mmol, 88.7%) as a syrup: TLC R_f 0.28 (EtOAc/hexane 1:1); FABMS (FAB-NBA + NaI) *m*/*z* 1313 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{71}H_{73}O_{17}P_3Na$ 1313.3958, found 1313.3972; $[\alpha]^{24}_D$ −17.6 ($CHCl_3$, c = 0.850).

D-*myo*-Inositol-1,4,5-trisphosphate (25). To a solution of **24** (81.3 mg, 0.065 mmol) in MeOH (5 mL) was added 20% $Pd(OH)_2$ on carbon (16.3 mg) at rt, and the mixture was hydrogenyzed at rt for 1 day. The solution was filtered, and the filtrate was concentrated to give **26** (26.8 mg, 0.064 mmol, 98.5%) as a syrup: ^{1}H NMR (400 MHz, D_2O + NaOD): δ 4.35 (1H, m), 4.17 (1H, dd, J = 15.7, 9.5 Hz), 3.92−3.88 (3H, m), 3.73 (1H, dd, J = 9.5, 2.6 Hz); ^{13}C NMR (100.58 MHz, D_2O + NaOD) δ 78.40, 76.20, 75.59, 73.52, 72.73, 71.71; FABMS (FAB-TEA + NaI) *m*/*z* 575 (M^+ + Na); FABHRMS (FAB-TEA + NaI) calcd for $C_6H_{15}O_{15}P_3Na_6$ 552.8609, found 552.8631; $[\alpha]^{24}_D$ −3.19 (H_2O, c = 0.26) Na salt.

Methyl 4,6-Di-*O*-methoxybenzylidene-2,3-di-*O*-methoxybenzyl-α-D-glucopyranoside. (26). To a solution of methyl 4,6-*O*-methoxybenzylidene-α-D-glucopyranoside (2.03 g, 6.506 mmol) in *N*,*N*-dimethylformamide−THF (66.0 mL, 5:1) were added sodium hydride (780.0 mg, 19.52 mmol) and *p*-methoxybenzyl chloride (2.70 mL, 19.52 mmol) at room temperature and the mixture stirred. The solution was allowed to stir at 90 °C for 30 min. The mixture was quenched with saturated NH_4Cl, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was evaporated. The remaining residue was purified on a column of silica gel (EtOAc/hexane 1:2) to give **26** (2.83 g, 5.124 mmol, 78.8%) as a solid: TLC R_f 0.28 (EtOAc/hexane 1:2); MS (EI) *m*/*z* 552 (M^+); HRMS (EI) calcd for $C_{31}H_{36}O_9$ 552.2359, found 552.2359; mp 128.6 °C; $[\alpha]^{24}_D$ −46.2 ($CHCl_3$, c = 0.750). Anal. Calcd for $C_{31}H_{36}O_9$: C, 67.38; H, 6.57. Found: C, 67.33; H, 6.68.

Methyl 2,3,4-Tri-*O*-methoxybenzyl-α-D-glucopyranoside (27). To a solution of **26** (134.7 mg, 0.244 mmol) in CH_3CN (2.50 mL) were added sodium cyanoborohydride (159.0 mg, 1.464 mmol), activated molecular sieves 3A (250.0 mg), and trimethylsilyl chloride (92.0 mg, 1.464 mmol) at −20 °C and the mixture stirred for 30 min. The reaction mixture was filtered through a Celite pad, and the filtrate was poured into the ice-cold saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was evaporated. The remaining residue was purified on a column of silica gel (EtOAc/hexane 1:1) to give **27** (86.4 mg, 0.156 mmol, 63.9%) as a syrup: TLC R_f 0.23 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 433 (M^+ − MPM); MS (FAB-NBA + NaI) *m*/*z* 577 (M^+ + Na); HRMS (FAB-NBA + NaI) calcd for $C_{31}H_{38}O_9Na$ 577.2413, found 577.2390; mp 79.5 °C; $[\alpha]^{24}_D$ +1.6 ($CHCl_3$, c = 1.060). Anal. Calcd for $C_{31}H_{38}O_9$: C, 67.13; H, 6.91. Found: C, 67.21; H, 6.95.

(*Z*)-Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-methoxybenzyl-α-D-*gluco*-hex-5-enopyranoside (28). To a solution of **27** (8.00 g, 14.44 mmol) in benzene−DMSO (140 mL, 1:1) were added anhydrous pyridine (2.30 mL, 28.88 mmol), trifluoroacetic acid (1.10 mL, 14.44 mmol), and finally, *N*,*N*-dicyclohexylcarbodiimide (17.9 g, 86.64 mmol). The mixture was stirred for 1 day at room temperature. After the addition of pentane (70.0 mL), the *N*,*N*-dicyclohexylurea was removed by filtration. The filtrate was poured into brine and diluted with benzene. The solution was dried over Na_2SO_4 and evaporated in vacuo. The crude methyl 2,3,4-tri-*O*-methoxybenzyl-α-D-*gluco*-hexodialdo-1,5-pyranoside thus obtained, without further purification, was treated with triethylamine (6.70 mL, 48.00 mmol), acetic anhydride (4.50 mL, 48.00 mmol) and 4-(dimethylamino)-pyridine (146.6 mg, 1.20 mmol) in 1,2-dichloroethane (120.0 mL) at reflux temperature for 3 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Chromatography (hexane/EtOAc 3:1) of the residue gave **28** (5.40 g, 9.097 mmol, 63.0%) as a syrup: TLC R_f 0.64 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 473 (M^+ − MPM); FABMS (FAB-NBA + NaI) *m*/*z* 617 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{33}H_{38}O_{10}Na$ 617.2362, found 617.2346; IR (neat) 1755.4 cm^{-1}; $[\alpha]^{24}_D$ −73.3 ($CHCl_3$, c = 0.870).

(1*R*,2*R*,3*S*,4*R*,5*S*)-2-Hydroxy-3,4,5-tri-*O*-(4-methoxybenzyl)-6-oxocyclohexyl Acetate (29). A mixture of **28** (5.10 g, 8.586 mmol) and $PdCl_2$ (152.3 mg, 0.859 mmol) in dioxane−water (90 mL, 2:1) was stirred at 60 °C for 3 h. After the reaction was finished, water was added and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Chromatography using (EtOAc/hexane 1:2) gave **29** (1.43 g, 2.466 mmol, 28.7%) as a solid: TLC R_f 0.36 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 459 (M^+ − MPM); FABMS (FAB-NBA + NaI) *m*/*z* 603 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{32}H_{36}O_{10}Na$ 603.2207, found 603.2233; IR (KBr) 1749.7, 1720.7 cm^{-1}; mp 131.8 °C; $[\alpha]^{24}_D$ −45.2 ($CHCl_3$, c = 1.060). Anal. Calcd for $C_{32}H_{36}O_{10}$: C, 66.19; H, 6.25. Found: C, 66.14; H, 6.27.

D-1-*O*-Acetyl-3,4,5-*O*-dimethoxybenzyl-*myo*-inositol (30). $Me_4NBH(OAc)_3$ (501.7 mg, 1.907 mmol) was dissolved in CH_3CN−AcOH (4.0 mL 1:1) and cooled to −40 °C. At this temperature, **29** (221.2 mg, 0.381 mmol) in CH_3CN (2.0 mL) was added, and the mixture was allowed to warm to room temperature and stirred for 3 h. Then saturated aqueous Rochelle salt (1.00 mL) was added and the mixture stirred for an additional 30 min. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Chromatography (EtOAc/hexane, 1:1) of the residue gave **30** (213.6 mg, 0.367 mmol, 96.3%) as a solid: R_f 0.32 (EtOAc/hexane 2:1); MS (EI) *m*/*z* 461 (M^+ − MPM); FABMS (FAB-NBA + NaI) *m*/*z* 605 (M + Na^+); HRMS (FAB-NBA + NaI) calcd for $C_{32}H_{38}O_{10}Na$ 605.2363, found 605.2377; IR (KBr) 1736.2 cm^{-1}; mp 150.8 °C; $[\alpha]^{24}_D$ +1.30 ($CHCl_3$, c = 1.010). Anal. Calcd for $C_{32}H_{38}O_{10}$: C, 65.97; H, 6.57. Found: C, 65.98; H, 6.55.

D-1-*O*-Acetyl-2,6-di-*O*-benzyloxymethyl-3,4,5-tri-*O*-methoxybenzyl-*myo*-inositol (31). To a solution of **30** (100.2 mg, 0.172 mmol) in 1,2-dichloroethane (3.50 mL) were added *N*,*N*-diisopropylethylamine 0.20 mL (1.204 mmol) and benzyl chloromethyl ether (0.15 mL, 1.032 mmol). The reaction mixture was stirred at reflux temperature for 3 h. After the

reaction was finished, water was added and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to dryness. Chromatography using (EtOAc/hexane 1:4) gave **31** (121.3 mg, 0.148 mmol, 86.0%): TLC R_f 0.82 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 701 (M^+ − MPM); FABMS (FAB-NBA + NaI) *m*/*z* 846 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{48}H_{54}O_{12}Na$ 845.3513, found 845.3522; IR (neat) 1740.0 cm^{-1}; $[\alpha]^{24}_D$ −45.5 ($CHCl_3$, *c* = 0.850).

D-2,6-Di-*O*-benzyloxymethyl-3,4,5-tri-*O*-methoxybenzyl-*myo*-inositol (32). To a solution of **31** (171.8 mg, 0.210 mmol) in MeOH (20.0 mL) was added 10 N NaOH (6.0 mL) at 0 °C. The solution was allowed to stir at room temperature for 2 h. The mixture was quenched with water, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was evaporated, and the remaining residue was purified on a column of silicagel (EtOAc/hexane 1:2) to give **32** (153.8 mg, 0.197 mmol, 94.3%) as a solid: TLC R_f 0.62 (EtOAc/hexane 1:1); MS (EI) *m*/*z* 659 (M^+ − MPM); FABMS (FAB-NBA + NaI) *m*/*z* 804 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{46}H_{52}O_{11}Na$ 803.3408, found 803.3409; mp 84.7 °C; $[\alpha]^{24}_D$ −47.8 ($CHCl_3$, *c* = 1.040).

D-2,6-Di-*O*-benzyloxymethyl-*myo*-inositol (33). To a solution of **32** (119.1 mg, 0.153 mmol) in CH_2Cl_2−water (15.8 mL 18:1) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (156.3 mg, 0.689 mmol) at 0 °C. The solution was allowed to stir at room temperature for 2 h. The mixture was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and dried over Na_2SO_4. The solvent was evaporated. The remaining residue was purified on a column of silicagel (EtOAc/hexane 1:4) to give **33** (60.3 mg, 0.144 mmol, 94.1%) as a solid: TLC R_f 0.23 (EtOAc/ hexane 1:1); FABMS (FAB-NBA + NaI) *m*/*z* 443 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{22}H_{28}O_8Na$ 443.1682, found 443.1667; mp 106.0 °C; $[\alpha]^{24}_D$ +20.2 ($CHCl_3$, *c* = 0.310). Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.85; H, 6.71. Found: C, 62.75; H, 6.59.

D-2,6-Di-*O*-benzyloxymethyl-1,3,4,5-tetrakis-*O*-(dibenzylphosphono)-*myo*-inositol (34). To a solution of **33** (12.2 mg, 0.029 mmol) in CH_2Cl_2 (1.0 mL) was added 1*H*-tetrazole (20.3 mg, 0.290 mmol) and dibenzyldiisopropylphosphoramidite (78 μL, 0.232 mmol) at room temperature and stirred 12 h. The solution was cooled (0 °C) and added NaH_2PO_4 (61.8 mg, 0.435 mmol) and *m*-CPBA (75.1 mg, 0.435 mmol). The reaction mixture was allowed to stir at room temperature for 2 h. The mixture was diluted with CH_2Cl_2, quenched with saturated Na_2SO_3, saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, washed with 1 N HCl. The organic phase was neutralized with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated. The remaining residue was purified on a column of silicagel (EtOAc/hexane 1:1) to give **34** (32.1 mg, 0.022 mmol, 75.9%) as a syrup: TLC R_f 0.32 (EtOAc/hexane 1:1); FABMS (FAB-NBA + NaI) *m*/*z* 1484 (M^+ + Na); FABHRMS (FAB-NBA + NaI) calcd for $C_{78}H_{80}O_{20}P_4Na$ 1483.4091, found 1483.4109; mp 106.0 °C; $[\alpha]^{24}_D$ −17.0 ($CHCl_3$, *c* = 0.805).

D-*myo*-Inositol-1,3,4,5-*O*-tetrakisphosphate (35). To a solution of **34** (15.2 mg, 0.010 mmol) in MeOH (2.0 mL) was added 20% $Pd(OH)_2$ on carbon(1.5 mg) at rt, and the mixture with hydrogenolyzed at rt for 2 days. The solution was filtered, and the filtrate was concentrated to give **35** (5.1 mg, 0.010 mmol, 98.1%) as a solid: ^{1}H NMR (400 MHz, CD_3OD) δ 4.71 (1H, dd, *J* = 18.7, 9.5 Hz), 4.53 (1 H, dd, *J* = 18.7, 9.2 Hz), 4.37 (1H, dd, *J* = 18.7, 9.2 Hz), 4.29 (1H, ddd, *J* = 9.5, 9.5, 2.6 Hz), 4.22 (1H, dd, *J* = 3.3, 2.6 Hz), 3.68 (1H, dd, *J* = 9.5, 3.3 Hz).^{13}C NMR (100.58 MHz, D_2O + NaOD) δ 81.89, 77.50, 74.11, 73.41, 72.78, 69.82. $[\alpha]^{24}_D$ −4.51 (H_2O, *c* = 0.13) Na salt.

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Supporting Information Available: Peak assignments in ^{1}H NMR and ^{13}C NMR for **4*E***, **4*Z***, **5*E***, **5*Z***, **6*E***, **6*Z***, **7a**−**d**, **8a**−**d**, **9a**, **7a**β−**7c**β, **7d**α, **8a**β, **8b**α, **9a**β, **7a**α, **7c**α, **7d**β, **8a**α, **8b**β, **8c**β, **9a**α, **10**−**17**, **18*E***, **18*Z***, **19**−**35**, D-*chiro*-inositol, *muco*-inositol, *epi*-inositol, *myo*-inositol, *scyllo*-inositol, *neo*-inositol, *allo*-inositol, L-*chiro*-inositol, and *cis*-inositol. This material is available free of charge via the Internet at http://pubs.acs.org.

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