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Efficient syntheses of optically pure *chiro*- and *allo*-inositol derivatives, azidocyclitols and aminocyclitols from *myo*-inositol

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Abstract

Efficient routes for the syntheses of optically pure and hitherto unknown L-*chiro*- and D-*allo*-inositol derivatives, azido- and aminocyclitols of L-*chiro*-configuration, diazido- and diaminocyclitols of D-*allo*-configuration from economically viable *myo*-inositol are described. These routes provide access to synthetically flexible 1,2:4,5-di-*O*-isopropylidene-*chiro*-inositol and 1,6:3,4-di-*O*-isopropylidene-*allo*-inositol, which are otherwise difficult to synthesize directly from their parent inositols. A one pot methodology that allows rapid access to both *chiro*- and *allo*-inositol derivatives has also been developed. Investigations on the glycosidase inhibitory properties of these novel azido- and amino-inositols unraveled the potentials of these classes of compounds as novel class of glycosidase inhibitors. Both D and L forms of these cyclitols could be synthesized from *myo*-inositol in gram scales and hence by exploiting the difference in reactivities of cis- and trans-ketals, a variety of protected derivatives, which are useful for the synthesis of unnatural phosphoinositols and natural products, can be synthesized.
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Keywords: Cyclitol; Inositol; Carbohydrate; Glycosidase inhibitor; Aminocyclitol

1. Introduction

A great deal of attention has been paid to the synthetic inositol chemistry due to the involvement of phosphorylated or glycosylated inositols in various biological processes. Several inositol phosphates and phospholipids occur in Nature. Apart from the well established roles of Ins(1,4,5)P_3 in cellular signal transduction[1,2] and glycosylphosphatidylinositols in protein anchoring,[3] the biological roles of majority of phosphoinositols and glycoinositols are yet to be unraveled. Many of the phosphoinositols are metabolized by different specific kinases and phosphatases resulting in site selective phosphorylation and/or dephosphorylation of these phosphoinositols. However, the biological significances of these phosphorylation–dephosphorylation cascades are unknown. The design and syntheses of novel ligands of the enzymes/receptors involved in these processes are necessary to unravel the finer details of cellular events. Thus one of the major foci of the synthetic inositol chemistry is the judicious design, synthesis and structure–activity relationship (SAR) studies of different structurally modified analogs of natural substrates of different metabolic enzymes and receptors. Inositols being cyclohexane hexols, there are nine isomeric possibilities differing in the relative orientation of hydroxyl groups. Naturally, ligands derived from these isomeric inositols became the target candidates for these studies. However, the facts that only four isomeric inositols occur naturally and the paucity of naturally occurring ones are major hurdles to such investigations. As a consequence, there have been several attempts to synthesize these inositols from different starting materials. In addition, inositols are increasingly being used as synthons for many natural products,[4] scaffolds for metal complexing agents,[5] gelators,[6] catalysts,[7] supramolecular assemblies,[8] etc. These novel applications of inositols also give further impact for developing efficient methodologies for their syntheses.

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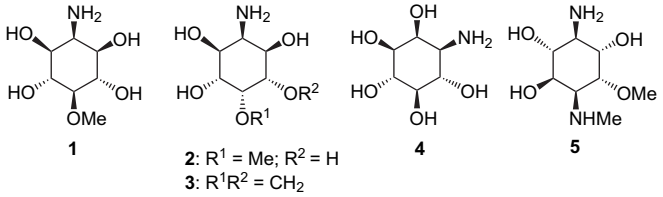


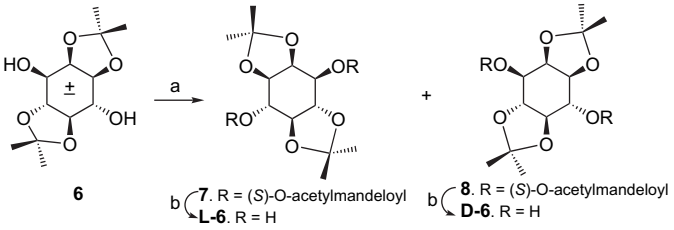
Chart 1. Aminocyclitol moieties of aminoglycoside antibiotics.

On the other hand, aminocyclitols have gained importance because of their glycosidase inhibitory properties[9] and antibacterial properties. Aminocyclitols forms the aglycons in many aminoglycoside antibiotics[10] and SAR studies[11,12] have established the importance of the aminocyclitol part for antibacterial activities. For instance, amino-inositols **1**–**5** (Chart 1) are the aminocyclitol part of antibiotics KA-3093, methoxyhygromycin, hygromycin A, minosaminomycin, and fortimicin, respectively. To control the bacterial resistance toward antibiotics, developing novel antibiotics using analogs of natural aminocyclitols forms an important area of medicinal chemistry research.[13] Also aminocyclitols are potential synthons for natural products like *Amarylladaceae* alkaloids (e.g., pancratistatin, narciclasine, lycoricidine, etc.). In addition, some of the synthetic azidocyclitols, the synthetic precursors for aminocyclitols, have been shown to possess potent anticancer properties.[14]

2. Results and discussions

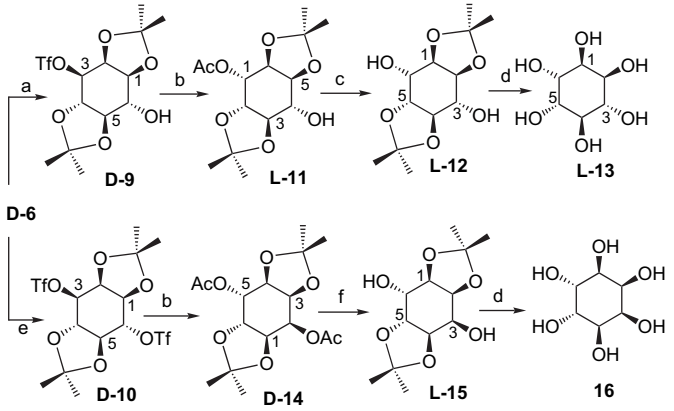
Due to the aforementioned importance of cyclitols and aminocyclitols, various elegant syntheses of isomeric inositols,[15] monoaminocyclitols,[16] and diaminocyclitols[17] from different starting materials have been reported. However, use of cheaply available *myo*-inositol as starting material for the synthesis of such cyclitols and aminocyclitols is advantageous. Since the regioselective protection–deprotection of *myo*-inositol hydroxyl groups with a wider range of protecting groups[18] and methods for optical resolution of protected *myo*-inositol derivatives[2c] are known, by choosing an appropriate optically pure *myo*-inositol derivative as the starting material, desirably protected isomeric inositol derivatives and aminocyclitols in optically pure form can be made. Although *scyllo*,[19] *neo*,[20] *cis*,[21] D-*chiro*[22] and L-*chiro*[23] inositols (or their derivatives) have been synthesized from *myo*-inositol, only a few of these reports[19b,22,23] deal with the syntheses of optically homogeneous derivatives. We herein report the full details of our synthesis of enantiomerically pure *chiro*- and *allo*-inositol derivatives and aminocyclitols.[24]

Racemic 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**6**),[25] due to its ease of preparation, difference in reactivity between two hydroxyl groups and the possibility for the selective deprotection of *trans* ketal in presence of the cis-ketal, has been chosen as the starting material for the synthesis of isomeric inositol derivatives and aminocyclitols via S_N2 substitution of mono and di-sulfonate derivatives of **6**. We have recently developed[26] an efficient method for the diastereomeric resolution of (±)-**6** without involving column chromatography.[24a] Acylation of (±)-**6** with (*S*)-*O*-acetylmandeloyl chloride provided diastereomeric di-(*S*)-*O*-acetylmandelate derivatives **7** and **8** (Scheme 1) from which **8** was crystallized from a mixture of ethyl acetate–hexane (3:7 v/v) solution and **7** was crystallized from chloroform solution of the concentrated mother liquor.[26a] Removal of the chiral auxiliaries by aminolysis with isobutylamine provided enantiomers of **6** in quantitative yields. The amides could be washed off with hexane and pure diols L-**6** and D-**6** could be obtained by crystallization from a mixture of dichloromethane and hexane. The use of cheaply available *O*-acetylmandelic acid as the chiral auxiliary and avoidance of chromatography for purification render inexpensive access to optically active derivatives D-**6** and L-**6**.



Scheme 1. (*S*)-*O*-Acetylmandeloyl chloride, Py, 0 °C; (b) isobutylamine, MeOH, reflux.

During the synthesis of *neo*-inositol, Potter et al. have observed an enhancement in yield and regioselectivity for trifluoromethanesulfonylation compared to other sulfonylations.[20] This report has prompted us to use trifluoromethanesulfonic (triflic) anhydride for sulfonylation. Regioselective sulfonylation of diol D-**6** with 1.1 equiv of triflic anhydride in the presence of pyridine provided 3-triflate D-**9** (Scheme 2) in excellent yield (90%). Although trace of ditriflate D-**10** (6%) was formed, monotriflate resulting from the sulfonylation of C6–OH was not observed. In agreement with previous observation,[20] a comparison of yields of previously reported tosylation[18] with our triflylation reveals that the yield and regioselectivity for triflylation is superior to those for other sulfonylations. It is worthy to note that such a high degree of



Scheme 2. (a) Tf_2O (1.1 equiv), Py, CH_2Cl_2, −20 °C; (b) KOAc, DMA, 70 °C; (c) MeOH, Et_3N, reflux; (d) TFA–H_2O (4:1), rt; (e) Tf_2O (2.2 equiv), Py, CH_2Cl_2, −20 °C; (f) NaOMe, MeOH, reflux.

regioselectivity during acylation, silylation, alkylation, and sulfonylation has not been observed for this diol previously.[18] Ditriflate D-**10** can be washed away with hexane. Ultra-pure crystalline D-**9** could be obtained by crystallization from CH_2Cl_2–hexane. However, D-**9** is very unstable at rt and hence a perfect combustion analysis was not possible. Also D-**9** always decomposed in solution during the acquisition of ^{13}C NMR. Also this compound did not melt on heating but charred in the temperature range 110–130 °C probably due to the decomposition before melting point. For this reason crude D-**9**, obtained by simply washing off the ditriflate D-**10**, was converted to the next product as soon as it was prepared.

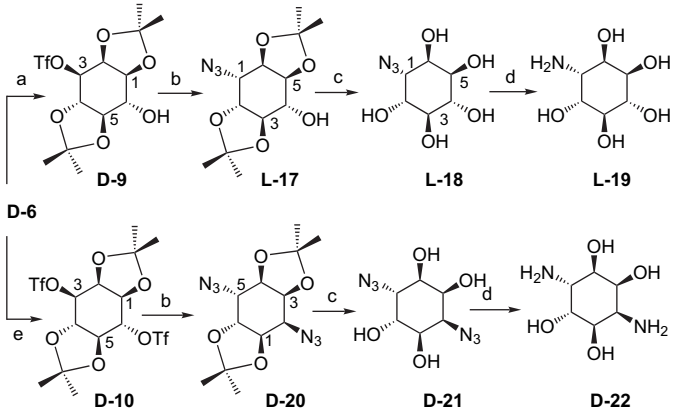
At first we attempted to substitute the triflyl group with acetate in S_N2 fashion to synthesize *chiro*-inositol derivatives. However, treatment of D-**9** with potassium acetate (KOAc) in DMF resulted in the formation of an inseparable mixture of formate and acetate. The use of DMF as formate anion equivalent in substitution of sulfonates has been documented in literature.[20,27] Potter et al.[20] used aq dimethylacetamide (DMA) as acetate anion equivalent to substitute the triflate group. An analogous approach using aq DMA to substitute the triflyl group in D-**9** was sluggish to be of practical use. However, a clean S_N2 substitution of triflate with acetate could be achieved by the use of KOAc in DMA. Evaporation of DMA under reduced pressure followed by aqueous work-up of the residue provided pure 1-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-L-*chiro*-inositol (L-**11**) in quantitative yield without the need of chromatography. Products arising from elimination or substitution (S_N1) with retention of configuration were not detected. The acetate moiety in L-**11** was removed by methanolysis and pure 1,2:4,5-di-*O*-isopropylidene-L-*chiro*-inositol (L-**12**) could be obtained quantitatively by simple evaporation of the solvents. Finally, acid hydrolysis of the ketal moieties and evaporation of the solvents provided pure L-*chiro*-inositol (L-**13**), which could be crystallized from a mixture of water and ethanol.

Sulfonylation of diol D-**6** with 2.2 equiv of triflic anhydride in the presence of pyridine provided the ditriflate D-**10** (Scheme 2). Treatment of D-**10** with KOAc in DMA provided D-2,5-di-*O*-acetyl-1,6:3,4-di-*O*-isopropylidene-*allo*-inositol (D-**14**) in quantitative yield. The acetate moieties were removed by methanolysis using catalytic amount of NaOMe in methanol. Neutralization of the reaction mixture with dry ice followed by evaporation to dryness and trituration with dichloromethane provided the D-1,6:3,4-di-*O*-isopropylidene-*allo*-inositol D-**15** in quantitative yield. *allo*-Inositol **16** being a *meso*-cyclitol, it was prepared from the racemic **15**. Thus (±)-**15**, prepared from (±)-**6** in a similar sequence as above, on acid hydrolysis afforded *allo*-inositol (**16**).

In light of the demand for various inositols for ligand synthesis in short time, we investigated the syntheses of *allo*- and *chiro*-inositol derivatives in one pot. A co-spotted TLC (Thin Layer Chromatography) analysis of individually synthesized *chiro*-acetate L-**11** and *allo*-diacetate D-**14** revealed that they are chromatographically separable. Hence we decided to synthesize L-**11** and D-**14** in one pot. Thus a mixture of monotriflate D-**9** and ditriflate D-**10** were synthesized by reacting the diol D-**6** with 1.5 equiv of triflic anhydride in pyridine. Treatment of the crude mixture of D-**9** and D-**10** thus obtained with KOAc in DMA, followed by work-up and chromatography provided acetate L-**11** (41%) and diacetate D-**14** (54%). Thus this procedure gives access to two important inositol derivatives essentially in two steps from diol D-**6**.

It is noteworthy that protected derivatives **11** and **12** cannot be obtained from *chiro*-inositol directly, as isopropylidenation is reported[18] to give C2 symmetric 1,2;5,6-di-*O*-isopropylidene-*chiro*-inositol (both cis), which is not expected to show any selectivity for cleavage. Although protection of *allo*-inositol is not known, 1,6:3,4-di-*O*-isopropylidene-*allo*-inositol (**15**), is not expected to be a product of di-isopropylidenation of *allo*-inositol (**16**) as other two diketals (with two cis-ketals) are expected to be more stable than **15**. Hence our routes provide access to protected derivatives (**11**,**12**,**14**, and **15**), which cannot be obtained directly from respective inositols. The relative lability of *trans*-isopropylidene over *cis*-isopropylidene[18] on mild acid hydrolysis or transketalization can be exploited to synthesize further set of partially protected inositol derivatives (cis-mono ketals) from these diketals. Such partially protected inositol derivatives are essential for the syntheses of phosphoinositols and natural products.

We then turned our attention to the synthesis of novel aminocyclitols. Nucleophilic substitution of the triflate D-**9** with sodium azide in DMF provided 1L-1-azido-1-deoxy-2,3:5,6-di-*O*-isopropylidene-*chiro*-inositol (L-**17,** Scheme 3). As in the case of substitution with acetate, compounds arising from elimination or S_N1 reaction were not observed. Contrary to the reaction of D-**9** with KOAc in DMF, competing substitution with formate anion was not observed in this case. This could be due to the large difference in nucleophilicities of azide and *O*-acyl anion. The formate being less nucleophilic may not be able to compete with highly nucleophilic azide anion for the S_N2 substitution of triflate. But since the difference in nucleophilicities of two *O*-acyl anions (formate and acetate) being small, formate anion competes with acetate during the substitution with KOAc in DMF. The ketal protecting groups in L-**17** were removed by acid hydrolysis and pure



Scheme 3. (a) Tf_2O (1.1 equiv), Py, CH_2Cl_2, −20 °C; (b) NaN_3, DMF, 70 °C; (c) TFA–H_2O (4:1), rt; (d) H_2, Pd–C, MeOH, rt; (e) Tf_2O (2.2 equiv), Py, CH_2Cl_2, −20 °C.

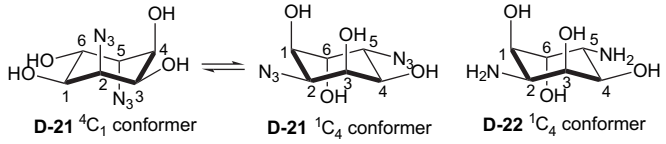


Chart 2. Conformational preferences of D-**21** and D-**22**.

1L-1-azido-1-deoxy-*chiro*-inositol (L-**18**) could be obtained as a gum in quantitative yield by simple evaporation of the solvents. Hydrogenolysis of the azide L-**18** provided 1L-1-amino-1-deoxy-*chiro*-inositol (L-**19**).

Similarly, treatment of the ditriflate D-**10** with NaN_3 in DMF provided 1D-2,5-di-azido-2,5-di-deoxy-1,6:3,4-di-*O*-isopropylidene-*allo*-inositol (D-**20**, Scheme 3) in 93% yield. Removal of the isopropylidene groups by acid hydrolysis provided 1D-2,5-diazido-2,5-di-deoxy-*allo*-inositol (D-**21**). Owing to the *allo* (3a/3e) configuration and hence the plausible dynamic interchange between two different chair conformations (Chart 2), the signals in both ^1H NMR and ^{13}C NMR of D-**21** were very broad. However, the signals were resolved at high temperature as expected. Finally, hydrogenolysis of D-**21** provided 1D-2,5-diamino-2,5-di-deoxy-*allo*-inositol (D-**22**). Surprisingly, D-**22** showed sharp peaks in the NMR spectra. Analysis of the $^3J_{HH}$ coupling constants suggested that D-**22** takes the chair conformation where both amino groups and C-4–OH are in equatorial orientation ($^1C_4$ conformation). Coupling constants of 10.5 Hz for H-4/H-5 coupling and 3.5 Hz for H-1/H-6 coupling are indicative of diaxial orientation of H-4 and H-5 and diequatorial orientation of H-1 and H-6. This is in agreement with the $^1C_4$ conformation of the cyclohexyl ring. Further evidence for such a conformation came from the observed cross-peaks between H-1 and H-3 in the COSY spectra due to the W-coupling.

The abilities of these azido-inositols and amino-inositols to inhibit various glycosidases were investigated. All of these compounds showed weak to moderate inhibition toward the enzymes tested. Inhibition of various glycosidases and glycogen phosphorylase by compounds L-**18**, L-**19**, D-**21**, D-**22**, and (±)-**22** is shown in Table 1. However, it is worthy to note that the azido-inositol L-**18** showed relatively good inhibition toward rat intestinal sucrase and isomaltase with the IC_{50} values of 0.66 and 0.54 mM, respectively. Also, the compounds L-**18**, D-**21**, and D-**22** showed about 50% inhibition at 1 mM toward rice α-glucosidase, rat intestinal sucrase, and rat intestinal isomaltase, respectively. Interestingly, the inhibition of some of the enzymes by (±)-**22** is better than that by D-**22**.

Although there are a few reports on the synthesis of various mono-amino[16] and dimaino-inositols,[17a–h] the glycosidase inhibitory activities of these derivatives have not been investigated. In general, the enzyme inhibitions by our azido- or amino-inositol are comparable with that by other cyclitol[28] or aminocyclitol[29] derivatives and more potent than amino-di-inositols[17i] and some of the aminocyclitols[30] but much less potent than conformationally restricted bicyclic aminocyclitol[31] or valienamine analogs.[32] Our results suggest that there is enough scope for investigation of various amino and azido-inositols as novel class of glycosidase inhibitors.

3. Conclusions

In conclusion, we have reported efficient routes for the syntheses of different protected *chiro*- and *allo*-inositol derivatives, monoazido- and monoamino-inositol of *chiro* configuration and diazido- and diamino-inositols of *allo* configuration in optically active form from *myo*-inositol. Since the *trans*-isopropylidene can be cleaved leaving the cis-ketal unaffected, by exploiting this selectivity, different derivatives for cyclitol and aminocyclitol based natural product and phosphoinositol syntheses can be made easily. A one pot method for the simultaneous preparation of both *chiro*- and *allo*-inositol derivative provides easy access to derivatives of two different inositols. Also another advantage is that the derivatives, which cannot be obtained directly from the respective inositols, can be obtained via our method through sulfonate inversion of the respective *myo*-inositol derivative. Preliminary investigation on the glycosidase inhibitory activity of the novel azido and aminocyclitols suggests that these classes of compounds have potential to be novel class of glycosidase inhibitors.

4. Experimental

4.1. General

All experiments were conducted under nitrogen atmosphere. Melting points were determined with a Yanaco Micro Melting Point Apparatus and are uncorrected. Flash column chromatography was performed using silica gel (Fuji Silysia,

Table 1
Enzyme inhibition rate (%) of amino- and azido-inositols at 1 mM

Enzyme	(±)-**22**	D-**21**	D-**22**	L-**18**	L-**19**
α-Glucosidase (rice, pH 5.0)	25.4	17.4	29.9	49.3	31.3
Rat intestinal maltase (pH 5.8)	18.8	0.0	3.8	26.2	0.0
Rat intestinal sucrase (pH 5.8)	20.0	47.9	34.4	61.5 (IC_{50}=0.66 mM)	32.8
Rat intestinal isomaltase (pH 5.8)	29.1	28.1	49.1	68.7 (IC_{50}=0.54 mM)	19.3
β-Glucosidase (almonds, pH 5.0)	11.1	21.7	7.6	0.0	0.0
Glycogen phosphorylase b (rabbit muscle)	21.7[a]	7.6[b]	11.4[b]	3.5[b]	3.2[b]
α-Fucosidase (human placenta)	0.4	12.9	9.5	20.1	19.9
β-Xylosidase (*Aspergillus niger*)	8.3	8.3	21.5	18.1	23.8

[a] Inhibition at 1 mg/mL.
[b] Inhibition at 0.4 mM.

Silica gel BW-300). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-DPX-400 instrument. Chemical shifts (δ_H values relative to tetramethylsilane and δ_C values relative to $CDCl_3$) and coupling constants (J values) are given in parts per million and hertz, respectively. Optical rotations were recorded in a JASCO P-1010 Polarimeter. Elemental analyses were carried out on a YANACO MT-5 elemental analyzer. Usual work-up refers to evaporation of the reaction solvent followed by dissolution of the residue in ethyl acetate and washing successively with water, dil HCl, satd $NaHCO_3$ solution, and brine followed by drying over anhyd $MgSO_4$ and concentration under reduced pressure.

4.2. Enzyme assay

The enzymes α-glucosidase (from rice, assayed at pH 5.0), β-glucosidase (from almonds, assayed at pH 5.0), α-fucosidase (from human placenta, assayed at pH 6.8), β-xylosidase (from *Aspergillus niger*, assayed at pH 5.0), *p*-nitrophenyl glycosides, and disaccharides were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). Brush border membranes prepared from rat small intestine according to the method of Kessler et al.[33] were assayed at pH 5.8 for rat intestinal maltase, isomaltase, and sucrase using maltose, isomaltose, and sucrose. The released D-glucose was determined colorimetrically using the Glucose CII-test Wako (Wako Pure Chemical Industries, Osaka, Japan). Other glycosidase activities were determined using an appropriate *p*-nitrophenyl glycoside as substrate. The reaction was stopped by adding 400 mM Na_2CO_3. The released *p*-nitrophenol was measured spectrometrically at 400 nm. Glycogen phosphorylase activity was assayed in the direction of glycogen breakdown from the rate of NADPH formation in an assay coupled to phosphoglucomutase and glucose 6-phosphate dehydrogenase.[34]

4.3. Preparation of S-O-acetyl-mandeloyl chloride

A solution of (*S*)-*O*-acetyl mandelic acid (194 mg, 1 mmol) in dichloromethane (5 mL) was cooled to 0 °C. To this solution added oxalyl chloride (105 μL, 1.1 mmol) and then a catalytic amount (10 μL) of DMF and the resulting mixture was stirred at 0 °C till the effervescence ceases (about 2 h). This solution was directly used for esterification. Pure *S*-*O*-acetylmandeloyl chloride can also be obtained by evaporating off the dichloromethane and extracting the residue with dry hexane followed by evaporation of the hexane extract.

4.4. Separation of 7 and 8

To a solution of diol (±)-**6** (520 mg, 2 mmol) in pyridine (10 mL), a solution of (*S*)-*O*-acetylmandeloyl chloride (893 mg, 4.2 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C and stirred for 3 h gradually allowing the reaction mixture to attain rt. After 3 h, ethyl acetate was added and washed successively with water, dil HCl, satd solution of $NaHCO_3$, and brine. The organic layer was dried over anhyd Na_2SO_4 and evaporated under reduced pressure to obtain a solid (1.23 g). Compound **8** (563 mg, 46%, mp 215–217 °C; $[\alpha]_D$ +64.4 (*c* 1, CH_2Cl_2))[26b] could be obtained by crystallization from a mixture of ethyl acetate and hexane (1:3 v/v). The concentrated mother liquor was re-dissolved in a mixture of $CHCl_3$ (10 mL) and hexane (20 mL) to get crystals of **7** (514 mg, 42%, mp 177 °C; $[\alpha]_D$ +53.2 (*c* 1, CH_2Cl_2)).[26b]

4.5. D-1,2:4,5-Di-O-isopropylidene-myo-inositol (D-6)

4.5.1. Method A

A suspension of **8** (800 mg, 1.3 mmol) and isobutylamine (2 mL) in methanol (10 mL) was refluxed for 1 h, when TLC showed complete disappearance of the starting material. The solvent and excess isobutylamine were evaporated off under reduced pressure and the residue thus obtained was chromatographed with ethyl acetate–hexane (8:2 v/v) as eluent to get pure D-**6** (334 mg, 99%). Mp 159–161 °C; $[\alpha]_D$ −21.8 (*c* 1, MeCN); lit.[35] values for enantiomer of D-**6** mp 159–161 °C; $[\alpha]_D$ 22 (*c* 1, MeCN).

4.5.2. Method B

To a suspension of **8** (1.84 g, 3 mmol) in dry methanol (50 mL) was added triethylamine (9 mL) and the mixture was stirred at rt overnight. The solvents were evaporated and the residue was washed with hexane to get pure diol D-**6** (0.781 g, 100%).

4.6. (±)-3-O-Trifluoromethanesulfonyl-1,2:4,5-di-O-isopropylidene-myo-inositol [(±)-9]

To a solution of diol (±)-**6** (2.6 g, 10 mmol) in a mixture of pyridine (20 mL) and dichloromethane (100 mL) at −20 °C was added triflic anhydride (1.93 mL) dropwise and the mixture was stirred overnight gradually warming it to rt. The solvents were evaporated off, the residue was dissolved in ethyl acetate and washed successively with water, dil HCl, satd $NaHCO_3$ solution, and brine, dried over anhyd $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed using 1:9 ethyl acetate–hexane to get ditriflate (712 mg, 13.6%) and further elution with 3:7 ethyl acetate–hexane provided the monotriflate (3.29 g, 84%).

In an easy method the ditriflate can effectively be removed by washing the residue with hexane (5×10 mL) and the remaining solid was very pure monotriflate. *Note*: it has been observed that the monotriflate, after work-up, is prone to decomposition via ketal cleavage and hence the next reaction has to be done immediately.

4.7. D-3-O-Trifluoromethanesulfonyl-1,2:4,5-di-O-isopropylidene-myo-inositol (D-9)

To a solution of diol D-**6** (1.3 g, 5 mmol) in a mixture of pyridine (10 mL) and dichloromethane (50 mL) at −20 °C, was added trifluoromethanesulfonic anhydride (985 μL, 5.1 mmol) dropwise and the solution was stirred at that temperature for 2 h. The mixture was then diluted with ethyl acetate (150 mL), washed with water, dil HCl, aq $NaHCO_3$, and

brine, dried over anhyd $MgSO_4$, and evaporated. The residue was washed with hexane (5×10 mL) and concentration of the combined hexane washings provided ditriflate D-**10** (131 mg, 6%). The residue remained after washing with hexane was pure monotriflate D-**9** (1.765 g, 90%). $[\alpha]_D$ 13 (*c* 1, MeOH); ^1H NMR ($CDCl_3$, 400 MHz): 1.38 (s, 3H, Me), 1.46 (s, 3H, Me), 1.48 (s, 3H, Me), 1.56 (s, 3H, Me), 2.45 (br, OH), 3.40 (dd, 10.25, 9.77 Hz, H-5), 3.94 (dd, 10.74, 6.38 Hz, H-6), 4.08–4.16 (m, 2H, H-1 and H-4), 4.57 (t, 4.40 Hz, H-2), 5.07 (dd, 10.24, 4.40 Hz, H-3).

4.8. 1-O-Acetyl-2,3:5,6-di-O-isopropylidene-L-chiro-inositol (L-*11*)

The triflate D-**9** (392 mg, 1 mmol) was stirred with potassium acetate (491 mg, 5 mmol) in dimethylacetamide (9 mL) at 70 °C for overnight. The solvent was evaporated under reduced pressure and the residue on usual work-up provided pure L-**11** (299 mg, 99%). Mp 126–128 °C; $[\alpha]_D$ −65.0 (*c* 1, $CHCl_3$); ^1H NMR (Me_2SO-d_6, 400 MHz): 1.24 (s, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 2.05 (s, 3H), 3.58 (m, H-4), 3.64–3.68 (overlapped, H-2 and H-3), 3.96 (dd, 5.9, 5.7 Hz, H-5), 4.22 (dd, 5.7, 1.8 Hz, H-6), 5.38 (t, 1.8 Hz, H-1), 5.62 (d, 5.5 Hz, OH); ^1H NMR (CD_3OD, 400 MHz): 1.33 (s, 3H), 1.37 (s, 3H), 1.42 (s, 3H), 1.47 (s, 3H), 2.10 (s, 3H), 3.73–3.81 (overlapped, H-2, H-3 and H-4), 4.06 (dd, 5.7, 5.6 Hz, H-5), 4.28 (dd, 5.6, 1.8 Hz, H-6), 5.55 (t, 1.8 Hz, H-1); ^1H NMR (Me_2CO-d_6, 400 MHz): 1.28 (s, 3H), 1.32 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 2.08 (s, 3H), 3.74–3.81 (overlapped, H-2, H-3 and H-4), 4.07 (t, 5.4 Hz, H-5), 4.28 (dd, 5.4, 1.8 Hz, H-6), 4.74 (d, 3.7 Hz, OH), 5.53 (t, 1.8 Hz, H-1); ^1H NMR ($CDCl_3$, 400 MHz): 1.34 (s, 3H), 1.40 (s, 3H), 1.46 (s, 3H), 1.49 (s, 3H), 2.11 (s, 3H), 2.73 (br, OH), 3.83–3.90 (overlapped, H-2, H-3 and H-4), 4.13 (dd, 6.4, 5.6 Hz, H-5), 4.23 (dd, 5.6, 2.4 Hz, H-6), 5.68 (t, 2.4 Hz, H-1); ^{13}C NMR ($CDCl_3$, 100 MHz): 20.55 ($COCH_3$), 25.54 (CH_3), 26.24 (CH_3), 26.86 (CH_3), 27.69 (CH_3), 66.17 (Ins *C*), 74.89 (Ins *C*), 75.21 (Ins *C*), 76.58 (Ins *C*), 77.22 (Ins *C*), 81.02 (Ins *C*), 109.81 (CMe_2), 111.91 (CMe_2), 169.20 (*C*OMe). Anal. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.33. Found: C, 55.96; H, 7.27.

4.9. 1,2:4,5-Di-O-isopropylidene-L-chiro-inositol (L-*12*)

The acetate L-**11** (200 mg, 0.66 mmol) was refluxed in a mixture of methanol (4 mL) and triethylamine (1 mL) for 2 h. The reaction mixture was cooled and the solvents were evaporated under reduced pressure to obtain pure L-**12** (171 mg, 99.3%) as a white solid. A small fraction of this solid was crystallized from a mixture of $CHCl_3$ and hexane. $[\alpha]_D$ −61.0 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 1.34 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.47 (s, 6H, 2×CH_3), 2.67 (br s, 6-OH), 3.06 (br s, 3-OH), 3.75 (dd, 9.2, 2.8 Hz, H-5), 3.80–3.95 (2H overlapped, H-3 and H-4), 4.15 (t, 5.6 Hz, H-2), 4.33 (dd, 5.6, 2.0 Hz, H-1), 4.48 (m, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz): 25.64 (CH_3), 26.58 (CH_3), 27.13 (CH_3), 27.88 (CH_3), 65.63 (Ins *C*), 74.72 (Ins *C*), 75.78 (Ins *C*), 77.26 (Ins *C*), 79.06 (Ins *C*), 81.2 (Ins *C*), 109.43 (CMe_2), 111.95 (CMe_2). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.21; H, 7.69.

4.10. L-chiro-Inositol (L-*13*)

Diketal L-**12** (100 mg, 0.38 mmol) was stirred in a mixture of TFA and H_2O (4:1 v/v, 3 mL) at rt for 3 h. Evaporation to dryness provided L-*chiro*-inositol (L-**13**, 69 mg) as a white solid. $[\alpha]_D$ −59.0 (*c* 1.2, H_2O); lit.[23] $[\alpha]_D$ −58.2 (*c* 1.3, H_2O).

4.11. (±)-3,6-Di-O-trifluoromethanesulfonyl-1,2:4,5-di-O-isopropylidene-myo-inositol [(±)-*10*]

To a solution of diol (±)-**6** (1.17 g, 4.5 mmol) in a mixture of pyridine (15 mL) and dichloromethane (75 mL) at −20 °C was added triflic anhydride (1.93 mL, 10 mmol) dropwise and the mixture was stirred overnight gradually warming the mixture to rt. The solvents were evaporated off and the residue was dissolved in ethyl acetate and washed successively with water, dil HCl, satd $NaHCO_3$ solution, and brine, dried over anhyd $MgSO_4$, and evaporated under reduced pressure. The crude residue thus obtained was chromatographed with 1:9 (v/v) ethyl acetate–hexane to get the ditriflate (±)-**10** (2.2 g, 93%) as a white solid. This solid did not show a sharp melting point. At 92 °C, the crystals shrinked, further heating resulted in browning of the crystals at 112–116 °C and finally the crystals got charred at 120 °C. ^1H NMR ($CDCl_3$, 400 MHz): 1.41 (s, 3H, Me), 1.47 (s, 3H, Me), 1.50 (s, 3H, Me), 1.59 (s, 3H, Me), 3.60 (dd, 10.8, 10.25 Hz, H-5), 4.19 (t, 10.8 Hz, H-4), 4.36 (dd, 6.35, 4.40 Hz, H-1), 4.62 (t, 4.40 Hz, H-2), 4.87 (dd, 10.8, 6.5 Hz, H-6), 5.08 (dd, 10.25, 4.40 Hz, H-3); ^{13}C NMR ($CDCl_3$): 25.51 (CH_3), 26.51 (CH_3), 26.54 (CH_3), 27.39 (CH_3), 74.02 (Ins *C*), 74.72 (Ins *C*), 75.79 (Ins *C*), 78.58 (Ins *C*), 81.40 (Ins *C*), 87.11 (Ins *C*), 112.28 (CMe_2), 114.74 (CMe_2), 118.38 (q, CF_3), 118.42 (q, CF_3). Anal. Calcd for $C_{14}H_{18}F_6O_{10}S_2$: C, 32.06; H, 3.46. Found: C, 31.91; H, 3.54.

4.12. D-3,6-Di-O-trifluoromethanesulfonyl-1,2:4,5-di-O-isopropylidene-myo-inositol (D-*10*)

To a solution of diol D-**6** (1.3 g, 5 mmol) in a mixture of pyridine (17 mL) and dichloromethane (83 mL) at −20 °C, was added trifluoromethanesulfonic anhydride (2.123 mL, 11 mmol) dropwise and the solution was stirred at that temperature for 2 h. The solvent was evaporated and the residue thus obtained was dissolved in ethyl acetate and washed successively with water, cold dil HCl, aq $NaHCO_3$, and brine, dried over anhyd $MgSO_4$, and the solvent was evaporated to get D-**10** (2.543 g, 97%) as a white powder. Since ^1H NMR showed no impurity, this was not purified further.

4.13. D-2,5-Di-O-acetyl-1,6:3,4-di-O-isopropylidene-allo-inositol (D-*14*)

The triflate D-**10** (1.049 g, 2 mmol) was stirred with potassium acetate (981 mg, 10 mmol) in dimethylacetamide

(16 mL) at 70 °C for overnight. The solvent was evaporated under reduced pressure and the residue on usual work-up provided pure D-**14** (688 mg, quant) as white solid. A small fraction of this solid was crystallized from a mixture of chloroform and hexane. Mp 140 °C; $[\alpha]_D$ −55.0 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 1.33 (s, 3H, Me), 1.42 (s, 3H, Me), 1.44 (s, 3H, Me), 1.49 (s, 3H, Me), 2.11 (s, 3H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 3.93 (dd, 10.2, 2.57 Hz, H-1), 4.24 (dd, 5.66, 1.60 Hz, H-4), 4.27 (dd, 10.20, 3.37 Hz, H-6), 4.37 (t, 5.67 Hz, H-3), 5.64 (dd, 5.65, 2.58 Hz, H-2), 5.74 (dd, 3.37, 1.60 Hz, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): 20.70 ($COCH_3$), 21.13 ($COCH_3$), 25.01 (CH_3), 25.88 (CH_3), 26.61 (CH_3), 26.64 (CH_3), 66.14 (Ins *C*), 66.75 (Ins *C*), 70.83 (Ins *C*), 72.24 (Ins *C*), 72.84 (Ins *C*), 77.02 (Ins *C*), 110.10 (CMe_2), 111.45 (CMe_2), 169.26 (OCOMe), 169.71 (OCOMe). Anal. Calcd for $C_{16}H_{24}O_8 \cdot 0.3H_2O$: C, 54.94; H, 7.09. Found: C, 54.86; H, 6.92.

4.14. (±)-2,5-Di-O-acetyl-1,6:3,4-di-O-isopropylidene-allo-inositol [(±)-14]

To a solution of ditriflate (±)-**10** (524 mg, 1 mmol) in DMA (10 mL), KOAc (491 mg, 5 mmol) was added and the mixture was stirred at 80 °C for 8 h. DMA was evaporated under reduced pressure and the residue was dissolved in ethyl acetate and washed successively with water and brine, dried over anhyd $MgSO_4$, and the solvent was evaporated. The residue thus obtained was chromatographed using ethyl acetate–hexane as eluent to get the diacetate (±)-**14** (300 mg, 87%). Mp 161 °C (sublimed).

4.15. L-1,2:4,5-Di-O-isopropylidene-allo-inositol (L-15)

The diacetate D-**14** (344 mg, 1 mmol) and catalytic amount of sodium methoxide (10 mg) were refluxed in methanol (10 mL) for 2 h. The reaction mixture was cooled, neutralized by the addition of solid CO_2, and then the solvents were evaporated under reduced pressure. Trituration of the residue with dichloromethane provided pure L-**15** (260 mg, 100%) as a white solid. A small fraction of this solid was crystallized from a mixture of ethyl acetate and hexane. Mp 136 °C; $[\alpha]_D$ −85.0 (*c* 1, $CHCl_3$); ^1H NMR (Me_2SO-d_6, 400 MHz): 1.26 (s, 3H, Me), 1.33 (s, 3H, Me), 1.34 (s, 3H, Me), 1.44 (s, 3H, Me), 3.80 (dd, 9.8, 1.5 Hz, H-4), 4.05–4.11 (overlapped, H-3 and H-5), 4.22 (dd, 4.4, 3.4 Hz, H-2), 4.82 (dd, 4.4, 0.5 Hz, H-6), 5.30 (dd, 4.4, 0.5 Hz, H-1); ^1H NMR (C_6D_6, 400 MHz): 1.15 (s, 3H, Me), 1.39 (s, 6H, 2×Me), 1.49 (s, 3H, Me), 3.86–3.90 (overlapped, H-2 and H-4), 4.16 (dd, 4.4, 2.4 Hz, H-3), 4.33 (dd, 5.9, 1.5 Hz, H-1), 4.53 (dd, 3.4, 1.5 Hz, H-6), 4.62 (dd, 9.8, 3.4 Hz, H-5); ^1H NMR ($CDCl_3$, 400 MHz): 1.40 (s, 3H, Me), 1.47 (s, 3H, Me), 1.52 (s, 3H, Me), 1.55 (s, 3H, Me), 2.42 (s, OH), 2.47 (s, OH), 3.95 (dd, 10.0, 2.4 Hz, H-4), 4.29 (dd, 6.0, 4.4 Hz, H-2), 4.33–4.38 (overlapped, H-3 and H-5), 4.41 (dd, 6.0, 1.6 Hz, H-1), 4.51 (dd, 3.2, 1.6 Hz, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz): 24.44 (CH_3), 25.73 (CH_3), 26.67 (CH_3), 26.75 (CH_3), 65.59 (Ins *C*), 65.95 (Ins *C*), 71.68 (Ins *C*), 73.32 (Ins *C*), 74.18 (Ins *C*), 78.56 (Ins *C*), 109.38 (CMe_2), 110.92 (CMe_2). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.19; H, 7.81.

4.16. (±)-1,2:4,5-Di-O-isopropylidene-allo-inositol [(±)-15]

Diacetate (±)-**14** (200 mg, 0.58 mmol) and sodium methoxide (10 mg) were reacted in methanol (6 mL) for 2 h as above to get (±)-**15** (131 mg, 87%).

4.17. allo-Inositol (16)

Compound (±)-**15** (100 mg, 0.38 mmol) was stirred with a mixture of TFA and water (4:1 v/v, 3 mL) for 3 h. Evaporation to dryness provided *allo*-inositol (**16**, 69 mg) as a white solid.

4.18. Synthesis of 1-O-acetyl-2,3:5,6-di-O-isopropylidene-L-chiro-inositol and D-2,5-di-O-acetyl-1,6:3,4-di-O-isopropylidene-allo-inositol in one pot

To a solution of diol D-**6** (260 mg, 1 mmol) and pyridine (2 mL) in CH_2Cl_2 (10 mL) was added Tf_2O (255 μL, 1.5 mmol) dropwise at −20 °C. The reaction mixture was stirred overnight at rt. The solvents were evaporated and the residue was dissolved in ethyl acetate, washed successively with water, cold dil HCl, satd aq $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. The crude mixture of D-**9** and D-**10** thus obtained was dissolved in DMA (7 mL) and reacted with KOAc (500 mg, 5.1 mmol) at 70–80 °C for 5 h. DMA was evaporated and usual work-up of the residue followed by column chromatography yielded L-**11** (124 mg, 41%) and D-**14** (186 mg, 54%).

4.19. (±)-1-Azido-1-deoxy-2,3:5,6-di-O-isopropylidene-chiro-inositol [(±)-17]

To a solution of (±)-**9** (3.295 g, 8.4 mmol) in DMF (50 mL) was added NaN_3 (1.3 g, 20 mmol) and the mixture was stirred at 70 °C for 5 h. DMF was then evaporated under diminished pressure and the residue was dissolved in ethyl acetate and washed successively with water and brine, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude azide thus obtained was crystallized from a mixture of dichloromethane and hexane to get pure (±)-**17** (2.17 g, 90.8%) as a colorless solid. Mp 128 °C.

4.20. L-1-Azido-1-deoxy-2,3:5,6-di-O-isopropylidene-chiro-inositol (L-17)

Using D-**9** (392 mg, 1 mmol) and NaN_3 (130 mg, 2 mmol) optically pure L-**17** (240 mg, 84%) could be obtained. Mp sublimed in the range 100–125 °C; $[\alpha]_D$ −10.1 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 1.34 (s, 3H, Me), 1.48 (s, 3H, Me), 1.49 (s, 3H, Me), 1.50 (s, 3H, Me), 3.84 (m, H-4), 3.88–3.94 (m, H-2 and H-3), 4.06 (t, 5.9 Hz, H-5), 4.18 (dd, 5.40, 1.95 Hz, H-6), 4.44 (t, 2.0 Hz, H-1); ^{13}C NMR ($CDCl_3$, 100 MHz): 25.5, 26.0, 26.9, 27.6, 56.9, 75.3, 75.5, 76.2,

77.6, 80.8, 109.7, 112.3; FABMS (M+1): 286. Anal. Calcd for $C_{12}H_{19}N_3O_5$: C, 50.52; H, 6.71; N, 14.73. Found: C, 50.31; H, 6.62; N, 14.68.

4.21. L-1-Azido-1-deoxy-chiro-inositol (L-**18**)

Compound L-**17** (143 mg, 0.5 mmol) was stirred in a mixture of TFA and H_2O (4:1 v/v, 2 mL) at rt for 4 h. Evaporation of the solvents provided L-**18** (102 mg, 99.4%) as a gum. $[\alpha]_D$ −11 (*c* 1, H_2O); ^{1}H NMR (D_2O, 400 MHz): 3.26–3.33 (m, 2H, H-3 and H-4), 3.38 (ddd, 8.8, 3.5, 1.0 Hz, H-5), 3.69 (dd, 8.8, 3.8 Hz, H-2), 3.81 (t, 3.8 Hz, H-1), 3.86 (t, 3.5 Hz, H-6); ^{13}C NMR (D_2O, 100 MHz): 64.5, 70.0, 70.1, 70.2, 72.6, 72.8. Anal. Calcd for $C_6H_{11}N_3O_5$: C, 35.12; H, 5.40; N, 20.48. Found: C, 34.99; H, 5.56; N, 20.41.

4.22. L-1-Amino-1-deoxy-chiro-inositol (L-**19**)

Compound L-**18** (51 mg, 0.25 mmol) was dissolved in wet methanol (2 mL) and stirred with 10% Pd–C (10 mg) under an atmosphere of hydrogen (hydrogen balloon) for 24 h. Filtered through a small pad of Celite, washed well with water and methanol. The combined filtrate was evaporated to dryness to get L-**19** (38 mg, 84%). $[\alpha]_D$ −85.2 (*c* 1.15, H_2O); ^{1}H NMR (D_2O, 400 MHz): 3.36 (br, H-1), 3.55–3.65 (m, 2H, H-3 and H-4), 3.75–3.85 (br, H-5), 3.85–3.90 (br, H-2), 4.05 (br, H-6); ^{13}C NMR (D_2O, 100 MHz): 54.4, 70.0, 70.2, 71.9, 72.4, 72.8. Anal. Calcd for $C_6H_{13}NO_5$: C, 40.22; H, 7.31; N, 7.82. Found: C, 40.01; H, 7.42; N, 7.67.

4.23. (±)-2,5-Di-azido-2,5-dideoxy-1,6:3,4-di-O-isopropylidene-allo-inositol [(±)-**20**]

To a solution of ditriflate (±)-**10** (967 mg, 1.84 mmol) in DMF (5 mL), NaN_3 (260 mg, 4 mmol) was added and the mixture was stirred at 70 °C for 5 h. DMF was evaporated under reduced pressure, the residue was dissolved in ethyl acetate and washed successively with water and brine, dried over anhyd $MgSO_4$, and the solvent was evaporated. The residue thus obtained was chromatographed using ethyl acetate–hexane as eluent to get the diazide (±)-**20** (548 mg, 96%) as a crystalline solid. Mp 132–135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.37 (s, 3H, Me), 1.50 (s, 6H, 2×Me), 1.61 (s, 3H, Me), 3.95 (dd, 10.0, 2.8 Hz, H-1), 4.15 (dd, 5.4, 1.6 Hz, H-4), 4.25 (dd, 5.4, 2.8 Hz, H-2), 4.29 (dd, 10.0, 3.6 Hz, H-6), 4.32 (t, 5.4 Hz, H-3), 4.46 (dd, 3.6, 1.6 Hz, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): 25.1, 25.2, 26.5, 26.7, 57.1, 60.5, 72.3, 72.5, 74.2, 77.3, 110.7, 112.2. Anal. Calcd for $C_{12}H_{18}N_6O_4$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.38; H, 5.81; N, 27.02.

4.24. D-2,5-Di-azido-2,5-di-deoxy-1,6:3,4-di-O-isopropylidene-allo-inositol (D-**20**)

By using D-**10** (524 mg, 1 mmol) and NaN_3 (195 mg, 3 mmol) in the above reaction optically pure D-**20** (288 mg, 93%) could be obtained. $[\alpha]_D$ −54.0 (*c* 1, $CHCl_3$).

4.25. (±)-2,5-Di-azido-2,5-di-deoxy-allo-inositol [(±)-**21**]

Diazide (±)-**20** (202 mg, 0.65 mmol) was dissolved in 50% aq TFA (4 mL) and the solution was stirred at rt overnight. Then the solvents were evaporated to give pure diazide (±)-**21** (150 mg, 100%) as a white gummy solid. ^{1}H NMR (D_2O, 400 MHz, rt): 3.70–4.05 (br, 4H), 4.05–4.25 (br, 2H); ^{1}H NMR (D_2O, 400 MHz, 80 °C): 3.80–3.86 (br, 1H), 3.88–3.98 (m, 2H), 4.03 (t, 1H), 4.12 (dd, 1H), 4.14–4.18 (m, 1H); ^{1}H NMR (CD_3OD, 400 MHz): 3.45–3.60 (br, 1H), 3.70–3.80 (m, 1H), 3.86 (dd, 9.70, 3.08 Hz, 1H), 3.95–4.00 (br, 1H), 4.00–4.05 (dd, 4.6, 3.0 Hz, 1H), 4.05–4.20 (br, 1H); ^{13}C NMR (D_2O, 100 MHz, 80 °C): 61.1, 62.2, 70.4, 70.7, 71.4, 72.0. Anal. Calcd for $C_6H_{10}N_6O_4$: C, 31.31; H, 4.38; N, 36.51. Found: C, 31.27; H, 4.44; N, 36.36.

4.26. D-2,5-Di-azido-2,5-di-deoxy-allo-inositol (D-**21**)

Use of D-**20** (100 mg, 0.32 mmol) in place of (±)-**20** and 80% aq TFA (2 mL) in the above reaction provided D-**21** (74 mg, quant). $[\alpha]_D$ 32.0 (*c* 1, H_2O).

4.27. (±)-2,5-Diamino-2,5-di-deoxy-allo-inositol [(±)-**22**]

To a solution of (±)-**21** (100 mg, 0.43 mmol) in methanol (3 mL) was added 10% Pd on carbon (20 mg) and suspension was stirred under an atmosphere of hydrogen (1 atm, H_2 balloon) at rt overnight. The mixture was filtered through a membrane filter washing the filter with methanol and water. The combined filtrates were evaporated to give diamino-inositol (±)-**22** (60 mg, 77%) as a semi-solid. ^{1}H NMR (D_2O, 400 MHz): 2.90 (br s, H-2), 2.98 (dd, 10.5, 2.75 Hz, H-5), 3.47 (dd, 10.5, 1.3 Hz, H-4), 3.74 (dd, 3.5, 1.6 Hz, H-1), 3.83 (dd, 1.3, 2.5 Hz, H-3), 3.89 (t, 3.50 Hz, H-6); ^{13}C NMR (D_2O, 100 MHz): 47.6, 47.7, 71.1, 72.0, 74.2, 74.3; FABMS (M+1): 179. Anal. Calcd for $C_6H_{14}N_2O_4$: C, 40.44; H, 7.92; N, 15.72. Found: C, 40.27; H, 8.06; N, 15.54.

4.28. D-2,5-Diamino-2,5-di-deoxy-allo-inositol (D-**22**)

Reaction of D-**21** (60 mg, 0.26 mmol) and Pd–C (12 mg) in methanol (3 mL) under hydrogen atmosphere as above provided D-**22** (38 mg, 82%). $[\alpha]_D$ 43.0 (*c* 1.5, H_2O).

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