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Efficient routes to optically active azido-, amino-, di-azido- and di-amino-cyclitols with *chiro*- and *allo*-configuration from *myo*-inositol

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Abstract—Efficient routes to hitherto unknown 1D-2,5-di-azido-di-deoxy-*allo*-inositol, 1D-2,5-di-amino-di-deoxy-*allo*-inositol, 1L-1-azido-1-deoxy-*chiro*-inositol and 1L-1-amino-1-deoxy-*chiro*-inositol were developed by using cheaply available *myo*-inositol as the starting material. Preliminary investigations on the enzyme inhibitory properties were done. The methodology reported is amenable to gram scale synthesis and thus can find application in natural product synthesis.
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Amino-cyclitols are important class of compounds because of their potential as glycosidase inhibitors,[1] antibiotics, anticancer agents etc. As glycosidases are involved in a variety of different biological processes, novel glycosidase inhibitors are drug leads for diabetes, cancer and many viral infections. Most of aminoglycoside antibiotics contain either a di-amino-cyclitol or mono-amino-cyclitol as an aglycon.[2] For instance, amino-inositols **1**–**5** (Chart 1) are the amino-cyclitol part of antibiotics KA-3093, methoxyhygromycin, hygromycin A, minosaminomycin, and fortimycin, respectively. SAR studies[3] in these types of antibiotics revealed that amino-inositol moiety is essential for antibiotic action and even the antibiotic activity is known to vary with the conformation of the amino-cyclitol moiety.[4] Since pathogens are known to develop resistance to antibiotics over a period of time, developing analogs of natural amino-cyclitols as novel potent antibiotics are in the forefront of medicinal chemistry.[5] On the other hand, synthetic azido-inositols have been shown to possess potent anticancer properties.[6] Also azido-cyclitols and amino-cyclitols are important intermediates for the synthesis of natural products like Amarilladaceae alkaloids (e.g., pancratistatin, narsciclasine, lycoricidine etc.). In addition, amino-cyclitols are thought to interfere with *myo*-inositol cycle. These facts stimulated interest in

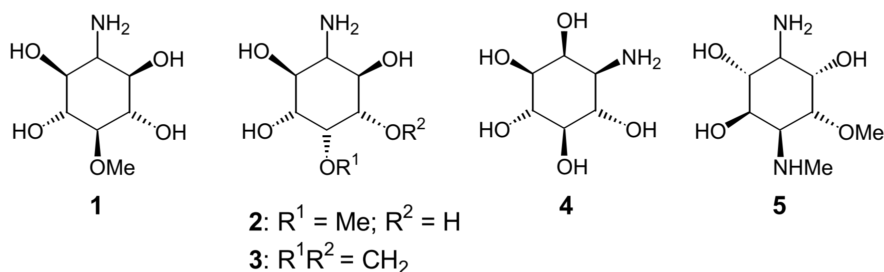

Chart 1.

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the efficient and practical synthesis of amino-cyclitols as potential candidates for the possible pharmaceutical applications and the efforts by various groups, round the globe, have culminated in the syntheses of different mono-amino[7] and di-amino[8] cyclitols from various starting materials. We herein report the syntheses and preliminary investigations of enzyme inhibitory properties of hitherto unknown 1D-2,5-di-azido-2,5-di-deoxy-*allo*-inositol, 1D-2,5-di-amino-2,5-di-deoxy-*allo*-inositol, 1L-1-azido-1-deoxy-*chiro*-inositol, and 1L-1-amino-1-deoxy-*chiro*-inositol.

Inositols, being structurally similar to the amino-cyclitols, represent ideal synthons for the synthesis of various amino- and azido-cyclitols. The known strategies for the selective protection–deprotection[9] and efficient resolution of *myo*-inositol prompted us to explore the syntheses of various amino- and azido-cyclitols from this cheaply available cyclitol. Diketal derivatives **6** and **7** (Chart 2) served as the important intermediates for various phosphoinositol syntheses and other derivatives, due to their ease of preparation, selectivity in reaction (or protection) between two hydroxyl groups and the possibility for the selective deprotection of *trans* ketal in presence of the *cis*. We have recently developed[10] an

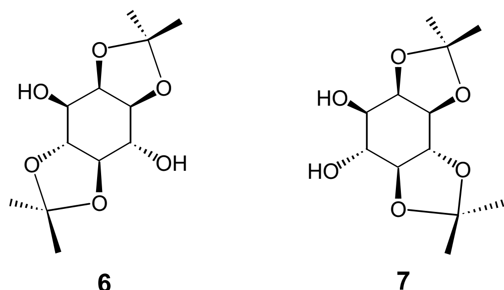
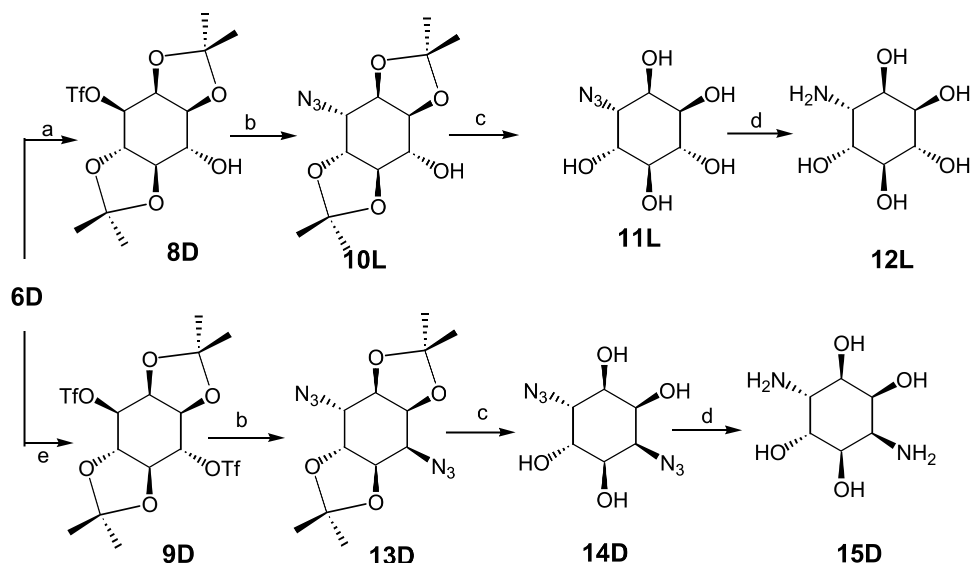


Chart 2.

efficient method for the resolution of racemic 1,2;4,5-di-*O*-isopropylidene-*myo*-inositol, **6** via diastereomeric separation of its S-*O*-acetylmandelate derivatives without involving column chromatography. Since relatively cheaper *O*-acetylmandelic acid has been used as chiral auxiliary and no chromatography is involved, optically active derivatives **6D** and **6L** could be obtained in an inexpensive way and served as starting materials for the syntheses of optically active isomeric inositols.[11]

The diol **6D** was regioselectively sulfonylated with 1 equiv of triflic anhydride in pyridine to get the monotriflate **8D** (Scheme 1) in excellent yield (90%) along with minor amount (6%) of ditriflate **9D**, which could be washed away with hexane. The crude **8D** thus obtained was crystallized from CH_2Cl_2–hexane to get pure white needles of **8D** ($[\alpha]_D$ 13, *c* 1, MeOH). Monotriflate resulting from the sulfonylation of C-6–OH was not observed. It is interesting that such a high degree of regioselectivity during acylation, silylation, alkylation, and sulfonylation has not been observed in this diol previously.[9] A comparison of yields of other sulfonates[9] with triflylate reveals that the regioselectivity observed for triflylation is better than that for other sulfonylations. Similar enhancement in yield and regioselectivity for triflylation compared to other sulfonylation has been observed previously during the synthesis of *neo*-inositol.[12] Inversion of the triflate in **8D** with sodium azide in DMF followed by aqueous work-up provided 1L-1-azido-1-deoxy-2,3;5,6-di-*O*-isopropylidene-*chiro*-inositol, **10L**[13] (84%, sublimed in the range 100–125 °C, $[\alpha]_D$ −10.1, *c* 1, $CHCl_3$). The structure of **10L** was further confirmed by solving its single crystal X-ray structure (Fig. 1). No trace of compounds (products arising from elimination or S_N1 reaction) other than **10L** was observed. Acid hydrolysis of the ketal moieties in **10L** followed by evaporation of the solvents provided pure 1L-1-azido-1-deoxy-*chiro*-inositol, **11L**[14] as a gum ($[\alpha]_D$ −11, *c* 1 H_2O) in quantitative yield. Finally 1L-1-amino-1-



Scheme 1. Reagents and conditions: (a) Tf_2O (1.1 equiv), pyr, 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), pyr, CH_2Cl_2, −20 °C.

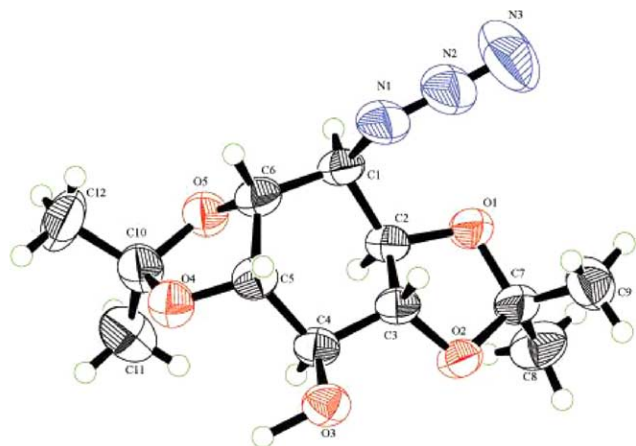


Figure 1. ORTEP diagram of **10L**.

deoxy-*chiro*-inositol, **12L**[15] ($[\alpha]_D$ −85.2, *c* 1.15, H_2O), was obtained by hydrogenolysis of the azide **11L** in good (84%) yield.

Similarly the ditriflate **9D** (97%) was prepared by sulfonylation of **6D** with 2.2 equiv of triflic anhydride in pyridine. After usual work-up, the crude reaction mixture was treated with NaN_3 in DMF followed by work-up and chromatography provided 1D-2,5-di-azido-2,5-di-deoxy-1,6;3,4-di-*O*-isopropylidene-*allo*-inositol, **13D**[16] in 93% yield (mp 132–135 °C, $[\alpha]_D$ −54, *c* 1, $CHCl_3$). In this case also, no product with retention of configuration has been isolated. Diazide **13D** on acid hydrolysis followed by evaporation of the solvents provided 1D-2,5-di-azido-2,5-di-deoxy-*allo*-inositol, **14D**[17] as a gum ($[\alpha]_D$ 32, *c* 1, H_2O) in quantitative yield. The signals in both ^{1}H NMR and ^{13}C NMR of **14D** were very broad. This is not unexpected based on the possible exchange between two different chair conformations due to the *allo* (3a/3e) configuration. The signals were resolved at high temperature as expected. The diazide **14D** on hydrogenolysis provided 1D-2,5-di-amino-2,5-di-deoxy-*allo*-inositol, **15D**[18] ($[\alpha]_D$ 43, *c* 1.5, H_2O). Unlike in the case of **14D**, **15D** showed sharp peaks in the NMR spectra. The $^3J_{HH}$ coupling constants suggest that **15D** takes the chair conformation where both amino groups and C-4–OH are in equatorial orientation. 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.

Inhibition of various glycosidases and glycogen phosphorylase by compounds **11L**, **12L**, **14D**, **15D**, and (±)-**15** is shown in Table 1. Although the inhibitory activities of these compounds were relatively weak, the azido-inositol **11L** showed relatively good inhibition toward rat intestinal sucrase and isomaltase with the IC_{50} values of 0.66 and 0.54 mM, respectively. However, investigations are underway to study whether the inhibition by **11L** is reversible or irreversible. Also, the compounds **11L**, **14D**, and **15D** showed about 50% inhibition at 1 mM toward rice α-glucosidase, rat intestinal sucrase and rat intestinal isomaltase, respectively. It is noteworthy that the inhibition of some of the enzymes by (±)-**15** is better than that by **15D**.

Although there are a few reports on the synthesis of various mono-amino[7] and di-amino-inositols,[8a–h] the glycosidase inhibitory activities of these derivatives are not known. In general, the enzyme inhibitions by our azido- or amino-inositols are comparable with that by other cyclitol[19] or amino-cyclitol[20] derivatives. But it is noteworthy that these simple compounds are more potent than amino-di-inositols[8i] and some of the amino-cyclitols[21] but much less potent than conformationally restricted bicyclic amino-cyclitol[22] or valeinamine analogs.[23]

In conclusion, we have reported efficient routes for the syntheses of amino- and azido-inositols with *chiro*- and *allo*-configuration in optically active form. Since the *trans* isopropylidene can be cleaved leaving the *cis* ketal unaffected, by exploiting this selectivity, different derivatives for natural product syntheses can be made. Preliminary investigation on the enzyme inhibitory activity of these azido- and amino-cyclitol was carried out. We are presently attempting to study the other biological activities of these derivatives, which will be reported in the near future elsewhere. Synthesis of amino-cyclitols based natural products are also on our future agenda.

Acknowledgements

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

Enzyme	(±)-**15**	**14D**	**15D**	**11L**	**12L**
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.

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13. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.34 (s, 3H); 1.48 (s, 3H); 1.49 (s, 3H); 1.50 (s, 3H); 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 Hz, 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.
14. ^{1}H NMR (D_2O, 400 MHz): 3.26–3.33 (m, 2H, H-3 and H-4); 3.38 (ddd, 8.8 Hz, 3.5 Hz, 1.0 Hz, H-5); 3.69 (dd, 8.8 Hz, 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.
15. ^{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.
16. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.37 (s, 3H); 1.50 (s, 6H); 1.61 (s, 3H); 3.95 (dd, 10.0 Hz, 2.8 Hz, H-1); 4.15 (dd, 5.4 Hz, 1.6 Hz, H-4); 4.25 (dd, 5.4 Hz, 2.8 Hz, H-2); 4.29 (dd, 10.0 Hz, 3.6 Hz, H-6); 4.32 (t, 5.4 Hz, H-3); 4.46 (dd, 3.6 Hz, 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. Elemental analysis: 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.
17. ^{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 Hz, 3.08 Hz, 1H); 3.95–4.00 (br, 1H); 4.00–4.05 (dd, 4.6 Hz, 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.
18. ^{1}H NMR (D_2O, 400 MHz); 2.90 (br s, H-2); 2.98 (dd, 10.5 Hz, 2.75 Hz, H-5); 3.47 (dd, 10.5 Hz, 1.3 Hz, H-4); 3.74 (dd, 3.5 Hz, 1.6 Hz, H-1); 3.83 (dd, 1.3 Hz, 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.
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