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Chiral building blocks from biomass: 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol

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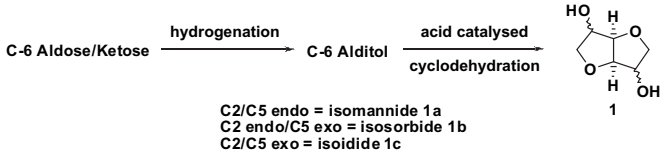
ABSTRACT

An efficient route towards the synthesis of 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4** has been developed resulting in significant improvements in both isolated yields and purity when compared to literature procedures. As a consequence, resin-grade 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4** has become available for laboratory scale step-growth polymer synthesis. Additionally, an interesting renewable chiral 2-amino-2-deoxy-1,4-3,6-dianhydroiditol **10**, has been isolated.

1. Introduction

Recently, the sharp increase in crude oil prices and increasing concerns about rising carbon dioxide levels and associated global warming effects have sparked a growing interest towards bio-based building blocks for the polymer industry. One group of renewable building blocks that gained considerable attention is the anhydro sugar polyols, also known as isohexides.[1] These isohexides can be obtained from C6-alditols such as sorbitol or mannitol via acid catalysed cyclodehydration (Scheme 1).[2] Of the three known isohexide isomers, only dianhydro-1,4-3,6-D-sorbitol or isosorbide is currently produced on (small) industrial scale.



Scheme 1.

These rigid bicyclic diols have several interesting properties in polymer applications.[3] Thiem and Lueders for instance have shown that incorporation of isohexides into polyesters such as PET results in a significant increase in glass transition temperature (T_g), which could widen the scope of applications of these materials.[4] Although the first investigations into the use of isohexides as building block for polymers have been reported as far back as in 1965,[5] it was the more recent extensive work by Dupont and Roquette on the incorporation of high purity isosorbide **1b** in polyesters that triggered renewed interest in these molecules.[6] Our group has also been actively involved in isosorbide chemistry for over ten years, with recently an increasing focus on applications in performance materials.[7]

Whereas the parent isohexides [isomannide **1a** (*endo–endo* conformation), isosorbide **1b** (*endo–exo* conformation), and to a lesser extent isoidide **1c** (*exo–exo* conformation)] have been studied extensively as bio-based monomers, only few reports have been made on the use of the corresponding dideoxy-diaminoisoidides.[9,13,19,20] This is undoubtedly due to the limited synthetic accessibility of these substances, combined with inadequate purities obtained with the known procedures. During our on-going investigations towards the viability of bio-based polyamides and polyurethanes with performance polymers characteristics, we required substantial amounts of high purity amino isohexides. This prompted us to reinvestigate the known literature procedures.

To date there are only three known synthetic routes[8,11,13] to unsubstituted isohexide diaminoisoidides. All of these procedures

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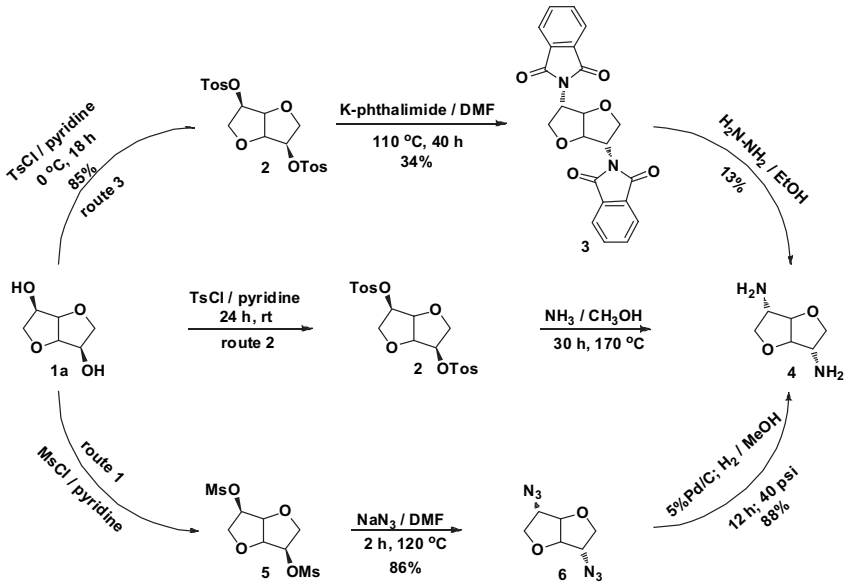
rely on introducing amine functionality by nucleophilic displacement of tosylated or mesylated hydroxyl groups. Since S_N2 reactions on an *exo*-leaving group are only effective with very small nitrogen nucleophiles (e.g., ammonia or azide anion),[2] often isomannide, with two *endo* hydroxyl functionalities is used in these reactions. The resulting symmetrical 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol will have the idide (*exo*–*exo*) conformation, which is expected to have advantageous effects when incorporated into step-growth polymers.[7]

The first known route involves conversion of the isohexide to the corresponding bismesylate **5**, followed by nucleophilic substitution with azide **6**.[8] Hydrogenation of the isohexide azides yields the corresponding 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditols **4** in 88% yield (Scheme 2).[9] The major drawback of this route is the potentially explosive character of the diazide, which prohibits its application on larger scale.[10] The second route consists of reacting isohexide bistosylates **2** with methanolic ammonia at 170 °C in a sealed vessel for 30 h (Scheme 2).[11] This method is severely hampered by the necessity to use a large volume autoclave in order to obtain reasonable amounts of product (50 g of 1,4:3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2** in 1.5 L methanolic ammonia). Although in the original paper no isolated yields were given, preliminary results in our own laboratories indicate that the isolated yields are in very low range (<20%).[12]

2. Results and discussion

The first step in the reaction sequence, the tosylation of isomannide, is virtually quantitative.[11] After recrystallisation from ethanol, the product can be obtained in high purity as colorless needles. The subsequent introduction of a nitrogen functionality via a nucleophilic displacement of the tosylate group is however less trivial. According to the procedure described by Cope and Shen (DMF, 110 °C, 40 h) the desired 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** (Scheme 2) was obtained in an unsatisfactory yield of only 34%.[13] In contrast, Kuszmann and Medgyes reported an isolated yield of 62% of the 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** starting from 1,4-3,6-dianhydro-2,5-di-*O*-mesyl-D-mannitol **5**.[14] However, while we obtained 1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2** in an isolated yield of >90% and in >99% purity after recrystallization, the 1,4-3,6-dianhydro-2,5-di-*O*-mesyl-D-mannitol **5** was obtained in only 83% yield. Furthermore, crude 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** was obtained in 94% yield from the 1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2**, while in case of the 1,4-3,6-dianhydro-2,5-di-*O*-mesyl-D-mannitol **5** the crude yield of 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** did not exceed 80%. Based on this study, we used 1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2** as a starting material.

In order to obtain insight in the selectivity of the reaction with potassium phthalimide, the reaction was first performed on small



Scheme 2. Synthetic routes to unsubstituted isohexide diaminoisoidides.

The third route comprises three steps starting from isomannide **1a**; tosylation, nucleophilic substitution with potassium phthalimide, and subsequent deprotection with hydrazine hydrate (Scheme 2).[13] This route also has severe drawbacks, such as low overall isolated yield in the second step (34% of the 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3**), and low isolated yield of high purity 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4** (<13%). However, this procedure was the most preferred with regard to scalability in order to obtain lab-scale quantities (>50 g) of resin-grade 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4** on short term. Obviously, more catalytic routes towards diamino isohexides are required to make these building blocks economically viable, the development of which is currently in progress in our laboratories.

scale (1.5 g) in deuterated solvents (DMF-d_6 and DMSO-d_6, 20 mL), and the progress of the reaction was followed by ^{1}H and ^{13}C NMR spectroscopy (Table 1). When the reaction was performed in DMF, the potassium phthalimide had only limited solubility, which severely hampered NMR analysis. As the solubility of the starting material (1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2**) and the desired product (2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3**) was excellent in DMSO, this became the solvent of choice. Furthermore, DMSO is known for its ability to solvate cations, an increase in the reactivity of the potassium phthalimide was anticipated.[15] A first series of small-scale experiments showed that at a temperature of 130 °C all of the NMR signals corresponding with the starting material had disappeared within 24 h. The resulting reaction mixture consisted mainly of 2,5-diphthalimido-

Table 1
Optimization of the synthesis of 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3**

Starting material (g, mmol)	Potasssium phthalimide (g, mmol, equiv)	Time (h)	Temp (°C)	Solvent	Molar yield ratio % in situ NMR (end of reaction) **3**:**7**
2 (1.64, 3.6)	(1.47, 7.9, 2.2)	48	130	DMSO-d_6	35:65
2 (0.55, 1.2)	(0.50, 2.7, 2.2)	42	110	DMF-d_7 (wet)	[a]
2 (1.64, 3.6)	(1.48, 8.0, 2.2)	25	130	DMSO-d_6(dry)	67:33

[a] The ratio between the 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** and phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7** could not be calculated because of huge amount of impurities present in the crude mixture.

2,5-dideoxy-1,4-3,6-dianhydroiditol **3**, phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7**, and minor amounts of other carbohydrate based species. Work-up of the crude reaction mixture with water (D_2O) and chloroform ($CDCl_3$), followed by NMR analysis showed that the aqueous phase contained a small amount of isoidide besides the expected potassium tosylate. The identification of isoidide was based on ^1H and ^{13}C NMR spectra of an authentic sample. NMR analysis of the organic phase showed that it contained predominantly 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** and phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7** in the ratio of 2:1. The *exo–exo* conformation of **3** and **7** was confirmed by ^1H-, HH-COSY and NOESY NMR analysis. Variation of reaction parameters such as time and temperature had little effect on the 2:1 ratio (Table 1). Optimal reaction conditions in DMSO thus far were stirring at 130 °C for 24 h, using 2.2 equiv of potassium phthalimide. Based on the optimized conditions, the reaction was performed on 50 g and 100 g scales (Table 2).

Apparently phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7** as well as isoidide were formed by hydrolysis of the tosylate group under the reaction conditions. Consequently, we investigated the effect of water in the reaction medium. Surprisingly, 1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2** remained intact in wet DMSO, and even the addition of a mild base (K_2CO_3) did not lead to any significant changes. However, when potassium hydroxide was added, fast degradation of the 1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2** was observed (together with significant darkening of the solution). After 2 h, the NMR signals of the starting material had disappeared; resulting in a multitude of unresolved carbohydrate and unsaturated signals, which were observed in the ^{13}C NMR spectrum, indicating complete degradation of the sample. Curiously, it was observed that even after a short time at room temperature the methyl signal of the tosylate group had disappeared, presumably due to perdeuteration, given the appearance of a small multiplet in the ^{13}C NMR spectrum at the original chemical shift value of the methyl signal.

It was envisaged that even a small amount of water in the reaction mixture will influence the hydrolysis of product **3** lead to by-products. Hence, in order to avoid the by-product formation by hydrolysis, the reaction was performed in fresh anhydrous DMSO (<0.005% water), which resulted in a significant increase in the isolated yield of the 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3**. Furthermore, it was found that selective precipitation of the 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** was more effective from chloroform than from ethanol.[13] All of these improvements resulted in an increase in isolated yield in this step to 84% (from 34%). Purification of the chloroform soluble fraction by column chromatography resulted in the isolation of phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7** in high purity (95% based in ^1H NMR).

The third step in the original synthesis is the deprotection of the 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** with hydrazine hydrate. Although this reaction is very efficient, the separation of the desired product **4** from the by-product (phthalhydrazide) resulted in very poor isolated yields (<20%) and purity (<95%) of 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4**.[16] Thus, we explored an alternative method for the deprotection of phthalimides; refluxing in 6 M HCl/glacial acetic acid.[17] Complete conversion of **8** was achieved after 24 h at reflux temperature. Upon cooling the reaction mixture, phthalic acid crystallizes from the solution, and can be efficiently removed by suction-filtration. The resulting mother liquor is subsequently evaporated under reduced pressure giving the crude 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol HCl salt **8** in very high yield (92%). Further purification of the crude 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol HCl salt **8** was achieved by dissolution/precipitation from methanolic/ethanolic HCl. Subsequent transformation of the HCl salt into the free 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4** was achieved by treatment with a (purified) basic ion exchange resin (Amberlyst® A26), which also removes residual phthalic acid. As a result, the desired 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4** was obtained in high yield (95%) and with high purity (99%). The overall isolated yield of the 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4** in four steps was thus increased from 14% to 47%.

In order to improve the total valorization of the biomass feed-stock we investigated the viability of our deprotection strategy on the phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7**. Despite the fact that isohexides have been reported to undergo ring-opening when treated with strong acids for prolonged time,[18] hydrolysis of the phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7** successfully yielded 2-amino-2-deoxy-1,4-3,6-dianhydroiditol HCl salt **9** in moderate yield.

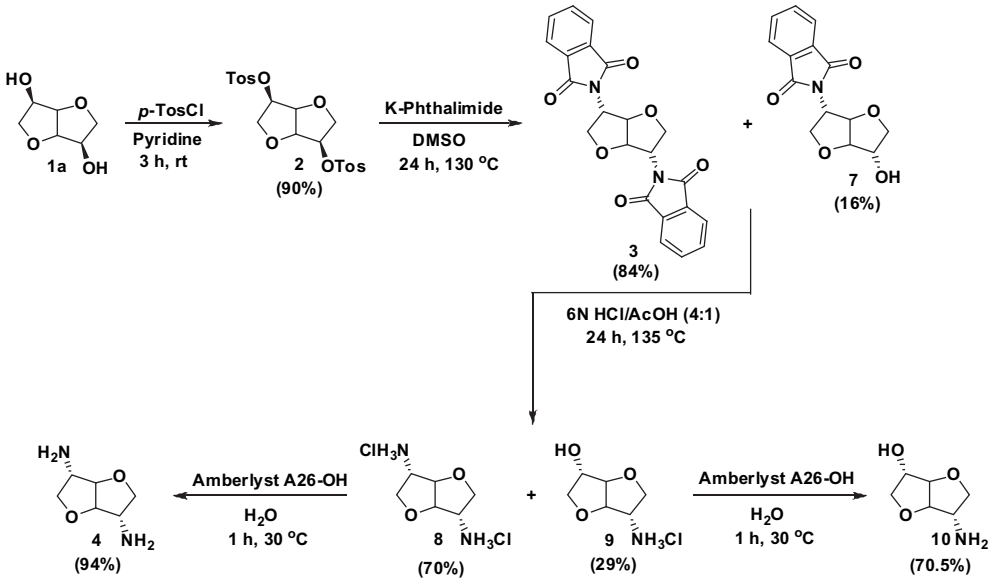
These results prompted us to further simplify our procedure. Starting from 50 g 1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2**, the substitution reaction with potassium phthalimide was performed in DMSO for 24 h at 130 °C. After completion, the reaction mixture was diluted with water and extracted with chloroform. The crude product mixture was subsequently hydrolysed in 6 M

Table 2
Synthesis of 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** and optimal reaction conditions

Starting material (g, mol)	Potasssium phthalimide (g, mol, equiv)	Time (h)	Temp (°C)	Solvent (dry)	Crude yield % **3** and **7** (g, mol)	Ratio[b]
2 (50, 0.11)	(44.3, 0.24, 2.2)	24	130	DMSO	94 (41.5, 0.10)	1:0
2[a] (50, 0.11)	(44.3, 0.24, 2.2)	24	130	DMSO	96 (42.7, 0.10)	1:0.15
2 (100.1, 0.22)	(88.7, 0.48, 2.2)	48	110	DMSO	95 (85, 0.21)	1:0.2
5 (15, 0.05)	(20, 0.10, 2.2)	24	130	DMSO	80 (16, 0.04)	1:0.2

[a] Refer synthesis of 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3**, *Route*:2 in the experimental procedure.
[b] The ratio between the 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** and phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7** in isolated crude mixture, according to ^1H NMR.

HCl/glacial acetic acid without prior separation of the bisphthalimide. After removal of the phthalic acid by filtration, the crude product contained the HCl salts of the 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **8**, the 2-amino-2-deoxy-1,4-3,6-dianhydroiditol **9** and residual phthalic acid (according to NMR analysis). Virtually pure 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol HCl salt **8** was obtained by selective precipitation from ethanolic HCl. Evaporation of the filtrate gave the crude 2-amino-2-deoxy-1,4-3,6-dianhydroiditol HCl salt **9** (Scheme 3). After treatment with Amberlyst® A26 resin and decolourization with activated carbon, 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4** was obtained in an overall yield of 47% (starting from the 1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2**) and in >99% purity (^{1}H NMR). Analogously, 2-amino-2-deoxy-1,4-3,6-dianhydroiditol HCl salt **9** was converted to pure 2-amino-2-deoxy-1,4-3,6-dianhydroiditol **10**.



Scheme 3. Synthesis of 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4** and 2-amino-2-deoxy-1,4-3,6-dianhydroiditol **10**.

3. Conclusions

Driven by a need for resin-grade 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol **4** we decided to re-design the unsatisfactory literature procedures. By using in situ NMR analysis of the reaction mixtures in the most critical step in the reaction sequence, we were able to significantly improve the yield. Furthermore, implementation of an alternative deprotection procedure for the phthalimide groups, followed by a highly selective purification procedure resulted in a significant increase in the isolated yield of high purity **4**. A radical integration of the synthetic sequence, by-passing time consuming separation/purification steps, further increased the overall isolated yield of **4** to 47% in four steps. Furthermore, we have shown the possibility to isolate another interesting chiral renewable building block, the 2-amino-2-deoxy-1,4-3,6-dianhydroiditol **10**. Currently, we are exploring more catalytic routes towards isohexide based diamines, as well as more selective routes to 2-amino-2-deoxy-1,4-3,6-dianhydroiditol **10**.

4. Experimental section

4.1. General information

Isomannide (Aldrich, 95%), *p*-toluene sulphonyl chloride (Fluka, 99%), potassium phthalimide (Fluka, ≥99%), DMSO (Aldrich, ≥99.9%, anhydrous), pyridine (Merck, p.a.), hydrochloric acid (reagent grade 37%, Sigma Aldrich), acetic acid (Merck; glacial; 100% p.a.), chloroform (Merck, p.a.), chloroform-*d* (99.8 atom% D Aldrich), DMSO-d_6 (99.9 atom% D, Aldrich) were stored on dried molecular sieves 4 Å. D_2O (>99.8%, Merck) was used as received, ethanol (Merck, p.a.), methanol (p.a. Merck), ethanolic HCl 1.25 N (Fluka), Silica gel (Alfa Aesar, 60; 0.040–0.063 mm; 230–400 mesh), Molecular sieves (Acros, 5 Å, 8–12 mesh), diethyl ether (Merck, 99.7%), magnesium sulfate (Acros Organics, 99% extra pure, dried, contains 3–4 mol of water), Celite® 545 coarse (Fluka), Sicapent (with indicator, Merck). Amberlyst® A26 (Aldrich) hydroxide form (Strongly basic, macroreticular resin with quaternary ammonium functionality from Rohm & Haas Co): prior to use, the resin was washed with demineralised water (100 mL) by sonification in an ultrasonic bath at room temperature for 10 min. The water layer was subsequently removed by decantation. This procedure was repeated five times, until the water layer remained colourless. Activated carbon (Norit SA2 94007-6, steam activated carbon with a high adsorptive capacity) was a gift from Norit Nederland BV. Isoidide (R&D product) was a gift from Roquette Freres. All the chemicals were used as received, unless denoted otherwise.

Fourier transform infrared (FT-IR) spectra were obtained on a Varian Scimitar 1000 FT-IR spectrometer equipped with a Pike MIRacle ATR Diamond/ZnSe single reflection plate and a DTSG-detector. The measurement resolution was set at 4 cm^{-1}, and the spectra were collected in the range 4000-650 cm^{-1} with 32 co-added scans. NMR spectra were recorded on a Bruker Avance III spectrometer operating at 400.17 MHz (^{1}H) and 100.62 MHz (^{13}C). Gas chromatography was performed on an Interscience Focus GC equipped with an AS 3000 series auto sampler. Injection volume 1 μL. Injector temperature 275 °C. Split ratio 1:33. Column flow (at 275 °C) 50 mL/min helium. GC column: Restek Rxi-5ms, 30 m×0.25 mm×0.25 μm. GC program (2,5-FDA.mth); hold 2 min at 70 °C, ramp 10 °C/min, final temperature 300 °C, hold 2 min. Total run time 27 min. Detector; FID at 300 °C. GC–MS analysis was performed on a Finnigan Mat GC8000 Top GC (He carrier gas, flow 1 mL/min, split flow 25 mL/min; Chrompack CP-Sil 5CB column, 30 m×0.25 mm×1.0 μm; GC program hold 2 min at 40 °C, ramp 10 °C/min, final temperature 300 °C) connected to a Finnigan Mat Automass II quadrupole mass selective detector (EI, mass range

40–400 Da, 150 ms sample speed). Electrospray Ionisation (ESI) mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Differential Scanning Calorimetry (DSC) measurements were conducted on a Perkin–Elmer Diamond series DSC. The temperature range used was 20 °C up to 200 °C at a heating rate of 10 °C/min.

4.2. Synthesis of 1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol 2

A 2-necked round-bottom flask was charged with a solution of isomannide (50 g, 0.34 mol) in 150 mL of pyridine under nitrogen atmosphere. The mixture was cooled to 0–5 °C. A solution of *p*-toluene sulphonyl chloride (130.5 g, 0.68 mol) in pyridine (350 mL) was added drop wise over 30 min. After 3 h, the reaction mixture was placed in a refrigerator over night. Then, the mixture was poured onto ice-water (2.5 L) and stirred for 1 h. The obtained sandy solid was subsequently grounded and washed thoroughly with water, dilute HCl (0.2 M), and finally water followed by suction-filtration. The crude product was recrystallized from ethanol yielding **2** as white needles. Yield: 140 g, 90%; mp 93–94 °C (lit.[20] mp 92–93 °C); ν_{max} (neat) 1595, 1370, 1192, 1171, 1113, 1054, 996 cm^{-1}; δ_H (400.17 MHz, $CDCl_3$) 7.79 (4H, d, *J* 8.0 Hz), 7.33 (4H, d, *J* 8.0 Hz), 4.86–4.79 (2H, m), 4.45 (2H, d, *J* 3.7 Hz), 3.89 (2H, dd, *J* 9.3, 6.8), 3.72 (2H, d, *J* 9.0 Hz), 2.43 (6H, s); δ_C (100.62 MHz, $CDCl_3$) 145.3, 133.0, 129.9, 127.9, 79.9, 77.8, 69.9, 21.5; HRMS (ESI): MH^+, found 455.0829. $C_{20}H_{23}O_8S_2$ requires 455.0834.

4.3. Synthesis of 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol 3 from 1,4-3,6-dianhydro-2,5-di-*O*-mesyl-D-mannitol 5

1,4-3,6-Dianhydro-2,5-di-*O*-mesyl-D-mannitol **5** was synthesized according to the procedure reported previously.[19] 1,4-3,6-Dianhydro-2,5-di-*O*-mesyl-D-mannitol **5** (15 g, 0.05 mol), potassium phthalimide (20 g, 0.10 mol) and DMSO (150 mL) were charged to the reactor under a continuous flow of nitrogen. The initially yellow suspension was subsequently stirred at 130 °C (internal temperature) for 24 h. During the course of the reaction the suspension became dark brown. After termination of the reaction, the dark brown solution was cooled down to room temperature, and poured into cold water (1 L) (pH 7/8). The resulting DMSO/water mixture was extracted with $CHCl_3$ (2×500 mL). The combined $CHCl_3$ layers were then subsequently washed with water (2×500 mL), dried over $MgSO_4$ and decolorized with activated carbon (30 min at room temperature). The resulting solution was then filtered over a G-3 filter funnel containing Celite. The brown filtrate was evaporated at reduced pressure using a rotatory evaporator, giving a crude solid product of 16.2 g (80%). The crude product was further purified by selective precipitation of 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** from 200 mL of chloroform. Yield: 15 g, 75% (purity 99% based on NMR); mp 244–245 °C (lit.[13] mp 243.4–243.6 °C); ν_{max} (neat) 3393, 3280, 1772, 1709, 1610, 1466, 1380, 1301, 1173, 1122, 1087, 1008 cm^{-1}; δ_H (400.17 MHz, $CDCl_3$) 7.90–7.84 (4H, m), 7.78–7.73 (4H, m), 5.39 (2H, s), 4.92 (2H, dd, *J* 7.3, 6.4 Hz), 4.37 (2H, dd, *J* 9.2, 7.7 Hz), 4.01 (2H, dd, *J* 9.3, 6.1 Hz); δ_C (100.62 MHz, $CDCl_3$) 167.5, 134.1, 131.6, 123.3, 88.0, 71.0, 55.6; HRMS (ESI): MH^+, found 405.1081. $C_{22}H_{17}N_2O_6$ requires 405.1087.

4.4. Synthesis of 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol 3 from 1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol 2

Route 1: 1,4-3,6-Dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2** (50 g, 0.11 mol), potassium phthalimide (45.4 g, 0.25 mol) and DMSO (Aldrich, ≥99.9%, anhydrous) (500 mL) were charged into the reactor under a continuous flow of nitrogen. The initially yellow suspension was subsequently stirred at 130 °C (internal temperature) for 24 h. During the course of the reaction the suspension became dark brown. After termination of the reaction, the dark brown solution was cooled down to room temperature, and poured into cold water (1 L) (pH 7/8). The resulting DMSO/water mixture was extracted with $CHCl_3$ (4×500 mL). The combined $CHCl_3$ layers were then subsequently washed with water (2×500 mL), dried over $MgSO_4$ and decolorized with activated carbon (30 min at room temperature). The resulting solution was then filtered over a G-3 filter funnel containing Celite. The brown filtrate was evaporated at reduced pressure using a rotatory evaporator, giving a crude solid product. The crude product was further purified by selective precipitation of 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** from 250 mL of chloroform.

Route 2: Potassium phthalimide (44.4 g, 0.24 mol) and DMSO (650 mL) was charged into the reactor under a continuous flow of nitrogen. The mixture was stirred at 130 °C (internal temperature) for 4 h. 150 mL of DMSO was distilled off under reduced pressure. The reaction mixture was cooled down to room temperature and 1,4-3,6-dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2** (50 g, 0.11 mol) was added. Again the mixture was stirred at 130 °C (internal temperature) for 24 h. After the completion of reaction, the dark brown solution was cooled down to room temperature, and poured into cold water (1 L) (pH 7/8). The resulting DMSO/water mixture was extracted with $CHCl_3$ (4×500 mL). The combined $CHCl_3$ layers were then subsequently washed with water (2×500 mL), dried over $MgSO_4$ and decolorized with activated carbon (30 min at room temperature). The resulting solution was then filtered over a G-3 filter funnel containing Celite. The brown filtrate was evaporated at reduced pressure using rotatory evaporator, giving a yellow solid. NMR analysis showed the presence of both bisphthalimide and monophthalimide in the crude mixture. The crude product was further purified by selective precipitation of 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** from 250 mL of chloroform. Yield: 38 g, 84%; mp 244–245 °C (lit.[13] mp 243.4–243.6 °C); ν_{max} (neat) 3393, 3280, 1772, 1709, 1610, 1466, 1380, 1301, 1173, 1122, 1087, 1008 cm^{-1}; δ_H (400.17 MHz, $CDCl_3$) 7.90–7.84 (4H, m), 7.78–7.73 (4H, m), 5.39 (2H, s), 4.92 (2H, dd, *J* 7.3, 6.4 Hz), 4.37 (2H, dd, *J* 9.2, 7.7 Hz), 4.01 (2H, dd, *J* 9.3, 6.1 Hz); δ_C (100.62 MHz, $CDCl_3$) 167.5, 134.1, 131.6, 123.3, 88.0, 71.0, 55.6; HRMS (ESI): MH^+, found 405.1081. $C_{22}H_{17}N_2O_6$ requires 405.1087.

4.5. Synthesis of phthalimido-2-deoxy-1,4-3,6-dianhydroiditol 7

The chloroform soluble fraction of the aforesaid reaction was purified by column chromatography over silica gel (ethyl acetate/petroleum ether (2:3)), yielding the phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7**. Yield: 4.8 g, 16%; mp 122–123 °C; ν_{max} (neat) 3393, 3280, 1772, 1709, 1610, 1466, 1380, 1301, 1173, 1122, 1087, 1008 cm^{-1}; δ_H (400.17 MHz, $CDCl_3$) 7.89–7.82 (4H, m), 7.77–7.72 (4H, m), 5.16 (2H, dd, *J* 4.4, 2.2 Hz), 4.82 (2H, d, *J* 4.4 Hz), 4.78 (2H, td, *J* 7.7, 2.2 Hz), 4.38 (2H, s), 4.21–4.13 (2H, m), 4.05 (2H dd, *J* 10.1, 3.4 Hz), 3.97–3.87 (4H, m); δ_C (100.62 MHz, $CDCl_3$) 166.8, 133.4, 130.8, 122.6, 88.4, 84.9, 72.9, 69.2, 55.6; HRMS (ESI): MH^+, found 276.0866. $C_{14}H_{14}NO_5$ requires 276.0872.

4.6. Synthesis of 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol dihydrochloride 8

A two-necked round-bottom flask was charged with crude mixture of **3** (41.2 g, 0.10 mol) and 250 mL 6 M HCl/AcOH (4:1). The stirred slight brownish suspension was then heated at 135 °C (oil bath temperature) for 24 h. After completion of the reaction, the slightly brown solution was cooled down to room temperature. During cooling crystallization of phthalic acid occurred. The

resulting suspension was filtered over a G-3 filter funnel. The brownish filtrate was washed thoroughly with diethyl ether (3×300 mL) to remove residual phthalic acid, and the aqueous phase was subsequently evaporated to dryness using a rotary film evaporator yielding a brown solid. This was dissolved in methanol (50 mL) at 50 °C. Next, ethanol (50 mL) was added, and the temperature was raised to distill off the methanol. Subsequently, an ethanolic HCl solution (100 mL) was added to precipitate the desired product. The resulting suspension was stirred for 10 min at 50 °C, filtered over a G-3 filter funnel and the precipitate was dried in a vacuum oven (<5 mbar, 24 h) over Sicapent yielding **8** as slightly brown solid in 99% purity according to NMR analysis. Yield **8**: 15.3 g, 70%; ν_{max} (neat) 3370, 2894, 1638, 1525, 1268, 1525, 1084, 1037 cm^{-1}; δ_H (400.17 MHz, D_2O) 5.04 (2H, s), 4.25 (2H, dd, *J* 10.7, 4.8 Hz), 4.08 (4H d, *J* 13.4 Hz); δ_C (100.62 MHz, D_2O) 87.2, 72.7, 58.5.

4.7. Synthesis of 2,amino-2-deoxy-1,4-3,6-dianhydroiditol hydrochloride 9

The filtrate of the aforesaid reaction was concentrated using a rotary evaporator, giving clear brown viscous homogeneous oil (1.4 g). Ethyl acetate was added to the oil, and after stirring for 10 min at room temperature the product precipitated. The mono hydrochloride amine salt **9** was isolated by filtration, and subsequently dried in a vacuum oven (<5 mbar, 24 h) over Sicapent yielding **9** as brownish solid in 98% purity according to NMR analysis. Yield **9**: 0.9 g, 29%; ν_{max} (neat) 3370, 2894, 1638, 1525, 1268, 1084, 1037 cm^{-1}; δ_H (400.17 MHz, D_2O) 4.69 (H, d, *J* 4.0 Hz), 4.61 (H, d, *J* 4.0 Hz), 4.39 (H, s), 4.00–3.89 (3H, m), 3.78 (H, dd, *J* 9.5, 1.8 Hz), 3.57 (H, dd, *J* 2.4, 1.8 Hz); δ_C (100.62 MHz, D_2O) 87.9, 86.6, 74.9, 74.1, 73.9, 56.8.

4.8. Synthesis of 2,5-diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol 4

2,5-Diamino-2,5-dideoxy-1,4-3,6-dianhydroiditol HCl salt **8** (15.3 g, 0.07 mol) was dissolved in demineralised water (200 mL) giving a slightly brown solution. To this solution activated carbon (100 mg) was added, and the resulting suspension was stirred for 30 min at 35 °C. Filtration over a glass filter (G-3) containing Celite, resulted in a clear colourless filtrate. To this filtrate freshly washed Amberlyst A-26-OH (60 g, 0.075 mol) was added, and the resulting suspension was sonified in an ultrasonic bath for 1 h at 30 °C. After completion of reaction, the aqueous solution was filtered over a glass filter (G-3) and the IEX-resin was washed thoroughly with water (3×50 mL). The combined clear colourless aqueous phases were evaporated to dryness using a rotary film evaporator yielding an off-white semi-solid **4**, which was further dried in vacuum oven (25 °C, <5 mbar) over sicapent for 24 h. The crude product was recrystallized from ethanol/methanol mixture (1:0.25) yielding **4** as white needles. Yield: 9.5 g, 94% (99% purity based on NMR); mp 60–62 °C (lit.[13] mp 59–60 °C); ν_{max} (neat) 3351, 2825, 1597, 1537, 1200, 1080, 1035 cm^{-1}; δ_H (400.17 MHz, D_2O) 4.74 (2H, s), 4.03 (2H, dd, *J* 10.3, 4.9 Hz), 3.84 (2H, dd, *J* 10.3, 2.5 Hz), 3.72 (2H, dd, *J* 4.7, 2.5 Hz); δ_C (100.62 MHz, D_2O) 86.2, 72.1, 56.3; HRMS (ESI): MH^+, found 145.0972. $C_6H_{13}N_2O_2$ requires 145.0977.

4.9. Synthesis of 2-amino-2-deoxy-1,4-3,6-dianhydroiditol 10

2-Amino-2-deoxy-1,4-3,6-dianhydroiditol HCl salt **9** (0.9 g, 0.005 mol) was dissolved in demineralised water (100 mL) giving a slightly brown solution. To this solution was added activated carbon (100 mg) and stirred for 30 min at 35 °C. The suspension was filtered over a glass filter (G-3) containing Celite, resulting a clear colourless filtrate. To this filtrate freshly washed Amberlyst A-26-OH (4 g, 0.005 mol) was added, and the resulting suspension was sonified in an ultrasonic bath for 1 h at 30 °C. After the completion of reaction, the aqueous solution was filtered over a glass filter (G-3) and the IEX-resin was washed thoroughly with water (3×50 mL). The combined clear colourless aqueous phases were evaporated to dryness using a rotary film evaporator to afford an off-white viscous-solid **10**. The product thus obtained was further dried in vacuum oven (25 °C, <5 mbar) over sicapent for 24 h. Yield: 0.5 g, 70.5%; ν_{max} (neat) 3365, 2885, 1624, 1565, 1235, 1080, 1025 cm^{-1}; δ_H (400.17 MHz, D_2O) 4.68 (H, d, *J* 1.6 Hz), 4.62 (H, s), 4.38 (H, s), 3.93 (3H, d, *J* 13.5 Hz), 3.77 (H, d J 9.6 Hz), 3.58 (H, s); δ_C (100.62 MHz, D_2O) 87.9, 86.6, 74.9, 74.1, 73.9, 56.8; HRMS (ESI): MH^+, found 146.0812. $C_6H_{12}NO_3$ requires 146.0817.

4.10. Experimental procedures for the synthesis of 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol 3 reaction followed by NMR

4.10.1. Reaction performed in DMSO-d_6. 1,4-3,6-Dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2** (1.64 g, 3.6 mmol) and potassium phthalimide (1.47 g, 7.9 mmol) were added to 20 mL DMSO-d_6 at room temperature, giving a yellow suspension. The temperature was raised to 130 °C, resulting in an orange colored solution. The reaction was stirred under nitrogen. NMR samples were taken at several time intervals. After 48 h, the reaction was cooled down to room temperature. To the solution 100 mL water was added, this was extracted with 3×30 mL $CHCl_3$. The combined organic layers were washed with 2×25 mL water. The organic layer was then dried over $MgSO_4$ and evaporated to dryness using a rotary film evaporator, giving yellow solid (0.725 g, 59% yield). NMR analysis showed that the ratio of products 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** and phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7** in 35:65%.

4.10.2. Reaction performed in DMF-d_7. 1,4-3,6-Dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2** (0.55 g, 1.2 mmol) and potassium phthalimide (0.50 g, 2.7 mmol) were added to 7.7 mL DMF-d_7 at room temperature, giving a white suspension. The temperature was raised to 110 °C, giving a brown/orange solution with a brown precipitate. The reaction was stirred under nitrogen. NMR samples were taken at several time intervals. After 42 h, the reaction was cooled down to room temperature. To the solution 100 mL water was added, this was extracted with 3×30 mL $CHCl_3$. The combined organic layers were washed with 2×25 mL water. The organic layer was then dried over $MgSO_4$ and evaporated to dryness using a rotary film evaporator, giving a yellow solid (0.5 g, >100% yield) NMR analysis showed that there were too many impurities. Therefore the ratio could not be determined.

4.10.3. Reaction performed in DMSO-d_6 (dry). 1,4-3,6-Dianhydro-2,5-di-*O*-*p*-tosyl-D-mannitol **2** (1.64 g, 3.6 mmol), potassium phthalimide (1.48 g, 8.0 mmol) were added to 20 mL DMSO-d_6 (distilled, high vacuum distillation, 0.05 mbar) at room temperature, giving a yellow suspension. The temperature was raised to 130 °C, giving an orange coloured solution. The reaction was stirred under nitrogen. NMR samples were taken at several time intervals. After 25 h, the reaction was cooled down to room temperature. To the solution 100 mL water was added, this was extracted with 3×30 mL $CHCl_3$. The organic layer was washed with 2×25 mL water. The organic layer was then dried over $MgSO_4$ and evaporated to dryness using a rotary film evaporator, giving yellow solid (1.0 g, 77% yield). NMR analysis showed that the ratio of products 2,5-diphthalimido-2,5-dideoxy-1,4-3,6-dianhydroiditol **3** and phthalimido-2-deoxy-1,4-3,6-dianhydroiditol **7** in 67:33%.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of **2**–**4**, **7**–**10**. Supplementary data related to this article can be found online version, at doi:10.1016/j.tet.2010.11.031.

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