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New Potent C_2-Symmetric Malaria Plasmepsin I and II Inhibitors

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Abstract—A series of malaria plasmepsin (Plm) I and II inhibitors containing a C_2-symmetric core structure have been synthesised and tested for protease inhibition activity. These compounds can be prepared using a straightforward synthesis involving a phenol nucleophilic ring opening of a diepoxide. Exemplar compounds synthesised exhibited remarkable inhibitory activity against both Plm I and II, notably **15c** with K_i values of 2.7 nM and 0.25 nM respectively, as well as showing >100-fold selectivity against Cathepsin D.

Introduction

Malaria is one of the most serious infectious diseases in the world today, affecting approximately 500 million people yearly.[1] Mortality from malaria exceeds 1 million people per year, most of them being children in Africa under the age of 4 years, a number that is continuously increasing due to the rapid spread of drug resistant parasites.[2–5] This underscores the paramount importance of discovering new pharmaceuticals active against both wild type and resistant parasite strains and consequently to identify novel molecular targets for drug discovery. Recently proteases have emerged as new and promising targets for antimalarials.[4,6–9] Of the four major species of the malaria parasite, *Plasmodium falciparum* is responsible for more than 95% of malaria-related mortality.[10,11] The intraerythrocytic stages of *Plasmodium* rely on red blood cell haemoglobin for nutrient supply.[12] Two homologous aspartic proteases, plasmepsin I and II (Plm I and Plm II) appear to initiate this haemoglobin degradation process in the parasite digestive acid vacuole, and blockages of these enzymes has been demonstrated to result in parasite death.[4,13–15] Today, at least 10 aspartic protease genes have been identified in the *P. falciparum* genome, potentially complicating the picture of target selection and target redundancy.[12,16] The crystal structure for Plm II has been solved both as zymogen proplasmepsin and in complex with pepstatin A, which is the classical non selective statine-based peptide aspartic protease inhibitor.[17,18] Although Pepstatin A and other related statine type containing peptide inhibitors as well as inhibitors containing hydroxyethylamine scaffolds have been described, only a limited number of non-peptide potent inhibitors of Plm II have been disclosed.[8,9,11,13,19–22] Moreover, there is today an increased awareness that Plm I is acting in synergy with Plm II, underscoring the importance to develop and characterise broad based inhibitors against Plm I and II. Cathepsin D (Cat D), a human protease in the endosomal-lysosomal pathway, exhibits an overall 35% sequence homology to Plm II, and thus, for development of Plm I and II inhibitors it is desirable to achieve a high selectivity against Cat D in order to minimize potential adverse effects. We herein report on a new class of inhibitors that potently inhibits both Plm I and II whilst showing excellent selectivity against Cat D.

Chemistry and Structure–Activity Relationship

As starting point for this work, an acyclic C_2-symmetric diol derived from D-mannitol was used which previously has been developed for the synthesis of HIV-1 protease inhibitors.[23] Although weak HIV-1 protease inhibition was generally observed, the potential of the template for the design and synthesis of aspartic protease inhibitors was demonstrated. The inhibitors in this

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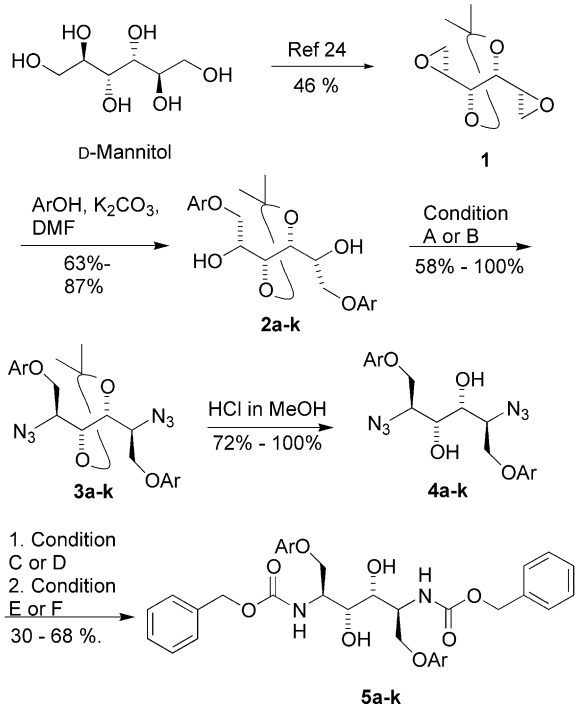
report were made starting from D-mannitol which was converted into a 3,4-*O*-protected diepoxide and subsequently ring-opened with phenol derivatives (Scheme 1). The resulting diols were then converted into the corresponding diazides, which were reduced and thereafter coupled to a series of selected acylating derivatives delivering the target inhibitor compounds (Schemes 1 and 3).

From readily available D-mannitol, the starting material 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol (**1**) was synthesised in three steps according to the procedure of Merrer et al.,[24] (Scheme 1). The diepoxide (**1**) was then reacted with phenols in DMF at 110 °C in the presence of potassium carbonate to give the diols **2a–k** in 63–81% yield (Table 1).[23]

The diols **2a–e** were converted to the corresponding diazides **3a–e** in 66% to quantitative yields, using Mitsunobu conditions with DIAD, triphenylphosphine, diphenylphosporazidate (DPPA) (Scheme 1, Condition A).[25] However, this methodology was less useful for the transformation of the diols **2f–k** into the diazides **3f–k** and low yields were encountered. Applying an alternative procedure, where the diols were treated with trifluoromethanesulfonic anhydride in the presence of pyridine followed by reaction with sodium azide in DMF delivered the diazides **3f–k** in 58–86% overall yields (Scheme 1, Condition B).

Hydrolysis of the isopropylidene acetal in **3a–k** by 3 M HCl in methanol gave the diazido diols **4a–k** in 73% to quantitative yields. Catalytic hydrogenolysis of **4a–d** over 10% palladium on carbon (Scheme 1, Condition C), afforded the corresponding diamino diols, that subsequently were transformed into the target compounds **5a–d**. To avoid reductive debromation of **4e**, H_2S in pyridine-triethylamine was used for selective reduction of the azido groups (Scheme 1, Condition D).[26] This method also proved useful for the diazide reduction of compounds **4f–k**.



Scheme 1. Synthesis of compound set I, **5a–k**. Condition: (A) Ph_3P, DIAD, THF; (B) 1.Tf_2O, pyridine, CH_2Cl_2 2. NaN_3, DMF; (C) 1. H_2, Pd/C, EtOAc 2. benzyl chloroformate, pyridine, CH_2Cl_2; (D) 1. H_2S, pyridine, Et_3N 2. *N*-(benzyloxycarbonyloxy)-succinimide, Et_3N, CH_2Cl_2.

Table 1. Reaction yields and synthetic method for compounds **2–5a–k**

Ar–	Compd (yields)			
Ph–	**2a**, 81%	**3a**, 100%[a]	**4a**, 95%	**5a**, 30%[c]
p-MeOPh–	**2b**, 63%	**3b**, 100%[a]	**4b**, 73%	**5b**, 48%[c]
p-CNPh–	**2c**, 79%	**3c**, 66%[a]	**4c**, 86%	**5c**, 51%[c]
m-MeOPh–	**2d**, 75%	**3d**, 98%[a]	**4d**, 100%	**5d**, 65%[c]
p-BrPh–	**2e**, 74%	**3e**, 95%[a]	**4e**, 87%	**5e**, 68%[d]
m-CNPh–	**2f**, 72%	**3f**, 84%[b]	**4f**, 100%	**5f**, 67%[d]
o-CNPh–	**2g**, 75%	**3g**, 86%[b]	**4g**, 81%	**5g**, 58%[d]
p-(thiazol-2-yl)Ph- (**10**)	**2h**, 80%	**3h**, 76%[b]	**4h**, 80%	**5h**, 47%[d]
m-(thiazol-2-yl)Ph- (**11**)	**2i**, 87%	**3i**, 73%[b]	**4i**, 72%	**5i**, 57%[d]
p-(thiazol-5-yl)Ph- (**12**)	**2j**, 63%	**3j**, 58%[b]	**4j**, 85%	**5j**, 45%[d]
m-(thiazol-5-yl)Ph- (**13**)	**2k**, 65%	**3k**, 70%[b]	**4k**, 92%	**5k**, 57%[d]

[a]Condition A (see Scheme 1).
[b]Condition B (see Scheme 1).
[c]Condition C (see Scheme 1).
[d]Condition D (see Scheme 1).

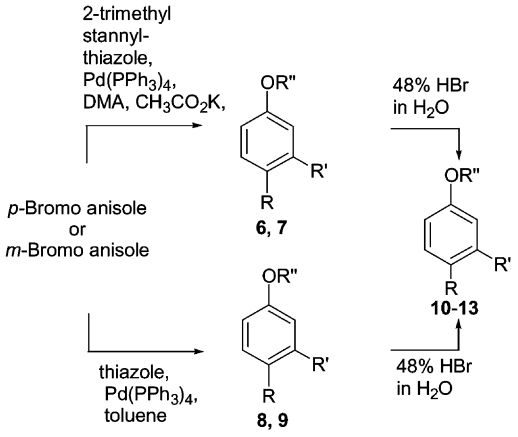
The target compounds **5a–d** were obtained in 30–65% overall yield over two steps, by reduction of the diazides, followed by reaction with benzyl chloroformate in the presence of pyridine in CH_2Cl_2. Reacting the corresponding diamine of **4e–k** with benzyl chlorofomate resulted in poor yields. However, using *N*-(benzyloxycarbonyloxy)-succinimide instead delivered the compounds **5e–k** in 45–68% overall yields.

To obtain the corresponding thiazole substituted phenols two different approaches were applied (Scheme 2). The *p*- and *m*-thiazole-2-yl-phenols **10** and **11** were synthesised from a Stille type coupling using 2-trimethylstannylthiazole, prepared in good yield by quenching 2-lithiothiazole with trimethyltin chloride.[27] The stannylated reagents were reacted with *p*- and *m*-bromoanisole in the presence of $Pd(Ph_3)_4$ affording the anisoles **6** and **7**.[28] Demethylation of the anisoles was subsequently achieved with 48% HBr in water after which phenols **10** and **11** were isolated in 63 and 61% overall yield respectively, over the two steps.

The *p*- and *m*-thiazole-5-yl-phenols **12** and **13** were prepared in two steps in 60 and 44% yields respectively by reacting thiazole with *p*- and *m*-bromanisole in the presence of $Pd(Ph_3)_4$[29] followed by 48% HBr in water (Scheme 2). The structures were confirmed by the presence of the ^1H NMR signals at 7.88 ppm (s, 1H) for **12** and 8.05 ppm for **13** (s, 1H), assigned to the C(4) proton of the thiazole ring. The isomeric thiazole-4-yl derivative would give rise to a doublet at ≈7.4 ppm [H-C(5)].

From this first set of compounds very promising inhibitors were rapidly identified (Table 2).

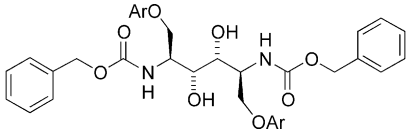
It was evident from the limited SAR available that the electron withdrawing cyano substituent attached to the



Cpd.	6	7	8	9	10	11	12	13
R		H		H		H		H
R'	H		H		H		H	
R''	Me	Me	Me	Me	H	H	H	H
Yield					63%*	61%*	60%*	44%*

Scheme 2. Synthesis of phenols **10–13**; * overall yields.

Table 2. Percentage inhibition at 0.5 μM against Plm I and II and inhibition constant for Plm I, Plm II and Cat D for compound set I



Compd	Ar–	% inh.at 0.5 μM		K_i (nM)		
		Plm I	Plm II	Plm I	Plm II	Cat D
5c	*p*-CNPh–	49	100	350	140	>6000
5f	*m*-CNPh–	19	5	nd	nd	nm
5g	*o*-CNPh–	2	0	nd	nd	nm
5h	*p*-(thiazol-2-yl)Ph–	3	0	nd	nd	nm
5j	*p*-(thiazol-5-yl)Ph–	0	2	nd	nd	nm
5k	*m*-(thiazol-2-yl)Ph–	5	0	nd	nd	nm

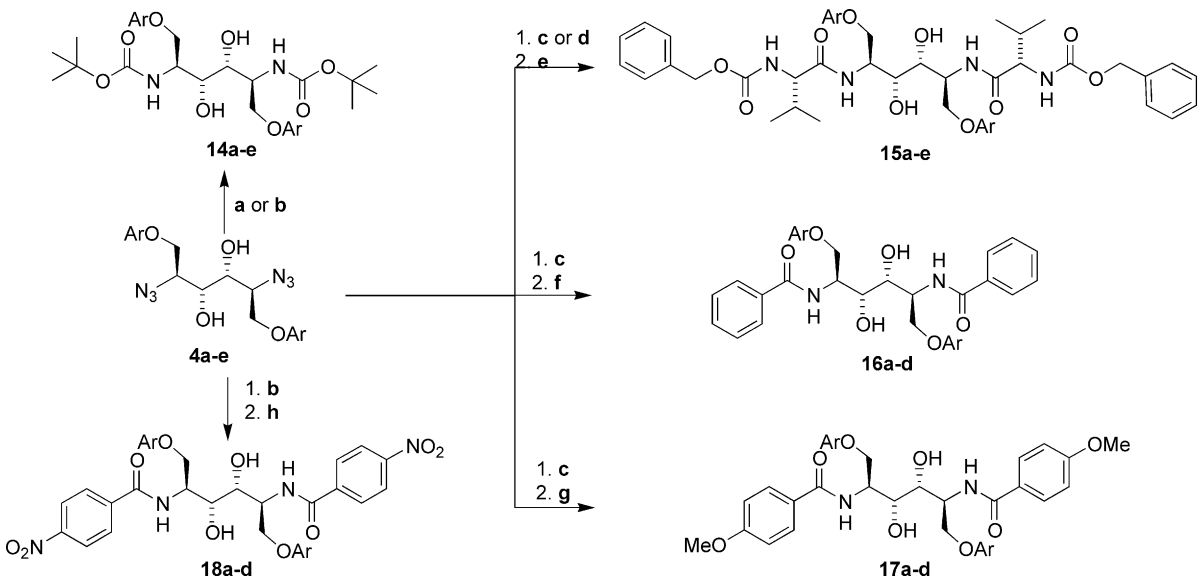
Compounds **5a–b**, **d–e** and **i** were found to be inactive; nd = not detected, nm = not measured.

phenoxy groups rendered the best activity. Thus inhibitor **5c**, having a *para* cyano phenoxy group, inhibits Plm I and II with K_i values of 350 and 140 nM, respectively, whilst the corresponding unsubstituted phenoxy groups as well as electron rich methoxy substituted phenoxy groups failed to exhibit inhibition activity towards Plm I and II to any degree. With these highly promising inhibition data at hand an expanded set of compounds were prepared. A limited number of the substituted phenoxy entities from the original set were retained while exploring replacements for the benzyloxycarbonyl moiety with amides and carbamates. It was also decided to maintain the C_2-symmetric feature that had shown promise from the initial compound set. The desired target molecules of the new series, compound set II, were obtained by reducing the appropriate diazides followed by coupling of the resulting diamines with the chosen acylating groups (Scheme 3 and Table 3).

Compounds **14a–d** were formed in 45–92% yield by reduction of the azido groups followed by in situ acylation of the resulting amine using hydrogen over 10% palladium on carbon in ethyl acetate in the presence of di-*tert*-butyl dicarbonate (Boc_2O) (Scheme 3, Table 3).[30] For **14e**, the diazide was reduced with H_2S and the diamine was isolated and subsequently reacted with Boc_2O. Compounds **15a–e** were obtained in 56–90% yield by coupling the diamines, from the reduced azides, vide supra, with the amino acid Z-Val-OH using PyBop as coupling reagent.[31]

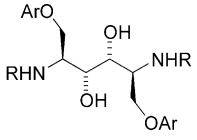
Finally, the diazides **4a–d** were converted to amides **16a–d**, **17a–d** and **18a–d** by reduction of the diazides, using hydrogen, over 10% palladium on carbon, and coupling of the resulting diamines with the anhydrides benzoic anhydride, *p*-methoxybenzoic anhydride and *p*-nitrobenzoic anhydride. The anhydrides used were prepared in a one-pot reaction by mixing the corresponding carboxylic acids with triphosgene in the presence of triethylamine in ethyl acetate, which produced the anhydrides in high yields.[32] Attempts to isolate compounds **16e**, **17e** and **18e** in pure form were unsuccessful, partly attributed to the very low solubility of the amides.

From this expanded compound set II even more potent inhibitors of Plm I and II were discovered (Table 4). Notably the Z-Val series of inhibitors, exemplified by **15c**, show remarkable Plm I and II inhibitory activity,



Scheme 3. Synthesis of compound set II, **14a–e**, **15a–e**, **16a–d**, **17a–d** and **18a–d** (a) H_2, Pd/C, $(Boc)_2O$, EtOAc; (b) 1. H_2S, pyridine, Et_3N 2. $(Boc)_2O$, Et_3N, EtOAc; (c) H_2, Pd/C, EtOAc; (d) H_2S, pyridine, Et_3N; (e) Z-Val-OH, PyBOP, DIPEA; CH_2Cl_2; (f) benzoic anhydride, CH_2Cl_2; (g) 4-methoxybenzoic anhydride, CH_2Cl_2; (h) 4-nitrobenzoic anhydride CH_2Cl_2.

Table 3. Reaction yields of amides and carabamate couplings for compound set II



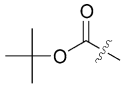
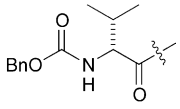
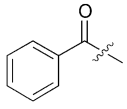
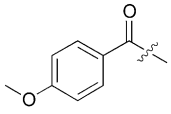
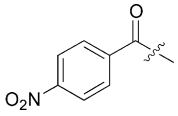
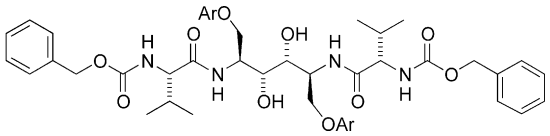
Ar–	R				
					
	Compound (yield)				
Ph–	**14a**, 92%	**15a**, 56%	**16a**, 93%	**17a**, 52%	**18a**, 97%
p-MeOPh–	**14b**, 45%	**15b**, 63%	**16b**, 56%	**17b**, 76%	**18b**, 50%
p-CNPh–	**14c**, 71%	**15c**, 73%	**16c**, 63%	**17b**, 59%	**18c**, 72%
m-MeOPh–	**14d**, 68%	**15d**, 71%	**16d**, 74%	**17d**, 57%	**18d**, 56%
p-BrPh–	**14e**, 61%	**15e**, 90%			

Table 4. Inhibition constants for Plm I, Plm II and Cat D for compound set II



Compd	Ar–	K_i(nM)		
		Plm I	Plm II	Cat D
15a	Ph–	29	86	>3000
15b	*p*-MeOPh–	9	23	>3000
15c	*p*-CNPh–	2.7	0.25	340
15d	*m*-MeOPh–	31	44	>3000
15e	*p*-BrPh–	58	23	1840

Compounds **14a–e**, **16a**,**b**,**d**, **17a–d** and **18a–d** were found to be inactive.

with K_i values of 2.7 and 0.25 nM respectively, as well as showing >100-fold selectivity against Cathepsin D. Plasmepsin II, although lacking the C_2-symmetry properties of the HIV-1 protease, shows the typical bilobal structure topology of eukaryotic aspartic proteases, and it has herein been documented that Plm II can bind with high affinity to C_2-symmetric inhibitors such as **15c**. Statine-based inhibitors like pepstatin A, show preference to lipofilic amino acids in the amino terminus, like Leu-Val-Val. It is highly likely that Z-Val occupy this site as well.

Conclusion

By exploring C_2-symmetric templates, we have discovered compounds that exhibit potent inhibition of

both Plm I and II. Moreover, selected inhibitors from this set of compounds show very favourable selectivity towards Cathepsin D. Another attractive feature is their relative simplicity, which could translate into favourable cost of goods. There thus appear to be a good foundation for further optimisation of this set of inhibitors.

Experimental

Plasmepsin assay and K_i determination

Pro-plasmepsin II was a generous gift from Helena Danielson (Department of Biochemistry, Uppsala University, Uppsala, Sweden) and the expression and purification of plasmepsin I will be published elsewhere.[33] Human liver cathepsin D was purchased from Sigma-Aldrich, Sweden. The activities of plasmepsin I (Plm I), plasmepsin II (Plm II) and cathepsin D (Cat D) was measured essentially as described earlier,[11] using a total reaction volume of 100 μL The concentration of pro-Plm II was 3 nM, the amount of Plm I was adjusted to give similar catalytic activity and 50 ng/mL pro-cathepsin D was used. The pro-sequence of Plm II was cleaved off by preincubation in assay reaction buffer (100 mM sodium acetate buffer (pH 4.5), 10% glycerol and 0.01% Tween 20) at room temperature for 40 min and Cat D was activated by incubation in the same reaction buffer at 37 °C for 20 min. The reaction was initiated by the addition of 3 μM substrate (DABCYL-Glu-Arg-Nle-Phe-Leu-Ser-Phe-Pro-EDANS, AnaSpec Inc, San Jose, CA, USA) and hydrolysis was recorded as the increase in fluorescence intensity over a 10 min time period, during which the rate increased linearly with time.

Stock solutions of inhibitors in DMSO were serially diluted in DMSO and added directly before addition of substrate, giving a final DMSO concentration of 1%.

IC_{50}-values were obtained by assuming competitive inhibition and fitting a Langmuir isotherm ($v_i/v_o = 1/(1+[I]/IC_{50})$) to the dose response data (Grafit), where v_i and v_o are the initial velocities for the inhibited and uninhibited reaction respectively and [I] is the inhibitor concentration.[34] The K_i was subsequently calculated by using $K_i = IC_{50}/(1+[S]/K_m)$[35] and K_m value determined according to Michaelis–Menten.

General

All glassware was dried over an open flame before use in connection with an inert atmosphere. Concentrations were performed under reduced pressure at <40 °C (bath temperature). Thin layer chromatography was performed using silica gel 60 F-254 plates with detection by UV and charring with 8% sulfuric acid. Silica gel (0.040–0.063 mm) was used for column chromatography. Me_4Si (0.0 ppm) was used as an internal standard in ^1H NMR and Me_4Si or $CDCl_3$ (77.0 ppm) were used in ^{13}C NMR. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. MALDI-TOF spectra were recorded on a Bruker Biflex III using 2′,4′,6′-trihydroxy-acetophenone monohydrate (THAP) as matrix. Unless stated otherwise, all materials were obtained from commercial suppliers and used without further purification. Compounds **2–4a–b** and **14a–b** were synthesised according to Zuccarello et al.[23]

General method for the preparation of compounds 2c–k. K_2CO_3 (0.5 equiv) was added to a stirred solution of 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol, **1**[24] (1 equiv) and phenol (3–4 equiv) in DMF (30 mL/g of **1**). The reaction mixture was heated at 110 °C for 4–5 h. The reaction mixture was, after cooling, added to saturated aqueous NH_4Cl and extracted with Et_2O. The organic phase was washed with H_2O (2×) and the combined aqueous layers were extracted with Et_2O (2×). The organic layers were combined dried with $MgSO_4$ and concentrated. Purification of the residue by silica gel column chromatography (solvent system A; toluene; toluene–EtOAc 6:1, solvent system B; toluene–EtOAc 3:1) gave the target compounds **2c–k**.

1,6-Di-*O*-(4-cyanophenyl)-3,4-*O*-isopropylidene-D-mannitol, 2c. The title compound was prepared in 79% yield (1.26 g, 2.97 mmol) according to general procedure, vide supra (solvent system A). $[\alpha]_D^{20}$ +23.6 (*c* 0.67, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.57–7.55 (d, 4H), 7.01–7.00 (d, 4H), 4.33–4.31 (d, 2H), 4.14–4.10 (dd, 2H), 4.03 (m, 4H), 3.91 (s, 2H) 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 134.2, 119.3, 115.6, 110.4, 104.5, 79.9, 71.8, 70.3, 27.2; anal. calcd for: ($C_{23}H_{24}N_2O_6$) C, 65.1, H, 5.7, N, 6.6. Found: C, 64.9, H, 5.7, N, 6.4.

3,4-*O*-Isopropylidene-1,6-di-*O*-(3-methoxyphenyl)-D-mannitol, 2d. The title compound was prepared in 75% yield (1.22 g, 2.82 mmol) according to general procedure, vide supra (solvent system A). $[\alpha]_D^{20}$ +32 (*c* 1.87, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.21–7.15 (m, 2H), 6.57–6.51 (m, 6H), 4.28–4.25 (d, 2H), 4.06–4.04 (m, 6H), 3.78 (s, 6H), 3.76 (s, 2H), 1.39 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 160.2, 130.2, 110.1, 107.1, 107.1, 101.5, 80.0, 71.9, 69.9, 55.5, 27.1; anal. calcd for: ($C_{23}H_{30}O_6$) C, 63.6, H, 7.0, found: C, 63.7, H, 7.0.

1,6-Di-*O*-(4-bromophenyl)-3,4-*O*-isopropylidene-D-mannitol, 2e. The title compound was prepared in 74% yield (1.48 g, 2.78 mmol) according to general procedure, vide supra (solvent system A). $[\alpha]_D^{20}$ +24 (*c* 1.03, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.35 (d, 4H), 6.83–6.81 (d, 4H), 4.25–4.22 (d, 2H), 4.02 (m, 6H), 3.68 (s, 2H), 1.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 132.5, 116.7, 113.6, 110.2, 80.0, 71.9, 70.1, 27.1. Anal. calcd for: ($C_{21}H_{24}Br_2O_6$) C, 47.4, H, 4.6., found: C, 47.3, H, 4.6.

1,6-Di-*O*-(3-cyanophenyl)-3,4-*O*-isopropylidene-D-mannitol, 2f. The title compound was prepared in 72% yield (246 mg, 0.58 mmol) according to general procedure, vide supra (solvent system A). $[\alpha]_D^{20}$ +27.1 (*c* 1.53, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.24–7.17 (m, 6H), 4.30–4.28 (d, 2H), 4.10–4.03 (m, 8H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 130.7, 125.2, 120.3, 118.8, 118.0, 113.4, 110.4, 79.9, 71.8, 70.3, 27.1; anal. calcd for: ($C_{23}H_{24}N_2O_6$) C, 65.1, H, 5.7, N, 6.6, found: C, 65.0, H, 5.7, N, 6.5.

1,6-Di-*O*-(2-cyanophenyl)-3,4-*O*-isopropylidene-D-mannitol, 2g. The title compound was prepared in 75% yield (257 mg, 0.60 mmol) according to general procedure, vide supra (solvent system A). $[\alpha]_D^{20}$ +34.5 (*c* 1.36, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.49 (m, 4H), 7.03–6.97 (m, 4H), 4.40–4.38 (dd, 2H), 4-34–4.33 (d, 2H), 4.19–4.11 (m, 6H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 134.7, 133.8, 121.3, 116.8, 113.0, 110.3, 102.3, 79.5, 71.7, 71.0, 27.1; anal. calcd for: ($C_{23}H_{24}N_2O_6$) C, 65.1, H, 5.7, N, 6.6, found: C, 65.0, H, 5.8, N, 6.7.

3,4-*O*-Isopropylidene-1,6-Di-*O*-(4-thiazol-2-yl-phenyl)-D-mannitol, 2h. The title compound was prepared in 80% yield (279 mg, 0.52 mmol) according to general procedure, vide supra (solvent system B). $[\alpha]_D^{20}$ +30.5 (*c* 0.72, MeOH–DCM 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.77 (d, 4H), 7.71–7.70 (d, 2H), 7.22–7.21 (d, 2H), 6.96–6.94 (d, 4H), 4.27–4.25 (dd, 2H), 4.07–4.03 (dd, 2H), 4.01–3.94 (m, 4H), 3.47 (s, 2H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 160.7, 143.2, 128.4, 126.6, 118.4, 115.3, 110.1, 80.0, 71.6, 70.2, 27.0; anal. calcd for: ($C_{27}H_{28}N_2O_6S_2$) C, 60.0, H, 5.2, N, 5.2, found: C, 60.1, H, 5.2, N, 5.0.

3,4-*O*-Isopropylidene-1,6-Di-*O*-(3-thiazol-2-yl-phenyl)-D-mannitol, 2i. The title compound was prepared in 87% yield (505 mg, 0.93 mmol) according to general procedure, vide supra (solvent system B). $[\alpha]_D^{20}$ +25.8 (*c* 1.77, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.83 (d, 2H) 7.55–7.53 (m, 2H), 7.49–7.46 (bd, 2H), 7.31–7.25 (m, 4H), 6.97–6.93 (m, 2H), 4.97 (s, 2H), 4.36–4.33 (d, 2H), 4.14–4.07 (m, 6H), 1.37 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 159.4, 143.7, 134.8, 130.2, 119,7, 119.3, 117.1, 112.5, 110.1, 80.1, 71.9, 70.3, 27.1; anal. calcd for: ($C_{27}H_{28}N_2O_6S_2$) C, 60.0, H, 5.2, N, 5.2, found: C, 60.3, H, 5.2, N, 5.1.

3,4-*O*-Isopropylidene-1,6-Di-*O*-(4-thiazol-5-yl-phenyl)-D-mannitol, 2j. The title compound was prepared in 63% yield (195 mg, 0.36 mmol) according to general procedure, vide supra (solvent system B). $[\alpha]_D^{20}$ +34.0 (*c* 0.67, MeOH–DCM 2:1); ^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD) δ 8.62 (s, 2H), 7.85 (s, 2H), 7.39–7.37 (d, 4H), 6.92–6.89 (d, 4H), 4.26–4.24 (d, 2H), 4.06–3.98 (m, 6H), 3.22 (bs, 2H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$:CD_3OD) δ 159.4, 151.8, 139.6, 137.7, 128.4, 123.8, 115.5, 110.1, 80.0, 71.6, 70.2, 27.1; anal. calcd for: ($C_{27}H_{28}N_2O_6S_2$) C, 60.0, H, 5.2, N, 5.2, found: C, 59.6, H, 5.6, N, 4.9.

3,4-*O*-Isopropylidene-1,6-Di-*O*-(3-thiazol-5-yl-phenyl)-D-mannitol, 2k. The title compound was prepared in 65% yield (164 mg, 0.30 mmol) according to general procedure, vide supra (solvent system B). $[\alpha]_D^{20}$ +25.8 (*c* 2.15, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 2H), 8.03 (s, 2H), 7.29–7.24 (t, 2H), 7.17–7.12 (m, 4H), 6.94–6.92 (dd, 2H), 4.8 (s, 2H), 4.36–4.34 (d, 2H), 4.16–4.09 (m, 6H), 1.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 152.5, 139.2, 132.4, 130.4, 120.0, 114.7, 113.9, 110.1, 80.2, 71.9, 70.3, 27.2; anal. calcd for: ($C_{27}H_{28}N_2O_6S_2$) C, 60.0, H, 5.2, N, 5.2, found: C, 59.5, H, 5.3, N, 5.3.

General method for the preparation of compounds 4c–e. To a stirred solution of triphenylphosphine (2 equiv) in THF under an argon atmosphere at 0 °C, diisopropylazodicarboxylate (DIAD) (5 equiv) was added dropwise during 5 min. The mixture was stirred for 30 min to yield a white precipitate of triphenylphosphine-DIAD complex. A solution of **2c–e** (1 equiv) in THF was added and the mixture was stirred for 15 min before diphenyl phosphorazidate (DPPA) (2.5 equiv) was added. The mixture was allowed to warm to room temperature. After stirring overnight, the solvent was removed and the crude material was purified by silica gel column chromatography (toluene; toluene–EtOAc 9:1) to give the target compounds **3c–e**. To **3c–e** (1 equiv) was added a cold (0 °C) solution of acetyl chloride (25 equiv) in MeOH (35 mL/mmol **3c–e**), which had been stirred for 10 min. After stirring for 4 h at room temperature, the reaction mixture was concentrated. The residue was purified by silica gel column chromatography (toluene; toluene–EtOAc 3:1) to give the target compounds **4c–e**.

2,5-Diazido-1,6-di-*O*-(4-cyanophenyl)-2,5-dideoxy-L-iditol, 4c. The title compound was prepared in a two step synthesis according to general procedure, vide supra. The intermediate **3c** was prepared in 66% yield (603 mg, 1.27 mmol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 134.4, 119.1, 115.6, 111.5, 105.3, 76.5, 68.6, 59.3, 27.0. The title compound was produced in 86% yield (472 mg, 1.09 mmol). $[\alpha]_D^{20}$ +14.8 (*c* 1.60, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD) δ 7.53–7.51 (d, 4H), 6.93–6.91 (d, 4H), 4.29–4.20 (m, 4H), 3.91–3.87 (m, 2H), 3.83–3.81 (m, 2H), 3.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$:CD_3OD) δ 161.8, 134.3, 119.1, 115.5, 104.6, 79.1, 68.6, 62.3; IR: 2229, 2103 cm^{-1}; anal. calcd for ($C_{20}H_{18}N_8O_4$) C, 55.3, H, 4.2, N, 25.8, found: C, 55.0, H, 4.1, N, 25.3.

2,5-Diazido-2,5-dideoxy-1,6-di-*O*-(3-methoxyphenyl)-L-iditol, 4d. The title compound was prepared in a two step synthesis according to general procedure, vide supra. The intermediate **3d** was prepared in 98% yield (874 mg, 1.80); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 159.4, 130.3, 111.14, 107.5, 106.9, 101.5, 77.2, 68.1, 59.8, 55.5, 27.1. The title compound was produced in 99% yield (545 mg, 1.23 mmol). $[\alpha]_D^{20}$ −1.25 (*c* 1.60, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.18 (t, 2H), 6.56–6.48 (m, 6H), 4.27–4.25 (m, 4H), 3.95–3.94 (m, 4H), 3.78 (s, 6H), 2.93–2.92 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 159.4, 130.3, 107.5, 106.9, 101.4, 69.2, 62.7, 55.6; IR: 2101 cm^{-1}; anal. calcd for: ($C_{20}H_{24}N_6O_4$) C, 54.1, H, 5.4, N, 18.9, found: C, 54.6, H, 5.5, N, 18.6.

1,6-Di-*O*-(4-bromophenyl)-2,5-diazido-2,5-dideoxy-L-iditol, 4e. The title compound was prepared in a two step synthesis according to general procedure, vide supra. The intermediate **3e** was prepared in 95% yield (831 mg, 1.43 mmol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 132.7, 116.7, 114.2, 111.3, 76.9, 68.4, 59.6, 27.1. The title compound was produced in 87% yield (488 mg, 0.90 mmol). $[\alpha]_D^{20}$ +11.9 (*c* 1.30, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.38 (d, 4H), 6.81–6.78 (d, 4H), 4.29–4.19 (m, 4H), 3.99–3.91 (m, 4H), 2.80–2.79 (d, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 132.7, 116.6, 114.3, 70.9, 68.5, 62.6; IR: 2103 cm^{-1}; anal. calcd for: ($C_{18}H_{18}Br_2N_6O_4$) C, 39.9, H, 3.4, N, 15.5, found: C, 39.6, H, 3.3, N, 15.9.

General method for the preparation of compounds 4f–k. To a stirred solution of **2f–k** (1 equiv) in DCM (4 mL) and pyridine (2 mL) at 0 °C was added triflic anhydride (4 eqiuv.) and the mixture was stirred for 1 h at 0 °C. The mixture was diluted with DCM and washed with saturated aqueous $NaHCO_3$ (1×) and H_2O (1×) and the combined aqueous layers were extracted with EtOAc (2×). All the organic layers were combined dried with $MgSO_4$ and concentrated. The residue was added to a solution of sodium azide (10 equiv) in DMF (3 mL) at 70 °C. After 2 h the mixture was filtrated through a plug of Celite, the solvent was removed and the crude material was purified by silica gel column chromatography (toluene; toluene–EtOAc 9:1) to give the target compounds **3f–k**.

To **3f–k** (1 equiv) was added a cold (0 °C) solution of acetyl chloride (25 equiv) in MeOH (35 mL/ mmol **3f–k**), which had been stirred for 10 min. After stirring for 4 h at room temperature, the reaction mixture was concentrated. The residue was purified by silica gel column chromatography (solvent system A; toluene; toluene–EtOAc 3:1, solvent system B; toluene; toluene–EtOAc 1:1) to give the target compounds **4f–k**.

2,5-diazido-1,6-di-*O*-(3-cyanophenyl)-2,5-dideoxy-L-iditol, 4f. The title compound was prepared in a two step synthesis according to general procedure, vide supra. The intermediate **3f** was prepared in 84% yield (186 mg, 0.40 mmol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 130.9, 125.7, 120.4, 119.9, 117.8, 114.1, 111.05, 70.7, 68.7, 59.3, 27.1. The title compound was produced in 99% yield (145 mg, 0.33 mmol) (solvent system A). $[\alpha]_D^{20}$ −7.6 (*c* 1.50, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.15 (m, 8H), 4.37–4.26 (m, 4H), 4.00–3.97 (m, 4H), 2.91 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 130.8, 125.7, 120.1, 118.5, 118.0, 113.7, 70.8, 69.7, 62.8; IR: 2233, 2101 cm^{-1}; anal. calcd for: ($C_{20}H_{18}N_8O_4$) C, 55.3, H, 4.2, N, 25.8. Found: C, 55.0, H, 4.3, N, 25.9.

1,6-Di-*O*-(2-cyanophenyl)-2,5-diazido-2,5-dideoxy-L-iditol, 4g. The title compound was prepared in a two step synthesis according to general procedure, vide supra. The intermediate **3g** was prepared in 86% yield (192 mg, 0.41 mmol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 134.7, 134.1, 122.0, 116.3, 112.7, 111.3, 102.5, 77.0, 68.8, 60.0, 27.2, The title compound was produced in 81% yield (89 mg, 0.20 mmol (solvent system A). $[\alpha]_D^{20}$ −14.9 (*c* 2.05, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.43 (m, 4H), 7.05–6.97 (m, 4H), 4.44–4.34 (m, 4H), 4.11 (bs, 4H), 3.52 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 134.9, 133.8, 121.8, 116.5, 112.7, 102.0, 70.7, 68.8, 62.8; IR: 2231, 2103 cm^{-1}; anal. calcd for: ($C_{20}H_{18}N_8O_4$)) C, 55.3, H, 4.2, N, 25.8, found: C, 55.5, H, 4.3, N, 25.9.

2,5-Diazido-2,5-dideoxy-1,6-di-*O*-(4-thiazol-2-yl-phenyl)-L-iditol 4h. The title compound was prepared in a two step synthesis according to general procedure, vide supra. The intermediate **3h** was prepared in 58% yield (101 mg, 0.17 mmol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 159.6, 143.6, 128.4, 127.6, 118.5, 115.2, 111.3, 77.0, 68.3, 59.7, 27.1. The title compound was produced in 80% yield (103 mg, 0.19 mmol) (solvent system B). $[\alpha]_D^{20}$ +4.09 (*c* 1.11, DCM–MeOH 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.84 (d, 4H), 7.82–7.81 (d, 2H), 7.26–7.25 (d, 2H), 6.92–6.89 (d, 4H), 4.27–4.25 (m, 4H), 3.97 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 159.7, 143.6, 128.4, 127.4, 118.6, 115.2, 70.8, 68.3, 63.5; IR: 2110 cm^{-1}; anal.calcd for: ($C_{24}H_{22}N_8O_4S_2$)) C, 52.3, H, 4.0, N, 20.4, found: C, 52.5, H, 4.1, N, 20.5.

2,5-Diazido-2,5-dideoxy-1,6-di-*O*-(3-thiazol-2-yl-phenyl)-L-iditol, 4i. The title compound was prepared in a two step synthesis according to general procedure, vide supra. The intermediate **3i** was prepared in 73% yield (239 mg, 0.41 mmol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 158.6, 143.9, 135.2, 130.4, 120.4, 119.3, 117.2, 112.0, 111.3, 76.8, 68.3, 59.7, 27.1. The title compound was produced in 72% yield (93 mg, 0.17 mmol) (solvent system B). $[\alpha]_D^{20}$ +2.2 (*c* 1.72, DCM–MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.85 (d, 2H), 7.52–7.47 (m, 4H), 7.30–7.26 (m, 4H), 6.93–6.90 (dd, 2H), 4.38–4.31 (m, 4H), 4.00 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168, 4, 158.7, 143.7, 134.9, 130.4, 120.3, 119,5, 117.3, 112.0, 70.9, 68.4, 62.8; IR: 2102 cm^{-1}; anal. calcd for: ($C_{24}H_{22}N_8O_4S_2$)) C, 52.3, H, 4.0, N, 20.4, found: C, 51.9, H, 4.1, N, 20.7.

2,5-Diazido-2,5-dideoxy-1,6-di-*O*-(4-thiazol-5-yl-phenyl)-L-iditol, 4j. The title compound was prepared in a two step synthesis according to general procedure, vide supra. The intermediate **3j** was prepared in 76% yield (132 mg, 0.22 mmol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 151.8, 139.1, 138.6, 128.6, 125.0, 115.5, 111.3, 77.0, 68.3, 59.7, 27.1. The title compound was prepared in 85% yield (86 mg, 0.16 mmol) according to general procedure, vide supra (solvent system B). $[\alpha]_D^{20}$ +2.36 (*c* 1.55, DCM–MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, CD_3OD) δ 8.72 (s, 2H), 7.91 (s, 2H), 7.45–7.43 (d, 4H), 6.90–6.88 (d, 4H), 4,26–4.13 (m, 4H), 3.92–3.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$,CD_3OD) δ 158.7, 152.0, 139.2, 137.5, 128.0, 124.0, 115.2, 70.5, 68.0, 62.8; IR: 2103 cm^{-1}; anal. calcd for: ($C_{24}H_{22}N_8O_4S_2$) C, 52.3, H, 4.0, N, 20.4, found: C, 52.5, H, 4.1, N, 20.6.

2,5-Diazido-2,5-dideoxy-1,6-di-*O*-(3-thiazol-5-yl-phenyl)-L-iditol, 4k. The title compound was prepared in a two step synthesis according to general procedure, vide supra. The intermediate **3k** was prepared in 70% yield (107 mg, 0.18 mmol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 152.5, 139.6, 139.1, 132.8. 130.6, 120.7, 114.6, 113.6, 111.3, 77.1, 68.3, 59.7, 27.1. The title compound was produced in 92% yield (84 mg, 0.16 mmol); $[\alpha]_D^{20}$ +2.73 (*c* 1.65, DCM–MeOH 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 2H), 8.00 (s, 2H), 7.29–7.26 (t, 2H), 7.15–7.13 (d, 2H), 7.05–7.04 (m, 2H), 6.88–6.86 (dd, 2H), 4.36–4.31 (m, 4H), 4.05–3.97 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 152.8, 139.3, 139.2, 132.5, 130.6, 120.5, 114.7, 113.5, 71.0, 68.2, 62.6; IR: 2106 cm^{-1}; anal. calcd for: ($C_{24}H_{22}N_8O_4S_2$) C, 52.3, H, 4.0, N, 20.4, found: C, 52.5, H, 4.2, N, 20.4.

General method for the preparation of compounds 5a–d. To 4a–d (1 equiv) in EtOAc was added a catalytic amount of Pd/C (10%). Hydrogen was added at atmospheric pressure to the system and the reaction mixture was stirred for 1 h. The suspension was then filtrated through Celite and the solvent was removed. To the diamines and Et_3N (4 equiv) in DCM was added benzyl chloroformate (2 equiv). After stirring over night the reaction mixture was concentrated and the residue was purified by silica gel column chromatography (DCM–MeOH 20:1) to give the target compounds 5a–d.

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-phenyl-L-iditol, 5a. The title compound was prepared in 30% yield (19 mg, 0.032 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 156.9, 136.4, 129.7, 128.7, 128.7, 128.4, 128.3, 121.6, 114.8, 71.5, 68.4, 67.4, 51.6; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{34}H_{36}N_2O_8$, 660.25, found: 639.22 (MK^+) 623.27 (MNa^+).

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-(4-methoxyphenyl)-L-iditol, 5b. The title compound was prepared in 48% yield (22 mg, 0.033 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 154.5, 152.5, 136.4, 128.8, 128.3, 115.9, 114.9, 71.5, 69.3, 67.3, 55.9, 51.6; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{36}H_{40}N_2O_{10}$, 600.27, found: 699.22 (MK^+) 683.28 (MNa^+).

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-1,6-di-*O*-(4-cyanophenyl)-2,5-dideoxy-L-iditol, 5c. The title compound was prepared in 51% yield (21 mg, 0.033 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 156.9, 136.4, 134.1, 128.6, 128.3, 128.0, 119.1, 115.6, 104.3, 69.9, 67.8, 67.1, 51.3; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{36}H_{34}N_4O_8$, 650.24, found: 689.25 (MK^+) 673.28 (MNa^+) 651.30 (MH^+).

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-(3-methoxyphenyl)-L-iditol, 5d. The title compound was prepared in 65% yield (26 mg, 0.040 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 159.6, 157.0, 136.4, 130.2, 128.8, 128.4, 128.3, 127.2, 107.3, 106.9, 101.3, 71.5, 68.5, 67.4, 55.5, 51.7; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{36}H_{40}N_2O_{10}$, 660.27, found: 699.31 (MK^+) 683.32 (MNa^+) 661.31 (MH^+).

General method for the preparation of compounds 5e–k. H_2S (g) was bubbled through a solution of 4e–k (1 equiv) in pyridine (3 mL) and Et_3N (1.5 mL) for 1 h. After stirring for additional 2 h the reaction mixture was concentrated. The residue was dissolved in DCM, and Et_3N (2.1 equiv) and *N*-(benzyloxycarbonyloxy)-succinimide was added. After stirring over night the reaction mixture was concentrated and the residue was purified by silica gel column chromatography (DCM–MeOH 40:1) to give the target compounds 5e–k.

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-1,6-di-*O*-(4-bromophenyl)-2,5-dideoxy-L-iditol, 5e. The title compound was prepared in 68% yield (44 mg, 0.058 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 156.9, 136.5, 132.3, 128.5, 128.1, 127.9, 116.6, 113.3, 69.9, 67.7, 67.0, 51.6; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{34}H_{34}Br_2N_2O_8$, 756.07, found: 779.00 (MNa^+).

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-1,6-di-*O*-(3-cyanophenyl)-2,5-dideoxy-L-iditol, 5f. The title compound was prepared in 67% yield (40 mg, 0.062 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 157.0, 140.9, 129.3, 129.0, 128.5, 128.2, 128.1, 127.8, 120.6, 119, 118.7, 112.8, 70.0, 67.6, 67.0, 51.1; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{36}H_{34}N_4O_8$, 650.25, found: 673.28 (MNa^+).

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-1,6-di-*O*-(2-cyanophenyl)-2,5-dideoxy-L-iditol, 5g. The title compound was prepared in 58% yield (43 mg, 0.066 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 157.0, 136.4, 134.7, 133.5, 133.4, 128.4, 128.3, 128.1, 127.9, 121.3, 121.2, 112.8, 69.6, 67.1, 67.0, 51.3; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{36}H_{34}N_4O_8$, 650.25, found: 673.30 (MNa^+).

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-(4-thiazol-2-yl-phenyl)-L-iditol, 5h. The title compound was prepared in 47% yield (26 mg, 0.034 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 160.2, 157.0, 143.0, 136.5, 128.5, 128.1,127.9, 126.6, 118.3, 115.1, 70.0, 67.6, 67.0, 51.7; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{40}H_{38}N_4O_8S_2$, 766.21, found: 789.25 (MNa^+) 767.27 (MH^+).

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-(3-thiazol-2-yl-phenyl)-L-iditol, 5i. The title compound was prepared in 57% yield (47 mg, 0.062 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 159.1, 157.0, 143.2, 136.5, 134.6, 130.1, 128.4, 128.0, 127.8, 119.6, 119.3, 116.9, 112.5, 70.1, 67.8, 66.9, 51.9; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{40}H_{38}N_4O_8S_2$, 766.21, found: 789.12 (MNa^+) 767.15 (MH^+).

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-(4-thiazol-5-yl-phenyl)-L-iditol, 5j. The title compound was prepared in 45% yield (31 mg, 0.040 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 157.2, 152.1, 139.8, 137.5, 136.8, 128.5, 128.3, 128.0, 127.8, 123.9, 115.5, 70.0, 67.7, 66.9, 51.7; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{40}H_{38}N_4O_8S_2$, 766.21, found: 789.26 (MNa^+) 767.28 (MH^+).

2,5-Bis[*N*-(benzyloxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-(3-thiazol-5-yl-phenyl)-L-iditol, 5k. The title compound was prepared in 57% yield (32 mg, 0.041 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 157.0, 152.6, 139.5, 138.6, 132.1, 130.2, 128.4, 128.0, 127.7, 119.8, 114.8, 113.4, 69.9, 67.7, 66.9, 51.7; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{40}H_{38}N_4O_8S_2$, 766.21, found: 789.23 (MNa^+) 767.26 (MH^+).

4-Thiazol-2-yl-phenol, 10. 4-Bromoanisole (700 μL, 5.35 mmol), tetrakis(triphenylphosphine)palladium (0) (100 mg, 0.09 mmol) and 2-trimethylstannylthiazole (2.0 g, 5.35 mmol) in toluene (25 mL) was refluxed over night. The mixture was filtrated through Celite and concentrated. The residue was purified by silica gel column chromatography (toluene; toluene–EtOAc 20:1) to give **6**; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 161.3, 143.6, 128.3, 126.8, 118.2, 114.5, 55.6. HBr in H_2O (48%, 15 mL) was added to the 2-(4-methoxyphenyl)thiazole and the mixture was stirred at reflux for 2 h. The mixture was added to $NaHCO_3$ (aq) and extracted with EtOAc (3×), dried with $MgSO_4$ and concentrated to give **10** (576 mg 3.26 mmol) as a white solid in 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.57 (m, 3H), 7.13–7.12 (d, 1H), 6.74–6.71 (d, 2H), 4.10 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, CD_3OD) δ 169.6, 159.3, 142.6, 128.3, 125.0, 118.0, 115.9.

3-Thiazol-2-yl-phenol, 11. 3-Bromoanisole (745 μL, 5.90 mmol), tetrakis(triphenylphosphine)palladium (0) (110 mg, 0.096 mmol) and 2-trimetylstannylthiazole (2.2 g, 5.89 mmol) in toluene (30 mL) was refluxed over night. The mixture was filtrated through Celite and concentrated. The residue was purified by silica gel column chromatography (toluene; toluene–EtOAc 20:1) to give **7**; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 160.3, 143.8, 135.0, 130.2, 119.4, 119.2, 115.5, 111.4, 55.6. HBr in H_2O (48%, 15 mL) was added to the 2-(3-methoxyphenyl)thiazole and the mixture was stirred at reflux for 2 h. The mixture was added to saturated aqueous $NaHCO_3$ and extracted with EtOAc (3×), dried with $MgSO_4$ and concentrated to give **11** (658 mg 3.72 mmol) as a white solid in 63% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.75 (dd, 1H), 7.38–7.19 (m, 4H), 6.89–6.87 (dd, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 157.7, 143.1, 134.3, 130.5, 119.4, 118.5, 117.9, 113.2.

4-Thiazol-5-yl-phenol, 12. 4-Bromoanisole (810 μL, 6.42 mmol), thiazole (2.3 mL, 32 mmol), potassium acetate (936 mg, 9.52 mmol) and tetrakis(triphenylphosphine)palladium (0) (300 mg, 0.26 mmol) in dimethylacetamide (20 mL) was heated to 100 °C and stirred over night. The mixture was filtrated through Celite and concentrated. The residue was purified by silica gel column chromatography (toluene; toluene–EtOAc 15:1) to give **8**; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 151.5, 139.4, 138.3, 128.5, 123.9, 114.8, 55.6. HBr in H_2O (48%, 15 mL) was added to the 5-(4-methoxyphenyl)thiazole and the mixture was stirred at reflux for 2 h. The mixture was added to saturated aqueous $NaHCO_3$ and extracted with EtOAc (3×), dried with $MgSO_4$ and concentrated to give **12** (540 mg 2.83 mmol) as a white solid in 44% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.89 (s, 1H), 7.40–7.38 (dd, 2H), 6.84–6.82 (dd, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 151.7, 140.4, 136.9, 128.4, 122.3, 116.1.

3-Thiazol-5-yl-phenol, 13. 3-Bromoanisole (540 μL, 4.28 mmol), thiazole (1.5 mL, 20.8 mmol), potassium acetate (624 mg, 6.34 mmol) and tetrakis(triphenylphosphine)palladium (0) (240 mg, 0.20 mmol) in dimethylacetamide (20 mL) was heated to 100 °C and stirred over night. The mixture was filtrated through Celite and concentrated. The residue was purified by silica gel column chromatography (toluene; toluene–EtOAc 20:1) to give **9**; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 152.3, 139.5, 139.4, 132.6, 130.4, 119.7, 114.0, 112.3, 55.6. HBr in H_2O (48%, 15 mL) was added to the 5-(3-methoxyphenyl)thiazole and the mixture was stirred at reflux for 2 h. The mixture was added to saturated aqueous $NaHCO_3$ and extracted with EtOAc (3×), dried with $MgSO_4$ and concentrated to give **13** (490 mg 2.57 mmol) as a white solid in 60% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.05, (s, 1H), 7.28–7.22 (m, 1H), 7.10–7.08 (m, 1H), 6.88–6.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 152.5, 138.7, 132.3, 130.6, 118.9, 116.3, 114.5.

General method for the preparation of compounds 14c and d. To 4c and d. (1 equiv) and *tert*-butoxycarbonyl anhydride (Boc_2O; 2.1 equiv) in EtOAc was added a catalytic amount of Pd/C (10%). Hydrogen was added at atmospheric pressure to the system and the reaction mixture was stirred for 3 h. The suspension was then filtrated through Celite, the solvent was removed and the crude material was purified by silica gel column chromatography (toluene–EtOAc 1:1) to give the target compounds **14c** and **d**.

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-1,6-di-*O*-(4-cyanophenyl)-2,5-dideoxy-L-iditol, 14c. The title compound was prepared in 71% yield (38 mg, 0.065 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 156.6, 132.5, 116.4, 113.7, 104.6, 80.5, 71.4, 68.4, 51.2, 28.5; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{30}H_{38}N_4O_8$, 582.27, found: 605.31 (MNa^+).

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-2,5-dideoxy-1,6-di-*O*-(3-methoxyphenyl)-L-iditol, 14d. The title compound was prepared in 68% yield (34 mg, 0.057 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 159.8, 130.1, 107.2, 106.9, 101,3, 71.1, 68.4, 55.5, 51.3, 28.5; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{30}H_{44}N_2O_{10}$, 592.30, found: 631.36 (MK^+) 615.40 (MNa^+).

2,5-Bis[*N*-(*tert*-butoxycarbonyl)amino]-1,6-di-*O*-(4-bromophenyl)-2,5-dideoxy-L-iditol, 14e. H_2S (g) was bubbled through a solution of **4e** (100 mg, 0.18 mmol) in pyridine (3 mL) and Et_3N (1.5 mL) for 1 h. After stirring for additional 2 h the reaction mixture was concentrated. The residue was dissolved in DCM (2 mL) and Et_3N (54 μL, 0.38 mmol) and *tert*-butoxycarbonyl anhydride (Boc_2O; 82 mg, 0.38 mmol) was added. After stirring overnight the mixture was concentrated and purified by silica gel column chromatography (DCM–MeOH 40:1) to give the target compounds **14e** as a white solid (76 mg, 0.11 mmol, 61%); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 156.7, 132.6, 116.7, 113.7, 80.6, 71.4, 68.4, 51.1, 28.6; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{28}H_{38}Br_2N_2O_8$, 688.10, found: 711.16 (MNa^+).

General method for the preparation of compounds 15a–d. To **4a–d** (1 equiv) in EtOAc was added a catalytic amount of Pd/C (10%). Hydrogen was added at atmospheric pressure to the system and the reaction mixture was stirred for 1 h. The suspension was then filtrated through Celite and the solvent was removed. DIPEA (4 equiv) was added to the diamines, Z–Val–OH (2 equiv) and PyBop (2 equiv) in DCM. After stirring over night the mixture was diluted with DCM and washed with $NaHCO_3$ (1×) and brine (1×), and the combined aqueous layers were extracted with DCM (2×). The organic layers were combined, dried with $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (DCM–MeOH 20:1) to give the target compounds **15a–d**.

2,5-Bis[*N*-(2-benzyloxycarbonylamino-3-methylbutyloxy)amino]-2,5-dideoxy-1,6-di-*O*-phenyl-L-iditol, 15a. The title compound was prepared in 56% yield (34 mg, 0.042 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 158.1, 156.6, 135.9, 129.0, 128.0, 127.7, 127.4, 114.1, 69.7, 66.5, 60.0, 50.1, 30.4, 18.7, 17.3; MS (MALDI-TOF) *m/z* mass calcd for: $C_{44}H_{54}N_4O_{10}$, 798.38, found: 836.36 (MK^+) 821.34 (MNa^+).

2,5-Bis[*N*-(2-benzyloxycarbonylamino-3-methylbutyloxy)amino]-2,5-dideoxy-1,6-di-*O*-(4-methoxyphenyl)-L-iditol, 15b. The title compound was prepared in 63% yield (37 mg, 0.043 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 157.0, 154.1, 152.7, 136.3, 128.6, 128.3, 128.0, 115.7, 114.7, 70.4, 67.8, 67.1, 60.9, 55.8, 50.8, 31.0, 19.3, 17.7; MS (MALDI-TOF) *m/z* mass calcd for: $C_{46}H_{58}N_4O_{12}$, 858.41, found: 897.34 (MK^+) 881.38 (MNa^+) 859.40 (MH^+).

2,5-Bis[*N*-(2-benzyloxycarbonylamino-3-methylbutyloxy)amino]-(4-cyanophenyl)-2,5-dideoxy-1,6-di-*O*-L-iditol, 15c. The title compound was prepared in 73% yield (64 mg, 0.076 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 162.0, 136.3, 134.0, 128.5, 128.2, 127.7, 119.1, 115.5, 104.1, 70.0, 67.3, 67.1, 61.0, 50.0, 30.7. 29.6, 19.1, 17.6; MS (MALDI-TOF) *m/z* mass calcd for: $C_{46}H_{52}N_6O_{10}$, 848.37, found: 871.42 (MNa^+).

2,5-Bis[*N*-(2-benzyloxycarbonylamino-3-methylbutyloxy)amino]-2,5-dideoxy-1,6-di-*O*-(3-methoxyphenyl)-L-iditol, 15d. The title compound was prepared in 71% yield (36 mg, 0.042 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 161.0, 159.7, 157.0, 136.4, 130.1, 128.7, 128.4, 128.3, 107.1, 107.0, 101.3, MS (MALDI-TOF) *m/z* mass calcd for: $C_{46}H_{58}N_4O_{12}$, 658.41, found: 881.43 (MNa^+).

2,5-Bis[*N*-(2-benzyloxycarbonylamino-3-methylbutyloxy)amino]-(4-bromophenyl)-2,5-dideoxy-1,6-di-*O*-L-iditol, 15e. H_2S (g) was bubbled through a solution of **4e** (81 mg, 0.15 mmol) in pyridine (3 mL) and Et_3N (1.5 mL) for 1 h. After stirring for additional 2 h. the reaction mixture was concentrated. The residue was dissolved in DCM (2 mL) and Z–Val–OH (73 mg, 0.29 mmol), PyBop (151 mg, 0.29 mmol) and DIPEA (100 μL, 0.6 mmol) was added. After stirring overnight the mixture was diluted with DCM and washed with $NaHCO_3$ (1×) and brine (1×) and the combined aqueous layers were extracted with DCM (2×). The organic layers were combined with the mixture above, dried with $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (DCM–MeOH 40:1) to give the target compound **15e** as a white solid (125 mg, 0.13 mmol, 90%); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 157.3, 156.7, 136.0, 131.8, 128.0, 127.6, 127.3, 116.1, 112.8, 69.6, 67.0, 66.6, 60.6, 50.0, 30.3, 18.6, 17.1; MS (MALDI-TOF) *m/z* mass calcd for: $C_{44}H_{52}Br_2N_4O_{10}$, 954.21, found: 977.21 (MNa^+).

General method for the preparation of compounds 16a–d, 17a–d, 18a–d. To **4a–d** (1 equiv) in EtOAc was added a catalytic amount of Pd/C (10%). Hydrogen was added at atmospheric pressure to the system and the reaction mixture was stirred for 1 h. The suspension was then filtrated through Celite and the solvent was removed. To the diamines and Et_3N (4 equiv) in DCM was added anhydride (2 eqiuv.). The mixture was stirred overnight and the formed precipitate was filtered of and the solid was washed with DCM to give the target compounds **16a–d, 17a–d** and **18 a–d**.

2,5-Bis[*N*-(benzoyl)amino]-2,5-dideoxy-1,6-di-*O*-phenyl-L-iditol, 16a. The title compound was prepared in 93% yield (26 mg, 0.048 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 158.4, 134.8, 130.5, 129.4, 129.0, 128.6, 127.2, 121.1, 114.6, 70.6, 66.7, 51.5; MS (MALDI-TOF) *m/z* mass calcd for: $C_{32}H_{32}N_2O_6$, 540.23, found: 579.12 (MK^+) 563.18 (MNa^+) 541.28 (MH^+).

2,5-Bis[*N*-(benzoyl)amino]-2,5-dideoxy-1,6-di-*O*-(4-methoxyphenyl)-L-iditol, 16b. The title compound was prepared in 56% yield (21 mg, 0.035 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 153.8, 152.4, 133.5, 131.7, 128.4, 127.0, 116.3, 115.4, 114.4, 70.5, 67.3, 53.5, 51.3; MS (MALDI-TOF) *m/z* mass calcd for: $C_{34}H_{36}N_2O_8$, 600.25, found: 639.16 (MK^+) 623.18 (MNa^+).

2,5-Bis[*N*-(benzoyl)amino]-(4-cyanophenyl)-2,5-dideoxy-1,6-di-*O*-L-iditol, 16c. The title compound was prepared in 63% yield (22 mg, 0.037 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 161.9, 134.0, 133.7, 132.0, 128.7, 127.2, 119.0, 115.5, 104.0, 70.2, 67.0, 51.5; MS (MALDI-TOF) *m/z* mass calcd for: $C_{34}H_{30}N_4O_6$, 590.25, found: 629.19 (MK^+) 613.25 (MNa^+).

2,5-Bis[*N*-(benzoyl)amino]-2,5-dideoxy-1,6-di-*O*-(3-methoxyphenyl)-L-iditol, 16d. The title compound was prepared in 74% yield (40 mg, 0.067 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 160.9, 159.9, 134.1, 131.9, 130.0, 128.7, 127.4, 107, 106.8, 101.1, 70.5, 66.8, 55.2, 51.5; MS (MALDI-TOF) *m/z* mass calcd for: $C_{34}H_{36}N_2O_8$, 600.25, found: 639.83 (MK^+) 623.28 (MNa^+) 601.30 (MH^+).

2,5-Bis[*N*-(4-methoxybenzoyl)amino]-2,5-dideoxy-1,6-di-*O*-phenyl-L-iditol, 17a. The title compound was prepared in 52% yield (23 mg, 0.038 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 162.3, 158.1, 129.1, 128.9, 120.7, 114.2, 113.4, 69.9, 66.3, 55.0, 51.1; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{34}H_{36}N_2O_8$, 600.25, found: 639.24 (MK^+) 623.29 (MNa^+) 601.32 (MH^+).

2,5-Bis[*N*-(4-methoxybenzoyl)amino]-2,5-dideoxy-1,6-di-*O*-(4-methoxyphenyl)-L-iditol, 17b. The title compound was prepared in 76% yield (37 mg, 0.056 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 162.0, 153.4, 152.1, 128.4, 114.9, 113.8, 112.9, 69.6, 66.7, 54.5, 54.4, 50.7; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{36}H_{40}N_2O_{10}$, 660.27, found: 699.20 (MK^+) 683.24 (MNa^+).

2,5-Bis[*N*-(4-methoxybenzoyl)amino]-1,6-di-*O*-(4-cyanophenyl)-2,5-dideoxy-L-iditol, 17c. The title compound was prepared in 59% yield (22 mg, 0.034 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 162.5, 159.7, 133.6, 128.7, 125.5, 119.6, 115.2, 113.5, 103.6, 70.0, 66.7, 54.9, 50.1; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{36}H_{34}N_4O_8$, 650.24, found: 689.15 (MK^+) 673.28 (MNa^+) 651.20 (MH^+).

2,5-Bis[*N*-(4-methoxybenzoyl)amino]-2,5-dideoxy-1,6-di-*O*-(3-methoxyphenyl)-L-iditol, 17d. The title compound was prepared in 57% yield (26 mg, 0.040 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 162.8,161.1, 160.0, 129.9, 129.2, 126.4, 113.9, 107.2, 107.0, 101.4; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{36}H_{40}N_2O_{10}$, 660.27, found: 683.29 (MNa^+).

2,5-Bis[*N*-(4-nitrobenzoyl)amino]-2,5-dideoxy-1,6-di-*O*-phenyl-L-iditol, 18a. The title compound was prepared in 97% yield (38 mg, 0.061 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 158.4, 149.8, 139.8, 129.6, 128.6, 123.6, 121.4, 114.7, 70.5, 66.9, 51.9; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{32}H_{30}N_4O_{10}$, 630.20, found: 669.09 (MK^+) 653.12 (MNa^+).

2,5-Bis[*N*-(4-nitrobenzoyl)amino]-2,5-dideoxy-1,6-di-*O*-(4-methoxyphenyl)-L-iditol, 18b. The title compound was prepared in 56% yield (28 mg, 0.040 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 155.8, 154.1, 149.3, 128.2, 123.3, 115.2, 114.4, 70.0, 67.0, 55.3, 51.4; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{34}H_{34}N_4O_{12}$, 690.22, found: 729.17 (MK^+) 713.14 (MNa^+).

2,5-Bis[*N*-(4-nitrobenzoyl)amino]-1,6-di-*O*-(4-cyanophenyl)-2,5-dideoxy-L-iditol, 18c. The title compound was prepared in 72% yield (28 mg, 0.041 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 161.8, 149.0, 139.8, 134.2, 128.9, 123.3, 119.1, 115.5, 102.9, 69.0, 67.1, 51.4; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{34}H_{28}N_6O_{10}$, 680.19, found: 703.22 (MNa^+).

2,5-Bis[*N*-(4-nitrobenzoyl)amino]-2,5-dideoxy-1,6-di-*O*-(3-methoxyphenyl)-L-iditol, 18d. The title compound was prepared in 56% yield (27 mg, 0.040 mmol) according to general procedure, vide supra; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 160.9, 159.6, 149.7, 139.6, 130.1, 128.7, 123.7, 106.8, 106.7, 101.2, 70.5, 66.7, 55.3, 51.7; MS (MALDI-TOF) *m*/*z* mass calcd for: $C_{34}H_{34}N_4O_{12}$, 690.22, found: 713.15 (MNa^+).

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References and Notes

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