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Synthesis of 3-amido-3-deoxy-β-D-talopyranosides: all-*cis*-substituted pyranosides as lectin inhibitors

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ABSTRACT

3-Deoxy-3-amino-β-D-talopyranosides have been synthesized for the first time. The amines were obtained from galactopyranosides through 2,3-anhydrogulosides that were opened to idosides followed by an oxidation/reductive amination sequence. From the amines, 11 corresponding 3-deoxy-3-arylamido-β-talopyranosides have been synthesized and evaluated as inhibitors against galectin-1, -2, -3, -4C, -4N, -7, -8N and -9N. The synthesized talosamides showed selectivity for Galectin-4C with three of the monosaccharides having dissociation constants at around 100 μM against the lectin, which is more than two orders of magnitude better than methyl β-galactoside and significantly better than the previous best galectin-4C monosaccharide inhibitor.

1. Introduction

Taloside-based compounds as lectin inhibitors appear of particular interest due to the fact that, as far as we know, there are no mammalian talose-containing glycoconjugates or talose-specific processing or recognizing proteins. Hence, talose-based compounds may not suffer from some of the poor pharmacological properties generally associated with carbohydrates. In order to investigate this hypothesis, we embarked on a project aiming at talose-based inhibitors of galectins.[1] Galectins have been implicated in cancer progression, immunity and inflammation,[2–5] and the underlying molecular mechanisms responsible have increasingly been understood, such as regulation of apoptosis, cell signalling, intracellular trafficking and cell adhesion.[6–14]

Taloside based, as opposed to galactoside based, galectin inhibitors were envisioned after observation of an extended binding pocket in the direction an axial 2OH of a bound saccharide (Fig. 1) would have in X-ray structures of several galectins.[15–18] GRID simulations later corroborated the finding and prompted us to synthesize a first generation of taloside-based galectin inhibitors.[1] Taloside inhibitors turned out to have different specificity than galactoside inhibitors to the galectin members, and among the highest-affinity monosaccharide inhibitors against galectin-4C (C-terminal domain) and 8N (N-terminal domain) were discovered to be talosides. So far, only a limited number of 2OH substituents on talosides have been synthesized and tested, thus the optimal 2OH substituent likely still remains to be found.

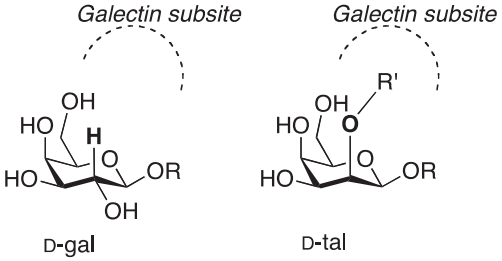

Fig. 1. Galectin interaction sites close to H2 of bound natural ligand monosaccharide D-galactose can be targeted by axial C2-functionalities of D-talopyranosides.

In this paper we present the synthesis and biological evaluation of 3-amido-3-deoxy-talosides. As mentioned, there seem to be no (or very few) mammalian taloside-processing or recognizing proteins, which may make taloside-based galectin inhibitors more metabolically resilient ligands. To increase stability further, we now report on the replacement of the affinity-enhancing 3-*O*-ester of the first generation taloside inhibitors with 3-*N*-amides. As an additional benefit, for some galectin members, 3-*N*-amides confer increased affinity compared to the corresponding 3-*O*-esters.[19–21] Finally, 3-*N*-β-talosides and consequently 3-*N*-amido-β-talosides

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have not been reported in the literature and this class of all-*cis* glycosides present challenging synthetic targets.

2. Synthesis

O-Glycosides. One may imagine several routes, both de novo and carbohydrate based, to obtain 3-*N*-amido-talosides. After surveying talose-related literature we settled on carbohydrate-based approaches. We have previous experience with 3-amido-β-galactosides, and have developed several routes to these targets.[22] Thus, perhaps the most obvious route to 3-amido-β-talosides would be through 3-amido-β-galactosides, which we have developed convenient routes to.[22] However, in our hands, all attempts at epimerizing (i.e., Lattrell–Dax and Mitsonobu reactions) the 2-OH of 3-amido-β-galactosides failed. Contrary to our amides, 2-OH epimerization to talosides have been reported from suitable protected all-*O*-galactosides.[23,24] Synthesis of the all-*cis*-substituted β-talosides by epimerization of galactose 2-OH proved a more daunting task than epimerization of 3-OH galactosides or gulosides. The resulting 1,3-diaxial interactions between 2,4-OH in talose presumably being a major impediment.[25] Instead, we decided on a route where the 1,3-diaxial relationship of 2-OH and 4-OH was installed in an intermediate idoside before the equatorial 3-NH_2 was installed through a substitution or oxidation/reductive amination sequence.

Thus, starting from benzylidene-protected methyl β-D-galactopyranoside **1** (Scheme 1), selective 3-OH tosylation followed by base-promoted oxirane formation afforded the 2,3-anhydro guloside **3** in excellent yield. Treatment with KOH under microwave conditions opened the oxirane **3** selectively at C2 to obtain idoside **4**, presumably due to a favourable chair-like transition state. Toluoylation quantitatively gave the 2-OH derivatized idoside **5** as the only observable isomer, likely explained by the activating effect of a vicinal *cis*-oxygen. All attempts at displacing the intermediate 3-OTf of idoside **5** with azide failed to produce the desired product. Consequently, we resorted to an oxidation/reductive amination sequence to obtain 3-amino-3-deoxy-β-taloside **7** for the first time. NOE-experiment confirmed the talo-configuration.

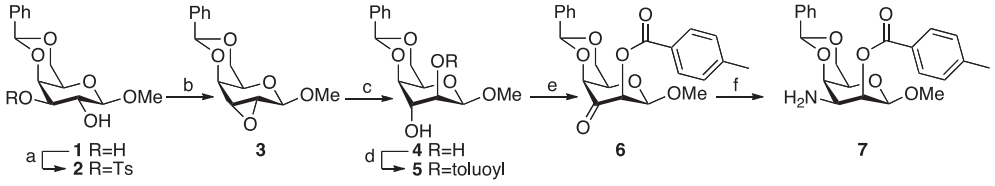
With key intermediate talo-amine **7** in hand, we were in position to acylate to form seven selected aromatic amides **10**–**16** (Table 1). The choice of amido structure was based on earlier observations that *m*- and *p*-substituted benzamides, together with 2-naphthamides, are optimal galactose 3-*N*-amido substituents for galectin-3 inhibition.[27,28] Hence, a representative panel of these particularly well galectin-3-binding aromatic 3-*N*-amide structures was selected for incorporation into the talose 3-*N*-amides. Acylation of **7** afforded protected talo-amides that were subsequently de-benzylidenated to give **17**–**23**. Four of these (**17**, **20**, **21** and **22**) were further saponified to furnish **24**–**27**.

S-Glycosides. Currently, the highest-affinity monosaccharide galectin inhibitors are in the low micromolar range.[29] To reach the nanomolar range, disaccharide (or higher) saccharides seem to be needed (for monovalent inhibitors). Thus, to allow for the incorporation of 3-amido-3-deoxy-talosides in disaccharides we synthesized one *S*-glycoside **34** as a talosyl donor. The synthetic strategy to *S*-glycoside **34** was essentially the same as for *O*-glycosides **10**–**16**. The only difference in route was that tetrabutylammonium nitrite (QNO_2) worked better than hydroxide for opening of oxirane **30** to idoside **31**. Perhaps not surprising given that the *trans* β-epoxy sulfide **30** (i.e., a mustard) was positioned to work against axial external nucleophilic epoxide opening, thus likely explaining the lowered tolerance to the combination of heat and basic nucleophiles compared to the corresponding *O*-methyl glycoside **3** (Scheme 3).

3. Biological evaluation

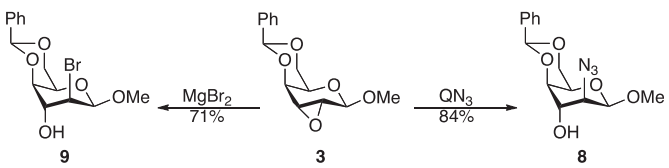
Compounds **17**–**27**, together with references methyl β-galactoside **29** and methyl β-taloside[1] **28**, were evaluated against galectin-1, -2, -3, -4C, -4N, -7, -8N, -9N in a fluorescence polarization assay[30] (Table 2).

For galectin-1, inhibitors **17** and **18** showed affinity slightly lower than 1 mM (compared to methyl β-galactoside **29** at >10 mM). Most of the inhibitors tested were in the 2–3 mM range. There was no clear preference with 2-O-toluoylation (**17**–**23**) or without (**24**–**27**), indicating that either talosides are not ideal against galectin-1 or that the 2-OH was not derivatized suitably here (previous work[1] with other 2-OH substituents showed no hits



Scheme 1. Synthesis of **3**-amino-taloside **7**. Reagents and conditions: (a) TsCl, pyridine (94%). (b) $(CH_3)_3SiOK$, DMF (98%). (c) KOH (aq, 5 M), MW (88%). (d) *p*-toluoyl chloride, pyridine (quant.). (e) Dess–Martin periodinane. (f) $NaBH_3CN$, NH_4OAc, trimethyl orthoformate, MeOH, THF (23% over two steps).

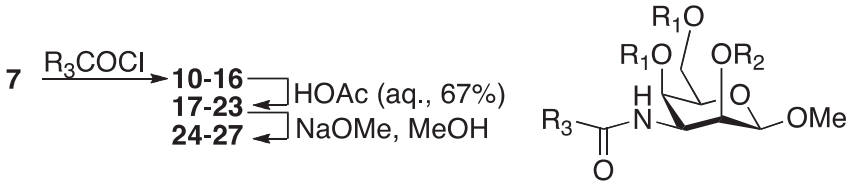
Incidentally, the opening of the 2,3-anhydro guloside **3** seems little investigated. Besides opening with the oxygen nucleophiles (hydroxide and nitrite) discussed here, nitrogen and halogen nucleophiles were successfully attempted (Scheme 2). Opening with tetrabutylammonium azide (QN_3) under microwave irradiation improved on the previously reported[26] yield of **8** while opening with bromide to obtain **9** has not been reported to our knowledge. Other nucleophiles may work and expand the scope of the ring opening of the 2,3-anhydro guloside **3**.



Scheme 2. Ring opening of oxirane **3**.

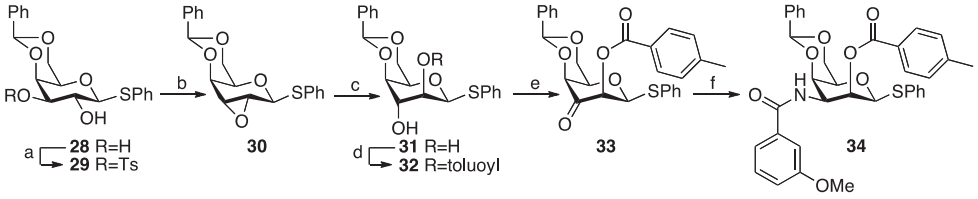
either). Given the close kinship, it is not surprising to see very similar affinities for galectin-2 as for galectin-1. Six inhibitors showed greater affinities than 1 mM for galectin-3, the best being **20** at 0.57 mM (compared to methyl β-galactoside **29** at 4.4 mM). Again, no clear preference was seen with or without 2-O-toluoylation. By far the best matches for these talosamide inhibitors were found against Gal-4C (C-terminal) with K_d down to ca. 100 μM for compounds **17**, **20** and **21**, and compounds **18** and **22** in the 200 μM range. Thus compared to the parent monosaccharide methyl β-galactoside **29**, there is a two order of magnitude improvement in affinity. It is clear that the axial 2-*O*-toluoyl contributes beneficially to overall binding, results that corroborate previous findings for structurally similar 3-*O*-esters.[1] For galectin-4N (N-terminal), affinities of the 2-*O*-toluoylated compounds **17**–**23** clustered around 1 mM (compared to methyl β-galactoside **29** at 6.6 mM), while the free 2-OH compounds **24**–**27** were decidedly worse. The taloside scaffold may likely not be ideal for galectin-7 as generally poor

Table 1
Synthesis of 3-amido-D-talopyranosides **10**–**27**



	10	**11**	**12**	**13**	**14**	**15**	**16**
R_1	CHPh	CHPh	CHPh	CHPh	CHPh	CHPh	CHPh
R_2	Toluoyl	Toluoyl	Toluoyl	Toluoyl	Toluoyl	Toluoyl	Toluoyl
R_3	**17** CF_3	**18** tBu	**19** OMe	**20** NO_2	**21**	**22**	**23** COOH
R_1	H	H	H	H	H	H	H
R_2	Toluoyl	Toluoyl	Toluoyl	Toluoyl	Toluoyl	Toluoyl	Toluoyl
R_3	As above	As above	As above	As above	As above	As above	As above

	24	**25**	**26**	**27**
R_1	H	H	H	H
R_2	H	H	H	H
R_3	As above	As above	As above	As above



Scheme 3. Synthesis of 3-amido-thio-taloside **34**. Reagents and conditions: (a) TsCl, pyridine (38%). (b) $(CH_3)_3SiOK$, DMF (73%). (c) QNO_2, DMF (56%). (d) *p*-Toluoyl chloride, pyridine (88%). (e) Dess–Martin periodinane. (f) i. $NaBH_3CN$, NH_4OAc, trimethyl *ortho*formate, MeOH, THF ii. *m*-anisoyl chloride, lutidine, DCM (18% from **32**).

inhibitors were seen for all talosamides tested. Given the poor affinities, any preference for 2-O-toluoylation is hard to discern. For galectin-8N and -9N, the highest-affinity compounds reached 0.32 mM (**27**) and 0.94 mM (**25**), respectively (compared to methyl β-galactoside **29** at 6.3 and 1.2 mM, respectively). For these galectins, there was a small but clear preference for the free 2-OH (**24**–**27**), an effect seen previously for galectin-8N with structurally similar 3-*O*-esters.[1] Also noted before is the interesting observation that galectin-8N in fact prefers methyl β-taloside (**28**) over methyl β-galactoside (**29**).

4. Concluding remarks

3-Deoxy-3-amino-β-D-talopyranosides have been synthesized for the first time from galactopyranosides via 2,3-anhydrogulosides. The gulosides were opened with hydroxide to idosides, followed by an oxidation/reductive amination sequence to give a 3-amino-taloside. From this amine, 11 corresponding 3-deoxy-3-arylamido-β-D-talopyranosides **17**–**27** were synthesized and evaluated as inhibitors against galectin-1, -2, -3, -4C, -4N, -7, -8N and -9N. The standout result was against galectin-4C with inhibition below 100 μM for these monosaccharides, offering two orders of magnitude improved affinity compared to the parent monosaccharide methyl β-galactoside. These talose C3 amides thus improve on the talose O3 esters reported previously in terms of affinity.[1] In analogy with tandem-repeat (two binding sites within the same polypeptide) galectin-8, where the two CRDs display very different selectivities but where both need to be present to result in strong avidity and cell signalling,[12,13] inhibiting the galectin-4C CRD may very well be enough to inhibit the cellular functions of intact galectin-4. Moreover, we believe the talosamides hold promise in terms of chemical hydrolytic stability as well as the apparent lack of mammalian talose-recognizing and processing proteins potentially offering reduced rate of systemic clearance.

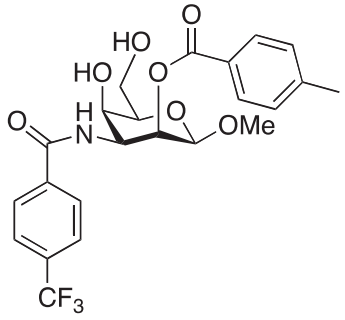
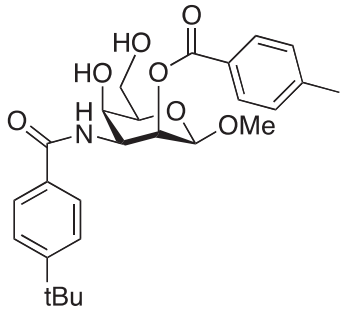
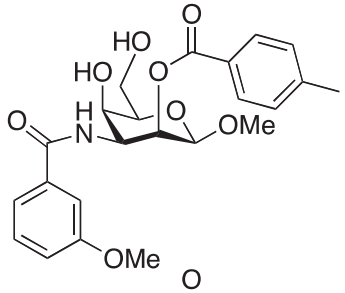
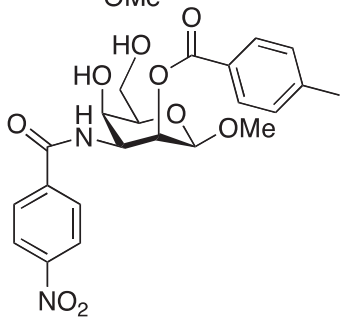
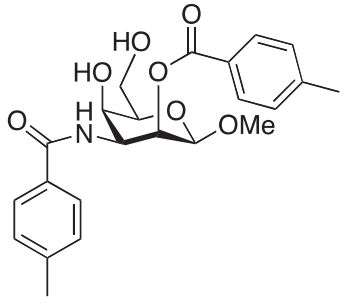
5. Experimental section

5.1. General methods

NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer at ambient temperature. ^{1}H NMR spectra were assigned using 2D-methods (COSY and NOESY). Chemical shifts are given in parts per million downfield from the signal for Me_4Si, with reference to residual $CHCl_3$, DMSO, HDO or CD_2HOD. HRMS was recorded on a Micromass Q-TOF micro spectrometer (ESI) and a JEOL SX-120 FAB spectrometer. Reactions were monitored by TLC using aluminium-backed silica gel plates (Merck 60 F_{254}) and visualized using UV light and by charring with ethanolic H_2SO_4 (ca. 7%). Preparative chromatography was performed using silica gel (Amicon Matrex 35–70 μm, 60 Å) columns. Preparative TLC was performed using glass-backed silica gel plates (200×200×1 mm, 60 F_{254}). DMF was distilled and stored over 4 Å M.S. Other solvents were dried by storing over activated M.S. Reagents were supplied by Sigma–Aldrich and used as is.

*5.1.1. Methyl 4,6-O-benzylidene-3-O-p-toluenesulfonyl-β-D-galactopyranoside (**2**).* Methyl 4,6-*O*-benzylidene-galactoside **1** (5.00 g, 17.7 mmol) was dissolved in pyridine (100 mL) at rt and *p*-

Table 2
Dissociation constants for compounds **17**–**29** to galectin-1, -2, -3, -4C, -4N, -7, -8N and -9N[a]

Compd	Structure	Galectins							
		1	2	3	4C	4N	7	8N	9N
17		1000±120	n.a.[b]	2300±340	120±26	1100±88	>4000	2000±2901	>4000
18		720±52	n.a.	2900±240	260±23	n.a.	2500±57	1000±61	3900±240
19		2900±240	2800±480	1800±180	670±61	1000±230	>4000	3300±61	>4000
20		1900±200	1700±8	570±110	94±16	900±210	>4000	4–10,000	>4000
21		2400±160	2600±590	910±190	120±4	1300±12	>4000	3100±11	>4000

(*continued on next page*)

Table 2 (*continued*)

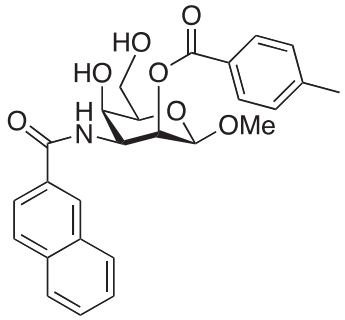
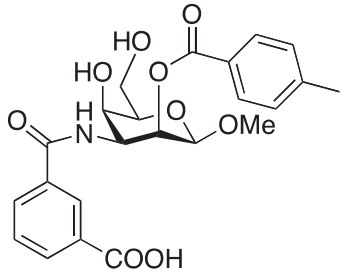
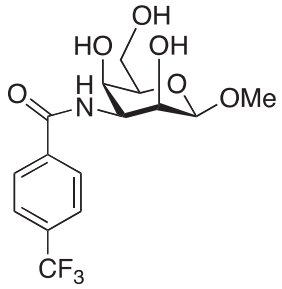
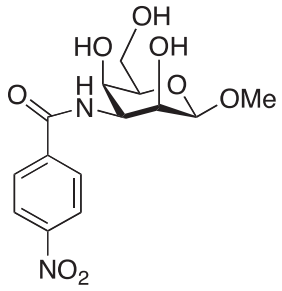
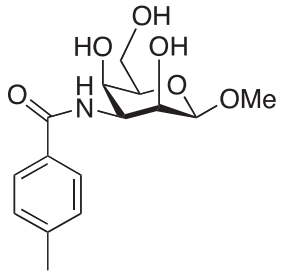
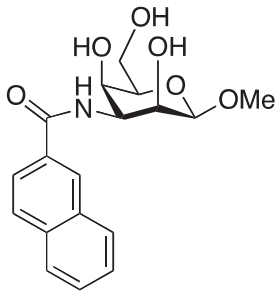
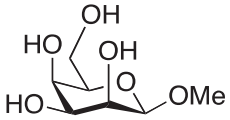
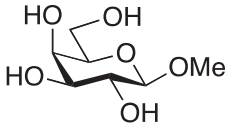
Compd	Structure	Galectins							
		1	2	3	4C	4N	7	8N	9N
22		2400±340	1700±180	900±500	220±120	1100±260	2–10,000	2000±250	>4000
23		2100±0	2000±370	720±110	620±110	760±160	1200±290	3100±23	>4000
24		2500±1100	2700±150	3000±280	1700±210	>4000	>4000	1100±12	4400±350
25		1700±81	1800±250	860±150	1100±99	2500±65	1400±380	820±100	940±86
26		>4000	4800±470	2500±130	2400±210	>4000	4–10,000	770±99	3300±130

Table 2 (*continued*)

Compd	Structure	Galectins							
		1	2	3	4C	4N	7	8N	9N
27		3300±170	2000±29	740±47	870±190	4–10,000	2700±360	320±55	2600±14
28[1]		>10,000	>10,000	10,000±3600	10,000±2000	>10,000	>10,000	1500±500	4600±100
29[1]		>10,000	13,000±3000	4400±800	>10,000	6600±200	4100±1700	6300±1500	1200±200

[a] Dissociation constants (μM) for compounds **17**–**29** binding to galectin-1, -2, -3, -4C, -4N, -7, -8N and -9N as measured in a fluorescence polarization assay[30] The average dissociation constants were calculated from 2 to 6 data points that gave 20–80% inhibition.
[b] Not available.

toluenesulfonyl chloride (6.09 g, 32.0 mmol) was added in portions over 43 h. Unreacted reagent was quenched by addition of excess H_2O and the reaction was concentrated and purified by column chromatography (toluene/acetone 100:10 to 100:20 to 100:30 gradient) to give tosylate **2**[31] in 94% yield (7.24 g); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, *J*=8.3 Hz, 2H, Ar*H*), 7.46–7.41 (m, 2H, Ar*H*), 7.37–7.32 (m, 3H, Ar*H*), 7.28 (d, 2H, Ar*H*), 5.38 (s, 1H, C*H*), 4.60 (dd, *J*=9.9, 3.8 Hz, 1H, *H*3), 4.37–4.32 (m, 2H, *H*4+*H*6), 4.24 (d, *J*=7.7 Hz, 1H, *H*1), 4.05 (dd, *J*=12.5, 1.8 Hz, 1H, *H*6), 3.98 (dd, *J*=9.9, 7.7 Hz, 1H, H2), 3.56 (s, 3H, OCH_3), 3.47 (d, *J*=1.1 Hz, 1H, *H*5), 2.42 (s, 3H, CH_3).

*5.1.2. Methyl 2,3-anhydro-4,6-O-benzylidene-β-D-gulopyranoside (**3**).* Potassium trimethylsilanoate (1.41 g, 11.0 mmol) was added to a stirred solution of tosylate **2** (3.19 g, 7.30 mmol) in DMF (73 mL) at rt. After 1.25 h, the reaction was diluted with CH_2Cl_2 (1.0 L) and washed with $NaHCO_3$ (satd, aq, 2×500 mL) and brine (500 mL). The organic phase was dried over $MgSO_4$ before being concentrated to give epoxide **3**[31] in 98% yield (1.89 g); ^{1}H NMR ($CDCl_3$) δ 7.57–7.51 (m, 2H, Ar*H*), 7.41–7.35 (m, 3H, Ar*H*), 5.60 (s, 1H, C*H*), 4.83 (app. s, 1H, *H*1), 4.35 (app. d, *J*=12.6 Hz, 1H, *H*6), 4.32 (t, *J*=1.9 Hz, 1H, *H*4), 4.10 (dd, *J*=12.7, 2.1 Hz, 1H, *H*6), 3.62 (s, 3H, OCH_3), 3.46 (br s, 1H, *H*3), 3.32–3.28 (m, 2H, *H*2+*H*5).

*5.1.3. Methyl 4,6-O-benzylidene-β-D-idopyranoside (**4**).* Epoxide **3** (900 mg, 3.41 mol) was stirred in KOH (5 M, 15 mL) in a microwave reactor at 140 °C for 30 min. The reaction was concentrated and purified by column chromatography (CH_2Cl_2/MeOH 100:5) to give idoside **4**[31] in 88% yield (850 mg); ^{1}H NMR (CD_3OD) δ 7.52–7.46 (m, 2H, Ar*H*), 7.39–7.34 (m, 3H, Ar*H*), 5.60 (s, 1H, C*H*), 4.75 (d, *J*=1.1 Hz, 1H, *H*1), 4.31 (dd, *J*=12.6, 1.6 Hz, 1H, *H*6), 4.18 (dd, *J*=12.6, 1.9 Hz, 1H, *H*6), 4.01–3.98 (m, 2H, tent. *H*3*H*4), 3.83 (app. s, 1H, tent. *H*2), 3.58 (s, 3H, OCH_3), 3.54 (br s, 1H, *H*5).

*5.1.4. Methyl 4,6-O-benzylidene-2-O-toluoyl-β-D-idopyranoside (**5**).* *p*-Toluoyl chloride (107 mL, 810 mmol) was added to a stirred solution of idoside **4** (190 mg, 670 mmol) in pyridine (7 mL) at 0 °C. After 1 h, H_2O (excess) was added, the reaction was concentrated, and purified by column chromatography (toluene/acetone 100:10) to give toluoate **5** in quantitative yield (270 mg); ^{1}H NMR ($CDCl_3$) δ 7.93 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.49–7.44 (m, 2H, Ar*H*), 7.32–7.15 (m, 5H, Ar*H*), 7.04 (d, *J*=8.4 Hz, 2H, Ar*H*), 5.56 (s, 1H, C*H*), 5.17 (br s, 1H, *H*2), 4.94 (app. s, 1H, *H*1), 4.51 (dd, *J*=12.5, 1.1 Hz, 1H, *H*6), 4.31 (br s, 1H, tent. *H*3), 4.18 (app. d, *J*=12.3 Hz, 1H, *H*6), 3.97 (app. s, 1H, tent. *H*4), 3.85 (d, *J*=1.5 Hz, 1H, tent. *H*5), 3.60 (s, 3H, OCH_3), 2.38 (s, 3H, C*H*3).

*5.1.5. Methyl 3-amino-4,6-O-benzylidene-3-deoxy-2-O-toluoyl-β-D-talopyranoside (**7**).* Dess–Martin periodinane (2.19 g, 5.2 mmol) was added to a stirred solution of toluoate **5** (1.38 g, 3.44 mmol) in CH_2Cl_2 (35 mL) at rt. After 3 h, the reaction was concentrated and purified by column chromatography (CH_2Cl_2/MeOH 100:5) to give crude methyl 4,6-*O*-benzylidene-2-*O*-toluoyl-*lyxo*-β-D-hexopyranosid-3-ulose **6**. $NaCNBH_3$ (1.08 g, 17.2 mmol) was added to a stirred solution of crude **6** (<3.44 mmol) and NH_4OAc (10.6 g, 138 mmol) in MeOH/THF (100:70 mL) and $CH(OMe)_3$ (35 mL) under nitrogen atmosphere and at rt. After 17 h, the reaction was concentrated and purified by repeated column chromatography (CH_2Cl_2/MeOH 100:5 to 100:10) to give intermediate amine **7** in 23% yield (0.32 g) from toluoate **5**; ^{1}H NMR ($CDCl_3$) δ 7.86 (d, *J*=8.2 Hz, 2H, Ar*H*), 7.63–7.57 (m, 2H, Ar*H*), 7.42–7.33 (m, 3H, Ar*H*), 6.96 (d, *J*=7.9 Hz, 2H, Ar*H*), 5.60 (s, 1H, C*H*), 5.41 (br d, *J*=3.0 Hz, 1H, *H*2), 4.50 (d, *J*=1.1 Hz, 1H, *H*1), 4.47 (dd, *J*=12.5, 1.3 Hz, 1H, *H*6), 4.18 (dd, *J*=12.6, 2.0 Hz, 1H, *H*6), 4.11 (br d, *J*=3.0 Hz, 1H, *H*4), 3.52 (s, 3H, OCH_3), 3.49 (app. d, *J*=1.1 Hz, 1H, *H*5), 3.35 (t, *J*=3.8 Hz, 1H, *H*3), 2.35 (s, 3H, CH_3).

5.2. Typical procedure for acylation of amines 10–16

*5.2.1. Methyl 4,6-O-benzylidene-3-deoxy-3-(2-naphthamido)-2-O-toluoyl-β-D-talopyranoside (**15**).* 2-Naphthoyl chloride (44 mg,

232 mmol) followed by pyridine (31 mL, 387 mmol) were added to a stirred solution of the intermediate amine **7** in CH_2Cl_2 (1 mL) under nitrogen atmosphere and at rt. After 24 h, the reaction was concentrated and purified by column chromatography (toluene/acetone100:20) to give amide **15** in 82% yield (31 mg); ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J=1.4 Hz, 1H, Ar*H*), 7.98 (d, J=8.2 Hz, 2H, Ar*H*), 7.83–7.78 (m, 2H, Ar*H*), 7.72 (d, J=8.0 Hz, 1H, Ar*H*), 7.68 (dd, J=8.6, 1.8 Hz, 1H, Ar*H*), 7.64–7.60 (m, 2H, Ar*H*), 7.57–7.36 (m, 5H, Ar*H*), 7.04 (d, J=7.9 Hz, 2H, Ar*H*), 6.93 (d, J=8.8 Hz, 1H, N*H*), 5.69 (dd, J=3.6, 0.7 Hz, 1H, *H*2), 5.63 (s, 1H, C*H*), 4.87 (dt, J=8.9, 3.9 Hz, 1H, *H*3), 4.70 (d, J=1.1 Hz, 1H, *H*1), 4.55 (dd, J=12.5, 1.2 Hz, 1H, *H*6), 4.29 (dd, J=3.9, 0.8 Hz, 1H, *H*4), 4.23 (dd, J=12.6, 2.0 Hz, 1H, *H*6), 3.66 (app. d, J=1.1 Hz, 1H, *H*5), 3.60 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3).

*5.2.2. Methyl 4,6-O-benzylidene-3-deoxy-3-(4-trifluoromethylbenzamido)-2-O-toluoyl-β-D-talopyranoside (**10**).* ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J=8.2 Hz, 2H, Ar*H*), 7.78–7.70 (m, 2H, Ar*H*), 7.63–7.56 (m, 4H, Ar*H*), 7.43–7.33 (m, 3H, Ar*H*), 7.06 (d, J=7.9 Hz, 2H, Ar*H*), 6.85 (d, J=8.7 Hz, 1H, N*H*), 5.64 (d, J=3.0 Hz, 1H, *H*2), 5.60 (s, 1H, C*H*), 4.80 (dt, J=8.7, 3.8 Hz, 1H, *H*3), 4.69 (d, J=1.1 Hz, 1H, *H*1), 4.55 (dd, J=12.6, 1.2 Hz, 1H, *H*6), 4.26 (dd, J=3.9, 0.8 Hz, 1H, *H*4), 4.22 (dd, J=12.6, 2.0 Hz, 1H, *H*6), 3.66 (app. d, J=1.1 Hz, 1H, *H*5), 3.59 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3).

*5.2.3. Methyl 4,6-O-benzylidene-3-deoxy-3-(4-tert-butylbenzamido)-2-O-toluoyl-β-D-talopyranoside (**11**).* ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J=8.2 Hz, 2H, Ar*H*), 7.64–7.54 (m, 4H, Ar*H*), 7.42–7.34 (m, 5H, Ar*H*), 7.04 (d, J=7.9 Hz, 2H, Ar*H*), 6.78 (d, J=8.9 Hz, 1H, N*H*), 5.63 (dd, J=3.6, 0.7 Hz, 1H, *H*2), 5.60 (s, 1H, C*H*), 4.82 (dt, J=8.9, 3.8 Hz, 1H, *H*3), 4.67 (d, J=1.1 Hz, 1H, *H*1), 4.52 (dd, J=12.5, 1.2 Hz, 1H, *H*6), 4.24–4.17 (m, 2H, *H*4*H*6), 3.64 (app. d, J=1.0 Hz, 1H, *H*5), 3.58 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3), 1.29 (s, 9H, ^{t}Bu).

*5.2.4. Methyl 4,6-O-benzylidene-3-deoxy-3-(3-methoxybenzamido)-2-O-toluoyl-β-D-talopyranoside (**12**).* ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J=8.2 Hz, 2H, Ar*H*), 7.62–7.57 (m, 2H, Ar*H*), 7.42–7.35 (m, 3H, Ar*H*), 7.26–7.15 (m, 2H, Ar*H*), 7.11 (dt, J=7.6, 1.0 Hz, 1H, Ar*H*), 7.01 (d, J=7.9 Hz, 2H, Ar*H*), 6.99 (ddd, J=8.3, 2.7, 1.0 Hz, 1H, Ar*H*) 6.78 (d, J=8.9 Hz, 1H, N*H*), 5.63 (dd, J=3.6, 0.6 Hz, 1H, *H*2), 5.61 (s, 1H, C*H*), 4.80 (dt, J=8.8, 3.9 Hz, 1H, *H*3), 4.68 (d, J=1.1 Hz, 1H, *H*1), 4.53 (dd, J=12.6, 1.3 Hz, 1H, *H*6), 4.24 (dd, J=4.0, 0.9 Hz, 1H, *H*4), 4.21 (dd, J=12.6, 2.0 Hz, 1H, *H*6), 3.68 (s, 3H, OCH$_3$), 3.64 (app. d, J=1.1 Hz, 1H, *H*5), 3.58 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3).

*5.2.5. Methyl 4,6-O-benzylidene-3-deoxy-3-(4-nitrobenzamido)-2-O-toluoyl-β-D-talopyranoside (**13**).* ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J=8.9 Hz, 2H, Ar*H*, aromatic region obscured by traces of residual reagent, which was removed after conversion to **20**), 7.96 (d, J=8.2 Hz, 2H, Ar*H*), 7.77 (d, J=8.9 Hz, 2H, Ar*H*), 7.60–7.55 (m, 2H, Ar*H*), 7.41–7.32 (m, 3H, Ar*H*), 7.07 (d, J=7.9 Hz, 2H, Ar*H*), 6.91 (d, J=8.6 Hz, 1H, N*H*), 5.64 (br d, J=3.5 Hz, 1H, *H*2), 5.60 (s, 1H, C*H*), 4.79 (dt, J=8.5, 3.8 Hz, 1H, *H*3), 4.69 (d, J=1.1 Hz, 1H, *H*1), 4.54 (dd, J=12.6, 1.1 Hz, 1H, *H*6), 4.27 (dd, J=3.8, 0.7 Hz, 1H, *H*4), 4.23 (dd, J=12.6, 2.0 Hz, 1H, *H*6), 3.66 (app. d, J=1.0 Hz, 1H, *H*5), 3.59 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3).

*5.2.6. Methyl 4,6-O-benzylidene-3-deoxy-3-(4-methylbenzamido)-2-O-toluoyl-β-D-talopyranoside (**14**).* ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J=8.2 Hz, 2H, Ar*H*, aromatic region obscured by traces of residual reagent, which was removed after conversion to **21**), 7.62–7.57 (m, 2H, Ar*H*), 7.52 (d, J=8.2 Hz, 2H, Ar*H*), 7.42–7.35 (m, 3H, Ar*H*), 7.15 (d, J=7.9 Hz, 2H, Ar*H*), 7.03 (d, J=7.9 Hz, 2H, Ar*H*), 6.76 (d, J=8.9 Hz, 1H, N*H*), 5.63 (d, J=3.6, 0.7 Hz, 1H, *H*2), 5.60 (s, 1H, C*H*), 4.80 (dt, J=8.9, 3.8 Hz, 1H, *H*3), 4.67 (d, J=1.1 Hz, 1H, *H*1), 4.52 (dd, J=12.6, 1.3 Hz, 1H, *H*6), 4.24 (dd, J=3.9, 0.9 Hz, 1H, *H*4), 4.21 (dd, J=12.6, 2.0 Hz, 1H, *H*6), 3.64 (app. d, J=1.2 Hz, 1H, *H*5), 3.58 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3), 2.34 (s, 3H CH_3).

*5.2.7. Methyl 4,6-O-benzylidene-3-deoxy-3-(3-carboxybenzamido)-2-O-toluoyl-β-D-talopyranoside (**16**).* ^{1}H NMR ($CDCl_3$) δ 8.41 (t, J=1.6 Hz, 1H, Ar*H*, aromatic region obscured by traces of residual reagent, which was removed after conversion to **23**), 8.18 (dt, J=7.7, 1.3 Hz, 1H, Ar*H*), 7.93 (d, J=8.3 Hz, 2H, Ar*H*), 7.82–7.73 (m, 1H, Ar*H*), 7.44 (t, J=7.7 Hz, 1H, Ar*H*), 7.40–7.33 (m, 5H, Ar*H*), 7.00 (d, J=8.0 Hz, 2H, Ar*H*), 6.91 (d, J=8.8 Hz, 1H, N*H*), 5.66 (br d, J=3.5 Hz, 1H, *H*2), 5.62 (s, 1H, C*H*), 4.83 (dt, J=8.7, 3.8 Hz, 1H, *H*3), 4.69 (d, J=1.0 Hz, 1H, *H*1), 4.54 (dd, J=12.6, 1.2 Hz, 1H, *H*6), 4.27 (dd, J=3.8, 0.9 Hz, 1H, *H*4), 4.23 (dd, J=12.5, 2.0 Hz, 1H, *H*6), 3.66 (br s, 1H, *H*5), 3.58 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3).

5.3. Typical procedure for debenzylidenation of amides 17–23

*5.3.1. Methyl 3-deoxy-3-(2-naphthamido)-2-O-toluoyl-β-D-talopyranoside (**22**).* Benzylidenated **15** (30.8 mg, 55.6 mmol) was stirred in HOAc (aq, 67%, 2.4 mL) at 70 °C for 17 h before being concentrated and purified by column chromatography (CH_2Cl_2/MeOH 100:5) to give ester **22** in 76% yield (19.6 mg); ^{1}H NMR (CD_3OD) δ 8.09 (br s, 1H, Ar*H*), 8.04 (d, J=2 Hz, Ar*H*), 7.87–7.81 (m, 2H, Ar*H*), 7.73–7.67 (m, 2H, Ar*H*), 7.56–7.46 (m, 2H, Ar*H*), 7.30 (d, J=8.0 Hz, 2H, Ar*H*), 5.73 (br d, J=3.9 Hz, 1H, *H*2), 4.79 (d, J=1.4 Hz, 1H, *H*1), 4.56 (t, J=3.6 Hz, 1H, *H*3), 3.99–3.89 (m, 3H, *H*4*H*6*H*6), 3.82 (ddd, J=6.7, 5.4, 1.2 Hz, 1H, *H*5), 3.57 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3); ESIMS m/z calcd for $[C_{26}H_{28}NO_7]^+$, 466.1866; found, 466.1858.

*5.3.2. Methyl 3-deoxy-3-(4-trifluoromethylbenzamido)-2-O-toluoyl-β-D-talopyranoside (**17**).* ^{1}H NMR (CD_3OD) δ 8.01 (d, J=8.2 Hz, 2H, Ar*H*), 7.83 (d, J=8.1 Hz, 2H, Ar*H*), 7.70 (d, J=8.2 Hz, 2H, Ar*H*), 7.30 (d, J=8.0 Hz, 2H, Ar*H*), 5.68 (d, J=3.7 Hz, 1H, *H*2), 4.77 (d, J=1.4 Hz, 1H, *H*1), 4.52 (t, J=3.6 Hz, 1H, *H*3), 3.97–3.86 (m, 3H, *H*4*H*6*H*6), 3.79 (ddd, J=6.8, 5.4, 1.3 Hz, 1H, *H*5), 3.56 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3); ESIMS m/z calcd for $[C_{23}H_{25}F_3NO_7]^+$, 484.1583; found, 484.1579.

*5.3.3. Methyl 3-deoxy-3-(4-tert-butylbenzamido)-2-O-toluoyl-β-D-talopyranoside (**18**).* ^{1}H NMR (CD_3OD) δ 8.02 (d, J=8.2 Hz, 2H, Ar*H*), 7.59 (d, J=8.7 Hz, 2H, Ar*H*), 7.42 (d, J=8.6 Hz, 2H, Ar*H*), 7.30 (d, J=8.0 Hz, 2H, Ar*H*), 5.66 (br d, J=3.4 Hz, 1H, *H*2), 4.77 (d, J=1.3 Hz, 1H, *H*1), 4.50 (t, J=3.6 Hz, 1H, *H*3), 3.96–3.86 (m, 3H, *H*4*H*6*H*6), 3.78 (br t, J=5.5 Hz, 1H, *H*5), 3.56 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3), 1.30 (s, 9H, ^{t}Bu); ESIMS m/z calcd for $[C_{26}H_{33}NO_7Na]^+$, 494.2155; found, 494.2161.

*5.3.4. Methyl 3-deoxy-3-(3-methoxybenzamido)-2-O-toluoyl-β-D-talopyranoside (**19**).* ^{1}H NMR (CD_3OD) δ 8.03 (d, J=8.2 Hz, 2H, Ar*H*), 7.33–7.13 (m, 5H, Ar*H*), 7.04–7.00 (m, 1H, Ar*H*), 5.67 (d, J=3.7 Hz, 1H, *H*2), 4.77 (d, J=1.4 Hz, 1H, *H*1), 4.49 (t, J=3.6 Hz, 1H, *H*3), 3.96–3.86 (m, 3H, *H*4*H*6*H*6), 3.79 (ddd, J=1.2, 5.4, 6.6 Hz, 1H, *H*5), 3.67 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 2.42 (s, 3H, CH_3); ESIMS m/z calcd for $[C_{23}H_{28}NO_8]^+$, 446.1815; found, 446.1805.

*5.3.5. Methyl 3-deoxy-3-(4-nitrobenzamido)-2-O-toluoyl-β-D-talopyranoside (**20**).* ^{1}H NMR (CD_3OD) δ 8.22 (d, J=9.0 Hz, 2H, Ar*H*), 8.00 (d, J=8.2 Hz, 2H, Ar*H*), 7.86 (d, J=9.0 Hz, 2H, Ar*H*), 7.29 (d, J=8.0 Hz, 2H, Ar*H*), 5.69 (d, J=3.6 Hz, 1H, *H*2), 4.77 (d, J=1.3 Hz, 1H, *H*1), 4.53 (t, J=3.6 Hz, 1H, *H*3), 3.96–3.86 (m, 3H, *H*4*H*6*H*6), 3.80 (ddd, J=1.2, 5.5, 6.7 Hz, 1H, *H*5), 3.56 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3); ESIMS m/z calcd for $[C_{22}H_{24}N_2O_9Na]^+$, 483.1380; found, 483.1368.

*5.3.6. Methyl 3-deoxy-3-(4-methylbenzamido)-2-O-toluoyl-β-D-talopyranoside (**21**).* ^{1}H NMR (CD_3OD) δ 8.01 (d, J=8.2 Hz, 2H, Ar*H*), 7.54 (d, J=8.2 Hz, 2H, Ar*H*), 7.29 (d, J=7.9 Hz, 2H, Ar*H*), 7.17 (d, J=7.9 Hz, 2H, Ar*H*), 5.66 (br d, J=3.7 Hz, 1H, *H*2), 4.76 (d, J=1.4 Hz,

1H, *H*1), 4.49 (t, *J*=3.6 Hz, 1H, *H*3), 3.96–3.86 (m, 3H, *H*4*H*6*H*6), 3.80 (ddd, *J*=1.2, 5.4, 6.8 Hz, 1H, *H*5), 3.55 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3), 2.34 (s, 3H, CH_3); ESIMS *m*/*z* calcd for $[C_{23}H_{28}NO_7]^+$, 430.1866; found, 430.1860.

*5.3.7. Methyl 3-deoxy-3-(3-carboxybenzamido)-2-O-toluoyl-β-D-talopyranoside (**23**).* ^{1}H NMR (CD_3OD) δ 8.33 (s, 1H, Ar*H*), 8.11 (d, *J*=7.8 Hz, 1H, Ar*H*), 8.01 (d, *J*=8.2 Hz, 2H, Ar*H*), 7.83 (d, *J*=7.8 Hz, 1H, Ar*H*), 7.46 (t, *J*=7.8 Hz, 1H, Ar*H*), 7.28 (d, *J*=8.0 Hz, 2H, Ar*H*), 5.69 (br d, *J*=3.6 Hz, 1H, *H*2), 4.77 (d, *J*=1.3 Hz, 1H, *H*1), 4.52 (t, *J*=3 Hz, 1H, *H*3), 3.96–3.86 (m, 3H, *H*4*H*6*H*6), 3.79 (br t, *J*=6.7 Hz, 1H, *H*5), 3.56 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3); ESIMS *m*/*z* calcd for $[C_{23}H_{26}NO_9]^+$, 460.1608; found, 460.1595.

5.4. Typical procedure for deacylation of amides 24–27

*5.4.1. Methyl 3-deoxy-3-(2-naphthamido)-β-D-talopyranoside (**27**).* NaOMe (1 M, 20 mL) was added to a stirred solution of ester **22** (9.0 mg, 19.3 mmol) in MeOH (1 mL) at rt. After 1.5 h, the reaction was concentrated and purified by column chromatography (CH_2Cl_2/MeOH 100:5 to 100:20 gradient) to give amide **27** in 94% yield (6.3 mg); ^{1}H NMR (CD_3OD) δ 8.46 (s, 1H, Ar*H*), 8.03–7.91 (m, 4H, Ar*H*), 7.64–7.55 (m, 2H, Ar*H*), 4.55 (d, *J*=0.8 Hz, 1H, *H*1), 4.26 (t, *J*=3.1 Hz, 1H, *H*3), 3.98 (br d, *J*=2.9 Hz, 1H, *H*2), 3.93 (br d, *J*=3.1 Hz, 1H, *H*4), 3.85–3.81 (m, 2H, *H*6*H*6), 3.68 (ddd, *J*=1.0, 5.6, 6.7 Hz, 1H, *H*5), 3.62 (s, 3H, OCH_3); ESIMS *m*/*z* calcd for $[C_{18}H_{22}NO_6]^+$, 348.1447; found, 348.1451.

*5.4.2. Methyl 3-deoxy-3-(4-trifluoromethylbenzamido)-β-D-talopyranoside (**24**).* ^{1}H NMR (CD_3OD) δ 8.06 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.81 (d, *J*=8.2 Hz, 2H, Ar*H*), 4.53 (d, *J*=0.9 Hz, 1H, *H*1), 4.21 (t, *J*=3.1 Hz, 1H, *H*3), 3.94 (br d, *J*=2.8 Hz, 1H, *H*2), 3.89 (br d, *J*=3.0 Hz, 1H, *H*4), 3.85–3.79 (m, 2H, *H*6*H*6), 3.65 (br t, *J*=6.7 Hz, 1H, *H*5), 3.61 (s, 3H, OCH_3); ESIMS *m*/*z* calcd for $[C_{15}H_{19}F_3NO_6]^+$, 366.1164; found, 366.1154.

*5.4.3. Methyl 3-deoxy-3-(4-nitrobenzamido)-β-D-talopyranoside (**25**).* ^{1}H NMR (CD_3OD) δ 8.35 (d, *J*=9.0 Hz, 2H, Ar*H*), 8.09 (d, *J*=9.0 Hz, 2H, Ar*H*), 4.53 (d, *J*=1.0 Hz, 1H, *H*1), 4.21 (t, *J*=3.0 Hz, 1H, *H*3), 3.95 (br d, *J*=2.9 Hz, 1H, *H*2), 3.89 (br d, *J*=3.1 Hz, 1H, *H*4), 3.85–3.79 (m, 2H, *H*6*H*6), 3.66 (ddd, *J*=1.0, 5.7, 6.7 Hz, 1H, *H*5), 3.61 (s, 3H, OCH_3); ESIMS *m*/*z* calcd for $[C_{14}H_{18}N_2O_8Na]^+$, 365.0961; found, 365.0963.

*5.4.4. Methyl 3-deoxy-3-(4-methylbenzamido)-β-D-talopyranoside (**26**).* ^{1}H NMR (CD_3OD) δ 7.78 (d, *J*=8.2 Hz, 2H, ArH), 7.31 (d, *J*=7.9 Hz, 2H, ArH), 4.52 (d, *J*=0.9 Hz, 1H, H1), 4.18 (t, *J*=3.1 Hz, 1H, H3), 3.92 (br d, *J*=2.9 Hz, 1H, H2), 3.86 (br d, *J*=3.1 Hz, 1H, *H*4), 3.83–3.79 (m, 2H, *H*6*H*6), 3.64 (br t, *J*=1 Hz, 1H, *H*5), 3.60 (s, 3H, OCH_3), 2.41 (s 3H, CH_3); ESIMS *m*/*z* calcd for $[C_{15}H_{22}NO_6]^+$, 312.1447; found, 312.1461.

*5.4.5. Phenyl 4,6-O-benzylidene-3-O-p-toluenesulfonyl-1-thio-β-D-galactopyranoside (**29**).* Phenyl 4,6-*O*-benzylidene-1-thio-galactoside **28** (1.00 g, 2.77 mmol) was dissolved in pyridine (15 mL) at rt and *p*-toluenesulfonyl chloride (1.59 g, 8.32 mmol) was added in portions over 24 h. Unreacted reagent was quenched by addition of excess H_2O and the reaction was concentrated and purified by column chromatography (toluene/acetone 100:5 to 100:10 to 100:15 gradient) to give tosylate **29** in 38% yield (0.53 g); ^{1}H NMR ($CDCl_3$) δ 7.80 (d, *J*=8.3 Hz, 2H, ArH), 7.66–7.62 (m, 2H, ArH), 7.39–7.19 (m, 5H, Ar*H*), 5.36 (s, 1H, C*H*), 4.61 (dd, *J*=9.5, 3.5 Hz, 1H, *H*3), 4.52 (d, *J*=9.4 Hz, 1H, *H*1), 4.40–4.34 (m, 2H, *H*4+*H*6), 4.00 (dd, *J*=12.4, 1.6 Hz, 1H, *H*6), 3.92 (ddd, *J*=9.4, 9.4, 2.5 Hz, 1H, *H*2), 3.56 (app. d, *J*=1.1 Hz, 1H, *H*5), 2.42 (s, 3H, CH_3), 2.29 (d, *J*=2.6 Hz, 1H, O*H*).

*5.4.6. Phenyl 2,3-anhydro-4,6-O-benzylidene-1-thio-β-D-gulopyranoside (**30**).* Potassium trimethylsilanoate (198 mg, 1.54 mmol) was added to a stirred solution of tosylate **29** (0.53 g, 1.03 mmol) in DMF (5 mL) at rt. After 1 h, the reaction was diluted with DCM (100 mL) and washed with $NaHCO_3$ (satd, aq, 2×100 mL) and brine (100 mL). The organic phase was dried over $MgSO_4$ before being concentrated and purified by column chromatography (toluene/acetone 100:10) to give epoxide **30** in 73% yield (256 mg); ^{1}H NMR ($CDCl_3$) δ 7.76–7.72 (m, 2H, Ar*H*), 7.60–7.56 (m, 2H, Ar*H*), 7.46–7.41 (m, 3H, Ar*H*), 7.25–7.15 (m, 3H, Ar*H*), 5.60 (s, 1H, C*H*), 5.20 (app. s, 1H, *H*1), 4.41 (br d, *J*=12.0 Hz, 1H, *H*6), 4.32 (t, *J*=1.7 Hz, 1H, *H*4), 4.08 (dd, *J*=12.7, 2.0 Hz, 1H, *H*6), 3.53 (d, *J*=3.8 Hz, 1H, *H*2), 3.44 (d, *J*=1.6 Hz, 1H, *H*5), 3.33 (br s, 1H, *H*3).

*5.4.7. Phenyl 4,6-O-benzylidene-1-thio-β-D-idopyranoside (**31**).* Epoxide **30** (100 mg, 292 mmol) and QNO_2 (421 mg, 1.46 mmol) in DMF (3 mL) were stirred in a microwave reactor at 120 °C for 30+20 min. The reaction was concentrated and purified by column chromatography (toluene/acetone 100:10) to give idoside **31** in 56% yield (58.5 mg); ^{1}H NMR ($CDCl_3$) δ 7.53–7.45 (m, 4H, Ar*H*), 7.37–7.22 (m, 6H, Ar*H*), 5.45 (s, 1H, C*H*), 5.29 (app. s, 1H, *H*1), 4.35 (dd, *J*=12.6, 1.2 Hz, 1H, *H*6), 4.14 (t, *J*=2.8 Hz, 1H, *H*3), 3.99 (dd, *J*=12.6, 1.8 Hz, 1H, *H*6), 3.97 (br d, *J*=3.0 Hz, 1H, *H*4), 3.83–3.66 (m, 3H, *H*2*H*5O*H*).

*5.4.8. Phenyl 4,6-O-benzylidene-2-O-toluoyl-1-thio-β-D-idopyranoside (**32**).* *p*-Toluoyl chloride (25 mL, 186 mmol) was added to a stirred solution of idoside **31** (58 mg, 161 mmol) in pyridine (2 mL) at rt. After 30 min, H_2O (×s) was added, the reaction was concentrated and purified by column chromatography (toluene/acetone 100:10) to give toluoate **32** in 88% yield (68 mg); ^{1}H NMR ($CDCl_3$) δ 7.99 (d, *J*=8.2 Hz, 2H, Ar*H*), 7.62–7.53 (m, 2H Ar*H*), 7.44–7.40 (m, 2H, Ar*H*), 7.32–7.23 (m, 5H, Ar*H*), 7.18–7.09 (m, 4H, Ar*H*), 5.50 (s, 1H, C*H*), 5.46 (d, *J*=1.5 Hz, 1H, *H*1), 5.26 (br s, 1H, *H*2), 4.49 (br d, *J*=12.6 Hz, 1H, *H*6), 4.34 (t, *J*=2.6 Hz, 1H, *H*3), 4.11 (dd, *J*=12.6, 1.9 Hz, 1H, *H*6), 3.97 (app. s, 1H, *H*4), 3.85 (app. d, *J*=1.2 Hz, 1H, *H*5), 2.41 (s, 3H, CH_3).

*5.4.9. Phenyl 4,6-O-benzylidene-2-O-toluoyl-1-thio-lyxo-β-D-hexopyranosid-3-ulose (**33**).* Dess–Martin periodinane (93 mg, 219 mmol) was added to a stirred solution of toluoate **32** (68 mg, 146 mmol) in DCM (2 mL) at rt. After 2 h, the reaction was concentrated and purified by column chromatography (toluene/acetone 100:10 to 100:20 gradient) to give crude ketone **33**.

*5.4.10. Phenyl 4,6-O-benzylidene-3-deoxy-3-(3-methoxybenzamido)-2-O-toluoyl-1-thio-β-D-talopyranoside (**34**).* $NaCNBH_3$ (61 mg, 973 mmol) was added to a stirred solution of crude ketone **33** (<146 mmol) and NH_4OAc (600 mg, 7.78 mmol) in MeOH/THF (1:1, 10 mL) and CH(OMe)$_3$ (2 mL) under nitrogen atmosphere and at rt. After 19 h, more $NaCNBH_3$ (61 mg, 973 mmol) was added. After another 3 h, the reaction was concentrated and redissolved in DCM (100 mL) before being washed with $NaHCO_3$ (satd, aq, 75 mL) and brine (2×75 mL). The aqueous phases were extracted with DCM (50 mL) and the pooled organic phases were dried over $MgSO_4$ before being concentrated and purified by column chromatography (DCM/MeOH 100:5 to 100:10) to give intermediate amine. *m*-Anisoyl chloride (23 mL, 162 mmol) followed by lutidine (26 mL, 227 mmol) were immediately added to a stirred solution of the intermediate amine in DCM (1 mL) under nitrogen atmosphere and at rt. After 16 h, more *m*-anisoyl chloride (23 mL, 162 mmol) and lutidine (26 mL, 227 mmol) were added and the reaction stirred another hour before being concentrated and purified by column chromatography (toluene/acetone 100:10 to 100:20 gradient) to give amide **34** in 18% yield (16 mg) from toluoate **32**; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J*=8.2 Hz, 2H, Ar*H*), 7.61–7.55 (m, 4H, Ar*H*), 7.42–7.14 (m, 9H, Ar*H*), 7.09 (d, *J*=7.8 Hz, 2H, Ar*H*), 6.99 (ddd, *J*=8.2, 2.6, 1.2 Hz, 1H, Ar*H*), 6.79 (d, *J*=7.8 Hz, 1H, N*H*), 5.86 (dd, *J*=3.6, 0.9 Hz, 1H, *H*2), 5.57 (s, 1H, C*H*), 5.11 (d, *J*=1.3 Hz, 1H, *H*1), 4.79 (dt, *J*=7.8, 3.8 Hz, 1H, *H*3), 4.53 (dd, *J*=12.6, 1.2 Hz, 1H, *H*6), 4.25 (br d,

J=3.8 Hz, 1H, $H4$), 4.17 (dd, J=12.6, 1.9 Hz, 1H, $H6$), 3.68 (s, 4H, $H5$+OCH_3), 2.41 (s, 3H, CH_3).

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Supplementary data

NMR-spectra can be found in the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.098.

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