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Preparation of new type of organocatalysts having a carbohydrate scaffold ☆

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ABSTRACT

The synthesis of nine new, bifunctional organocatalysts having carbohydrate scaffolds has been accomplished. In these catalysts both of the catalytic amino and thiourea functions are directly attached to a carbohydrate core. The activities of the newly prepared catalysts were tested in a Michael addition.

1. Introduction

In recent years, organocatalysis, the acceleration of various chemical reactions by catalytic amounts of organic molecules, emerged as one of the rapidly developing areas of organic chemistry.[1] With the aid of organocatalysis a large number of chemical reactions could then be performed in stereoselective manner. Particularly great attention has been paid to the development of new, efficient catalysts. A special class of these catalysts is the so called bifunctional organocatalysts in which H-bond donor and Lewis base functionalities are combined in a single asymmetric molecular scaffold. Several different bifunctional catalysts have been designed, synthesized, and tested. Most of these molecules have a combination of thiourea and amine groups as catalytic functionalities which are presented on a single chemical entity. The very first example of these catalysts has been described by Takemoto[2] in this molecule the catalytic centers are connected to a cyclohexane scaffold (compound **A**, Fig. 1). Later some different chiral scaffolds such as binaphtyl[3] or cinchona alkaloids[4] (compounds **B** and **C**, Fig. 1) were investigated and the catalysts based on these scaffolds showed promising results in asymmetric synthesis, particularly, in catalyzing Michael and aza-Henry reactions.

To date only a limited number of scaffolds have been used to synthesize bifunctional organocatalysts. Monosaccharides as commercially available, inexpensive molecules of diverse chirality can be considered as obvious candidates for chiral scaffolds. Organocatalysts based on a D-glucosamine scaffold carrying urea and imine as catalytic functionalities were described by Kunz in 2007.[5] Enantioselective Strecker and Mannich reactions were performed using these catalysts.[5]

Thiourea–amine type bifunctional organocatalysts containing a monosaccharide unit were prepared and their catalytic activities were investigated recently.[6] In these cases, the carbohydrate moiety was located on the periphery of the catalyst molecule and not in-between the two catalytic centers (compounds **D** and **E**, Fig. 2). To our knowledge there is only one example in the literature where a monosaccharide residue was used as a scaffold to connect thiourea and amine functionalities thereby defining the selectivity of the catalyzed reaction (compound **F**, Fig. 2).[7] In this study the use of urea derivatives, however, provided higher yields and selectivity than the corresponding thiourea derivative.[7] Up to now, there are no examples of bifunctional thiourea-amine organocatalysts where the core scaffold is a monosaccharide unit and the use of the catalyst results in high yield and high enantioselectivity catalyzing a chemical reaction.

We have initiated the preparation of new—bifunctional—thiourea–amine catalysts starting from D-glucose. In these molecules the two catalytic centers are connected with a carbohydrate residue. Using these catalysts the enantioselectivity of the catalyzed reaction will be influenced only by the carbohydrate moiety. The possible effect arising from carbohydrate chirality

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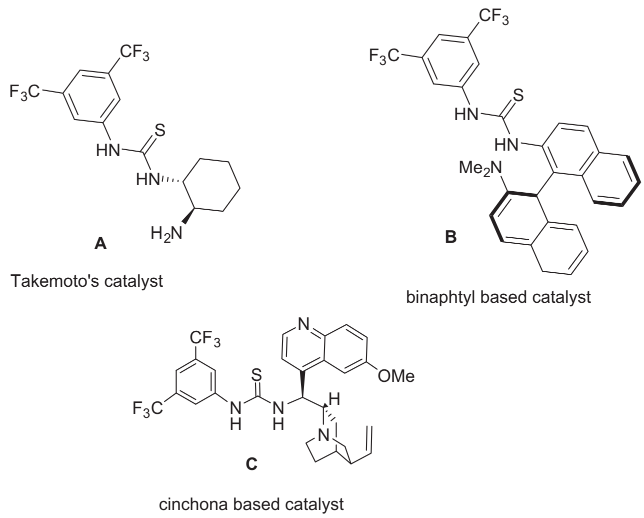


Figure 1. Representative examples of bifunctional organocatalysts.

was taken into consideration in the design, by placing the catalytic groups at various positions of the carbohydrate scaffold. Thus the synthesis of molecules having the amino and thioureido groups in positions 4 and 6 (**G** and **H**, Fig. 3), or in positions 2 and 3 (**I**, Fig. 3), respectively, was planned. The catalytic groups are distanced by three carbon–carbon bonds in the first case, whereas they are separated by two C–C bonds in the latter. In the case of **G** and **H**, the synthetic route was designed to afford both the 4-amino-6-thioureido (**G**) and the 6-amino-4-thioureido (**H**) derivatives from the same starting material.

2. Results and discussion

For the preparation of the targeted catalysts having the catalytic groups in the 4 and 6 positions, methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside[8] (**1**, Scheme 1) was selected as starting material which is easily available from commercial methyl α-D-glucopyranoside in a few steps in high yields.

The synthesis of the 4-amino-6-thioureido type compounds started with the preparation of the 6-azido derivative (**2**). Reaction of compound **1** with sodium azide in DMF at elevated temperature resulted in the formation of the 6-azido derivative (→**2**, Scheme 1) in almost quantitative yield. The benzoate protecting group from compound **2** was removed with NaOMe in MeOH affording derivative **3** in high yield. 4-Amino derivatives were prepared by S_N2 replacement with primary amines via the 4-*O*-triflate in a one-pot manner. Treatment of **3** with triflic anhydride in CH_2Cl_2 in the presence of pyridine at 0 °C afforded the crude 4-*O*-triflate, which was reacted directly with cyclohexylamine or benzylamine in the solvent mixture of CH_2Cl_2/DMF to yield the 4-cyclohexylamino (**4**) and 4-benzylamino (**5**) derivatives, respectively. The

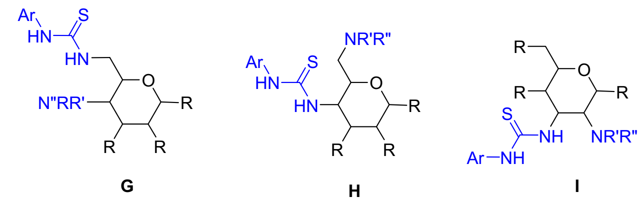
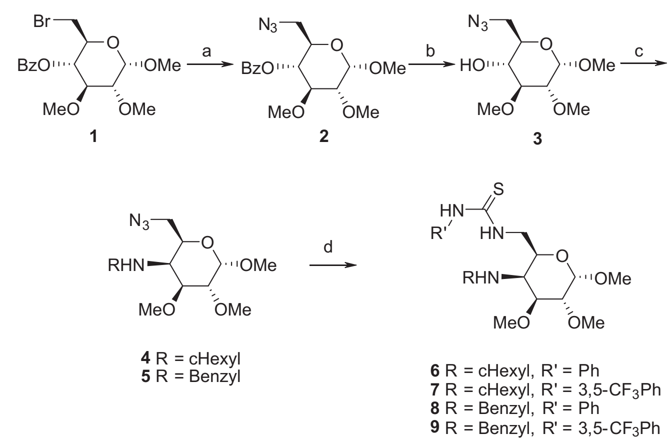


Figure 3. General structures of the targeted organocatalysts.



Scheme 1. Reagents and conditions: (a) NaN_3, DMF, 70 °C, 6 h, 94%; (b) NaOMe, MeOH, rt, 1 h, 80%; (c) (i) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 2 h, (ii) amine, DMF, 45 °C, 10 h, 50–70%; (d) (i) propanedithiol, MeOH, rt, 48 h (**6** and **7**), or PPh_3, H_2O, THF, 80 °C, (**8** and **9**), (ii) isothiocyanate, MeOH, rt, 4 h, 30–50%.

azido function of compound **4** was reduced to amine with propanedithiol in methanol[9] and the 6-amino derivative was reacted with phenyl isothiocyanate (**4** → **6**) or 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**4** → **7**) affording the bifunctional organocatalyst candidates.

For the reduction of azido function of compound **5**, the use of triphenylphosphine was found more advantageous, as reduction with propanedithiol resulted in impurities which were difficult to separate from the amino derivative. The amino derivative of compound **5** was reacted with phenyl isothiocyanate or 3,5-bis(trifluoromethyl)phenyl isothiocyanate affording derivatives **8** and **9**, respectively.

For the preparation of the 6-amino-4-thioureido type target molecule nucleophilic substitution of the bromo function of compound **1** with piperidine was performed to afford **10** in high yield (Scheme 2). This reaction was significantly slower than the substitution of **1** with sodium azide. The removal of the benzoate protecting group from **10** by Zemplén's method required elevated temperature, but afforded compound **11** in good yield. The azido function was introduced at position **4** by S_N2 reaction via a triflate intermediate. Treatment of **11** with Tf_2O, as described for **4**, followed by reaction of the crude with sodium azide in DMF

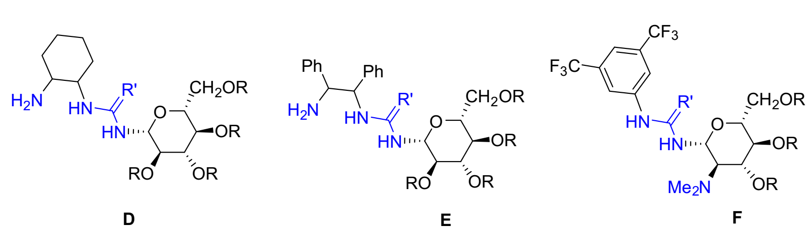
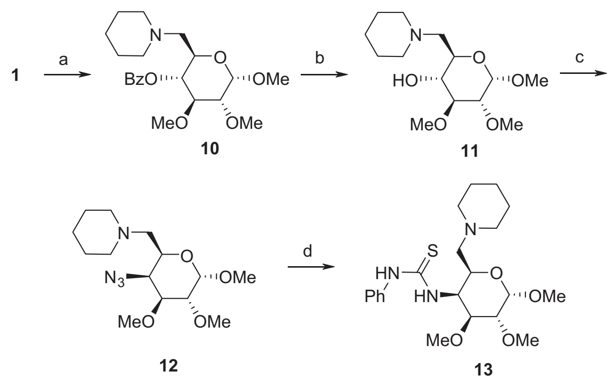


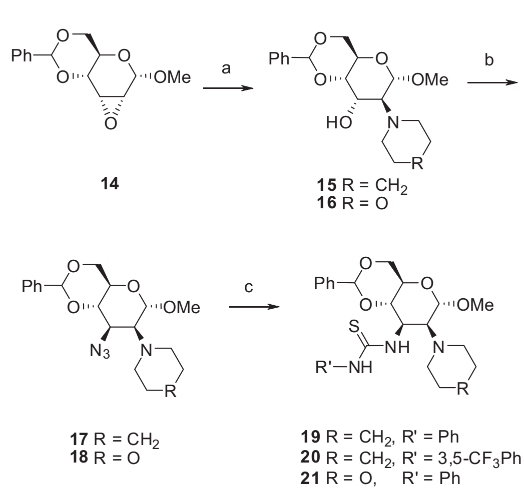
Figure 2. Monosaccharide-containing bifunctional organocatalysts.



Scheme 2. Reagents and conditions: (a) piperidine, DMF, 70 °C, 50 h, 90%; (b) NaOMe, MeOH, reflux, 2 h, 85%; (c) (i) Tf_2O, pyridine, DCM, 0 °C, 2 h, (ii) NaN_3, DMF, 45 °C, 72 h, 40%; (d) (i) propanedithiol, MeOH, rt, 48 h, (ii) phenyl isothiocyanate, MeOH, rt, 8 h, 69%.

afforded the 4-azido *galacto* epimer (**11** → **12**). The stereochemistry was proven by the two small coupling constants of the H-4 in the ^{1}H NMR spectrum ($J_{3,4}$ 2.3 Hz $J_{4,5}$ <1 Hz,) while the presence on the azido group was indicated by the upfield shift of the C-4 signal in the ^{13}C NMR spectrum. The transformation of the azido function into thiourea derivative was performed as in the case of compound **6**. Treatment of **12** with propanedithiol resulted in the formation of the 4-amino intermediate which was reacted with phenyl isothiocyanate to form compound **13** as a catalyst candidate.

The preparation of the 2-amino-3-thioureido derivatives started from the *allo*-epoxide **14**[10] (Scheme 3) as starting material which is easily available from commercial methyl α-D-glucopyranoside in a few steps in high yields. The epoxide was opened with piperidine or with morpholine according to a literature procedure[11] affording the *altro* derivatives **15** and **16** in high yields. The preparation of the 3-azido derivatives was accomplished by using Mistunobu conditions as only low yields were obtained in preliminary trials to introduce the azide by the displacement of the 3-*O*-triflate intermediate (data not shown). Compounds **15** and **16** were treated with diisopropyl azodicarboxylate and triphenylphosphine then with diphenylphosphoryl azide[12] to form the 3-azido derivatives **17** and **18**, respectively. The azido functions of compounds **17** and **18** were reduced with triphenylphosphine, the resulting 3-amino derivatives were subsequently treated with phenyl



Scheme 3. Reagents and conditions: (a) piperidine or morpholine, $LiClO_4$, MeCN, 90 °C, 24 h, 80–90%; (b) (i) PPh_3, DIAD, THF, 0 °C, (ii) DPPA, THF, rt, 24 h, 60–80%; (c) (i) PPh_3, THF, H_2O, 80 °C, (ii) isothiocyanate, MeOH, rt, 8 h, 60–80%.

isothiocyanate or 3,5-bis(trifluoromethyl)phenyl isothiocyanate affording the target compounds (**17** → **19**, **17** → **20**, **18** → **21,** and **18** → **22**).

The catalytic activity of the prepared new, monosaccharide-based bifunctional organocatalysts was tested on the Michael addition of acetylacetone to β-nitrostyrene (→**23**, Scheme 4). This reaction is commonly used as test in evaluating newly developed organocatalysts.[13] Based on preliminary experiments dichloromethane was selected as solvent for the reaction. The use of other solvents such as toluene, THF, MeCN, or diethyl ether resulted in much longer reaction times (data not shown). The stereochemistry of the products was determined by comparison of their optical rotation values (Table 1) with literature references[13b] together with the comparison of the chiral HPLC retention times with literature references.[13c,d] The enantiomeric excess was determined by chiral HPLC.

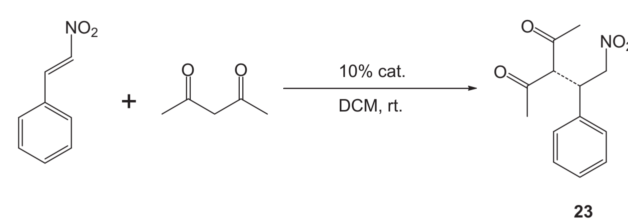
The catalytic activity of the synthesized compounds is summarized in Table 1. Only those compounds which have secondary amine groups were able to promote the reaction to give good yields (Table 1, entries 1, 2, and 3). Tertiary amine-containing derivatives afforded very low yield or no reaction at all (entries 4, 5, and 6). The active catalysts favored the formation of the product having the S configuration, the enantioselectivity, however, was low. Further examination of the catalytic activity of prepared compounds on different reactions is in progress, and will be reported in due course.

In conclusion, the synthesis of a new family of monosaccharide-based bifunctional organocatalysts has been achieved. Thiourea and amine functionalities were used as catalytic centers connected by a monosaccharide unit thereby replacing the commonly employed cyclohexane unit. The activities of the newly prepared catalysts were tested on a model reaction, where some of the compounds afforded high yields, although with low enantioselectivity.

3. Experimental

3.1. General

Commercially available starting materials were used without further purification. Solvents were dried according to standard



Scheme 4. Reagents and conditions: β-nitrostyrene, 1.1 equiv acetylacetone, 10 mol % catalyst, CH_2Cl_2, rt, 24 h.

Table 1
Summary of the catalytic activity of selected catalyst candidates

Entry	Catalyst	Yield[a]	ee%	$[\alpha]_D^{25}$ Values
1	6	70%	18.7%	13.9 (*c* 0.5, $CHCl_3$)
2	7	78%	14.1%	8.0 (*c* 0.5, $CHCl_3$)
3	9	50%	12.9%	7.8 (*c* 0.65, $CHCl_3$)
4	19	<5%	n.d.	n.d.
5	20	None	—	—
6	21	None	—	—

n.d.: not determined.
[a] Reaction times were 24 h in all cases. Without the use of catalyst no product formation was observed.

procedures. Melting points (uncorrected) were determined on a Griffin apparatus. Optical rotations were measured with a Jasco-Optical activity AA-10R polarimeter. NMR spectra were recorded on a Varian Gemini 2000 (200 MHz for ^{1}H and 50 MHz for ^{13}C) and on a Varian Unity-Inova (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer in $CDCl_3$ as solvent. All chemical shifts are quoted in ppm downfield from the characteristic signals (^{1}H: 0.00 ppm (TMS), ^{13}C: 77.00 ppm ($CDCl_3$)). Kieselgel 60 (E. Merck, Darmstadt, Germany) was used for column chromatography and DC-Alufolien Kieselgel 60 F_{256} plates were used for TLC. MS spectra were recorded on an Applied Biosystems 3200 QTRap spectrometer. Enantiomeric excesses were determined on a Waters 600 HPLC instrument. (Diacel Chiralpack AD column, hexane/*i*-propanol 80:20, flow rate: 1 mL/min, λ = 210 nm).

3.2. Methyl 6-azido-4-*O*-benzoyl-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (2)

NaN_3 (260 mg, 4.0 mmol) was added to a solution of **1** (780 mg, 2.0 mmol) in dry DMF (10 mL) and the mixture was stirred for 6 h at 70 °C. The mixture was allowed to cool to rt then it was diluted with EtOAc (100 mL) and washed with water (3 × 50 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated, and the product was obtained after column chromatography (toluene–acetone; 95:5) as a syrup (660 mg, 94%). $[\alpha]_D^{25}$ 52.5 (*c* 0.69, $CHCl_3$); ^{1}H NMR: δ 8.06, 7.60, and 7.46 (m, 5H, aromatic), 5.09 (dd, 1H, $J_{3,4}$ 9.4 Hz, $J_{4,5}$ 9.9 Hz, H-4), 4.93 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.99 (ddd, 1H, $J_{5,6}$ 5.4 and 2.6 Hz, H-5), 3.74 (dd, 1H, $J_{2,3}$ 9.2 Hz, H-3), 3.56, 3.52 and 3.48 (each s, each 3H, 3 OMe), 3.38 (m, 2H, H-2 and H-6a), 3.27 (dd, 1H, J_{gem} 13.3 Hz, H-6b); ^{13}C NMR: δ 165.4 (C=O), 133.4, 129.8, 129.3, and 128.5 (aromatic), 97.6 (C-1), 81.3 (C-2), 80.7 (C-3), 71.8 (C-4), 69.2 (C-5), 61.0, 59.3 and 55.5 (3 OMe), 51.3 (C-6); MS: Calcd for: $C_{16}H_{21}N_3O_6$ 351, found: 352 $[M+H]^+$, 374 $[M+Na]^+$, 725 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{21}N_3O_6$: C, 54.69; H, 6.02. Found: C, 54.82; H, 6.05.

3.3. Methyl 6-azido-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (3)

NaOMe (50 mg) was added to a solution of **2** (660 mg, 1.88 mmol) in dry MeOH (20 mL). The mixture was stirred for 1 h at rt. Then the mixture was neutralized with Amberlite IR-120 (H^+). The resin was filtered off and washed with MeOH. The filtrate was concentrated and the product was isolated by column chromatography (toluene–acetone; 4:1). **3** (370 mg, 80%) was obtained as a colorless syrup: $[\alpha]_D^{25}$ 117.0 (*c* 0.58, $CHCl_3$);^{1}H NMR: δ 4.81 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.70 (m, 1H, H-5), 3.60, 3.46 and 3.41 (each s, each 3H, 3 OMe), 3.50 (dd, 1H, J_{gem} 13.2 Hz, H-6a), 3.44–3.30 (m, 3H, H-3, H-4 and H-6b) 3.20 (dd, 1H, $J_{2,3}$ 9.2 Hz, H-2) 2.18 (br s, 1H, 4-OH); ^{13}C NMR: δ 97.3 (C-1), 82.6 (C-3), 81.7 (C-2), 70.4 and 70.3 (C-4 and C-5), 61.1, 58.4 and 55.3 (3 OMe), 51.4 (C-6); MS: Calcd for: $C_9H_{17}N_3O_5$ 247, found: 270 $[M+Na]^+$, 517 $[2M+Na]^+$. Anal. Calcd for $C_9H_{17}N_3O_5$: C, 43.72; H, 6.93. Found: C, 43.67; H, 6.95.

3.4. Methyl 6-azido-4-cyclohexylamino-4,6-dideoxy-2,3-di-*O*-methyl-α-D-galactopyranoside (4)

A solution of Tf_2O (1.63 mL, 9.7 mmol) in CH_2Cl_2 (5 mL) was added to a solution of **3** (1.61 g, 6.7 mmol) in a mixture of pyridine (3.2 mL) and CH_2Cl_2 (20 mL) at 0 °C, then the mixture was stirred for 2 h at 0 °C. TLC (hexane–EtOAc; 1:1) showed the formation of a new apolar derivative. Cyclohexylamine (6 mL) in DMF (20 mL) was added to the mixture and stirring was continued for 10 h at 45 °C. Then the mixture was concentrated and the residue was purified by column chromatography (hexane–EtOAc; 1:1) to provide **4** (1.1 g, 51%) as a pale yellow syrup. $[\alpha]_D^{25}$ 136.4 (*c* 0.64, $CHCl_3$); ^{1}H NMR: δ 4.86 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.78 (m, 1H, H-5), 3.60 (dd, 1H, J_{gem} 12.2 Hz, H-6a), 3.51 (dd, 1H, $J_{2,3}$ 9.5 Hz, $J_{3,4}$ 3.6 Hz, H-3), 3.44, 3.42, and 3.41 (each s, each 3H, 3 OMe), 3.35 (dd, 1H, H-2), 3.16 (dd, 1H, H-6b) 3.08 (dd, 1H, $J_{4,5}$ ~1 Hz, H-4), 2.25 (m, 1H, cyclohexyl C*H*), 1.80–1.50 and 1.20–0.70 (m, 10 H, cyclohexyl CH_2); ^{13}C NMR: δ 97.3 (C-1), 79.1 (C-3), 77.1 (C-2), 70.3 (C-5), 58.6, 57.8 and 55.2 (3 OMe), 56.8 (cyclohexyl *C*H) 53.7 (C-4), 52.2 (C-6), 34.5, 33.6, 25.8, 25.2, 25.0 (5 cyclohexyl *C*H_2); MS: Calcd for: $C_{15}H_{28}N_4O_4$ 328, found: 329 $[M+H]^+$; HRMS: $[M+H]^+$ calcd for 329.2189, found: 329.2191.

3.5. Methyl 6-azido-4-benzylamino-4,6-dideoxy-2,3-di-*O*-methyl-α-D-galactopyranoside (5)

Compound **3** (1.61 g, 6.7 mmol) was converted into the 4-*O*-triflate intermediate as described for compound **4**. A solution of benzylamine (6 mL) in DMF (20 mL) was added to the triflate intermediate and the mixture was stirred for 10 h at 45 °C. Then the mixture was concentrated and the residue was purified by column chromatography (hexane–EtOAc; 1:1) to give 5 (1.67 g, 76%) as a pale yellow syrup: $[\alpha]_D^{25}$ 117.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR: δ 7.40–7.20 (m, 5H, aromatic), 4.95 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 3.85 (m, 3H, H-5 and benzyl CH_2), 3.70 and 3.22 (each dd, 2H, $J_{5,6}$ 8.8 and 4.2 Hz, J_{gem} 12.5 Hz, H-6a), 3.60 (dd, 1H, $J_{2,3}$ 9.9 Hz, $J_{3,4}$ 4.2 Hz, H-3), 3.48, 3.44 and 3.28 (each s, each 3H, 3 OMe), 3.43 (dd, 1H, H-2), 3.10 (dd, 1H, $J_{4,5}$ 1.3 Hz, H-4); ^{13}C NMR: δ 140.1, 128.3, and 127.1 (aromatic), 97.5 (C-1), 79.4 (C-3), 77.1 (C-2), 70.2 (C-5), 58.6, 57.4 and 55.2 (3 OMe), 55.4 (C-4), 54.4 (benzyl *C*H_2), 52.3 (C-6); MS: Calcd for: $C_{16}H_{24}N_4O_4$ 336, found: 337 $[M+H]^+$. Anal. Calcd for $C_{16}H_{24}N_4O_4$: C, 57.13; H, 7.19. Found: C, 57.07; H, 7.18.

3.6. Methyl 4-cyclohexylamino-4,6-dideoxy-2,3-di-*O*-methyl-6-(*N′*-phenyl)thioureido-α-D-galactopyranoside (6)

Propanedithiol (2.0 mL) was added to a solution of **4** (0.8 g, 2.4 mmol) in MeOH (20 mL) at rt and the mixture was stirred for 48 h at rt. When TLC (hexane–EtOAc, 1:1) showed the formation of the 6-amino derivative the mixture was filtered, the filtrate was evaporated, and the residue was purified by column chromatography (CH_2Cl_2–MeOH–water; 8:5:1) to afford the amino derivative (0.65 g). Phenyl isothiocyanate (400 μL) was added to a solution of the amino derivative (650 mg) in MeOH (10 mL) at rt. The mixture was stirred for 4 h then concentrated. After column chromatography (CH_2Cl_2–MeOH–water; 8:5:1) of the residue a white solid was obtained, which was recrystallized from EtOAc to yield **6** (450 mg, 42%, over two steps): mp 160–162 °C; $[\alpha]_D^{25}$ 84.7 (*c* 0.54, $CHCl_3$); ^{1}H NMR: δ 8.36 (br s, 1H, NH), 7.42–7.20 (m, 5H, aromatic), 4.80 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.32 (br s, 1H, H-6a), 3.86 (m, 1H, H-5), 3.57 (dd, 1H, $J_{2,3}$ 10.2 Hz, $J_{3,4}$ 4.7 Hz, H-3), 3.48 (m, 1H, H-6b), 3.46, 3.42, and 3.20 (each s, each 3H, 3 OMe), 3.30 (dd, 1H, H-2), 3.14 (dd, 1H, H-4), 2.28 (m, 1H, cyclohexyl C*H*), 1.80–1.50 and 1.20–0.70 (m, 10H, cyclohexyl CH_2); ^{13}C NMR: δ 180.0 (C=S), 136.3, 129.8, 126.8, and 125.0 (aromatic), 97.4 (C-1), 79.0 (C-3), 77.1 (C-2), 68.0 (C-5), 58.5, 58.0 and 54.9 (3 OMe), 56.9 (cyclohexyl *C*H) 54.5 (C-4), 47.2 (C-6), 34.0, 33.3, 25.7, 25.0, 24.9 (5 cyclohexyl *C*H_2); MS: Calcd for: $C_{22}H_{35}N_3O_4S$ 437, found: 438 $[M+H]^+$. Anal. Calcd for $C_{22}H_{35}N_3O_4S$: C, 60.38; H, 8.06. Found: C, 60.42; H, 8.04.

3.7. Methyl 4-cyclohexylamino-4,6-dideoxy-2,3-di-*O*-methyl-6-(*N′*-3,5-bis(trifluoromethyl)phenyl)thioureido-α-D-galactopyranoside (7)

Compound **4** (0.8 g, 2.4 mmol) was converted into the 6-amino derivative as described for compound **6**. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (400 μL) was added to a solution of the 6-amino derivative (0.65 g) in MeOH (10 mL) at rt. The mixture was stirred for 4 h then concentrated and the product was isolated after column chromatography (hexane–EtOAc; 1:2) as a white solid. The solid was recrystallized from EtOAc to yield **7** (530 mg, 35%, over two steps): mp 189–191 °C; $[\alpha]_D^{25}$ 39.7 (*c* 0.51, $CHCl_3$); ^{1}H NMR: δ 10.18 (br s, 1H, 6-NH), 8.95 (br s, 1H, NH), 7.84 (s, 2H, aromatic) 7.68 (s, 1H, aromatic), 4.95 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.40 (m, 1H, H-6a), 3.96 (m, 1H, H-5), 3.65 (dd, 1H, $J_{2,3}$ 10.4 Hz, $J_{3,4}$ 4.7 Hz, H-3), 3.55, 3.46 and 3.44 (each s, each 3H, 3 OMe), 3.45 (m, 1H, H-6b), 3.28 (dd, 1H, H-2), 3.22 (dd, 1H, H-4), 2.37 (m, 1H, cyclohexyl C*H*), 1.60–1.44 and 1.20–0.50 (m, 10H, cyclohexyl CH_2); ^{13}C NMR: δ 178.8 (C=S), 139.5 (aromatic quaterner), 132.8 (q, 2C, $^2J_{C,F}$ 33 Hz, C-3″ and C-5″), 122.9 (q, 2C, $^1J_{C,F}$ 271 Hz, 2CF_3), 122.8 (m, 2C, C-2″ and C-6″), 118.4 (m, 1 C, C-4″), 97.7 (C-1), 79.4 (C-3), 77.2 (C-2), 65.5 (C-5), 58.7, 58.6 and 55.5 (3 OMe), 57.0 (cyclohexyl *C*H) 54.3 (C-4), 49.3 (C-6), 33.2, 32.8, 25.5, 24.8, 24.6 (5 cyclohexyl *C*H_2); MS: Calcd for: $C_{24}H_{33}F_6N_3O_4S$ 573, found: 574 [M+H]$^+$. Anal. Calcd for $C_{24}H_{33}F_6N_3O_4S$: C, 50.25; H, 5.80. Found: C, 50.31; H, 5.82.

3.8. Methyl 4-benzylamino-4,6-dideoxy-2,3-di-*O*-methyl-6-(*N*′-phenyl)thioureido-α-D-galactopyranoside (8)

Triphenylphosphine (1.2 g, 4.6 mmol) was added to a solution of **5** (1.0 g, 3.0 mmol) in THF (20 mL) at rt and the mixture was stirred for 2 h at 80 °C. When TLC (hexane–EtOAc; 1:1) showed the absence of the starting material water (2 mL) was added to the mixture and the stirring was continued for 4 h at 80 °C. The mixture was concentrated, the residue was purified by column chromatography (CH_2Cl_2–MeOH–water 8:5:1) affording the 6-amino derivative (0.7 g). Phenyl isothiocyanate (225 μL) was added to a solution the 6-amino-derivative (485 mg) in MeOH (10 mL) at rt. The mixture was stirred for 24 h then concentrated and the product was obtained after column chromatography (CH_2Cl_2–MeOH–water 8:5:1) as a white solid. The solid was recrystallized from CH_2Cl_2/hexane to yield **8** (281 mg, 31%, over two steps) as white crystals: mp 100–102 °C; $[\alpha]_D^{25}$ 116.9 (*c* 0.65, $CHCl_3$); ^{1}H NMR: δ 8.18 (s, 1H, N*H*Ph), 7.40–7.18 (m, 10H, aromatic), 6.92 (d, 1H, 6-N*H*), 4.78 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.34 (br s, 1H, H-6a), 3.89 (m, 1H, H-5), 3.80 (ABq, 2H, benzyl CH_2), 3.68 (m, 1H, H-6b), 3.59 (dd, 1H, $J_{2,3}$ 10.3 Hz, $J_{3,4}$ 3.6 Hz, H-3), 3.44, 3.25 and 3.17 (each s, each 3H, 3 OMe), 3.35 (dd, 1H, H-2), 3.13 (dd, 1H, H-4), 1.66 (br s, 1H, 4-NH); ^{13}C NMR: δ 180.4 (C=S), 139.7, 136.1, 129.9, 128.4, 127.1 and 125.2 (aromatic), 97.6 (C-1), 79.0 (C-3), 77.0 (C-2), 68.6 (C-5), 58.7, 57.4 and 55.0 (3 OMe), 56.2 (C-4), 54.9 (benzyl *C*H_2), 47.1 (C-6); MS: Calcd for: $C_{23}H_{31}N_3O_4S$ 445, found: 446 [M+H]$^+$. Anal. Calcd for $C_{23}H_{31}N_3O_4S$: C, 62.00; H, 7.01. Found: C, 62.07; H, 7.02.

3.9. Methyl 4-benzylamino-4,6-dideoxy-2,3-di-*O*-methyl-6-(*N*′-3,5-bis(trifluoromethyl)phenyl)thioureido-α-D-galactopyranoside (9)

Compound **5** (1.0 g 3.0 mmol) was converted into the 6-amino derivative as described for **8**. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (350 μL) was added to a solution of the 6-amino derivative (497 mg) in MeOH (10 mL) at rt. The mixture was stirred for 10 min, during this time a light brown precipitate was formed. The solid was filtered and was purified by recrystallization from EtOAc/hexane to afford **9** (868 mg, 70%, over two steps) as white crystals: mp 180–182 °C; $[\alpha]_D^{25}$ 69.9 (*c* 0.89, $CHCl_3$); ^{1}H NMR: δ 9.28 (br s, 1H, NH), 8.66 (br s, 1H, NH), 7.50–7.40 (m, 8H, aromatic) 4.90 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.40 (m, 1H, H-6a), 4.00 (m, 1H, H-5), 3.84 and 3.55 (each m, 2H, benzyl CH_2), 3.70 (dd, 1H, $J_{2,3}$ 10.2 Hz, $J_{3,4}$ 4.7 Hz, H-3), 3.65 (m, 1H, H-6b), 3.51, 3.41 and 3.40 (each s, each 3H, 3 OMe), 3.34 (dd, 1H, H-2), 3.22 (dd, 1H, H-4), 2.00 (br s, 1H, 4-NH); ^{13}C NMR: δ 179.6 (C=S), 139.5 (aromatic quaterner), 132.8 (C-3″ and C-5″), 129.2, 128.8, 128.1, and 127.6 (aromatic), 123.2 (q, 2C, $^1J_{C,F}$ 271 Hz, 2CF_3), 121.4 (m, 2C, C-2″ and C-6″), 114.9 (m, 1 C, C-4″), 98.0 (C-1), 79.1 (C-3), 77.9 (C-2), 66.1 (C-5), 59.4 (C-4), 59.0, 58.4 and 55.8 (3 OMe), 55.7 (benzyl *C*H_2), 49.1 (C-6); MS: Calcd for: $C_{25}H_{29}F_6N_3O_4S$ 581, found: 582 [M+H]$^+$. Anal. Calcd for $C_{25}H_{29}F_6N_3O_4S$: C, 51.63; H, 5.03. Found: C, 51.51; H, 5.00.

3.10. Methyl 4-*O*-benzoyl-6-deoxy-2,3-di-*O*-methyl-6-piperidino-α-D-glucopyranoside (10)

Piperidine (720 μL, 7.3 mmol) was added to a solution of **1** (1.12 g, 2.88 mmol) in dry DMF (5 mL) and the mixture was stirred for 50 h at 70 °C. Then the mixture was allowed to cool to rt, it was diluted with toluene (100 mL) and washed with water (2 × 30 mL), the organic layer was dried over $MgSO_4$, filtered, and concentrated. Column chromatography (toluene–acetone; 3:1) of the residue afforded **10** (1.01 g, 90%) as a syrup: $[\alpha]_D^{25}$ 80.2 (*c* 0.63, $CHCl_3$); ^{1}H NMR: δ 8.05, 7.55 and 7.42 (m, 5H, aromatic), 5.00 (dd, 1H, $J_{3,4}$ 9.4 Hz, $J_{4,5}$ 9.9 Hz, H-4), 4.86 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.03 (m, 1H, H-5), 3.66 (dd, 1H, $J_{2,3}$ 9.4 Hz, H-3), 3.51, 3.46 and 3.43 (each s, each 3H, 3 OMe), 3.31 (dd, 1H, H-2), 2.50 and 2.36 (each dd, 2H, J_{gem} 13.4 Hz, H-6), 2.33, 1.46 and 1.30 (each m, 10H, 5 piperidine CH_2); ^{13}C NMR: δ 165.5 (C=O), 133.1, 129.7 and 128.3 (aromatic), 97.5 (C-1), 81.4 (C-2), 81.0 (C-3), 73.2 (C-4), 66.9 (C-5), 60.8, 59.2 and 55.5 (3 OMe), 60.1 (C-6), 55.1, 25.7 and 24.1 (5 piperidine CH_2); MS: Calcd for: $C_{21}H_{31}NO_6$ 393, found: 394 [M+H]$^+$. Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94. Found: C, 64.03; H, 7.92.

3.11. Methyl 6-deoxy-2,3-di-*O*-methyl-6-piperidino-α-D-glucopyranoside (11)

NaOMe (50 mg) was added to a solution of **10** (1.0 g, 2.54 mmol) in dry MeOH (20 mL) at rt, then the mixture was stirred for 2 h at reflux. The mixture was concentrated and the residue was purified by column chromatography (CH_2Cl_2–MeOH; 95:5 → 8:2) to give **11** (618 mg, 85%) as a colorless syrup: $[\alpha]_D^{25}$ 73.4 (*c* 0.63, $CHCl_3$); ^{1}H NMR: δ 4.68 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.60 (m, 1H, H-5), 3.56, 3.42 and 3.32 (each s, each 3H, 3 OMe), 3.40 (m, 2H, H-3 and H-4), 3.10 (dd, 1H, H-2), 2.60 (m, 2H, J_{gem} 12.3 Hz, H-6), 2.55, 2.30, 1.50 and 1.33 (each m, 10 H, 5 piperidine CH_2); ^{13}C NMR: δ 97.5 (C-1), 82.0 (C-3), 81.0 (C-2), 71.1 (C-4), 64.4 (C-5), 63.1 (C-6), 60.8, 58.6 and 55.0 (3 OMe), 55.4, 25.7 and 23.3 (5 piperidine CH_2); MS: Calcd for: $C_{14}H_{27}NO_5$ 289, found: 290 [M+H]$^+$, 312 [M+Na]$^+$. Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.11; H, 9.40. Found: C, 58.10; H, 9.37.

3.12. Methyl 4-azido-4,6-dideoxy-2,3-di-*O*-methyl-6-piperidino-α-D-galactopyranoside (12)

A solution of Tf_2O (1.89 mL, 11.3 mmol) in CH_2Cl_2 (5 mL) was added to a solution of **11** (2.16 g 7.5 mmol) in a mixture of pyridine (3.6 mL) and CH_2Cl_2 (50 mL) at 0 °C and the mixture was stirred for 2 h at 0 °C. Sodium azide (980 mg) in DMF (50 mL) was added to the mixture and stirring was continued for 72 h at 45 °C. Then the mixture was concentrated and the residue was purified by column chromatography (CH_2Cl_2–MeOH, 95:5) to yield **12** (700 mg, 30%) as a pale yellow syrup: $[\alpha]_D^{25}$ 104.8 (*c* 0.65, $CHCl_3$); ^{1}H NMR δ: 4.72 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.10 (dd, 1H, $J_{3,4}$ 2.3 Hz $J_{4,5}$ <1 Hz, H-4), 3.90 (m, 1H, H-5), 3.69 (dd, 1H, $J_{2,3}$ 9.8 Hz, H-3), 3.58, 3.56 and 3.40 (each s, each 3H, 3 OMe), 3.50 (m, 1H, H-2), 2.50 (m, 6H, H-6 and 2 piperidine CH_2), 1.60 and 1.40 (each m, 6H, 3 piperidine CH_2); ^{13}C NMR: δ 98.2 (C-1), 79.8 (C-3), 78.1 (C-2), 66.3 (C-5), 61.7 (C-4), 59.7 (C-6), 59.4, 58.4 and 55.8 (3 OMe), 55.6, 26.2 and 24.4 (5 piperidine *C*H_2); MS: Calcd for: $C_{14}H_{26}N_4O_4$ 314, found: 315 [M+H]$^+$, 332 [M+NH_4]$^+$. Anal. Calcd for $C_{14}H_{26}N_4O_4$: C, 53.49; H, 8.34. Found: C, 53.42; H, 8.32.

3.13. Methyl 4,6-dideoxy-2,3-di-*O*-methyl-6-piperidino-4-(*N'*-phenyl)thioureido-α-D-galactopyranoside (13)

Propanedithiol (200 μL) was added to a solution of **12** (300 mg, 0.95 mmol) in MeOH (5 mL) at rt and the mixture was stirred for 72 h at 50 °C. When TLC (CH_2Cl_2–MeOH, 95:5) showed the formation of the 4-amino derivative, the mixture was filtered and the filtrate was concentrated. The residue was dissolved in MeOH (10 mL) and phenyl isothiocyanate (200 μL) was added to the solution. The mixture was stirred for 8 h at rt, then it was concentrated and the residue was purified by column chromatography (CH_2Cl_2–MeOH; 95:5) to afford **13** (280 mg, 69% over two steps) as a syrup: $[\alpha]_D^{25}$ 122.5 (*c* 0.59, $CHCl_3$); ^{1}H NMR: δ 8.78 (br s, 1H, NH), 7.45–7.20 (m, 5H, aromatic), 6.51 (br s, 1H, NH), 5.30 (br s, 1H, H-4), 4.80 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1), 4.10 (m, 1H, H-5), 3.67 (dd, 1H, $J_{2,3}$ 10.3 Hz, $J_{3,4}$ 4.4 Hz, H-3), 3.53, 3.50 and 3.38 (each s, each 3H, 3 OMe), 3.11 (m, 1H, H-2), 2.66 (dd, 1H, H-6a), 2.46 (m, 5H, H-6b and 2 piperidine C*H*$_2$), 1.58 and 1.42 (each m, 6H, 3 piperidine C*H*$_2$); ^{13}C NMR: δ 181.5 (C=S), 136.7, 129.6, 126.5 and 126.6 (aromatic), 97.6 (C-1), 78.2 (C-3), 77.6 (C-2), 65.9 (C-5), 59.1 (C-6), 58.9, 58.1 and 55.6 (3 OMe), 54.5 (C-4), 54.9, 25.3 and 23.7 (5 piperidine *C*H$_2$); MS: Calcd for: $C_{21}H_{33}N_3O_4S$ 423, found: 424 $[M+H]^+$. Anal. Calcd for $C_{21}H_{33}N_3O_4S$: C, 59.55; H, 7.85. Found: C, 59.58; H, 7.89.

3.14. Methyl 4,6-*O*-benzylidene-2-deoxy-2-piperidino-α-D-altropyranoside (15)

Piperidine (6.73 mL) and $LiClO_4$ (3.62 g) were added to a solution of **14** (4.5 g, 17.0 mmol) in MeCN (50 mL) at rt and the mixture was stirred for 24 h at 90 °C. Then the mixture was concentrated, the residue was redissolved in EtOAc (300 mL), and washed with water (3 × 150 mL), the organic layer was dried, filtered, and concentrated. After column chromatography (CH_2Cl_2–MeOH; 95:5) **15** (5.7 g, 95%) was obtained as white crystals:. mp 83–85 °C (hexane/EtOAc), lit.[11] mp 117–118 °C; $[\alpha]_D^{25}$ 74.3 (*c* 0.64, $CHCl_3$); lit.[11] $[\alpha]_D^{25}$ 90.8 (*c* 1.3, CH_2Cl_2); ^{1}H NMR: δ 7.54–7.32 (m, 5 H, aromatic), 5.64 (s, 1H, –C*H*Ph), 4.80 (s, 1H, H-1), 4.32 (dd, 1H, J_{gem} 10.1 Hz, H-6a), 4.13 (m, 2H, H-3 and H-5), 3.90 (dd, 1H, $J_{3,4}$ 2.9 Hz, $J_{4,5}$ 9.8 Hz, H-4), 3.80 (dd, 1H, H-6b), 3.40 (s, 3H, OMe), 3.18 (d, 1H, $J_{3,OH}$ 4.7 Hz, 3-OH), 2.84 (d, 1H, $J_{2,3}$ 2.1 Hz, H-2), 2.70 and 2.55 (each m, each 2 H, 2 –C*H*$_2$–), 1.60 and 1.45 (m, 6H, –C*H*$_2$–); ^{13}C NMR: δ 137.4, 129.1, 128.2 and 126.2 (aromatic), 102.1 (–*C*HPh), 101.2 (C-1), 77.8 (C-4), 69.4 (C-6), 67.8 (C-2), 65.6 and 57.7 (C-3 and C-5), 55.3 (OMe), 51.8, 26.5 and 24.2 (5 –*C*H$_2$); MS: Calcd for: $C_{19}H_{27}NO_5$ 349, found: 350 $[M+H]^+$.

3.15. Methyl 4,6-*O*-benzylidene-2-deoxy-2-morpholino-α-D-altropyranoside (16)

Morpholine (5.9 mL) and $LiClO_4$ (3.62 g) were added to a solution of **14** (4.5 g, 17.0 mmol) in MeCN (50 mL) at rt and the mixture was stirred for 24 h at 90 °C. Then the mixture was concentrated and the residue was taken up in EtOAc (300 mL) and washed with water (3 × 150 mL), the organic layer was dried, filtered, and concentrated. Purification of the residue by column chromatography (CH_2Cl_2–MeOH; 95:5) afforded **16** (5.0 g, 84%) as white crystals:. mp 117–119 °C (hexane), lit.[11] mp 118–119 °C; $[\alpha]_D^{25}$ 73.2 (*c* 0.71, $CHCl_3$); lit.[11] $[\alpha]_D^{25}$ 71.7 (*c* 1.2, CH_2Cl_2); ^{1}H NMR: δ 7.54–7.32 (m, 5H, aromatic), 5.64 (s, 1H, –C*H*Ph), 4.83 (s, 1H, H-1), 4.32 (dd, 1H, J_{gem} 10.1 Hz, H-6a), 4.16 (m, 2H, H-3 and H-5), 3.92 (dd, 1H, $J_{3,4}$ 3.1 Hz, $J_{4,5}$ 9.8 Hz, H-4), 3.79 (dd, 1H, H-6b), 3.70 (t, 4H, –C*H*$_2$OC*H*$_2$–), 3.42 (s, 3H, OMe), 3.17 (d, 1H, $J_{3,OH}$ 6.6 Hz, 3-OH), 2.79 (d, 1H, $J_{2,3}$ 1.9 Hz, H-2), 2.70 and 2.60 (each m, each 2H, 2 –C*H*$_2$–); ^{13}C NMR: δ 137.2, 129.0, 128.2 and 126.2 (aromatic), 102.2 (–*C*HPh), 100.0 (C-1), 77.4 (C-4), 69.2 (C-6), 67.2 (–*C*H$_2$O*C*H$_2$–), 67.0 (C-2), 65.9 and 57.8 (C-3 and C-5), 55.4 (OMe), 51.1 (2 × –*C*H$_2$); MS: Calcd for: $C_{18}H_{25}NO_6$ 351, found: 352 $[M+H]^+$.

3.16. Methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-2-piperidino-α-D-mannopyranoside (17)

Diisopropyl azodicarboxylate (1.33 mL, 6.8 mmol) was added to a solution of **15** (2.0 g, 5.73 mmol) and PPh_3 (1.79 g, 6.87 mmol) in THF (50 mL) at 0 °C and the mixture was stirred for 20 min at 0 °C. Then diphenylphosphoryl azide (1.48 mL, 6.86 mmol) in THF (12 mL) was added and the mixture was stirred for 24 h at rt. Then the mixture was concentrated, the residue was taken up in EtOAc (300 mL), and washed with sat. $NaHCO_3$ solution (150 mL), the organic layer was dried, filtered, and concentrated. Column chromatography (CH_2Cl_2–EtOAc; 95:5) of the residue followed by recrystallization from hexane/EtOAc afforded **17** (1.27 g, 60%) as white crystals: mp 161–163 °C; $[\alpha]_D^{25}$ 17.8 (*c* 0.89, $CHCl_3$); ^{1}H NMR: δ 7.55–7.33 (m, 5H, aromatic), 5.60 (s, 1H, –C*H*Ph), 4.70 (s, 1H, H-1), 4.32 (dd, 1H, J_{gem} 9.9 Hz, H-6a), 4.20 (m, 1H, H-5), 4.13 (m, 1H, H-3), 4.01 (dd, 1H, $J_{3,4}$ 3.8 Hz, $J_{4,5}$ 9.8 Hz, H-4), 3.74 (dd, 1H, H-6b), 3.38 (s, 3H, OMe), 2.86 (d, 1H, $J_{2,3}$ 1.2 Hz, H-2), 2.72 and 2.55 (each m, each 2H, 2 –C*H*$_2$–), 1.60 and 1.45 (m, 6H, –C*H*$_2$–); ^{13}C NMR: δ 137.1, 129.1, 128.3 and 126.1 (aromatic), 102.2 (–*C*HPh), 101.3 (C-1), 77.7 (C-4), 69.4 (C-6), 67.4 (C-2), 58.0 (C-5), 56.0 (C-3), 55.2 (OMe), 51.7, 26.5 and 24.2 (5 –*C*H$_2$); MS: Calcd for: $C_{19}H_{26}N_4O_4$ 374, found: 375 $[M+H]^+$. Anal. Calcd for $C_{19}H_{26}N_4O_4$: C, 60.95; H, 7.00. Found: C, 60.99; H, 7.01.

3.17. Methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-2-morpholino-α-D-mannopyranoside (18)

Compound **16** (2.0 g, 5.73 mmol) was converted into the azido derivative as described for **17**. Column chromatography (CH_2Cl_2–EtOAc, 95:5) followed by crystallization from hexane/EtOAc afforded **18** (1.49 g, 69%) as white crystals: mp 164–166 °C; $[\alpha]_D^{25}$ 26.2 (*c* 0.62, $CHCl_3$); ^{1}H NMR: δ 7.54–7.34 (m, 5H, aromatic), 5.61 (s, 1H, –C*H*Ph), 4.72 (s, 1H, H-1), 4.30 (dd, 1H, J_{gem} 10.0 Hz, H-6a), 4.21 (m, 1H, H-5), 4.11 (m, 1H, H-3), 4.04 (dd, 1H, $J_{3,4}$ 3.6 Hz, $J_{4,5}$ 9.2 Hz, H-4), 3.73 (dd, 1H, H-6b), 3.70 (t, 4 H, –C*H*$_2$OC*H*$_2$–), 3.38 (s, 3H, OMe), 2.81 (d, 1H, $J_{2,3}$ 1.3 Hz, H-2), 2.75 and 2.64 (each m, each 2H, 2 –C*H*$_2$–); ^{13}C NMR: δ 137.0, 129.2, 128.3 and 126.1 (aromatic), 102.3 (–*C*HPh), 100.0 (C-1), 77.4 (C-4), 69.2 (C-6), 67.3 (–*C*H$_2$O*C*H$_2$–), 66.5 (C-2), 58.1 (C-5), 56.5 (C-3), 55.4 (OMe), 50.9 (2 –*C*H$_2$); MS: Calcd for: $C_{18}H_{24}N_4O_5$ 376, found: 377 $[M+H]^+$. Anal. Calcd for $C_{18}H_{24}N_4O_5$: C, 57.44; H, 6.43. Found: C, 57.57; H, 6.44.

3.18. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-piperidino-3-(*N'*-phenyl)thioureido-α-D-mannopyranoside (19)

Triphenylphosphine (1.51 g, 5.7 mmol) was added to a solution of **17** (1.2 g, 3.2 mmol) in THF (15 mL) at rt and the mixture was stirred for 2 h at 80 °C. When TLC (hexane:EtOAc; 1:1) showed the absence of the starting material water (0.75 mL) was added to the mixture and the stirring was continued for 4 h at 80 °C. Evaporation of the solvent and column chromatography (CH_2Cl_2–MeOH; 98:2) of the residue afforded the 3-amino derivative (900 mg). Phenyl isothiocyanate (300 μL) was added to a solution of the amino derivative (600 mg) in MeOH (10 mL) at rt. The mixture was stirred for 30 min, then concentrated, and the product was isolated by column chromatography (CH_2Cl_2–MeOH; 98:2). Compound **19** (733 mg, 71%) was obtained as a syrup: $[\alpha]_D^{25}$ 18.7 (*c* 0.82, $CHCl_3$); ^{1}H NMR: δ 8.2 (br s, 1H, NH), 7.80–7.00 (m, 10H, aromatic), 5.65 (s, 1H, –C*H*Ph), 4.76 (s, 1H, H-1), 4.20 (m, 2H, H-4 and H-6a), 3.79 (dd, 1H, H-6b), 3.65 (br s, 1H, H-5), 3.33 (br s, 3H, OMe), 2.80–2.50 (m, 4H, H-2, H-3 and 2 –C*H*$_2$–), 1.58 and 1.45 (m, 6 H, –C*H*$_2$–); ^{13}C NMR: δ 181.0 (C=S), 137.6, 137.1, 131.9, 131.8, 131.7, 128.4, and 126.0 (aromatic), 101.6 (–CHPh), 99.4 (C-1), 76.0 (C-4), 69.2 (C-6), 66.2 (C-2), 59.4 (C-5), 55.6 (OMe), 52.0 (2 -CH_2), 51.8 (C-3), 26.3 and 24.1 (3 –CH_2); MS: Calcd for: $C_{26}H_{33}N_3O_4S$ 483, found: 484 $[M+H]^+$. Anal. Calcd for $C_{26}H_{33}N_3O_4S$: C, 64.57; H, 6.88. Found: C, 64.37; H, 6.91.

3.19. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-piperidino-3-(*N*′-3,5-bis(trifluoromethyl)phenyl)thioureido-α-D-mannopyranoside (20)

Compound **17** was converted into the 3-amino derivative as described for compound **19**. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (470 μL) was added to a solution of the 3-amino derivative (600 mg) in MeOH (10 mL) at rt. The mixture was stirred for 30 min then concentrated. Column chromatography (CH_2Cl_2–EtOAc; 98:2) of the residue provided **20** (900 mg, 81%) as a syrup: $[\alpha]_D^{25}$ −41.7 (*c* 0.69, $CHCl_3$); ^1H NMR: δ 8.76 (br s, 1H, NH), 7.70–7.30 (m, 8H, aromatic), 5.70 (s, 1H, –C*H*Ph), 4.86 (s, 1H, H-1), 4.30 (m, 2H, H-4 and H-6a), 4.10 (m, 1H, H-5), 3.82 (dd, 1H, H-6b), 3.40 (br s, 3H, OMe), 2.80–2.55 (m, 4H, H-2, H-3 and 2 –CH_2–), 1.58 and 1.45 (m, 6H, –CH_2–); ^{13}C NMR: δ 183.2 (C=S), 136.5 (aromatic), 131.0 (C-3″ and C-5″), 128.5, 128.3 and 128.1 (aromatic), 122.8 (q, 2C, $^1J_{C,F}$ 271 Hz, 2CF_3), 123.1 (m, 2C, C-2″ and C-6″), 102.8 (–*C*HPh), 99.3 (C-1), 77.5 (C-4), 69.1 (C-6), 66.4 (C-2), 59.8 (C-5), 55.5 (OMe), 53.1 (C-3), 52.0 (2 –CH_2), 26.4 and 24.1 (3 –CH_2); MS: Calcd for: $C_{28}H_{31}F_6N_3O_4S$ 619, found: 620 $[M+H]^+$. Anal. Calcd for $C_{28}H_{31}F_6N_3O_4S$: C, 54.28; H, 5.04. Found: C, 54.16; H, 5.04.

3.20. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-morpholino-3-(*N*′-phenyl)thioureido-α-D-mannopyranoside (21)

Compound **18** (2.46 g, 6.5 mmol) was converted into the 3-amino derivative (1.34 g) as described for **19**. Phenyl isothiocyanate (130 μL) was added to a solution of the crude amino derivative (251 mg) in MeOH (8 mL) at rt. The mixture was stirred for 30 min, the product, which formed as a precipitate, was filtered and was recrystallized from EtOAc/hexane to afford **21** (167 mg, 29% over two steps) as white crystals: mp 192–193 °C; $[\alpha]_D^{25}$ 45.9 (*c* 0.84, $CHCl_3$); ^1H NMR: δ 8.40 (br s, 1H, NH), 7.50–7.20 (m, 10H, aromatic), 5.65 (s, 1H, –C*H*Ph), 4.67 (s, 1H, H-1), 4.20 (m, 2H, H-4 and H-6a), 3.78 (t, 1H, H-6b), 3.70 (t, 4H, –CH_2OCH_2–), 3.60 (br s, 1H, H-5), 3.10 (s, 3H, OMe), 2.80 and 2.60 (m, 6H, H-2, H-3 and 2 –CH_2–); ^{13}C NMR: δ 180.6 (C=S), 137.0, 129.4, 128.7, 128.0, 125.9, and 125.1 (aromatic), 101.6 (–*C*HPh), 98.2 (C-1), 75.2 (C-4), 69.0 (C-6), 67.2 (–*C*H_2O*C*H_2–), 65.4 (C-2), 59.5 (C-5), 55.7 (OMe), 51.4 (C-3), 51.2 (2 –CH_2); MS: Calcd for: $C_{25}H_{31}N_3O_5S$ 485, found: 486 $[M+H]^+$, 508 $[M+Na]^+$. Anal. Calcd for $C_{25}H_{31}N_3O_5S$: C, 61.83; H, 6.43. Found: C, 61.87; H, 6.54.

3.21. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-morpholino-3-(*N*′-3,5-bis(trifluoromethyl)phenyl)thioureido-α-D-mannopyranoside (22)

Compound **18** (2.46 g, 6.5 mmol) was converted into the 3-amino derivative (1.34 g) as described for **19**. 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (720 μL) was added to a solution of the crude amino derivative (920 mg) in MeOH (10 mL) at rt. The mixture was stirred for 30 min then concentrated. Column chromatography (CH_2Cl_2–EtOAc; 98:2 → 95:5) of the residue afforded **22** (733 mg, 27%) as a syrup: $[\alpha]_D^{25}$ −23.4 (*c* 0.74, $CHCl_3$); ^1H NMR: δ 8.70 (br s, 1H, NH), 7.50–7.10 (m, 8H, aromatic), 5.70 (s, 1H, –C*H*Ph), 4.78 (s, 1H, H-1), 4.35 (m, 2H, H-4 and H-6a), 3.81 (dd, 1H, H-6b), 3.70 (m, 5H, H-5 and 2 × –CH_2–), 3.40 (br s, 3H, OMe), 2.80–2.60 (m, 6H, H-2, H-3 and 2 –CH_2–); ^{13}C NMR: δ 183.1 (C=S), 136.2 (aromatic), 130.2 (C-3″ and C-5″), 128.9, 128.6 and 128.3 (aromatic), 122.8 (q, 2C, $^1J_{C,F}$ 270 Hz, 2CF_3), 123.1 (m, 2C, C-2″ and C-6″), 102.8 (–*C*HPh), 98.5 (C-1), 77.4 (C-4), 69.0 (C-6), 67.2 (–*C*H_2O*C*H_2–), 65.8 (C-2), 59.1 (C-5), 55.6 (OMe), 52.8 (C-3), 51.2 (2 –CH_2); MS: Calcd for: $C_{27}H_{29}F_6N_3O_5S$ 621, found: 622 $[M+H]^+$; HRMS: $[M+Na]^+$ calcd for 644.1624, found: 644.1629.

3.22. General procedure for the Michael addition

Organocatalyst (0.02 mmol) was added to a solution of β-nitrostyrene (0.2 mmol) in CH_2Cl_2 (0.5 mL) under Ar at rt. The mixture was stirred for 5 min, then acetylacetone (0.22 mmol) was added, and stirring was continued for 24 h at rt. The mixture was concentrated and the product was isolated by column chromatography (Hexane–EtOAc; 7:3). The ratio of the formed enantiomers was determined by chiral HPLC method: t_{major}: 9.3 min t_{minor}: 12.5 min.

3.23. (*S*)-3-(2-Nitro-1-phenylethyl)-pentane-2,4-dione (23)

^1H NMR: δ 7.35–7.15 (m, 5H, aromatic), 4.62–4.58 (m, 2H), 4.36 (d, *J* = 10.8 Hz, 1H), 4.28–4.20 (m, 1H), 2.30 (s, 3H), 1.95 (s, 3H); ^{13}C NMR: δ 201.7, 201.0, 136.0, 129.3, 128.5, 128.0, 78.1, 70.7, 42.8, 30.4, 29.5.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2013.12.026.

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