Novel carbohydrate-based bifunctional organocatalysts for nucleophilic addition to nitroolefins and imines†

Alessandra Puglisi,†a Maurizio Benaglia,*a Laura Raimondi,a Luigi Lay*b and Laura Polettia

Introduction

The development of new and efficient chiral catalytic systems represents a tumultuously expanding area in present day organic chemistry. In particular, the design of chiral efficient multifunctional organocatalysts has received a great deal of attention.1 Several approaches to achieve this goal were inspired by Nature’s extraordinarily efficient enzyme-catalyzed transformations, in which multistep processes are readily performed, in sharp contrast to the lengthy and tedious procedures of organic synthesis. The key elements that are able to guarantee enzymes’ extraordinary efficiency are poly-functionalization, pre-organization and cooperativity. Like many other groups, we have been actively engaged in the attempt to reproduce Nature’s efficiency in performing catalytic transformations by building new bifunctionalized chiral catalysts, where two organic residues will co-operate to promote stereoselective reactions and thus perform as polyfunctional, synergic organocatalysts.2 Examples of highly successful catalytic systems developed in the last few years are bifunctional (thio)urea–tertiary amine organocatalysts, employed in a great variety of stereoselective transformations.3

Glucosamine has been selected as a cheap and readily available chiral scaffold for the synthesis of a series of novel enantiomerically pure bifunctional organocatalysts bearing a tertiary amino group in proximity to a (thio)urea group. The catalytic behaviour of these compounds, both as neutral and N-protonated species, was investigated using the addition of acetylacetone to β-nitrostyrene as a model reaction. Under optimized experimental conditions, chemical yields up to 93% and enantioselectivities up to 89% were obtained. Semiempirical (AM1) computational studies allowed to find a theoretical rationale for the chemical and stereochemical behaviour of the catalyst of choice. These catalysts were also preliminarily investigated as promoters in the addition of diethyl malonate to the N-Boc imine of benzaldehyde, affording the product in up to 81% ee.

In this context, however, it must be noted that only a very limited set of chiral scaffolds have been used for the construction of such catalytic systems, which were mostly derived from 1,2-diamino cyclohexane, cinchona alkaloids, and 1,1'-binaphthyl 2,2'-diamine. Since all of these scaffolds have some drawbacks, mostly in term of cost and the necessity of complex synthetic manipulation, the search for alternative chiral structures suitable for the design of novel multifunctional organocatalysts is still a topic of front-line interest.

Carbohydrates are primarily involved in inflammatory processes, bacterial and viral invasions, tumour growth and metastasis, and many other crucial biological events.4 Due to their enormous structural diversity, oligo- and polysaccharides play a fundamental role in signal transduction and vital molecular recognition phenomena, thus offering exciting new therapeutic opportunities in biomedical fields.5 Due to their crucial biological roles carbohydrates, especially mono- and disaccharides, possess a unique set of chemical and structural features that make them particularly attractive as molecular scaffolds. They are readily available in a variety of diastereomeric forms, chiral and conformationally rigid molecules providing a well defined three-dimensional spatial arrangement of substituents and various multi-configured hydroxyl groups for chemical modification. We therefore reasoned that carbohydrates could offer extraordinary possibilities as basic structures onto which new metal-free catalysts can be developed, for their low cost, potential polyfunctionalization, and easy possibility of different modifications for fine tuning of steric, electronic and solubility properties. To the best of our knowledge, there is only one report describing the use of β-glucosamine as starting material for the synthesis of a new class of bifunctional catalysts able to promote the Strecker and Mannich reaction with imines.6 In this pioneering work Kunz et al. explored the preparation of carbohydrate-based organocatalysts, where the
monosaccharide effectively replaced the more frequently used 1,2-diamino cyclohexane scaffold and was the only stereocontrolling element present in the molecule.7

More recently, a few contributions have explored the use of saccharide-substituted chiral thiourea–amine compounds as promoters of stereoselective Michael additions to nitroolefins,8 and aza-Henry reactions.9 It must be noted, however, that in these catalysts either the chiral 1,2-diamino cyclohexane or other amino acid-derived enantiopure diamine scaffolds were retained as the crucial element for the stereocontrol of the reaction, while carbohydrates have, in all cases, been introduced only as an additional element possibly useful for a fine tuning of the catalytic properties of the molecule.

Based on these considerations and inspired by the seminal work by Kunz et al.,6 we decided to investigate the synthesis of a new family of (thio)urea–amine organocatalysts,10 where both catalytic residues were connected by an enantiomerically pure saccharide-based scaffold, as an alternative chiral skeleton to diamino cyclohexane (Fig. 1).

Results and discussion

When designing the novel metal-free catalysts, we selected as a starting material the cheap, readily available in large quantities D-glucosamine, which, by introduction of a second amino function, allows the construction of a bifunctional amine–(thio)urea-containing catalyst. Its polyfunctionalization offers several possible structural modifications to be explored for the development and fine tuning of the novel enantiomerically pure organocatalysts (Fig. 1).

The bifunctional catalysts of type B were synthesized according to the following strategy (Scheme 1). First, commercial D-glucosamine was converted into the 1-azido-2-N-allyloxycarbonyl derivative 1 as previously described.6 Next, Zemplén O-deacetylation of glycosyl azide 1 provided 2, and the 3, 4, and 6-hydroxyls were suitably functionalised with various protecting groups, in order to modulate the polarity, the rigidity and the hydrogen-bonding ability of the saccharide scaffold, and to evaluate their influence on the behaviour of the resulting organocatalysts (Fig. 1).

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Accordingly, the highly polar O-acetylated scaffold 1, and its deacetylated derivative 2, both suitable to act as hydrogen-bonding acceptors, were employed for the synthesis of organocatalysts 10 and 13, respectively. On the other hand, silyl and alkyl ether protecting groups dampen the polarity of the saccharide scaffold and might interfere with its hydrogen-bonding capacity. Intermediate 2 was therefore converted into 3 by treatment with triethylsilyl trifluoromethanesulfonate in the presence of sym-collidine (Scheme 1).

Moreover, since semiempirical calculations suggested that the steric hindrance of the substituents on the glycosyl moiety may play a crucial role in the catalytic activity, small size alkyl ethers, such as methyl groups were introduced on 2 under classical Williamson conditions to afford 4. Finally, the importance of the rigidity of the saccharide scaffold was investigated with the preparation of glycosyl azide 5 by introduction of the 4,6-O-benzylidene acetal followed by 3-O-silylation (Scheme 1).

Having the properly protected saccharide scaffolds in our hands, we approached their conversion into bifunctional organocatalysts of type B reported in Fig. 2. Preliminary investigations suggested that the best sequence was the initial installation of the (thio)ureido linkage, followed by the generation of the tertiary amine. Since our aim was to mimic the Takemoto catalyst (A in Fig. 1), glycosyl azide 1 was reacted with triphenylphosphine followed by the addition of 3,5-bis-trifluoromethyl phenylisothiocyanate (Scheme 2).
Scheme 2  The synthesis of glucosaminylurea-based organocatalysts. (a) PPh₃, ArNCS, THF (6: 45%, 7: 60%, 8: 36%, 14: 71%); (b) Pd(PPh₃)₄, Bu₃SnH, AcOH, CH₂Cl₂, then HCHO, NaCNBH₃, THF (9: 67%, 10: 52%, 11: 47%, 12: 61%); (c) NaOMe, MeOH, (qu).

**Fig. 2**  The proposed stereoselection model for acetylacetone addition to β-nitrostyrene.

We observed the exclusive generation of the urea-linked compound 6, which was confirmed by NMR spectroscopy as well as by mass spectrometry (ESI source) analysis. In particular, in the ¹³C-NMR spectrum the signal corresponding to the quaternary carbon of the new linkage appeared at 158 ppm, a chemical shift fully consistent with a urea function.

Eventually, organocatalyst 10 was achieved by palladium(0)-catalyzed removal of the Aloc group and subsequent N-dimethylation by reductive amination with formaldehyde and sodium cyanoborohydride (Scheme 2). The same sequence was successfully applied to glycosyl azides 3 and 5, leading to glucosaminylurea-based organocatalysts 11 and 12 via 7 and 8, respectively, while organocatalyst 13 was obtained by standard O-deacetylation of 10. In contrast, O-methylated organocatalyst 14 was achieved from 4 in higher yield when N-dimethylation was performed before the formation of the ureido linkage.

Finally, we investigated a different route to obtain the (thio)ureido-linked organocatalyst. The silylated saccharide scaffold 3 was converted into glycosyl azide 15 by deprotection of the 2-amino group and N-dimethylation in 57% yield over two steps. Next, catalytic hydrogenation of the anomeric azide onto 15 was performed in the presence of the aryl isothiocyanate to afford glucosaminylthiourea organocatalyst 16 (Scheme 3).

Partial epimerization of the transient anomeric amine, however, occurred during the hydrogenation step, and organocatalyst 16 was obtained as an α,β mixture, evidenced by NMR analysis.

In the next stage of our endeavor, the catalytic properties of the bifunctional organocatalyst were tested in the stereoselective addition of activated nucleophiles to nitroolefins. The catalytic activity of compounds 10–14 and 16 was first evaluated in the model reaction between trans β-nitrostyrene 17 and acetylacetone (Scheme 4); the reaction was typically performed in the presence of 10 mol% of catalyst for 18 h in dichloromethane at room temperature; the results obtained with chiral bifunctional catalysts of type B are reported in Table 1.

The poly-acetylated compound 10 was able to promote the reaction in modest yield and stereoselectivity. Derivatives bearing less sterically demanding hydroxyl groups were shown to catalyze the acetylacetone addition with improved efficiency; better yields were obtained with catalysts 14 and 13, although with low enantioselectivity. The possibility that coordinating hydroxyl groups may interfere with the action of the bifunctional catalyst that should activate the reactive substrates by realizing a hydrogen...
bond network, was considered responsible for the disappointing results. Indeed, the use of sugar-derived compounds with non-coordinating protecting groups at the hydroxy residues, such as silyl ethers afforded better results. Catalyst coordinating protecting groups at the hydroxy residues, such as thiourea-based catalyst derivative was shown to behave better than the corresponding reaction in 89% ee, a level of stereoselection comparable to with an even lower enantioselectivity (57% ee in DCM (entry 8, Table 2); in this case the product was isolated increasing the catalyst loading up to 30% (entry 7, Table 2) or was lowered.

In acetylacetone as solvent, even when the reaction temperature was lowered, more polar solvents like diethyl ether or by running the reaction the solvents of choice; lower stereoselectivities were observed in solvents (Table 2). Dichloromethane and toluene proved to be the behavior of the catalyst of choice, when the reaction temperature was lowered.

Unfortunately, the chemical yield was not improved either by increasing the catalyst loading up to 30% (entry 7, Table 2) or by performing the reaction with a great excess of acetylacetone in DCM (entry 8, Table 2); in this case the product was isolated with an even lower enantioselectivity (57% ee vs. 89% ee, entry 2 as determined by HPLC on a chiral stationary phase; yields and ee are the average of duplicate experiments.

Table 3 The addition of acetylacetone to β-nitrostyrenes catalyzed by 11

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R$</th>
<th>Product</th>
<th>Yield%/d</th>
<th>ee%/d</th>
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<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>18</td>
<td>93</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>20</td>
<td>71</td>
<td>82</td>
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<tr>
<td>3</td>
<td>OMe</td>
<td>22</td>
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<td>55</td>
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<tr>
<td>4</td>
<td>Cl</td>
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<tr>
<td>5</td>
<td>CF$_3$</td>
<td>26</td>
<td>78</td>
<td>85</td>
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</table>

Typical experimental conditions: 0.1 mol equiv. of catalyst, 5 mol equiv. of β-nitrostyrene, 1 mol equiv. of acetylacetone, 18 h reaction time in DCM at 25 °C. Yields of isolated products. As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments.

As expected, the product was obtained in higher yields, both with persilylated catalyst 11 and catalyst 13 and the same level of stereoselectivity (45% ee). A more polar reaction medium (such as acetylacetone) compared to dichloromethane negatively affected the coordination action of the catalyst towards the nitrostyrene.

By looking for the best experimental conditions, the catalytic behavior of the catalyst of choice 11 was investigated in different solvents (Table 2). Dichloromethane and toluene proved to be the solvents of choice; lower stereoselectivities were observed in more polar solvents like diethyl ether or by running the reaction in acetylacetone as solvent, even when the reaction temperature was lowered.

Unfortunately, the chemical yield was not improved either by increasing the catalyst loading up to 30% (entry 7, Table 2) or by performing the reaction with a great excess of acetylacetone in DCM (entry 8, Table 2); in this case the product was isolated with an even lower enantioselectivity (57% ee vs. 89% ee, entry 2 as determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments.

Table 2 Optimization studies for the organocatalytic addition of acetylacetone to β-nitrostyrene 17

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield%/d</th>
<th>ee%/d</th>
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<td>Et$_2$O</td>
<td>27</td>
<td>18</td>
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<tr>
<td>2</td>
<td>11</td>
<td>DCM</td>
<td>25</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>Et$_2$O</td>
<td>21</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>Toluene</td>
<td>23</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>neat</td>
<td>30</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>DCM</td>
<td>n.d.</td>
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<tr>
<td>7</td>
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Typical experimental conditions: 0.1 mol equiv. of catalyst, 0.1 mol equiv. of β-nitrostyrene, 1 mol equiv. of acetylacetone, 18 h reaction time in DCM at 25 °C. Yields of isolated products. As determined by HPLC on a chiral stationary phase; yields and ee are average of duplicate experiments.

Reaction was run at 0 °C. Reaction was run with 30% mol amount of catalyst. Reaction was run with 10 mol equiv. of acetylacetone for 1 mol equiv. of nitrostyrene. Reaction was run with 5 mol equiv. of nitrostyrene for 1 mol equiv. of acetylacetone.

Table 1 The stereoselective addition of acetylacetone to β-nitrostyrene 17 at RT in DCM

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield%/a</th>
<th>ee%/a</th>
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<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>35</td>
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</tr>
<tr>
<td>9</td>
<td>11</td>
<td>70</td>
<td>45</td>
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</table>

Typical experimental conditions: 0.1 mol equiv. of catalyst, 1 mol equiv. of β-nitrostyrene, 1 mol equiv. of acetylacetone, 18 h reaction time in DCM at 25 °C. Yields of isolated products. As determined by HPLC on a chiral stationary phase; yields and ee are the average of duplicate experiments. Reaction was run without solvent.
with nitroolefins bearing electron donating groups (see entries 4–5 of Table 3 in comparison with entry 3).

At this stage it is very difficult to propose any hypothesis of rationalization of the stereochemical course of the reaction, also in view of the fact that the present multifunctionalized catalysts probably present more than one possible mechanism of action. These compounds are thought to operate as bifunctional catalysts; for example for the addition of acetylacetone to trans β-nitrostyrene it is quite reasonable to postulate a transition state depicted in Fig. 2. The nitrostyrene activation through double hydrogen bond coordination with the urea group and deprotonation of the 1,3-diketone by the basic amino group of the 1,2-diaminocyclohexane moiety should keep the two reagents close enough to allow the catalyst to control the absolute stereochemistry of the process.

Working on this hypothesis, we performed some preliminary calculations with MM as well as with semiempirical methods, and were able to underline some critical features for the reaction promoted by sugar-derived catalysts.

A complete conformational analysis of catalysts 10 and 11, performed with an MMFFS force field, as included in the MacroModel package, revealed the reason for the scarce stereoselectivity of the reaction promoted by catalyst 6: in fact, not only the basic dimethylamino group, but also the three acetyl moieties can act as Lewis bases in this case.

With the acetylacetone enolate binding in four different positions, and thus four different relative orientations of the reactants being accessible, a significant lack of facial stereoselectivity is predicted, in agreement with the experimental data (Tables 1 and 2). On the other hand, oxygen atoms protected as silyl ethers are not basic, thus other catalysts such as 11, 12 and 16 are much more stereoselective.

To further investigate the origin of the reaction stereoselectivity, theoretical calculations were performed on the two adducts between catalyst 11, trans β-nitrostyrene and acetylacetone enolate, leading to the (R) and (S) products. Due to the size of the problem, the semiempirical AM1 Hamiltonian was selected. In an exploratory study performed on the Takemoto catalyst (Fig. 1), we observed a significant correspondence between the energy difference of the two diastereoisomeric ternary adducts and the final enantiomeric choice in the addition of ethyl malonate to trans β-nitrostyrene. In the case of the sugar-derived catalyst 11, two structures A and B were fully optimized, and characterized as minima, for the adducts leading to products (R) and (S), respectively (Fig. 3).  

![Fig. 3 AM1 structures A and B for the ternary complexes leading to the (R) and (S) adducts, respectively.](image)

The origin of the stereocontrol seems to depend upon the steric hindrance due to the silylated protecting groups of the carbohydrate oxygens; the small energy difference between complexes A and B (0.03 kcal mol⁻¹) increases to 2.9 kcal mol⁻¹ when the complexes of (R) and (S)-18 with catalyst 11 are considered (structures A' and B' in Fig. 4), favoring the (R) product. Another feature of the reaction is revealed by these calculations: the complexes between reaction product (R) or (S)-18 and catalyst 11 are extremely stable; in particular, decomplexation of A' to give (R)-18 and catalyst 11 requires about 8 kcal mol⁻¹. For this reason, an excess of trans β-nitrostyrene is recommended to obtain a reasonable reaction yield, in accordance with the experimental findings in Table 2.

![Fig. 4 AM1 structures A' and B' for the complexes of (R) and (S)-18 with catalyst 11, respectively.](image)

In order to further explore the catalytic behavior of this novel class of catalysts in more challenging transformations, the addition of activated nucleophiles to imines was studied; in particular, we focused our attention on reactions of imines with 1,3-dicarboxylic esters.

The addition of diethyl malonate to the N-Boc imine of benzaldehyde was investigated; the reaction was typically performed in dichloromethane at room temperature for 12 h in the presence of 10 mol% of catalyst to afford the corresponding Mannich product 27, that was isolated by flash chromatography; the results are reported in Scheme 5.

Once again, compounds bearing hydroxyl groups able to act as hydrogen bonding acceptors, like catalyst 14, promoted the reaction with low enantioselectivity, although in good chemical yield. In contrast, molecules bearing more sterically demanding hydroxyl protecting groups catalyzed the addition to Boc-imines in lower yields. However, for this transformation the silyl ether was shown to be the protecting group of choice, in order to guarantee good levels of stereoselection. With catalysts 16 and 12 the product was isolated with good enantioselectivity with 75% and 77% ee, respectively, but it was with catalyst 11 that the best results were observed: the expected β-amino ester was obtained in 81% enantioselectivity after an 18 h reaction at room temperature.

In conclusion, the synthesis of a new family of chiral bifunctional organocatalysts was successfully realized, starting from a readily available, cheap, enantiomerically pure material such as d-glucosamine. For the first time, the saccharide unit was employed as a chiral scaffold alternative to 1,2-trans-diaminocyclohexane, bearing two catalytic residues located in a well defined spatial arrangement. The activity of the novel catalysts was investigated in a model reaction: the addition of acetylacetone to nitrostyrene; in the best conditions, enantioselectivities up to 89% were obtained. The same metal-free catalysts were then employed in the addition of activated nucleophiles to imines: in the reaction of diethyl malonate with N-Boc imines and the products were isolated in up to 81% ee. An attempt to rationalize the stereochemical outcome...
of the reaction and the behaviour of the novel catalysts was also proposed on the basis of preliminary semiempirical (AM1) studies. We believe that these results represent only the first step towards the development of new carbohydrate-based metal-free catalytic systems, which may offer several attractive features, like ready availability, low cost, polyfunctionalization, the presence of several well defined stereocenters and the possibility of different facile modifications for the fine tuning of their catalytic properties.

Experimental Section

Computational

All MMFFS calculations were run with the MacroModel package; conformational analyses were performed with the stochastic MCMM method, with all exocyclic dihedral angles set as variables; convergence was considered achieved when all structures within 3 kcal mol⁻¹ from the global minimum were sampled several times. AM1 calculations were run with the Gaussian03 package.²⁹ All located structures were characterized as minima by means of a full vibrational analysis.

General

All reactions were carried out in oven-dried glassware with magnetic stirring under a nitrogen atmosphere, unless otherwise stated. All commercially available reagents, including dry solvents, were used as received. Organic extracts were dried over sodium sulfate, filtered, and concentrated under vacuum to yield a yellow glass. The complete removal of the acetyl groups was ascertained by NMR analysis and the compound was identified as a glassy solid.

2-[N-allyloxycarbonyl-2-amino-2-deoxy-β-D-glucopyranosyl azide (2)]

Compound 1 (1.95 g, 4.7 mmol) was dissolved in dry methanol under an inert atmosphere and a 1 M solution of MeONa in MeOH was added at rt until basic pH was reached. After the disappearance of the starting material (TLC analysis), the reaction was quenched with IR-120 resin (H⁺ form), filtered and concentrated under reduced pressure, obtaining compound 2 as a yellow glass (1.35 g, 97%). The complete removal of the acetyl groups was ascertained by NMR analysis and the compound was used in the following steps without further characterization.

2-[N-allyloxycarbonyl-2-amino-2-deoxy-3,4,6-tri-O-triethylsilyl-β-D-glucopyranosyl azide (3)]

Compound 2 (705 mg, 2.45 mmol) was dissolved in dry DMF under an inert atmosphere and cooled to ~20 °C. Sym-collidine (3.89 mL, 29.4 mmol) and TESOTf (3.05 mL, 3.47 mmol) were slowly dropped into the solution. After 24 h the reaction was quenched by pouring it into NaHCO₃-saturated solution and extracted with EtOAc. The combined organic layers were washed with water, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (elucent Hex/EtOAc 9:1) providing compound 3 (1.50 g, 97%) as a glassy solid.

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α₀ = -32.15° (c 0.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.88–6.00 (m, 1H, CH₃α), 5.55 (d, 1H, JₙH₂ = 9.4 Hz, NH), 5.37–5.20 (m, 1H, CH₃β₁), 4.98 (d, 1H, J₁₂ = 4.8 Hz, H-1), 4.61–4.58 (m, 2H, CH₂α₂), 4.15 (bt, 1H, J₂₃ = 9.5 Hz, H-6a), 3.91 (t, 1H, J = 3.8 Hz, H-4), 3.38–3.79 (m, 2H, H-6b, H-3), 3.74–3.69 (m, 1H, H-5), 3.63–3.58 (m, 1H, H-2), 1.03–0.92 (m, 27H, CH₃TES), 0.73–0.50 (m, 18H, CH₃TES); ¹³C NMR (100.6 MHz, CDCl₃) δ 117.5, 88.0, 80.1, 72.7, 69.3, 65.7, 62.5, 54.5, 6.8, 4.7. ESI-MS 654.2 g mol⁻¹
Synthesis of glucosaminyl ureas – general procedure

The glucosyl azide (1 mmol) and triphenylphosphine (1.1 mmol) were dissolved in dry THF under a nitrogen atmosphere and stirred overnight at rt. 3,5-Bis-trifluoromethylphenyl isothiocyanate (1 mmol) was added and the reaction was stirred for a further 3 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography, obtaining the pure urea derivative.

\[
N\text{-}[\text{N-allyloxycarbonyl-2-amino-2-deoxy-3,4,6-tri-O-triethylsilyl-}
\beta\text{-D-glucopyranosyl}], N\text{'-}[3\text{-bis-trifluoromethyl}]
\text{phenyl urea (7)}
\]

Chromatographic purification of urea 7 was performed using Hex/EtOAc 95 : 5 + 1% TEA as eluent (yield 60%).

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\alpha_0 = -3.69^\circ \text{ (c 1.0, CHCl}_3) ; \quad 'H\text{ NMR (400 MHz, CDCl}_3) \delta 7.91 (s, 2H, Ar), 7.74 (s, 1H, Ar), 7.49 (bd, 1H, NH), 6.36 (bs, 1H, NH), 5.96–5.88 (m, 1H, H\text{a}), 5.65 (bs, 1H, NH), 5.36–5.23 (m, 2H, CH\text{a}), 4.68–4.56 (m, 3H, CH\text{a}l l, H-6a), 4.38 (bs, 1H, H-6b), 4.08 (bt, 1H, H-1), 3.95–3.83 (m, 2H, H-2, H-3), 3.57 (bs, 1H, H-5), 3.44 (bt, 1H, H-4), 3.12 (m, 5H), 2.7 (m, 5CH\text{a}l l), 1.75 (s, 3H), 1.5 (t, 2H), 0.83 (m, 6H), 0.76–0.66 (m, 12H, CH\text{a}l l), 0.41 (q, 9H, J = 7.9 Hz, 3 CH\text{a}l l) ; \quad ^{13}\text{C NMR (100.6 MHz, CDCl}_3) \delta 157.2, 117.8, 81.8, 71.0, 68.8, 68.4, 66.3, 58.7, 52.3, 6.7, 6.4, 4.5, 4.0; \quad \text{ESI-MS 883.5 g mol}^{-1} \text{(Na)}. \quad \text{Anal. calcd for C}_{37}\text{H}_{63}\text{F}_6\text{N}_3\text{O}_7\text{Si}_3 (860.16): C, 51.66; H, 7.38; N, 4.89%; Found: C, 51.69; H, 7.35; N, 4.80%.
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Removal of the Aloc group and \(N\text{-},N\text{-dimethylation – general procedure}

The starting urea (1 eq.) was dissolved in dry dichloromethane, then Pd(PPh\text{3})\text{4} (0.02 eq.), AcOH (2.4 eq.) and Bu\text{3}SnH (1.1 eq.) were charged in a 10 mL round bottom flask under nitrogen. DCM (0.5 mL) was added and, after 5 min stirring at the indicated temperature, diethyl malonate (0.058 mL, 0.38 mmol, 2 eq.) was added until basic pH was reached. The mixture was extracted with EtOAc, the combined organic layers were washed with water and brine, dried (Na\text{2}SO\text{4}), filtered and concentrated under reduced pressure. The crude product was purified with flash chromatography on silica gel (1 × 16 cm silica, petroleum ether : AcOEt 7 : 3, flow rate = 1 mL min\text{−1}, P = 21 bar, \(\lambda = 210 \text{ nm})): t\text{_{minor}} = 11.14 min, [\alpha]_{D}^{20} = -13.98^\circ \text{ (c 0.1, CHCl}_3) \text{.}

General procedure for the Mannich reaction of diethyl malonate with inines

Bifunctional catalyst (0.019 mmol, 0.1 eq.) and Boc-imine (0.19 mmol, 1 eq.) were charged in a 10 mL round bottom flask under nitrogen. DCM (0.5 mL) was added and, after 5 min stirring at 23 °C for 18 h, then the solvent was evaporated in vacuo and the crude product was purified by flash chromatography on silica gel.

References

A reasonable explanation for this result is that the initially-formed anomerically pure glucosyl amine to be coupled with the aryl isothiocyanate failed.