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Graphical Abstract

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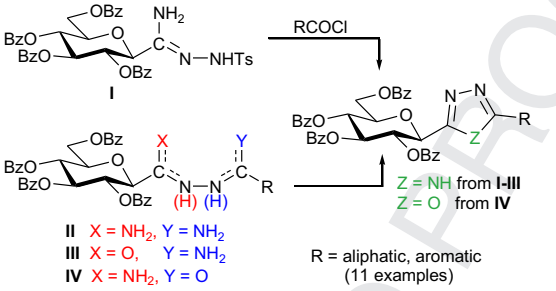

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C-(β-D-Glucopyranosyl)formamidrazones, formic acid hydrazides and their transformations into 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles: a synthetic and computational study

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ABSTRACT

Synthesis of *O*-perbenzoylated 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles, precursors of potent inhibitors of glycogen phosphorylase, was studied by ring closures of N^1-acyl-carboxamidrazone type intermediates. Reactions of *C*-(β-D-glucopyranosyl)formimidate or *C*-(β-D-glucopyranosyl)formamidine with acid hydrazides as well as acylation of *C*-(β-D-glucopyranosyl)formamidrazone by acid chlorides unexpectedly gave the corresponding 1,3,4-oxadiazoles instead of 1,2,4-triazoles. The desired triazoles were obtained in reactions of *C*-(β-D-glucopyranosyl)formamidine or *C*-(β-D-glucopyranosyl)formyl chloride with arenecarboxamidrazones, and also in acylations of N^1-tosyl-*C*-(β-D-glucopyranosyl)formamidrazone with acid chlorides. Theoretical calculations (B3LYP and M06-2X DFT with the standard 6-31G(d,p) basis set) on simple model compounds with methyl and phenyl substituents to understand the bifurcation of the ring closure of N^1-acyl-carboxamidrazones indicated that in general the reaction led to 1,2,4-triazoles. However, the probability of the 1,3,4-oxadiazole forming pathway was shown to be significantly higher with N^1-benzoyl-acetamidrazones, which were closest analogues of the intermediates resulting in *C*-glucosyl-1,3,4-oxadiazoles. It was thereby demonstrated that the substitution pattern of the N^1-acyl-carboxamidrazones played a fundamental role in determining the direction of the ring closing reaction.

1. Introduction

The 1,2,4-triazole motif is an attractive heterocycle in drug design. A large number of 1,2,4-triazole derivatives with proven or potential pharmaceutical utilization against various diseases (e.g., fungal, bacterial, viral, and parasitic infections, inflammatory and immuno disorders, neuropathic lesions, epilepsy, cancer, diabetes, obesity, hypertension, allergy, etc.) have been reported.[1,2] The widespread and successful application of this heteroaromatic ring is due especially to its high resistance to metabolic degradation and ability to participate in diverse favourable interactions (e.g., hydrogen and coordination bonds, van der Waals and ion–dipole interactions, cation–π and π–π stackings) in biological systems.[2]

As part of an ongoing program aimed at exploring the inhibitory effects of azole type *C*- and *N*-β-D-glucopyranosyl heterocycles towards glycogen phosphorylase enzyme[3–10] (GP, a validated molecular target for the treatment of type 2 *diabetes mellitus*[11]), we set out to prepare and test 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles. For a rationalization of the design of such compounds as GP inhibitors, the reader is kindly referred to our recent preliminary communication.[12]

The most common synthetic procedure for the formation of 3,5-disubstituted-1,2,4-triazoles is based on the intramolecular ring closure of acyl-amidrazones. This type of intermediate can be obtained by reactions of carboxylic acid derivatives (e.g., acid chlorides, (thio)amides, nitriles, (thio)imidates, amidines) with hydrazide or amidrazone reagents.[13]

The above synthetic pathways were employed in syntheses of *C*-glycofuranosyl-1,2,4-triazoles, as well. Thus, 3-glycofuranosyl-5-substituted-1,2,4-triazoles were obtained from *C*-glycofuranosyl (thio)formimidates with hydrazide or amidrazone reagents with or without isolation of the intermediate acyl-amidrazones.[14–17] Preparation of 5-amino-3-(β-D,L-ribofuranosyl)-1,2,4-triazole was performed by the reaction of 2,5-anhydro-3,4-*O*-isopropylidene-D,L-allonolactone with aminoguanidine.[18] Synthesis of a pseudo C-

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nucleoside, 3-[(4*R*)-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-erythrofuranos-4-*C*-yl]-5-phenyl-1,2,4-triazole was achieved by condensation of the corresponding 4-*C*-thiocarbamoyl furanose derivative and benzhydrazide.[19] In addition, cyclization of substituted N^1-acyl-*C*-glycofuranosyl formamidrazones obtained from the corresponding formimidate[20] or spiro-1,3-oxazin-4-one[21] precursors afforded 1,3,5-trisubstituted *C*-glycofuranosyl-1,2,4-triazoles.

As another alternative, reactions of glycosyl cyanides with 1-aza-2-azoniaallene salts (generated in situ from chloroalkyl azo compounds by $SbCl_5$)[22,23] or with hydrazonoyl chlorides in the presence of $Yb(OTf)_3$[24] furnished *C*-glycosyl-1,2,4-triazoles. This method was used only for the preparation of 1,3,5-trisubstituted-1,2,4-triazoles both with furanoid and pyranoid sugar rings.

To the best of our knowledge, the synthesis of 3-*C*-glycopyranosyl-5-substituted-1,2,4-triazoles has not yet been reported.[12] Herein we disclose our experiences on the preparation of these target compounds via *C*-(β-D-glucopyranosyl)formamidrazone and formic acid hydrazide type intermediates. Computational studies to elucidate the behaviour of some amidrazone derivatives in ring closing steps yielding either 1,2,4-triazole or 1,3,4-oxadiazole are also presented.

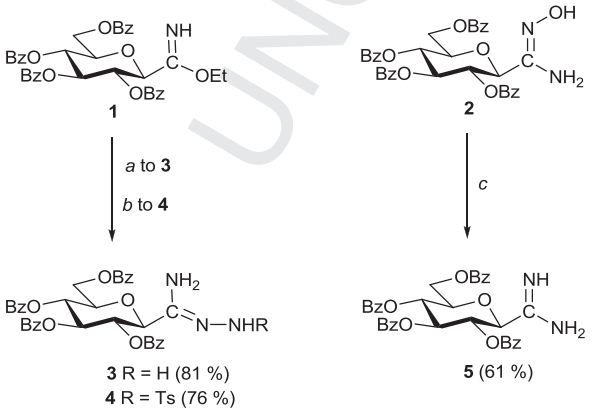
2. Results and discussion

2.1. Syntheses

In preliminary experiments, heterocyclizations of the easily available *O*-perbenzoylated β-D-glucopyranosyl cyanide[25] as well as *C*-(β-D-glucopyranosyl)thioformamide[9,26] were studied in analogy with literature examples. However, attempted transformations of the glucosyl cyanide into 1,2,4-triazole with benzhydrazide or its benzosulfonate salt brought about reactions neither with conventional heating (experiments carried out following published procedures for the transformation of (hetero)aromatic nitriles[27,28]) nor with microwave activation. The corresponding thioamide remained also intact on treatment with benzhydrazide even at elevated temperature (conditions adapted from reports for non-sugar[29,30] or ribofuranose[19] based compounds) as well as under microwave irradiation.

Therefore, application of more reactive precursors such as *O*-perbenzoylated *C*-(β-D-glucopyranosyl)formimidate,[9] (**1**), -formamidrazones (**3**, **4**), -formamidine (**5**) and *C*-(β-D-glucopyranosyl) formyl chloride,[31] (**13**), was envisaged for the construction of the target triazoles.

Synthesis of formamidrazone **3** was carried out by the treatment of ethyl *C*-(β-D-glucopyranosyl)formimidate[9] (**1**) with hydrazine hydrate in EtOH (Scheme 1). The reaction of formimidate **1** with tosylhydrazide in anhydrous CH_2Cl_2 gave N^1-tosylated formamidrazone **4** in high yield. Formamidine **5** was produced from *C*-(β-D-glucopyranosyl)formamidoxime[32] (**2**) in a *one-pot* reaction by adapting a literature method applied for non-sugar based compounds.[33] Thus, acetylation of **2** followed by reductive cleavage of the N–O bond by transfer hydrogenation gave **5** in good yield (Scheme 1).



Scheme 1. Reagents and conditions: (a) $NH_2NH_2{\cdot}H_2O$, EtOH, rt; (b) $TsNHNH_2$, dry CH_2Cl_2, rt; (c) (1) Ac_2O, AcOH, rt, (2) 10% Pd(C), HCOOK, MeOH, rt.

Following literature analogies,[15] the cyclization of formimidate **1**[9] with benzhydrazide (**6a**) was probed first in different solvents ($PhCH_3$, 1,4-dioxane, DMF) at elevated temperature (Scheme 2). However, these experiments led to the formation of the known 5-phenyl-2-(2′,3′,4′,6′-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-oxadiazole[5] **8a** instead of the expected 1,2,4-triazole.

Next, formamidine **5** was reacted with benzhydrazide (**6a**) in several solvents ($PhCH_3$, 1,4-dioxane, DMF, EtOH, pyridine) at high temperature to get the target triazole, however, complex reaction mixtures were obtained in each case. Therefore, the coupling of **5** with benzhydrazide (**6a**) was carried out in pyridine at ambient temperature providing intermediate N^1-benzoyl-formamidrazone **7a** (Scheme 2). Ring closure of **7a** was then accomplished by heating in DMF to yield 1,3,4-oxadiazole **8a** instead of 1,2,4-triazole **11a**.

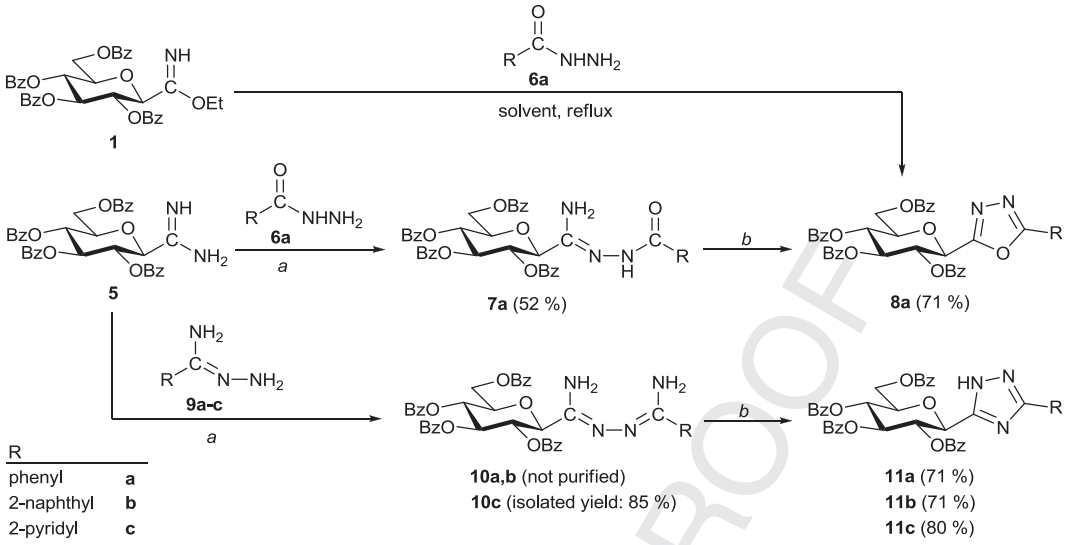
To exclude the possibility of the formation of the oxadiazole, the reaction of amidine **5** with arenecarboxamidrazones **9** was also investigated (Scheme 2). For these experiments benzamidrazone (**9a**) as well as naphthalene-2-carboxamidrazone (**9b**) were prepared from the corresponding carboximidates[34] and hydrazine reagents as described in the experimental part, while pyridine-2-carboxamidrazone[35] (**9c**) was obtained from pyridine-2-carbonitrile and hydrazine hydrate in EtOH. Treatment of amidine **5** with **9a–c** in pyridine furnished N^1-arenecarboximido-formamidrazones **10a–c**, which were cyclized, without being purified, in anhydrous DMF to give the corresponding 1,2,4-triazoles **11a–c** in high yields (Scheme 2). To determine the exact structure of an intermediate by NMR spectroscopy, column chromatographic purification of amidrazone **10c** was also performed.

Although this route seems to represent a reliable and high-yielding method, its utilization in the synthesis of variously substituted triazoles has been limited by the availability of the necessary amidrazone reagents.

Because of the above difficulty, we set out to study the transformation of formamidrazone **3** with readily available acid chlorides. However, ring closure of **3** with benzoyl chloride on heating in toluene (route i in Table 1, entry 1) gave oxadiazole **8a**. Surprisingly, the formally reversed reaction, where *C*-(β-D-glucopyranosyl)formyl chloride[31] **13** (freshly prepared from formic acid **12** in thionyl chloride) was cyclized with arenecarboxamidrazones **9a,c** (route iii) yielded the desired triazoles **11a** and **11c** (entries 4 and 7), respectively. Taking into account the lengthy preparation of **13** this route offered no advantage over the construction of triazoles **11** in reactions of amidine **5** with arenecarboxamidrazones (Scheme 2).

The above transformations were also carried out in two steps including the isolation of the intermediates of the reactions. Treatment of amidrazone **3** with benzoyl chloride at rt afforded acyl-amidrazone **7a** (also obtained from amidine **5**, cf. Scheme 2), which was cyclized to **8a** on route ii (entries 2 and 3). Coupling of acid chloride **13** with arenecarboxamidrazones **9a,c** at rt gave **14a,c**, respectively. Subsequent cyclization of **14a** on heating in toluene or in DMF gave triazole **11a** on route iv (entries 5 and 6).

Furthermore, transformation of acyl-amidrazones bearing the same substituents on both carbon atoms was also examined. Treatment of glucosyl formyl chloride **13** with glucosyl formamidrazone **3** in toluene at rt yielded intermediate **14d** from which bis-*C*-glucosyl-1,2,4-triazole **11d** was obtained in the ring closing step (Table 1, entries 8 and 9). Similarly to **13**, cyclization of N^1-benzoyl-benzamidrazone (**15**) prepared from benzamidrazone



Scheme 2. Reagents and conditions: (a) dry pyridine, rt; (b) dry DMF, 140 °C.

(**9a**) and benzoyl chloride (Scheme 3) resulted in disubstituted triazole **16**.

To understand the unexpected behaviour of the intermediates in the cyclization steps computational studies were carried out, as described later.

To find a relatively short and reliable preparation of the target compounds, we turned to a method reported to transform N^1-tosylated aromatic and aliphatic carboxamidrazones by aliphatic acid chlorides into 1-tosyl-1,2,4-triazoles in anhydrous chloroform in the presence of pyridine.[36] Thus, reactions of tosyl-amidrazone **4** with acid chlorides towards the desirable *C*-glycosyl-triazoles were studied. Cleavage of the *N*-tosyl group was foreseen by using TBAF, which is usually applied for N-desulfonylation of nitrogen heterocycles.[37]

On cyclization of **4** with most of the studied aromatic acid chlorides, the tosyl moiety was also split off. Thus, instead of the expectable tosylated triazoles **17a**,**b**,**e**,**g**–**i**, the target compounds **11a**,**b**,**e**,**g**–**i** could be isolated (Table 2). Treatment of **4** with 4-acetoxybenzoyl chloride or acetoxyacetyl chloride resulted in mixtures of the tosylated (**17f**,**j**) and the free triazoles (**11f**,**j**), respectively. Therefore, after work-up of the reaction mixtures, the crudes were treated with TBAF to remove the tosyl group, thus providing compounds **11f** and **11j**, respectively. In the reaction of **4** with acetyl chloride the 5-methyl-3-(2′,3′,4′,6′-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1-tosyl-1,2,4-triazole (**17k**) was obtained exclusively, from which removal of the tosyl group by TBAF furnished triazole **11k**.

On pivaloylation (Scheme 4), total consumption of the starting material **4** required higher temperature and the use of DMAP, and the intermediate N^3-pivaloyl-N^1-tosyl-formamidrazone (**18l**) could be isolated. Amidrazone **18l** was then cyclized by heating in *m*-xylene with simultaneous loss of the tosyl moiety to yield triazole **11l**.

2.2. Computational studies

In order to get a deeper insight into the unexpected formation of 1,3,4-oxadiazoles in cyclizations of some acyl-amidrazones computational studies have been undertaken. To the best of our knowledge, no similar theoretical calculations can be found in the literature except a paper on the tautomerism and the role of water molecules in tautomeric interconversions of aliphatic carboxamidrazones.[38]

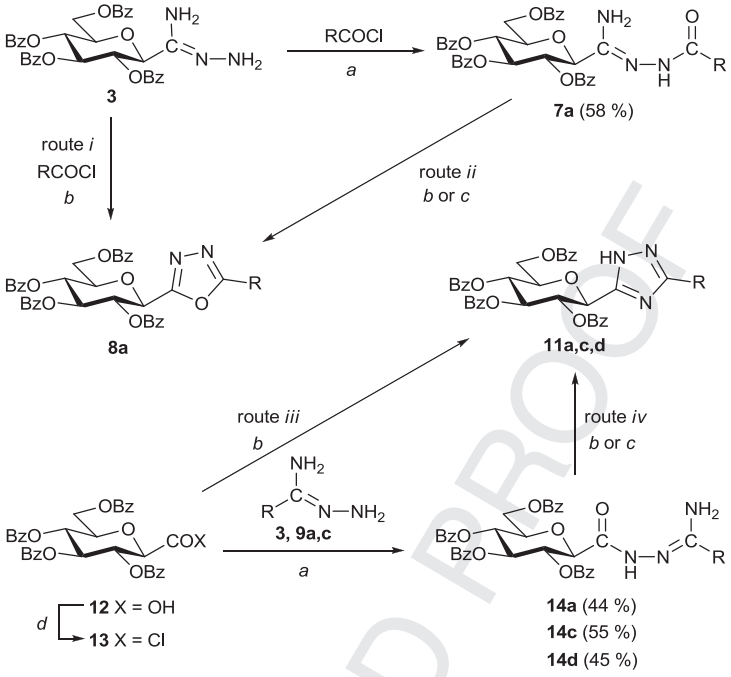
2.2.1. Amidrazones. While computational studies on simple amidrazone derivatives were reported,[38] we did not find any theoretical calculations for benzamidrazone. In order to get comparable results, acetamidrazone[38] was recalculated with smaller 6-31G(d,p) basis set, which was used throughout this work.

For acetamidrazone and benzamidrazone the two plausible tautomeric forms **I** and **II**, with *Z* and *E* geometries, respectively, representing the most stable structures according to Tavakol's work,[38] were optimized at different levels and the same basis set (Table 3). Tautomer **I** proved consistently more stable than **II** independently from the substituents and the applied level of calculations. The obtained energy differences (ΔE) between **I** and **II** were in the range of 3.6–4.9 kcal/mol. These results depended mainly on the level of the applied theory and only slightly on the substituent.

2.2.2. Reactions of amidrazones and acyl chlorides. Calculations were performed on the formation of acyl-amidrazone derivatives from the most stable amidrazone tautomer **I** (Scheme 5). Computationally, the mechanism of this reaction consists of two distinct steps. The first step is the nucleophilic attack of a nitrogen on the acyl carbon and the second one is a proton abstraction by the outgoing chloride. Hereafter only the first step is investigated expansively presuming that this is the rate-limiting step. Because of the eight different TS-s (taking into account the stereochemical differences in **TS I** and **TS II**) and for the sake of simplicity only the TS energies are compared to the sum of the lowest energy amidrazone (**I**) and acyl-chloride (**III**) structures (Table 4). In this reaction N^1 was found to be the most efficient nucleophile yielding much lower TS (**TS II** towards **V**) energy than N^3 (**TS I** towards **IV**). Therefore, acyl-amidrazone **V** was used to study the ring closure reactions. It should be noted that the negative energy value in Table 4 is the consequence of the chosen reference energy. It means that the local first order saddle point on the Born–Oppenheimer energy surface has smaller ZPVE corrected energy than the sum of the reactants' ZPVE corrected energies.

2.2.3. Acyl-amidrazone tautomerism. Plausible non-ionic tautomers (**Vc**–**VIIIc**) of N^1-acetyl-acetamidrazone are shown in Scheme 6 (no other structures were studied at this stage assuming that the substituents have no substantial effect on the tautomeric equilibria). Calculations were carried out for the energy content of these tautomers as well as for their ammonia-assisted interconversion (vide infra). Tautomer **Vc** was found to be the most stable, while all

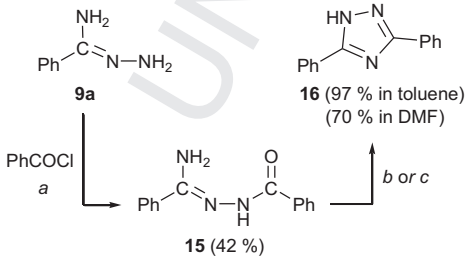
Table 1
Ring closures of amidrazones **3** and **9a**,**c** with acid chlorides



a) dry toluene, rt; *b*) dry toluene, 90 °C; *c*) dry DMF, 140 °C; *d*) $SOCl_2$, reflux

Entry	R	Route	Conditions and yields (%)		
				8	**11**
1.		i	b	66	—
2.	**a**	ii	b	68	—
3.		ii	c	71[a]	—
4.		iii	b	Traces[b]	60
5.		iv	b	—	90
6.		iv	c	—	85
7.	**c**	iii	b	—	58
8.	**d**	iv	b	Traces[b]	76
9.		iv	c	—	73

[a] Previously presented result (Scheme 2).
[b] The compound was detectable by TLC, but its amount was estimated to be less than 5%.



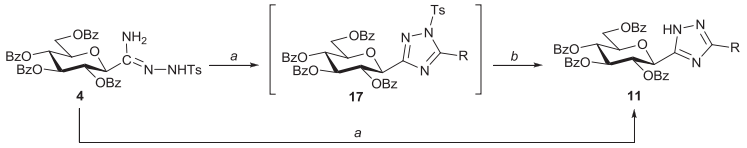
Scheme 3. Reagents and conditions: (a) dry toluene, rt; (b) dry toluene, 90 °C; (c) dry DMF, 140 °C.

other ones (**VIc**–**VIIIc**) represented arrangements of significantly higher energies. Therefore, at rt and even in the range of the reaction temperatures, the acyl-amidrazones may exist with high probability almost exclusively in tautomeric form **V**.

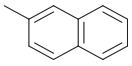
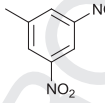
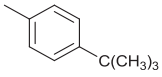
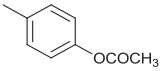
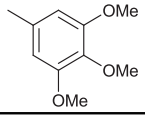
In each case the tautomeric interconversion energies were significantly lower when a 'mediator' molecule with hydrogen acceptor and, in its protonated form, hydrogen donor character (e.g. a primary amino group of the amidrazone itself or ammonia) helped the hydrogen transfer. Therefore, the transition state energies indicated in Scheme 6 correspond to the NH_3 mediated tautomeric interconversion barriers.

2.2.4. Ring closure of acyl-amidrazones. According to our synthetic experiences (cf. Table 1) the ring closure reactions of acyl-amidrazones result in either 1,3,4-oxadiazole or 1,2,4-triazole derivatives depending on the nature of the R^1 and R^2 substituents. Thus, a formal interchange of aliphatic and aromatic substituents

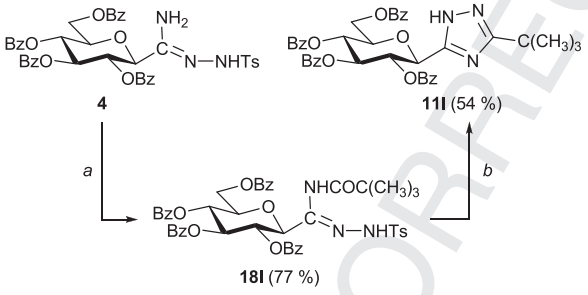
Table 2
Synthesis of 3-substituted-5-(2′,3′,4′,6′-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazoles from N^1-tosyl-amidrazone **4**



a) 1.5 equiv. RCOCl, 1.8 equiv. dry pyridine, dry $CHCl_3$, 0 °C to rt; *b*) TBAF, dry THF, reflux

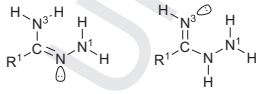
	R	Conditions and yields (%)			R	Conditions and yields (%)	
			11 (from **4**)				**11** (from **4**)
a		a	69	**h**		a	57
b		a	56	**i**		a	55
e		a	58	**j**	$-CH_2OCOCH_3$	a, b[a]	61
f		a, b[a]	60	**k**	-CH3	a	69 (**17k**)[b]
g		a	54			b	88 (from **17k**)[c]

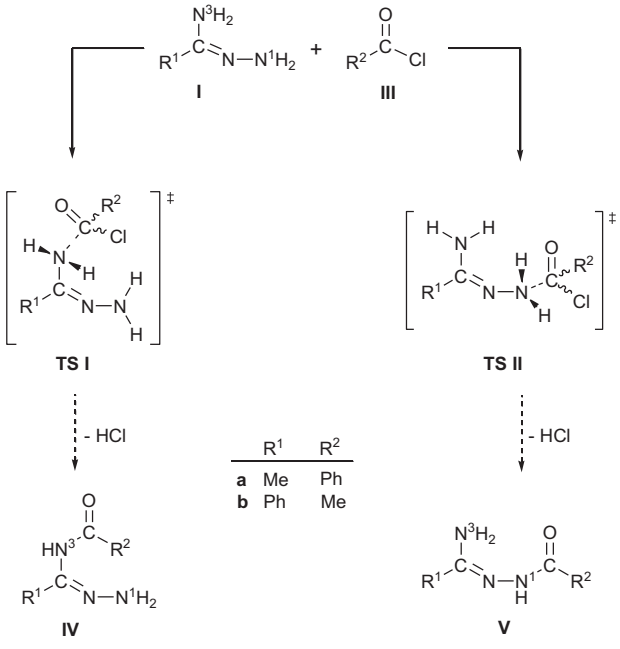
[a] The crude mixture obtained from amidrazone **4** and acid chloride was treated with TBAF.
[b] Tosylated triazole **17k** was exclusively obtained under reaction conditions a.
[c] Triazole **11k** was achieved from the isolated tosylated triazole **17k**.



Scheme 4. Reagents and conditions: (a) $(CH_3)_3CCOCl$, dry $CHCl_3$, dry pyridine, DMAP, reflux; (b) *m*-xylene, 120 °C.

Table 3
Absolute and relative energies (in atomic units and kcal/mol, respectively) for tautomers of acetamidrazone and benzamidrazone in their most stable configuration calculated at B3LYP, M06-2X and MP2 levels of theory using 6-31G(d,p) basis set

R^1	Method	 **I** (*Z*)	**II** (*E*)	ΔE ($E_{II}-E_I$) [kcal/mol]
		E [a.u.]		
Me	B3LYP	−244.558690	−244.552170	4.09
	M06-2X	−244.439737	−244.433532	3.89
	MP2	−243.818627	−243.810768	4.93
Ph	B3LYP	−436.247242	−436.240747	4.08
	M06-2X	−436.052092	−436.046349	3.60
	MP2	−434.918724	−434.911741	4.38

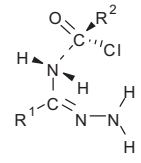


Scheme 5. Acylation of the most stable amidrazone tautomer **I**.

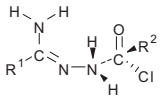
may switch the mechanism over to the formation of either an oxadiazole or a triazole. While a direct contribution of these substituents in the reaction (i.e. by cleavage or formation of bonds) cannot be assumed, their fine tuning influence on the transition state energies (stabilization or destabilization of the TS-s due to the aromatic/non-aromatic character of the groups) may affect the direction of the ring formation. In order to understand how the

Table 4
Transition state energies[a] [kcal/mol] for the acyl-amidrazone formations leading to products **IV** (**TS I**) and **V** (**TS II**) (cf. Scheme 5)

Method

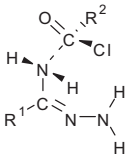


(*S*)

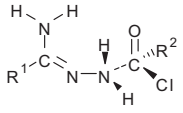


(*S*)

	TS Ia	TS Ib	TS IIa	TS IIb
B3LYP	12.15	17.64	4.12	7.64
M06-2X	6.95	12.14	0.22	2.67



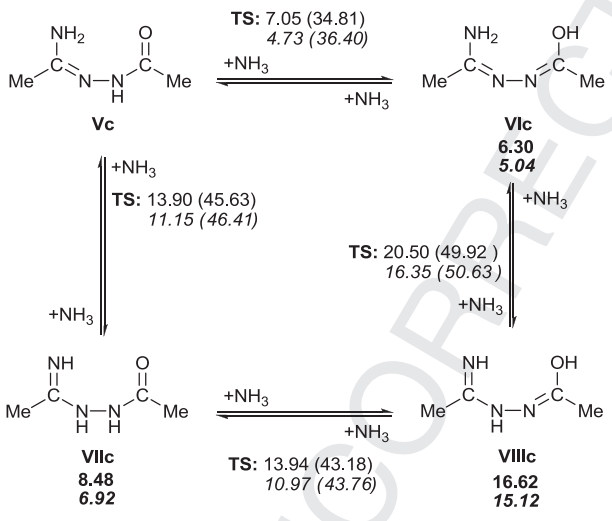
(*R*)



(*R*)

	TS Ia	TS Ib	TS IIa	TS IIb
B3LYP	13.20	15.99	3.93	4.92
M06-2X	8.82	11.33	0.30	−0.30

[a] Relative values compared to the sum of the lowest energy amidrazone (**I**) and acid chloride (**III**) structures.



Scheme 6. Energies [kcal/mol] for tautomers **Vc**–**VIIIc** of N^1-acetyl-acetamidrazone and their ammonia-assisted interconversion (see text). Relative energies as compared to **Vc** are shown in bold, transition state energies are indicated as plain numbers on the arrows. Upper and lower numbers refer to results of B3LYP and M06-2X calculations, respectively. Numbers in parentheses refer to the non-assisted transition state energies.

different substituents act on the TS-s, further calculations were carried out.

Ring closure of acyl-amidrazones **V** can be bifurcate (Scheme 7) and, depending on the attack of the carbonyl oxygen on the amidrazone carbon (route A) or that of N^3 on the carbonyl carbon (route C), may lead to the formation of an oxadiazole (**XII**) or a triazole (**XIV**, **XV**), respectively. Similarly to the cases of computation of tautomeric interconversions of acyl-amidrazones (cf. Scheme 6), assistance by a participating ammonia molecule was found to be advantageous in the ring closing reactions (route D), as well. Thus, calculations were performed with and without the participation of an NH_3 molecule in each pathway (routes A–D), for which transition states are shown in Scheme 7, and the respective numerical values are collected in Table 5.

In route A, initial attack of the oxygen onto the amidrazone carbon formally results in a special product **X** via **TS VI**. The energy level of **TS VI** was not affected by the presence of NH_3. The unusual bonding network of **X** should undergo a reorganization by a H shift along the ring (mediated by ammonia through **TS III**) leading to intermediate **IX**, which, on losing ammonia via **TS V**, results in the final product oxadiazole **XII**. In this route, formation of intermediate **X** is the rate determining step in all but the **Xa** B3LYP/6-31G(d,p) cases (Table 5). However, only **Xa** and **Xd** proved computationally stable, i.e., geometry optimization structures **Xb** and **Xc** did not keep their ring structure and acyl-amidrazones **Vb** and **Vc** were retrieved. The presence of ammonia opened up an alternative path to oxadiazole **XII** (route B via **TS VII**→**XI**→**TS IV**→**IX**→**TS V**) wherein the loss of ammonia from the ring closed intermediate **IX** through **TS V** proved the rate determining step.

In route C, N^3 of **V** attacks the carbonyl carbon to form intermediate **XIII** via **TS VIII**. Further loss of water from **XIII** assisted by ammonia in two orientations (**TS X** or **TS XI**) gives either tautomer **XIV** or **XV** of the final product triazole. On this route the ring formation via **TS VIII** is the slowest step. Formation of **XIII** is facilitated in the presence of ammonia (route D) since the energies for **TS IX** are ~15–20 kcal/mol lower than those of **TS VIII**, however, the ring formation via **TS IX** still remains rate determining.

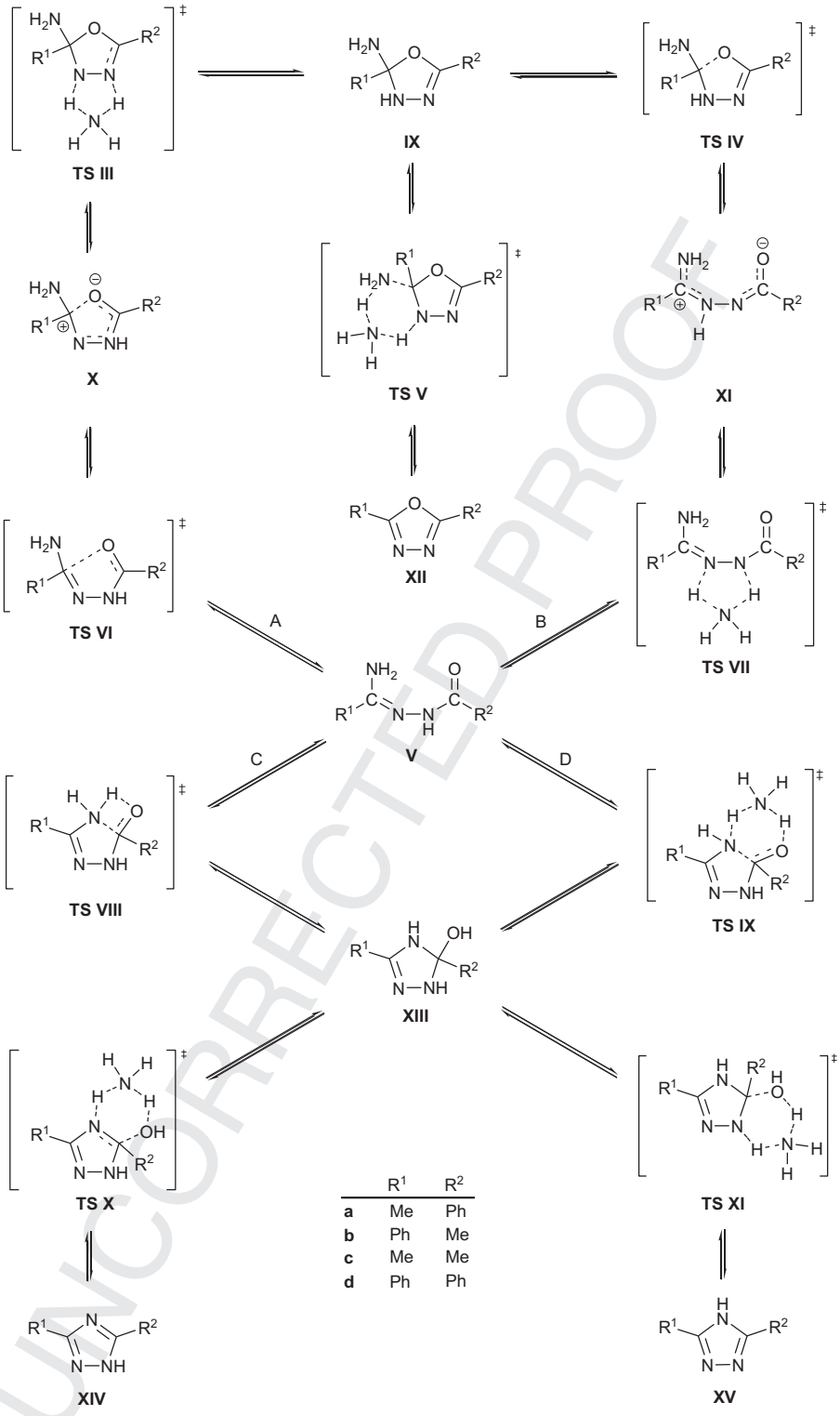
The data in Table 5 clearly demonstrate that route B is more favourable than route A and route D is more favourable than route C when a 'helper' ammonia molecule is present in our model systems. Hence, when 'helper' groups (e.g., primary amino group of acyl-amidrazones) are present in the 'real' reaction mixture the routes B and D cannot be ignored as well.

A comparison of the rate determining steps of the oxadiazole and triazole forming pathways is given in Table 6. The 'direct' ring formations favour the oxadiazole with the substituents **a** since in this case **TS VIa** has a significantly lower energy than **TS VIIIa**. This finding directly reflects the experimental outcome of the ring closing reaction involving *N*-acyl-(*C*-glucopyranosyl)formamidrazone **7a** (cf. Scheme 2 and Table 1) resulting in 1,3,4-oxadiazole **8a**. On the other hand, with the substituent pair **d**, no significant difference of the energies of **TS VId** and **TS VIIId** could be pointed out, while the instability of intermediates **Xb** and **Xc** makes the formation of oxadiazoles **XIIb** and **XIIc** highly improbable.

The highest energy transition states on the ammonia-assisted pathways are **TS V** (to oxadiazole **XII** on route B) and **TS IX** (to triazoles **XIV** and **XV** on route D). **TS IX** leading to triazole formation is consistently lower in energy than those leading to oxadiazole formation (**TS V**), and this difference is the smallest for the substituent pair **a**.

Since the applied levels of theory prefer the 'ammonia-assisted' pathways rather than the 'direct' ones, it can be concluded that for the model substituents **a**–**d** the triazole formation is more advantageous than the oxadiazole formation. In fact this kind of reaction is frequently used for the preparation of substituted triazoles (cf. the introductory section). On the other hand, the extent of triazole preference is substituent dependent and might be shifted to the oxadiazole formation with the appropriate substituent combination and experimental conditions. Our data indicate that if there is any chance for oxadiazole formation, it probably will take place first with substituent pairs similar to **a**, exactly as it was found for the R^1=(β-D-glucopyranosyl) and R^2=phenyl substituent combination.

It should be noted finally that the levels of theory we could apply for modelling the reaction paths leading to oxadiazole and



Scheme 7. Formation of 1,3,4-oxadiazoles (**XII**) or 1,2,4-triazoles (**XIV** or **XV**) from acyl-amidrazones (**V**).

triazole products are supposed to work well for calculation of relative transition state energy barriers for the same type of bond breakage and formation. On the other hand, comparing different kinds of reaction barriers (e.g., oxadiazole vs triazole formation) the predictive powers of these methods are more limited. Nevertheless, from this computational study the fundamental role of the relative position of methyl and phenyl substituents (i.e., model non-aromatic vs model aromatic) on the corresponding transition state energy stabilization–destabilization (i.e., on the reaction path selection) was undoubtedly demonstrated.

3. Conclusion

Syntheses of new types of *C*-glucopyranosyl formic acid derivatives, namely formamidrazone and formamidine allowed, together with the known formimidate and formyl chloride, to

Table 5
Relative transition state energies and energy differences [kcal/mol] for the 'direct' and ammonia-assisted ring closures and eliminations on the oxadiazole and on the triazole formation pathways

Substituents	Method	Oxadiazole paths (routes A and B)					Triazole paths (routes C and D)			
		TS III	**TS IV**	**TS V**	**TS VI**	**TS VII**	**TS VIII**	**TS IX**	**TS X**	**TS XI**
a (R^1=Me; R^2=Ph)	B3LYP	37.62	25.88	33.35	36.58	16.65	41.80	29.68	25.79	28.79
	M06-2X	33.72	26.00	27.77	37.80	15.36	41.20	22.76	21.83	25.53
b (R^1=Ph; R^2=Me)	B3LYP	—	22.11	39.51	—	14.69	42.27	26.80	21.99	25.44
	M06-2X	—	21.94	33.10	—	12.71	40.66	20.87	17.94	22.72
c (R^1=R^2=Me)	B3LYP	—	24.37	38.01	—	16.82	43.72	30.47	27.49	24.18
	M06-2X	—	24.64	32.32	—	15.74	42.60	—	—	20.66
d (R^1=R^2=Ph)	B3LYP	39.21	23.70	35.20	39.71	14.69	40.22	26.08	23.58	26.90
	M06-2X	34.61	23.72	29.20	40.10	12.89	39.28	19.40	19.11	23.81

Table 6
Comparison of the highest relative transition state energies [kcal/mol] for the 'direct' and 'ammonia-assisted' ring closures on the oxadiazole and on the triazole formation pathways

Substituents	Method	Route A versus route C (direct)	Route A: stable intermediate **X**?	Route B versus route D (ammonia-assisted)
		ΔE ($E_{TS\ VIII}$–$E_{TS\ VI}$)		ΔE ($E_{TS\ IX}$–$E_{TS\ V}$)
a (R^1=Me R^2=Ph)	B3LYP	5.22	Yes	−3.67
	M06-2X	3.40	Yes	−5.01
b (R^1=Ph R^2=Me)	B3LYP	—	No	−12.71
	M06-2X	—	No	−12.23
c (R^1=R^2=Me)	B3LYP	—	No	−7.54
	M06-2X	—	No	—
d (R^1=R^2=Ph)	B3LYP	0.51	Yes	−9.12
	M06-2X	−0.82	Yes	−9.80

evaluate ring closing reactions of acyl-amidrazones Glc–C(NH_2)=N–NH–C(=O)-Ar and Glc–C(=O)–NH–N=C(NH_2)–Ar. The former intermediates were shown to be transformed to the corresponding 1,3,4-oxadiazoles while the latter ones gave the expected 1,2,4-triazoles. This bifurcation of the ring closure, depending on the substitution pattern of the acyl-amidrazone intermediate, had no comparable precedents in the literature, therefore, theoretical calculations were invoked to explain the findings (see below). A practical synthesis of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles was elaborated using the reaction of N^1-tosyl-*C*-glucopyranosyl formamidrazone with various acid chlorides.

Density functional quantum chemical calculations on the ring closure reactions of acyl-amidrazones were carried out. It was demonstrated computationally that even if the most advantageous reaction paths led to 1,2,4-triazole products, both the 'direct' and the 'ammonia-assisted' routes indicated the existence of an alternative 1,3,4-oxadiazole pathway. Calculations for the ring closure of Me–C(NH_2)=N–NH–C(=O)–Ph showed the highest probability for oxadiazole formation in good agreement with the experimental findings.

4. Experimental

4.1. General methods

Melting points were measured on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at rt. NMR spectra were recorded with a Bruker 360 (360/90 MHz for ^{1}H/^{13}C) spectrometer. Chemical shifts are referenced to Me_4Si (^{1}H), or to the residual solvent signals (^{13}C). IR spectra were recorded with a Jasco FT-IR 4100 spectrophotometer. Microanalyses were performed on an Elementar Vario Micro Cube. ESI-MS spectra were measured with a Thermo Scientific LTQ XL instrument. TLC was performed on DC-Alurolle Kieselgel 60 F_{254} (Merck) plates, visualized under UV light and by gentle heating. For column chromatography Kieselgel 60 (Merck, particle size 0.063–0.200 mm) was used. Dichloromethane and toluene were distilled from P_4O_{10} and stored over 4 Å molecular sieves and pressed sodium plates, respectively. Anhydrous pyridine and DMF were purchased from Aldrich. Ethyl *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formimidate[9] (**1**), *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formamidoxime[32](**2**), *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formic acid[31] (**12**) and pyridine-2-carboxamidrazone[35] (**9c**) were synthesized according to published procedures.

4.2. Synthesis of benzamidrazone 9a and naphthalene-2-carboxamidrazone 9b

(A) The corresponding arenecarboximidate[34] (3.36 mmol) was dissolved in anhydrous MeOH (10 mL), hydrazine acetate (3.36 mmol, 1 equiv) was added, and the mixture was stirred at rt for 3 h. The solvent was removed under diminished pressure, and the crude product was used freshly without further purification in general procedure II for the synthesis of triazoles **11a,b**.

(B) Benzimidate[34] (1.00 g, 6.70 mmol) and hydrazine hydrate (0.33 mL, 6.70 mmol) were stirred in anhydrous EtOH (20 mL) at rt overnight. The solvent was then removed, and the remaining syrup was crystallized on addition of cold hexane to give 0.78 g (86%) of benzamidrazone (**9a**) as a pale yellow solid. Mp: 73–75 °C (from *n*-hexane) (lit.[39] mp: 75–76 °C); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.71–7.69 (2H, m, aromatics), 7.32–7.30 (3H, m, aromatics), 5.58 (2H, br s, NH_2), 4.96 (2H, br s, NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 147.5 (C=N), 135.4, 128.9, 128.5 (2), 125.7 (2) (aromatics).

4.3. Syntheses of precursors

*4.3.1. C-(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl)formamidrazone (**3**).* Ethyl *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formimidate[9] (**1**, 1.00 g, 1.53 mmol) and hydrazine hydrate (75 μL, 1.53 mmol) were stirred in anhydrous EtOH (20 mL) at rt, and the reaction was monitored by TLC (1:1 EtOAc/hexane). After completion of the reaction (1 day) the precipitate was filtered off,

and washed with EtOH to give 0.79 g (81%) white solid. Mp: 135–137 °C (from EtOH); $[\alpha]_D$ −19 (*c* 0.52, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3470, 3380 (br signals, NH); ^1H NMR (DMSO-d_6) δ (ppm): 8.00 (2H, d, *J*=7.3 Hz, aromatics), 7.83–7.78 (4H, m, aromatics), 7.70–7.37 (14H, m, aromatics), 5.94–5.85, 5.68 (3×1H, 3 pseudo t, *J*=9.2, 9.2 Hz in each, H-2, H-3, H-4), 5.41 (2H, s, NH_2), 4.65 (2H, br s, NH_2), 4.46 (3H, s, H-5, H-6a, H-6b), 4.37 (1H, d, *J*=9.2 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.0, 165.6, 165.3, 165.1 (C=O), 147.9 (C=N), 133.4–133.1, 129.7–129.6, 129.4, 129.1, 128.8, 128.6, 128.3–128.2 (aromatics), 77.9, 76.1, 73.6, 70.4, 69.2 (C-1–C-5), 63.0 (C-6). MS-ESI (*m*/*z*): calcd for $C_{35}H_{32}N_3O_9^+$ $[M+H]^+$: 638.21. Found: 638.21.

*4.3.2. N^1-Tosyl-C-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)formamidrazone (**4**).* Ethyl *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formimidate[9] (**1**, 1.00 g, 1.53 mmol) and *p*-toluenesulfonylhydrazide (0.43 g, 2.3 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL), stirred at rt, and monitored by TLC (1:1 EtOAc/hexane). After completion of the reaction (3 days) the solvent was removed, and the residue was purified by column chromatography (2:3 EtOAc/hexane) to give colourless oil. Yield: 0.92 g (76%); R_f: 0.52 (1:1 EtOAc-hexane); $[\alpha]_D$ −50 (*c* 0.21, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3463, 3379 (br signals, NH); ^1H NMR ($CDCl_3$) δ (ppm): 8.01 (2H, d, *J*=7.9 Hz, aromatics), 7.90 (2H, d, *J*=7.9 Hz, aromatics), 7.81–7.77 (4H, m, aromatics), 7.50–7.17 (14H, m, aromatics), 6.86 (2H, d, *J*=7.9 Hz, aromatics), 5.98 (1H, pseudo t, *J*=9.2, 9.2 Hz, H-2 or H-3 or H-4), 5.80–5.66 (4H, m, H-2 and/or H-3 and/or H-4, NH_2), 4.62 (1H, dd, *J*=11.9, 2.6 Hz, H-6a), 4.51 (1H, dd, *J*=11.9, 5.3 Hz, H-6b), 4.40 (1H, d, *J*=9.2 Hz, H-1), 4.24 (1H, ddd, *J*=9.2, 5.3, 2.6 Hz, H-5), 2.20 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.1, 165.6, 165.2, 165.0 (C=O), 157.3 (C=N), 143.0, 134.7, 133.3–132.9, 129.7–129.4, 129.2, 128.9, 128.7, 128.5, 128.4, 128.2–127.6 (aromatics), 76.8, 76.0, 73.6, 70.3, 69.0 (C-1–C-5), 63.0 (C-6), 21.4 (CH_3). MS-ESI (*m*/*z*): calcd for $C_{42}H_{38}N_3O_{11}S^+$ $[M+H]^+$: 792.22. Found: 792.67.

*4.3.3. C-(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl)formamidine (**5**).* *C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formamidoxime[32] (**2**, 3.19 g, 5.0 mmol) and acetic anhydride (0.52 mL, 5.5 mmol) were stirred in glacial acid (10 mL) at rt for 10 min. Potassium formate was prepared in situ from K_2CO_3 (3.46 g, 25 mmol) and formic acid (1.90 mL, 50 mmol) in MeOH (7.5 mL), the above solution of the acetylated amidoxime and 0.50 g 10% Pd(C) were added, stirred at rt and monitored by TLC (1:1 EtOAc/hexane and 9:1 $CHCl_3$/MeOH). After completion of the reaction (1 h) the mixture was diluted with MeOH and filtered through a Celite pad then the filtrate was concentrated. The residue was dissolved in EtOAc (200 mL), extracted with water (200 mL) then with brine (200 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated. The crude product was crystallized by a mixture of $CHCl_3$/hexane to give a white solid. Yield: 1.90 g (61%). Mp: 153–155 °C (from $CHCl_3$/hexane); $[\alpha]_D$ +53 (*c* 0.23, DMSO); IR (KBr) ν_{max} (cm^{-1}): 3420 (br, NH); ^1H NMR (DMSO-d_6) δ (ppm): 9.82 (3H, br s, amidine NH, NH_2), 8.06–7.40 (20H, m, aromatics), 6.09, 5.94, 5.81 (3×1H, 3 pseudo t, *J*=9.2, 9.2 Hz in each, H-2, H-3, H-4), 4.96 (1H, d, *J*=9.2 Hz, H-1), 4.74 (1H, ddd, *J*=9.2, 5.3, 2.6 Hz, H-5), 4.61–4.53 (2H, m, H-6a, H-6b); ^{13}C NMR (DMSO-d_6) δ (ppm): 165.4, 165.3, 165.0, 164.7, 164.6 (C=O, C=N), 134.2–133.4, 129.5–128.6, 128.4, 128.2, 127.8 (aromatics), 74.6, 74.0, 73.6, 70.2, 68.1 (C-1–C-5), 62.4 (C-6). MS-ESI (*m*/*z*): calcd for $C_{35}H_{31}N_2O_9^+$ $[M+H]^+$: 623.20. Found: 623.50.

*4.3.4. N^1-Benzoyl-C-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl) formamidrazone (**7a**).*

(A) *C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formamidine (**5**, 0.20 g, 0.32 mmol) and benzhydrazide (**6a**, 66 mg, 0.48 mmol, 1.5 equiv) were stirred in anhydrous pyridine (4 mL) at rt, and monitored by TLC (9:1 $CHCl_3$/MeOH). After completion of the reaction (3 days) the mixture was concentrated under diminished pressure, traces of pyridine were removed by repeated co-evaporations with toluene. The crude product was purified by column chromatography (2:1 EtOAc/hexane) to yield 0.12 g (52%) white solid.

(B) *C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formamidrazone (**3**, 0.20 g, 0.31 mmol) and benzoyl chloride (40 μL, 0.34 mmol, 1.1 equiv) were stirred in anhydrous toluene (6 mL) at rt, and monitored by TLC (1:1 EtOAc/hexane). After completion of the reaction (4 days) the solvent was removed and the residue was purified by column chromatography (2:1 EtOAc/hexane then EtOAc) to yield 0.14 g (58%) white solid. Mp: 193–195 °C; $[\alpha]_D$ −6 (*c* 0.53, DMSO); IR (KBr) ν_{max} (cm^{-1}): 3464, 3323 (br signals, NH); ^1H NMR (DMSO-d_6) δ (ppm): 9.82 (1H, s, NH), 8.03–7.39 (25H, m, aromatics), 6.62 (2H, s, NH_2), 6.05–5.94, 5.74 (3×1H, 3 pseudo t, *J*=9.2, 9.2 Hz in each, H-2, H-3, H-4), 4.64–4.49 (4H, m, H-1, H-5, H-6a, H-6b); ^{13}C NMR (DMSO-d_6) δ (ppm): 165.4, 165.1, 164.8 (2), 162.8 (C=O), 149.0 (C=N), 134.4, 133.7–133.4, 130.8, 129.4–127.4 (aromatics), 77.9, 74.5, 74.3, 70.3, 68.9 (C-1–C-5), 62.9 (C-6). MS-ESI (*m*/*z*): calcd for $C_{42}H_{36}N_3O_{10}^+$ $[M+H]^+$: 742.24. Found: 742.19.

*4.3.5. N^1-(Pyridine-2-carboximido)-C-(2,3,4,6-tetra-O-benzoil-β-D-glucopyranosyl)formamidrazone (**10c**).* *C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formamidine (**5**, 0.10 g, 0.16 mmol) and pyridine-2-carboxamidrazone[35] (**9c**, 22 mg, 0.16 mmol) were stirred in anhydrous pyridine (3 mL) at rt, and monitored by TLC (9:1 $CHCl_3$/MeOH). After completion of the reaction (16 h) the mixture was concentrated under diminished pressure, traces of pyridine were removed by repeated co-evaporations with toluene. The crude product was purified by column chromatography (1:1 EtOAc/hexane) to yield 0.10 g (85%) pale yellow syrup. R_f: 0.82 (9:1 $CHCl_3$/MeOH); $[\alpha]_D$ +183 (*c* 0.21, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3490, 3374 (NH); ^1H NMR ($CDCl_3$) δ (ppm): 8.45 (1H, d, *J*=4.0 Hz, Py–H-6), 8.16 (1H, d, *J*=7.9 Hz, Py–H-3), 8.05 (2H, d, *J*=7.9 Hz, aromatics), 7.95–7.93 (4H, m, aromatics), 7.86 (2H, d, *J*=7.9 Hz, aromatics), 7.64–7.20 (14H, m, aromatics), 6.03, 5.93 (2×1H, 2 pseudo t, *J*=9.2, 9.2 Hz in each, H-2 and/or H-3 and/or H-4), 5.78–5.73 (3H, m, H-2 or H-3 or H-4, NH_2), 5.50 (2H, br s, NH_2), 4.68 (1H, dd, *J*=11.9, 2.6 Hz, H-6a), 4.56–4.51 (2H, m, H-1, H-6b), 4.27 (1H, ddd, *J*=9.2, 5.3, 2.6 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.1, 165.8, 165.3, 165.2 (C=O), 153.2, 152.5, 150.7 (2×C=N, Py–C-2), 147.9 (Py–C-6), 136.0 (Py–C-4), 133.4–133.1, 129.8–129.7, 129.4 (2), 128.8, 128.7, 128.4–128.2 (aromatics), 124.3, 120.8 (Py–C-3, Py–C-5), 77.4, 76.2, 74.1, 70.1, 69.3 (C-1–C-5), 63.1 (C-6). MS-ESI (*m*/*z*): calcd for $C_{41}H_{36}N_5O_9^+$ $[M+H]^+$: 742.25. Found: 742.20.

*4.3.6. General procedure I for the synthesis of N′-carboximido-C-(2,3,4,6-tetra-O-benzoil-β-D-glucopyranosyl)formic acid hydrazides (**14**).* *C*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)formic acid[31] (**12**, 0.20 g, 0.32 mmol) was heated in thionyl chloride (5 mL) at reflux temperature for 1 h then the excess of the reagent was evaporated. Traces of thionyl chloride were removed by repeated co-evaporations with toluene. The residue was dissolved in anhydrous toluene (6 mL) and an amidrazone **3** or **9** (1–1.5 equiv) was added, the mixture was stirred at rt and monitored by TLC (2:1 toluene/AcOH). After 1 day the solvent was removed and the crude product was purified by column chromatography.

*4.3.7. N′-Benzenecarboximido-C-(2,3,4,6-tetra-O-benzoil-β-D-glucopyranosyl)formic acid hydrazide (**14a**).* From acid **12** (0.20 g, 0.32 mmol) and benzamidrazone (**9a**, 65 mg, 0.48 mmol) according to general procedure I. Purified by column chromatography (7:3

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EtOAc/hexane) to yield 0.11 g (44%) white solid. Mp: 164–166 °C; $[\alpha]_D$ −6 (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 8.06 (2H, dd, *J*=7.3, 1.3 Hz, aromatics), 7.96–7.93 (4H, 2dd, *J*=7.3, 1.3 Hz in each, aromatics), 7.84 (2H, dd, *J*=7.3, 1.3 Hz, aromatics), 7.71 (2H, dd, *J*=7.3, 1.9 Hz, aromatics), 7.59–7.25 (15H, m, aromatics), 6.01, 5.77–5.71 (3×1H, 3 pseudo t, *J*=9.9, 9.2 Hz in each, H-2, H-3, H-4), 5.59 (2H, br s, NH_2), 4.73 (1H, dd, *J*=12.6, 2.6 Hz, H-6a), 4.55 (1H, dd, *J*=12.6, 5.3 Hz, H-6b), 4.37 (1H, d, *J*=9.9 Hz, H-1), 4.23 (1H, ddd, *J*=9.9, 5.3, 2.6 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.5, 166.2, 165.7, 165.2, 163.3 (C=O), 156.7 (C=N), 133.5–132.9, 130.9, 129.9–129.7, 129.3, 129.0, 128.8, 128.6, 128.5–128.3, 126.7, 126.4 (aromatics), 77.1, 76.5, 73.6, 71.0, 69.1 (C-1–C-5), 62.9 (C-6). MS-ESI (*m*/*z*): calcd for $C_{42}H_{36}N_3O_{10}^+$ $[M+H]^+$: 742.24. Found: 742.25.

*4.3.8. N′-(Pyridine-2-carboximido)-C-(2,3,4,6-tetra-O-benzoil-β-D-glucopyranosyl)formic acid hydrazide (**14c**).* From acid **12** (0.20 g, 0.32 mmol) and pyridine-2-carboxamidrazone[35] (**9c**, 65 mg, 0.48 mmol) according to general procedure I. Purified by column chromatography (2:1 EtOAc/hexane) to yield 0.13 g (55%) white solid. Mp: 188–190 °C; $[\alpha]_D$ −23 (*c* 0.20, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3438 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 8.55 (1H, d, *J*=4.6 Hz, Py–H-6), 8.25 (1H, d, *J*=8.6 Hz, Py–H-3), 8.10 (2H, d, *J*=7.3 Hz, aromatics), 7.99–7.95 (2×2H, 2 d, *J*=7.3, 7.3 Hz in each, aromatics), 7.84 (2H, d, *J*=7.3 Hz, aromatics), 7.72–7.28 (14H, m, aromatics, Py–H-4, Py–H-5), 6.45 (2H, s, NH_2), 6.00, 5.76–5.70 (3×1H, 3 pseudo t, *J*=9.2, 9.2 Hz in each, H-2, H-3, H-4), 4.82 (1H, dd, *J*=12.6, 2.6 Hz, H-6a), 4.58 (1H, dd, *J*=12.6, 5.3 Hz, H-6b), 4.41 (1H, d, *J*=9.2 Hz, H-1), 4.23 (1H, ddd, *J*=9.2, 5.3, 2.6 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ (ppm): 167.0, 166.0, 165.7, 165.2, 162.3 (C=O), 152.3, 149.7, 147.8 (C=N, Py–C-2, Py–C-6), 136.6 (Py–C-4), 133.6–133.3, 130.1–128.2 (aromatics), 124.9, 121.5 (Py–C-3, Py–C-5), 77.2, 76.2, 73.3, 70.6, 68.7 (C-1–C-5), 62.6 (C-6). MS-ESI (*m*/*z*): calcd for $C_{41}H_{35}N_4O_{10}^+$ $[M+H]^+$: 743.23. Found: 743.18.

*4.3.9. N′-(2′,3′,4′,6′-Tetra-O-benzoil-β-D-glucopyranosylcarboximido)-C-(2,3,4,6-tetra-O-benzoil-β-D-glucopyranosyl)formic acid hydrazide (**14d**).* From acid **12** (0.20 g, 0.32 mmol) and C-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)formamidrazone (**3**, 0.20 g, 0.32 mmol) according to general procedure I. Purified by column chromatography (5:4 EtOAc-hexane) to yield 0.18 g (45%) white solid. Mp: 139–141 °C; $[\alpha]_D$ −36 (*c* 0.51, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3448, 3376 (br signals, NH); ^1H NMR ($CDCl_3$) δ (ppm): 8.14–7.70 (16H, m, aromatics), 7.54–7.21 (24H, m, aromatics), 6.01–5.93 (2×1H, 2 pseudo t, *J*=9.2, 9.2 Hz in each, H-2 and/or H-2′ and/or H-3 and/or H-3′ and/or H-4 and/or H-4′), 5.78 (1H, pseudo t, *J*=9.9, 9.2 Hz, H-2 or H-2′ or H-3 or H-3′ or H-4 or H-4′), 5.71–5.58 (5H, m, H-2 and/or H-2′ and/or H-3 and/or H-3′ and/or H-4 and/or H-4′, NH_2), 4.67–4.43 (5H, m, H-1 or H-1′, H-6a, H-6b, H-6′a, H-6′b), 4.25–4.19 (2H, m, H-5 or H-5′, H-1 or H-1′), 4.11 (1H, ddd, *J*=9.2, 5.3, 2.6 Hz, H-5 or H-5′); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.6, 166.1 (2), 165.6 (3), 165.1, 165.0, 162.6 (C=O), 155.0 (C=N), 133.5–133.1, 129.9–129.6, 129.4, 129.1, 128.9, 128.7, 128.6, 128.5–128.2 (aromatics), 77.1, 76.3 (2), 76.2, 73.6, 73.0, 70.8, 70.5, 69.1, 68.7 (C-1–C-5, C-1′–C-5′), 62.9, 62.8 (C-6, C-6′). MS-ESI (*m*/*z*): calcd for $C_{70}H_{58}N_3O_{19}^+$ $[M+H]^+$: 1244.37. Found: 1245.00.

*4.3.10. N^1-Benzoyl-benzamidrazone (**15**).* Benzamidrazone (**9a**, 0.20 g, 1.48 mmol) and benzoyl chloride (172 μL, 1.48 mmol) were suspended in anhydrous toluene (6 mL), the mixture was stirred at rt and monitored by TLC (2:1 EtOAc/hexane). After two days the solvent was removed and the residue was purified by column chromatography (95:5 EtOAc/MeOH) to yield 0.15 g (42%) white solid. Mp: 166–168 °C; ^1H NMR (DMSO-d_6) δ (ppm): 10.02 (1H, br s, NH), 7.89–7.84 (4H, m, aromatics), 7.54–7.43 (6H, m, aromatics), 6.72 (2H, br s, NH_2); ^{13}C NMR (DMSO-d_6) δ (ppm): 163.0, 151.6 (C=O, C=N), 134.8, 130.6, 129.6, 128.0, 127.5, 126.5 (aromatics). MS-ESI (*m*/*z*): calcd for $C_{14}H_{14}N_3O^+$ $[M+H]^+$: 240.11. Found: 240.25.

4.4. Syntheses of 1,2,4-triazoles

*4.4.1. General procedure II for the synthesis of 5-substituted-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazoles (**11**) from C-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)formamidine (**5**).* C-(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl)formamidine (**5**, 0.70 g, 1.12 mmol) and an arenecarboxamidrazone **9** (2.24 mmol, 2 equiv) were dissolved in anhydrous pyridine (15 mL), the mixture was stirred at rt, and monitored by TLC (9:1 $CHCl_3$/MeOH). After completion of the reaction (16 h) the solvent was removed. Without further purification the obtained crude amidrazone **10** was dissolved in anhydrous DMF (15 mL), and heated at 140 °C for 0.5 h. The mixture was then cooled to rt, diluted with water (30 mL), and extracted with diethyl ether (5×20 mL). The combined organic phase was dried over $MgSO_4$, concentrated under diminished pressure, and the crude product was purified by column chromatography.

*4.4.2. General procedure III for the synthesis of 5-substituted-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazoles (**11**) from C-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)formic acid (**12**).* C-(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl)formic acid[31] (**12**, 0.20 g, 0.32 mmol) was heated in thionyl chloride (5 mL) at reflux temperature for 1 h then the excess of the reagent was evaporated. Traces of thionyl chloride were removed by repeated co-evaporations with toluene. The residue was dissolved in anhydrous toluene (4 mL), carboxamidrazone **9** (1–1.5 equiv) was added, and the mixture was heated at 90 °C. After completion of the reaction monitored by TLC (EtOAc and 1:1 EtOAc/hexane) the solvent was removed and the crude product was purified by column chromatography.

*4.4.3. General procedure IV for the synthesis of 5-substituted-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazoles (**11**) from N′-carboximido-C-(2,3,4,6-tetra-O-benzoil-β-D-glucopyranosyl) formic acid hydrazides (**14**).* An acid hydrazide **14** (50 mg) was heated in anhydrous toluene (2 mL) at 90 °C or in anhydrous DMF (2 mL) at 140 °C and the reaction was monitored by TLC (2:1 EtOAc/hexane). After completion of the reaction the solvent was removed under diminished pressure and the residue was purified by column chromatography.

*4.4.4. General procedure V for the synthesis of 5-substituted-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazoles (**11**) from N^1-tosyl-C-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)formamidrazone (**4**).* N^1-Tosyl-C-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)formamidrazone (**4**, 0.50 g, 0.63 mmol) was dissolved in anhydrous $CHCl_3$ (10 mL) and anhydrous pyridine (92 μL, 1.14 mmol, 1.8 equiv) was added. The mixture was cooled in an ice bath, and a solution of an acid chloride (0.95 mmol, 1.5 equiv) in anhydrous $CHCl_3$ (5 mL) was added dropwise over 15 min. Subsequently the mixture was stirred at rt and monitored by TLC (1:1 EtOAc/hexane). After total consumption of the starting material (2 days) the mixture was diluted with $CHCl_3$ (15 mL) and extracted with water (2×15 mL). The organic phase was dried over $MgSO_4$, concentrated under diminished pressure, and the crude product was purified by column chromatography.

*4.4.5. 5-Phenyl-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11a**).*

(A) From amidine **5** (0.70 g, 1.12 mmol) and benzamidrazone (**9a**, 0.30 g, 2.24 mmol) according to general procedure II. Purified

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by column chromatography (1:2 EtOAc-hexane) to yield 0.58 g (71%) white solid.

(B) From acid **12** (0.20 g, 0.32 mmol) and benzamidrazone (**9a**, 43 mg, 0.32 mmol) according to general procedure III. Reaction time: 20 h. Purified by column chromatography (1:2 EtOAc/hexane) to yield 0.14 g (60%) white solid.

(C) From acid hydrazide **14a** (50 mg, 0.07 mmol) in anhydrous toluene according to general procedure IV. Reaction time: 8 h. Purified by column chromatography (1:2 EtOAc/hexane) to yield 44 mg (90%) white solid.

(D) From acid hydrazide **14a** (40 mg, 0.05 mmol) in anhydrous DMF according to general procedure IV. Reaction time: 4 h. Purified by column chromatography (1:2 EtOAc/hexane) to yield 33 mg (85%) white solid.

(E) From tosyl-amidrazone **4** (0.55 g, 0.70 mmol) and benzoyl chloride (121 μL, 1.04 mmol) according to general procedure V. Purified by column chromatography (3:7 EtOAc/hexane) to yield 0.35 g (69%) white solid. Mp: 219–221 °C; $[\alpha]_D$ +14 (*c* 0.22, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3438 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 12.70 (1H, br s, triazole NH), 7.93–7.75 (9H, m, aromatics), 7.46 (1H, t, *J*=7.9 Hz, aromatic), 7.37–7.11 (15H, m, aromatics), 6.35, 6.15, 6.00 (3×1H, 3 pseudo t, *J*=9.2, 9.2 Hz in each, H-2′, H-3′, H-4′), 5.38 (1H, d, *J*=9.2 Hz, H-1′), 4.63–4.56 (2H, m, H-6′a, H-6′b), 4.45 (1H, ddd, *J*=9.2, 5.3, 2.6 Hz, H-5′); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.3, 166.1, 165.3, 165.1 (C=O), 158.0, 157.7 (triazole C-3, C-5), 133.4–133.0, 129.9–129.7, 129.2, 129.1, 128.7, 128.6–128.1, 127.8, 126.4 (aromatics), 76.7, 74.5, 74.2, 71.3, 69.5 (C-1′–C-5′), 63.2 (C-6′). Anal. Calcd for $C_{42}H_{33}N_3O_9$ (723.73): C, 69.70; H, 4.60; N, 5.81. Found: C, 69.82; H, 4.49; N, 5.73.

4.4.6. *5-(2-Naphthyl)-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11b**).*

(A) From amidine **5** (0.50 g, 0.80 mmol) and naphthalene-2-carboxamidrazone (**9b**, 0.30 g, 1.61 mmol) according to general procedure II. Purified by column chromatography (1:2 EtOAc/hexane) to yield 0.44 g (71%) white solid.

(B) From tosyl-amidrazone **4** (0.50 g, 0.63 mmol) and 2-naphthoyl chloride (0.18 g, 0.95 mmol) according to general procedure V. Purified by column chromatography (1:2 EtOAc/hexane) to yield 0.27 g (56%) white solid. Mp: 222–224 °C; $[\alpha]_D$ −1 (*c* 0.22, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3437 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 8.19 (1H, s, aromatic), 7.95–7.83 (9H, m, aromatics), 7.64–7.08 (17H, m, aromatics), 6.45, 6.24, 6.08 (3×1H, 3 pseudo t, *J*=10.6, 9.2 Hz in each, H-2′, H-3′, H-4′), 5.47 (1H, d, *J*=9.2 Hz, H-1′), 4.67–4.59 (2H, m, H-6′a, H-6′b), 4.49 (1H, ddd, *J*=10.6, 5.3, 2.6 Hz, H-5′); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.4, 166.0, 165.2, 165.2 (C=O), 158.0, 157.7 (triazole C-3, C-5), 133.8, 133.3–132.9, 132.8, 129.8–129.6, 129.2, 129.1, 128.7, 128.3–128.1, 127.5, 126.8, 126.3, 125.0, 123.3 (aromatics), 76.8, 74.5, 74.2, 71.4, 69.6 (C-1′–C-5′), 63.2 (C-6′). Anal. Calcd for $C_{46}H_{35}N_3O_9$ (773.78): C, 71.40; H, 4.56; N, 5.43. Found: C, 71.52; H, 4.46; N, 5.30.

4.4.7. *5-(2-Pyridyl)-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11c**).*

(A) From amidine **5** (0.15 g, 0.24 mmol) and pyridine-2-carboxamidrazone (**9c**, 33 mg, 0.24 mmol) according to general procedure II. Purified by column chromatography (1:1 EtOAc/hexane) to yield 0.14 g (80%) white solid.

(B) From acid **12** (1.20 g, 1.92 mmol) and pyridine-2-carboxamidrazone (**9c**, 0.39 g, 2.88 mmol) according to general procedure III. Purified by column chromatography (1:1 EtOAc/hexane) to yield 0.81 g (58%) white solid. Mp: 229–231 °C; $[\alpha]_D$ −37 (*c* 0.22, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3445 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 13.77 (1H, br s, triazole NH), 8.61 (1H, d, *J*=5.3 Hz, Py–H-6), 8.14 (1H, d, *J*=7.9 Hz, Py–H-3), 7.98, 7.93, 7.87 (3×2H, 3d, *J*=7.9 Hz in each, aromatics), 7.81–7.75 (3H, m, aromatics), 7.50–7.19 (13H, m, aromatics), 6.28, 6.08, 5.92 (3×1H, 3 pseudo t, *J*=9.2, 9.2 Hz in each, H-2′, H-3′, H-4′), 5.20 (1H, d, *J*=9.2 Hz, H-1′), 4.67 (1H, dd, *J*=11.9, 2.6 Hz, H-6′a), 4.58 (1H, dd, *J*=11.9, 5.3 Hz, H-6′b), 4.42 (1H, ddd, *J*=9.2, 5.3, 2.6 Hz, H-5′); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.2, 165.9, 165.2, 164.7 (C=O), 160.2, 154.8 (triazole C-3, C-5), 149.3 (Py–C-6), 145.6 (Py–C-2), 137.7 (Py–C-4), 133.3–132.9, 129.7–129.6, 129.5, 129.2, 129.0, 128.9, 128.3–128.2 (aromatics), 125.1, 122.2 (Py–C-3, Py–C-5), 76.6, 74.7, 74.6, 71.3, 69.7 (C-1′–C-5′), 63.5 (C-6′). Anal. Calcd for $C_{41}H_{32}N_4O_9$ (724.71): C, 67.95; H, 4.45; N, 7.73. Found: C, 67.81; H, 4.32; N, 7.69.

4.4.8. *3,5-Bis-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11d**).*

(B) From acid hydrazide **14d** (60 mg, 0.05 mmol) in anhydrous toluene according to general procedure IV. Reaction time: 10 h. Purified by column chromatography (2:3 EtOAc/hexane) to yield 45 mg (76%) white amorphous solid.

(A) From acid hydrazide **14d** (56 mg, 0.05 mmol) in anhydrous DMF according to general procedure IV. Reaction time: 8 h. Purified by column chromatography (2:3 EtOAc/hexane) to yield 40 mg (73%) white amorphous solid. R_f: 0.45 (1:1 EtOAc/hexane); IR (KBr) ν_{max} (cm^{-1}): 3438 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 7.96, 7.90, 7.81, 7.77 (4×4H, 4 d, *J*=7.9 Hz in each, aromatics), 7.51–7.20 (24 H, m, aromatics), 5.98, 5.73, 5.72 (3×2H, 3 pseudo t, *J*=9.9, 9.2 Hz in each, 2×H-2′, 2×H-3′, 2×H-4′), 5.04 (2H, d, *J*=9.9 Hz, 2×H-1′), 4.57 (2H, dd, *J*=12.6, 2.6 Hz, 2×H-6′a), 4.49 (2H, dd, *J*=12.6, 5.3 Hz, 2×H-6′b), 4.26 (2H, ddd, *J*=9.9, 5.3, 2.6 Hz, 2×H-5′); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.3, 165.8, 165.1, 164.9 (C=O), 156.4 (triazole C-3, C-5), 133.4, 133.1–133.0, 129.8–129.7, 129.4, 129.1, 128.8, 128.7, 128.4–128.2, (aromatics), 76.8, 73.9, 73.7, 71.2, 69.4 (C-1′–C-5′), 63.3 (C-6′). Anal. Calcd for $C_{70}H_{55}N_3O_{18}$ (1226.19): C, 68.57; H, 4.52; N, 3.43. Found: C, 68.71; H, 4.63; N, 3.34.

4.4.9. *5-(4-tert-Butylphenyl)-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11e**).*

From tosyl-amidrazone **4** (0.10 g, 0.13 mmol) and 4-*tert*-butylbenzoyl chloride (34 μL, 0.19 mmol) according to general procedure V. Purified by column chromatography (3:7 EtOAc/hexane) to yield 57 mg (58%) white amorphous solid. R_f: 0.41 (2:3 EtOAc/hexane); $[\alpha]_D$ −3 (*c* 0.36, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3437 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 8.62 (1H, br s, triazole NH), 7.94–7.89 (4H, m, aromatics), 7.84–7.81 (4H, m, aromatics), 7.72 (2H, d, *J*=7.9 Hz, aromatics), 7.49–7.15 (14H, m, aromatics), 6.31, 6.13, 5.99 (3×1H, 3 pseudo t, *J*=10.6, 9.2 Hz in each, H-2′, H-3′, H-4′), 5.35 (1H, d, *J*=9.2 Hz, H-1′), 4.67–4.56 (2H, m, H-6′a, H-6′b), 4.45 (1H, ddd, *J*=9.2, 5.3, 2.6 Hz, H-5′), 1.27 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.3, 166.1, 165.3, 165.0 (C=O), 157.9, 157.5 (triazole C-3, C-5), 153.4, 133.3–132.9, 129.8–129.6, 129.3, 129.1, 128.8, 128.3–128.1, 126.2, 125.6, 124.7 (aromatics), 76.7, 74.6, 74.2, 71.3, 69.6 (C-1′–C-5′), 63.3 (C-6′), 34.7 ($C(CH_3)_3$), 31.0 ($C(CH_3)_3$). Anal. Calcd for $C_{46}H_{41}N_3O_9$ (779.83): C, 70.85; H, 5.30; N, 5.39. Found: C, 70.93; H, 5.41; N, 5.28.

4.4.10. *5-(4-Acetoxyphenyl)-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11f**).*

From tosyl-amidrazone **4** (0.20 g, 0.25 mmol) and 4-acetoxybenzoyl chloride (75 mg, 0.38 mmol) according to general procedure V. After extraction and evaporation the crude mixture was dissolved in THF (6 mL), 1 M solution of Bu_4NF in THF (0.50 mL) was added and the mixture was refluxed for

3 h, then the solvent was removed under diminished pressure. The residue was purified by column chromatography (1:4 EtOAc/toluene) to yield 0.12 g (60%) white amorphous solid. R_f: 0.33 (1:3 EtOAc/toluene); $[\alpha]_D$ −8 (*c* 0.11, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 7.93 (2H, d, *J*=8.0 Hz, aromatics), 7.90–7.87 (4H, m, aromatics), 7.81 (2H, d, *J*=7.4 Hz, aromatics), 7.74 (2H, d, *J*=8.0 Hz, aromatics), 7.42 (1H, t, *J*=7.3 Hz, aromatics), 7.35–7.06 (11H, m, aromatics), 6.98 (2H, *J*=8.6 Hz, aromatics), 6.37, 6.21, 6.05 (3×1H, 3 pseudo t, *J*=9.9, 9.2 Hz in each, H-2′, H-3′, H-4′), 5.40 (1H, d, *J*=9.9 Hz, H-1′), 4.62 (2H, m, H-6′a, H-6′b), 4.48 (1H, ddd, *J*=9.9, 5.5, 4.3 Hz, H-5′), 2.21 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 169.1, 166.2, 165.9, 165.1, 165.0 (C=O), 157.7, 156.9 (triazole C-3, C-5), 151.7, 133.2–132.8, 129.7–129.4, 129.0, 128.8, 128.8, 128.6, 128.5, 128.2–127.6, 125.3, 125.1, 121.7 (aromatics), 76.5, 74.4, 74.0, 71.3, 69.5 (C-1′–C-5′), 63.2 (C-6′), 20.8 (CH_3). Anal. Calcd for $C_{44}H_{35}N_3O_{11}$ (781.76): C, 67.60; H, 4.51; N, 5.38. Found: C, 67.69; H, 4.62; N, 5.26.

*4.4.11. 3-(2′,3′,4′,6′-Tetra-O-benzoyl-β-D-glucopyranosyl)-5-(3,4,5-trimethoxyphenyl)-1,2,4-triazole (**11g**).* From tosyl-amidrazone **4** (0.20 g, 0.25 mmol) and 3,4,5-trimethoxybenzoyl chloride (87 mg, 0.38 mmol) according to general procedure V. Purified by column chromatography (3:7 EtOAc/hexane) to yield 0.11 g (54%) white solid. Mp: 125–127 °C; $[\alpha]_D$ +10 (*c* 0.39, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 8.65 (1H, br s, triazole NH), 7.93–7.91 (6H, m, aromatics), 7.75 (2H, d, *J*=6.6 Hz, aromatics), 7.50–7.22 (10H, m, aromatics), 7.08–7.05 (4H, m, aromatics), 6.23, 6.14, 5.99 (3×1H, 3 pseudo t, *J*=10.6, 9.2 Hz in each, H-2′, H-3′, H-4′), 5.31 (1H, d, *J*=9.2 Hz, H-1′), 4.67–4.62 (2H, m, H-6′a, H-6′b), 4.42 (1H, ddd, *J*=9.2, 5.3, 4.0 Hz, H-5′), 3.80 (3H, s, OMe), 3.62 (6H, s, 2×OMe); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.4, 165.9, 165.2, 165.0 (C=O), 158.3, 157.0 (triazole C-3, C-5), 153.2, 139.2, 133.4–133.0, 129.8–129.5, 129.1, 129.0, 128.7, 128.6, 128.3–128.0, 123.6, 103.4 (aromatics), 76.9, 74.2, 74.1, 71.4, 69.5 (C-1′–C-5′), 63.3 (C-6′), 60.7 (OMe), 55.8 (2×OMe). Anal. Calcd for $C_{45}H_{39}N_3O_{12}$ (813.80): C, 66.41; H, 4.83; N, 5.16. Found: C, 66.34; H, 4.96; N, 5.28.

*4.4.12. 5-(4-Nitrophenyl)-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11h**).* From tosyl-amidrazone **4** (1.70 g, 2.15 mmol) and 4-nitrobenzoyl chloride (0.60 g, 3.20 mmol) according to general procedure V. Purified by column chromatography (3:7 EtOAc/hexane) to yield 0.94 g (57%) yellow solid. Mp: 183–185 °C; $[\alpha]_D$ +35 (*c* 0.22, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3430 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 8.08 (2H, d, *J*=8.7 Hz, aromatics), 8.00–7.89 (8H, m, aromatics), 7.75 (2H, d, *J*=7.8 Hz, aromatics), 7.53–7.45 (3H, m, aromatics), 7.37–7.25 (7H, m, aromatics), 7.07–7.03 (2H, m, aromatics), 6.16, 6.02, 5.93 (3×1H, 3 pseudo t, *J*=9.7, 9.5 Hz in each, H-2′, H-3′, H-4′), 5.24 (1H, d, *J*=9.7 Hz, H-1′), 4.73–4.63 (2H, m, H-6′a, H-6′b), 4.42 (1H, ddd, *J*=9.7, 5.4, 2.7 Hz, H-5′); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.7, 165.8, 165.4, 165.2 (C=O), 159.0, 155.4 (triazole C-3, C-5), 148.0, 135.6, 133.5–133.2, 130.0–129.5, 128.9, 128.4–128.0, 127.0, 123.7 (aromatics), 77.2, 73.7, 73.5, 71.4, 69.3 (C-1′–C-5′), 63.3 (C-6′). Anal. Calcd for $C_{42}H_{32}N_4O_{11}$ (768.72): C, 65.62; H, 4.20; N, 7.29. Found: C, 65.73; H, 4.28; N, 7.17.

*4.4.13. 5-(3,5-Dinitrophenyl)-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11i**).* From tosyl-amidrazone **4** (1.70 g, 2.15 mmol) and 3,5-dinitrobenzoyl chloride (0.74 g, 3.22 mmol) according to general procedure V. Purified by column chromatography (3:7 EtOAc/hexane) to yield 0.90 g (55%) yellow solid. Mp: 107–109 °C; $[\alpha]_D$ +4.5 (*c* 0.47, MeOH); IR (KBr) ν_{max} (cm^{-1}): 3429 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 8.86 (2H, s, aromatics), 8.02–7.94 (6H, m, aromatics), 7.80 (2H, d, *J*=8.2 Hz, aromatics), 7.56–7.30 (10H, m, aromatics), 7.16–7.12 (2H, m, aromatics), 6.18, 5.94–5.88 (3×1H, 3 pseudo t, *J*=9.7, 9.6 Hz in each, H-2′, H-3′, H-4′), 5.27 (1H, d, *J*=9.8 Hz, H-1′), 4.69 (2H, m, H-6′a, H-6′b), 4.45 (1H, ddd, *J*=9.5, 5.4, 2.6 Hz, H-5′); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.7, 165.8, 165.6, 165.3 (C=O), 158.4, 154.7 (triazole C-3, C-5), 148.6, 133.9–133.3, 129.8–129.6, 129.0, 128.8, 128.5–128.2, 125.9, 118.6 (aromatics), 77.1, 73.4, 73.3, 71.1, 69.2 (C-1′–C-5′), 63.2 (C-6′). Anal. Calcd for $C_{42}H_{31}N_5O_{13}$ (813.72): C, 61.99; H, 3.84; N, 8.61. Found: C, 61.89; H, 3.93; N, 8.71.

*4.4.14. 5-(Acetoxymethyl)-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11j**).* From tosyl-amidrazone **4** (1.00 g, 1.26 mmol) and acetoxyacetyl chloride (204 μL, 1.89 mmol) according the general procedure V. After extraction and evaporation the crude mixture was dissolved in THF (30 mL), 1 M solution of Bu_4NF in THF (2.53 mL) was added and the mixture was refluxed for 1.5 h, then the solvent was removed under diminished pressure. The residue was purified by column chromatography (1:1 EtOAc/hexane) to yield 0.55 g (61%) white amorphous solid. R_f: 0.45 (2:3 EtOAc/hexane); $[\alpha]_D$ +16 (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 10.19 (1H, br s, triazole NH), 7.94–7.90 (6H, m, aromatics), 7.71 (2H, d, *J*=7.0 Hz, aromatics), 7.43–6.88 (12H, m, aromatics), 6.36, 6.22, 6.12 (3×1H, 3 pseudo t, *J*=9.6, 8.8 Hz in each, H-2′, H-3′, H-4′), 5.36 (1H, d, *J*=9.6 Hz, H-1′), 5.10 (2H, s, CH_2), 4.71–4.62 (2H, m, H-6′a, H-6′b), 4.49 (1H, ddd, *J*=9.6, 4.9, 2.6 Hz, H-5′), 1.87 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 170.3, 166.0, 165.6, 164.9, 164.7 (C=O), 157.1, 154.3 (triazole C-3, C-5), 133.1–132.8, 129.6–129.2, 129.0, 128.5, 128.2, 128.1–127.7 (aromatics), 76.6, 74.1, 73.9, 71.3, 69.3 (C-1′–C-5′), 63.2 (C-6′), 57.3 (CH_2), 20.0 (CH_3). Anal. Calcd for $C_{39}H_{33}N_3O_{11}$ (719.69): C, 65.09; H, 4.62; N, 5.84. Found: C, 65.18; H, 4.73; N, 5.73.

*4.4.15. 5-Methyl-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11k**).* The tosyl-amidrazone **4** (0.60 g, 0.76 mmol) treated with acetyl chloride (81 μL, 1.14 mmol) according to general procedure V gave 5-methyl-3-(2′,3′,4′,6′-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1-tosyl-1,2,4-triazole (**17k**). The crude product was purified by column chromatography (3:7 EtOAc/hexane) to yield 0.43 g (69%) of white amorphous solid. R_f: 0.67 (1:1 EtOAc/hexane); $[\alpha]_D$ +89 (*c* 0.23, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 7.99, 7.90, 7.81 (3×2H, 3d, *J*=7.9 Hz in each, aromatics), 7.74–7.72 (4H, m, aromatics), 7.54–7.25 (12H, m, aromatics), 7.05 (2H, d, *J*=7.9 Hz, aromatics), 6.02, 5.95, 5.80 (3×1H, 3 pseudo t, *J*=10.6, 9.2 Hz in each, H-2′, H-3′, H-4′), 4.97 (1H, d, *J*=9.2 Hz, H-1′), 4.60 (1H, dd, *J*=11.9, 2.6 Hz, H-6′a), 4.51 (1H, dd, *J*=11.9, 5.3 Hz, H-6′b), 4.28 (1H, ddd, *J*=9.2, 5.3, 2.6 Hz, H-5′), 2.71 (3H, s, CH_3), 2.28 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.1, 165.8, 165.1, 164.4 (C=O), 159.1, 157.0 (triazole C-3, C-5), 146.4 (TsC_qCH_3), 133.4–133.0, 130.0–129.6, 129.4, 129.0, 128.8, 128.7, 128.3–128.0 (aromatics), 76.7, 74.4, 74.0, 70.7, 69.4 (C-1′–C-5′), 63.4 (C-6′), 21.7 (CH_3), 14.5 (CH_3). Anal. Calcd for $C_{44}H_{37}N_3O_{11}S$ (815.84): C, 64.78; H, 4.57; N, 5.15. Found: C, 64.89; H, 4.44; N, 5.23.

This triazole **17k** (0.35 g, 0.43 mmol) was dissolved in THF (10 mL), a 1 M solution of Bu_4NF in THF (0.86 mL, 0.86 mmol) was added and the mixture was refluxed. After completion of the reaction (2 h) monitored by TLC (1:1 EtOAc/hexane), the solvent was removed under diminished pressure, and the residue was purified by column chromatography (3:2 EtOAc/hexane) to yield 0.25 g (88%) colourless syrup. R_f: 0.43 (3:1 EtOAc/hexane); $[\alpha]_D$ +43 (*c* 0.22, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3437 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 12.03 (1H, br s, triazole NH), 7.92–7.90 (4H, m, aromatics), 7.80–7.78 (4H, m, aromatics), 7.50–7.18 (12H, m, aromatics), 6.28, 6.08, 5.95 (3×1H, 3 pseudo t, *J*=9.8, 9.8 Hz in each, H-2′, H-3′, H-4′), 5.18 (1H, d, *J*=9.2 Hz, H-1′), 4.62–4.53 (2H, m, H-6′a, H-6′b), 4.40 (1H, ddd, *J*=9.2, 5.3, 2.6 Hz, H-5′), 2.35 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.3, 166.0, 165.2, 165.0 (C=O), 158.5, 154.7 (triazole C-3, C-5), 133.3–133.0, 129.8–129.7, 129.4, 129.0, 128.8, 128.3–128.2 (aromatics), 76.6, 74.7, 74.3, 71.1, 69.5 (C-1′–C-5′), 63.4 (C-6′), 12.1 (CH_3). Anal. Calcd for $C_{37}H_{31}N_3O_9$ (661.66): C, 67.16; H, 4.72; N, 6.35. Found: C, 67.29; H, 4.60; N, 6.24.

*4.4.16. 5-(tert-Butyl)-3-(2′,3′,4′,6′-tetra-O-benzoyl-β-D-glucopyranosyl)-1,2,4-triazole (**11l**).* Tosyl-amidrazone **4** (1.00 g, 1.26 mmol) and pivaloyl chloride (0.46 mL, 3.79 mmol, 3 equiv) were dissolved in anhydrous $CHCl_3$ (20 mL), anhydrous pyridine (0.37 mL, 4.55 mmol, 3.6 equiv) and 4-dimethylaminopyridine (7.7 mg, 0.06 mmol, 5 mol %) were added, and the mixture was stirred at rt for 1 h, then refluxed for 6 h. After completion of the reaction (monitored by TLC, 1:1 EtOAc/hexane) the mixture was diluted with $CHCl_3$ (30 mL) and extracted with water (2×20 mL). The organic phase was dried over $MgSO_4$, concentrated under diminished pressure, and the crude product was purified by column chromatography (3:7 EtOAc/hexane) to yield 0.86 g (77%) N^3-(pivaloyl)-N^1-tosyl-C-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)formamidrazone (**18l**) as a pale yellow oil. R_f: 0.28 (3:7 EtOAc/hexane); $[\alpha]_D$ +6 (*c* 0.37, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3399 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 10.00 (1H, s, NH), 8.07 (2H, d, *J*=7.9 Hz, aromatics), 7.99 (1H, s, NH), 7.92 (2H, d, *J*=7.9 Hz, aromatics), 7.73 (2H, d, *J*=7.9 Hz, aromatics), 7.66 (2H, d, *J*=7.9 Hz, aromatics), 7.62–7.21 (14H, m, aromatics), 6.75 (2H, d, *J*=7.9 Hz, aromatics), 5.90, 5.68, 5.33 (3×1H, 3 pseudo t, *J*=9.9, 9.2 Hz in each, H-2, H-3, H-4), 4.70 (1H, dd, *J*=12.6, 2.0 Hz, H-6a), 4.53 (1H, d, *J*=9.9 Hz, H-1), 4.46 (1H, dd, *J*=12.3, 4.6 Hz, H-6b), 4.20 (1H, ddd, *J*=9.9, 4.6, 2.0 Hz, H-5), 2.11 (3H, s, CH_3), 1.28 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 179.2 (C=$OC(CH_3)_3$), 166.0, 165.6, 165.1, 164.7 (C=O), 143.0, 135.3, 134.6 (C=N, TsC_q), 133.7–133.1, 129.8–128.1, 127.2 (aromatics), 78.6, 76.4, 73.1, 69.5, 68.6 (C-1–C-5), 62.2 (C-6), 40.1 ($C(CH_3)_3$), 27.4 ($C(CH_3)_3$), 21.6 (CH_3). MS-ESI (*m*/*z*): calcd for $C_{47}H_{46}N_3O_{12}S^+$ $[M+H]^+$: 876.28. Found: 876.67.

The above amidrazone **18l** (0.32 g, 0.36 mmol) was heated in xylene (6 mL) at 120 °C for 2 h. The solvent was removed and the crude product was purified by column chromatography (2:3 EtOAc/hexane) to give the title compound **11l** as a pale yellow oil. Yield: 0.14 g (54%); R_f: 0.31 (4:6 EtOAc/hexane); $[\alpha]_D$ +25 (*c* 0.42, $CHCl_3$); IR (KBr) ν_{max} (cm^{-1}): 3431 (br, NH); ^1H NMR ($CDCl_3$) δ (ppm): 9.88 (1H, br s, triazole NH), 7.92, 7.89, 7.81, 7.75 (4×2H, 4d, *J*=8.0 Hz in each, aromatics), 7.49–7.05 (12H, m, aromatics), 6.30, 6.12, 6.04 (3×1H, 3 pseudo t, *J*=9.9, 9.2 Hz in each, H-2′, H-3′, H-4′), 5.33 (1H, d, *J*=9.9 Hz, H-1′), 4.70–4.59 (2H, m, H-6′a, H-6′b), 4.45 (1H, ddd, *J*=9.2, 4.9, 2.6 Hz, H-5′), 1.24 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ (ppm): 166.3, 166.0, 165.4, 164.8 (C=O), 157.9 (triazole C-3, C-5), 133.3–132.8, 129.9–129.6, 129.3, 129.7, 128.7, 128.3–128.0 (aromatics), 76.6, 74.5, 74.3, 71.5, 69.7 (C-1′–C-5′), 63.5 (C-6′), 32.1 ($C(CH_3)_3$), 28.8 ($C(CH_3)_3$). Anal. Calcd for $C_{40}H_{37}N_3O_9$ (703.74): C, 68.27; H, 5.30; N, 5.97. Found: C, 68.39; H, 5.41; N, 5.91.

*4.4.17. 3,5-Diphenyl-1,2,4-triazole (**16**).*

(A) The amidrazone **15** (40 mg, 0.17 mmol) was heated in anhydrous toluene (2 mL) and the reaction was monitored by TLC (EtOAc and 1:4 EtOAc/hexane). After completion of the reaction (2 days) the solvent was removed under diminished pressure and the residue was purified by column chromatography (1:4 EtOAc/hexane) to yield 36 mg (97%) of **16** as a white solid.

(B) The amidrazone **15** (40 mg, 0.17 mmol) was heated in anhydrous DMF (2 mL) and the reaction was monitored by TLC (EtOAc and 1:4 EtOAc/hexane). After 10 h the solvent was removed under diminished pressure and the residue was purified by column chromatography (1:4 EtOAc/hexane) to yield 26 mg (70%) of **16** as a white solid. Mp: 188–190 °C (lit.[40] mp: 188–189 °C). ^1H and ^{13}C NMR data correspond to the reported spectra.[40]

4.5. 5-Phenyl-2-(2′,3′,4′,6′-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,3,4-oxadiazole (8a)

(A) The amidrazone **3** (0.10 g, 0.16 mmol) and benzoyl chloride (20 μL, 0.17 mmol, 1.1 equiv) were dissolved in anhydrous toluene (3 mL), the mixture was heated at 90 °C and monitored by TLC (1:1 EtOAc/hexane). After completion of the reaction (5 h) the solvent was removed and the residue was purified by column chromatography (1:3 EtOAc/hexane) to yield 75 mg (66%) white solid.

(B) The amidrazone **7a** (50 mg, 0.07 mmol) was heated in anhydrous toluene (2 mL) at 90 °C for 6 h. The reaction mixture was concentrated under diminished pressure and the residue was purified by column chromatography (1:3 EtOAc/hexane) to give 33 mg (68%) white solid.

(C) The amidrazone **7a** (50 mg, 0.07 mmol) was heated in DMF (1.5 mL) at 140 °C for 0.5 h. The reaction mixture was then cooled to rt, diluted with water (10 mL), and extracted with diethyl ether (5×10 mL). The combined organic phase was dried over $MgSO_4$, concentrated under diminished pressure, and the crude product was purified by column chromatography (1:3 EtOAc/hexane) to give 35 mg (71%) white solid. ^1H and ^{13}C NMR data correspond to the reported spectra.[5]

4.6. Computational studies

Series of B3LYP[41–44] and M06-2X[45] DFT theoretical calculations on substituted formamidrazones, acyl-amidrazones (on their formation, tautomerism, and ring closure reactions) were carried out using the standard 6-31G(d,p) basis set. For substituted amidrazones MP2 calculations were performed as well. The GAUSSIAN '09 suite of software[46] was used for all calculations. The existence of local minima on the potential energy surfaces and the first order transition state geometries, which connect them were proven in each case by the calculation of analytical second derivatives. All of the energy and energy difference values shown in the figures and tables are zero-point vibrational energy (ZPVE) corrected values and are given in kcal/mol units. In the calculations the aromatic (phenyl and 2-pyridyl) and non-aromatic (β-D-glucopyranosyl) substituents were modelled through simple phenyl (Ph) and methyl (Me) groups, respectively. For the calculation of the relative energies and the barrier height of transition states, the lowest energy of the system (e.g., at conformational or tautomeric energies) or the sum of the lowest energies of subsystems (e.g., at bimolecular reactions) were chosen as references.

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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.tet.2013.09.099.

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