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Regioselective synthesis of 5-trifluoromethyl-1,2,3-triazole nucleoside analogues via TBS-directed 1,3-dipolar cycloaddition reaction

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ABSTRACT

Herein described was a straightforward method for the highly regioselective synthesis of 5-trifluoromethyl-1,2,3-triazole nucleoside analogues, which featured the utilization of tert-butyldimethylsilyl (TBDMS) group as the directing group in the 1,3-dipolar cycloaddition reactions. 4-tert-Butyldimethylsilyl-5-trifluoromethyl-1,2,3-triazole nucleoside analogues were generated as the only cycloaddition products in moderate yields (15–79%) via the treatment of glycosyl azides with 3,3,3-trifluoro-1-tert-butyldimethylsilylpropyne **1** in toluene at 85 °C. Removal of TBS groups in these triazole cycloadducts with tetrabutylammonium fluoride (TBAF) smoothly afforded the various 5-trifluoromethyl-1,5-disubstituted 1,2,3-triazole nucleoside analogues in good yields (40–88%).

1. Introduction

Naturally occurring nucleosides and their synthetic analogues have been the intensive research interest due to their highly potential biological activity as antitumor and antiviral agents [1]. Among them nucleosides bearing a five-member ring nucleobase are of great interest due the fact that they have exhibited unique biological activities [2]. In the past years, many highly bioactive triazole nucleosides have been synthesized and biologically evaluated for virus and hepatitis therapies [3–6]. For example, 1,2,3-triazole TSAO analogue displayed very strong bioactivity for inhibition of HIV-1 in CEM and MT-4 cells [4a] and 1,2,4-triazole ribavirin derivative has been reported to be very potent for treatment of drug-resistant pancreatic cancer [6a] (Fig. 1).

On the other hand, introduction of a trifluoromethyl group into some nucleosides has drawn considerable attention in view of the remarkable changes in the bioactivity and stability of the corresponding compounds [7]. Thus, development of methodology for synthesizing trifluoromethylated triazolo nucleoside analogues has been of interest of organic chemists, medicinal chemists and pharmacologists. So far, the most versatile method to access triazole-based nucleoside analogues has been the Huisgen 1,3-dipolar cycloaddition of glycosyl azides with alkynes [8]. This classic thermal cycloaddition, however, usually suffers from the formation of regioisomeric mixture of products when azides were treated with unsymmetrical acetylene [9]. Although the regioselective synthesis of the 4-trifluoromethyl-substituted 1,2,3-triazoles has been made by several groups [10], to the best of our knowledge the regioselective incorporation of a CF_3 group into 5-position of 1,2,3-triazolo moiety of nucleosides has never been explored [11]. Indeed, the strong electron-withdrawing property of trifluoromethyl group makes it more accessible to 4-position of triazole ring. Recently, Hlasta et al. [12] reported the use of trimethylsilyl group as regiodirecting group to control the regioselectivity in synthesizing 1,5-disubstituted 4-trimethylsilyl 1,2,3-triazoles via the cycloaddition reaction of 1-trimethylsilylacetylenes and organoazides. Inspired by Hlasta's work, we were interested to investigate the viability of utilizing the trifluoromethylated acetylene as an efficient building block to regioselective preparation of 5-trifluoromethylated 1,2,3-triazoles. Herein described was our methodology of practically constructing 5-trifluoromethyl 1,5-disubstituted 1,2,3-triazole nucleoside analogues via tert-butyldimethylsilyl(TBS)-directed 1,3-dipolar cycloaddition reaction.

2. Results and discussion

We first prepared the 3,3,3-trifluoro-1-tert-butyldimethylsilylpropyne **1** as the dipolarophile for cycloaddition reaction. According to a modified procedure reported by Hanamoto and

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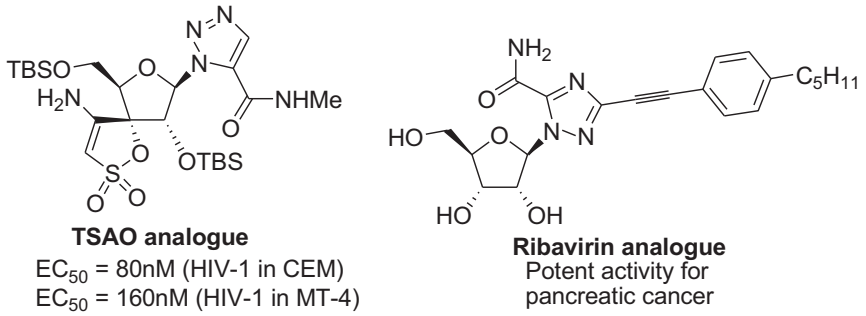
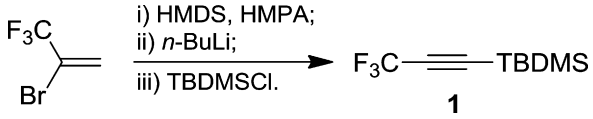


Fig. 1. Highly bioactive triazolo nucleoside analogues.



Scheme 1. Synthesis of **1** from 2-bromo-3,3,3-trifluoropropene.

Yamada [13], **1** could be provided by addition of commercially available 2-bromo-3,3,3-trifluoropropene to a solution of in situ generated lithium hexamethyldisilazide (LiHMDS) in THF using hexamethylphosphoramide (HMPA) as additive, followed by addition of tert-butyldimethylsilyl chloride(TBDMSCl). ^{19}F NMR spectroscopy of the reaction mixture illustrated that the reaction proceeded smoothly. However, it was unexpectedly difficult to isolate **1** from other components by fractional distillation due to their close boiling points. ^{1}H, ^{13}C and ^{19}F NMR showed that **1** was contaminated by the hexamethyldisilazane (HMDS) and other unknown compounds, which were also confirmed by the GC–MS analysis (Scheme 1) [14].

Although the purification of the compound **1** was unsuccessful, we believed that the cycloaddition between organic azides and the crude compound **1** should be chemospecific, thus purification of **1** was not necessary [15]. To investigate the reactivity of **1** for 1,3-dipolar cycloaddition, readily available benzyl azide **2** was chosen as the model substrate. We were pleased to find that the cycloaddition, when performed in toluene at 85 °C for 30 h, provided the desired triazole cycloadduct **3** as the single regioisomer product (Scheme 2). The regiochemistry assignment of the compound **3** was determined by HMBC experiment [16]. Increasing reaction temperature from 85 °C to reflux temperature or performing the reaction in THF provided the product in very low yield along with some complicated byproducts.

The promising result obtained from the cycloaddition of benzyl azide **2** with **1** stimulated us to extend the reaction to glycosyl azide substrates. Thus, a series of O-protected glycosyl azides **6a–6c** [17], **6d** [18], **6e–6g** [19] and **6h** [20] were prepared according to the reported procedures and used for cycloaddition reaction. It should be pointed out that for non-participating benzyl group protected glycosyl azide **6c**, anomeric mixture (α/β 1:1) was obtained. O-Acyl glycosyl azide **6e** was also contaminated by about 10% of 1,2-cis anomer [19b]. ^{n}-Octyl azide **4** was used as a control and the results were summarized in Table 1. We were pleased to find that all the glycosyl azides provided the desired cycloadducts

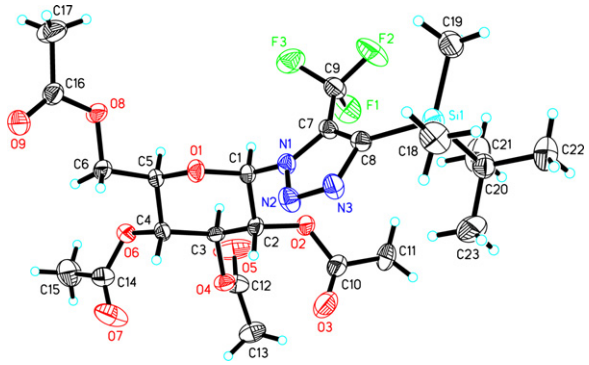
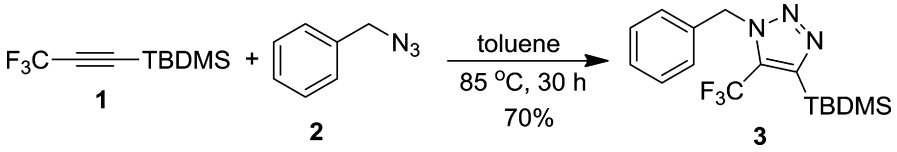


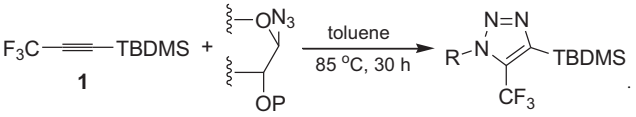
Fig. 2. ORTEP drawing of the X-ray crystallographic structure of **7a**.

in moderate yields (Table 1, entries 2–9), albeit lower yields compared to **4** (Table 1, entry 1). Of all the O-protected glycosyl azides, glycopyranosyl azides **6a** and **6b** (Table 1, entries 2 and 3) were more reactive in the cycloaddition reaction than glycofuranosyl azides **6e** and **6f** (Table 1, entries 6–8), although higher potential bioactivity should be expected from the latter ones. The lower reactivity of **6e** and **6f** was ascribed to the larger steric hindrance of furanose ring in the transition state of cycloaddition than that of their pyranose counterparts. Additionally, it was found that all the O-acyl glycosyl azides reacted smoothly to afford the corresponding cycloadducts with retention of configuration at the anomeric carbon (Table 1, entries 2 and 3 and entries 5–8). Lower yield (37%) was resulted for O-benzyl glucosyl azide **6c** (anomeric mixture 1:1) to afford the corresponding mixture **7c** of two α/β anomers (Table 1, entry 4) which may due to more crowded steric environment of azido group caused by benzyl group in **6c** than that caused by acetyl group in **6a** or **6b** [21]. It should be noted that cycloaddition reaction also proceeded well for the azides **6d** and **6h**, where azido groups were not attached to anomeric carbon (Table 1, entries 5 and 9), and the corresponding 1,2,3-triazole nucleosides **7d** and **7h** were provided in 70% and 54% yield, respectively. Most importantly, all the cycloaddition reactions exhibited very excellent regioselectivity and exclusively delivered the 5-trifluoromethyl-1,4,5-trisubstituted 1,2,3-triazoles. The absolute structure of compound **7a** was confirmed by X-ray diffraction analysis (Fig. 2) [22]. The excellent regioselectivities undoubtedly illustrated that the transition state of herein described 1,3-dipolar cycloaddition was mainly directed by TBS



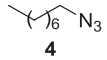
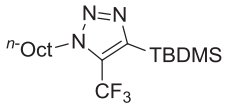
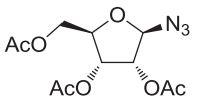
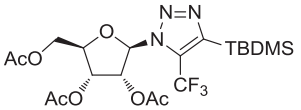
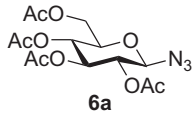
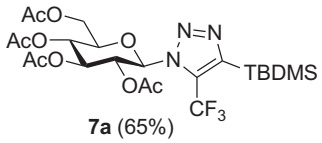
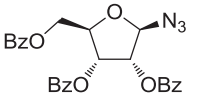
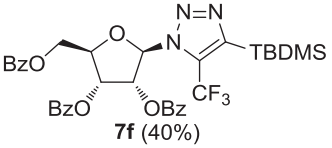
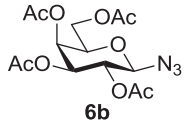
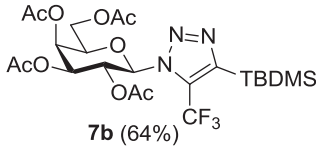
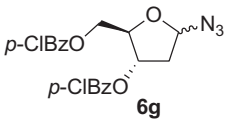
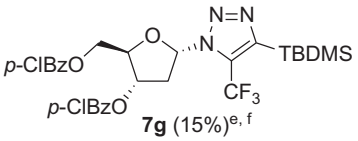
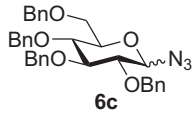
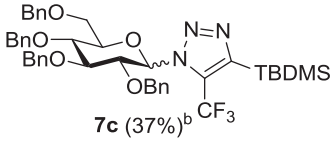
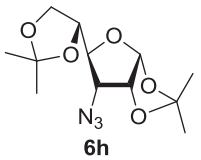
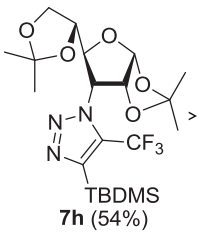
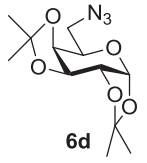
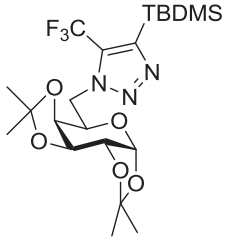
Scheme 2. Model cycloaddition reaction between **1** and benzyl azide **2**.

Table 1
Cycloaddition between glycosyl azides and 3,3,3-trifluoro-1-tert-butyldimethylsilylpropyne **1**.[a]



P = protecting group,
R = glycosyl group

6 **7**

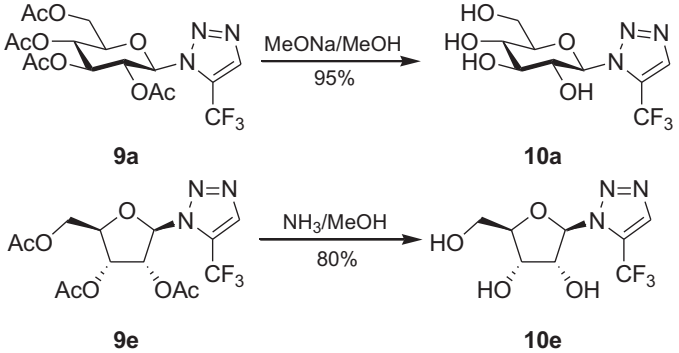
Entry	Glycosyl azides	Products	Entry	Glycosyl azides	Products
1	 **4**	 **5** (79 %)	6	 **6e**	 **7e** (47%)[c, d]
2	 **6a**	 **7a** (65%)	7	 **6f**	 **7f** (40%)
3	 **6b**	 **7b** (64%)	8	 **6g** α:β 1:5	 **7g** (15%)[e, f]
4	 **6c** α:β 1:1	 **7c** (37%)[b]	9	 **6h**	 **7h** (54%)
5	 **6d**	 **7d** (70%)	–	–	–

[a] Isolated yield based on glycosyl azide, average of two runs.
[b] α/β ratio 1:1 determined by ^{1}H NMR and ^{19}F NMR.
[c] Less than 10% of α isomer was observed based on ^{1}H and ^{19}F NMR analysis.
[d] Product was contaminated by another regioisomer when at reflux temperature and/or extended time (48 h).
[e] p-ClBz: p-ClC$_6$H$_4$CO.
[f] Only α cycloadduct was isolated based on ^{1}H NMR and ^{19}F NMR analysis.

group (rather than CF_3 group) by means of a combination of steric hindrance and electronical bias between α and β position of acetylene, as proposed elsewhere [12].

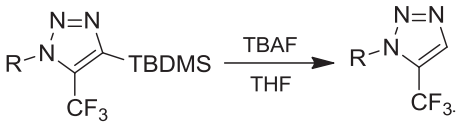
With the prepared 4-(tert-butyldimethylsilyl)-5-trifluoromethyl-1,2,3-triazoles in hand, removal of silyl groups in the products was carried out via treatment with TBAF and the corresponding 5-trifluoromethyl substituted 1,2,3-triazole nucleoside analogues were afforded in moderate to good yields (Table 2) [23].

Finally, the global deprotection of the sugar moieties in the 5-trifluoromethyl substituted 1,2,3-triazole nucleoside analogues was examined briefly. Considering that global deprotection of acetyl groups from the sugar moieties of all 1,2,3-triazole nucleoside analogues would be achieved by standard conditions,



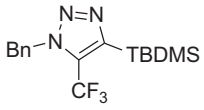
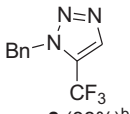
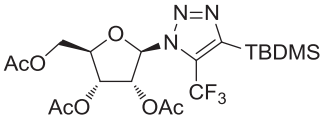
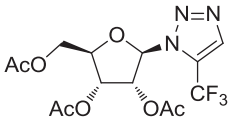
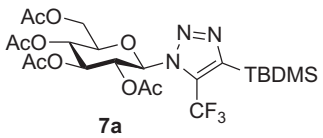
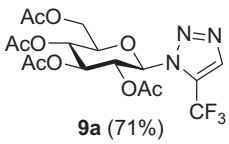
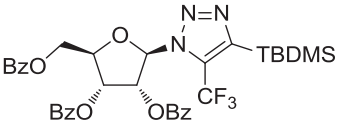
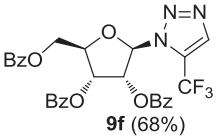
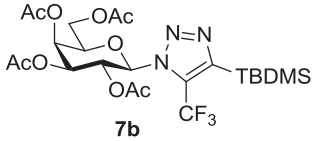
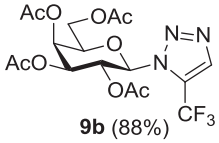
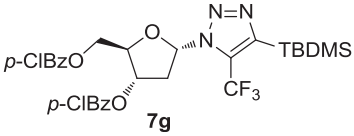
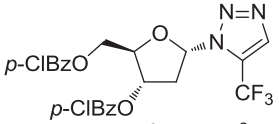
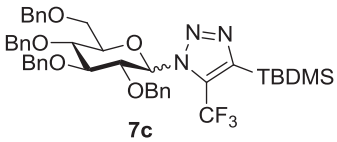
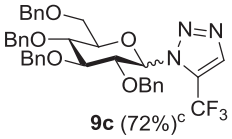
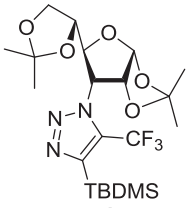
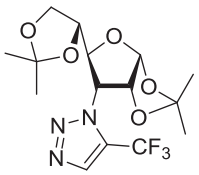
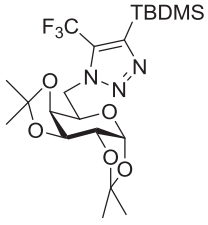
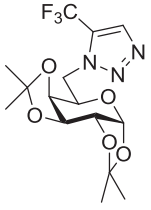
Scheme 3. Deprotection of acetyl groups in compounds **9a** and **9e**.

Table 2
Desilylation of 4-(tert-butyldimethylsilyl)-5-trifluoromethyl-1,2,3-triazoles.[a]



7 **9**

R=glycosyl group

Entry	Substrates	Products	Entry	Substrates	Products
1	 **3**	 **8** (88%)[b]	6	 **7e**	 **9e** (64%)[d]
2	 **7a**	 **9a** (71%)	7	 **7f**	 **9f** (68%)
3	 **7b**	 **9b** (88%)	8	 **7g**	 **9g** (40%)[e]
4	 **7c**	 **9c** (72%)[c]	9	 **7h**	 **9h (50%)**
5	 **7d**	 **9d** (80%)	–	–	–

[a] Isolated yield based on the glycosyl triazole.
[b] Use aqueous HF as desilylating reagent.
[c] α/β ratio 1:1.3 determined by ^{1}H NMR and ^{19}F NMR.
[d] Less than 5% of α isomer was observed based on ^{1}H and ^{19}F NMR analysis.
[e] p-ClBz: p-ClC_6H_4CO.

only glucopyranosyl 9a and glucofuranosyl 9e were chosen as our model substrates to examine the final deprotection of acetyl groups by Zemplen reagent [24a] and NH_3/MeOH solution [24b], respectively. Thus the desired 5-trifluoromethyl-1,2,3-triazoles nucleoside analogues 10a and 10e were afforded in 95% and 85% yield, respectively (Scheme 3).

3. Conclusion

In summary, a straightforward method for highly regioselective synthesis of trifluoromethylated 1,2,3-triazole nucleoside analogues has been developed. This method afforded a practical and efficient route to construct the 5-trifluoromethyl substituted 1,2,3-triazole ring. Various 5-trifluoromethylated 1,2,3-triazole nucleoside analogues were prepared according to this methodology. Antivirus and cytotoxicity evaluation of the obtained 5-trifluoromethylated 1,2,3-triazole nucleoside analogues are currently in progress and will be reported soon.

4. Experimental

4.1. General

Unless otherwise indicated, all reagents were obtained from commercial available sources and were used without further purification. THF was distilled from sodium/benzophenone ketyl and toluene was distilled from sodium immediately before use. All reactions were carried out in flame-dried glassware under a nitrogen atmosphere. IR spectra of liquids were recorded as thin film on KBr plates and IR spectra of solids were recorded as KBr

pellets with a Nicolet 380 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-400 spectrometer with tetramethylsilane (TMS) as an internal standard. ^{19}F NMR spectra were recorded on Bruker AM-400 spectrometer with $CFCl_3$ as an external standard and low field is positive. Low-resolution mass spectra (LRMS) and GC–MS were recorded on Shimadzu QP-2010. High-resolution mass spectra (HRMS) were measured on FTMS-7.0 or Waters Micromass GCT, respectively. GC–HRMS were measured on Waters Micromass GCT Premier. Elemental analyses were taken on a Vario EL III elementary analysis instrument.

4.2. 3,3,3-Trifluoro-1-tert-butyldimethylsilylpropyne (1)

Hexamethyldisilazane (HMDS, 17.6 mL, 84.3 mmol) and hexamethylphosphoramide (HMPA, 0.9 mL, 5.17 mmol) were added successively into THF (100 mL). Then, ^{n}-BuLi (1.6 M in hexane solution, 52.8 mL, 84.48 mmol) was added dropwise at 0 °C. After the mixture was stirred for 0.5 h at 0 °C, the whole solution was cooled to −78 °C and 2-bromo-3,3,3-trifluoropropene (4 mL, 38.7 mmol) in THF (30 mL) was added slowly over 1 h via syringe pump. After stirring for 30 min, tert-butylchlorodimethylsilane (5.29 g, 35.1 mmol) in THF (30 mL) was added dropwise. The reaction mixture was stirred for additional 30 min at −78 °C and hexane (200 mL) was added successively to the resulting mixture before it warmed to room temperature. The resulting solution was washed carefully with saturated NH_4Cl aqueous solution. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting oil residue was purified by Vigreux distillation (bp 94–101 °C/760 mmHg) to give crude **1** as a cloudy oil (ca. 11 g, 31% determined by GC–MS analysis of final fractional components) that can be used directly without further purification. Characterization data of compound **1** in the crude product were obtained by NMR and GC–MS analysis of final fractional components: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H, $C(CH_3)_3$), 0.22 (s, 6H, 2 CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 115.4 (q, J = 257.6 Hz, CF_3), 95.0 (q, J = 5.4 Hz, acetylene C-1), 93.1 (q, J = 50.5 Hz, acetylene C-2), 28.1 (tert-butyl-CH_3), 18.7 (tert-butyl-C), −3.2 (Si-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −50.8 (s, 3F, CF_3); GC–MS (ESI): m/z 208.1 $[M]^+$; GC–HRMS-EI: m/z $[M]^+$ calcd for $C_9H_{15}F_3Si$: 208.0895. Found: 208.0892.

4.3. General procedure for 1,3-dipolar cycloaddition between organic azides and 3,3,3-trifluoro-1-tert-butyldimethylsilylpropyne (1)

Into a 50 mL round-bottom flask equipped with a condenser was added organic azide (1.0 equiv), 3,3,3-trifluoro-1-tert-butyldimethylsilylpropyne **1** (1.0 equiv based on GC–MS analysis) and toluene (10 mL, ca. 0.2 M). The mixture was stirred at 85 °C for 30 h before cooled to room temperature. After removal of the solvent, the residue was diluted with ethyl acetate, washed with brine and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent gave a residue which was purified by flash column chromatography on silica gel to give the 5-trifluoromethyl-substituted cycloadduct.

4.3.1. 1-Benzyl-4-(tert-butyldimethylsilyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (3)

IR (KBr, cm^{-1}) ν_{max} 3093, 3068, 3036, 2957, 2859, 1637, 1524, 1471, 1255, 1169, 1134, 725, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.32 (m, 3H, phenyl-H), 7.26–7.24 (m, 2H, phenyl-H), 5.68 (s, 2H, benzyl-CH_2), 0.94 (s, 9H, $C(CH_3)_3$), 0.35 (s, 6H, 2 CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.2 (triazole C-4), 133.2 (phenyl-C), 131.6 (q, J = 39.2 Hz, triazole C-5), 127.8 (phenyl-C), 127.6 (phenyl-C), 126.6 (phenyl-C), 119.8 (q, J = 270.1 Hz, CF_3), 52.4 (benzyl-CH_2), 25.4 (tert-butyl-CH_3), 16.1 (tert-butyl-C), −6.3 (Si-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −55.1 (s, 3F, CF_3); MS (EI): m/z (%) 77.0 (9), 91.0 (100), 127.0 (13). 285.0 (28); anal. calcd for $C_{16}H_{22}F_3N_3Si$: C, 56.28; H, 6.49; N, 12.31. Found: C, 56.54; H, 6.55; N, 12.49.

4.3.2. 4-(tert-Butyldimethylsilyl)-1-octyl-5-(trifluoromethyl)-1H-[1,2,3]-triazole (5)

IR (KBr, cm^{-1}) ν_{max} 2931, 2861, 1464, 1258, 1174, 1133; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (t, J = 7.2 Hz, 2H, octyl-CH_2), 1.98–1.91 (m, 2H, octyl-CH_2), 1.34–1.27 (m, 10H, 5 octyl-CH_2), 0.94 (s, 9H, $C(CH_3)_3$), 0.88 (t, J = 6.8 Hz, 3H, octyl-CH_3), 0.35 (s, 6H, 2 CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.6 (triazole C-4), 132.5 (q, J = 39.0 Hz, triazole C-5), 121.0 (q, J = 268.5 Hz, CF_3), 50.1 (C-1), 31.7, 30.1, 29.0, 28.9, 26.5 (C-2,3,4,5,6), 26.4 (tert-butyl-CH_3), 22.6 (C-7), 17.2 (tert-butyl-C), 14.0 (C-8), −5.2 (Si-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −55.6 (s, 3F, CF_3); MS (EI): m/z (%) 43.1 (23), 57.1 (26), 69.0 (95), 196.0 (52), 307.1 (100); anal. calcd for $C_{17}H_{32}F_3N_3Si$: C, 56.17; H, 8.87; N, 11.56. Found: C, 56.39; H, 9.18; N, 11.65.

4.3.3. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-4-(tert-butyldimethylsilyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (7a)

IR (KBr, cm^{-1}) ν_{max} 2956, 2860, 1755, 1238, 1169, 1141, 1096; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00–5.95 (m, 1H, H-2), 5.84–5.82 (d, J = 9.2 Hz, 1H, H-1), 5.44–5.39 (m, 1H, H-4), 5.29–5.24 (m, 1H, H-3), 4.27–4.22 (dd, J = 12.8, 4.8 Hz, 1H, H-6), 4.21–4.18 (dd, J = 12.8, 2.4 Hz, 1H, H-6′), 3.98 (ddd, J = 10.4, 5.2, 2.4 Hz, 1H, H-5), 2.08 (s, 3H, acetyl-CH_3), 2.07 (s, 3H, acetyl-CH_3), 2.04 (s, 3H, acetyl-CH_3), 1.86 (s, 3H, acetyl-CH_3), 0.93 (s, 9H, $C(CH_3)_3$), 0.36 (s, 6H, 2 CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.5 (acetyl-CO), 169.2 (acetyl-CO), 168.2 (acetyl-CO), 167.2 (acetyl-CO), 146.1 (triazole C-4), 132.6 (q, J = 40.4 Hz, triazole C-5), 119.5 (q, J = 269.4 Hz, CF_3), 83.8 (C-1), 74.1, 72.2, 68.8, 66.6 (C-2,3,4,5), 60.4 (C-6), 25.3 (tert-butyl-CH_3), 19.5 (2 acetyl-CH_3), 19.2 (acetyl-CH_3), 16.2 (tert-butyl-C), −6.3 (Si-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −55.2 (s, 3F, CF_3); MS (EI): m/z (%) 43.1 (88), 109.0 (54), 115.0 (9), 127.0 (19), 169 (100), 331.0 (6), 524.0 (10); anal. calcd for $C_{23}H_{34}F_3N_3O_9Si$: C, 47.50; H, 5.89; N, 7.22. Found: C, 47.45; H, 6.26; N, 7.05.

4.3.4. 1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-4-(tert-butyldimethylsilyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (7b)

IR (KBr, cm^{-1}) ν_{max} 2956, 2936, 2860, 1740, 1371, 1218, 1174, 1141, 1082; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10–6.06 (m, 1H, H-2), 5.84 (d, J = 9.2 Hz, 1H, H-1), 5.54–5.53 (m, 1H, H-4), 5.25 (dd, J = 10, 3.6 Hz, 1H, H-3), 4.23–4.14 (m, 3H, H-5, H-6, H-6′), 2.20 (s, 3H, acetyl-CH_3), 2.05 (s, 3H, acetyl-CH_3), 2.02 (s, 3H, acetyl-CH_3), 1.87 (s, 3H, acetyl-CH_3), 0.94 (s, 9H, $C(CH_3)_3$), 0.37 (s, 6H, 2 CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.3 (acetyl-CO), 170.2 (acetyl-CO), 170.0 (acetyl-CO), 168.3 (acetyl-CO), 147.2 (triazole C-4), 133.3 (q, J = 40.8 Hz, triazole C-5), 120.5 (q, J = 269.4 Hz, CF_3), 85.9 (C-1), 74.1, 71.4, 67.3, 66.9 (C-2,3,4,5), 61.3 (C-6), 26.4 (tert-butyl-CH_3), 20.6 (2 acetyl-CH_3), 20.2 (acetyl-CH_3), 17.2 (tert-butyl-C), −5.2 (Si-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −55.0 (s, 3F, CF_3); MS (EI): m/z (%) 43.1 (100), 109.0 (44), 115.0 (8), 127.0 (29), 169.0 (98), 229.0 (17), 331.0 (20), 524.0 (8); anal. calcd for $C_{23}H_{34}F_3N_3O_9Si$: C, 47.50; H, 5.89; N, 7.22. Found: C, 47.60; H, 5.96; N, 7.14.

4.3.5. 1-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-4-(tert-butyldimethylsilyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (7c)

Mixture of α/β anomers. Major isomer: IR (KBr, cm^{-1}) ν_{max} 3088, 3063, 3030, 2929, 2859, 1949, 1873, 1807, 1744, 1605, 1253, 1166, 1092, 734, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–6.94 (m, 20H, 4 OBn-H), 6.23 (d, J = 6 Hz, 1H, H-1), 5.05–4.89 (m, 3H, OBn-CH_2, H-3), 4.78–4.44 (m, 6H, 3 OBn-CH_2), 3.94–3.89 (m, 2H, H-2, H-5), 3.80–3.72 (m, 2H, H-4, H-6), 3.56 (dd, J = 11.2, 0.8 Hz, 1H, H-6), 0.99 (s, 9H, $C(CH_3)_3$), 0.44 (s, 3H, CH_3, satellite peak observed), 0.40 (s, 3H, CH_3, satellite peak observed); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.1 (triazole C-4), 138.5 (phenyl-C),

138.2 (phenyl-C), 137.6 (phenyl-C), 137.4 (phenyl-C), 128.5 (2 phenyl-C), 128.4 (2 phenyl-C), 128.0 (phenyl-C), 127.9 (2 phenyl-C), 127.8 (phenyl-C), 127.7 (2 phenyl-C), 127.6 (phenyl-C), 127.4 (phenyl-C), 120.7 (q, J = 269.1 Hz, CF_3), 86.2 (C-1), 82.6, 80.0, 78.7, 77.3 (C-2,3,4,5), 75.8 (OBn-CH_2), 75.3 (OBn-CH_2), 74.0 (OBn-CH_2), 73.5 (OBn-CH_2), 68.0 (C-6), 26.5 (tert-butyl-CH_3), 17.2 (tert-butyl-C), −5.1 (Si-CH_3), one triazole carbon not observed under the ^{13}C NMR conditions; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −54.7 (s, 3F, CF_3); MS (EI): m/z (%) 77.0 (10), 91.0 (100), 127.0 (16), 160.0 (5), 285.0 (32); anal. calcd for $C_{43}H_{50}F_3N_3O_5Si$: C, 66.73; H, 6.51; N, 5.43. Found: C, 66.29; H, 6.36; N, 5.02.

4.3.6. 1-(6-Deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-6-yl)-4-(tert-butyldimethylsilyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (7d)

IR (KBr, cm^{-1}) ν_{max} 2983, 2932, 2859, 1462, 1380, 1249, 1172, 1127; ^1H NMR (400 MHz, $CDCl_3$) δ 5.47 (d, J = 5.6 Hz, 1H, H-1), 4.67–4.64 (m, 3H, H-3, H-6, H-6′), 4.44–4.41 (m, 1H, H-5), 4.32 (dd, J = 4.8, 2.4 Hz, 1H, H-2), 4.28 (dd, J = 8, 2 Hz, 1H, H-4), 1.50 (s, 3H, isopropylidene-CH_3), 1.44 (s, 3H, isopropylidene-CH_3), 1.36 (s, 3H, isopropylidene-CH_3), 1.29 (s, 3H, isopropylidene-CH_3), 0.92 (s, 9H, $C(CH_3)_3$), 0.36 (s, 6H, 2 CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.8 (triazole C-4), 136.0 (q, J = 39.2 Hz, triazole C-5), 123.2 (q, J = 269.2 Hz, CF_3), 112.3 (isopropylidene-C), 111.4 (isopropylidene-C), 98.5 (C-1), 73.4, 73.2, 72.8, 69.3 (C-2,3,4,5), 52.1 (C-6), 28.7 (isopropylidene-CH_3), 28.3 (isopropylidene-CH_3), 28.2 (isopropylidene-CH_3), 27.3 (isopropylidene-CH_3), 26.9 (tert-butyl-CH_3), 19.5 (tert-butyl-C), −2.9 (Si-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −55.0 (s, 3F, CF_3); MS (MALDI): m/z 494.4 $[M+H]^+$; HRMS-MALDI: m/z $[M+H]^+$ calcd for $C_{21}H_{35}F_3N_3O_5Si$: 494.2293; found: 494.2300; anal. calcd for $C_{21}H_{34}F_3N_3O_5Si$: C, 51.10; H, 6.94; N, 8.51. Found: C, 51.00; H, 7.23; N, 8.49.

4.3.7. 1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-4-(tert-butyldimethylsilyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (7e)

Major isomer: IR (KBr, cm^{-1}) ν_{max} 2956, 2931, 2859, 1753, 1229, 1167, 1139; ^1H NMR (400 MHz, $CDCl_3$) δ 6.16 (d, J = 2 Hz, 1H, H-1), 6.13 (dd, J = 5.2, 2.4 Hz, 1H, H-3), 5.84 (dd, J = 6.4, 5.2 Hz, 1H, H-2), 4.51–4.46 (m, 1H, H-4), 4.38 (dd, J = 12.4, 3.2 Hz, 1H, H-5), 4.15 (dd, J = 12.4, 4.4 Hz, 1H, H-5′), 2.15 (s, 3H, acetyl-CH_3), 2.12 (s, 3H, acetyl-CH_3), 2.00 (s, 3H, acetyl-CH_3), 0.95 (s, 9H, $C(CH_3)_3$), 0.35 (s, 6H, 2 CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5 (acetyl-CO), 169.3 (2 acetyl-CO), 147.0 (triazole C-4), 134.0 (triazole C-5, no split observed), 121.9 (CF_3, no split observed), 89.4 (C-1), 81.3, 74.6, 70.8 (C-2,3,4), 62.6 (C-5), 26.4 (tert-butyl-CH_3), 20.6 (acetyl-CH_3), 20.5 (acetyl-CH_3), 17.2 (tert-butyl-C), −5.2 (Si-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −54.8 (s, 3F); MS (EI): m/z (%) 43.1 (89), 69.1 (8), 97.0 (46), 117.0 (13),139.0 (100), 157.0 (38), 259.0 (14), 452.0 (16); anal. calcd for $C_{20}H_{30}F_3N_3O_7Si$: C, 47.14; H, 5.93; N, 8.25. Found: C, 47.30; H, 6.06; N, 8.18.

4.3.8. 1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-4-(tert-butyldimethylsilyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (7f)

IR (KBr, cm^{-1}) ν_{max} 3091, 3068, 3036, 2956, 2931, 2888, 2859, 1635, 1523, 1254, 1169, 1135, 1058, 780, 725; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03–7.92 (m, 6H, phenyl-H), 7.61–7.33 (m, 9H, phenyl-H), 6.46 (dd, J = 5.2, 1.6 Hz, 1H, H-3), 6.43 (d, J = 1.6 Hz, 1H, H-1), 6.37 (dd, J = 4.8, 7.2 Hz, 1H, H-2), 4.95–4.91 (m, 1H, H-4), 4.71 (dd, J = 12.4, 4 Hz, 1H, H-5), 4.57 (dd, J = 5.6, 12.4 Hz, 1H, H-5′), 0.96 (s, 9H, $C(CH_3)_3$), 0.36 (s, 6H, 2 CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.2 (benzoyl-CO), 165.0 (benzoyl-CO), 146.4 (triazole C-4), 133.9 (phenyl-C), 133.6 (phenyl-C), 133.2 (phenyl-C), 129.9 (2 phenyl-C), 129.8 (phenyl-C), 129.4 (phenyl-C), 128.7 (phenyl-C), 128.6 (2 phenyl-C), 128.5 (phenyl-C), 128.4 (phenyl-C), 89.7 (C-1), 81.2, 75.7, 71.7 (C-2,3,4), 63.5 (C-5), 26.4 (tert-butyl-CH_3), 17.2 (tert-butyl-C), −5.3 (Si-CH_3), one triazole carbon and CF_3 carbon not observed under the ^{13}C NMR conditions; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −54.7 (s, 3F, CF_3); MS (EI): m/z (%) 57.1 (5), 77.0 (11), 91.0 (100), 127.0 (16), 160.0 (5), 285.0 (31); anal. calcd for $C_{35}H_{36}F_3N_3O_7Si$: C, 60.42; H, 5.22; N, 6.04. Found: C, 60.03; H, 5.23; N, 5.81.

4.3.9. 1-(2-Deoxy-3,5-di-O-(4-chlorobenzoyl)-α-D-ribofuranosyl)-4-(tert-butyldimethylsilyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (7g)

IR (KBr, cm^{-1}) ν_{max} 3100, 3070, 3041, 2956, 2931,2859, 1925, 1721, 1594, 1266, 1238, 1169, 1136, 758, 683; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99–7.93 (m, 4H, phenyl-H), 7.46–7.36 (m, 4H, phenyl-H), 6.50 (dd, J = 6.8, 4 Hz, 1H, H-1), 5.98–5.94 (m, 1H, H-3), 4.68–4.64 (m, 1H, H-4), 4.55 (dd, J = 4.8, 12 Hz, 1H, H-5), 4.44 (dd, J = 12, 6.4 Hz, 1H, H-5′), 3.69 (ddd, J = 4, 7.2, 14.4 Hz, 1H, H-2), 2.83 (ddd, J = 5.2, 7.2, 14.4 Hz, 1H, H-2′), 0.95 (s, 9H, $C(CH_3)_3$), 0.36 (s, 6H, 2 CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.5 (benzoyl-CO), 167.3 (benzoyl-CO), 149.1 (2 phenyl-C), 142.5 (phenyl-C), 142.0 (phenyl-C), 135.4 (triazole C-4), 133.5 (2 phenyl-C), 131.3 (phenyl-C), 131.1 (phenyl-C), 130.1 (q, J = 39.5 Hz, triazole C-5), 123.0 (q, J = 269.3 Hz, CF_3), 89.8 (C-1), 85.9, 77.4, 66.3 (C-2,3,4), 39.9 (C-5), 28.7 (tert-butyl-CH_3), 19.5 (tert-butyl-C), −2.9 (Si-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −54.8 (s, 3F, CF_3); GC–MS (EI): m/z (%) 53.1 (18), 81.0 (100), 111.0 (15), 139.0 (57), 235.9 (12); MS (ESI): m/z 665.9 $[M+Na]^+$; HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{28}H_{30}Cl_2F_3N_3O_5SiNa$: 666.1176. Found: 666.1180.

4.3.10. 1-(3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl)-4-(tert-butyldimethylsilyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (7h)

IR (KBr, cm^{-1}) ν_{max} 2987, 2956, 2934, 2889, 2860, 1528, 1464, 1383, 1254, 1169, 1132, 1069; ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (d, J = 4 Hz, 1H, H-1), 5.36 (dd, J = 8.8, 4 Hz, 1H, H-3 or H-2), 4.92 (dd, J = 9.2, 5.6 Hz, 1H, H-4), 4.81–4.79 (m, 1H, H-5), 4.36–4.32 (m, 1H, H-2 or H-3), 4.00 (dd, J = 8.8, 6.4 Hz, 1H, H-6), 3.5 (dd, J = 8.8, 6.4 Hz, 1H, H-6′), 1.52 (s, 3H, isopropylidene-CH_3), 1.28 (s, 3H, isopropylidene-CH_3), 1.25 (s, 3H, isopropylidene-CH_3), 1.17 (s, 3H, isopropylidene-CH_3), 0.90 (s, 9H, $C(CH_3)_3$), 0.38 (s, 3H, CH_3), 0.33 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.4 (triazole C-4), 133.2 (q, J = 39.5 Hz, triazole C-5), 121.0 (q, J = 268.8 Hz, CF_3), 113.8 (isopropylidene-C), 109.8 (isopropylidene-C), 104.7 (C-1), 79.1, 75.4, 65.9 (C-2,3,4), 61.2 (C-5, C-6), 27.0 (isopropylidene-CH_3), 26.4 (isopropylidene-CH_3), 26.3 (isopropylidene-CH_3), 25.8 (isopropylidene-CH_3), 25.0 (tert-butyl-CH_3), 17.1 (tert-butyl-C), −5.2 (Si-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −55.6 (s, 3F, CF_3); MS (ESI): m/z 494.0 $[M+H]^+$; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{21}H_{35}F_3N_3O_5Si$: 494.2293. Found: 494.2308.

4.4. Preparation of 5-trifluoromethyl-1,5-disubstituted-1,2,3-triazoles

4.4.1. 1-Benzyl-5-(trifluoromethyl)-1H-[1,2,3]-triazole (8)

To a solution of 3 (103 mg, 0.3 mmol) in THF (3 mL) was added hydrofluoric acid (0.13 mL, 40% aq., 3 mmol). After the starting material had been consumed, the mixture was diluted with H_2O. The aqueous solution was extracted with ethyl acetate (3 mL × 3 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the crude product was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1:20, v/v) to afford 8 (60 mg, 88%) as a light yellow oil. IR (KBr, cm^{-1}) ν_{max} 3062, 3025, 2954, 2925, 2854, 1636, 1562, 1248, 1172, 1139, 720, 694; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H, triazole C5-H), 7.37–7.34 (m, 3H, phenyl-H), 7.29–7.26 (m, 2H, phenyl-H), 5.66 (s, 2H, benzyl-CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.6 (triazole C-4), 133.6 (phenyl-C), 129.0 (phenyl-C),

128.9 (phenyl-C), 127.8 (phenyl-C), 119.8 (q, J = 268.1 Hz, CF_3), 53.6 (benzyl-CH_2), one triazole carbon not observed under the ^{13}C NMR conditions; ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.8 (s, 3F, CF_3); MS (EI): m/z (%) 77.0 (9), 91.0 (100), 130.0 (72), 178.0 (23), 198.0 (22), 227.0 (9); anal. calcd for $C_{10}H_8F_3N_3$: C, 52.87; H, 3.55; N, 18.50. Found: C, 53.01; H, 3.73; N, 18.64.

*4.4.2. General procedure for the preparation of 5-trifluoromethyl-1,5-disubstituted 1,2,3-triazoles nucleoside analogues (**9**)*

Tetrabutylammonium fluoride (TBAF, 1.9 equiv) was added to a solution of 7 (1.0 equiv) in THF (3 mL, ca. 0.1 M). The mixture was stirred at room temperature for 1 h, then washed with brine and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the crude product was purified by flash column chromatography on silica gel to give the desired 5-trifluoromethyl-1,5-disubstituted 1,2,3-triazole nucleoside analogues 9.

*4.4.2.1. 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (**9a**).* IR (KBr, cm^{-1}) ν_{max} 2964, 2927, 2852, 1749, 1571, 1224, 1153, 1039; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H, triazole C5-H), 5.87–5.80 (m, 2H, H-1, H-2), 5.43 (m, 1H, H-4), 5.26 (m, H-3), 4.23–4.22 (m, 2H, H-6, H-6′), 4.00 (ddd, J = 10.0, 4.4, 3.2 Hz, 1H, H-5), 2.07 (s, 6H, acetyl-CH_3), 2.04 (s, 3H, acetyl-CH_3), 1.88 (s, 3H, acetyl-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5 (acetyl-CO), 170.1 (acetyl-CO), 169.2 (acetyl-CO), 168.5 (acetyl-CO), 135.3 (triazole C-4), 128.7 (q, J = 42.2 Hz, triazole C-5), 119.5 (q, J = 268.8 Hz, CF_3), 85.5 (C-1), 75.3, 72.8, 69.8, 67.5 (C-2,3,4,5), 61.4 (C-6), 20.6 (2 acetyl-CH_3), 20.2 (2 acetyl-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −58.2 (s, 3F, CF_3); MS (EI): m/z (%) 43.0 (100), 69.1 (5), 97.0 (20), 115.0 (11), 139.0 (41), 157.0 (11), 169.0 (8); anal. calcd for $C_{17}H_{20}F_3N_3O_9$: C, 43.69; H, 4.31; N, 8.99. Found: C, 43.79; H, 4.66; N, 8.87.

*4.4.2.2. 1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (**9b**).* IR (KBr, cm^{-1}) ν_{max} 2976, 2930, 1724, 1594, 1277, 1172, 1090; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H, triazole C5-H), 5.93–5.86 (m, 2H, H-1, H-2), 5.55–5.54 (m, 1H, H-4), 5.26 (dd, J = 8.8, 2.4 Hz, 1H, H-3), 4.25–4.15 (m, 3H, H-5, H-6, H-6′), 2.21 (s, 3H, acetyl-CH_3), 2.05 (s, 3H, acetyl-CH_3), 2.03 (s, 3H, acetyl-CH_3), 1.90 (s, 3H, acetyl-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4 (acetyl-CO), 170.1 (acetyl-CO), 170.0 (acetyl-CO), 168.7 (acetyl-CO), 135.6 (triazole C-4), 128.6 (q, J = 42.4 Hz, triazole C-5), 119.5 (q, J = 268.4 Hz, CF_3), 86.7 (C-1), 74.3, 70.9, 67.3, 66.7 (C-2,3,4,5), 61.2 (C-6), 20.6 (2 acetyl-CH_3), 20.5 (acetyl-CH_3), 20.2 (acetyl-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −58.0 (s, 3F, CF_3); MS (EI): m/z (%) 43.1 (100), 69.1 (8), 97.0 (18), 115.0 (11), 139.0 (34), 157.0 (10), 169.0 (5); anal. calcd for $C_{17}H_{20}F_3N_3O_9$: C, 43.69; H, 4.31; N, 8.99. Found: C, 43.86; H, 4.36; N, 8.64.

*4.4.2.3. 1-(2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (**9c**).* Mixture of α/β anomers. Major isomer: IR (KBr, cm^{-1}) ν_{max} 3145, 3031, 2917, 2868, 1955, 1877, 1812, 1741, 1562, 1247, 1142, 1096, 742, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H, triazole C5-H), 7.34–6.94 (m, 20H, 4 OBn-H), 6.09 (d, J = 6 Hz, 1H, H-1), 4.99–4.84 (m, 3H, OBn-CH_2, H-3), 4.74–4.36 (m, 6H, 3 OBn-CH_2), 3.88–3.84 (m, 2H, H-2, H-5), 3.78–3.69 (m, 2H, H-4, H-6), 3.51–3.48 (m, 1H, H-6′); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.9 (phenyl-C), 140.5 (phenyl-C), 140.2 (phenyl-C), 139.5 (phenyl-C), 136.9 (triazole C-4), 131.6 (q, J = 42.5 Hz, triazole C-5), 131.0 (phenyl-C), 130.9 (2 phenyl-C), 130.8 (phenyl-C), 130.7 (phenyl-C), 130.6 (phenyl-C), 130.4 (phenyl-C), 130.3 (phenyl-C), 130.2 (2 phenyl-C), 130.1 (phenyl-C), 130.0 (phenyl-C), 122.0 (q, J = 269.1 Hz, CF_3), 88.3 (C-1), 84.8, 81.9, 80.4, 79.5 (C-2,3,4,5), 78.3 (OBn-CH_2), 77.5 (OBn-CH_2), 76.5 (OBn-CH_2), 75.9 (OBn-CH_2), 70.7 (C-6); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −58.2 (s, 3F, CF_3); MS (MALDI): m/z 682.2 $[M+Na]^+$; HRMS-MALDI: m/z $[M+Na]^+$ calcd for $C_{37}H_{36}F_3N_3O_5Na$: 682.2499. Found: 682.2518.

*4.4.2.4. 1-(6-Deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-6-yl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (**9d**).* IR (KBr, cm^{-1}) ν_{max} 2989, 2937, 1635, 1562, 1458, 1257, 1214, 1164, 1070; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H, triazole C5-H), 5.46 (d, J = 5.2 Hz, 1H, H-1), 4.68 (dd, J = 8, 2.4 Hz, 1H, H-3), 4.66–4.64 (m, 2H, H-6, H-6′), 4.44–4.40 (m, 1H, H-5), 4.34 (dd, J = 5.6, 2.4 Hz, 1H, H-2), 4.29 (dd, J = 8, 2.4 Hz, 1H, H-4), 1.51 (s, 3H, isopropylidene-CH_3), 1.45 (s, 3H, isopropylidene-CH_3), 1.37 (s, 3H, isopropylidene-CH_3), 1.28 (s, 3H, isopropylidene-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.4 (triazole C-4), 131.0 (q, J = 41.2 Hz, triazole C-5), 122.1 (q, J = 268.6 Hz, CF_3), 112.4 (isopropylidene-C), 111.4 (isopropylidene-C), 98.5 (C-1), 73.3, 73.2, 72.6, 69.2 (C-2,3,4,5), 52.2 (C-6), 28.2 (isopropylidene-CH_3), 28.1 (isopropylidene-CH_3), 27.2 (isopropylidene-CH_3), 26.9 (isopropylidene-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −58.5 (s, 3F, CF_3); MS (EI): m/z 379.1 $[M]^+$; HRMS-EI: m/z $[M]^+$ calcd for $C_{15}H_{20}F_3N_3O_5$: 379.1355. Found: 379.1350.

*4.4.2.5. 1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (**9e**).* Major isomer: IR (KBr, cm^{-1}) ν_{max} 2956, 2850, 1743, 1588, 1371, 1236, 1147, 1112; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H, triazole C5-H), 6.17 (dd, J = 5.2, 2.8 Hz, 1H, H-2), 6.13 (d, J = 2.8 Hz, 1H, H-1), 5.79 (t, J = 5.8 Hz, 1H, H-3), 4.54–4.50 (m, 1H, H-4), 4.39 (dd, J = 12.4, 3.2 Hz, 1H, H-5), 4.16 (dd, J = 12, 4 Hz, H-5′) 2.15 (s, 3H, acetyl-CH_3), 2.14 (s, 3H, acetyl-CH_3), 2.02 (s, 3H, acetyl-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5 (acetyl-CO), 169.5 (acetyl-CO), 169.2 (acetyl-CO), 134.6 (triazole C-4), 128.7 (q, J = 42.8 Hz, triazole C-5), 119.5 (q, J = 269.9 Hz, CF_3), 89.3 (C-1), 81.7, 74.1, 70.8 (C-2,3,4), 62.5 (C-5), 20.6 (acetyl-CH_3), 20.5 (acetyl-CH_3), 20.4 (acetyl-CH_3); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −58.3 (s, 3F, CF_3); MS (EI): m/z (%) 43.1 (100), 69.1 (5), 85.0 (22), 97.0 (11), 115.0 (19), 139.0 (15), 157.0 (9); anal. calcd for $C_{14}H_{16}F_3N_3O_7$: C, 42.54; H, 4.08; N, 10.63. Found: C, 42.92; H, 4.08; N, 10.54.

*4.4.2.6. 1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (**9f**).* IR (KBr, cm^{-1}) ν_{max} 3147, 3063, 3034, 2954, 1728, 1601, 1263, 1119, 1069, 1024, 709, 686; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–7.94 (m, 7H, phenyl-H, triazole C5-H), 7.61–7.35 (m, 9H, phenyl-H), 6.53 (dd, J = 4.8, 1.6 Hz, 1H, H-2), 6.39 (d, J = 1.2 Hz, 1H, H-1), 6.30 (t, J = 6.4 Hz, 1H, H-3), 4.96–4.92 (m, 1H, H-4), 4.74 (dd, J = 4, 12 Hz, 1H, H-5), 4.56 (dd, J = 4.8, 12.8 Hz, 1H, H-5′); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.1 (benzoyl-CO), 165.1 (benzoyl-CO), 165.0 (benzoyl-CO), 134.6 (2 phenyl-C), 134.0 (phenyl-C), 133.7 (phenyl-C), 133.3 (phenyl-C), 129.9 (phenyl-C), 129.8 (phenyl-C), 129.3 (phenyl-C), 128.7 (phenyl-C), 128.6 (phenyl-C), 128.5 (phenyl-C), 128.4 (phenyl-C), 119.5 (q, J = 272.0 Hz, CF_3), 89.6 (C-1), 81.6, 75.2, 71.6 (C-2,3,4), 63.2 (C-5), two triazole carbons not observed under the ^{13}C NMR conditions; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −58.2 (s, 3F, CF_3); MS (EI): m/z (%) 57.1 (5), 77.0 (7), 91.0 (100), 113.0 (16), 181.0 (10), 252.0 (7); anal. calcd for $C_{29}H_{22}F_3N_3O_7$: C, 59.90; H, 3.81; N, 7.23. Found: C, 59.69; H, 3.84; N, 6.84.

*4.4.2.7. 1-(2-Deoxy-3,5-di-O-(4-chlorobenzoyl)-α-D-ribofuranosyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (**9g**).* IR (KBr, cm^{-1}) ν_{max} 3148, 3095, 3066, 2950, 2927, 2854, 1924, 1719, 1594, 1266, 1091, 758, 684; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, triazole C5-H), 7.93 (AA′BB′, J = 8.8 Hz, 4H, phenyl-H), 7.44–7.41 (m, 4H, phenyl-H), 6.50–6.48 (m, 1H, H-1), 5.66–5.62 (m, 1H, H-3), 4.75 (dd, J = 8.4, 4 Hz, 1H, H-4), 4.67 (dd, J = 12, 3.6 Hz, 1H, H-5), 4.61 (dd, J = 12, 4.8 Hz, 1H, H-5′), 3.50–3.45 (m, 1H, H-2), 3.14–3.06 (m,

1H, H-2′); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.2 (benzoyl-CO), 165.0 (benzoyl-CO), 140.3 (phenyl-C), 139.8 (phenyl-C), 135.0 (phenyl-C), 134.9 (triazole C-4), 131.2 (phenyl-C), 129.0 (phenyl-C), 128.8 (phenyl-C), 128.7 (phenyl-C), 128.1 (q, J = 43.4 Hz, triazole C-5), 127.5 (phenyl-C), 119.7 (q, J = 268.0 Hz, CF_3), 87.7 (C-1), 83.9, 74.9, 63.9 (C-2,3,4), 37.1 (C-5); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −58.3 (s, 3F, CF_3); MS (ESI): m/z 551.9 $[M+Na]^+$; HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{22}H_{16}Cl_2F_3N_3O_5Na$: 552.0311. Found: 552.0314.

*4.4.2.8. 1-(3-Deoxy-1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-yl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (**9h**).* IR (KBr, cm^{-1}) ν_{max} 2987, 2937, 1744, 1566, 1376, 1216, 1162, 1109; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, triazole C5-H), 6.05 (d, J = 4 Hz, 1H, H-1), 5.44 (dd, J = 8.8, 4 Hz, 1H, H-3 or H-2), 4.97 (dd, J = 9.2, 5.6 Hz, 1H, H-4), 4.86–4.84 (m, 1H, H-5), 4.46–4.42 (m, 1H, H-2 or H-3), 4.06 (dd, J = 8.8, 6.4 Hz, 1H, H-6), 3.60 (dd, J = 8.8, 5.6 Hz, 1H, H-6′), 1.57 (s, 3H, isopropylidene-CH_3), 1.32 (s, 3H, isopropylidene-CH_3), 1.31 (s, 3H, isopropylidene-CH_3), 1.27 (s, 3H, isopropylidene-CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.2, 128.2 (q, J = 41.3 Hz, triazole C-5), 119.9 (q, J = 268.3 Hz, CF_3), 113.9 (isopropylidene-C), 110.0 (isopropylidene-C), 104.7 (C-1), 79.1, 75.2, 65.8, 61.2 (C-2,4,5,6), 27.0 (isopropylidene-CH_3), 26.3 (isopropylidene-CH_3), 25.7 (isopropylidene-CH_3), 24.8 (isopropylidene-CH_3), one glycosyl carbon not observed under the ^{13}C NMR conditions; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −59.0 (s, 3F, CF_3); MS (EI): m/z 379.1 $[M]^+$; HRMS-EI: m/z $[M]^+$ calcd for $C_{15}H_{20}F_3N_3O_5$: 379.1355. Found: 379.1358.

4.5. Deprotection of the sugar moieties

4.5.1. 1-(β-D-Glucopyranosyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (10a)

To the peracetate protected compound 9a (63 mg, 0.14 mmol) was added a solution of 0.005 M sodium methoxide (1.6 mg, 0.03 mmol) in dry methanol (6 mL). The pale yellow solution was stirred at room temperature for 4 h and subsequently neutralized by dropwise addition of AcOH (pH ∼ 6). Filtration and evaporation of solvent to dryness under reduced pressure afforded the desired 10a (38 mg, 95%) as a colorless syrup. IR (KBr, cm^{-1}) ν_{max} 3338 (br.), 2932, 2880, 1568, 1336, 1264, 1147, 1043; ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H, triazole C5-H), 5.46 (d, J = 8.8 Hz, 1H, H-1), 4.21 (t, J = 8.8 Hz, 1H, H-2), 3.77 (dd, J = 12, 2.4 Hz, 1H, H-4), 3.60 (dd, J = 5.6, 12.8 Hz, 1H, H-6), 3.52–3.46 (m, 2H, H-5, H-6′), 3.43–3.39 (m, 1H, H-3); ^{13}C NMR (100.6 MHz, CD_3OD) δ 134.0 (triazole C4), 129.0 (q, J = 41.5 Hz, triazole C5), 119.7 (q, J = 268.0 Hz, CF_3), 87.5 (C-1), 80.0, 77.1, 71.6, 69.5 (C-2,3,4,5), 60.9 (C-6). ^{19}F NMR (376.5 MHz, CD_3OD) δ −59.7 (s, 3F, CF_3); MS (ESI): m/z 322.0 $[M+Na]^+$; HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_9H_{12}F_3N_3O_5Na$: 322.0621. Found: 322.0634.

4.5.2. 1-(β-D-Ribofuranosyl)-5-(trifluoromethyl)-1H-[1,2,3]-triazole (10e)

To the peracetate protected compound 9e (71 mg, 0.18 mmol) was added a solution of 7 N NH_3/MeOH (2 mL, 14 mmol). The mixture was stirred at room temperature until TLC shows the complete consumption of the starting material. After removal of the solvent in vacuo, the crude product was purified by flash column chromatography on silica gel (methanol/dichloromethane, 1:10, v/v) to give the desired 10e (38 mg, 80%) as a colorless syrup. Major isomer: IR (KBr, cm^{-1}) ν_{max} 3301, 2937, 1565, 1337, 1231, 1145, 1042; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H, triazole C5-H), 5.81 (d, J = 4 Hz, 1H, H-1), 5.32 (dd, J = 5.6, 9.6 Hz, 1H, H-2), 4.79–4.77 (m, 2H, H-3, H-4), 4.24–4.21 (m, 1H, H-5), 4.00–3.96 (m, 1H, H-5′); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 135.1 (triazole C4), 127.8 (q, J = 41.3 Hz, triazole C4), 119.8 (q, J = 268.2 Hz, CF_3), 91.4 (C-1), 86.8, 74.0, 70.6 (C-2, 3, 4), 61.5 (C-5); ^{19}F NMR (376.5 MHz, DMSO-d_6) δ −57.3 (s, 3F, CF_3); MS (ESI): m/z 292.0 $[M+Na]^+$; HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_8H_{10}F_3N_3O_4Na$: 292.0516. Found: 292.0529.

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