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# Efficient Synthesis of 1,2,3-Triazole-Fused Bicyclic Compounds from Aldoses

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We would like to report an expedient synthesis of 1,2,3-triazole-fused bicyclic compounds starting from naturally occurring carbohydrates. These imino sugars were prepared in four steps from *glyco*-ynitols, readily available from monosaccharides. The title compounds were prepared by intramolecular 1,3-dipolar cycloaddition of azidoalkynes in a one-pot substitution/thermal cyclization procedure.

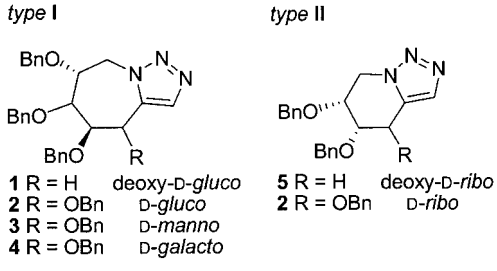


## Introduction

1,2,3-Triazoles are attractive motifs, which, because of their chemical properties and structure, should find many applications in organic chemistry. Not present in natural products, they are remarkably stable to metabolic transformations. Furthermore, 1,2,3-triazole moieties are emerging as powerful pharmacophores in their own right.[1] Our group has now been involved in the synthesis of carbohydrate derivatives for a couple of years[2–7] and, in continuation of our studies on their utilization, we became interested in the synthesis of polyhydroxylated structures incorporating the 1,2,3-triazole motif.

Known methods for the regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles include the treatment of azides with active methylene compounds,[8] followed by introduction of functional groups, and 1,3-dipolar cycloadditions between azides and alkynes.[9]

Here we report the efficient synthesis of *glyco*-1,2,3-triazoles **1**–**6**, prepared by intramolecular 1,3-dipolar cycloadditions of carbohydrate derivatives readily available from aldohexoses (type **I**) and aldopentoses (type **II**) (Scheme 1). Such carbohydrate mimics belong to the family of imino sugars, which have been shown to be very potent inhibitors of glycosidases[10] and glycosyltransferases.[11] These sugar-derived 1,2,3-triazoles[12–15] can also be regarded as potential precursors to analogues of some important alkaloid antibiotics.




Scheme 1.

## Results and Discussion

The 1,2,3-triazole-fused bicyclic carbohydrate-derived compounds **1**–**6** were prepared by intramolecular 1,3-dipolar cycloadditions of azidoalkynes. Such azidoalkynes are readily available via *glyco*-ynitols, starting from tritylated aldoses, through one-carbon chain-elongation without creation of a new stereogenic center, followed by the activation and the azido substitution of the primary hydroxy group (Scheme 2).

We have recently reported the synthesis of 1,1-dibromoalkenes from partially protected and unprotected aldoses[5] and their transformation into *glyco*-ynitols.[6] These compounds are interesting scaffolds that can be used in many transformations. We first used these compounds to synthesize 1,6- and 1,7-enynes, which in turn afforded polyhydroxylated 1-vinylcyclopentenes and 1-vinylcyclohexenes through ring-closing enyne metathesis.[7] We would now like to describe the use of the *glycol*-ynitols for the rapid preparation of sugar-derived 1,2,3-triazoles.

We first devoted our efforts toward the synthesis of compound **1** (Scheme 3). Starting from 2-deoxy-6-*O*-trityl-D-glucose, the dibromo olefin was obtained by treatment of the hemiacetal with (dibromomethyl)triphenylphosphonium bromide in the presence of zinc in 1,4-dioxane under reflux.[5] Treatment of this olefin with *n*-butyllithium in THF at low temperature afforded the corresponding alkyne.[6] In the next step, this *glyco*-ynitol was subjected to a classical benzylation reaction, followed by deprotection of the primary hydroxy group by acidic treatment, affording **7**.[7] Activation of the primary hydroxy group by a tosylate was next introduced by treatment of **7** with *p*-toluenesulfon-

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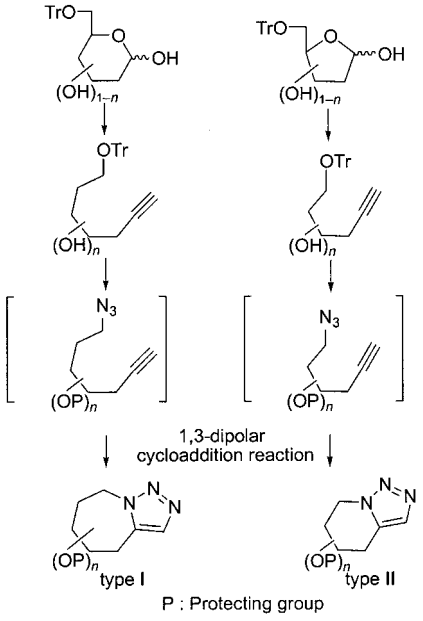
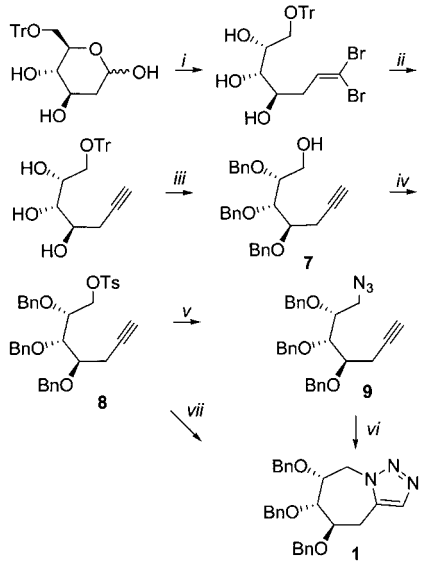


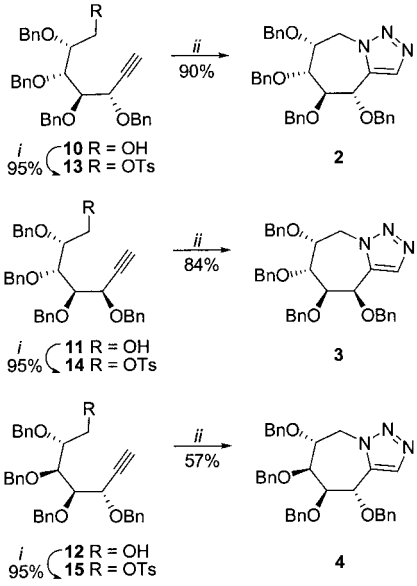

Scheme 2.




Scheme 3. Reagents and conditions: *i*) $Ph_3PCHBr_3$, Zn, 1,4-dioxane, reflux, 76%. *ii*) *n*BuLi, THF, –70 °C, 92%. *iii*) 1) BnBr, TBAI, NaH, DMF; 2) HCl concd., $CHCl_3$/MeOH, 76%. *iv*) TsCl, Py, room temp., 95%. *v*) $NaN_3$, DMF, 80 °C, 5 min, 60%. *vi*) Toluene, reflux, 24 h, 92%. *vii*) $NaN_3$, DMF, 120 °C, 3 h, 70%.

yl chloride in pyridine at room temperature, with tosylate **8** being obtained in a very good yield (95%). By addition of sodium azide in DMF at 80 °C, **8** was transformed into the azido compound **9**, which was isolated in moderate yield (60%). We think that this modest result could be partly due to the easy cyclization of this intermediate. When the azidoalkyne **9** was heated at reflux in toluene, 1,3-dipolar cyclization occurred to give the deoxy-*gluco*-1,2,3-triazole **1** in 92% yield. The structure of bicycle **1** was resolved by NMR spectroscopy experiments, with the characteristic resonances observed at $\delta$ = 135.0, 135.1, and 46.6 ppm attributed to C-3, C-3a, and C-8, respectively, and those at $\delta$ = 7.46 (s) and 4.76 (m) attributed to 3-H and 8a-H and 8b-H, respectively. This structure was also confirmed by a characteristic ion at *m*/*z* = 478.6, attributed to $[M + Na]^+$, in its mass spectrum (FAB-MS). Since isolation of **9** turned out to give only a moderate yield, we thought and hoped that introduction of the azide and direct conversion into the 1,2,3-triazole in a one-pot procedure might improve the overall yield of these transformations. Indeed, when **8** was treated with sodium azide in DMF at 120 °C the reaction proceeded to completion after 3 h, and **1** was isolated in an improved 70% overall yield (Scheme 3).

We then decided to extend these reaction conditions to three other aldohexoses (Scheme 4). Use of *p*-TsCl in pyridine thus allowed the conversion of **10** into tosylate **13**, which was treated with sodium azide in DMF at 120 °C for 1 h 45 min to provide the triazole **2** in 85% overall yield. NMR spectroscopy and mass spectrometry were used to established this structure. We were pleased to note that the presence of an alkoxy group on the carbon atom α to the triple bond did not negatively affect the course of the cyclisation. By the same sequence, *manno*-ynitol **11** and *galacto*-ynitol **12** were converted into the corresponding *manno*-1,2,3-triazole **3** and *galacto*-1,2,3-triazole **4** in 80% and 54% overall yields, respectively. In the case of *galacto*-derived **12**, we noticed a drop in reactivity, which forced us to increase the reaction time (60 h) and to use an excess of reagent ($NaN_3$, 6 equiv.). Those measures resulted in a slightly poorer yield because of the appearance of unidentified side products. The structures **2**, **3**, and **4** were also confirmed by $^1H$ and $^{13}C$ NMR spectroscopy, and characteristic ions at *m*/*z* = 584.4 in their respective mass spectra (FAB-MS) were attributed to $[M + Na]^+$.

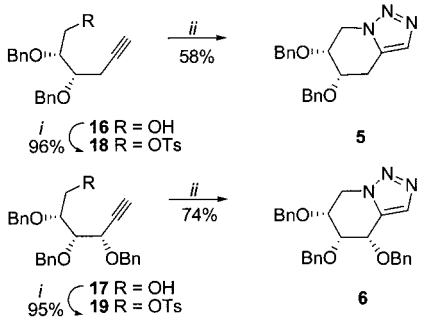



Scheme 4. Reagents and conditions: *i*) TsCl, Py, room temp., 24 h. *ii*) $NaN_3$, DMF, 120 °C.

After our work with hexoses, we turned to the synthetic transformation of pentoses into 1,2,3-triazoles. By use of

the same synthetic procedure we achieved the synthesis of two *glyco*-1,2,3-triazoles **5** and **6** from aldopentoses (Scheme 5). The D-*ribose* derivatives **16** and **17** were treated with *p*-TsCl in the presence of pyridine at room temperature for 24 h to afford tosylates **18** and **19** in 96% and 95% yields, respectively. One-pot $S_N2$ displacement of the corresponding tosylates with $NaN_3$, followed by the 1,3-dipolar cycloaddition, afforded 1,2,3-triazoles **5** and **6**, isolated in this case in yields of 58% and 74%, respectively.




Scheme 5. Reagents and conditions: *i*) TsCl, Py, room temp., 24 h. *ii*) $NaN_3$, DMF, 120 °C, 1 h.

## Conclusions

In summary, we have achieved the synthesis of several new chiral 1,2,3-triazole-fused bicyclic compounds in a few steps from commercially available monosaccharides (pentoses and hexoses). Those 1,2,3-triazole-fused bicyclic carbohydrate-derived compounds possess a predefined stereochemistry and were obtained in satisfactory overall yields by a versatile procedure. We have it in mind to investigate other preparations of new bi- and polycyclic compounds derived from carbohydrates by such an approach.

## Experimental Section

**General Remarks:** Unless otherwise specified, materials were purchased from commercial suppliers and were used without further purification. Reactions with moisture-sensitive materials were conducted in oven-dried glassware under argon. Flash chromatography was carried out on Kieselgel 60 (230–400 mesh, Merck) and analytical thin-layer chromatography (TLC) was performed on E. Merck glass-backed silica gel sheets (Silica Gel 60 $F_{254}$). Melting points are uncorrected. Optical rotations were measured with a sodium lamp ($\lambda$ = 589 nm) and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75 MHz, respectively. Spectra were recorded in $CDCl_3$ or [$D_6$]DMSO and chemicals shifts ($\delta$) are expressed in ppm relative to residual $CHCl_3$ or an internal standard. All signals in the $^{13}$C NMR spectra were assigned through C,H-correlated spectra. IR spectra were recorded with neat films (NaCl cell) and KBr pellets (solids). Infusion electrospray mass spectra in the positive-ion mode were obtained with an updated (3.6 GHz TDC) Q-TOF hybrid quadrupole/time-of-flight instrument, fitted with a pneumatically assisted electrospray ion source (Z-spray).

**General Procedure 1 for the Synthesis of Compounds 8, 13–15, and 18–19:** *p*-Toluenesulfonyl chloride (2 equiv.) was added to a pyridine (1 mL) solution of the starting material (**7**, **10**–**12**, **16**–**17**;[7] 1 mmol) immersed in a water bath. After having been stirred under argon at room temperature for 24 h, the reaction mixture was concentrated. The crude residue was purified by flash chromatography.

**(2*R*,3*S*,4*R*)-2,3,4-Tri-*O*-benzyl-1-*O*-(tolyl-4-sulfonyl)hept-6-yne-1,2,3,4-tetrol (8):** Compound **8** was prepared from **7** (129 mg, 0.3 mmol) by General Procedure 1. The crude residue was purified by flash chromatography (hexane/EtOAc, 9:1), and **8** was obtained as a colorless oil in 95% yield (170 mg). $R_f$ = 0.36 (hexane/EtOAc, 8:2). $[\alpha]_D^{27}$ = –14 (*c* = 0.5, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ = 7.40–7.30 (m, 19 H, $C_6H_5$), 4.84–4.42 (d, 6 H, PhC$H_2$), 4.50 (dd, $J_{1a,1b}$ = 10.5, $J_{1a,2}$ = 5.0 Hz, 1 H, 1a-H), 4.28 (dd, $J_{1a,1b}$ = 10.5, $J_{1b,2}$ = 2.3 Hz, 1 H, 1b-H), 3.96 (ddd, $J_{1a,2}$ = 5.0, $J_{1b,2}$ = 2.3, $J_{2,3}$ = 8.6 Hz, 1 H, 2-H), 3.94 (dd, $J_{2,3}$ = 8.6, $J_{3,4}$ = 2.8 Hz, 1 H, 3-H), 3.85 (dt, $J_{3,4}$ = $J_{4,5a}$ = 2.8, $J_{4,5b}$ = 6.7 Hz, 1 H, 4-H), 2.61 (m, 2 H, 5a-H, 5b-H), 2.08 (t, $J_{7,5a}$ = $J_{7,5b}$ = 2.7 Hz, 1 H, 7-H), 1.21 (s, 3 H, $SO_2$PhC$H_3$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 145.1, 138.5, 133.3, 128.9, 128.8, 128.7, 128.5, 128.1 ($C_6H_5$), 81.1 (C-6), 79.1 (C-2), 77.7 (C-4), 77.6 (C-3), 75.4–72.6 (Ph$CH_2$), 71.4 (C-1, C-7), 22.0 ($SO_2$Ph$CH_3$), 20.6 (C-5) ppm. MS: *m*/*z* = 607.7 [*M* + Na]$^+$. $C_{35}H_{36}O_6S$ (584.72): calcd. C 71.89, H 6.21, S 5.48; found C 72.03, H 6.43, S 5.72.

**(2*R*,3*R*,4*R*,5*S*)-2,3,4,5-Tetra-*O*-benzyl-1-*O*-(tolyl-4-sulfonyl)hept-6-yne-1,2,3,4,5-pentol (13):** Compound **13** was prepared from **10** (134 mg, 0.25 mmol) by General Procedure 1. The crude residue was purified by flash chromatography (hexane/EtOAc, 87:13) and **13** was obtained as a colorless oil in 95% yield (165 mg). $R_f$ = 0.45 (hexane/EtOAc, 8:2). $[\alpha]_D^{27}$ = +22 (*c* = 0.25, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ = 7.40–7.30 (m, 24 H, $C_6H_5$), 5.07–4.43 (d, 8 H, PhC$H_2$), 4.55 (dd, $J_{4,5}$ = 7.3, $J_{5,7}$ = 2.0 Hz, 1 H, 5-H), 4.49 (dd, $J_{1a,1b}$ = 10.7, $J_{1a,2}$ = 2.3 Hz, 1 H, 1a-H), 4.26 (dd, $J_{1a,1b}$ = 10.7, $J_{1b,2}$ = 5.5 Hz, 1 H, 1b-H), 4.18 (dd, $J_{2,3}$ = 5.5, $J_{3,4}$ = 3.4 Hz, 1 H, 3-H), 3.93 (dt, $J_{1a,2}$ = 2.3, $J_{2,3}$ = $J_{1b,2}$ = 5.5 Hz, 1 H, 2-H), 3.89 (dd, $J_{4,5}$ = 7.3, $J_{3,4}$ = 3.4 Hz, 1 H, 4-H), 2.64 (d, $J_{5,7}$ = 2.0 Hz, 1 H, 7-H), 1.21 (s, 3 H, $SO_2$PhC$H_3$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 145.0, 138.6, 138.5, 133.3, 128.9, 128.7, 128.5, 128.2 ($C_6H_5$), 81.1 (C-4), 80.6 (C-6), 79.3(C-3), 77.8 (C-2), 77.2 (C-7), 75.0, 74.9, 72.4, 71.0 (Ph$CH_2$), 71.4 (C-5), 69.9 (C-1), 22.2 ($SO_2$Ph$CH_3$) ppm. MS: *m*/*z* = 713.9 [*M* + Na]$^+$. $C_{42}H_{42}O_7S$ (690.84): calcd. C 73.02, H 6.13, S 4.64; found C 73.31, H 6.29, S 4.75.

**(2*R*,3*R*,4*R*,5*R*)-2,3,4,5-Tetra-*O*-benzyl-1-*O*-(tolyl-4-sulfonyl)hept-6-yne-1,2,3,4,5-pentol (14):** Compound **14** was prepared from **11** (303 mg, 0.56 mmol) by General Procedure 1. The crude residue was purified by flash chromatography (hexane/EtOAc, 87:13) and **14** was obtained as a colorless oil in 95% yield (370 mg). $R_f$ = 0.47 (hexane/EtOAc, 8:2). $[\alpha]_D^{27}$ = –32 (*c* = 0.5, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ = 7.40–7.30 (m, 24 H, $C_6H_5$), 5.07–4.43 (d, 8 H, PhC$H_2$), 4.58 (m, 1 H, 1a-H), 4.53 (dd, $J_{4,5}$ = 4.7, $J_{5,7}$ = 2.7 Hz, 1 H, 5-H), 4.30 (dd, $J_{1a,1b}$ = 10.8, $J_{1b,2}$ = 5.4 Hz, 1 H, 1b-H), 4.29 (dd, $J_{2,3}$ = 5.4, $J_{3,4}$ = 3.4 Hz, 1 H, 3-H), 3.47 (dt, $J_{1a,2}$ = 2.1, $J_{2,3}$ = $J_{1b,2}$ = 5.4 Hz, 1 H, 2-H), 3.44 (dd, $J_{4,5}$ = 4.7, $J_{3,4}$ = 3.4 Hz, 1 H, 4-H), 2.65 (d, $J_{5,7}$ = 2.7 Hz, 1 H, 7-H), 1.21 (s, 3 H, $SO_2$PhC$H_3$) ppm. $^{13}$C NMR ($CDCl_3$): $\delta$ = 145.2, 138.6, 138.5, 133.3, 128.9, 128.8, 128.7, 128.2 ($C_6H_5$), 81.6 (C-6), 80.8 (C-4), 78.3 (C-3), 77.7 (C-2), 76.7 (C-7), 75.0–71.0 (Ph$CH_2$), 69.8 (C-1), 69.3 (C-5), 22.0 ($SO_2$Ph$CH_3$) ppm. MS: *m*/*z* = 713.9 [*M* + Na]$^+$. $C_{42}H_{42}O_7S$ (690.84): calcd. C 73.02, H 6.13, S 4.64; found C 73.28, H 6.41, S 4.82.

**(2*R*,3*S*,4*R*,5*S*)-2,3,4,5-Tetra-*O*-benzyl-1-*O*-(tolyl-4-sulfonyl)hept-6-yne-1,2,3,4,5-pentol (15):** Compound **15** was prepared from **12** (410 mg, 0.76 mmol) by General Procedure 1. The crude residue was purified by flash chromatography (hexane/EtOAc, 87:13) and **15** was obtained as a colorless oil in 95% yield (500 mg). $R_f$ = 0.42

(hexane/EtOAc, 8:2). $[\alpha]_D^{29}$ = +24 ($c$ = 0.4, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ = 7.40–7.30 (m, 24 H, $C_6H_5$), 5.07–4.43 (d, 8 H, PhC$H_2$), 4.55 (dd, $J_{4,5}$ = 7.3, $J_{5,7}$ = 2.2 Hz, 1 H, 5-H), 4.54 (dd, $J_{1a,1b}$ = 10.7, $J_{1a,2}$ = 3.0 Hz, 1 H, 1a-H), 4.27 (dd, $J_{1a,1b}$ = 10.7, $J_{1b,2}$ = 4.0 Hz, 1 H, 1b-H), 4.08 (m, 3 H, 2-H, 3-H, 4-H), 2.70 (d, $J_{5,7}$ = 2.2 Hz, 1 H, 7-H), 1.21 (s, 3 H, $SO_2$PhC$H_3$) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 145.0, 138.6, 138.5, 133.3, 128.8, 128.7, 128.5, 128.2 ($C_6H_5$), 81.7 (C-4), 81.6 (C-6), 77.9, 77.4 (C-2, C-3), 76.9 (C-7), 75.0, 74.9, 72.4, 71.0 (Ph$CH_2$), 71.3 (C-1), 69.6 (C-5), 22.2 ($SO_2$Ph$CH_3$) ppm. MS: $m/z$ = 713.9 $[M + Na]^+$. $C_{42}H_{42}O_7S$ (690.84): calcd. C 73.02, H 6.13, S 4.64; found C 73.33, H 6.29, S 4.82.

**(2*R*,3*S*)-2,3-Di-*O*-benzyl-1-*O*-(tolyl-4-sulfonyl)hex-5-yne-1,2,3-triol (18):** Compound **18** was prepared from **16** (143 mg, 0.46 mmol) by General Procedure 1. The crude residue was purified by flash chromatography (hexane/EtOAc, 9:1) and **18** was obtained as a solid in 96% yield (200 mg). $R_f$ = 0.20 (hexane/EtOAc, 9:1). $[\alpha]_D^{27}$ = +1 ($c$ = 1, $CHCl_3$). M.p. 87–92 °C. $^1H$ NMR ($CDCl_3$): $\delta$ = 7.40–7.30 (m, 14 H, $C_6H_5$), 4.71–4.48 (d, 4 H, PhC$H_2$), 4.38 (dd, $J_{1a,1b}$ = 10.6, $J_{1a,2}$ = 2.6 Hz, 1 H, 1a-H), 4.25 (dd, $J_{1a,1b}$ = 10.6, $J_{1b,2}$ = 4.7 Hz, 1 H, 1b-H), 3.84 (ddd, $J_{1a,2}$ = 2.6, $J_{1b,2}$ = 4.7, $J_{2,3}$ = 8.0 Hz, 1 H, 2-H), 3.70 (dt, $J_{2,3}$ = 8.0, $J_{3,4a}$ = 2.6, $J_{3,4b}$ = 8.0 Hz, 1 H, 3-H), 2.61 (m, 2 H, 4a-H, 4b-H), 2.04 (t, $J_{4a,6}$ = $J_{4b,6}$ = 2.6 Hz, 1 H, 6-H), 1.24 (s, 3 H, $SO_2$PhC$H_3$) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 145.2, 138.0, 130.3, 128.9, 128.4, 128.3 ($C_6H_5$), 80.6 (C-5), 77.6 (C-2), 75.7 (C-3), 73.3, 72.5 (Ph$CH_2$), 71.1 (C-6), 69.1 (C-1), 22.0 ($SO_2$Ph$CH_3$), 20.7 (C-4) ppm. MS: $m/z$ = 487.6 $[M + Na]^+$. $C_{27}H_{28}O_5S$ (464.57): calcd. C 69.80, H 6.07, S 6.90; found C 70.12, H 6.25, S 7.20.

**(2*R*,3*S*,4*S*)-2,3,4-Tri-*O*-benzyl-1-*O*-(tolyl-4-sulfonyl)hex-5-yne-1,2,3,4-tetrol (19):** Compound **19** was prepared from **17** (327 mg, 0.78 mmol) by General Procedure 1. The crude residue was purified by flash chromatography (hexane/EtOAc, 9:1) and **19** was obtained as a colorless oil in 95% yield (420 mg). $R_f$ = 0.35 (hexane/EtOAc, 8:2). $[\alpha]_D^{27}$ = +32 ($c$ = 0.6, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ = 7.40–7.35 (m, 19 H, $C_6H_5$), 4.92–4.52 (d, 6 H, PhC$H_2$), 4.56 (dd, $J_{3,4}$ = 8.8, $J_{4,6}$ = 2.1 Hz, 1 H, 4-H), 4.42 (dd, $J_{1a,1b}$ = 10.5, $J_{1a,2}$ = 4.7 Hz, 1 H, 1a-H), 4.25 (dd, $J_{1a,1b}$ = 10.5, $J_{1b,2}$ = 2.1 Hz, 1 H, 1b-H), 3.91 (m, 2 H, 2-H, 3-H), 2.58 (d, $J_{4,6}$ = 2.1 Hz, 1 H, 6-H), 2.50 (s, 3 H, $SO_2$PhC$H_3$) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 145.2, 138.2, 137.9, 137.8, 130.8, 128.9, 128.8, 128.7, 128.5, 127.4 ($C_6H_5$), 80.0 (C-5), 79.5, 77.1 (C-2, C-3), 76.6 (C-6), 74.6, 73.1, 71.5 (Ph$CH_2$), 70.7 (C-4), 69.8 (C-1), 22.2 ($SO_2$Ph$CH_3$) ppm. MS: $m/z$ = 593.7 $[M + Na]^+$. $C_{34}H_{34}O_6S$ (570.70): calcd. C 71.56, H 6.00, S 5.62; found C 71.82, H 6.23, S 5.82.

**(2*R*,3*S*,4*R*)-1-Azido-2,3,4-tri-*O*-benzylhept-6-yne-2,3,4-triol (9):** Sodium azide (40 mg, 0.62 mmol) was added to a DMF (7 mL) solution of **8** (200 mg, 0.34 mmol). After having been stirred at 80 °C under argon for 5 min, the reaction mixture was concentrated. After extraction with EtOAc/$H_2O$, the combined organic extracts were dried ($Na_2SO_4$) and concentrated. The crude residue was purified by flash chromatography (hexane/EtOAc, 94:6) and **9** was obtained as a colorless oil in 60% yield (90 mg). $R_f$ = 0.71 (hexane/EtOAc, 8:2). $[\alpha]_D^{30}$ = +3 ($c$ = 0.9, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ = 7.40–7.30 (m, 15 H, $C_6H_5$), 4.84–4.42 (d, 6 H, PhC$H_2$), 3.98 (dd, $J_{2,3}$ = 6.3, $J_{3,4}$ = 3.0 Hz, 1 H, 3-H), 3.88 (dt, $J_{3,4}$ = $J_{4,5a}$ = 3.0, $J_{4,5b}$ = 6.7 Hz, 1 H, 4-H), 3.69 (dd, $J_{1a,1b}$ = 13.3, $J_{1a,2}$ = 5.2 Hz, 1 H, 1a-H), 3.48 (dd, $J_{1a,1b}$ = 13.3, $J_{1b,2}$ = 2.7 Hz, 1 H, 1b-H), 3.85 (m, 1 H, 2-H), 2.63 (dd, $J_{4,5a}$ = 3.0, $J_{5a,7}$ = 2.6 Hz, 1 H, 5a-H), 2.61 (dd, $J_{4,5b}$ = 6.7, $J_{5b,7}$ = 2.6 Hz, 1 H, 5b-H), 2.09 (t, $J_{5a,7}$ = $J_{5b,7}$ = 2.6 Hz, 1 H, 7-H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 138.9, 138.8, 128.8, 128.7, 128.5, 128.2 ($C_6H_5$), 81.2 (C-6), 79.2, 79.1 (C-2, C-3), 77.8 (C-4), 75.6, 72.7, 72.1 (Ph$CH_2$), 71.3 (C-7), 51.3 (C-1), 20.7 (C-5) ppm. MS: $m/z$ = 478.4 $[M + Na]^+$. $C_{28}H_{29}N_3O_3$ (455.55): calcd. C 73.82, H 6.42, N 9.22; found C 73.89, H 6.59, N 9.35.

**General Procedure 2 for the Synthesis of Compounds 1–6:** Sodium azide (2 equiv.) was added to a DMF (7 mL) solution of one of the tosylated compounds (**8**, **13**–**15**, **18**–**19**; 0.05 mmol). The reaction mixture was stirred under argon at 120 °C. The reaction was monitored by TLC, and after completion, the solvent was evaporated. The residue was diluted with EtOAc and washed with $H_2O$. The combined organic layers were dried ($Na_2SO_4$) and concentrated. The crude residue was purified by flash chromatography to give the desired compounds **1**–**6**.

**(5*R*,6*S*,7*R*)-5,6,7-Tris(benzyloxy)-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*]azepine (1):** Compound **1** was prepared from **8** (166 mg, 0.28 mmol) by General Procedure 2. The crude residue was purified by flash chromatography (hexane/EtOAc, 70:30) and **1** was obtained as a colorless oil in 70% yield (90 mg). $R_f$ = 0.25 (hexane/EtOAc 6:4). $[\alpha]_D^{27}$ = –57 ($c$ = 0.8, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ = 7.46 (s, 1 H, 3-H), 7.40–7.30 (m, 15 H, $C_6H_5$), 4.84–4.42 (d, 6 H, PhC$H_2$), 4.76 (m, 2 H, 8a-H, 8b-H), 4.06 (br d, $J_{5,6}$ = 5.9 Hz, 1 H, 6-H), 3.92 (ddd, 1 H, 7-H), 3.85 (dt, $J_{4a,5}$ = 1.3, $J_{4b,5}$ = 5.9, $J_{5,6}$ = 5.9 Hz, 1 H, 5-H), 3.18 (dd, $J_{4a,5}$ = 1.3, $J_{4a,4b}$ = 15.6 Hz, 1 H, 4a-H), 3.06 (dd, $J_{4b,5}$ = 5.9, $J_{4a,4b}$ = 15.6 Hz, 1 H, 4b-H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 138.9, 138.0, 137.8, 128.9, 128.8, 128.7, 128.5, 128.2 ($C_6H_5$), 135.1 (C-3a), 135.0 (C-3), 79.0 (C-6), 75.1 (C-7), 74.7 (C-5), 75.5, 72.4, 72.3 (Ph$CH_2$), 46.6 (C-8), 22.1 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 1460, 1239, 1060, 800 $cm^{-1}$. MS: $m/z$ = 478.6 $[M + Na]^+$. $C_{28}H_{29}N_3O_3$ (455.55): calcd. C 73.82, H 6.42, N 9.22; found C 73.91, H 6.50, N 9.30.

**(4*S*,5*R*,6*S*,7*R*)-4,5,6,7-Tetrakis(benzyloxy)-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*]azepine (2):** Compound **2** was prepared from **13** (153 mg, 0.24 mmol) by General Procedure 2. The crude residue was purified by flash chromatography (hexane/EtOAc, 75:25) and **2** was obtained as a solid in 90% yield (120 mg). $R_f$ = 0.15 (hexane/EtOAc, 8:2). M.p. 105–108 °C. $[\alpha]_D^{28}$ = +14 ($c$ = 1.2, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ = 7.71 (s, 1 H, 3-H), 7.40–7.30 (m, 20 H, $C_6H_5$), 5.12 (dd, $J_{8a,8b}$ = 14.1, $J_{7,8a}$ = 8.3 Hz, 1 H, 8a-H), 4.99 (d, $J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 4.84–4.62 (d, 8 H, PhC$H_2$), 4.58 (dd, $J_{8a,8b}$ = 14.1, $J_{7,8b}$ = 2.0 Hz, 1 H, 8b-H), 4.12 (m, $J_{6,7}$ = 5.8 Hz, 2 H, 6-H, 7-H), 4.08 (t, $J_{4,5}$ = $J_{5,6}$ = 5.8 Hz, 1 H, 5-H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 139.4, 139.0, 138.7, 138.6, 128.6, 128.2, 128.0, 127.9, 127.7 ($C_6H_5$), 135.5 (C-3a), 134.6 (C-3), 82.5, 78.6 (C-6, C-7), 74.6 (C-5), 74.5, 74.0, 73.1, 71.6 (Ph$CH_2$), 73.9 (C-4), 47.2 (C-8) ppm. IR (KBr): $\tilde{\nu}$ = 3050, 1460, 1239, 1060, 800 $cm^{-1}$. MS: $m/z$ = 584.4 $[M + Na]^+$. $C_{35}H_{35}N_3O_4$ (561.67): calcd. C 74.84, H 6.28, N 7.48; found C 75.02, H 6.50, N 7.54.

**(4*R*,5*R*,6*S*,7*R*)-4,5,6,7-Tetrakis(benzyloxy)-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*]azepine (3):** Compound **3** was prepared from **14** (360 mg, 0.52 mmol) by General Procedure 2. The crude residue was purified by flash chromatography (hexane/EtOAc, 75:25) and **3** was obtained as a colorless oil in 84% yield (247 mg). $R_f$ = 0.14 (hexane/EtOAc, 8:2). $[\alpha]_D^{28}$ = –71 ($c$ = 0.3, $CHCl_3$). $^1H$ NMR ($C_2D_6OS$): $\delta$ = 7.75 (s, 1 H, 3-H), 7.40–7.30 (m, 20 H, $C_6H_5$), 5.01 (d, $J_{4,5}$ = 2.1 Hz, 1 H, 4-H), 4.80–4.62 (d, 8 H, PhC$H_2$), 4.78 (dd, $J_{8a,8b}$ = 13.1, $J_{7,8a}$ = 8.1 Hz, 1 H, 8a-H), 4.62 (dd, $J_{8a,8b}$ = 13.1, $J_{7,8b}$ = 1.8 Hz, 1 H, 8b-H), 4.22 (m, 2 H, 6-H, 7-H), 4.08 (m, 1 H, 5-H) ppm. $^{13}C$ NMR ($C_2D_6OS$): $\delta$ = 139.2, 139.0, 138.9, 138.5, 128.9, 128.7, 128.6, 128.5, 128.3 ($C_6H_5$), 134.9 (C-3a), 134.6 (C-3), 82.5, 78.6 (C-6, C-7), 74.6 (C-5), 74.5, 74.0, 73.1, 71.6 (Ph$CH_2$), 73.8 (C-4), 47.8 (C-8) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 1460, 1239, 1060, 800 $cm^{-1}$. MS: $m/z$ = 584.4 $[M + Na]^+$. $C_{35}H_{35}N_3O_4$ (561.67): calcd. C 74.84, H 6.28, N 7.48; found C 75.12, H 6.55, N 7.54.

**(4*S*,5*R*,6*R*,7*R*)-4,5,6,7-Tetrakis(benzyloxy)-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*]azepine (4):** Compound **4** was prepared from **15** (500 mg, 0.72 mmol) by General Procedure 2. The crude residue was purified by flash chromatography (hexane/EtOAc, 75:25) and **4** was obtained as a colorless oil in 57% yield (230 mg). $R_f$ = 0.2 (hexane/EtOAc, 7:3). $[\alpha]_D^{27}$ = +18 (*c* = 0.4, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ = 7.74 (s, 1 H, 3-H), 7.40–7.30 (m, 20 H, $C_6H_5$), 4.90 (d, $J_{4,5}$ = 5.8 Hz, 1 H, 4-H), 4.80–4.62 (d, 8 H, PhC$H_2$), 4.70 (m, $J_{8a,8b}$ = 14.1, $J_{7,8a}$ = 8.3, $J_{7,8b}$ = 2.0 Hz, 2 H, 8a-H, 8b-H), 4.15 (m, $J_{7,8a}$ = 8.3, $J_{7,8b}$ = 2.0, $J_{5,6}$ = 3.0 Hz, 2 H, 6-H, 7-H), 4.08 (dd, $J_{4,5}$ = 5.8, $J_{5,6}$ = 3.0 Hz, 1 H, 5-H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 139.4, 139.0, 138.7, 138.6, 129.2, 129.0, 128.7, 128.2, 127.6 ($C_6H_5$), 135.5 (C-3a), 134.0 (C-3), 82.5, 78.6 (C-6, C-7), 74.6 (C-5), 74.5, 74.0, 73.1, 71.6 (Ph*C*$H_2$), 73.9 (C-4), 52.0 (C-8) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 1460, 1239, 1060, 800 $cm^{-1}$. MS: *m*/*z* = 584.4 [*M* + Na]$^+$. $C_{35}H_{35}N_3O_4$ (561.67): calcd. C 74.84, H 6.28, N 7.48; found C 75.12, H 6.60, N 7.64.

**(5*S*,6*R*)-5,6-Bis(benzyloxy)-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]-pyridine (5):** Compound **5** was prepared from **18** (200 mg, 0.43 mmol) by General Procedure 2. The crude residue was purified by flash chromatography (hexane/EtOAc, 4:6) and **5** was obtained as a solid in 58% yield (120 mg). $R_f$ = 0.25 (hexane/EtOAc, 6:4). $[\alpha]_D^{27}$ = –5 (*c* = 0.85, $CHCl_3$). M.p. 108–111 °C. $^1H$ NMR ($CDCl_3$): $\delta$ = 7.48 (s, 1 H, 3-H), 7.40–7.30 (m, 10 H, $C_6H_5$), 4.75 (m, 4 H, PhC$H_2$), 4.62 (dd, $J_{7a,7b}$ = 13.5, $J_{6,7a}$ = 5.6 Hz, 1 H, 7a-H), 4.39 (dd, $J_{7a,7b}$ = 13.5, $J_{6,7b}$ = 4.0 Hz, 1 H, 7b-H), 4.15 (ddd, $J_{6,7a}$ = 5.6, $J_{6,7b}$ = 4.0, $J_{5,6}$ = 1.6 Hz, 1 H, 6-H), 4.05 (ddd, $J_{4b,5}$ = 4.8, $J_{4a,5}$ = 7.5, $J_{5,6}$ = 1.6 Hz, 1 H, 5-H), 3.20 (dd, $J_{4a,5}$ = 7.5, $J_{4a,4b}$ = 16.3 Hz, 1 H, 4a-H), 2.99 (dd, $J_{4b,5}$ = 4.8, $J_{4a,4b}$ = 16.3 Hz, 1 H, 4b-H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 138.1, 138.0, 129.0, 128.5, 128.4, 128.1, 128.0 ($C_6H_5$), 132.0 (C-3a), 131.5 (C-3), 73.3 (C-5), 73.1 (C-6), 72.4, 71.9 (Ph*C*$H_2$), 48.0 (C-7), 23.6 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3050, 1450, 1250, 1060, 800 $cm^{-1}$. MS: *m*/*z* = 358.4 [*M* + Na]$^+$. $C_{20}H_{21}N_3O_2$ (335.40): calcd. C 71.62, H 6.31, N 12.53; found C 71.32, H 6.27, N 12.40.

**(4*S*,5*R*,6*R*)-4,5,6-Tris(benzyloxy)-4,5,6,7-tetrahydro[1,2,3]triazolo-[1,5-*a*]pyridine (6):** Compound **6** was prepared from **19** (448 mg, 0.78 mmol) by General Procedure 2. The crude residue was purified by flash chromatography (hexane/EtOAc, 6:4) and **6** was obtained as a solid in 74% yield (260 mg). $R_f$ = 0.22 (hexane/EtOAc, 6:4). $[\alpha]_D^{23}$ = –15 (*c* = 1.2, $CHCl_3$). M.p. 114–116 °C. $^1H$ NMR ($CDCl_3$): $\delta$ = 7.75 (s, 1 H, 3-H), 7.40–7.30 (m, 15 H, $C_6H_5$), 4.75 (d, 6 H, PhC$H_2$), 4.63 (m, $J_{7a,7b}$ = 12.0, $J_{6,7a}$ = 10.5 Hz, 1 H, 7a-H), 4.58 (dd, $J_{4,5}$ = 3.0, $J_{5,6}$ = 5.8 Hz, 1 H, 5-H), 4.44 (dd, $J_{7a,7b}$ = 12.0, $J_{6,7b}$ = 2.0 Hz, 1 H, 7b-H), 4.37 (d, $J_{4,5}$ = 3.0 Hz, 1 H, 4-H), 3.91 (ddd, $J_{6,7a}$ = 10.5, $J_{6,7b}$ = 2.0, $J_{5,6}$ = 5.8 Hz, 1 H, 6-H) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 138.3, 137.6, 138.1, 129.1, 128.8, 128.6, 128.3, 128.1 ($C_6H_5$), 134.5 (C-3a), 132.2 (C-3), 74.7 (C-6), 74.0, 72.3, 72.0 (Ph*C*$H_2$), 72.6 (C-4), 71.7 (C-5), 46.2 (C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3050, 1450, 1250, 1060, 800 $cm^{-1}$. MS: *m*/*z* = 464.5 [*M* + Na]$^+$. $C_{27}H_{27}N_3O_3$ (441.52): calcd. C 73.45, H 6.16, N 9.52; found C 73.62, H 6.20, N 9.54.

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