Sulfonium Triflate Mediated Glycosidations of Aryl 2-Azido-2-deoxy-1-thio-D-mannosides

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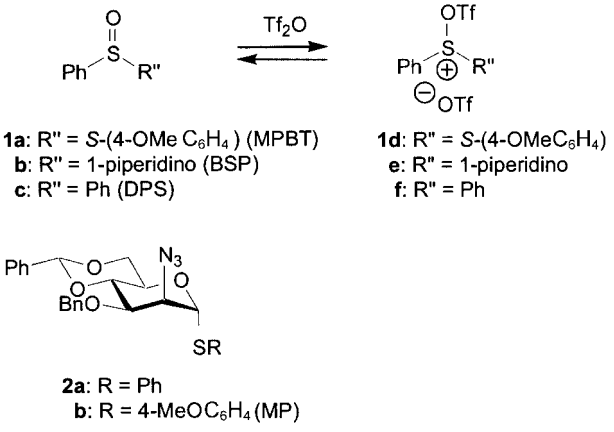
The effectiveness in terms of yield and stereoselectivity of (phenylsulfinyl)piperidine (BSP) **1b**/ trifluoromethanesulfonic anhydride (Tf_2O) and diphenyl sulfoxide (DPS) **1c**/ Tf_2O-mediated glycosidations of 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-thiomannosides **2a/b** is described. Application of the BSP/Tf_2O activator led to productive condensations using *p*-methoxyphenyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-thiomannoside (**2b**) as a donor, while the more powerful DPS/Tf_2O combination gave similar results using both *p*-methoxyphenyl and phenyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-thiomannosides **2a/b**.

Introduction

The development of synthetic procedures for the efficient and stereoselective introduction of glycosidic linkages is a major aim in carbohydrate chemistry.[1–7] Although considerable progress has been made in the last decades, a general glycosylation procedure that enables the assembly of any given oligosaccharide or glycoconjugate, if at all possible, remains to be established. The outcome of a glycosylation event, in terms of yield and stereoselectivity, depends on solvent systems, temperature, the nature of the donor and acceptor and the applied protective group strategy. Apart from this, the leaving group at the anomeric center of the donor in combination with the activator system can be a decisive factor in the outcome of a glycosylation reaction.

Recently, Crich and coworkers reported major advances in the stereoselective construction of β-D-mannopyranosides[8–10] and β-L-rhamnopyranosides.[11] For steric and electronic reasons these linkages are notoriously difficult to prepare. Application of the 4,6-benzylidene protecting group[12] in armed[13] thiomannoside donors in combination with *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT)/ trifluoromethanesulfonic anhydride (Tf_2O) (**1a**, Scheme 1) and 2,6-bis(*tert*-butyl)-4-methylpyridine (DTBMP) as non-nucleophilic base led to the introduction of β-glycosidic linkages in high excess.[10] The same group found an improvement of this procedure in the development of the more potent activator system 1-(phenylsulfinyl)piperidine (BSP) and Tf_2O (**1b**, Scheme 1) in combination with tris(*tert*-butyl)pyrimidine (TTBP) as acid scavenger, capable of activation and coupling of disarmed[14] glycosides and able to effectuate selective β-mannoside formation. With the objective to develop an efficient procedure to install β-mannosamine linkages employing orthogonally protected thioglycosides, our attention was focussed on the use of 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-thiomannosides **2** as suitable glycosyl donors.[15]



Scheme 1.

In a preliminary report, we disclosed our results in the study of the two-step MPBT/Tf_2O-promoted the glycosylations of 2-azido-2-deoxy-thiomannosides **2a/b** with several acceptor molecules.[16] It turned out that phenyl thiomannoside **2a** could not be activated using the MPBT/Tf_2O system, probably due to the electron withdrawing effect of the azide function. Effective condensations employing this activator were accomplished by the use of donor **2b**, in which

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the disarmed nature is counterbalanced by the introduction of a methoxy group on the phenyl ring, thereby enhancing the nucleophilicity of the anomeric sulfur atom. The outcome of this study raised the question whether the BSP/Tf_2O activator system could effect the formation of β-mannosamine linkages with equal efficiency.[17]

Subjection of *S*-phenyl donor **2a** tothe BSP/Tf_2O protocol did not lead to reproducible results. Complete activation of **2a** could not always be attained, presumably due to untraceable, subtle variations in the experimental conditions. For instance, we employed the BSP/Tf_2O protocol on **2a** using methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4**) as the acceptor (Figure 1). The desired disaccharide **11** was isolated in an α:β ratio of 1:1 in 72% yield.[18] In an attempt to encourage the formation of the kinetically favored β-anomer, the activation temperature was lowered to –78 °C. After activation and acceptor addition only small amounts of dimer **11** (< 10%) were isolated. Screening of the activation step by TLC analysis after activation for 5 min revealed two major spots with nearly identical polarity. Identification of these products after warming of the reaction mixture to room temperature by standard work-up and purification afforded starting compound **2a** (27% based on starting material) and the 2-azidoglucal **3** (48%), which originates from elimination of the C-2 proton in the transient contact ion pair.[19,20] These findings urged us to employ the BSP/Tf_2O protocol in the condensation of the more reactive *S*-methoxyphenyl donor **2b** with acceptors **4**–**9**. The results of these glycosylations are summarized in Table 1.

Condensation of **2b** with **4** afforded the disaccharide **11** in 91% yield and an α:β ratio of 1:4 (Entry 1). A similar result was obtained in the condensation of the less reactive acceptor methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (**5**) (Entry 2). Coupling of **2b** with phytosphingosine derivative **6** gave solely the β-anomer **13** in 80% yield. Glycosylation of the sterically demanding 3′-OH in diacetone glucose **7** to afford the disaccharide **14** proceeded equally efficient but with less stereoselectivity. In the condensation of **2b** with the glucosazide acceptor **8**, the stereochemistry of the glycosylation reaction was completely reversed to give α-dimer **15** in 66% yield and no β-product was observed (Entry 5). Glycosylation of the corresponding 1,6-anhydro-glucosazide **9** gave disaccharide **16** in 75% yield and an α:β ratio of 1:4.

The assumption that the lack of reactivity of **2a** towards the BSP/Tf_2O combination originates from a stabilizing effect of the piperidine nitrogen lone pair on the sulfur cation **1e** guided us to the finding, that the diphenyl sulfoxide (DPS)/Tf_2O activator system, as originally applied in Gin's innovative dehydrative glycosylation,[21] is a more powerful thiophile. In the first instance, the protocol developed by Gin and coworkers for dehydrative couplings, was used for the activation of phenyl thiomannoside **2a**. Thus, to a solution of 1.0 equiv. donor **2a**, 2.8 equiv. of DPS and 3.0 equiv. TTBP in dichloromethane at –60 °C was added 1.4 equiv. of Tf_2O. Within 5 min, TLC analysis indicated complete activation, and the glycosyl acceptor **4** was added at the same temperature. Indeed, condensation of **2a** with **4** under these conditions led to disaccharide **11** in 88% yield and α:β ratio of 1:4 (Entry 1, Table 2), with no detectable formation of the glucal **3** as a side product. Using this protocol, acceptors **5**, **7**, **9** and **10** (Entries 2–5) were condensed uneventfully with **2a** to provide the disaccharides **12**, **14**, **16** and **17**, respectively. The results of these condensation reactions do not deviate substantially from those obtained with the BSP activation of **2b**. To enable an unambiguous comparison of the BSP/Tf_2O and DPS/Tf_2O systems, we treated **2a** with 1.1 equiv. of the DPS/Tf_2O reagent at –60 °C, added **4** and isolated **11** in 77% yield in a slightly less pronounced β-selectivity of 1:3 (Entry 6). We also executed the condensation of the same reactants with 1.1 equiv. DPS/Tf_2O combination at –78 °C to afford the disaccharide **11** in 78% yield in a 1:4 α:β ratio (Entry 7). Finally, application of the DPS/Tf_2O activator combination in the activation of the (*p*-methoxyphenyl)thiomannoside **2b** and subsequent coupling with **9** afforded the disaccharide **16** in 70% yield and a 1:4 α:β ratio (Entry 8).

In summary, we have demonstrated that both disarmed thiomannosides **2a** and **2b** can be employed as suitable donors in the stereoselective formation of β-linked 2-azido-2-deoxy-D-mannosides. Thiomannosides **2a** and **2b** can be smoothly activated and coupled under the guidance of the highly potent DPS/Tf_2O reagent combination. Alternatively, BSP/Tf_2O activation of **2b** leads to comparable results, whereas application of this system in the glycosidation of **2a** leads to irreproducable outcomes. The degree of stereoselectivity in the glycosidation of **2a** and **2b** seems to be mainly governed by the stereochemical nature of the ac-

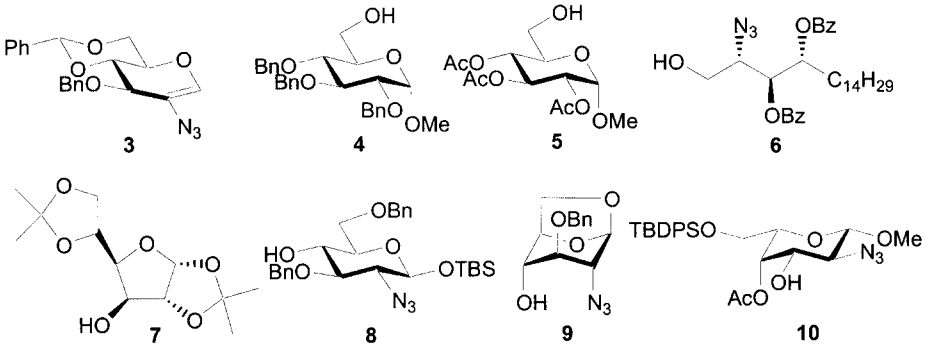
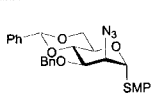
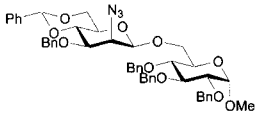
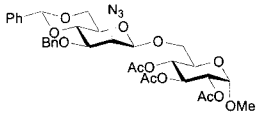
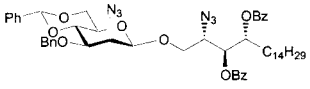
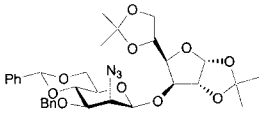
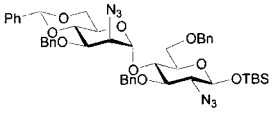
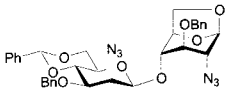


Figure 1. Elimination product **3** and glycosyl acceptors **4**–**10**.

Table 1. BSP/Tf_2O-promoted glycosidations of thiomannoside **2b**.

Entry	Donor	Acceptor	Product	Yield (%)	α:β ratio
1	 **2b**	**4**	 **11**	91	1:4
2	**2b**	**5**	 **12**	96	1:4
3	**2b**	**6**	 **13**	80	β
4	**2b**	**7**	 **14**	89	1:2
5	**2b**	**8**	 **15**	66	α
6	**2b**	**9**	 **16**	75	1:4

ceptor. Condensation of primary acceptors **4**,**5** and **6** led to good β-selectivity culminating in the pure β-product **13**. Contrary, glycosylation of secondary acceptors reduced the β-selectivity and gave in case of the sterically congested acceptor **8** solely the α-product. In the condensation of the sterically more accesible secondary alcohols **9** and **10**, a better β-selectivity was observed.

Experimental Section

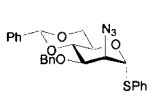
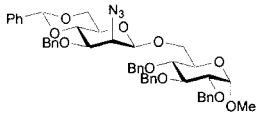
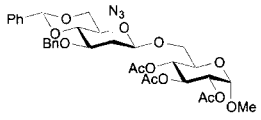
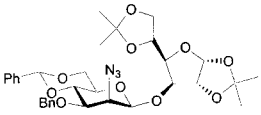
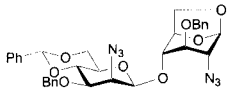
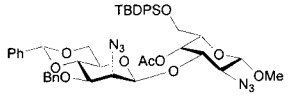
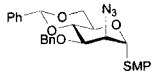
General Methods: Dichloromethane was refluxed with P_2O_5 and distilled before use. BSP and TTBP were synthesized as described by Crich et al.[14,22] Trifluoromethanesulfonic anhydride was stirred for 3 hours with P_2O_5 and subsequently distilled. All other chemicals (Fluka, Acros, Merck, Aldrich, Sigma) were used as received. Reactions were performed under inert gas and strictly anhydrous conditions. Traces of water from reagents used in reactions that require anhydrous conditions were removed by coevaporation with toluene and dichloroethane. Molecular sieves (3 Å) were flame-dried before use. Column chromatography was performed on Fluka silica gel 60 (0.040–0.063 mm). TLC analysis was conducted on DC-alufolien (Merck, Kieselgel 60 F_{254}). Compounds were visualized by UV absorption (254 nm), by spraying with 20% H_2SO_4 in ethanol or with a solution of $(NH_4)_6Mo_7O_{24}•4H_2O$ 25g/L, followed by charring at ±140 °C. ^1H and ^{13}C NMR spectra were recorded with a Jeol JNM-FX-200 (200 and 50 MHz), a Bruker DPX 300 (300 and 75 MHz) or a Bruker AV 400 (400 and 100 MHz). NMR spectra were recorded in $CDCl_3$ with chemical shifts (δ) relative to tetramethylsilane unless stated otherwise. Mass spectra were recorded with an Finnigan LTQ-FT (Thermo Electron). Optical rotations were recorded with a Propol automatic polarimeter. IR spectra were recorded with a Shimadzu FTIR-8300 and are reported in cm^{-1}. Melting points were measured with a Büchi melting point apparatus.

General Procedures for Glycosylations

Protocol A: To a stirred mixture of the thioglycoside **2b** (0.2 mmol), BSP (0.22 mmol), TTBP (0.44 mmol) and 3-Å MS at –60 °C in DCM (4 mL) was added Tf_2O (0.22 mmol). After stirring for 10 min at this temperature, a solution of the acceptor (0.3 mmol) in DCM (1.5 mL) was added dropwise and the mixture was warmed to 0 °C after which Et_3N (200 μL) was added. The mixture was filtered, washed with satd. aq. $NaHCO_3$ and the organics were dried ($MgSO_4$), filtered and the volatiles were removed in vacuo. The glycosides were isolated by column chromatography.

Protocol B: To a stirred mixture of the thioglycoside **2a** (0.2 mmol), DPS (0.56 mmol), TTBP (0.44 mmol) and 3-Å MS at –60 °C in DCM (4 mL) was added Tf_2O (0.56 mmol). After stirring for 10 min at this temperature, a solution of the acceptor (0.3 mmol) in DCM (1.5 mL) was added dropwise and the mixture was warmed to 0 °C after which Et_3N (200 μL) was added. The mixture was filtered, washed with satd. aq. $NaHCO_3$ and the organics were

Table 2. DPS/Tf_2O-promoted glycosidations of thiomannosides **2a/b**.

Entry	Donor	Acceptor	Product	Yield (%)	α:β ratio
1	 **2a**	**4**	 **11**	88	1:4
2	**2a**	**5**	 **12**	93	1:4
3	**2a**	**7**	 **14**	91	1:2
4	**2a**	**9**	 **16**	70	1:5
5	**2a**	**10**	 **17**	74	1:4
6	**2a**	**4**	**11**	77	1:3
7	**2a**	**4**	**11**	77	1:4
8	 **2b**	**9**	**16**	70	1:4

dried ($MgSO_4$), filtered and the volatile solvents were removed in vacuo. The glycosides were isolated by column chromatography.

Protocol C: To a stirred mixture of the thioglycoside **2a** (0.2 mmol), DPS (0.22 mmol), TTBP (0.44 mmol) and 3-Å MS at –60 °C in DCM (4 mL) was added Tf_2O (0.22 mmol). After stirring for 10 min at this temperature, a solution of the acceptor (0.3 mmol) in DCM (1.5 mL) was added dropwise and the mixture was warmed to 0 °C after which Et_3N (200 μL) was added. The mixture was filtered, washed with satd. aq. $NaHCO_3$ and the organics were dried ($MgSO_4$), filtered and the volatile solvents were removed in vacuo. The glycosides were isolated by column chromatography.

Protocol D: Identical to protocol C, except that the activation and reaction temperature was –78 °C.

Protocol E: Identical to protocol C, with the exception that instead of donor **2a**, donor **2b** was used.

Phenyl 2-Azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (2a):[16] White solid. M.p. 96 °C. R_f = 0.69 (ethyl acetate/light petroleum, 1:4 v/v). $[a]_D^{25}$ = +39.4 (*c* = 0.1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2854, 2110, 1581, 1373, 1099, 983, 694 cm^{-1}. ^1H NMR: δ (ppm) = 7.46 (m, 15 H, $H_{arom.}$), 5.66 (s, 1 H, –C*H*Ph), 5.46 (s, 1 H, H-1), 4.96 (d, *J* = 12.0 Hz, 1 H, –C*H*Ph), 4.78 (d, *J* = 12.0 Hz, 1 H, –C*H*Ph), 4.46 (m, 1 H, H-5), 4.21 (m, 4 H, H-2, H-3, 2× H-6), 3.87 (t, *J* = 9.9 Hz, 1 H, H-4). ^{13}C NMR: δ (ppm) = 137.9, 137.5, 132.9, 131.8, 129.3, 129.0, 128.5, 128.2, 128.0, 127.9, 127.6, 126.2, 101.6, 87.0, 79.1, 75.9, 73.3, 68.2, 65.1, 64.0. ESI-HRMS calcd. for $C_{26}H_{25}N_3O_4S$ [M + NH_4]: 493.1910; found 493.1885.

***p*-Methoxyphenyl 2-Azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (2b):**[16] Pale yellow solid. M.p. 107 °C. R_f = 0.60 (ethyl acetate/light petroleum, 1:4 v/v) $[a]_D^{25}$ = +82.2 (*c* = 1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2861, 2102, 1591, 1244, 1089, 746, 696 cm^{-1}. ^1H NMR: δ (ppm) = 7.50 (m, 2 H), 7.34 (m, 10 H, $H_{arom.}$), 6.85 (d, *J* = 8.8 Hz, 2 H, $H_{arom.}$), 5.63 (s, 1 H, –C*H*Ph), 5.26 (s, 1 H, H-1), 4.92 (d, *J* = 12.4 Hz, 1 H, –C*H*Ph), 4.74 (d, *J* = 12.4 Hz, 1 H, –C*H*Ph), 4.36 (m, 1 H, H-5), 4.19 (m, 4 H, H-2, 2× H-6, H-3), 3.83 (t, *J* = 10.2 Hz, 1 H, H-4), 3.76 (s, 3 H, OCH_3). ^{13}C NMR: δ (ppm) = 160.1, 137.9, 137.5, 135.1, 129.0, 128.5, 128.2, 127.8, 127.6, 126.1, 122.7, 101.6, 87.8, 79.2, 75.8, 73.3, 68.3, 65.0, 63.8, 55.2. ESI-HRMS calcd. for $C_{27}H_{27}N_3O_5S$ [M + NH_4]: 523.2015; found 523.1977.

1,5-Anhydro-2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-*arabino*-hex-1-enitol (3): To a stirred mixture of **2a** (0.2 mmol), BSP (0.22 mmol) and TTBP (0.44 mmol) and 3-Å MS at –60 °C in DCM (4 mL) was added Tf_2O (0.22 mmol). After stirring for 10 min, Et_3N was added. The reaction mixture was warmed to room temp., washed with satd. aq. $NaHCO_3$ and the organics were dried ($MgSO_4$), filtered and concentrated. Column chromatography (light petroleum → ethyl acetate/light petroleum, 1:9 v/v) afforded the glucal **3** (35 mg, 96 μmol, 48%) as a colorless oil and

2a (26 mg, 54 μmol, 27%). **3:** R_f = 0.80 (ethyl acetate/toluene, 1:6 v/v). $[\alpha]_D^{25}$ = +4.9 (*c* = 1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 3080, 3040, 2110, 1925, 1640, 840 cm^{-1}. ^1H NMR: δ (ppm) = 7.42 (m, 4 H, $H_{arom.}$), 7.36 (m, 6 H, $H_{arom.}$), 6.43 (d, *J* = 1.2 Hz, 1 H, H-1), 5.61 (s, 1 H, –C*H*Ph), 4.93 (d, *J* = 10.8 Hz, 1 H, –C*H*Ph), 4.77 (d, *J* = 10.8 Hz, 1 H, –C*H*Ph), 4.56 (dd, *J* = 7.0, 1.2 Hz, 1 H, H-3), 4.38 (dd, *J*= 10.0, 4.8 Hz, 1 H, H-6), 4.15 (dd, *J* = 10.0, 7.0 Hz, 1 H, H-4), 3.89 (m, 1 H, H-5), 3.84 (dd, *J* = 10.0, 3.8 Hz, 1 H, H-6). ^{13}C NMR: δ (ppm) = 136.4, 129.2, 129.0, 128.3, 128.2, 127.9, 127.5, 127.1, 126.0, 116.9, 107.2, 101.1, 80.4, 74.4, 73.6, 69.1, 68.1. ESI-HRMS calcd. for $C_{20}H_{19}N_3O_4$ [M + NH_4]: 383.1714; found 383.1756.

Methyl 6-*O*-(2-Azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (11)

Protocol A: 11α: Yield 30 mg, 36 μmol, 18%; **11β**: Yield 121 mg, 146 μmol, 73%. **Protocol B: 11α:** Yield 29 mg, 35 μmol, 18%; **11β:** Yield 116 mg, 140 μmol, 70%. **Protocol C: 11α:** Yield 32 mg, 38 μmol, 19%; **11β**: Yield 96 mg; 116 μmol, 58%. **Protocol D: 11α**: Yield 25 mg, 31 μmol, 16%; **11β**: Yield 102 mg, 123 μmol, 61%. **Protocol E: 11α:** Yield 23 mg, 28 μmol, 14%; **11β:** Yield 93 mg, 112 μmol, 56%. **11α:** Colorless oil. R_f = 0.67 (ethyl acetate/light petroleum, 1:3 v/v). $[\alpha]_D^{25}$ = +6.6 (*c* = 0.5, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2871, 2104, 1452, 1365,1068, 696 cm^{-1}. ^1H NMR: δ (ppm) = 7.38–7.24 (m, 25 H, $H_{arom.}$), 5.54 (s, 1 H, –C*H*Ph), 5.03–4.59 (m, 8 H, –C*H*Ph), 4.55 (d, *J* = 3.8 Hz, 1 H, H-1), 4.27 (dd, *J* = 10.5, 5.0 Hz, 1 H, H-6′), 4.23 (s, 1 H, H-1′), 4.08 (t, *J* = 8.5 Hz, 1 H, H-3), 3.83 (m, 2 H, H-6, H-4′), 3.81 (t, *J* = 10.4 Hz, 1 H, H-6′), 3.76 (m, 1 H, H-5), 3.72 (d, *J* = 2.9 Hz, 1 H, H-2′), 3.59 (dd, *J* = 11.3, 6.1 Hz, 1 H, H-3′), 3.49 (m, 2 H, H-2, H-6), 3.53 (t, *J* = 8.6 Hz, 1 H, H-4), 3.59 (m, 1 H, H-5′), 3.34 (s, 3 H, OCH_3). ^{13}C NMR: δ (ppm) = 138.5, 137.9, 137.8, 137.6, 136.5, 132.2, 129.3, 128.8, 128.7,127.5, 125.9, 125.2, 125.0, 101.5, 99.3, 97.8, 82.0, 79.8, 78.4, 77.4, 75.7, 75.0, 74.9, 74.5, 73.3, 73.2, 67.1, 66.2, 63.9, 62.5, 55.1. ESI-HRMS calcd. for $C_{48}H_{51}N_3O_{10}$ [M + NH_4]: 847.3918; found 847.3904. **11β:** White foam. R_f = 0.55 (ethyl acetate/light petroleum, 1:3 v/v). $[\alpha]_D^{25}$ = +18.6 (*c* = 0.5, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2852, 2104, 1452, 1359, 1273, 1028, 696 cm^{-1}. ^1H NMR: δ (ppm) = 7.37–7.24 (m, 25 H, $H_{arom.}$), 5.55 (s, 1 H, –C*H*Ph), 5.03–4.57 (m, 8 H, –C*H*Ph), 4.55 (d, *J* = 3.8 Hz, 1 H, H-1), 4.26 (dd, *J* = 10.5, 5.0 Hz, 1 H, H-6′), 4.18 (s, 1 H, H-1′), 4.05 (t, *J* = 8.5 Hz, 1 H, H-3), 3.85 (m, 2 H, H-6, H-4′), 3.80 (t, *J* = 10.4 Hz, 1 H, H-6′), 3.75 (m, 1 H, H-5), 3.70 (d, *J* = 2.9 Hz, 1 H, H-2′), 3.59 (dd, *J* = 11.3, 6.1 Hz, 1 H, H-3′), 3.49 (m, 2 H, H-2, H-6), 3.52 (t, *J* = 8.6 Hz, 1 H, H-4), 3.33 (s, 3 H, OCH_3), 3.32 (m, 1 H, H-5′). ^{13}C NMR: δ (ppm) = 138.7, 138.5, 138.1, 137.3, 129.0, 128.6, 128.5, 128.4. 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 126.0, 101.5, 100.3, 97.9, 82.1, 79.9, 78.5, 75.7, 74.6, 73.4, 72.9, 69.5, 68.5, 68.4, 67.3, 63.5, 55.2. ESI-HRMS calcd. for $C_{48}H_{51}N_3O_{10}$ [M + NH_4]: 847.3918; found 847.3882.

Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-mannopyranosyl)-α-D-glucopyranoside (12)

Protocol A: 12α: Yield: 26 mg, 38 μmol, 19%; **12β**: Yield: 127 mg, 154 μmol, 77%. **Protocol B: 12α:** Yield: 31 mg, 37 μmol, 18%; **12β:** 102 mg, 149 μmol, 75%. **12α:** Colorless oil. R_f 0.48 (ethyl acetate/light petroleum, 1:1 v/v). $[\alpha]_D^{25}$ = –1.8 (*c* = 0.5, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2854, 2107, 1438, 1030, 934 cm^{-1}. ^1H NMR: δ (ppm) = 7.55–7.36 (m, 10 H, $H_{arom.}$), 5.60 (s, 1 H, –C*H*Ph), 5.46 (t, *J* = 9.7 Hz, 1 H, H-3), 5.08 (t, *J* = 9.7 Hz, 1 H, H-4), 4.90 (m, 3 H, H-1, H-2, –C*H*Ph), 4.80 (s, 1 H, H-1′), 4.74 (d, *J* = 8.0 Hz, 1 H, C*H*Ph), 4.19 (dd, *J* = 10.1, 4.5 Hz, 1 H, H-6′), 4.10 (m, 2 H, H-5, H-6), 3.92 (m, 2 H, H-4′, H-6′), 3.81 (t, *J* = 10.4 Hz, 1 H, H-6), 3.78 (m, 2 H, H-3′, H-5′), 3.49 (d, *J* = 11.3 Hz, 1 H, H-2′), 3.35 (s, 3 H, OCH_3), 2.04 (s, 3 H, Ac), 2.02, (s, 3 H, Ac), 1.98 (s, 3 H, Ac). ^{13}C NMR: δ (ppm) = 171.4, 170.8, 139.1, 137.2, 128.9, 128.8.0, 128.3, 128.2, 127.9, 126.3, 125.9, 125.6, 100.8, 99.9, 96.4, 78.2, 76.3, 72.7, 71.1, 70.0, 69.3, 69.0, 67.9, 55.1, 20.7. ESI-HRMS calcd. for $C_{33}H_{39}N_3O_{13}$ [M + Na]: 708.2381; found 708.2394. **12β:** White solid. R_f 0.37 (ethyl acetate/light petroleum, 1:1 v/v). $[\alpha]_D^{25}$ = +6.8 (*c* = 1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2856, 2111, 1456, 1221, 1027, 931 cm^{-1}. ^1H NMR: δ (ppm) = 7.55–7.36 (m, 10 H, $H_{arom.}$), 5.57 (s, 1 H, –C*H*Ph), 5.49 (t, *J* = 9.8 Hz, 1 H, H-3), 4.82 (m, 5 H, H-4, H-1, H-2, –C*H*Ph), 4.57 (s, 1 H, H-1′), 4.29 (dd, *J* = 10.4, 4.8 Hz, 1 H, H-6′), 4.09 (m, 1 H, H-5), 4.08 (dd, *J* = 10.0, 3.6 Hz, 1 H, H-6), 4.00 (t, *J* = 10.0 Hz, 1 H, H-6′), 3.87 (t, *J* = 10.2 Hz, 1 H, H-4′), 3.73 (dd, *J* = 10.0, 3.6 Hz, 1 H, H-6), 3.52 (dd, *J* = 10.6, 7.1 Hz, 1 H, H-3′), 4.43 (d, *J* = 7.1 Hz, 1 H, H-2′), 3.38 (s, 3 H, OCH_3), 3.34 (m, 1 H, H-5′), 2.05 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 1.99 (s, 3 H, Ac). ^{13}C NMR: δ (ppm) = 170.1, 169.9, 169.6, 137.7, 137.2, 129.1, 129.0, 128.5, 128.2, 127.7, 125.9, 125.3, 125.2, 101.5, 100.7, 96.6, 78.3, 76.0, 72.9, 70.8, 69.9, 68.8, 68.7, 67.6, 55.3, 20.6. ESI-HRMS calcd. for $C_{33}H_{39}N_3O_{13}$ [M + Na]: 708.2381; found 708.2389.

(2*S*,3*S*,4*R*)-1-*O*-(2-Azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranosyl)-2-azido-3,4-di-*O*-benzoylphytosphingosine (13)

Protocol A: Yield: 147 mg, 160 μmol, 80%. Colorless oil. R_f 0.66 (ethyl acetate/light petroleum, 1:9 v/v). $[\alpha]_D^{25}$ –33.2 (*c* = 0.5, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2910, 2114, 1724, 1263, 1095, 731, 702 cm^{-1}. ^1H NMR: δ (ppm) = 8.06 (m, 4 H, $H_{arom.}$), 7.28 (m, 16 H, $H_{arom.}$), 5.62 (m, 2 H, H-3, H-4), 5.55 (s, 1 H, C*H*Ph), 4.83 (d, *J* = 12.4 Hz, 1 H, –C*H*Ph), 4.70 (d, *J* = 12.4 Hz, 1 H, –C*H*Ph), 4.56 (s, 1 H, H-1′), 4.24 (d, *J* = 2.2 Hz, 1 H, H-2′), 4.16 (m, 4 H, 2× H-1, H-3′, H-2), 3.93 (m, 3 H, 2× H-6, H-4), 3.28 (m, 1 H, H-5′), 1.87 (t, *J* = 6.6 Hz, 2 H, 2× H-5), 1.23 (m, 22 H, –CH_2–), 0.87 (t, *J* = 5.8 Hz, 3 H, –CH_3). ^{13}C NMR: δ (ppm) = 165.7, 165.0, 138.2, 133.4, 133.2, 129.2, 129.0, 128.9, 128.7, 127.6, 101.4, 99.7, 78.2, 76.1, 72.1, 72.6, 68.9, 68.1, 67.2, 62.0, 60.9, 60.2, 55.3, 31.8, 29.5, 25.2, 22.5, 14.0. ESI-HRMS calcd. for $C_{52}H_{64}N_6O_9$ [M + NH_4]: 934.5079; found 934.5021.

3-*O*-(2-Azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-mannopyranosyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (14)

Protocol A: 14α: Yield: 37 mg, 59 μmol, 29%; **14β:** 74 mg, 119 μmol 60%. **Protocol B: 14α:** Yield: 38 mg, 61 μmol, 31%; **14β:** 76 mg, 121 μmol, 60%. **14α:** Colorless oil. R_f = 0.56 (ethyl acetate/light petroleum, 1:1 v/v). $[\alpha]_D^{25}$ = +14.0 (*c* = 1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2912, 2106, 1589, 1229, 1016, 698 cm^{-1}. ^1H NMR: δ (ppm) = 7.46–7.31 (m, 10 H, $H_{arom.}$), 5.86 (d, *J* = 3.8 Hz, 1 H, H-1), 5.64 (s, 1 H, –C*H*Ph), 5.07 (s, 1 H, H-1′), 4,89 (d, *J* = 10.2 Hz, 1 H, –C*H*Ph), 4.74 (d, *J* = 10.2 Hz, 1 H, –C*H*Ph), 4.54 (d, *J* = 3.8 Hz, 1 H, H-2), 4,41 (m, 1 H, H-5), 4.38 (m, 2 H, H-4, H-3), 4.33 (dd, *J* = 10.2, 4.5 Hz, 1 H, H-6′), 4.18 (t, *J* = 6.4 Hz, 1 H, H-6), 4.09 (m, 5 H, H-4′, H-6, H-2′, H-6′, H-5′), 3.82 (dd, *J* = 9.5, 3.8 Hz, 1 H, H-3′), 1.49 (s, 3 H, –CH_3), 1.46 (s, 3 H, –CH_3), 1.39 (s, 3 H, –CH_3), 1.31 (s, 3 H, –CH_3). ^{13}C NMR: δ (ppm) = 137.8, 137.0, 129.0, 128.5, 128.4, 128.0, 127.8, 126.2, 112.1, 108.4, 105.2, 100.6, 98.0, 82.4, 80.6, 80.2, 78.4, 76.4, 73.2, 73.2, 68.6, 67.7, 66.3, 63.5, 26.7, 26.5, 26.3, 25.5. ESI-HRMS calcd. for $C_{32}H_{39}N_3O_{10}$ [M + NH_4]: 643.2979; found 643.3008. **14β:** Colorless oil. R_f = 0.45 (ethyl acetate/light petroleum, 1:1 v/v). $[\alpha]_D^{25}$ = –107.8 (*c* = 1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2918, 2108, 1456, 1375, 1265, 1084, 731 cm^{-1}. ^1H NMR: δ (ppm) = 7.50–7.33 (m, 10 H, $H_{arom.}$), 5.94 (d, *J* = 3.8 Hz, 1 H, H-1), 5.59 (s, 1 H, –C*H*Ph), 4.91 (d, *J* = 10.2 Hz, 1 H, –C*H*Ph), 4.73 (d, *J* = 10.2 Hz, 1 H, –C*H*Ph), 4.68 (d, *J* = 1.0 Hz, 1 H, H-1′), 4.50 (d, *J* = 3.8 Hz, 1 H, H-2), 4,37 (m, 1 H, H-5), 4.33 (m, 2 H, H-4, H-3), 4.27 (dd, *J* = 10.2, 4.5 Hz, 1 H, H-6′), 4.18 (t,

J = 6.4 Hz, 1 H, H-6), 4.07 (m, 2 H, H-4′, H-6), 3,90 (d, J = 3.5 Hz, 1 H, H-2′), 3.86 (t, J = 10.2 Hz, 1 H, H-6′), 3.77 (dd, J = 9.5, 3.8 Hz, 1 H, H-3′), 3.33 (m, 1 H, H-5′), 1.50 (s, 3 H, –CH_3), 1.45 (s, 3 H, –CH_3), 1.38 (s, 3 H, –CH_3), 1.32 (s, 3 H, –CH_3). ^{13}C NMR: δ (ppm) = 137.7, 137.1, 129.0, 128.5, 128.3, 127.9, 127.7, 126.0, 112.0, 108.6, 105.0, 101.5, 98.1, 82.6, 80.4, 80.3, 78.4, 76.4, 73.1, 73.0, 68.3, 67.5, 66.0, 63.5, 26.7, 26.5, 26.3, 25.5. ESI-HRMS calcd. for $C_{32}H_{39}N_3O_{10}$ [M + NH_4]: 643.2979; found 643.3058.

***tert*-Butyldimethylsilyl 2-Azido-4-*O*-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranosyl)-3,6-di-*O*-ben-zyl-2-deoxy-β-D-glucopyranoside (15)**

Protocol A: Yield: 114 mg, 130 μmol, 66%. Colorless oil. R_f = 0.61 (ethyl acetate/light petroleum, 1:9 v/v). $[\alpha]_D^{25}$ = –9.8 (c = 1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2928, 2856, 2110, 2106, 1497, 1454, 1253, 1064 cm^{-1}. ^{1}H NMR: δ (ppm) = 7.48 (m, 5 H, $H_{arom.}$), 7.37 (m, 15 H, $H_{arom.}$), 5.58 (s, 1 H, –CHPh), 5.15 (s, 1 H, H-1′), 4.99 (d, J = 11.2 Hz, 1 H, –CHPh), 4.78 (d, J = 11.2 Hz, 1 H, –CHPh), 4.56 (m, 4 H, –CHPh), 4.53 (d, J = 8.8 Hz, 1 H, H-1), 4.08 (m, 2 H, H-4′, H-6′), 3.96 (dd, J = 9.6, 3.7 Hz, 1 H, H-3′), 3.76 (m, 3 H, H-5′, H-4, H-3), 3.72 (d, J = 3.7 Hz, 1 H, H-2′), 3.65 (d, J = 3.0 Hz, 2 H, 2× H-6), 3.36 (m, 3 H, H-5, H-2, H-6′), 0.95 (s, 9 H, –C$H_3$$t$Bu), 0.17 (s, 3 H, Si–C$H_3$), 0.16 (s, 3 H, Si–C$H_3$). ^{13}C NMR: δ (ppm) = 138.0, 137.4, 129.3, 129.0, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.7, 127.5, 127.5, 127.4, 126.0, 101.5, 100.6, 97.2, 82.6, 78.9, 75.8, 75.6, 74.8, 74.4, 73.6, 73.2, 68.9, 68.6, 68.5, 64.7, 62.7, 25.6, 17.9, –4.3, –5.2. ESI-HRMS calcd. for $C_{46}H_{56}N_6O_9Si$ [M + NH_4]: 882.4222; found 882.4181.

2-Azido-4-*O*-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranosyl)-3-*O*-benzyl-2-deoxy-β-D-anhydroglucose (16)

Protocol A: 16α: Yield: 19 mg, 30 μmol, 15%; **16β**: yield: 78 mg, 120 μmol, 60%. **Protocol B: 16α:** Yield: 15 mg, 24 μmol, 12%; **16β:** Yield 77 mg, 116 μmol, 58%. **16α:** White foam. R_f = 0.53 (ethyl acetate/light petroleum, 1:4 v/v). $[\alpha]_D^{25}$ = +2.4 (c = 1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2926, 2156, 2104, 1265, 1139, 1026 cm^{-1}. ^{1}H NMR: δ (ppm) = 7.40 (m, 2 H, $H_{arom.}$), 7.29 (m, 13 H, $H_{arom.}$), 5.62 (s, 1 H, –CHPh), 5.55 (s, 1 H, H-1), 4.83 (d, J = 12.0 Hz, 1 H, –CHPh), 4.69 (m, 3 H, H-1′, –CHPh), 4.61 (d, J = 5.2 Hz, 1 H, H-5), 4.53 (d, J = 12.0 Hz, 1 H, –CHPh), 4.21 (m, 2 H, H-6′, H-3), 4.12 (m, 2 H, H-6, H-4′), 3.98 (dd, J = 3.6, 1.2 Hz, 1 H, H-2′), 3.88 (m, 2 H, H-5′, H-6′), 3.77 (dd, J = 7.6, 6.0 Hz, 1 H, H-6), 3.60 (s, H-4), 3.57 (t, J = 1.6 Hz, 1 H, H-3), 3.16 (s, 1 H, H-2). ^{13}C NMR: δ (ppm) = 138.4, 137.5, 137.3, 129.9, 129.0, 128.7, 128.38, 128.4, 128.2, 127.8, 127.7, 127.5, 101.7, 100.6, 99.0, 78.8, 77.3, 75.9, 75.2, 74.4, 73.40, 72.5, 68.5, 65.2, 64.7, 62.6, 58.8. ESI-HRMS calcd. for $C_{33}H_{34}N_6O_8$ [M + NH_4]: 660.2782; found 660.2779. **16β:** White foam. R_f = 0.32 (ethyl acetate/light petroleum, 1:4 v/v). $[\alpha]_D^{25}$ = –26.4 (c = 1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2872, 2108, 2104, 1456, 1265, 1085 cm^{-1}. ^{1}H NMR: δ (ppm) = 7.41 (m, 2 H, $H_{arom.}$), 7.29 (m, 13 H, $H_{arom.}$), 5.52 (s, 1 H, –CHPh), 5.46 (s, 1 H, H-1), 4.78 (d, J = 12.4 Hz, 1 H, –CHPh), 4.76 (s, 1 H, H-1′), 4.67 (d, J = 12.4 Hz, 1 H, –CHPh), 4.58 (d, J = 5.4 Hz, 1 H, H-5), 4.54 (s, 2 H, –CHPh), 4.18 (dd, J = 10.4, 4.8 Hz, 1 H, H-6′), 4.05 (m, 2 H, H-6, H-2′), 3.98 (t, J = 9.4 Hz, 1 H, H-4′), 3.86 (s, 1 H, H-4), 3.83 (t, J = 10.2 Hz, 1 H, H-6′), 3.75 (m, 2 H, H-3, H-6), 3.65 (dd, J = 9.6, 3.6 Hz, H-3′), 3.23 (m, 1 H, H-5′), 3.12 (s, 1 H, H-2). ^{13}C NMR: δ (ppm) = 138.1, 137.5, 137.2, 129.0, 128.2, 127.9, 127.9, 127.7, 127.5, 125.9, 101.6, 100.9, 96.9, 78.3, 77.7, 76.0, 73.0, 72.7, 72.5, 71.8, 68.2, 67.6, 64.7, 62.8, 60.3, 58.8. ESI-HRMS calcd. for $C_{33}H_{34}N_6O_8$ [M + NH_4]: 660.2782; found 660.2781.

Methyl 4-*O*-Acetyl-2-azido-3-*O*-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-D-mannopyranosyl)-6-*O*-*tert*-butyldiphenylsilyl-2-deoxy-β-L-galactopyranoside (17)

Protocol B: 17α: Yield: 25 mg, 30 μmol, 14%. **17β:** Yield: 102 mg, 118 μmol, 60%. **17α:** Colorless oil. R_f = 0.71 (ethyl acetate/light petroleum, 1:3 v/v). $[\alpha]_D^{25}$ = +6.2 (c = 1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2985, 2976, 2076, 1746, 1381, 1247, 1076, 1043 cm^{-1}. ^{1}H NMR: δ (ppm) = 7.61 (m, 4 H, $H_{arom.}$), 7.38 (m, 16 H, $H_{arom.}$), 5.60 (s, 1 H, –CHPh), 5.40 (d, J = 1.6 Hz, 1 H, H-4), 5.03 (s, 1 H, H-1′), 4.89 (d, J = 12.4 Hz, 1 H, –CHPh), 4.72 (d, J = 12.4 Hz, 1 H, –CHPh), 4.23 (dd, J = 10.2, 4.8 Hz, 1 H, H-6′), 4.18 (d, J = 7.6 Hz, 1 H, H-1), 4.10 (t, J = 9.2 Hz, 1 H, H-4′), 4.00 (m, 3 H, H-2′, H-6′, H-3′), 3.81 (m, 2 H, H-6, H-3), 3.74 (m, 1 H, H-5′), 3.66 (t, J = 6.8 Hz, 1 H, H-6), 3.62 (m, 1 H, H-5), 3.56 (m, 4 H, OCH_3, H-2), 1.93 (s, 3 H, Ac), 1.05 (s, 9 H, –C$H_3$$t$Bu). ^{13}C NMR: δ (ppm) = 169.3, 138.3, 138.1, 135.5, 133.1, 132.9, 129.9, 129.8, 129.4, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 103.3, 101.7, 100.8, 78.9, 75.9, 75.0, 73.9, 73.4, 73.3, 68.4, 68.0, 64.6, 63.3, 62.7, 61.5, 57.2, 26.7, 20.5, 19.1. ESI-HRMS calcd. for $C_{45}H_{52}N_6O_{10}Si$ [M + NH_4]: 882.3852; found 882.3879. **17β:** White foam. R_f = 0.51 (ethyl acetate/light petroleum, 1:3 v/v). $[\alpha]_D^{25}$ = –44.2 (c = 1, $CHCl_3$). IR (thin film): $\tilde{\nu}$ = 2986, 2976, 2078, 1746, 1380, 1247, 1074, 1047 cm^{-1}. ^{1}H NMR: δ (ppm) = 7.63 (m, 4 H, $H_{arom.}$), 7.39 (m, 16 H, $H_{arom.}$), 5.63 (s, 1 H, –CHPh), 5.48 (d, J = 3.2 Hz, 1 H, H-4), 4.89 (d, J = 12.0 Hz, 1 H, –CHPh), 4.84 (d, J = 1.2 Hz, 1 H, H-1′), 4.75 (d, J = 12.0 Hz, 1 H, –CHPh), 4.34 (dd, J = 10.8, 5.2 Hz, 1 H, H-6′), 4.16 (d, J = 8.0 Hz, 1 H, H-1), 4.02 (t, J = 9.6 Hz, 1 H, H-4′), 3.92 (m, 2 H, H-2′, H-6′), 3.81 (m, 3 H, H-3, H-6, H-3′), 3.69 (t, 1 H, 8.0 Hz, H-6), 3.65 (m, 1 H, H-5), 3.55 (m, 4 H, OCH_3, H-2), 3.38 (m, 1 H, H-5′), 2.10 (s, 3 H, Ac), 1.05 (s, 9 H, –C$H_3$$t$Bu). ^{13}C NMR: δ (ppm) = 170.6, 137.8, 137.2, 135.5, 135.4, 132.8, 132.5, 129.9, 129.8, 129.0, 128.9, 128.4, 128.2, 102.8, 101.5, 97.4, 78.1, 76.5, 75.8, 72.9, 72.8, 68.3, 67.4, 64.8, 63.0, 61.8, 61.1, 57.2, 26.7, 20.7, 19.0. ESI-HRMS calcd. for $C_{45}H_{52}N_6O_{10}Si$ [M + NH_4]: 882.3852; found 882.3867.

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