JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00006 • Publication Date (Web): 13 Feb 2018

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Total Synthesis of Nucleoside Antibiotics Plicacetin and Streptcytosine A

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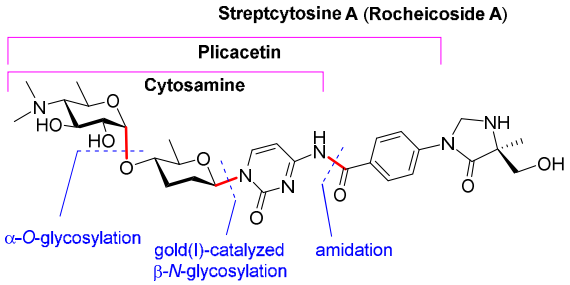


ABSTRACT: Disaccharide nucleoside antibiotics plicacetin and streptcytosine A (also named rocheicoside A) were effectively synthesized through the common precursor cytosamine. The amosamine and amicetose moieties were efficiently assembled through an α-selective *O*-glycosylation while the cytosine nucleus was subsequently introduced through a β-selective gold (I)-catalyzed *N*-glycosylation. Further microwave-assisted amidation reactions completed the modular syntheses.

INTRODUCTION

Amicetin (Fig. 1) was isolated in the early 1950s as the first member of the amicetin family antibiotics,[1a] which are produced in the fermentation broth of various species of *Streptomyces*, *Arthrobacter*, and *Nocardia*.[1-12] The structures of amicetin and its simpler congeners, such as plicacetin

(**1**),[1c,d] were elucidated via extensive degradation and transformation studies in the 1960s.[2-4] In 1981, the structure of amicetin was unambiguously confirmed by X-ray diffraction analysis,[5] and in 2007, a detailed NMR structure determination was reported.[6] Other members of the amicetin family antibiotics include oxamicetin,[7] norplicacetin,[8] oxyplicacetin,[9] SF2457,[10] and cytosaminomycins A-D.[11] More recently, streptcytosine A (**2**) was isolated from a culture broth of *Streptomyces* sp. TPU1236A collected in Okinawa, Japan;[12a] this compound was later isolated from *Streptomyces rochei* 06CM016 collected in the Mediterranean sea and named rocheicoside A (Figure 1).[12b] These antibiotics share a common disaccharide pyrimidine nucleoside motif, namely cytosamine, in which amosamine is α-(1→4)-linked to amicetose, itself β-(1→N^1)-linked to a cytosine nucleus. The NH_2 group of the amosamine residue could be mono- or di-methylated, the C-3 of the amicetose residue could be hydroxylated, and the N^7 on cytosine could be acylated, thus constituting the molecular diversity of these compounds. As antibiotics, they demonstrated antibacterial and antiviral activities both *in vitro* and *in vivo*, more specifically against tuberculosis, herpes, and polio.[1,6-11,13] Amicetin has shown to stabilize polysomes and prevent their breakdown induced by other antibiotics.[14] More importantly, they have proven to inhibit protein biosynthesis of both prokaryotic and eukaryotic ribosomes by binding to the peptidyl transferase centre.[15] Recently, NMR spectroscopy and unconstrained molecular modelling provided direct evidences for the specific binding of amicetin to two 35mer ribosomal RNA motifs of *Halobacterium halobium* and *Escherichia coli* 23S rRNAs.[16] Nevertheless, further biological studies are hampered by the fact that these compounds are produced in heterogeneous mixtures and in small quantities, which renders their accessibility difficult. As a consequence, chemical synthesis of these molecules with a well-defined structure and in appreciable amount is of great interest.

To date, several important sugar segments of amicetin antibiotics have been chemically synthesized,

i.e., amicetose,[3] amicetose nucleoside,[17] and aminosamine.[2,18] In 2001, Sugimura *et al.* reported the synthesis of cytosamine (**3**), which is thought to be a common intermediate of this class of antibiotics, via a glycosylation between an amosamine-type glycosyl fluoride donor and an amicetose nucleoside acceptor.[19] The glycosylation was promoted by 5.0 equiv. of AgOTf/$SnCl_2$ in Et_2O/dichloroethane (room temperature, 40 h) and provided the desired α-glycoside in 52% yield together with the β-anomer (11%) and the remaining acceptor (11%). The total synthesis of plicacetin (**1**) has been reported by Stevens *et al.* in 1972.[20] In their synthesis, cytosamine (**3**) was prepared by coupling an amosamine-type β-glycosyl chloride donor with an amicetose nucleoside acceptor in molten states, under diminished pressure, and in the presence of Dowex 1-X2 (HO^-). The corresponding α-linked disaccharide was obtained in 38% yield after extensive purification; subsequent transformations led to cytosamine and finally plicacetin (**1**).[1d]

The paucity of reports indicates the difficulty of chemically synthesizing this class of antibiotics. Indeed, when designing a retro-synthetic pathway, several problems arise: the construction of α-linkage between an amosamine donor and an amicetose acceptor, the installation of the cytosine nucleus in a regio- and β-selective manner with an amicetose donor lacking neighboring participation, and the introduction of pendant motifs on the poorly reactive NH_2 of the cytosine nucleus. These considerations prompted us to investigate the chemical synthesis of the amicetin family antibiotics. Herein we report the total synthesis of plicacetin (**1**) and streptcytosine A (rocheicoside A, **2**). Their syntheses were achieved via the common intermediate cytosamine (**3**), which was effectively constructed by a high β-selective glycosylation between disaccharide *o*-hexynylbenzoate donor **4** and cytosine derivative **5** under gold(I)-catalysis (Fig. 1).[21,22] Disaccharide **4** was synthesized by coupling amicetose acceptor **8** with amosamine-type donors (**6** and **7**), which was installed with *p*-methoxybenzyl groups (PMB) to facilitate an α-selective glycosylation.

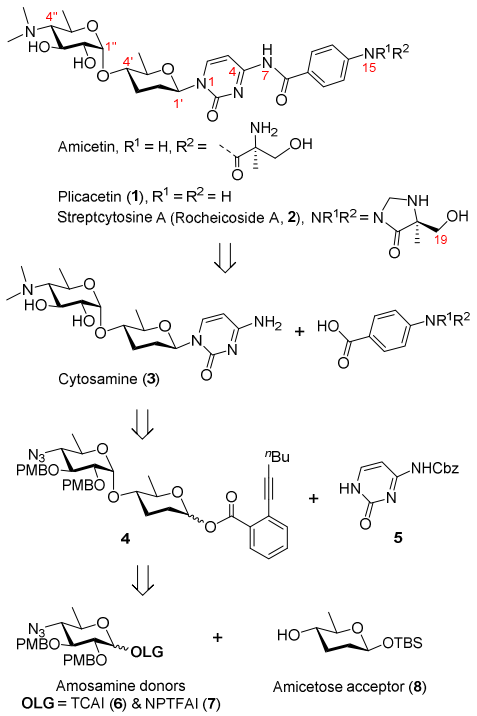
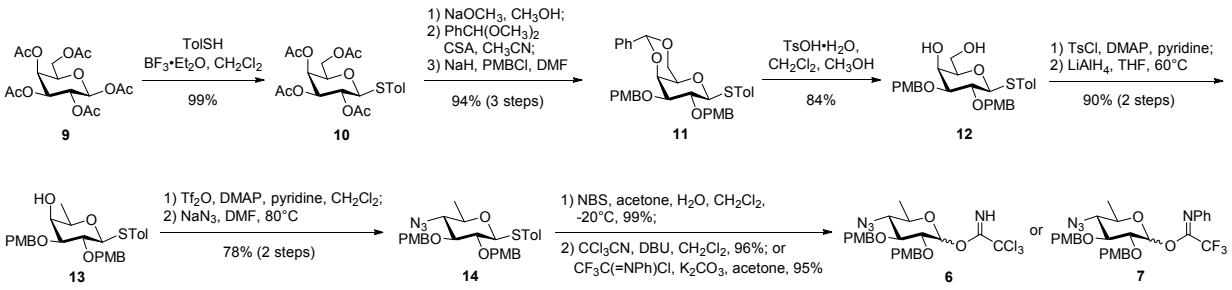


Figure 1. Plicacetin (**1**) and streptcytosine A (rocheicoside A, **2**) and a retrosynthetic analysis. Cbz = carboxybenzyl, NPTFAI = *N*-phenyltrifluoroacetimidate, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TCAI = trichloroacetimidate.

RESULTS AND DISCUSSION

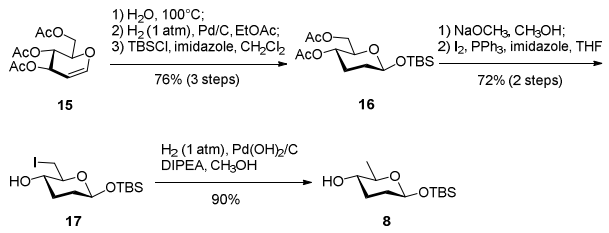
Amosamine-type donors **6** and **7** were synthesized from thiogalactoside **14** (Scheme 1). Compound **14** was prepared from commercially available penta-*O*-acetyl-β-D-galactopyranose (**9**) via a similar approach as the one reported by Sugimura *et al.*[19] Thus, β-acetate **9** was glycosylated with *p*-toluenethiol under the promotion of $BF_3{\cdot}OEt_2$ to provide thiogalactoside **10** (99%).[23] After removal of the acetyl groups, the 4,6-hydroxyl groups were selectively protected as benzylidene acetal and the free 2,3-hydroxyl groups were protected with PMB ethters, leading to the fully protected galactoside **11** in 94% overall yield from **10**.[24] Cleavage of the benzylidene acetal with $TsOH{\cdot}H_2O$ gave the 4,6-diol **12** (84%).[25] The primary 6-OH underwent selective tosylation and subsequent reduction with $LiAlH_4$ in THF at 60 ºC to afford the 6-deoxy galactoside **13** in 90% overall yield for two steps. Substitution of the 4-OH

with azide was accomplished via a 4-*O*-triflate intermediate, leading to 4,6-di-deoxy-thioglycoside **14** (78%, two steps). Finally, thioglycoside **14** was smoothly hydrolyzed in the presence of *N*-bromosuccinimide in a solvent mixture of acetone/H_2O/CH_2Cl_2 at -20 ºC, and the resulting hemiacetal was reacted with Cl_3CCN or $CF_3C(=NPh)Cl$ under standard basic conditions[26] to yield amosamine-type imidate donors **6** and **7**, respectively.



Scheme 1. Synthesis of amosamine donors **6** and **7**. CSA = camphorsulfonic acid, DBU = 1,8-biazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, NBS = *N*-bromosuccinimide, Tf = trifluoromethanesulfonyl, Tol = tolyl, Ts = *p*-toluenesulfonyl.

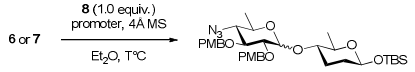
Amicetose acceptor **8** was obtained in a straightforward manner from commercially available 3,4,6-tri-*O*-acetyl-D-glucal **15** (Scheme 2). Ferrier-type reaction of **15** under a condition of H_2O at 100 ºC provided the corresponding hemiacetal, which upon hydrogenation and TBS-protection led to the 2,3-dideoxy β-glycoside **16** in 76% overall yield for three steps. After removal of the acetyl groups, the resultant primary alcohol was treated with I_2/PPh_3 and imidazole in THF to give 6-iodo-glycoside **17** in 72% yield (for two steps). Finally, reduction of the iodide was achieved via hydrogenolysis over $Pd(OH)_2$/C in the presence of DIPEA, giving amicetose acceptor **8** (90%).



Scheme 2. Synthesis of amicetose acceptor **8**. DIPEA = *N,N*-diisopropylethylamine.

Amicetose acceptor **8** was subjected to glycosylation with amosamine-type donors **6** and **7** in the presence of 4Å MS in Et_2O, a solvent which has been proven to favor the α-selective glycosylation (Table 1).[27] When acceptor **8** was coupled with donor **6** (2.1 equiv.) at -40 ºC under the promotion of TMSOTf (0.05 equiv.), disaccharide **18** was isolated in 88% yield and with a high α/β selectivity of 7.5:1 (entry 1). It is noteworthy that, under these reaction conditions, side products, *e.g.*, the *C*-glycoside derivatized from an intramolecular Friedel-Crafts reaction,[28] were formed and isomerization of the anomeric positions occurred under a prolonged reaction time, thus decreasing the yield of **18** and rendering the purification difficult. Taking into account these observations, acceptor **8** and donor **7** were glycosylated at -60 ºC under the promotion of TBSOTf (0.05 equiv.). Under these conditions, the previous byproducts as well as isomerization were not detected and disaccharide **18** was isolated in a better yield (92%) and still in an excellent α-selectivity (α/β = 8:1, entry 2). The isomers **18α** and **18β** could be separated on silica gel and their configurations were confirmed by ^{1}H NMR analysis. The *amosamine* anomeric proton of **18β** appeared as a doublet at δ 4.38 ppm with J = 7.6 Hz; the one of **18α** appeared downfield at δ 4.79 ppm, however, its J value could not be calculated due to overlapping with the CH_2 signals of the PMB groups and the anomeric proton of the amicetose moiety.

Table 1. Glycosylation of amicetose acceptor **8** with amosamine donors **6** and **7**.

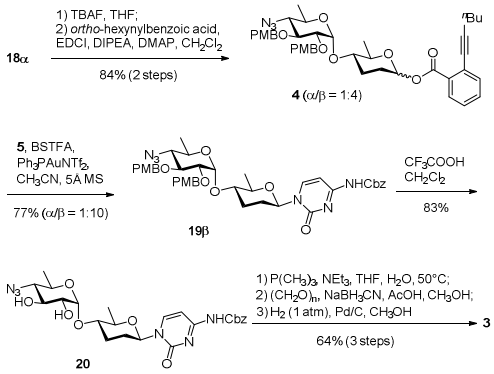


18

Entry	Donor (equiv.)[a]	Promoter (equiv.)[b]	T°C	Yield[c]	α/β[d]
1	**6** (2.1)	TMSOTf (0.05)	-40	88%	7.5:1
2	**7** (1.5)	TBSOTf (0.05)	-60	92%	8:1

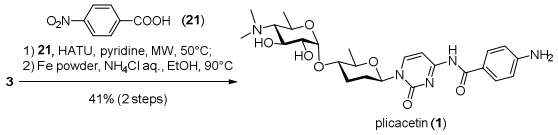
[a] Calculated based on acceptor **8**. [b] Calculated based on donors **6** and **7**. [c] Isolated yield of **18**. [d] Ratio of the isolated α and β isomers. MS = molecular sieves, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

Disaccharide **18α** was used to prepare the common intermediate cytosamine (**3**) (Scheme 3). Thus, **18α** was desilylated with a solution of TBAF in THF, and *o*-hexynylbenzoic acid was introduced to the corresponding hemiacetal to afford *o*-hexynylbenzoate donor **4** (84%, 2 steps). Donor **4** was subjected to glycosylation with silylated cytosine **5**[29] under the catalysis of $Ph_3PAuNTf_2$ (0.2 equiv.). To our delight, nucleoside **19** was isolated in a good 77% yield with an excellent β-selectivity (α/β = 1:10), most likely favored by the use of acetonitrile as solvent.[30] The isomers **19α** and **19β** could be separated on silica gel, and the β-configuration was confirmed by ^{1}H NMR analysis, wherein the anomeric proton appeared as a doublet at δ 5.74 ppm with J = 9.8 Hz. Isomer **19β** was then treated with CF_3COOH in CH_2Cl_2 to provide 2'',3''-diol **20** (83%). Finally, reduction of the azide under Staudinger conditions, followed by reductive dimethylation of the nascent amine with paraformaldehyde and $NaBH_3CN$ in $AcOH/CH_3OH$ and subsequent reductive cleavage of the Cbz group (H_2/Pd/C) led to cytosamine (**3**) in 64% yield for three steps.



Scheme 3. Synthesis of cytosamine (**3**). BSTFA = *N,O*-bis(trimethylsilyl)trifluoroacetamide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, TBAF = *tetra*-*n*-butylammonium fluoride.

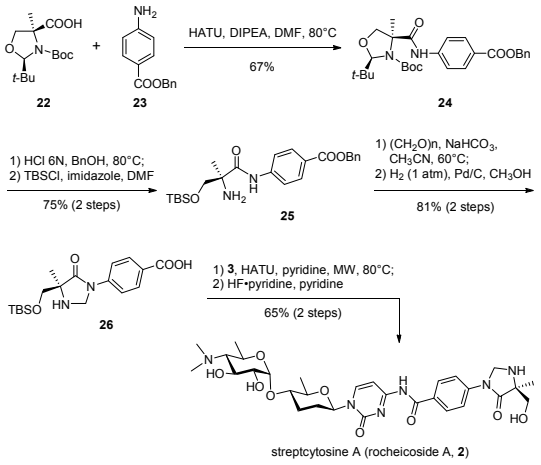
With cytosamine (**3**) at hand, the synthesis of plicacetin (**1**) was achieved in two steps (Scheme 4). Attempts to couple **3** with 4-nitrobenzoyl chloride failed even at elevated temperature, which can be rationalized by the poor nucleophilicity of the amino group of the cytosine moiety in **3**. Nevertheless, **3** could be coupled with 4-nitrobenzoic acid (**21**) in the presence of HATU under heating conditions, although a long reaction time was required. To our delight, the reaction time could be greatly shortened by using microwave (50 ºC, 5 min). Subsequent reduction of the nitro group using Fe powder and an aqueous solution of NH_4Cl in EtOH at 90 ºC furnished plicacetin (**1**) in 41% yield (for two steps).



Scheme 4. Synthesis of plicacetin (**1**). HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate.

To complete the synthesis of streptcytosine A (rocheicoside A, **2**), the carboxylic acid segment was prepared (Scheme 5). Compound **22**, obtained from L-serine methyl ester hydrochloride,[31] was coupled with benzyl 4-aminobenzoate (**23**)[32] in the presence of HATU and DIPEA in DMF at 80 ºC to afford

amide **24** (67%). The oxazolidine ring, which showed to be very stable, was opened under forced conditions employing an aqueous solution of 6N HCl in BnOH at 80 ºC. Subsequent protection of the primary alcohol with a TBS group provided the corresponding amido-amine **25** in 75% yield (for two steps). Reaction of **25** with paraformaldehyde and $NaHCO_3$ in CH_3CN at 60 ºC gave the corresponding imidazolidinone intermediate, which upon hydrogenolysis over Pd/C in CH_3OH provided the carboxylic acid segment **26** (81%, 2 steps). Cytosamine (**3**) and **26** were successfully coupled together in the presence of HATU and pyridine at 80 ºC under microwave conditions. The microwave was performed for 5 minutes, 3 times, in order to minimize side reactions. At this stage, the amide bonds remained fragile under both strong acidic and basic conditions. Nevertheless, HF·pyridine could smoothly remove the TBS group without affecting the amide bonds, thus providing streptcytosine A (rocheicoside A, **2**) in 65% yield (for two steps). Its NMR spectra were in accordance with those reported for the natural product.[12]



Scheme 5. Synthesis of streptcytosine A (rocheicoside A, **2**).

CONCLUSION

In conclusion, we reported the total synthesis of plicacetin (**1**) and the first total synthesis of

streptcytosine A (rocheicoside A, **2**), two antibiotics of the amicetin family. Our approach involved: 1) a α-selective *O*-glycosylation between amosamine imidate donors (**6** and **7**) and amicetose acceptor **8**; 2) formation of the common intermediate cytosamine (**3**) via a β-selective gold(I)-catalyzed *N*-glycosylation between disaccharide *o*-alkynylbenzoate donor **4** and cytosine (**5**); 3) amidation between **3** and the appropriate carboxylic acid segment under microwave conditions. Following this approach, the syntheses of other members are undergoing in our laboratory. We assume that the access to these biologically active natural compounds in pure forms and appropriate amount will help scientists to elucidate their structure-activity relationship as well as to design more potent analogs.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under N_2 or argon with anhydrous solvents in flame-dried glassware, unless otherwise noted. Dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), *N,N*-dimethylformamide (DMF), and methanol (CH_3OH) were dried over activated 4Å molecule sieves; triethylamine (NEt_3) and pyridine were dried over potassium hydroxide; tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium. The chemicals used were reagent grade as supplied, except where noted. Analytical thin-layer chromatography (TLC) was conducted with silica gel 60 F254 pre-coated glass plates (0.25 mm) and visualized by exposure to UV light (254 nm) or by staining with sulfuric acid, ceric ammonium molybdate, or potassium permanganate ($KMnO_4$) ethanolic solutions. Silica gel (particle size 0.037−0.048 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded at 400, 500, or 600 MHz and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded at 100, 125, or 150 MHz. Data for ^{13}C NMR spectra are

reported in terms of chemical shift. NMR spectra were referenced using $(CH_3)_4Si$ (0 ppm), residual $CDCl_3$ (^{1}H NMR δ = 7.26 ppm, ^{13}C NMR δ = 77.16 ppm), CD_3OD (^{1}H NMR δ = 3.31 ppm, ^{13}C NMR δ = 49.00 ppm), and DMSO-*d6* (^{1}H NMR δ = 2.50 ppm, ^{13}C NMR δ = 39.52 ppm). High resolution mass spectra were recorded on ESI-TOF spectrometers. Optical rotations were measured on a polarimeter using either $CHCl_3$ or CH_3OH as solvents.

Commercially available compounds **9**, **15**, and **21** were purchased, while compounds **5**, **22**, and **23** were synthesized according to literature procedures.[29,31,32]

*Tolyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside (**10**).* To a solution of D-galactose pentaacetate (**9**) (20.0 g, 51.2 mmol) and 4-tolyl mercaptan (TolSH) (7.00 g, 56.32 mmol) in CH_2Cl_2 (200 mL) was added $BF_3{\cdot}OEt_2$ (16.14 mL, 128.00 mmol) at 0 ºC. The mixture was stirred at room temperature for 6 h and then quenched at 0 ºC by addition of saturated aqueous $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 1:1) to provide **10** as a colorless liquid (23.0 g, 99%): $[\alpha]_D^{28}$ = +16.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.7 Hz, 2H), 5.40 (d, *J* = 2.1 Hz, 1H), 5.21 (t, *J* = 9.9 Hz, 1H), 5.03 (dd, *J* = 9.8, 2.8 Hz, 1H), 4.64 (d, *J* = 9.9 Hz, 1H), 4.18 (dd, *J* = 11.1, 7.0 Hz, 1H), 4.10 (dd, *J* = 11.1, 6.4 Hz, 1H), 3.90 (t, *J* = 6.4 Hz, 1H), 2.34 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.3, 170.2, 169.6, 138.6, 133.3, 129.8, 128.8, 87.1, 74.5, 72.2, 67.4, 67.4, 61.7, 21.3, 21.0, 20.8, 20.8, 20.7; HRMS (ESI) calcd for $C_{21}H_{30}O_9NS$ $[M+NH_4]^+$ 472.1636, found 472.1632.

*Tolyl 2,3-di-O-p-methoxybenzyl-4,6-O-benzylidene-1-thio-β-D-galactopyranoside (**11**).* To a solution of **10** (39.16 g, 86.16 mmol) in CH_3OH (300 mL) was added $NaOCH_3$ (465 mg, 8.64 mmol). The mixture was stirred for about 1 h at room temperature and then neutralized with DOWEX 50W (H^+-form). After removal of the resin by filtration, concentration of the filtrate afforded the corresponding 2,3,4,6-tetraol, which was used for the next step without further purification.

The crude tetraol was treated with benzaldehyde dimethylacetal (19.40 mL, 129.24 mmol) and camphorsulfonic acid (1.00 g, 4.31 mmol) in CH_3CN (600 mL) overnight at room temperature. After addition of NEt_3, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, and filtered. The filtrate was partially evaporated until apparition of a solid. Petroleum ether was added to the mixture, which was then stored at -20 ºC for 30 min. The solid was finally filtered, washed with petroleum ether, and used for the next step.

The aforementioned solid was dissolved in DMF (400 mL), and NaH (60% in mineral oil, 9.61 g, 240.35 mmol) was added at 0 ºC. After 30 min of stirring at 0 ºC, *p*-methoxybenzyl chloride (27.04 mL, 200.29 mmol) was added to the reaction mixture, and stirring was continued overnight at room temperature. The reaction was quenched by addition of CH_3OH. The mixture was neutralized with saturated aqueous NH_4Cl and then extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by crystallization (CH_2Cl_2/petroleum ether) to provide **11** as a light yellow solid (50 g, 94%): $[\alpha]_D^{28}$ = -22.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 2H), 7.56 (d, *J* = 3.8 Hz, 2H), 7.44–7.37 (m, 5H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.50 (s, 1H), 4.69 (s, 4H), 4.58 (d, *J* = 9.5 Hz, 1H), 4.37 (d, *J* =

12.2 Hz, 1H), 4.13 (d, *J* = 2.8 Hz, 1H), 3.98 (d, *J* = 11.9 Hz, 1H), 3.98-3.92 (m, 4H), 3.81 (s, 3H), 3.61 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.38 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 159.3, 138.0, 137.6, 133.4, 130.9, 130.3, 129.8, 129.7, 129.5, 129.0, 128.9, 128.1, 126.7, 113.8, 113.8, 101.3, 86.7, 81.1, 75.2, 75.1, 73.8, 71.5, 69.8, 69.5, 55.3, 55.3, 21.2; HRMS (ESI) calcd for $C_{36}H_{38}NaO_7S$ $[M+Na]^+$ 637.2230, found 637.2236.

*Tolyl 2,3-di-O-p-methoxybenzyl-1-thio-β-D-galactopyranoside (**12**).* $TsOH{\cdot}H_2O$ (3.55 g, 18.67 mmol) was added to a solution of compound **11** (16.40 g, 26.68 mmol) in CH_2Cl_2 (90 mL) and CH_3OH (90 mL) at room temperature. After stirring for 2 h, the mixture was neutralized by addition of NEt_3 and then concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 4:1 to 1:1) to provide **12** as a white foam (11.77 g, 84%): $[\alpha]_D^{28}$ = +4.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.94-6.84 (m, 4H), 4.76 (d, *J* = 9.9 Hz, 1H), 4.67 (d, *J* = 10.0 Hz, 1H), 4.64 (s, 2H), 4.57 (d, *J* = 9.7 Hz, 1H), 4.02 (s, 1H), 3.98–3.90 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.69 (t, *J* = 9.2 Hz, 1H), 3.60–3.51 (m, 1H), 3.45 (s, 1H), 2.72 (s, 1H), 2.42 (d, *J* = 4.3 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 159.4, 137.8, 132.5, 130.5, 123.0, 129.9, 129.8, 129.7, 114.1, 113.9, 88.0, 82.2, 78.1, 76.8, 75.4, 72.0, 67.4, 62.8, 55.4, 55.4, 21.2; HRMS (ESI) calcd for $C_{29}H_{34}NaO_7S$ $[M+Na]^+$ 549.1917, found 549.1919.

*Tolyl 2,3-di-O-p-methoxybenzyl-6-deoxy-1-thio-β-D-galactopyranoside (**13**).* Tosyl chloride (6.39 g, 33.52 mmol) was added to a solution of **12** (11.77 g, 22.35 mmol) and DMAP (273 mg, 2.23 mmol) in pyridine

(150 mL) at 0 ℃. The mixture was stirred at room temperature overnight and then quenched with H_2O at 0℃. After evaporation of the solvents under reduced pressure, the crude residue was diluted with EtOAc and washed with saturated aqueous $CuSO_4$. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 4:1 to 2:1) to afford the corresponding 6-*O*-Ts derivative (14.79 g, 97%).

$LiAlH_4$ (1.23 g, 32.50 mmol) was added to a solution of the aforementioned 6-*O*-Ts galactoside (14.75 g, 21.66 mmol) in dry THF (100mL) at 0 ℃, and the mixture was stirred at 60 ºC for 5 h. The reaction was quenched by careful addition of EtOAc and saturated aqueous potassium sodium tartrate (Seignette's salt) at 0℃. After filtration through Celite®, THF was removed under reduced pressure, and the resulting mixture was extracted with CH_2Cl_2 several times. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 4:1 to 2:1) to yield **13** as a colorless liquid (10.34 g, 93%): $[\alpha]_D^{28}$ = +5.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.91–6.84 (m, 4H), 4.75 (d, *J* = 9.9 Hz, 1H), 4.65 (dd, *J* = 9.0, 5.3 Hz, 1H), 4.63 (s, 2H), 4.51 (d, *J* = 9.7 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.77 (d, *J* = 2.6 Hz, 1H), 3.61 (t, *J* = 9.3 Hz, 1H), 3.52 (dt, *J* = 13.3, 4.9 Hz, 2H), 2.32 (s, 3H), 1.35 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 159.5, 137.7, 132.8, 130.7, 130.2, 130.0, 130.0, 129.7, 129.7, 114.1, 113.9, 88.0, 82.8, 76.7, 75.4, 74.3, 72.0, 69.6, 55.5, 55.4, 21.3, 16.9. HRMS (ESI) calcd for $C_{29}H_{34}NaO_6S$ $[M+Na]^+$ 533.1968, found 533.1971.

*Tolyl 2,3-di-O-p-methoxybenzyl-4-azido-4,6-dideoxy-1-thio-β-D-glucopyranoside (**14**).* DMAP (2.47 g,

2.02 mmol) and Tf_2O (6.84 mL, 40.50 mmol) were added to a solution of **13** (10.34 g, 20.25 mmol) in CH_2Cl_2 (80 mL) and pyridine (16 mL, 202.49 mmol) at 0℃. The mixture was allowed to stir at room temperature overnight and was finally quenched by addition of H_2O at 0 ºC. After removal of solvents, the crude compound was dissolved in EtOAc and washed with saturated aqueous $CuSO_4$. The organic layer was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 6:1) to furnish the corresponding 4-OTf galactoside as a colorless liquid (10.60 g, 81%).

Sodium azide (1.28 g, 19.79 mmol) was added to a solution of the aforementioned 4-OTf galactoside (10.60 g, 16.49 mmol) in DMF (90 mL), and the mixture was stirred at 80 ºC. After 2.5 h, DMF was evaporated under reduced pressure, and the resulting residue was diluted with CH_2Cl_2 and washed with saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 6:1) to afford **14** as a white solid (8.47 g, 96%): $[\alpha]_D^{25}$ = +48.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.93–6.87 (m, 4H), 4.87 (d, *J* = 10.0 Hz, 1H), 4.83 (d, *J* = 10.3 Hz, 1H), 4.77 (d, *J* = 10.2 Hz, 1H), 4.68 (d, *J* = 10.0 Hz, 1H), 4.54 (d, *J* = 9.5 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.50 (t, *J* = 8.9 Hz, 1H), 3.44 (t, *J* = 9.1 Hz, 1H), 3.21 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.14 (t, *J* = 9.5 Hz, 1H), 2.35 (s, 3H), 1.37 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 138.1, 132.8, 130.3, 130.0, 129.9, 129.8, 129.7, 114.02, 88.0, 84.6, 80.8, 75.5, 75.2, 74.9, 67.9, 55.4, 55.4, 21.3, 18.9; HRMS (ESI) calcd for $C_{29}H_{33}N_3NaO_5S$ $[M+Na]^+$ 558.2033, found 558.2036.

*2,3-Di-O-p-methoxybenzyl-4-azido-4,6-dideoxy-α/β-D-glucopyranosyl trichloroacetimidate (**6**).*

N-Bromosuccinimide (5.94 g, 33.38 mmol) was added to a mixture of **14** (5.96 g, 11.12 mmol) in acetone (50 mL), H_2O (5 mL), and CH_2Cl_2 (20 mL) at -20 ºC. After stirring for 2 h, a saturated aqueous $Na_2S_2O_3$ was added to quench the reaction. The two layers were separated and the aqueous one was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 8:1 to 2:1) to afford the corresponding hemiacetal as a white liquid (4.97 g, 99%).

CCl_3CN (1.45 mL, 14.55 mmol) and DBU (87 μL, 0.58 mmol) were added to a solution of the aforementioned hemiacetal (1.25 g, 2.91 mmol) in CH_2Cl_2 (5 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure. The residue was purified by a quick silica gel column chromatography (petroleum ether/EtOAc with 1% NEt_3, 8:1) to afford imidate **6** as a light yellow liquid (1.62 g, 96%). Because of stability reason, donor **6** was used directly for glycosylation without characterization.

2,3-Di-O-p-methoxybenzyl-4-azido-4,6-dideoxy-α/β-D-glucopyranosyl N-phenyltrifluoroacetimidate (7).

$CF_3(C{=}NPh)Cl$ (445 μL, 4.05 mmol) and K_2CO_3 (1.12 g, 8.10 mmol) were added to a solution of the aforementioned hemiacetal (870 mg, 2.03 mmol) in acetone (10 mL), and the mixture was stirred vigorously at room temperature for 1 h. The mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc with 1% NEt_3, 8:1) to yield imidate **7** as a yellow liquid (1.16 g, 95%). Because of stability reason, donor **7** was used directly for glycosylation without characterization.

*tert-Butyldimethylsilyl 2,3-dideoxy-4,6-di-O-acetyl-β-D-glucopyranoside (**16**).* 3,4,6-Triacetylglucal (**15**)

(10 g, 36.72 mmol) was suspended in H_2O (200 mL) and refluxed at 100 ºC until **15** was consumed. H_2O was removed under reduced pressure to provide the corresponding Ferrier-type hemiacetal, which was used for the next step without further purification.

10% Pd/C (1.50 g) was added to a solution of the aforementioned hemiacetal in EtOAc (200 mL), and the suspension was stirred under H_2 atmosphere. After 5 h, Pd/C was removed by filtration. The filtrate was concentrated under reduced pressure to provide the corresponding lactol as a viscous liquid, which was used for the next step without further purification.

TBSCl (7.60 g, 50.44 mmol) and imidazole (4.66g, 68.46 mmol) were added to a solution of the aforementioned crude lactol in CH_2Cl_2 (200 mL) at 0 ºC. The mixture was stirred at room temperature. After 4 h, the mixture was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 16:1 to 8:1) to afford **16** as a colorless liquid (9.67 g, 76%): $[\alpha]_D^{28}$ = +6.75 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (dd, *J* = 7.8, 0.6 Hz, 1H), 4.61 (td, *J* = 9.9, 4.8 Hz, 1H), 4.15–4.10 (m, 2H), 3.65–3.59 (m, 1H), 2.19–2.12 (m, 1H), 2.02 (s, 3H), 2.00 (s, 3H), 1.85–1.79 (m, 1H), 1.60 (tdd, *J* = 12.9, 8.8, 3.8 Hz, 1H), 1.54–1.42 (m, 1H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.1, 96.7, 75.1, 67.8, 63.7, 32.3, 27.2, 25.9, 21.2, 20.9, 18.2, -4.1, -5.0; HRMS (ESI) calcd for $C_{16}H_{30}NaO_6Si$ $[M+Na]^+$ 369.1704, found 369.1707.

*tert-Butyldimethylsilyl 2,3,6-trideoxy-6-iodo-β-D-glucopyranoside (**17**).* $NaOCH_3$ (151 mg, 27.91 mmol) was added to a solution of **16** (9.67 g, 27.91 mmol) in CH_3OH (50 mL) and the mixture was stirred for 4 h at room temperature. The mixture was neutralized with DOWEX 50W (H^+-form). The resin was then filtered off. The filtrate was concentrated under reduced pressure to provide the corresponding 4,6-diol,

which was used for the next step without further purification.

PPh_3 (18.30 g, 69.77 mmol) and imidazole (9.5 g, 139.55 mmol) were added to a solution of the aforementioned 4,6-diol in THF (100 mL). A solution of I_2 (11.33 g, 44.65 mmol) in THF (20 mL) was added slowly to the mixture at 0 ºC. After 30 min of stirring, another portion of I_2 (3.54 g, 13.95 mmol) in THF (5 mL) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous NaS_2O_3 and saturated aqueous $NaHCO_3$ at 0 ºC. The THF was removed under reduced pressure and the resulting aqueous mixture was extracted with CH_2Cl_2 twice. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 6:1) to provide **17** as a colorless liquid (7.72 g, 72%): $[\alpha]_D^{22}$ = +16.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 8.9, 2.1 Hz, 1H), 3.59 (dd, *J* = 10.1, 2.0 Hz, 1H), 3.41 (dd, *J* = 11.1, 7.1 Hz, 1H), 3.28–3.16 (m, 2H), 2.08–2.01 (m, 1H), 1.84 (ddd, *J* = 12.1, 5.6, 3.0 Hz, 1H), 1.67–1.46 (m, 3H), 0.90 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.1, 79.7, 70.2, 33.3, 31.4, 26.0, 18.2, 6.8, -3.6, -5.0; HRMS (ESI) calcd for $C_{12}H_{25}INaO_3Si$ $[M+Na]^+$ 395.0510, found 395.0511.

*tert-Butyldimethylsilyl 2,3,6-trideoxy-β-D-glucopyranoside (**8**).* 20% $Pd(OH)_2/C$ (662 mg) and DIPEA (9.31 mL, 53.34 mmol) were added to a solution of **17** in CH_3OH (40 mL), and the mixture was stirred under H_2 atmosphere. After 8h, $Pd(OH)_2/C$ was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 6:1) to yield **8** as a colorless liquid (3.94 g, 90%): $[\alpha]_D^{22}$ = -7.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (dd, *J* = 9.1, 2.1 Hz, 1H), 3.29–3.23 (m, 2H), 2.05–1.99 (m, 1H), 1.85–1.79 (m, 1H), 1.62–1.55 (m, 1H), 1.49–1.40 (m, 1H), 1.28 (d, *J* = 5.7 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s,

3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 96.7, 76.1, 71.6, 33.5, 31.4, 26.0, 18.3 (2C), -4.0, -5.0. HRMS (ESI) calcd for $C_{12}H_{26}NaO_3Si$ $[M+Na]^+$ 269.1543, found 269.1545.

tert-Butyldimethylsilyl

*(2',3'-Di-O-p-methoxybenzyl-4'-azido-4',6'-dideoxy-α-D-glucopyranosyl)-(1'→4)-2,3,6-trideoxy-β-D-glucopyranoside (**18α**).* (**6**+**8**, Table 1, entry 1): Freshly activated 4Å molecular sieves (2.00 g) was added to a solution of **6** (1.61 g, 2.80 mmol) and **8** (332 mg, 1.35 mmol) in Et_2O (10 mL). The mixture was cooled to -40 ºC and stirred at this temperature for 50 min. Then, TMSOTf (25 μL, 0.14 mmol) was added and the mixture was stirred at -40 ºC. After 30 min, the reaction was quenched by addition of NEt_3. The mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 60:1 to 16:1) to afford **18α** (690 mg, 78%) and **18β** (92 mg, 10%) as colorless liquids.

(**7**+**8**, Table 1, entry 2): Freshly activated 4Å molecular sieves (300 mg) was added to a solution of **7** (183 mg, 0.30 mmol) and **8** (50 mg, 0.20 mmol) in Et_2O (2 mL). The mixture was cooled to -60 ºC and stirred at this temperature for 40 min. Then, TBSOTf (4 μL, 0.015 mmol) was added and the mixture was stirred at -60 ºC. After 25 min, the reaction was quenched by addition of NEt_3. The mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 60:1 to 16:1) to afford **18α** (108 mg, 82%) and **18β** (13 mg, 10%) as colorless liquids.

18α: $[\alpha]_D^{27}$ = +104.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.92–6.82 (m, 4H), 4.86 (d, *J* = 10.0 Hz, 1H), 4.82–4.76 (m, 2H), 4.73 (d, *J* = 10.1 Hz,

1H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 3.79 (s, 6H), 3.74 (t, *J* = 9.5 Hz, 1H), 3.61–3.53 (m, 2H), 3.49 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.27 (td, *J* = 10.2, 4.4 Hz, 1H), 3.05 (t, *J* = 9.8 Hz, 1H), 2.11–2.04 (m, 1H), 1.91–1.84 (m, 1H), 1.54 (tdd, *J* = 13.0, 9.3, 3.8 Hz, 1H), 1.46–1.36 (m, 1H), 1.28 (d, *J* = 6.1 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 159.5, 130.4, 130.1, 130.0, 129.9, 114.0, 113.9, 110.1, 96.6, 93.0, 79.5, 75.4, 74.2, 74.1, 73.0, 68.1, 66.5, 55.4, 33.0, 26.5, 25.9, 19.0, 18.4, 18.2, -4.0, -5.0; HRMS (ESI) calcd for $C_{34}H_{51}N_3NaO_8Si$ $[M+Na]^+$ 680.3338, found 680.3339.

*(2',3'-Di-O-p-methoxybenzyl-4'-azido-4',6'-dideoxy-α-D-glucopyranosyl)-(1'→4)-2,3,6-trideoxy-α/β-D-glucopyranoside o-(hex-1-ynyl)benzoate (**4**).* TBAF (1M in THF, 2.60 mL, 2.60 mmol) was added to a solution of **18α** (1.14 g, 1.73 mmol) in THF (20 mL), and the mixture was stirred at room temperature. After 3 h, THF was evaporated under reduced pressure and the resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 2:1) to provide the corresponding hemiacetal (894 mg, 95%) as a colorless liquid.

The aforementioned hemiacetal (690 mg, 1.27 mmol) was dissolved in CH_2Cl_2 (10 mL) and DIPEA (1.64 mL, 12.70 mmol), *o*-hexynylbenzoic acid (473 mg, 2.54 mmol), EDCI (730 mg, 3.81 mmol), and DMAP (1.64 mL, 12.70 mmol) were added. The resulting mixture was stirred overnight at room temperature and then quenched by addition of saturated aqueous $NaHCO_3$. The two layers were separated and the aqueous one was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 60:1 to 16:1) to yield **4** as a light yellow liquid (814 mg, 88%, β/α = 4:1). As the major isomer, a portion of **4β** could be separated from the mixture.

4β: $[\alpha]_D^{29}$ = +92.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.51 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.43 (td, *J* = 7.6, 1.3 Hz, 1H), 7.35–7.31 (m, 2H), 7.30–7.25 (m, 3H), 6.91–6.85 (m, 4H), 5.99 (dd, *J* = 9.2, 2.3 Hz, 1H), 4.87 (d, *J* = 10.0 Hz, 1H), 4.80 (d, *J* = 3.6 Hz, 1H), 4.76–4.69 (m, 2H), 4.57 (d, *J* = 11.6 Hz, 1H), 3.81 (s, 3H), 3.81 (s, 3H), 3.78 (dd, *J* = 5.3, 3.2 Hz, 1H), 3.76 (t, *J* = 7.5 Hz, 1H), 3.59 (dq, *J* = 12.4, 6.2 Hz, 1H), 3.51 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.37–3.31 (m, 1H), 3.07 (t, *J* = 9.8 Hz, 1H), 2.48 (t, *J* = 7.1 Hz, 2H), 2.21–2.16 (m, 1H), 2.15–2.10 (m, 1H), 1.81–1.73 (m, 1H), 1.61 (tdd, *J* = 14.2, 9.9, 5.5 *Hz*, 4H), 1.54–1.46 (m, 2H), 1.32 (d, *J* = 6.2 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 159.7, 159.5, 134.6, 132.0, 131.1, 130.6, 130.4, 130.1, 130.1, 129.9, 127.2, 125.2, 114.1, 114.0, 96.7, 94.6, 93.5, 79.6, 79.5, 79.3, 75.5, 75.0, 74.0, 73.2, 68.1, 66.7, 55.4, 55.4, 30.9, 28.9, 25.6, 22.3, 19.7, 19.1, 18.5, 13.8; HRMS (ESI) calcd for $C_{41}H_{49}N_3NaO_9$ $[M+Na]^+$ 750.3361, found 750.3354.

*1-[2",3"-Di-O-p-methoxybenzyl-4"-azido-4",6"-dideoxy-α-D-glucopyranosyl)-(1"→4')-2',3',6'-trideoxy -β-D-glucopyranosyl]-N^4-carboxybenzylcytosine (**19β**)*. Freshly activated 5Å molecular sieves (800 mg) was added to a solution of donor **4** (α/β mixture, 460 mg, 0.63 mmol) in CH_3CN (4 mL) and the resulting mixture was stirred at room temperature for 40 min. In a separate flask, BSTFA (1.03 mL, 3.79 mmol) was added to a suspension of NHCbz-cytosine **5** (465mg, 1.90 mmol) in CH_3CN (4 mL) and the mixture was heated at 40 ºC until it became clear. The solution of the silylated cytosine was cooled to room temperature and added to the mixture of **4**. Then, a solution of $Ph_3PAuNTf_2$ (46 mg, 0.063 mmol) in CH_3CN (0.20 mL) was added, followed by the addition of BSTFA (0.50 mL, 1.90 mmol). The resulting mixture was stirred at room temperature for 1 day. Then, another portion of $Ph_3PAuNTf_2$ (46 mg, 0.063 mmol) was added and stirring was continued for 2 days (until complete consumption of donor **4**). The

mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 8:1 to 1:2) to provide **19β** as a white foam (339 mg, 70%) and **19α** as a white gel (35 mg, 7%). **19β**: $[\alpha]_D^{28}$ = +160.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.4 Hz, 1H), 7.41–7.37 (m, 5H), 7.35–7.31 (m, 2H), 7.29–7.21 (m, 3H), 6.94–6.84 (m, 4H), 5.74 (d, *J* = 9.8 Hz, 1H), 5.22 (s, 2H), 4.87 (d, *J* = 10.1 Hz, 1H), 4.79 (d, *J* = 3.6 Hz, 1H), 4.75–4.70 (m, 2H), 4.55 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 6H), 3.80–3.77 (m, 1H), 3.75 (t, *J* = 9.4 Hz, 1H), 3.61–3.55 (m, 1H), 3.52 (dd, *J* = 9.6, 3.7 Hz, 1H), 3.31 (td, *J* = 10.5, 4.3 Hz, 1H), 3.08 (t, *J* = 9.8 Hz, 1H), 2.40–2.30 (m, 1H), 2.22–2.13 (m, 1H), 1.62 (qd, *J* = 13.3, 3.8 Hz, 1H), 1.43–1.35 (m, 2H), 1.34 (d, *J* = 6.1 Hz, 3H), 1.27 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 159.7, 159.5, 154.4, 152.3, 144.0, 135.0, 130.3, 130.1, 129.9, 128.8, 128.4, 114.1, 114.0, 95.0, 93.1, 83.3, 79.6, 79.4, 77.1, 75.5, 73.8, 73.3, 68.1, 67.9, 66.7, 55.4, 55.4, 30.7, 26.6, 18.9, 18.5; HRMS (ESI) calcd for $C_{40}H_{46}N_6NaO_{10}$ $[M+Na]^+$ 793.3168, found 793.3166.

*1-[4"-Azido-4",6"-dideoxy-α-D-glucopyranosyl)-(1"→4')-2',3',6'-trideoxy-β-D-glucopyranosyl]-N^4-carboxybenzylcytosine (**20**)*. CF_3COOH (0.60 mL) was added to a solution of **19β** (425 mg, 0.55 mmol) in CH_2Cl_2 (12 mL) at 0º C and the mixture was stirred at room temperature for about 30 min. Then, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ at 0 ºC and extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 20:1) to provide **20** as a white foam (244 mg, 83%): $[\alpha]_D^{28}$ = +172.5 (*c* 1.1, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.05 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.1 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.33–7.30 (m, 2H), 5.72 (d, *J* = 7.9 Hz, 1H), 5.21 (s, 2H), 4.96 (d, *J* = 3.7 Hz, 1H), 3.73–3.69 (m, 1H), 3.67 (t, *J* = 9.5 Hz, 1H), 3.61 (dt, *J* = 12.4,

6.2 Hz, 1H), 3.47 (dd, *J* = 9.7, 3.8 Hz, 1H), 3.37 (td, *J* = 9.5, 4.4 Hz, 1H), 2.99 (t, *J* = 9.8 Hz, 1H), 2.40–2.28 (m, 1H), 2.17–2.04 (m, 1H), 1.70–1.55 (m, 2H), 1.31 (d, *J* = 6.1 Hz, 3H), 1.27 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 164.6, 156.8, 154.4, 145.8, 136.9, 129.5, 129.4, 129.2, 97.1, 96.5, 84.4, 78.2, 75.6, 73.6, 73.2, 69.9, 68.6, 67.9, 30.9, 27.8, 19.1, 18.6; HRMS (ESI) calcd for $C_{24}H_{30}N_6NaO_8$ $[M+Na]^+$ 553.2017, found 553.2018.

*Cytosamine (**3**).* $(CH_3)_3P$ (1M in THF, 0.92 mL, 0.92 mmol) and NEt_3 (0.32 mL, 2.30 mmol) were added to a solution of **20** (244 mg, 0.46 mmol) in THF (5 mL)/H_2O (1 mL) and the mixture was stirred at 50 ºC. After 2 h, the mixture was concentrated under reduced pressure to give the crude 4''-NH_2 derivative, which was used for the next step without further purification.

CH_3OH (5 mL), $(CH_2O)_n$ (69 mg, 2.30 mmol), $NaBH_3CN$ (144 mg, 2.30 mmol), and AcOH (79 μL, 1.38 mmol) were mixed with the aforementioned amine. The resulting mixture was stirred overnight at room temperature. The reaction was then quenched with saturated aqueous $NaHCO_3$. The two layers were separated and the aqueous one was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 20:1 to 15:1) to provide the corresponding 4''-$N(CH_3)_2$ derivative as a light yellow liquid (244 mg, 99%).

10% Pd/C (40 mg) was added to a solution of the aforementioned 4''-$N(CH_3)_2$ derivative (104 mg, 0.19 mmol) in CH_3OH (4 mL). The mixture was stirred under H_2 atmosphere for 8 h at room temperature. Then, Pd/C was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by RP-18 column chromatography (H_2O/CH_3OH, 1:2) to afford **3** as a white solid (50 mg, 64%): $[\alpha]_D^{26}$ = +159.5 (*c* 1.0, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.68 (d, *J* = 7.5 Hz, 1H), 5.90 (d, *J* = 7.5

Hz, 1H), 5.72 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.90 (d, *J* = 3.8 Hz, 1H), 3.87 (t, *J* = 9.8 Hz, 1H), 3.81 (dt, *J* = 12.2, 6.1 Hz, 1H), 3.69 (dq, *J* = 12.2, 6.1 Hz, 1H), 3.41 (dd, *J* = 9.5, 3.8 Hz, 1H), 3.38–3.32 (m, 1H), 2.46 (s, 6H), 2.38–2.32 (m, 1H), 2.13 (t, *J* = 10.1 Hz, 1H), 2.05–1.97 (m, 1H), 1.68 (ddd, *J* = 15.5, 13.2, 3.1 Hz, 1H), 1.64–1.54 (m, 1H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 167.5, 157.7, 142.5, 96.2, 96.1, 83.8, 78.2, 75.1, 74.6, 71.8, 70.2, 67.3, 42.4, 30.7, 27.9, 19.7, 19.2; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{31}N_4O_6$ 399.2238, found 399.2244.

*Plicacetin (**1**).* Compound **3** (11 mg, 0.028 mmol) was mixed with *p*-nitrobenzoic acid (**21**) (7 mg, 0.041 mmol), HATU (19 mg, 0.050 mmol), and pyridine (0.50 mL), and the resulting mixture in a sealed flask was heated under microwave at 50 ºC (monitored with an external surface sensor) for 5 min. Then, pyridine was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 40:1) to afford the corresponding amide.

A solution of NH_4Cl (0.74 mg, 0.014 mmol) in H_2O (0.20 mL) and Fe powder (8 mg, 0.14 mmol) were added to a solution of the aforementioned amide in EtOH (2 mL). The mixture was heated at 90 ºC for 30 min, and was then cooled down to room temperature and filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by RP-18 column chromatography (H_2O/CH_3OH + 0.05% CF_3COOH, 6:4) to afford **1** as a colorless liquid (6 mg, 41%): $[\alpha]_D^{21}$ = +77.0 (*c* 0.15, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 2H), 5.77 (d, *J* = 7.9 Hz, 1H), 5.01 (d, *J* = 3.8 Hz, 1H), 4.09 (dt, *J* = 12.0, 6.3 Hz, 1H), 3.95 (dd, *J* = 10.2, 9.4 Hz, 1H), 3.75 (dq, *J* = 12.2, 6.1 Hz, 1H), 3.54 (dd, *J* = 9.2, 3.9 Hz, 1H), 3.48–3.40 (m, 1H), 3.11 (t, *J* = 10.2 Hz, 1H), 3.00 (s, 6H), 2.44–2.33 (m, 1H), 2.21–2.12 (m, 1H), 1.79–1.61 (m, 2H), 1.46 (d, *J* = 6.2 Hz, 3H), 1.37 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100

MHz, CD_3OD) δ 168.7, 164.6, 156.3, 154.8, 146.3, 131.5, 121.1, 114.8, 98.5, 96.7, 84.6, 78.2, 76.6, 73.9, 72.0, 67.9, 64.0, 45.4, 30.9, 28.0, 19.2, 19.0; HRMS (ESI) calcd for $C_{25}H_{35}N_5NaO_7$ $[M+Na]^+$ 540.2429, found 540.2430.

*(2R,4S)-2-tert-Butyl-3-tert-butoxycarbonyl-4-methyl-4-[(p-(benzyloxycarbonyl)phenyl)carbamoyl]-oxazol idine (**24**).* Benzyl 4-aminobenzoate (**23**) (1.42 g, 6.26 mmol), HATU (2.54 g, 6.68 mmol), and DIPEA (3.65 mL, 20.90 mmol) were added to a solution of **22** (1.20 g, 4.18 mmol) in DMF (15 mL) and the reaction mixture was stirred at 80 ºC overnight. DMF was evaporated under reduced pressure, the resulting residue was dissolved in CH_2Cl_2, and washed successively with aqueous HCl 1N and saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 8:1) to afford **24** as a yellow solid (1.40 mg, 67%): $[\alpha]_D^{22}$ = -104.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.46–7.42 (m, 2H), 7.41–7.36 (m, 2H), 7.35–7.30 (m, 1H), 5.35 (s, 2H), 5.21 (s, 1H), 4.80 (d, *J* = 7.7 Hz, 1H), 3.81 (d, *J* = 9.0 Hz, 1H), 1.72 (s, 2H), 1.53 (s, 9H), 0.91 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 166.1, 155.9, 142.7, 136.3, 131.1, 128.7, 128.3, 128.2, 125.6, 118.9, 98.1, 83.0, 76.2, 68.2, 66.7, 38.3, 28.3, 26.3, 22.2; HRMS (ESI) calcd for $C_{28}H_{36}N_2NaO_6$ $[M+Na]^+$ 519.2466, found 519.2460.

*(S)-Benzyl 4-(2-amino-2-methyl-3-(tert-butyldimethylsilyloxy)-propanamido)benzoate (**25**).* Benzyl alcohol (1 mL) was added to a suspension of **24** (137 mg, 0.28 mmol) in aqueous HCl (6 N, 1 mL), and the mixture was heated at 80 ºC until **24** was totally consumed. The mixture was then extracted with EtOAc. The organic layer was discarded, and the aqueous one was concentrated under reduced pressure

to provide the corresponding amino-alcohol intermediate as the hydrochloride salt, which was used for the next step without further purification.

TBSCl (151 mg, 0.55 mmol) and imidazole (75 mg, 1.10 mmol) were added to a solution of the aforementioned amino-alcohol in DMF (2 mL). The mixture was stirred overnight at room temperature. Then, DMF was evaporated under reduced pressure and the resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc + 1% NEt_3, 4:1) to afford **25** as a yellow liquid (93 mg, 75%): $[\alpha]_D^{22}$ = -48.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.04 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.46–7.43 (m, 2H), 7.41–7.37 (m, 2H), 7.36–7.31 (m, 1H), 5.35 (s, 2H), 4.10 (d, J = 9.5 Hz, 1H), 3.39 (d, J = 9.5 Hz, 1H), 1.32 (s, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 166.2, 142.4, 136.3, 131.1, 128.7, 128.3, 128.3, 125.3, 118.6, 69.8, 66.7, 59.7, 25.9, 23.3, 18.3, -5.3; HRMS (ESI) calcd for $C_{24}H_{35}N_2O_4Si$ $[M+H]^+$ 443.2361, found 443.2359.

*(S)-4-[4-((tert-Butyldimethylsilyloxy)methyl)-4-methyl-5-oxoimidazolidin-1-yl]benzoic acid (**26**)*. Compound **25** (300 mg, 0.68 mmol) was mixed with $(CH_2O)_n$ (20 mg, 0.68 mmol), solid $NaHCO_3$ (86 mg, 0.68 mmol), and CH_3CN (4 mL). The mixture was heated at 60 ºC overnight. The salts were filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (petroleum ether/EtOAc + 1% NEt_3, 4:1) to afford the corresponding imidazolidinone intermediate as a colorless liquid (93 mg, 86%).

10% Pd/C (26 mg) was added to a solution of the aforementioned imidazolidinone intermediate (265 mg, 0.58 mmol) in CH_3OH (5 mL). The resulting suspension was stirred under H_2 atmosphere overnight at room temperature. After complete consumption of the imidazolidinone intermediate, Pd/C was filtered off. The filtrate was concentrated under reduced pressure to afford **26** as a white solid (198 mg, 94%):

$[\alpha]_D^{21}$ = -44.75 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 2H), 4.89 (q, *J* = 7.7 Hz, 1H), 4.02 (d, *J* = 10.2 Hz, 1H), 3.58 (d, *J* = 10.2 Hz, 1H), 1.26 (s, 3H), 0.81 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 170.4, 142.2, 131.3, 125.8, 117.8, 77.4, 77.2, 76.9, 66.9, 65.8, 62.4, 25.8, 18.4, 18.2, -5.4, -5.4; HRMS (ESI) calcd for $C_{18}H_{29}N_2O_4Si$ $[M+H]^+$ 365.1891, found 365.1888.

*Streptcytosine A (rocheicoside A, **2**)*. Cytosamine **3** (9 mg, 0.022 mmol) was mixed with acid **26** (16 mg, 0.045 mmol), HATU (19 mg, 0.050 mmol), and pyridine (0.40 mL). The resulting mixture in a sealed flask was heated under microwave at 80 ºC (monitored with an external surface sensor) for 5 min. The heating conditions were repeated for two additional times. After that, pyridine was evaporated under reduced pressure. The resulting residue was purified by Sephadex LH-20 (CH_2Cl_2/CH_3OH, 1:1) to afford the corresponding amide intermediate.

HF·pyridine (70% HF, 20 μL) was added to a solution of the aforementioned amide in pyridine at 0 ºC. The mixture was stirred at room temperature overnight, pyridine was then evaporated under reduced pressure. The resulting residue was purified by RP-18 column chromatography (H_2O/CH_3OH, 1:2) to afford **2** as a colorless liquid (8 mg, 65%): $[\alpha]_D^{21}$ = +83.0 (*c* 0.2, CH_3OH); ^{1}H NMR (600 MHz, DMSO-*d6*) δ 8.17 (d, *J* = 6.5 Hz, 1H), 8.04 (d, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 6.5 Hz, 1H), 5.71 (dd, *J* = 10.7, 1.5 Hz, 1H), 4.80 (dd, *J* = 12.2, 5.6 Hz, 2H), 4.71 (d, *J* = 7.5 Hz, 1H), 3.75 (t, *J* = 9.7 Hz, 1H), 3.66–3.60 (m, 3H), 3.32 (d, *J* = 10.9 Hz, 1H), 3.30–3.23 (m, 2H), 2.37 (s, 9H), 1.24 (d, *J* = 6.1 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 3H), 1.09 (s, 3H); ^{13}C NMR (150 MHz, DMSO-*d6*) δ 176.7, 166.6, 163.3, 154.3, 145.7, 142.2, 129.8, 127.9, 117.5, 96.8, 94.8, 82.4, 76.6, 73.3, 73.0, 70.2, 68.3, 65.9, 65.8, 65.3, 62.8, 42.3, 29.3, 26.7, 19.3, 19.0, 18.7; HRMS (ESI) calcd for $C_{30}H_{43}N_6O_9$ $[M+H]^+$ 631.3086,

found 631.3093.

ASSOCIATED CONTENT

Supporting Information

Comparison of the ^{13}C NMR data of streptcytosine A (rocheicoside A, **2**) with those reported for the natural product, and the ^{1}H and ^{13}C NMR spectra of all new compounds (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (21432012 & 21621002), the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20020000), and the K .C. Wong Education Foundation is acknowledged.

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