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# Donor-Bound Glycosylation for Various Glycosyl Acceptors: Bidirectional Solid-Phase Semisynthesis of Vancomycin and Its Derivatives

**Takayuki Doi,* Atsushi Kinbara, Hitoshi Inoue, and Takashi Takahashi*[a]**

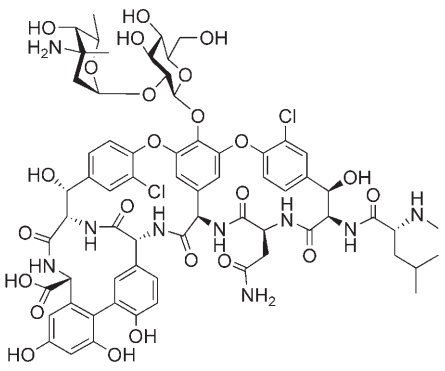
**Abstract:** The glycosidation of a polymer-supported glycosyl donor, *N*-phenyltrifluoroacetimidate, with various glycosyl acceptors is reported. The application of the polymer-supported *N*-phenyltrifluoroacetimidate is demonstrated in the synthesis of vancomycin derivatives. 2-*O*-[2-(azidomethyl)benzoyl]glycosyl imidate was attached to a polymer support at the 6-position by a phenylsulfonate linked with a C13 alkyl spacer. Solid-phase glycosidation with a vancomycin aglycon, selective deprotection of the 2-(azidomethyl)-benzoyl group, and glycosylation of the resulting 2-hydroxy group with a vancosamine unit were performed. Nucleophilic cleavage from the polymer support with acetate, chloride, azido, and thioacetate ions provided vancomycin derivatives in pure form after simple purification. The semisynthesis of vancomycin was achieved by deprotection of the acetate derivative.

**Keywords:** antibiotics · glycopeptides · glycosylation · solid-phase synthesis · vancomycin

## Introduction

To create chemical diversity in drug discovery, glycosylated natural products are important because a wide range of carbohydrates can be introduced to a variety of their aglycons.[1] Several diverse routes for altering glycosyl donors in a natural product have been demonstrated.[2] In contrast, Kakinuma and co-workers recently reported the enzymatic glycosidation of vicenisamine as a glycosyl donor with diverse aglycons of macrolides and steroids to construct a variety of vicenisaminide products.[3] On the other hand, solid-phase oligosaccharide synthesis has been advanced to provide combinatorial carbohydrate libraries.[4] We demonstrated that a bidirectional strategy[5] that constitutes a hybrid between the donor- and the acceptor-bound strategies and a diversity linker that can be displaced with various nucleophiles are effective for the construction of a 44-member trisaccharide library.[6] Although the donor-bound strategy with thioglycosides, glycosyl fluorides, trichloroacetimidates, phosphates, and glycals has been reported,[5–12] we investigated a more-appropriate polymer-supported donor to achieve the glycosidation with a wide range of diverse aglycon structures. We report herein a polymer-supported *N*-phenyltrifluoroacetimidate as an efficient glycosyl donor in solid-phase glycosidation with various glycosyl acceptors and applied it to the bidirectional strategy toward the semisynthesis of vancomycin and its derivatives by using a phenylsulfonate linker.

Vancomycin is a glycopeptide antibiotic that is used clinically. As vancomycin-resistant bacterial strains pose a serious threat to human health, modification of its structure to overcome this problem was studied.[13] The total synthesis of vancomycin and its aglycon and its semisynthesis from the aglycon were also accomplished.[14–18] Recently, acceptor-bound solid-phase synthesis of vancomycin derivatives[19] as



vancomycin (**1**)

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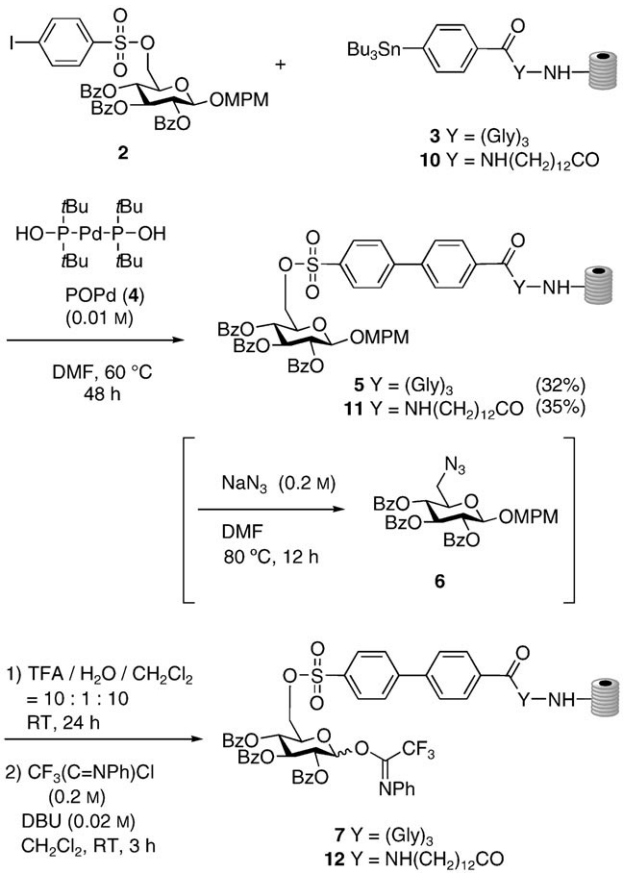
well as enzymatic reconstruction of vancomycin[20] and its application to library synthesis by utilizing chemical diversification[21] were demonstrated.

## Results and Discussion

We chose glycosyl imidates as polymer-supported donors in the synthesis of vancomycin derivatives as a trichloroacetimidate was utilized in the solution-phase and acceptor-bound solid-phase synthesis of vancomycin.[15d,19] Glycosyl *N*-phenyltrifluoroacetimidates are stable for handling and are strongly activated with TMSOTf or $BF_3{\cdot}OEt_2$;[22] hence, we utilized them in the unique *N*-glycosylation of primary amides.[23] Initially, the preparation of polymer-supported glycosyl *N*-phenyltrifluoroacetimidate **7** was investigated (Scheme 1). 2,3,4-Tri-*O*-benzoyl-6-*O*-(4-iodobenzenesulfonyl)glucose derivative **2** was immobilized by Migita–Stille coupling[24] with POPd catalyst (**4**)[25] and polymer-supported 4-(tributylstannyl)benzamide **3** linked with a triglycine spacer on polystyrene-based SynPhase™ lanterns.[26,27] The phenylsulfonate is a diversity linker when it is cleaved with various nucleophiles such as $R^-$, $N_3^-$, $AcO^-$, $H^-$, $CN^-$, $I^-$, and so on, as we demonstrated in the combinatorial syntheses of vitamin $D_3$ and trisaccharide libraries.[6,7,28] The loading yield of the coupling product **5** was determined to be 32% after nucleophilic cleavage from the polymer support with $NaN_3$. Removal of the MPM group in **5** with TFA/$H_2O$ followed by treatment with *N*-phenyltrifluoroacetimidoyl chloride and DBU afforded polymer-supported glycosyl donor **7**. In the presence of $Cs_2CO_3$ or NaH instead of DBU, 1,6-anhydroglucose was cleaved from the polymer support by intramolecular etherification under basic conditions.

Glycosidation of **7** with various glycosyl acceptors, 2,6-dimethoxyphenol (**8a**), monosaccharides **8b** and **8c**, tyrosine (**8d**), serine (**8e**), primary alcohol **8f**, and cholesterol (**8g**), using TMSOTf were investigated (Scheme 2). The products **9a–g** were obtained after nucleophilic cleavage with $NaN_3$ from the polymer support. Except for **9c**,[29] the glycosidations proceeded in good to excellent yields based on **5** even though disarmed glycosyl donor **7**, which is fully protected



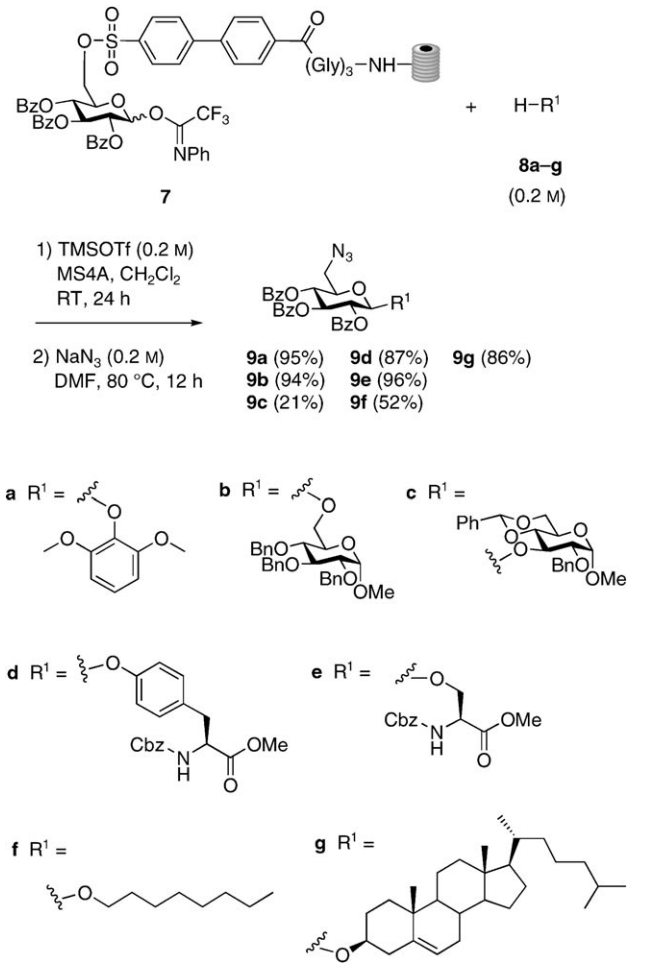

Scheme 1. Preparation of polymer-supported glycosyl *N*-phenyltrifluoroacetimidates **7** and **12**. Bz = benzoyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N*,*N*-dimethylformamide, MPM = 4-methoxyphenylmethyl, TFA = trifluoroacetic acid.

with benzoyl groups, was used. The β-glycosidic bonds were selectively formed by an anchoring effect of the 2-*O*-benzoyl group. The stereochemistry was proved by $^1H$ NMR spectroscopic analysis. No epimerization was observed at the α position of amino acid esters **9d** and **9e**.

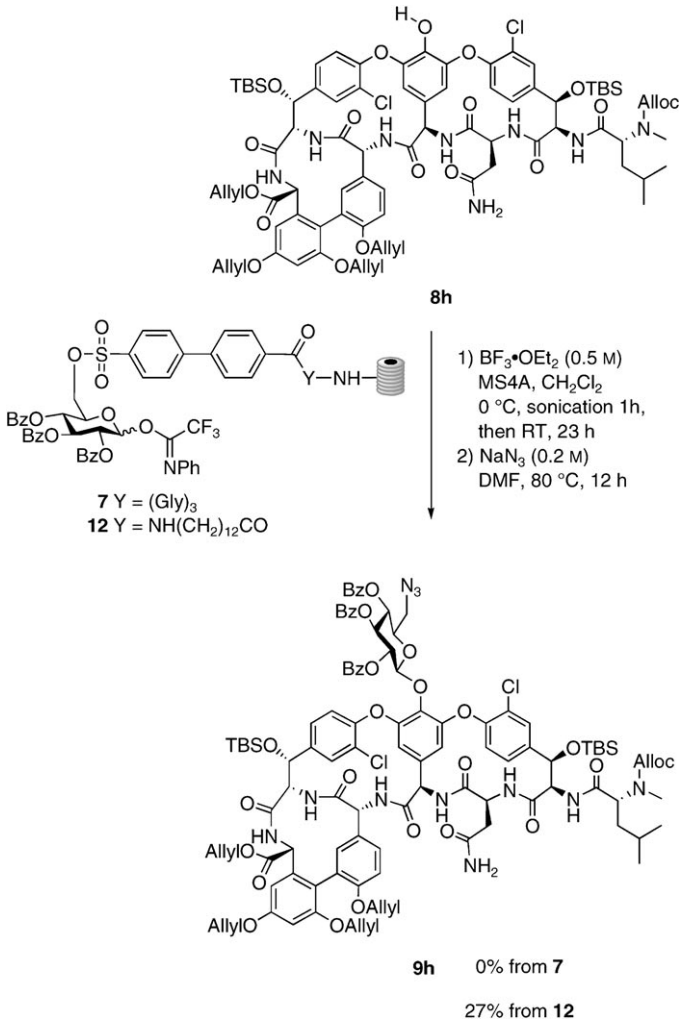
Next, we attempted the glycosidation of **7** with vancomycin aglycon **8h**, which was prepared from the acid cleavage of the disaccharide moiety from a fully protected vancomycin derivative by a reported method with some modification.[17,19] The lanterns **7** were treated with **8h** using TMSOTf or $BF_3{\cdot}OEt_2$ (Scheme 3). The lanterns were sufficiently washed with several solvents and were treated with $NaN_3$. None of the desired product **9h** was obtained, and aglycon **8h** was unexpectedly recovered. It is conceivable that the aglycon may have bound to the triglycine spacer to avoid glycosidation on the polymer support, because it is known that vancomycin binds to the D-Ala–D-Ala terminus in a peptidoglycan precursor.[13] Therefore, new glycosyl donor **12**, which has an alkyl spacer, was prepared from **10** (35% loading) in a similar manner (Scheme 1). Glycosidation of **12** with **8h** (0.2 M) was performed using $BF_3{\cdot}OEt_2$ (0.5 M) with sonication for 1 h at 0 °C and with agitation for another 23 h at room temperature.[30] After being sufficiently

**Abstract in Japanese:**
固相上にN-フェニルトリフルオロアセトイミダートを合成し，種々の糖受容体についてグリコシル化を高収率で達成した．2位を2-(アジドメチル)ベンゾイル基で保護し，6位をフェニルスルホナートリンカーを介し固相に担持したグルコースのイミダートに対し，バンコマイシンアグリコンのグリコシル化，2位のアジドベンゾイル基の選択的脱保護に続いて，遊離となった2位水酸基とバンコサミンとのグリコシル化を行った．最後にアセタート，塩化物，アジド，チオアセタートイオンにより固相から求核的切り出しを行い，バンコマイシン誘導体の合成を達成した．アセタート誘導体については，すべての保護基を脱保護し，バンコマイシンの部分合成に成功した．




Scheme 2. Donor-bound solid-phase glycosidation of **7** with various glycosyl acceptors **8a–g**. Bn = benzyl, Cbz = benzyloxycarbonyl, MS4A = 4-Å molecular sieves, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.




Scheme 3. Glycosidation of polymer-supported **7** and **12** with vancomycin aglycon **8h**. Alloc = allyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.

washed with several solvents to recover unreacted aglycon **8h**, the lanterns were treated with $NaN_3$ in DMF (0.2 M, 80 °C, 12 h). The crude product obtained was easily purified by silica-gel chromatography and gel-permeation chromatography (GPC) to isolate the desired glycoside **9h** in 27% overall yield.[31] Although the yield was low, the purification was very simple because there was no unreacted **8h** observed in the crude product in the solid-phase synthesis. In contrast, in solution-phase synthesis, it was difficult to separate the unreacted aglycon **8h** and the product **9h** by chromatography.

To synthesize vancomycin derivatives by bidirectional glycosylation, new polymer-supported donor **18** was prepared (Scheme 4). The AZMB group[32] was introduced at the 2-position in **18** because it can be assisted for β glycosidation by an anchoring effect and be selectively removed in the presence of acetyl and phenylsulfonyl groups prior to glycosylation with a vancosamine unit. Stereoselective epoxidation of glucal **13** with dimethyldioxirane followed by epoxide opening with 2-trimethylsilylethanol afforded the 2-hydroxy-free glucoside.[33] Protection of the alcohol with AZMBCl and removal of the TBS group (IBr/MeOH/$CH_2Cl_2$)[34] at the 6-position afforded **14**. After sulfonylation of **14** with 4-iodophenylsulfonyl chloride, the resulting iodide **15** was coupled with polymer-supported phenylstannane **10** by using $[PdCl_2(CH_3CN)_2]$ as a catalyst. The loading yield of **16** was determined to be 36% by isolation of **17** obtained by complete cleavage with LiCl from the polymer support. Acid treatment of **16** followed by formation of *N*-phenyltrifluoroacetimidate provided polymer-supported glycosyl donor **18**. Glycosidation of **18** with vancomycin aglycon **8h** ($BF_3{\cdot}OEt_2$/MS4A/$CH_2Cl_2$) was performed under the optimized conditions described previously to afford **19** (Scheme 5). Selective removal of the AZMB group ($PBu_3$/$H_2O$/THF) followed by glycosylation of the resulting alcohol **20** with vancosamine fluoride **21** afforded **22**.[15d,19a] Nucleophilic displacement of the phenylsulfonate linker with the nucleophiles $AcO^-$, $Cl^-$, $N_3^-$, and $AcS^-$ furnished the desired vancomycin derivatives **23–26**, respectively, in 26–31% overall yields from **16**. As there was no monosaccharide derivative observed after the cleavage, the second glycosyla-

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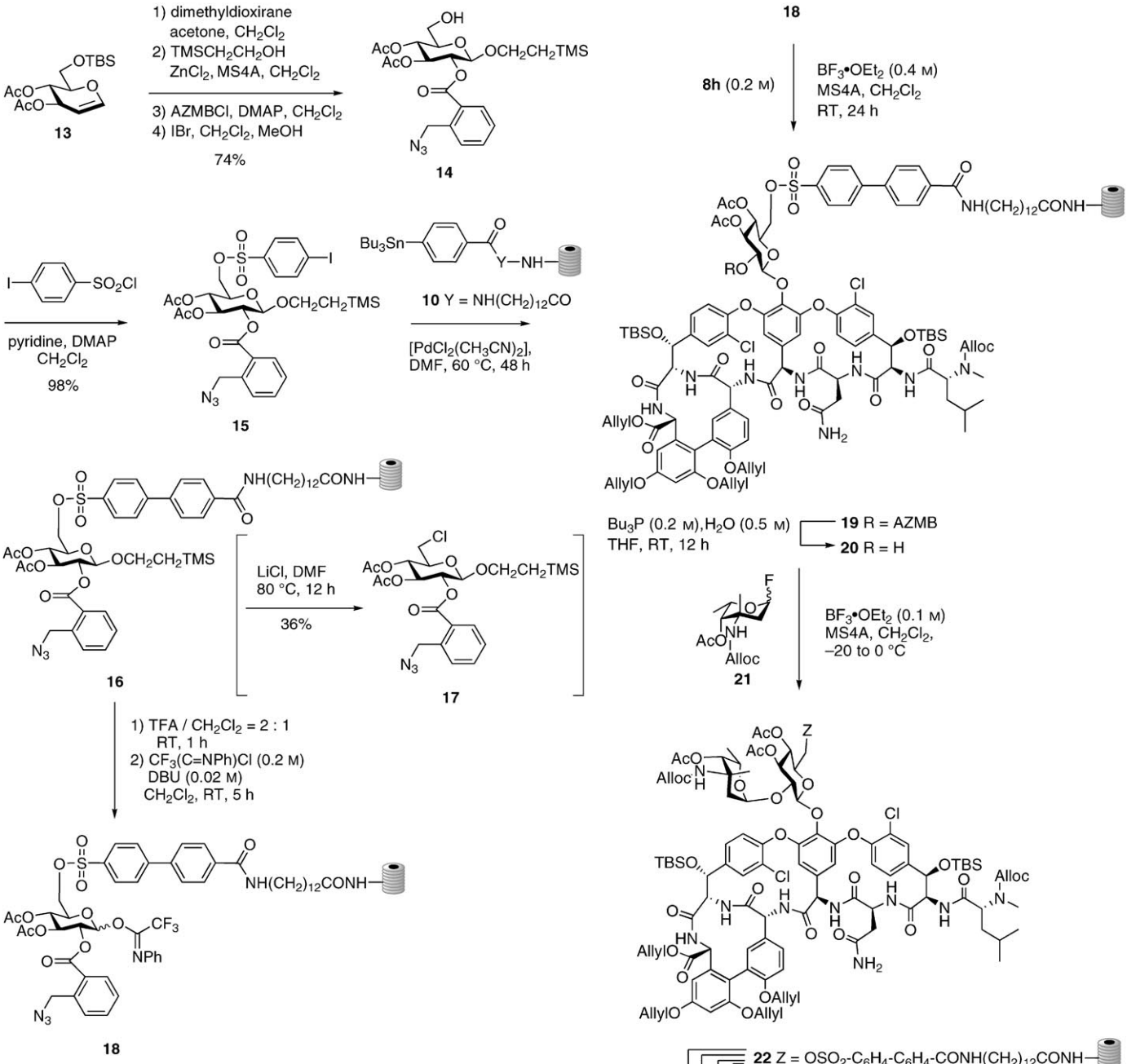


Scheme 4. Preparation of 2-*O*-AZMB derivative **18** on a polymer support. AZMB = 2-(azidomethyl)benzoyl, DMAP = 4-dimethylaminopyridine.

tion on the polymer support proceeded quantitatively. Deprotection of **23** was carried out as follows: Removal of 1) the TBS groups (HF·pyridine), 2) the acetyl groups ($N_2H_4$·$H_2O$/allyl alcohol/MeOH/THF), and 3) the allyl ester, allyl ether, and Alloc groups ([$Pd(PPh_3)_4$]/*N,N′*-dimethylbarbituric acid/1,4-dioxane/$H_2O$)[35] provided vancomycin (**1**)·TFA salt in 70% overall yield. The spectra and HPLC data of the synthetic vancomycin·TFA salt were in good agreement with those of the natural product.

Scheme 5. Synthesis of vancomycin (**1**) and its derivatives **23**–**26**. Reagents and reaction conditions: a) NaOAc (0.5 M), [15]crown-5 (0.1 M), DMF, 80 °C, 24 h; b) LiCl (0.2 M), DMF, 80 °C, 12 h; c) $Bu_4NN_3$ (0.2 M), DMF, 80 °C, 12 h; d) KSAc (0.2 M), DMF, 60 °C, 12 h; e) i) HF·pyridine, 60 °C, 12 h; ii) $N_2H_4$·$H_2O$/allyl alcohol/MeOH/THF = 0.16:1:1:1; iii) [$Pd(PPh_3)_4$] (50 mol %), *N,N′*-dimethylbarbituric acid (10 equiv), 1,4-dioxane, $H_2O$, room temperature, 7 h.

  

## Conclusions

In summary, we have demonstrated a solid-phase synthesis of functionalized glycosides through donor-bound glycosidation by utilizing an *N*-phenyltrifluoroacetimidate. In this study, palladium-catalyzed Migita–Stille coupling to immobilize a monosaccharide, glycosidation of the polymer-supported glycosyl imidates with various glycosyl acceptors, and cleavage from the phenylsulfonate linker with nucleophiles were performed. On the basis of this method, bidirectional glycosylation for the semisynthesis of vancomycin and its derivatives was achieved. Therefore, this method can be utilized in the combinatorial library synthesis of vancomycin analogues with modification of the vancosamine unit. Moreover, the bidirectional strategy enables both assembly of oligisaccharides and aglycons in a combinatorial synthesis of glycosylated bioactive compounds.

## Experimental Section

*General Techniques*

NMR spectra were recorded on a JEOL Model ECP-400 (400 MHz for $^1$H, 100 MHz for $^{13}$C) instrument in the indicated solvent. Chemical shifts are reported in parts per million (ppm) relative to the signal for internal tetramethylsilane (0.00 ppm for $^1$H) for solutions in $CDCl_3$. The solvents used were chloroform (7.26 ppm), acetone (2.04 ppm), and $D_2O$ (HOD 4.50 ppm at 323 K) for $^1$H NMR and [D]chloroform (77.1 ppm) and $D_2O$ with [$D_6$]acetone (29.3 ppm) as internal standard for $^{13}$C NMR spectroscopy. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrophotometer. Only the strongest and/or structurally important absorptions are reported, in cm$^{-1}$. Optical rotations were measured with a JASCO P-1020 polarimeter. All reactions were monitored by thin-layer chromatography carried out on 0.2-mm E. Merck silica-gel plates (60F-254) with UV light, visualized by *p*-anisaldehyde, ceric sulfate, or 10% ethanolic phosphomolybdic acid. Merck silica gel was used for column chromatography. GPC for qualitative and quantitative analysis was performed on a Japan Analytical Industry Model LC 605 chromatograph (recycling preparative HPLC), with a Japan Analytical Industry Model RI-5 refractive-index detector and a Japan Analytical Industry Model 310 UV detector with a polystyrene gel column (JAIGEL-1H, 20 mm × 600 mm), using chloroform as a solvent (3.5 mL min$^{-1}$). ESI-TOF mass spectra were measured with an Applied Biosystems TK-3500 Biospectrometry Workstation. High-resolution ESI-TOF mass spectra were calibrated with angiotensin I (Sigma), bradykinin (Sigma), and neurotensin (Sigma) as internal standards.

*Syntheses*

**2**: 4-Iodobenzenesulfonyl chloride (8.38 g, 27.7 mmol, 2.0 equiv), pyridine (5.60 mL, 69.4 mmol, 5.0 equiv) and DMAP (0.19 g, 1.39 mmol, 0.1 equiv) were added to a solution of *p*-methoxyphenylmethyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranoside (8.50 g, 13.9 mmol, 1.0 equiv) in $CH_2Cl_2$ (41.7 mL) at 0 °C under argon. After being stirred for 19 h at room temperature, the reaction mixture was poured into ice-cooled aqueous HCl (1 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was recrystallized from chloroform/hexane to give **2** (11.4 g, 13.1 mmol, 94%) as a white solid. $[\alpha]_D^{25} = +13.6$ ($c = 1.01$, $CHCl_3$); FTIR (solid): $\tilde{\nu} = 3068$, 2946, 1923, 1732, 1613, 1514, 1363, 968, 810, 708 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$–$7.88$ (m, 19H, aromatic), 7.13 (d, $J_{Hb,Hc} = 8.70$ Hz, 2H, Hc), 6.74 (d, $J_{Hb,Hc} = 8.70$ Hz, 2H, Hb), 5.75 (dd, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, 1H, 3-H), 5.48 (dd, $J_{1\text{-}H,2\text{-}H} = 8.22$ Hz, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, 1H, 2-H), 5.38 (dd, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, 1H, 4-H), 4.80 (d, $J_{Hd,Hd'} = 12.1$ Hz, 1H, Hd), 4.73 (d, $J_{1\text{-}H,2\text{-}H} = 8.22$ Hz, 1H, 1-H), 4.57 (d, $J_{Hd,Hd'} = 12.1$ Hz, 1H, Hd′), 4.28 (dd, $J_{5\text{-}H,6\text{-}H} = 2.42$ Hz, $J_{6\text{-}H,6'\text{-}H} = 11.1$ Hz, 1H, 6-H), 4.24 (dd, $J_{5\text{-}H,6'\text{-}H} = 3.87$ Hz, $J_{6\text{-}H,6'\text{-}H} = 11.1$ Hz, 1H, 6′-H), 4.00 (ddd, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, $J_{5\text{-}H,6\text{-}H} = 2.42$ Hz, $J_{5\text{-}H,6'\text{-}H} = 3.87$ Hz, 1H, 5-H), 3.79 ppm (s, 3H, Ha); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 165.7$, 165.3, 165.0, 159.6, 138.6, 135.2, 133.8, 133.4, 133.3, 130.0, 129.9, 129.8, 129.8, 129.3, 128.8, 128.6, 128.5, 128.4, 128.4, 128.3, 114.0, 98.7 (anomeric), 72.7, 72.2, 71.5, 70.4, 69.4, 68.6, 55.3 ppm; HRMS (ESI-TOF): calcd for $C_{41}H_{35}IO_{12}SNa$: 901.0786 $[M+Na]^+$; found: 901.0783.

**3**: TFA·$NH_2$–polystyrene lanterns (D series, loading: 34.0 μmol per unit, batch no.: 1640–1 A) were treated with 10% diisopropylethylamine (DIPEA) in DMF/$CH_2Cl_2$ (1:1, 2 × 15 min) at room temperature. Then, the lanterns were washed with DMF (3 × 5 min) and $CH_2Cl_2$ (2 × 5 min) and dried in vacuo to give $NH_2$–polystyrene lanterns. The $NH_2$–polystyrene lanterns were treated with a solution of Fmoc-Gly-OH (0.10 M), DIC (0.10 M) and HOBt (0.10 M) in DMF at room temperature (Fmoc = 9-fluorenylmethoxycarbonyl, DIC = diisopropyl carbodiimide, HOBt = 1-hydroxybenzotriazole). After being left for 24 h, the lanterns were washed with DMF (3 × 5 min) and $CH_2Cl_2$ (3 × 5 min) and dried in vacuo. The above Fmoc-protected lanterns were treated with 20% piperidine in DMF for 20 min at room temperature. After filtration, the lanterns were washed with DMF (3 × 5 min) and $CH_2Cl_2$ (3 × 5 min) and dried in vacuo. The above procedure was repeated three times to give $NH_2$-$(Gly)_3$ lanterns. The $NH_2$-$(Gly)_3$ lanterns obtained were treated with a solution of 4-(tributylstannyl)benzoic acid (0.20 M), DIC (0.20 M), and HOBt (0.20 M) in DMF at room temperature. After being left for 24 h, the lanterns were washed with DMF (3 × 5 min), THF/$H_2O$ (3:1, 3 × 5 min), MeOH (3 × 5 min), and $CH_2Cl_2$ (3 × 5 min) and dried in vacuo to give **3**.

**5**: The lanterns **3** (11 units) were treated with a solution of **2** (1.41 g, 1.60 mmol, 0.20 M) and **4** (40.1 mg, 0.08 mmol, 0.01 M) in DMF (8.00 mL) at 60 °C under argon. After being left for 48 h at the same temperature, the lanterns were washed with DMF (3 × 5 min), THF/$H_2O$ (3:1, 3 × 5 min), MeOH (3 × 5 min), and $CH_2Cl_2$ (3 × 5 min) and dried in vacuo to give **5**.

**6**: The lanterns **5** (1 unit) were treated with $NaN_3$ (9.75 mg, 0.15 mmol, 0.10 M) in DMF (1.50 mL) at 80 °C under argon. After being left for 12 h at the same temperature, the reaction mixture was poured into ice-cooled aqueous HCl (1 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (0–10% ethyl acetate in toluene) to give **6** (7.0 mg, 11 μmol, 32%, loading = 11 μmol per unit) as a colorless oil. $[\alpha]_D^{24} = -16$ ($c = 0.79$, $CHCl_3$); FTIR (solid): $\tilde{\nu} = 3441$, 2955, 2103, 1731, 1602, 1515, 1451, 1263, 1028, 822, 704 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$–$7.90$ (m, 15H, aromatic), 7.15 (d, $J_{Hb,Hc} = 8.21$ Hz, 2H, Hc), 6.74 (d, $J_{Hb,Hc} = 8.21$ Hz, 2H, Hb), 5.80 (dd, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, 1H, 3-H), 5.56 (dd, $J_{1\text{-}H,2\text{-}H} = 8.22$ Hz, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, 1H, 2-H), 5.44 (dd, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, 1H, 4-H), 4.88 (d, $J_{Hd,Hd'} = 12.1$ Hz, 1H, Hd), 4.80 (d, $J_{1\text{-}H,2\text{-}H} = 8.22$ Hz, 1H, 1-H), 4.68 (d, $J_{Hd,Hd'} = 12.1$ Hz, 1H, Hd′), 3.94 (ddd, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, $J_{5\text{-}H,6\text{-}H} = 8.22$ Hz, $J_{5\text{-}H,6'\text{-}H} = 1.45$ Hz, 1H, 5-H), 3.78 (s, 3H, Ha), 3.61 (dd, $J_{5\text{-}H,6\text{-}H} = 8.22$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, 6-H), 3.30 ppm (dd, $J_{5\text{-}H,6'\text{-}H} = 1.45$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, 6′-H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 165.8$, 165.4, 165.1, 159.6, 133.7, 133.3, 130.0, 130.0, 129.8, 129.3, 128.8, 128.6, 128.6, 128.4, 128.4, 113.9, 98.6 (anomeric), 74.4, 72.8, 71.8, 70.5, 70.2, 55.3, 51.5 ppm; HRMS (ESI-TOF): calcd for $C_{35}H_{31}N_3O_9Na$: 660.1953 $[M+Na]^+$; found: 660.1959.

**7**: The lanterns **5** (7 units) were treated with TFA/$H_2O$/$CH_2Cl_2$ (10:1.0:10, 3.00 mL, 0.30 mL, 3.00 mL) at room temperature. After being left for 12 h at the same temperature, the lanterns were washed with $NEt_3$/$CH_2Cl_2$ (1:9, 5 min), THF (3 × 5 min), and $CH_2Cl_2$ (3 × 5 min) and dried in vacuo to give lactol-linked lanterns. The obtained lactol-linked lantern (1 unit) was treated with a solution of *N*-phenyltrifluoroacetimidoyl chloride (38 μL, 0.30 mmol, 0.20 M) and DBU (4.5 μL, 0.03 mmol, 0.02 M) in $CH_2Cl_2$ (1.50 mL) at 0 °C under argon. After being left for 5 h at room temperature, the lantern was washed with $CH_2Cl_2$ (3 × 5 min) and dried in vacuo to give **7**.

  

General procedure for solid-phase glycosidation of **7** with **8**: The lanterns **7** (1 unit) were washed with dry toluene and dried in vacuo for 30 min. A solution of **8** (0.30 mmol, 0.20 M) in dry $CH_2Cl_2$ (1.50 mL) was added to the above lanterns and pulverized activated MS4A at room temperature under argon, and the mixture was stirred for 20 min to remove trace amounts of water. The reaction mixture was then cooled to 0 °C. An activator (TMSOTf, 0.30 mmol, 0.20 M) was slowly added to the reaction mixture at the same temperature. After being stirred for 24 h at room temperature, the reaction mixture was neutralized with $NEt_3$ at 0 °C. After filtration, the glycosylated lantern was washed with $NEt_3/CH_2Cl_2$ (1:1, 3× 1 min), $CH_2Cl_2$ (5×5 min), THF (5×10 min), and $CH_2Cl_2$ (5×5 min) and dried in vacuo to give the glycoside lantern. This lantern (1 unit) was treated with $NaN_3$ (9.8 mg, 0.15 mmol, 0.10 M) in DMF (1.50 mL) at 80 °C under argon. After being left for 12 h at the same temperature, the reaction mixture was poured into ice-cooled aqueous HCl (1 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel to afford the 6-position-modified glycoside.

**9a**: Acceptor: **8a**, activator: TMSOTf, yield: 6.8 mg, 11 μmol, 95% over 4 steps. $[\alpha]_D^{19} = +13$ ($c = 0.80$, $CHCl_3$); FTIR (solid): $\tilde{\nu} = 3441$, 2939, 2102, 1730, 1601, 1480, 1259, 1069, 709, 554 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.28$–8.01 (m, 15H, aromatic), 7.00 (t, $J_{Hb,Hc} = 8.22$ Hz, 1H, Hc), 6.51 (d, $J_{Hb,Hc} = 8.22$ Hz, 2H, Hb), 5.94 (dd, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, 1H, 3-H), 5.85 (dd, $J_{1\text{-}H,2\text{-}H} = 7.25$ Hz, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, 1H, 2-H), 5.62 (dd, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, 1H, 4-H), 5.42 (d, $J_{1\text{-}H,2\text{-}H} = 7.25$ Hz, 1H, 1-H), 3.91 (ddd, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, $J_{5\text{-}H,6\text{-}H} = 7.73$ Hz, $J_{5\text{-}H,6'\text{-}H} = 2.44$ Hz, 1H, 5-H), 3.67 (s, 6H, Ha), 3.58 (dd, $J_{5\text{-}H,6\text{-}H} = 7.73$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, 6-H), 3.28 (dd, $J_{5\text{-}H,6'\text{-}H} = 2.44$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, 6′-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 165.9$, 165.4, 165.1, 153.3, 133.6, 133.3, 133.1, 129.9, 129.9, 129.8, 129.8, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3, 124.9, 105.1, 102.0 (anomeric), 74.3, 73.1, 72.5, 70.3, 55.9, 51.5 ppm; HRMS (ESI-TOF): calcd for $C_{35}H_{31}N_3O_{10}Na$: 676.1902 $[M+Na]^+$; found: 676.1902.

**9b**: Acceptor: **8b**, activator: TMSOTf, yield: 9.9 mg, 10 μmol, 94% over 4 steps. $[\alpha]_D^{20} = +5.81$ ($c = 1.67$, $CHCl_3$); FTIR (neat): $\tilde{\nu} = 2928$, 2102, 1733, 1603, 1453, 1280, 1028, 751, 711 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta =$ 7.02–7.91 (m, 30H, aromatic), 5.85 (dd, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, 1H, B-3), 5.57 (dd, $J_{1\text{-}H,2\text{-}H} = 7.73$ Hz, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, 1H, B-2), 5.42 (dd, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, 1H, B-4), 4.90 (d, $J_{Ha,Ha'} = 11.1$ Hz, 1H, BnHa), 4.82 (d, $J_{1\text{-}H,2\text{-}H} = 7.73$ Hz, 1H, B-1), 4.74 (d, $J_{Hb,Hb'} = 12.1$ Hz, 1H, BnHb), 4.69 (d, $J_{Ha,Ha'} = 11.1$ Hz, 1H, BnHa′), 4.60 (d, $J_{Hb,Hb'} = 12.1$ Hz, 1H, BnHb′), 4.56 (d, $J_{1\text{-}H,2\text{-}H} = 3.38$ Hz, 1H, A-1), 4.49 (d, $J_{Hc,Hc'} = 11.1$ Hz, 1H, BnHc), 4.27 (d, $J_{Hc,Hc'} = 11.1$ Hz, 1H, BnHc′), 4.21 (dd, $J_{5\text{-}H,6\text{-}H} =$ 1.93 Hz, $J_{6\text{-}H,6'\text{-}H} = 10.6$ Hz, 1H, A-6), 3.93 (ddd, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, $J_{5\text{-}H,6\text{-}H} =$ 8.22 Hz, $J_{5\text{-}H,6'\text{-}H} = 2.42$ Hz, 1H, B-5), 3.89 (dd, $J_{2\text{-}H,3\text{-}H} = 9.18$ Hz, $J_{3\text{-}H,4\text{-}H} =$ 9.18 Hz, 1H, A-3), 3.79 (dd, $J_{5\text{-}H,6'\text{-}H} = 4.51$ Hz, $J_{6\text{-}H,6'\text{-}H} = 10.6$ Hz, 1H, A-6′), 3.72 (ddd, $J_{4\text{-}H,5\text{-}H} = 9.18$ Hz, $J_{5\text{-}H,6\text{-}H} = 1.93$ Hz, $J_{5\text{-}H,6'\text{-}H} = 4.51$ Hz, 1H, A-5), 3.62 (dd, $J_{5\text{-}H,6\text{-}H} = 8.22$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, B-6), 3.45 (dd, $J_{1\text{-}H,2\text{-}H} = 3.38$ Hz, $J_{2\text{-}H,3\text{-}H} = 9.18$ Hz, 1H, A-2), 3.41 (dd, $J_{3\text{-}H,4\text{-}H} = 9.18$ Hz, $J_{4\text{-}H,5\text{-}H} = 9.18$ Hz, 1H, A-4), 3.22 (dd, $J_{5\text{-}H,6'\text{-}H} = 2.42$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, B-6′), 3.20 (s, 3H, OMe); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 165.9$, 165.4, 164.9, 138.9, 138.3, 138.3, 133.8, 133.4, 133.33, 129.9, 129.8, 129.2, 128.8, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.0, 127.6, 127.6, 101.1, 98.1 (anomeric B), 82.0 (anomeric A), 79.8, 77.3, 75.7, 74.8, 74.6, 73.5, 72.7, 71.9, 70.4, 69.5, 68.4, 55.0, 51.4 ppm; HRMS (ESI-TOF): calcd for $C_{55}H_{53}N_3O_{13}Na$: 986.3471 $[M+Na]^+$; found: 986.3474.

**9c**: Acceptor: **8c**, activator: TMSOTf, yield: 2.0 mg, 2.3 μmol, 21% over 4 steps. $[\alpha]_D^{21} = +37.7$ ($c = 1.15$, $CHCl_3$); FTIR (neat): $\tilde{\nu} = 2939$, 2104, 1733, 1602, 1452, 1279, 1070, 754, 710 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta =$ 7.10–7.89 (m, 25H, aromatic), 5.69 (dd, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, 1H, B-3), 5.64 (s, 1H, Ha), 5.46 (dd, $J_{1\text{-}H,2\text{-}H} = 7.25$ Hz, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, 1H, B-2), 5.42 (dd, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, 1H, B-4), 5.16 (d, $J_{1\text{-}H,2\text{-}H} = 7.25$ Hz, 1H, B-1), 5.09 (dd, $J_{1\text{-}H,2\text{-}H} = 3.87$ Hz, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, 1H, A-2), 4.99 (d, $J_{1\text{-}H,2\text{-}H} = 3.87$ Hz, 1H, A-1), 4.51 (dd, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, 1H, A-3), 4.30 (dd, $J_{5\text{-}H,6\text{-}H} = 4.35$ Hz, $J_{6\text{-}H,6'\text{-}H} = 10.2$ Hz, 1H, A-6), 3.91 (dd, $J_{5\text{-}H,6'\text{-}H} = 4.35$ Hz, $J_{6\text{-}H,6'\text{-}H} = 10.2$ Hz, 1H, A-6′), 3.79–3.84 (m, 3H, A-4, A-5, B-5), 3.44 (dd, $J_{5\text{-}H,6\text{-}H} = 7.25$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, B-6), 3.34 (s, 3H, OMe), 3.20 (dd, $J_{5\text{-}H,6'\text{-}H} = 2.42$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, B-6′); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 165.8$, 165.5, 165.4, 164.9, 137.5, 133.7, 133.4, 133.3, 132.9, 129.9, 129.8, 129.7, 129.6, 129.2, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 126.5, 101.7, 100.6 (anomeric B), 97.6 (anomeric A), 79.7, 75.5, 73.8, 73.6, 72.9, 72.2, 70.3, 69.0, 62.5, 55.5, 51.4 ppm; HRMS (ESI-TOF): calcd for $C_{48}H_{43}N_3O_{14}Na$: 908.2637 $[M+Na]^+$; found: 908.2639.

**9d**: Acceptor: **8d**, activator: TMSOTf, yield: 7.9 mg, 9.6 μmol, 87% over 4 steps. $[\alpha]_D^{21} = +21.0$ ($c = 1.09$, $CHCl_3$); FTIR (neat): $\tilde{\nu} = 74.2$, 72.6, 71.7, 70.2, 67.1, 54.8, 52.4, 51.5, 37.5. FT-IR (neat) 3427, 2104, 1732, 1646, 1511, 1281, 1262, 1069, 803, 711 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.28$–7.97 (m, 20H, aromatic), 7.00 (d, $J_{Hf,Hg} = 8.70$ Hz, 2H, Hf), 6.94 (d, $J_{Hf,Hg} = 8.70$ Hz, 2H, Hg), 5.94 (dd, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, 1H, 3-H), 5.76 (dd, $J_{1\text{-}H,2\text{-}H} = 8.22$ Hz, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, 1H, 2-H), 5.55 (dd, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, 1H, 4-H), 5.36 (d, $J_{1\text{-}H,2\text{-}H} = 8.22$ Hz, 1H, 1-H), 5.19 (d, $J_{Hb,Hc} = 7.73$ Hz, 1H, Hb), 5.09 (s, 2H, Ha), 4.62 (ddd, $J_{Hb,Hc} = 7.73$ Hz, $J_{Hc,Hd} = 5.80$ Hz, $J_{Hc,Hd'} = 5.80$ Hz, 1H, Hc), 4.05 (ddd, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, $J_{5\text{-}H,6\text{-}H} = 7.25$ Hz, $J_{5\text{-}H,6'\text{-}H} = 1.93$ Hz, 1H, 5-H), 3.69 (s, 3H, He), 3.59 (dd, $J_{5\text{-}H,6\text{-}H} = 7.25$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, 6-H), 3.44 (dd, $J_{5\text{-}H,6'\text{-}H} = 1.93$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, 6′-H), 3.08 (dd, $J_{Hc,Hd} = 5.80$ Hz, $J_{Hd,Hd'} = 19.8$ Hz, 1H, Hd), 3.04 ppm (dd, $J_{Hc,Hd'} = 5.80$ Hz, $J_{Hd,Hd'} = 19.8$ Hz, 1H, Hd′); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 171.9$, 165.8, 165.4, 165.1, 156.0, 133.8, 133.4, 130.6, 129.9, 129.9, 129.1, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 117.8, 99.9 ppm (anomeric); HRMS (ESI-TOF): calcd for $C_{45}H_{40}N_4O_{12}Na$: 851.2535 $[M+Na]^+$; found: 851.2533.

**9e**: Acceptor: **8e**, activator: TMSOTf, yield: 7.9 mg, 11 μmol, 96% over 4 steps. $[\alpha]_D^{24} = +19$ ($c = 0.91$, $CHCl_3$); FTIR (neat): $\tilde{\nu} = 3431$, 3033, 2104, 1716, 1603, 1514, 1452, 1284, 1069, 756 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.26$–7.94 (m, 20H, aromatic), 5.85 (dd, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, 1H, 3-H), 5.43–5.48 (m, 3H, 2-H, 4-H, Hb), 5.05 (d, $J_{Ha,Ha'} = 12.1$ Hz, 1H, Ha), 4.96 (d, $J_{Ha,Ha'} = 12.1$ Hz, 1H, Ha′), 4.80 (d, $J_{1\text{-}H,2\text{-}H} = 7.73$ Hz, 1H, 1-H), 4.49 (ddd, $J_{Hb,Hc} = 8.22$ Hz, $J_{Hc,Hd} = 1.93$ Hz, $J_{Hc,Hd'} = 2.90$ Hz, 1H, Hc), 4.39 (dd, $J_{Hc,Hd} = 1.93$ Hz, $J_{Hd,Hd'} = 10.2$ Hz, 1H, Hd), 3.94 (ddd, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, $J_{5\text{-}H,6\text{-}H} = 7.32$ Hz, $J_{5\text{-}H,6'\text{-}H} = 2.44$ Hz, 1H, 5-H), 3.89 (dd, $J_{Hc,Hd'} = 2.90$ Hz, $J_{Hd,Hd'} = 10.2$ Hz, 1H, Hd′), 3.70 (s, 3H, He), 3.52 (dd, $J_{5\text{-}H,6\text{-}H} = 7.32$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.7$ Hz, 1H, 6-H), 3.34 ppm (dd, $J_{5\text{-}H,6'\text{-}H} = 2.44$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.7$ Hz, 1H, 6′-H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 169.9$, 165.8, 165.3, 165.1, 155.9, 129.9, 129.8, 129.8, 129.1, 129.0, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 101.3 (anomeric), 74.3, 72,4, 71.7, 70.1, 69.5, 67.1, 54.1, 52.8, 51.2 ppm; HRMS (ESI-TOF): calcd for $C_{39}H_{36}N_4O_{12}Na$: 775.2222 $[M+Na^+]$; found: 775.2217.

**9f**: Acceptor: **8f**, activator: TMSOTf, yield: 3.6 mg, 5.7 μmol, 52% over 4 steps. $[\alpha]_D^{24} = -6.8$ ($c = 0.58$, $CHCl_3$); FTIR (neat): $\tilde{\nu} = 2929$, 2101, 1733, 1603, 1452, 1262, 1028, 709 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.26$–7.96 (m, 15H, aromatic), 5.87 (dd, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, 1H, 3-H), 5.51 (dd, $J_{1\text{-}H,2\text{-}H} = 7.73$ Hz, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, 1H, 2-H), 5.44 (dd, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, 1H, 4-H), 4.83 (d, $J_{1\text{-}H,2\text{-}H} = 7.73$ Hz, 1H, 1-H), 3.94–3.99 (m, 2H, 5-H, Ha), 3.58 (dd, $J_{5\text{-}H,6\text{-}H} = 7.73$ Hz, $J_{6\text{-}H,6'\text{-}H} =$ 13.5 Hz, 1H, 6-H), 3.53–3.57 (m, 1H, Ha′), 3.30 (dd, $J_{5\text{-}H,6'\text{-}H} = 2.42$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, 6′-H), 1.47–1.57 (m, 2H, Hb), 1.09–1.28 (m, 10H, Hc), 0.83 ppm (t, $J_{Hc,Hd} = 7.25$ Hz, 3H, Hd); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta = 165.9$, 165.5, 165.1, 133.7, 133.3, 133.2, 129.9, 129.8, 129.8, 129.4, 128.9, 128.7, 128.6, 128.4, 128.4, 101.2 (anomeric), 74.3, 72.8, 71.9, 70.6, 70.4, 51.5, 31.8, 29.4, 29.3, 29.2, 25.9, 22.7, 14.1 ppm; HRMS (ESI-TOF): calcd for $C_{35}H_{39}N_3O_8Na$: 652.2629 $[M+Na]^+$; found: 652.2622.

**9g**: Acceptor: **8g**, activator: TMSOTf, yield: 8.4 mg, 9.5 μmol, 86% over 4 steps. $[\alpha]_D^{24} = +28$ ($c = 0.77$, $CHCl_3$); FTIR (neat): $\tilde{\nu} = 2939$, 2099, 1734, 1602, 1451, 1283, 1095, 1069, 707 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta =$ 7.26–7.96 (m, 15H, aromatic), 5.89 (dd, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, 1H, 3-H), 5.47 (dd, $J_{1\text{-}H,2\text{-}H} = 7.73$ Hz, $J_{2\text{-}H,3\text{-}H} = 9.67$ Hz, 1H, 2-H), 5.42 (dd, $J_{3\text{-}H,4\text{-}H} = 9.67$ Hz, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, 1H, 4-H), 5.27–5.28 (m, 1H, Hc), 4.94 (d, $J_{1\text{-}H,2\text{-}H} = 7.73$ Hz, 1H, 1-H), 3.95 (ddd, $J_{4\text{-}H,5\text{-}H} = 9.67$ Hz, $J_{5\text{-}H,6\text{-}H} =$ 8.22 Hz, $J_{5\text{-}H,6'\text{-}H} = 2.42$ Hz, 1H, 5-H), 3.55–3.64 (m, 2H, 6-H, Ha), 3.27 (dd, $J_{5\text{-}H,6'\text{-}H} = 2.42$ Hz, $J_{6\text{-}H,6'\text{-}H} = 13.5$ Hz, 1H, 6′-H), 2.10–2.36 (m, 2H, Hb), 0.96–2.04 (m, 26H, cholesterol), 0.92 (s, 3H, Hh), 0.91 (d, $J =$ 8.70 Hz, 3H, Hf), 0.87 (d, $J = 1.93$ Hz, 3H, Hd or He), 0.85 ppm (d, $J =$ 1.45 Hz, 3H, Hd or He), 0.65 (s, 3H, Hg); $^{13}C$ NMR (100 MHz, $CDCl_3$):

  

$\delta$ = 165.9, 165.5, 165.1, 140.5, 133.7, 133.3, 133.3, 129.9, 129.8, 129.8, 129.5, 128.9, 128.6, 128.5, 128.4, 122.1, 100.1 (anomeric), 80.3, 74.1, 72.9, 72.1, 70.6, 56.8, 56.2, 51.5, 50.2, 42.4, 39.8, 39.6, 38.9, 37.3, 36.8, 36.3, 35.9, 32.0, 31.9, 29.6, 28.3, 28.1, 24.4, 23.9, 22.9, 22.6, 21.1, 19.4, 18.8, 11.9 ppm; HRMS (ESI-TOF): calcd for $C_{54}H_{67}N_3O_8Na$: 908.4820 $[M+Na]^+$; found: 908.4813.

**8h**: Vancomycin (**1**)·HCl (1.0 g, 0.67 mmol, 1.0 equiv) was dissolved in $H_2O$ (13.5 mL) and 1,4-dioxane (8.08 mL). $NaHCO_3$ (0.17 g, 2.02 mmol, 3.0 equiv) was added to the reaction solution, followed by a solution of *N*-(allyloxycarbonyloxy)succinimide (0.50 M) in 1,4-dioxane (5.4 mL, 2.7 mmol, 4.0 equiv) at room temperature. After the reaction mixture was stirred for 12 h at the same temperature, ether (100 mL) was added. The resulting mixture was stirred for 10 min, and then the organic layer was separated, concentrated in vacuo, and dried under high vacuum for 12 h to give crude *N*,*N*′-di-Allocvancomycin as a pale-pink solid. This solid was used for the next reaction without further purification. $NaHCO_3$ (0.11 g, 1.4 mmol, 2.0 equiv) was added to a solution of the crude *N*,*N*′-di-Allocvancomycin in DMF (10 mL) at room temperature under argon. This suspension was stirred for 20 min under high vacuum, and then allyl bromide (0.29 mL, 3.4 mmol, 5.0 equiv) was added at room temperature. After being stirred for 12 h at the same temperature, the mixture was concentrated in vacuo. The residue was dried under high vacuum for 12 h to give crude *N*,*N*′-di-Allocvancomycin allyl ester as a yellow oil. This oil was used for the next reaction without further purification. $Cs_2CO_3$ (1.10 g, 3.37 mmol, 5.0 equiv) was added to a solution of the crude *N*,*N*′-di-Allocvancomycin allyl ester in DMF (10 mL) at room temperature under argon. This suspension was stirred for 20 min under high vacuum, and then allyl bromide (2.3 mL, 27 mmol, 40 equiv) was added at room temperature. After the reaction mixture was stirred for 24 h at the same temperature, $H_2O$ (120 mL) was added. The white suspension obtained was centrifuged at 5000 rpm for 1 h. The precipitate was collected and dried under high vacuum to give crude *N*,*N*′-di-Alloc-tri-*O*-allylvancomycin allyl ester as a pale-yellow solid. 2,6-Lutidine (3.5 mL, 30 mmol, 45 equiv) and TBSOTf (2.32 mL, 10.1 mmol, 15 equiv) were added to a solution of the crude *N*,*N*′-di-Alloc-tri-*O*-allylvancomycin allyl ester in DMF (13.5 mL) and $CH_2Cl_2$ (13.5 mL) at 0 °C under argon. After being stirred for 24 h at room temperature, the reaction mixture was diluted with $CH_2Cl_2$ (67 mL). Aqueous HCl (1 M, 33 mL) was added to the resulting solution at 0 °C. After being stirred for 1 h at the same temperature, the reaction mixture was poured into aqueous HCl (3 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (30–100% ethyl acetate in hexane) to give semipure *N*,*N*′-di-Alloc-tri-*O*-allyl-hexa-*O*-*tert*-butyldimethylsilylvancomycin allyl ester (0.63 g, 0.25 mmol, 38% over 4 steps) as a white solid. $Me_2S$ (3.8 mL) was added to a solution of this semipure allyl ester in $CH_2Cl_2$ (3.8 mL), followed by TFA (3.8 mL) at room temperature under argon. After being stirred for 3 h at the same temperature, the reaction mixture was concentrated in vacuo and azeotropically evaporated with toluene. The residue was purified by chromatography on silica gel (30–100% ethyl acetate in hexane) to give **8h** (0.24 g, 0.15 mmol, 58%) as a white solid. TLC: $R_f$ = 0.22 (5% MeOH in $CHCl_3$); $[\alpha]_D^{24}$ = +4.8 ($c$ = 0.90, $CHCl_3$); FTIR (solid): $\tilde{\nu}$ = 3408, 2956, 1746, 1680, 1648, 1487, 1235, 838, 780 $cm^{-1}$; $^1H$ NMR (400 MHz, [$D_6$]acetone): $\delta$ = 8.26 (br s, 1H), 7.95 (br s, $J$ = 4.83 Hz, 1H), 7.51–7.53 (m, 3H), 7.36 (br s, 1H), 7.26 (d, $J$ = 7.73 Hz, 1H), 7.10–7.12 (m, 2H), 6.77–7.03 (m, 4H), 6.70 (d, $J$ = 1.93 Hz, 1H), 6.44 (d, $J$ = 1.93 Hz, 1H), 5.72–6.13 (m, 8H), 5.06–5.57 (m, 15H), 4.96 (d, $J$ = 6.28 Hz, 1H), 4.77 (dd, $J$ = 5.32, 14.0 Hz, 1H), 4.60–4.68 (m, 6H), 4.40–4.52 (m, 5H), 2.92 (s, 3H), 2.54 (dd, $J$ = 3.38, 15.5 Hz, 1H), 2.38 (dd, $J$ = 4.34, 15.5 Hz, 1H), 1.61–1.64 (m, 2H), 1.48–1.54 (m, 1H), 0.95 (s, 9H), 0.89–0.92 (m, 12H), 0.85 (d, $J$ = 5.28 Hz, 3H), 0.13 (s, 6H), 0.11 (s, 3H), 0.09 ppm (s, 3H); $^{13}C$ NMR (100 MHz, [$D_6$]acetone): $\delta$ = 171.8, 170.9, 170.6(3), 170.6(0), 168.4, 167.5, 159.4, 158.2, 156.9, 156.4, 151.4, 151.3, 149.0, 147.2, 140.9, 139.1, 136.5, 135.7, 135.4, 134.0, 133.8, 133.7, 133.4, 132.6, 129.8, 129.5, 128.9, 128.9, 128.5, 127.5, 127.3, 127.2, 125.9, 125.2, 124.4, 124.0, 122.2, 118.2, 117.2, 117.0, 116.9, 116.5, 114.4, 106.3, 105.8, 105.3, 101.0, 74.2, 73.6, 69.1, 69.1, 69.0, 66.4, 65.6, 63.7, 59.5, 57.0, 56.9, 55.0, 54.6, 51.6, 37.6, 36.6, 30.0, 25.9, 25.7, 25.1, 23.1, 22.2, 18.6, −4.97, −5.15, −5.33 ppm; HRMS (ESI-TOF): calcd for $C_{81}H_{100}Cl_2N_8O_{19}Si_2Na$ 1637.5913 $[M+Na]^+$; found: 1637.5915.

**10**: TFA·$NH_2$–polystyrene lanterns (D series, loading: 34.0 μmol per unit, batch no.: 1640–1A) were treated with 10% DIPEA in DMF/$CH_2Cl_2$ (1:1, 2×15 min) at room temperature. After filtration, the lanterns were washed with DMF (3×5 min) and $CH_2Cl_2$ (3×5 min) and dried in vacuo to give $NH_2$–polystyrene lanterns. These lanterns were treated with a solution of Fmoc-12-aminododecanic acid (0.10 M), DIC (0.10 M), and HOBt (0.10 M) in DMF at room temperature. After being left for 24 h, the lanterns were washed with DMF (3×5 min) and $CH_2Cl_2$ (3×5 min) and dried in vacuo. The above procedure was repeated twice to give Fmoc-NH-$C_{12}H_{22}$-lanterns. The Fmoc-protected lanterns were treated with 20% piperidine in DMF for 20 min at room temperature. After filtration, the lanterns were washed with DMF (3×5 min) and $CH_2Cl_2$ (3×5 min) and dried in vacuo. The obtained lanterns were treated with a solution of 4-(tributylstannyl)benzoic acid (0.20 M), DIC (0.20 M), and HOBt (0.20 M) in DMF at room temperature. After being left for 24 h, the lanterns were washed with DMF (3×5 min), THF/$H_2O$ (3:1, 3×5 min), MeOH (3×5 min), and $CH_2Cl_2$ (3×5 min) and dried in vacuo to give **10**.

**11**: The lanterns **10** (11 units) were treated with a solution of **2** (1.41 g, 1.60 mmol, 0.20 M) and **4** (40 mg, 80.0 μmol, 0.01 M) in DMF (8 mL) at 60 °C under argon. After being left for 48 h at the same temperature, the lanterns were washed with DMF (3×5 min), THF/$H_2O$ (3:1, 3×5 min), MeOH (3×5 min), and $CH_2Cl_2$ (3×5 min) and dried in vacuo to give **11**.

**6**: The lanterns **11** (1 unit) were treated with $NaN_3$ (19.5 mg, 0.30 mmol, 0.20 M) in DMF (1.50 mL) at 80 °C under argon. After being left for 12 h at the same temperature, the reaction mixture was poured into ice-cooled aqueous HCl (1 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (0–10% ethyl acetate in toluene) to give **6** (7.7 mg, 12 μmol, 35%, loading = 12 μmol per unit) as a colorless oil.

**12**: The lanterns **11** (3 units) were treated with TFA/$H_2O$/$CH_2Cl_2$ (10:1.0:10, 3.0, 0.30, 3.0 mL) at room temperature. After being left for 12 h at the same temperature, the lanterns were washed with $NEt_3$/$CH_2Cl_2$ (1:9, 5 min), THF (3×5 min), and $CH_2Cl_2$ (3×5 min) and dried in vacuo to give lactol-linked lanterns. These lanterns (1 unit) were treated with a solution of *N*-phenyltrifluoroacetimidoyl chloride (38 μL, 0.30 mmol, 0.20 M) and DBU (4.5 μL, 0.03 mmol, 0.02 M) in $CH_2Cl_2$ at 0 °C under argon. After being left for 5 h at room temperature, the lantern was washed with $CH_2Cl_2$ (3×5 min) and dried in vacuo to give **12**.

**9h**: The lanterns **12** (1 unit) were washed with dry toluene and dried in vacuo for 30 min. They and pulverized activated MS4A were added a solution of **8h** (0.49 g, 0.30 mmol, 0.20 M) in dry $CH_2Cl_2$ (1.50 mL) at room temperature under argon, and the mixture was stirred for 20 min to remove trace amounts of water. The reaction mixture was then cooled to 0 °C. $BF_3$·OEt (95 μL, 0.75 mmol, 0.50 M) was slowly added to the reaction mixture at the same temperature. After being sonicated for 1 h at the same temperature and stirred for 23 h at room temperature, the reaction mixture was neutralized with $NEt_3$ at 0 °C. After the filtration, the glycosylated lantern was washed with $NEt_3$/$CH_2Cl_2$ (1:1, 3×1 min), $CH_2Cl_2$ (5×5 min), THF (5×10 min), and $CH_2Cl_2$ (5×5 min) and dried in vacuo to give the vancomycin pseudoaglycon linked lantern. This lantern (1 unit) was treated with $NaN_3$ (9.8 mg, 0.15 mmol, 0.10 M) in DMF (1.5 mL) at 80 °C under argon. After being left for 12 h at the same temperature, the reaction mixture was poured into ice-cooled aqueous HCl (1 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (40–100% ethyl acetate in hexane) and GPC to give **9h** (6.6 mg, 3.2 μmol, 27% over 4 steps) as a white solid. TLC: $R_f$ = 0.23 (5% MeOH in $CHCl_3$); FTIR (solid): $\tilde{\nu}$ = 3416, 2972, 2106, 1737, 1645, 1487, 1261, 1068, 710 $cm^{-1}$; $^1H$ NMR (400 MHz, [$D_6$]acetone): $\delta$ = 6.71–7.97 (m, 28H), 6.70 (d, $J$ = 1.94 Hz, 1H), 6.43 (d, $J$ = 1.94 Hz, 1H), 5.76–6.14 (m, 10H), 5.06–5.62 (m, 17H), 4.98 (dd, $J$ =

  

6.28, 18.4 Hz, 1H), 4.77 (dd, $J$=5.32, 13.4 Hz, 1H), 4.59–4.70 (m, 6H), 4.46–4.51 (m, 6H), 3.40–3.72 (m, 2H), 2.82 (s, 3H), 2.40–2.55 (m, 2H), 1.50–1.64 (m, 3H), 0.85–1.00 (m, 24H), 0.10–0.18 ppm (m, 12H); HRMS (ESI-TOF): calcd for $C_{108}H_{121}Cl_2N_{11}O_{26}Si_2Na$: 2136.7292 $[M+Na]^+$; found: 2136.7289.

**14**: A solution of **13** (1.39 g, 4.40 mmol, 1.0 equiv) in $CH_2Cl_2$ (15.0 mL) was added to a solution of freshly prepared dimethyldioxirane (DMDO) in acetone at −78 °C under argon. After being stirred for 30 min at 0 °C, the reaction mixture was concentrated in vacuo at the same temperature. The residue was used for the next reaction without further purification. A mixture of the residue, (2-trimethylsilyl)ethanol (1.74 mL, 12.1 mmol, 3.0 equiv), and pulverized activated MS4A in dry $CH_2Cl_2$ (20 mL) was stirred for 20 min at 0 °C under argon to remove trace amounts of water. Then $ZnCl_2$ (1.38 g, 10.1 mmol, 2.5 equiv) (dried azeotropically with toluene) was added to the reaction mixture in one portion at the same temperature. After being stirred for 1 h at the same temperature, the reaction mixture was neutralized with $NEt_3$ and filtered through a pad of celite. The filtrate was concentrated in vacuo, and the residue was used for the next reaction without further purification. DMAP (2.47 g, 20.2 mmol, 5.0 equiv) and a solution of 2-(azidomethyl)benzoyl chloride (AZMBCl) (6.5 mmol, 1.6 equiv) in $CH_2Cl_2$ (19 mL) were added to a solution of the residue in $CH_2Cl_2$ (12 mL) at 0 °C under argon. After being stirred for 2 h at room temperature, the reaction mixture was poured into ice-cooled aqueous HCl (1 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used for the next reaction without further purification. A solution of IBr (1.25 g, 6.06 mmol, 1.5 equiv) in $CH_2Cl_2$ (6.60 mL) was added to a solution of the residue in MeOH (40 mL) at 0 °C under argon. After being stirred for 5 h at room temperature, the reaction mixture was diluted with $CH_2Cl_2$, poured into saturated aqueous $NaHCO_3$ and 10% aqueous $Na_2S_2O_3$, and the aqueous phase was extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (10–70% ethyl acetate in hexane) to give **14** (1.57 g, 3.00 mmol, 74% over 4 steps) as a colorless oil. $[\alpha]_D^{23}=+19$ ($c$=0.82, $CHCl_3$); FTIR (neat): $\tilde{\nu}$=3453, 2955, 2103, 1750, 1733, 1643, 1242, 1080, 839 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.91 (d, $J_{Hd,He}$=7.73 Hz, 1H, He), 7.57 (dd, $J_{Hb,Hc}$=7.73 Hz, $J_{Hc,Hd}$=7.73 Hz, 1H, Hc), 7.50 (d, $J_{Hb,Hc}$=7.73 Hz, 1H, Hb), 7.41 (dd, $J_{Hc,Hd}$=7.73 Hz, $J_{Hd,He}$=7.73 Hz, 1H, Hd), 5.43 (dd, $J_{2\text{-}H,3\text{-}H}$=9.67 Hz, $J_{3\text{-}H,4\text{-}H}$=9.67 Hz, 1H, 3-H), 5.22 (dd, $J_{1\text{-}H,2\text{-}H}$=8.22 Hz, $J_{2\text{-}H,3\text{-}H}$=9.67 Hz, 1H, 2-H), 5.11 (dd, $J_{3\text{-}H,4\text{-}H}$=9.67 Hz, $J_{4\text{-}H,5\text{-}H}$=9.67 Hz, 1H, 4-H), 4.84 (d, $J_{Ha,Ha'}$=15.0 Hz, 1H, Ha), 4.69 (d, $J_{Ha,Ha'}$=15.0 Hz, 1H, Ha′), 4.68 (d, $J_{1\text{-}H,2\text{-}H}$=8.22 Hz, 1H, 1-H), 3.99 (dt, $J_{Hf,Hf'}$=6.77 Hz, $J_{Hf,Hg}$=9.67 Hz, 1H, Hf), 3.79 (dd, $J_{5\text{-}H,6\text{-}H}$=1.45 Hz, $J_{6\text{-}H,6'\text{-}H}$=12.6 Hz, 1H, 6-H), 3.55–3.67 (m, 3H, 5-H, 6′-H, Hf′), 2.07 (s, 3H, Ac), 1.96 (s, 3H, Ac), 0.83–0.96 (m, 2H, Hg), −0.06 ppm (s, 9H, Hh); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=170.3, 169.6, 164.9, 138.7, 137.5, 135.2, 133.1, 131.0, 130.0, 129.3, 128.3, 128.2, 102.0, 100.2 (anomeric), 72.5, 71.8, 71.6, 68.8, 68.1, 67.8, 52.9, 20.6, 20.6, 18.0, −1.39 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{33}N_3O_9SiNa$: 546.1878 $[M+Na]^+$; found: 546.1883.

**15**: 4-Iodobenzenesulfonyl chloride (2.08 g, 6.88 mmol, 3.0 equiv), pyridine (0.93 mL, 11.5 mmol, 5.0 equiv), and DMAP (28 mg, 0.23 mmol, 0.1 equiv) were added to a solution of **14** (1.20 g, 2.29 mmol, 1.0 equiv) in $CH_2Cl_2$ (12 mL) at 0 °C under argon. After being stirred for 12 h at room temperature, the reaction mixture was poured into ice-cooled aqueous HCl (1 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (0–10% ethyl acetate in toluene) to give **15** (1.77 g, 2.29 mmol, 98%) as a colorless oil. $[\alpha]_D^{26}=+17$ ($c$=0.90, $CHCl_3$); FTIR (neat): $\tilde{\nu}$=2953, 2103, 1755, 1571, 1368, 1233, 1055, 837 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.93 (d, $J_{Hi,Hj}$=8.22 Hz, 2H, Hi), 7.89 (d, $J_{Hd,He}$=7.73 Hz, 1H, He), 7.62 (d, $J_{Hi,Hj}$=8.22 Hz, 2H, j), 7.57 (dd, $J_{Hb,Hc}$=7.73 Hz, $J_{Hc,Hd}$=7.73 Hz, 1H, Hc), 7.50 (d, $J_{Hb,Hc}$=7.73 Hz, 1H, Hb), 7.40 (dd, $J_{Hc,Hd}$=7.73 Hz, $J_{Hd,He}$=7.73 Hz, 1H, Hd), 5.36 (dd, $J_{2\text{-}H,3\text{-}H}$=9.67 Hz, $J_{3\text{-}H,4\text{-}H}$=9.67 Hz, 1H, 3-H), 5.16 (dd, $J_{1\text{-}H,2\text{-}H}$=7.73 Hz, $J_{2\text{-}H,3\text{-}H}$=9.67 Hz, 1H, 2-H), 5.00 (dd, $J_{3\text{-}H,4\text{-}H}$=9.67 Hz, $J_{4\text{-}H,5\text{-}H}$=9.67 Hz, 1H, 4-H), 4.82 (d, $J_{Ha,Ha'}$=14.5 Hz, 1H, Ha), 4.67 (d, $J_{Ha,Ha'}$=14.5 Hz, 1H, Ha′), 4.61 (d, $J_{1\text{-}H,2\text{-}H}$=7.73 Hz, 1H, 1-H), 4.18 (dd, $J_{5\text{-}H,6\text{-}H}$=2.90 Hz, $J_{6\text{-}H,6'\text{-}H}$=11.1 Hz, 1H, 6-H), 4.10 (dd, $J_{5\text{-}H,6'\text{-}H}$=5.80 Hz, $J_{6\text{-}H,6'\text{-}H}$=11.1 Hz, 1H, 6′-H), 3.95 (dt, $J_{Hf,Hf'}$=7.73 Hz, $J_{Hf,Hg}$=9.67 Hz, 1H, Hf), 3.82 (ddd, $J_{4\text{-}H,5\text{-}H}$=9.67 Hz, $J_{5\text{-}H,6\text{-}H}$=2.90 Hz, $J_{5\text{-}H,6'\text{-}H}$=5.80 Hz, 1H, 5-H), 3.52 (dt, $J_{Hf,Hf'}$=7.73 Hz, $J_{Hf',Hg}$=9.67 Hz, 1H, Hf′), 2.03 (s, 3H, Ac), 1.95 (s, 3H, Ac), 0.84–0.89 (m, 2H, Hg), −0.05 ppm (s, 9H, Hh); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=170.4, 170.2, 165.1, 137.5, 133.0, 131.0, 129.9, 128.3, 128.2, 100.4 (anomeric), 74.2, 72.7, 72.2, 69.0, 67.8, 52.8, 20.7, 20.6, 18.1, −1.43 ppm; HRMS (ESI-TOF): calcd for $C_{29}H_{100}IN_3O_{11}SSiNa$: 812.0777 $[M+Na]^+$; found: 812.0765.

**16**: The lanterns **10** (10 units) were treated with a solution of **15** (1.11 g, 1.40 mmol, 0.20 M) and $[Pd(MeCN)_2Cl_2]$ (18 mg, 0.07 mmol, 0.01 M) in DMF (7 mL) at 60 °C under argon. After being left for 48 h at the same temperature, the lanterns were washed with DMF (3×5 min), THF/$H_2O$ (3:1, 3×5 min), MeOH (3×5 min), and toluene (3×5 min) and dried in vacuo to give **16**.

**17**: The lanterns **16** (1 unit) were treated with LiCl (13 mg, 0.30 mmol, 0.20 M) in DMF (1.5 mL) at 80 °C under argon. After being left for 12 h at the same temperature, the reaction mixture was poured into ice-cooled aqueous HCl (1 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (0–10% ethyl acetate in toluene) to give **17** (6.7 mg, 12 μmol, 36%, loading=12 μmol per unit) as a colorless oil. $[\alpha]_D^{23}=+35.1$ ($c$=1.11, $CHCl_3$); FTIR (neat): $\tilde{\nu}$=2953, 2103, 1755, 1571, 1368, 1233, 1055, 837 $cm^{-1}$; $^1H$ NMR (400 MHz, CDCl3): $\delta$=7.91 (d, $J_{Hd,He}$=7.73 Hz, 1H, He), 7.57 (dd, $J_{Hb,Hc}$=7.73 Hz, $J_{Hc,Hd}$=7.73 Hz, 1H, Hc), 7.50 (d, $J_{Hb,Hc}$=7.73 Hz, 1H, Hb), 7.41 (dd, $J_{Hc,Hd}$=7.73 Hz, $J_{Hd,He}$=7.73 Hz, 1H, Hd), 5.39 (dd, $J_{2\text{-}H,3\text{-}H}$=9.67 Hz, $J_{3\text{-}H,4\text{-}H}$=9.67 Hz, 1H, 3-H), 5.23 (dd, $J_{1\text{-}H,2\text{-}H}$=8.22 Hz, $J_{2\text{-}H,3\text{-}H}$=9.67 Hz, 1H, 2-H), 5.08 (dd, $J_{3\text{-}H,4\text{-}H}$=9.67 Hz, $J_{4\text{-}H,5\text{-}H}$=9.67 Hz, 1H, 4-H), 4.83 (d, $J_{Ha,Ha'}$=14.9 Hz, 1H, Ha), 4.69 (d, $J_{Ha,Ha'}$=14.9 Hz, 1H, Ha′), 4.68 (d, $J_{1\text{-}H,2\text{-}H}$=8.22 Hz, 1H, 1-H), 4.00 (dt, $J_{Hf,Hf'}$=6.77 Hz, $J_{Hf,Hg}$=9.67 Hz, 1H, Hf), 3.78 (ddd, $J_{4\text{-}H,5\text{-}H}$=9.67 Hz, $J_{5\text{-}H,6\text{-}H}$=2.42 Hz, $J_{5\text{-}H,6'\text{-}H}$=10.1 Hz, 1H, 5-H), 3.57–3.67 (m, 3H, 6-H, 6′-H, Hf′), 2.07 (s, 3H, Ac), 1.96 (s, 3H, Ac), 0.86–0.98 (m, 2H, Hg), −0.05 ppm (s, 9H, Hh); $^{13}C$ NMR (100 MHz, CDCl3): $\delta$=170.4, 169.6, 165.0, 137.5, 133.0, 131.0, 129.9, 128.3, 128.2, 100.2 (anomeric), 73.8, 72.8, 72.1, 70.5, 67.8, 52.9, 43.4, 20.7, 20.6, 18.1, −1.41 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{32}ClN_3O_8SiNa$: 564.1539 $[M<M<Na]^+$; found: 564.1543.

**18**: The lanterns **16** (10 units) were treated with TFA/$CH_2Cl_2$ (2.0:1.0, 10, 5 mL) at room temperature. After being left for 1 h at the same temperature, the lanterns were washed with $NEt_3/CH_2Cl_2$ (1.0:9.0, 5 min), THF (3×5 min), and $CH_2Cl_2$ (3×5 min) and dried in vacuo to give lactol-linked lanterns. These lanterns (1 unit) were treated with a solution of *N*-phenyltrifluoroacetimidoyl chloride (38 μL, 0.30 mmol, 0.20 M) and DBU (4.5 μL, 0.03 mmol, 0.02 M) in $CH_2Cl_2$ at 0 °C under argon. After being left for 5 h at room temperature, the lantern was washed with $CH_2Cl_2$ (3×5 min) and dried in vacuo to give **18**.

**21**: Vancomycin (**1**) hydrochloride (1.0 g, 0.67 mmol, 1.0 equiv) was dissolved in $H_2O$ (14 mL) and 1,4-dioxane (8.1 mL). $NaHCO_3$ (0.17 g, 2.0 mmol, 3.0 equiv) was added to the reaction solution, followed by a solution of *N*-(allyloxycarbonyloxy)succinimide (0.50 M) in 1,4-dioxane (5.4 mL, 2.7 mmol, 4.0 equiv) at room temperature. After the reaction mixture was stirred for 12 h at the same temperature, ether (100 mL) was added. The resulting mixture was stirred for 10 min, and then the aqueous layer was separated, concentrated in vacuo, and dried under high vacuum for 12 h to give crude *N*,*N*′-di-Allocvancomycin as a pale-pink solid. This solid was used for the next reaction without further purification. HCl (1 M) in MeOH was added to a solution of the crude *N*,*N*′-di-Allocvancomycin in MeOH (10 mL) at room temperature under argon. After being stirred for 20 min at the same temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ at 0 °C, and the aqueous phase was extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (0–70% ethyl acetate in hexane) to afford 3-(*N*-allyloxycarbonyl)-L-vancosamine methyl glycosides (0.16 g, 0.62 mmol, 92% over 2 steps, α/β=2:1) as a colorless oil.

  

Data for α,β mixture: FTIR (neat): $\tilde{\nu}$ = 3410, 2985, 2939, 1793, 1713, 1506, 1013, 758 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): α anomer (major): $\delta$ = 5.84–5.94 (m, 1H, Hc), 5.38 (brs, 1H, Ha), 5.27 (dd, $J_{Hc,Hd'}$ = 16.9 Hz, $J_{Hd,Hd'}$ = 1.45 Hz, 1H, Hd′), 5.18 (dd, $J_{Hc,Hd}$ = 10.1 Hz, $J_{Hd,Hd'}$ = 1.45 Hz, 1H, Hd), 4.70 (d, $J_{1\text{-}H,2\text{-}H}$ = 4.35 Hz, 1H, 1-H), 4.59 (brd, $J_{Hb,Hc}$ = 5.80 Hz, 2H, Hb), 4.08 (brq, $J_{5\text{-}H,6\text{-}H}$ = 6.77 Hz, 1H, 5-H), 3.25–3.36 (m, 4H, 4-H, Hf), 2.15 (d, $J_{2\text{-}H,2'\text{-}H}$ = 14.5 Hz, 1H, 2′-H), 1.80 (dd, $J_{1\text{-}H,2\text{-}H}$ = 4.35 Hz, $J_{2\text{-}H,2'\text{-}H}$ = 14.5 Hz, 1H, 2-H), 1.60 (s, 3H, He), 1.24 ppm (d, $J_{5\text{-}H,6\text{-}H}$ = 6.77 Hz, 3H, 6-H); HRMS (ESI-TOF): calcd for $C_{12}H_{21}NO_5Na$: 282.1312 $[M+Na]^+$; found: 282.1313. Pyridine (0.50 mL, 6.2 mmol, 10 equiv), $Ac_2O$ (0.35 mL, 3.7 mmol, 6.0 equiv), and DMAP (7.3 mg, 0.06 mmol, 0.1 equiv) were added to a solution of 3-(*N*-allyloxycarbonyl)-α,β-L-vancosamine methyl glycoside (0.16 g, 0.62 mmol, 1.0 equiv) in $CH_2Cl_2$ (6.2 mL) at 0 °C under argon. After being stirred for 12 h at room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (0–70% ethyl acetate in hexane) to give 4-*O*-acetyl-3-(*N*-allyloxycarbonyl)-α,β-L-vancosamine methyl glycoside (0.17 g, 0.57 mmol, 92%, α/β = 2:1) as a colorless oil.[17] Data for α,β mixture: FTIR (neat): $\tilde{\nu}$ = 2988, 2943, 1744, 1648, 1528, 1373, 1249, 1055 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): α anomer (major): $\delta$ = 5.84–5.94 (m, 1H, Hc), 5.27 (dd, $J_{Hc,Hd'}$ = 16.9 Hz, $J_{Hd,Hd'}$ = 1.45 Hz, 1H, Hd′), 5.20 (dd, $J_{Hc,Hd}$ = 10.6 Hz, $J_{Hd,Hd'}$ = 1.45 Hz, 1H, Hd), 4.96 (brs, 1H, 4-H), 4.80 (d, $J_{1\text{-}H,2\text{-}H}$ = 4.35 Hz, 1H, 1-H), 4.71 (brs, 1H, Ha), 4.52 (dd, $J_{Hb,Hb'}$ = 13.0 Hz, $J_{Hb,Hc}$ = 5.32 Hz, 1H, Hb), 4.45 (dd, $J_{Hb,Hb'}$ = 13.0 Hz, $J_{Hb',Hc}$ = 5.80 Hz, 1H, Hb′), 4.11 (brq, $J_{5\text{-}H,6\text{-}H}$ = 6.77 Hz, 1H, 5-H), 3.33 (s, 3H, Hf), 2.16 (s, 3H, Ac), 2.12 (d, $J_{2\text{-}H,2'\text{-}H}$ = 13.5 Hz, 1H, 2′-H), 1.95 (dd, $J_{1\text{-}H,2\text{-}H}$ = 4.35 Hz, $J_{2\text{-}H,2'\text{-}H}$ = 13.5 Hz, 1H, 2-H), 1.70 (s, 3H, He), 1.14 ppm (d, $J_{5\text{-}H,6\text{-}H}$ = 6.77 Hz, 3H, 6-H); HRMS (ESI-TOF): calcd for $C_{14}H_{23}NO_6Na$: 324.1418 $[M+Na]^+$; found: 324.1425. $BF_3{\cdot}OEt_2$ (108 μL, 0.86 mmol, 1.5 equiv) was added to a solution of 4-*O*-acetyl-3-(*N*-allyloxycarbonyl)-α,β-L-vancosamine methyl glycoside (0.17 g, 0.57 mmol, 1.0 equiv) in MeCN (5.70 mL) and $H_2O$ (0.57 mL) at 0 °C under argon. After being stirred for 12 h at room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (0–70% ethyl acetate in hexane) to give 4-*O*-acetyl-3-(*N*-allyloxycarbonyl)-α,β-L-vancosamine (0.15 g, 0.54 mmol, 95%, α/β = 1:2) as a colorless oil. Data for α,β mixture: FTIR (neat): $\tilde{\nu}$ = 3327, 2989, 2944, 1733, 1533, 1375, 1250, 1103, 1061 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): β anomer (major) ; $\delta$ = 5.83–5.93 (m, 1H, Hc), 5.27 (d, $J_{Hc,Hd'}$ = 17.4 Hz, 1H, Hd′), 5.20 (d, $J_{Hc,Hd}$ = 10.6 Hz, 1H, Hd), 4.97–4.99 (m, 2H, 1-H, 4-H), 4.79 (brs, 1H, Ha), 4.52 (brd, $J_{Hb,Hb'}$ = 13.0 Hz, 1H, Hb), 4.45 (dd, $J_{Hb,Hb'}$ = 13.0 Hz, $J_{Hb',Hc}$ = 5.80 Hz, 1H, Hb′), 3.90 (brq, $J_{5\text{-}H,6\text{-}H}$ = 6.28 Hz, 1H, 5-H), 2.14–2.15 (m, 4H, 2-H, Ac), 1.76 (s, 3H, He), 1.68 (dd, $J_{1\text{-}H,2'\text{-}H}$ = 10.1 Hz, $J_{2\text{-}H,2'\text{-}H}$ = 12.1 Hz, 1H, 2′-H), 1.17 ppm (d, $J_{5\text{-}H,6\text{-}H}$ = 6.28 Hz, 3H, 6-H); HRMS (ESI-TOF): calcd for $C_{13}H_{21}NO_6Na$: 310.1261 $[M+Na]^+$; found: 310.1261. Diethylaminosulfur trifluoride (DAST; 28 μL, 0.21 mmol, 1.5 equiv) was added to a solution of 4-*O*-acetyl-3-(*N*-allyloxycarbonyl)-α,β-L-vancosamine (41 mg, 0.14 mmol, 1.0 equiv) in $CH_2Cl_2$ (2.8 mL) at 0 °C under argon. After being stirred for 1 h at the same temperature, the reaction mixture was diluted with $CH_2Cl_2$ and poured into saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with ethyl acetate. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was very labile to silica gel. Therefore, crude **21** (α/β = 15:1) was used for the glycosylation without further purification. Data for crude α,β mixture: $^1H$ NMR (400 MHz, $CDCl_3$): α anomer (major): $\delta$ = 5.84 (m, 1H, Hc), 5.73 (dd, $J_{1\text{-}H,2'\text{-}H}$ = 3.38 Hz, $J_{1\text{-}H,F}$ = 53.2 Hz, 1H, 1-H), 5.28 (brd, $J_{Hc,Hd'}$ = 17.4 Hz, 1H, Hd′), 5.21 (brd, $J_{Hc,Hd}$ = 10.2 Hz, 1H, Hd), 4.98 (brs, 1H, 4-H), 4.81 (brs, 1H, Ha), 4.53 (dd, $J_{Hb,Hb'}$ = 13.1 Hz, $J_{Hb,Hc}$ = 5.80 Hz, 1H, Hb), 4.46 (dd, $J_{Hb,Hb'}$ = 13.1 Hz, $J_{Hb',Hc}$ = 5.80 Hz, 1H, Hb′), 4.33 (brq, $J_{5\text{-}H,6\text{-}H}$ = 6.28 Hz, 1H, 5-H), 2.44 (dd, $J_{2\text{-}H,2'\text{-}H}$ = 14.5 Hz, $J_{2\text{-}H,F}$ = 7.25 Hz, 1H, 2-H), 2.17 (s, 3H, Ac), 2.01 (ddd, $J_{1\text{-}H,2'\text{-}H}$ = 3.38 Hz, $J_{2\text{-}H,2'\text{-}H}$ = 14.5 Hz, $J_{2'\text{-}H,F}$ = 40.6 Hz, 1H, 2′-H), 1.72 (s, 3H, He), 1.18 (d, $J_{5\text{-}H,6\text{-}H}$ = 6.28 Hz, 3H, 6-H).

**22**: The lanterns **18** (14 units, 23%, loading = 7.8 μmol per unit) were washed with dry toluene and dried in vacuo for 30 min. They and pulverized activated MS4A were added to a solution of **8h** (3.00 g, 1.86 mmol, 0.20 M) in dry $CH_2Cl_2$ (9.3 mL) at room temperature under argon, and the mixture was stirred for 20 min to remove trace amounts of water. The reaction mixture was then cooled to 0 °C. $BF_3{\cdot}OEt$ (0.47 mL, 3.7 mmol, 0.40 M) was slowly added to the reaction mixture at the same temperature. After being stirred for 24 h at room temperature, the reaction mixture was neutralized with $NEt_3$ at 0 °C. After filtration, the glycosylated lantern was washed with $NEt_3/CH_2Cl_2$ (1:1, 3×1 min), $CH_2Cl_2$ (5×5 min), THF (5×10 min), and $CH_2Cl_2$ (5×5 min) and dried in vacuo to give **19**. The above lanterns (13 units) were treated with $Bu_3P$ (0.96 mL, 3.9 mmol, 0.20 M) and $H_2O$ (0.18 mL, 9.75 mmol, 0.50 M) in THF (20 mL) at room temperature. After being left for 12 h at the same temperature, the lanterns were washed with THF/$H_2O$ (3:1, 3×5 min), THF (3×5 min), and $CH_2Cl_2$ (3×5 min) and dried in vacuo to give **20**. The lanterns **20** (4 units) were washed with dry toluene and dried in vacuo for 30 min. They and pulverized activated MS4A were added to a solution of **21** (crude, 0.80 mmol, 0.20 M) in dry $CH_2Cl_2$ (4 mL) at 0 °C, and the mixture was stirred for 20 min to remove trace amounts of water. The reaction mixture was then cooled to −20 °C. $BF_3{\cdot}OEt$ (51 μL, 0.40 mmol, 0.10 M) was slowly added to the reaction mixture at the same temperature.[19] After being stirred for 1 h at the same temperature, the reaction mixture was warmed to 0 °C and stirred for 7 h, then neutralized with $NEt_3$ at 0 °C. After filtration, the glycosylated lantern was washed with $NEt_3/CH_2Cl_2$ (1:1, 3×1 min), $CH_2Cl_2$ (5×5 min), THF (5×10 min), and $CH_2Cl_2$ (5×5 min) and dried in vacuo to give **22**.

General procedure for nucleophilic cleavage: A nucleophile (shown below) was added to **22** (1 unit) in DMF (1.50 mL) at room temperature under argon. After being stirred, the reaction mixture was poured into ice-cooled aqueous HCl (1 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with $H_2O$, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel and GPC to afford vancomycin protected by glucose modified at the 6-position.

**23**: Nucleophile: NaOAc (0.50 M) and [15]crown-5 (0.10 M), conditions: 80 °C, 24 h, yield: 4.9 mg, 2.3 μmol, 29% over 6 steps. FTIR (solid): $\tilde{\nu}$ = 2926, 1745, 1675, 1503, 1260, 1101, 1063, 942, 805, 697 $cm^{-1}$; HRMS (ES I-TOF): calcd for $C_{106}H_{135}Cl_2N_9O_{32}Si_2Na$: 2194.8021 $[M+Na]^+$; found: 2194.7991.

**24**: Nucleophile: LiCl (0.20 M), conditions: 80 °C, 12 h, yield: 5.1 mg, 2.3 μmol, 30% over 6 steps. FTIR (solid): $\tilde{\nu}$ = 2925, 1727, 1683, 1504, 1261, 1095, 1026, 800, 756, 524 $cm^{-1}$; HRMS (ESI-TOF): calcd for $C_{104}H_{132}Cl_3N_9O_{30}Si_2Na$: 2170.7577 $[M+Na]^+$; found: 2170.7548.

**25**: Nucleophile: $Bu_4N{\cdot}N_3$ (0.20 M), conditions: 80 °C, 12 h, yield: 4.4 mg, 2.0 μmol, 26% over 6 steps; FTIR (solid): $\tilde{\nu}$ = 2927, 2107, 1726, 1674, 1505, 1376, 1260, 1101, 1029, 803, 731 $cm^{-1}$; HRMS (ESI-TOF): calcd for $C_{104}H_{132}Cl_2N_{12}O_{30}Si_2Na$: 2177.7980 $[M+Na]^+$; found: 2177.7980.

**26**: Nucleophile: KSAc (0.20 M), conditions: 60 °C, 12 h, yield: 5.0 mg, 2.3 μmol, 29% over 6 steps. FTIR (solid): $\tilde{\nu}$ = 2927, 1736, 1648, 1486, 1385, 1251, 1216, 1090, 1026, 839, 776, 595 $cm^{-1}$; HRMS (ESI-TOF): calcd for $C_{106}H_{135}Cl_2N_9O_{31}SSi_2Na$: 2210.7793 $[M+Na]^+$; found: 2210.7789.

**1**·TFA: HF·pyridine (0.10 mL) was added to a solution of **23** (12 mg, 5.5 μmol, 1.0 equiv) in dry pyridine (1.00 mL) at room temperature under argon. After being stirred for 12 h at 60 °C, the reaction mixture was poured into ice-cooled aqueous HCl (1 M), and the aqueous phase was extracted with ethyl acetate. The extract was washed with $H_2O$, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. A mixture of $N_2H_4{\cdot}H_2O$, allyl alcohol, MeOH, and THF (1 mL, 0.16:1:1:1) was added to the residue at room temperature under argon. After being stirred for 6 h, the reaction mixture was neutralized with AcOH at the same temperature and concentrated in vacuo. The residue was purified by reverse-phase column chromatography (Bond Leut-C18: 0–100% MeOH in $H_2O$) to give hexaol. *N,N′*-dimethylbarbituric acid (8.62 mg, 55 μmol, 10 equiv) and $[Pd(PPh_3)_4]$ (3.2 mg, 2.8 μmol, 0.5 equiv) were added to a solution of the above residue in 1,4-dioxane at room temperature under argon. After the reaction mixture was stirred for 5 min, $H_2O$ was added (2×0.2 mL). After being stirred for 7 h, the re-

  

action mixture was concentrated in vacuo. The residue was purified by reverse-phase column chromatography (Bond Leut-C18: 0–40% MeOH in $H_2O$) followed by reverse-phase HPLC (C18 column, gradient solvent system 0–20 min, 0–100% MeCN (0.10% TFA) in $H_2O$ (0.10% TFA), flow rate 10 mL min$^{-1}$, $t_R$ 8.84 min) to afford **1**·TFA (5.0 mg, 3.3 μmol, 59% over 3 steps) as a white solid. $[\alpha]_D^{26} = +19$ ($c = 0.29$, $H_2O$); FTIR (solid): $\tilde{\nu} = 3254, 2968, 2465, 1664, 1489, 1419, 1202, 1134, 1063, 1026, 842, 722, 556$ cm$^{-1}$; $^1$H NMR (400 MHz, $D_2O$ at 323 K): $\delta = 7.51$–$7.70$ (m, 5H), 7.24 (d, $J = 8.22$ Hz, 1H), 6.92–7.11 (m, 3H), 6.58 (d, $J = 1.93$ Hz, 1H), 6.47 (d, $J = 1.56$ Hz, 1H), 6.00 (br s, 1H), 5.81 (br s, 1H), 5.34–5.52 (m, 8H), 4.84 (q, $J = 6.28$ Hz, 1H), 4.68 (m, 2H), 4.24 (s, 1H), 4.81 (t, $J = 7.25$ Hz, 1H), 3.80 (m, 3H), 3.65 (t, $J = 9.18$ Hz, 1H), 3.45 (s, 1H), 2.78 (s, 3H), 2.09 (dd, $J = 3.35$, 14.5 Hz, 1H), 2.03 (br d, $J = 14.5$ Hz, 1H), 1.78–1.85 (m, 1H), 1.66–1.73 (m, 1H), 1.52–1.62 (m, 1H), 1.44 (s, 3H), 1.15 (d, $J = 6.28$ Hz, 3H), 0.88 (d, $J = 6.28$ Hz, 3H), 0.83 ppm (d, $J = 6.28$ Hz, 3H); $^{13}$C NMR (100 MHz, $D_2O$): $\delta = 174.1$, 174.0, 171.0, 170.5, 169.5, 169.1, 168.4, 162.5 (q, $J_{C,F} = 35.8$ Hz, $CF_3CO_2H$), 156.6, 155.2, 154.2, 152.6, 149.1, 140.3, 135.3, 135.0, 128.8, 128.1, 127.8, 127.1, 126.8, 126.4, 125.9, 124.3, 123.5, 120.7, 117.8, 117.5, 116.1 (q, $J_{C,F} = 292$ Hz, $CF_3CO_2H$), 107.2, 103.3, 97.6, 79.2, 75.8, 71.2, 70.6, 68.9, 63.8, 60.4, 57.1, 54.6, 54.3, 51.4, 38.7, 35.8, 32.8, 31.5, 23.7, 22.1, 21.5, 21.2, 16.1 ppm; HRMS (ESI-TOF): calcd for $C_{66}H_{75}Cl_2N_9O_{24}Na$: 1470.4194 $[M+Na]^+$; found: 1470.4194; elemental analysis: calcd (%) for $C_{68}H_{75}Cl_2F_3N_9O_{25}\cdot 13H_2O$: C 45.87, H 5.72, N 7.08; found: C 45.67, H 5.96, N 7.08.

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