Solid- and Solution-Phase Synthesis of Vancomycin and Vancomycin Analogues with Activity against Vancomycin-Resistant Bacteria

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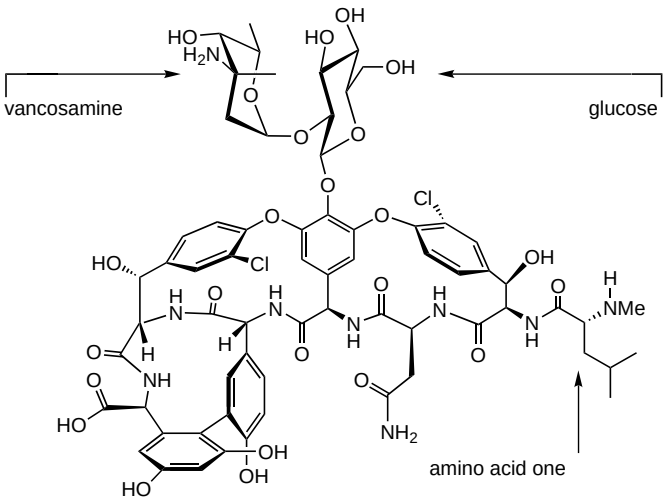
Abstract: Vancomycin, the prototypical member of the glycopeptide family of antibiotics, is a clinically used antibiotic employed against a variety of drug-resistant bacterial strains including methicillin-resistant *Staphylococcus aureus* (MRSA). The recent emergence of vancomycin resistance, viewed as a growing threat to public health, prompted us to initiate a program aimed at restoring the potency of this important antibiotic through chemical manipulation of the vancomycin structure. Herein, we describe the development of synthetic technology based on the design of a novel selenium safety catch linker, application of this technology to a solid-phase semisynthesis of vancomycin, and the solid- and solution-phase synthesis of vancomycin libraries. Biological evaluation of these compound libraries led to the identification of a number of in vitro highly potent antibacterial agents effective against vancomycin-resistant bacteria. In addition to aiding these investigations, the solid-phase chemistry described herein is expected to enhance the power of combinatorial chemistry and facilitate chemical biology and medicinal chemistry studies.

Keywords: antibiotics · biological evaluation · combinatorial synthesis · synthesis design · vancomycin

Introduction

Vancomycin[1] (**1**, Figure 1), the prototypical member of the glycopeptide class[2] of antibiotics, has been clinically used for the past 40 years to treat infection by Gram-positive bacteria. Its utility against methicillin-resistant *Staphylococcus aureus* (MRSA) has made it the drug of last resort for the treatment of this scourge.[3] However, the recent emergence of vancomycin-resistant *Enterococci* (VRE)[4] and vancomycin-intermediate resistant *Staphylococcus aureus* (VISA)[5] is raising serious public health concerns.[6] Accordingly, there is currently a vigorous effort to develop novel antibacterial drugs with activity against VRE and VISA.[7–9] Vancomycin's antibacterial activity stems from its ability to inhibit bacterial cell-wall peptidoglycan biosynthesis. Specifically, vancomycin binds to the terminal D-Ala-D-Ala fragment of the immature cell wall through an intricate network of five hydrogen bonds (Figure 2), and thereby inhibits cell wall construction.[10] This inhibition eventually leads to bacterial death due to the weakened cell wall's loss of ability to withstand high osmotic pressure. Vancomycin resistance (van A and van B) is primarily conferred through the mutation of the terminal D-Ala-



1 : vancomycin

Figure 1. Chemical structure of vancomycin (**1**).

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D-Ala to a terminal D-Ala-D-Lac.[11] This structural change results in the loss of one hydrogen bond from the vancomycin/peptide complex (Figure 2), thereby decreasing vancomycin's affinity for the cell-wall by a thousand-fold, and, as a consequence, rendering the antibiotic ineffective against such mutants.

In contemplating new weapons against bacteria, several strategies may be considered to reinstate the antibacterial activity of vancomycin against VRE and VISA. One of the most obvious tactics to potentially accomplish this goal would be to modify the binding surface between vancomycin and its ligand within the cell wall. Attractive as it may seem the re-engineering of the binding pocket of vancomycin through a systematic replacement of internal amino acids, its implementation, appears at present as synthetically complex, although a number of attempts along these lines have been made.[12–14] A second, more practical approach to restoring antibacterial activity to vancomycin-type structures has been explored by scientists at Eli Lilly[15] and rationalized by Williams.[16] Specifically, it was recognized that peripheral modification of the vancomycin core (particularly at the N-terminal D-LeuNMe residue, and more so at the vancosamine nitrogen) could enhance the antibiotic's activity against VRE. Specifically, it was observed that lypophilic anchors such as those present on the naturally occurring glycopeptide antibiotic teicoplanin[17] facilitate the delivery of the molecule at its site of action within the cell wall and thus improve its effectiveness against bacteria. A third approach for restoring and enhancing the antibacterial activity of vancomycin is through covalent dimerization, a strategy that will be further discussed in the following article.[18]

Results and Discussion

As mentioned above peripheral modification of vancomycin can lead to striking improvements in antibacterial activity, particularly against drug-resistant strains. However, there has been little modification of the constitution of the sugar moieties themselves. The absence of such studies is undoubtedly due to the synthetic challenges associated with modifying these domains of the molecule; although, some progress has been made toward this goal by coaching the biosynthetic machinery of the producing organism to produce certain modified analogues.[19] Enabled by our recent total synthesis of vancomycin,[20, 21] we decided to pursue the design and construction of such vancomycin variants. We reasoned that a solid-phase semisynthesis of vancomycin could even further facilitate the construction of compound libraries for biological screening, and therefore, considered such an endeavor. Despite the recent advances in the area of solid-phase synthesis of natural products, the highly complex nature of the vancomycin molecule necessitated the development of new chemistry applicable to the problem at hand.[22] A practical solid-phase semisynthesis of vancomycin, therefore, became our initial objective.[23]

Solid-phase semisynthesis of vancomycin: Cognizant that the appropriate choice of linking[24] and protecting group strategies would be crucial for the success of a solid-phase semisynthesis of vancomycin and analogues thereof, we decided, by analogy to our solution-phase synthesis of vancomycin, to employ persilylation as a means of protection and chose to link vancomycin to the solid phase through its C-terminus. The next issue we addressed was the nature of the linker itself. Requirements of such a linker included both acid and base stability, cleavage under mild conditions, and compatibility with silicon protecting groups. In principle, the photocleavable resin linkers **2** and **3**[25] (Figure 3) met these stringent criteria. However, while protected vancomycin, prepared as shown in Scheme 1, was readily loaded onto resin **2**, through Mitsunobu reaction, cleavage of the substrate could not be effected. Conversely, resin **3** could only be loaded

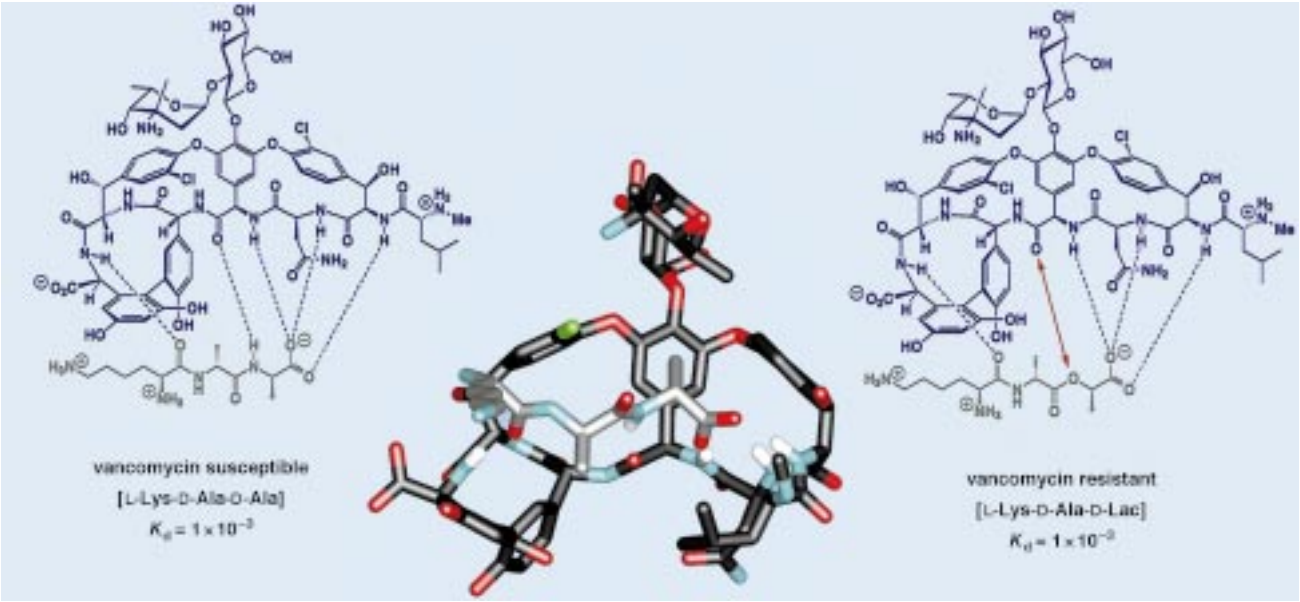

Figure 2. The hydrogen-bond network between vancomycin (dark structure) and the tripeptide L-Lys-D-Ala-D-Ala in ChemDraw format (left) and as a wire frame representation (center). The diagram on the right depicts the hydrogen-bond network between vancomycin and L-Lys-D-Ala-D-Lac.

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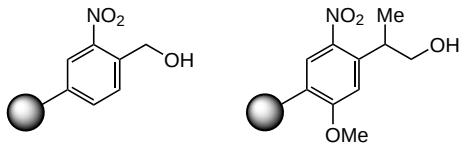
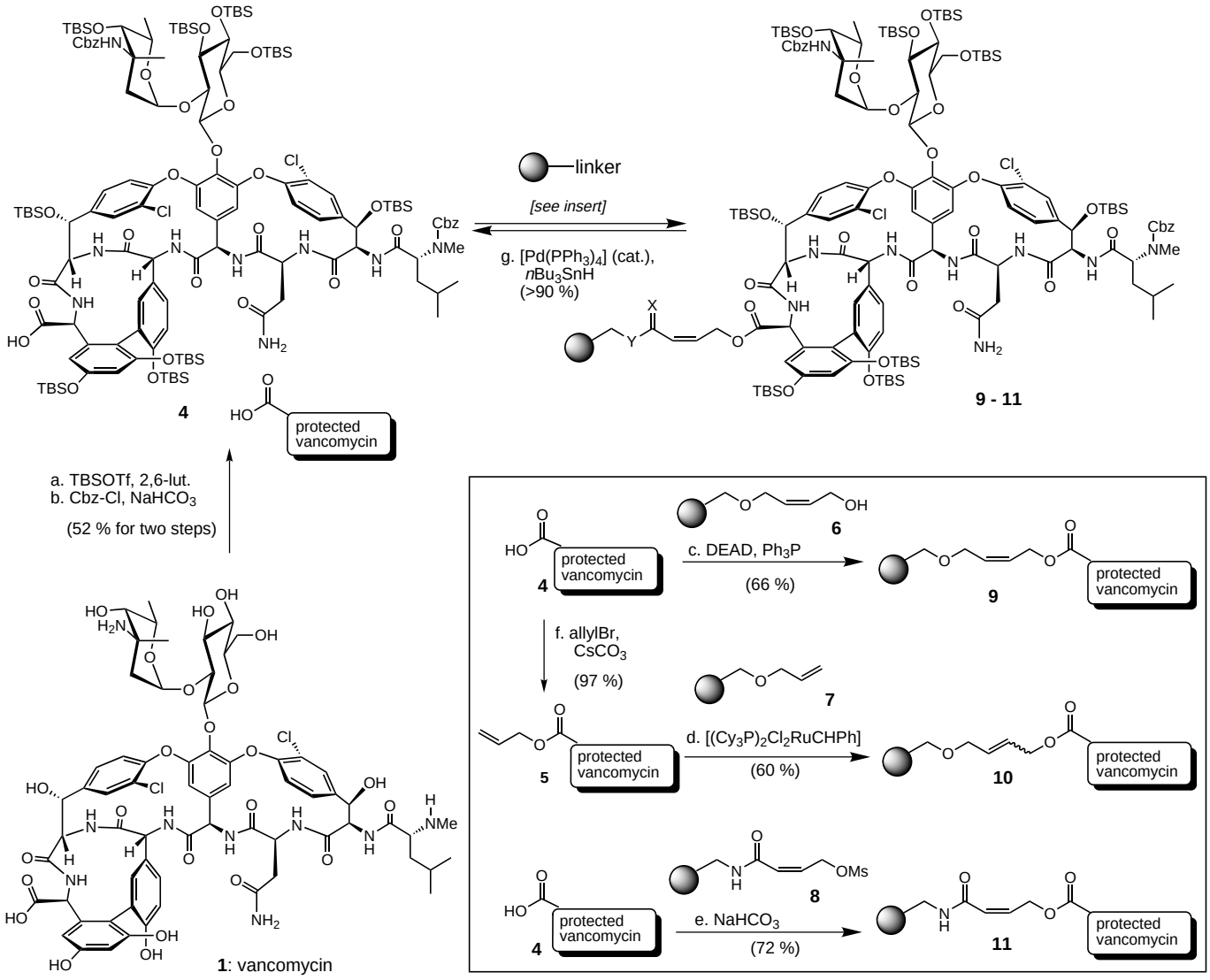


2 3

Figure 3. Photolabile linkers that failed to solve the vancomycin linker problem.

with a suitable vancomycin scaffold in low yield, presumably due to increased steric congestion. Unable to reach an acceptable compromise between loading and cleavage conditions, we turned our attention to the allyl linkers **6**, **7**, and **8** (Scheme 1).[26] Onto all three resins (**6**–**8**) a suitably protected vancomycin derivative could be efficiently loaded under mild conditions employing either Mitsunobu, olefin cross-metathesis, or alkylation reactions, respectively (see Scheme 1, insert). Importantly, vancomycin derivatives could be cleaved easily from all of the allyl resins upon exposure to palladium(0)-mediated allyl transfer conditions {[$Pd(PPh_3)_4$], nBu_3SnH}. Unfortunately, as events transpired during the solid-phase synthesis, problems with all three linkers, **6**–**8**, emerged along the charted solid-phase sequence. Specifically, after the glycosidation procedure which required Lewis acidic conditions ($BF_3 \cdot Et_2O$), the vancomycin-loaded resins **9** and **10** (Scheme 1) suffered from low cleavage efficiency, a fact attributed to a presumed [3,3]-sigmatropic rearrangement[27] as depicted in Figure 4. It was after several unsuccessful attempts to reverse this latter reaction or to otherwise improve the cleavage yield that we turned to acrylate linker, **8**, and the corresponding vancomycin-loaded resin **11** (Scheme 1). In this case the trouble-causing [3,3]-sigmatropic rearrangement was expected to be electronically disfavored,



Scheme 1. Loading of vancomycin onto a variety of allyl ester resins. a) TBSOTf (excess), 2,6-lut. (120 equiv), CH_2Cl_2/DMF 10:1, 23 °C, sonication, 8 h; b) Cbz-Cl (5.0 equiv), $NaHCO_3$ (10.0 equiv), 1,4-dioxane/H_2O 3:1, 23 °C, 3 h, 52 % over two steps; c) **6** (7.0 equiv), DEAD (7.0 equiv), Ph_3P (7.0 equiv), THF, −15 °C, 1.5 h, 66 %; d) **7** (10.0 equiv), [$(Cy_3P)_2Cl_2RuCHPh$] (2 × 0.1 equiv), benzene, 65 °C, 15 h, 60 %; e) **8** (4.0 equiv), $NaHCO_3$ (10.0 equiv), 4 Å MS, 23 °C (vacuum), 0.5 h; then 65 °C, 18 h, 72 %; f) allylBr (10.0 equiv), $NaHCO_3$ (10.0 equiv), 4 Å MS, DMF, 23 °C (vacuum), 0.5 h; then 8 h, 97 %; g) [$Pd(PPh_3)_4$] (0.1 equiv), nBu_3SnH (4.0 equiv), CH_2Cl_2, 0.5 h, 94 %. Cbz = benzyloxycarbonyl, Cy = cyclohexyl, DEAD = diethyl azodicarboxylate, DMF = *N*,*N*′-dimethylformamide, 2-6-lut. = 2-6-lutidine, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl.

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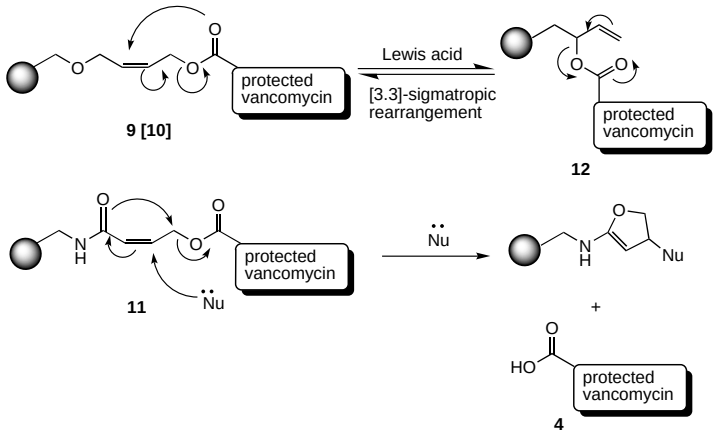


Figure 4. Presumed side reactions of allyl linkers **9**, **10**, and **11**.

and indeed the cleavage efficiency from the resin was not diminished after glycosidation. However, during further manipulation, this allylic acrylate resin was found to suffer premature cleavage, presumably due to nucleophilic addition to the acrylate moiety as rationalized in Figure 4. Reluctantly, we were forced, at this juncture, to conclude that despite the efficient loading and cleavage protocols offered by these novel allyl and acrylate resins, they were not appropriate for the solid-phase semisynthesis of vancomycin.

In searching for a solution to this problem, it occurred to us that a facile oxidation/elimination sequence involving the recently described phenylselenenyl resin[28] could be adopted to design a masked allyl group (see Figure 5). This pro-allyl

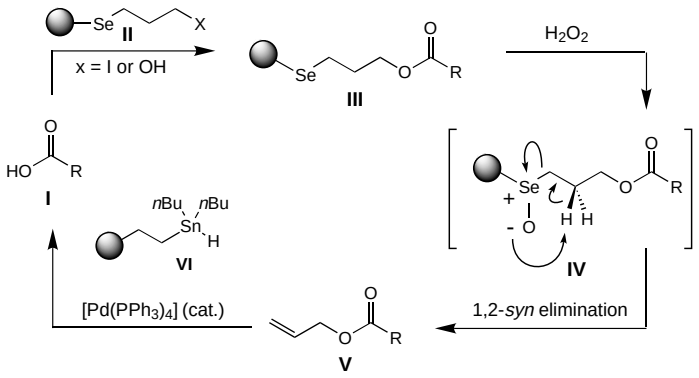
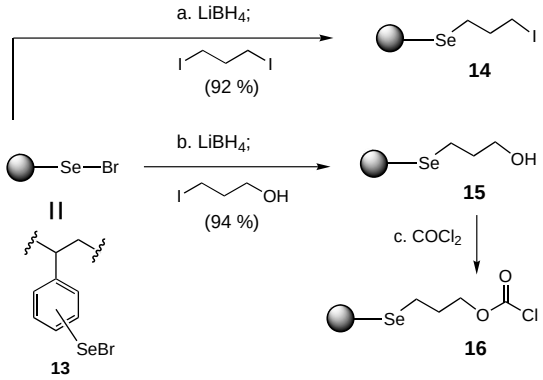


Figure 5. Conceptual framework for selenium-based pro-allyl and pro-alloc safety catch resins.

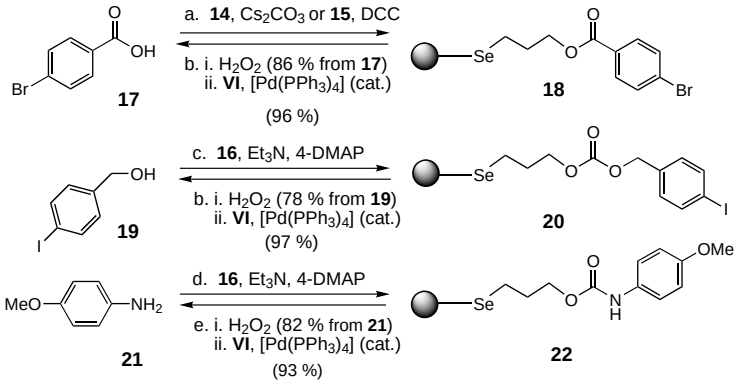
safety catch linker would retain the advantages of allyl protection for the C-terminus, but should be more stable to chemical manipulation and subsequent elaboration. The requisite pro-allyl selenium resin was easily prepared from the known selenium bromide resin **13** as shown in Scheme 2. Thus, treatment of resin **13** with $LiBH_4$ provided the corresponding lithio-selenium species which was quenched by either 1,3-diiodopropane or 3-iodopropanol to give resin **14** or **15**, respectively, and in high yield. Resin **15** was converted into the corresponding polymer-bound chloroformate by exposure to phosgene. In model reactions (see Scheme 3), both loading and cleavage proceeded smoothly for the pro-allyl and pro-alloc resins. Thus, loading of resin **14** or resin **15** with 4-bromobenzoate in the presence of Cs_2CO_3 or DCC, respectively, and subsequent cleavage with H_2O_2 and removal of the allyl group with polymer-bound tin hydride[22k, 29] and catalytic amounts of $[Pd(PPh_3)_4]$ gave **17** in 83% overall yield. The use of polymer-bound tin hydride instead of a soluble source of nBu$_3$SnH facilitates the removal of tin by-products as required for reliable biological assays. In a similar manner, pro-alloc resin was loaded with 4-iodobenzyl alcohol



Scheme 2. Synthesis of pro-allyl and pro-alloc selenium resins. a) $LiBH_4$ (1.5 equiv), THF, 0 °C, 0.5 h, wash; then 1,3-diiodopropane (4.0 equiv), THF/DMF 1:1, 23 °C, 5 h, 92%; b) $LiBH_4$ (1.5 equiv), THF, 0 °C, 0.5 h, wash; then 3-iodopropanol (4.0 equiv), THF/DMF 1:1, 23 °C, 5 h, 94%; c) $COCl_2$ (4.0 equiv), THF, 23 °C, 5 h.

(**19**) or methoxyaniline (**21**) in the presence of triethylamine and catalytic amounts of 4-DMAP to give, after cleavage and deprotection, **19** and **21** in 75 and 76% overall yield, respectively (Scheme 3). More importantly, loading of the protected vancomycin derivative **4** onto resin **14** employing $CsHCO_3$ and 4 Å MS gave polymer-bound vancomycin derivative **23** in 86% yield (Scheme 4). Cleavage facilitated by the action of H_2O_2, followed by removal of the C-terminal allyl group employing $[Pd(PPh_3)_4]$ and nBu$_3$SnH) gave non-asilylated bis-Cbz vancomycin **4** in 77% overall yield without any of the apparent drawbacks associated with the allyl and acrylate resins described above.

With a suitable linking strategy now operational, we were in a position to focus our attention on completing the solid-phase semisynthesis of vancomycin. Scheme 5 details the successful deglycosidation/reglycosidation sequence starting with the vancomycin loaded resin **23**. Thus, exposure of **23** to $TFA/Me_2S/CH_2Cl_2$ (1:1:1) caused hydrolysis of both sugar moieties and provided the polymer-bound phenol **24**. Glycosidation of this polymer-bound vancomcyin scaffold with trichloroacetimidate **25** (6.0 equiv) in the presence of $BF_3 \cdot Et_2O$ (9.0 equiv) gave the polymer-bound monosaccharide **26** in >90% yield. Liberation of the C-2 alloc-protected hydroxyl group proceeded smoothly under standard palla-

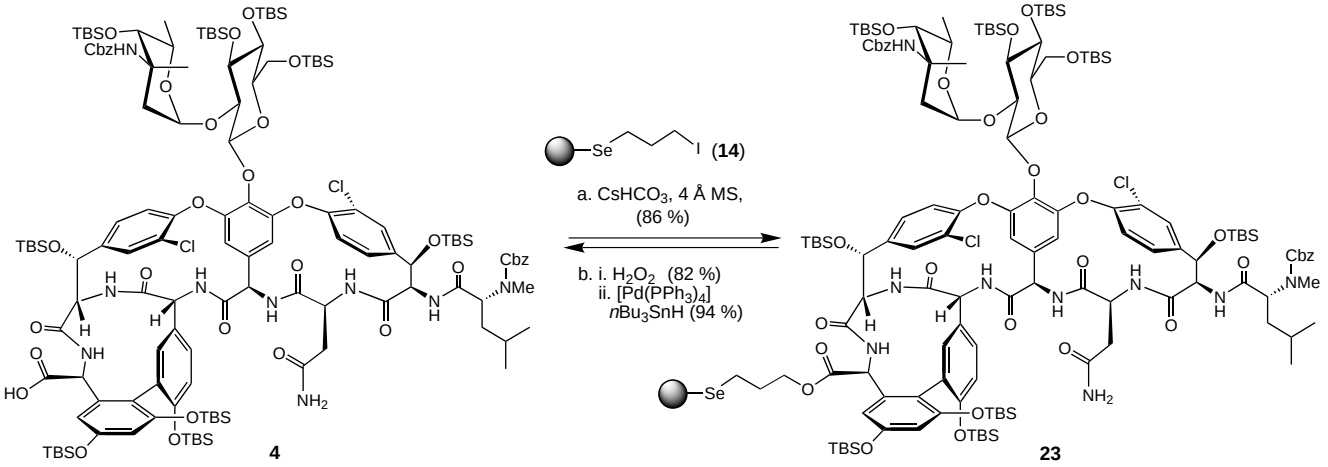


Scheme 3. Loading and cleavage of pro-allyl and pro-alloc resins. a) **4** (1.0 equiv), **17** (4.0 equiv), Cs_2CO_3 (4.0 equiv), DMF, 50 °C, 5 h or **15** (1.0 equiv), **17** (4.0 equiv), DCC (4.0 equiv), DMF, 23 °C, 15 h; b) i. H_2O_2 (2.0 equiv), THF, 23 °C, 2 h; Me_2S (4.0 equiv), 23 °C, 10 h, 86% from **14** and 78% from **15**; ii. **VI** (3.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), CH_2Cl_2, 23 °C, 0.5 h, 96% for **17** and 97% for **19**; c) **16** (4.0 equiv), Et_3N (5.0 equiv), 4-DMAP (0.1 equiv), 23 °C, 6 h; d) **16** (4.0 equiv), Et_3N (5.0 equiv), 4-DMAP (0.1 equiv), 23 °C, 3 h; e) i. H_2O_2 (2.0 equiv), THF, 23 °C, 2 h; Me_2S (4.0 equiv), 23 °C, 10 h, 82% from **21**; ii. **VI** (3.0 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), AcOH (4.0 equiv), CH_2Cl_2, 23 °C, 0.5 h, 93%. DCC = dicyclohexyldiimide, 4-DMAP = 4-dimethylaminopyridine.

dium-catalyzed allyl transfer conditions {$[Pd(PPh_3)_4]$, $n$$Bu_3SnH$} to give polymer-bound acceptor **27** in >95% yield. This result underscores the importance of the selenium-based safety catch allyl resin in terms of simplifying the choice of C-2 glucose protecting group. Glycosidation of the newly formed acceptor **27** with vancosamine glycosyl fluoride **28** (4.0 equiv) under the influence of $BF_3 \cdot Et_2O$ gave the fully protected, polymer-bound vancomycin derivative **29** in >85% yield. Oxidative cleavage of resin **29** with H_2O_2 yielded the allyl protected vancomycin derivative **5** in 80% yield. Treatment of the released compound **5** with K_2CO_3 in MeOH induced cleavage of the acetates and the phenol-bound silyl groups, and subsequent removal of the remaining TBS groups with CsF in DMF gave the bis-Cbz-*O*-allyl ester derivative **30** in 53% overall yield. Removal of the C-terminal allyl protecting group {$[Pd(PPh_3)_4]$, $n$$Bu_3SnH$}, followed by transfer hydrogenation (10% Pd/C, NH_3CO_2H), provided synthetic vancomycin (**1**) in 76% overall yield for the two steps. The four-step deprotection sequence proceeded smoothly and required only two purifications (after the CsF step, and then at the final stage).

Semisynthesis of vancomycin monosaccharide analogues: The development of the solid-phase semisynthesis of vancomycin provided a convenient route through which various vancomycin analogues could be rapidly accessed. Our initial proposal was to replace vancomycin's disaccharide segment with a new saccharide unit in order to furnish a vancomycin monosaccharide library. The synthesis proceeded as summarized in Scheme 6.

Thus, persilylation of vancomycin hydroxyl groups followed by alloc protection of both basic nitrogens (a choice that will save a deprotection step) yielded vancomycin derivative **31**. Compound **31** was then loaded onto the selenium resin **14**, via the carboxylic acid group, by the action of $CsHCO_3$ and 4 Å MS and from the resulting conjugate was removed the glycosyl moiety (TFA/Me_2S/CH_2Cl_2 1:1:1) to give intermediate **32**. For the purposes of introducing amino sugar moieties we chose to employ suitably protected azide sugars. Thus, for the attachment of the sugar moieties onto the phenol scaffold **32** we utilized the corresponding trichloroacetimidates (**33**, see Figure 6) in the presence of excess $BF_3 \cdot Et_2O$ which gave polymer-bound vancomycin glycosides **34**. An azide reduction-acylation sequence was then used to produce a number of analogues. Thus, polymer-bound azide **34** was treated with Et_3P under carefully controlled conditions (5.0 equiv Et_3P, THF/H_2O 10:1, 23 °C) to avoid acyl transfer from the neighboring position, and subsequently acylated with a variety of acid chlorides (RCOCl) to afford a series of polymer-bound amides **35** (azide reduction under standard Staudinger conditions (Ph_3P, 60 °C) resulted in complete transfer of the neighboring acetate to give the undesired hydroxy acet-



Scheme 4. Application of the pro-allyl selenium-based safety catch linker to the vancomycin problem. a) **14** (8.0 equiv), $CsHCO_3$ (5.0 equiv), DMF, 23 °C (vacuum), 0.5 h, 50 °C, 5 h, 86%; b) i. H_2O_2 (2.0 equiv), THF, 23 °C, 2 h; Me_2S (4.0 equiv), 23 °C, 48 h, 82%; ii. $[Pd(PPh_3)_4]$ (0.1 equiv), $n$$Bu_3SnH$ (4.0 equiv), CH_2Cl_2, 0.5 h, 94%.

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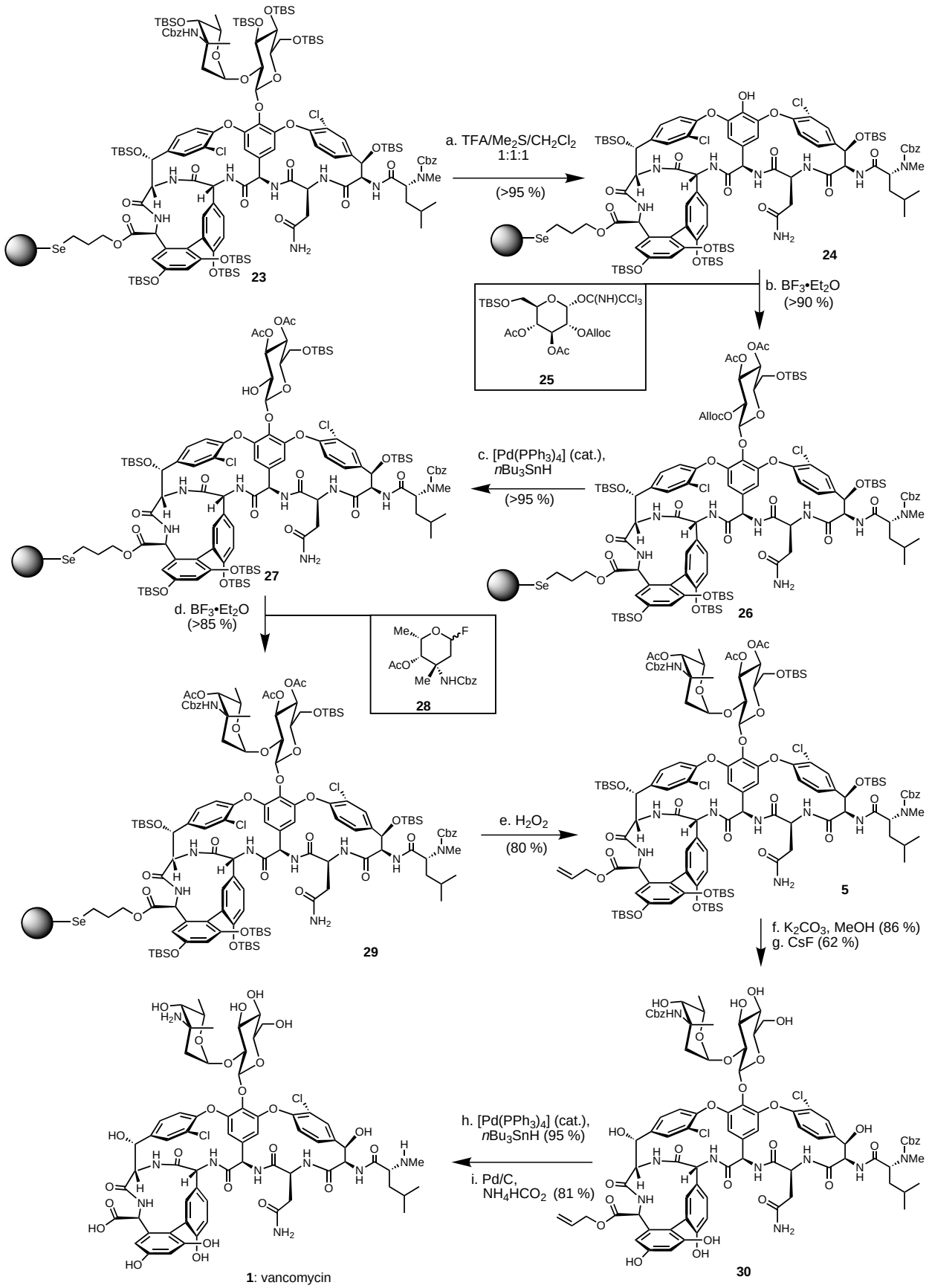
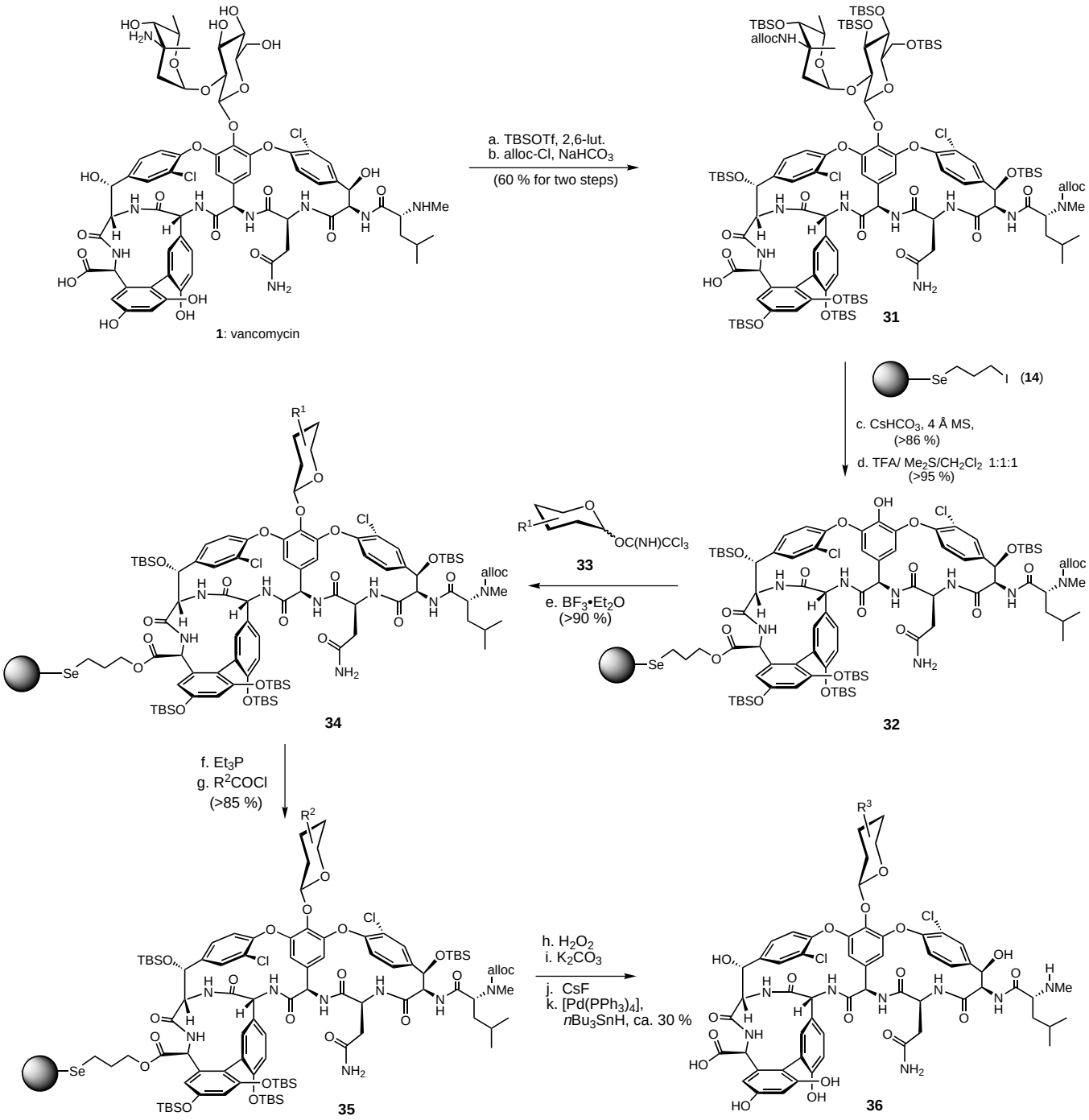


Scheme 5. Solid-phase semisynthesis of vancomycin (**1**). a) TFA/Me_2S/CH_2Cl_2 1:1:1, 23 °C, 3 h, >95 %; b) **25** (6.0 equiv), $BF_3 \cdot Et_2O$ (9.0 equiv), 4 Å MS, $-40 \rightarrow 0$ °C, 12 h, >90 %; c) $[Pd(PPh_3)_4]$ (0.1 equiv), nBu_3SnH (10.0 equiv), CH_2Cl_2, 23 °C, 2 h, >95 %; d) **28** (4.0 equiv), $BF_3 \cdot Et_2O$ (6.0 equiv), 4 Å MS, $-40 \rightarrow 0$ °C, 4 h, >85 %; e) H_2O_2, THF, 23 °C, 48 h, 80 %; f) K_2CO_3, MeOH, 23 °C, 6 h, 86 %; g) CsF, DMF, 23 °C, 15 h, 62 %; h) $[Pd(PPh_3)_4]$ (0.1 equiv), nBu_3SnH, DMF, 23 °C, 1 h, 95 %; i) 10 % Pd/C, NH_4HCO_2, H_2O/AcOH 1:1, 23 °C, 4 h, 81 %. Ac = acetate, TFA = trifluoroacetic acid.



Scheme 6. Solid-phase semisynthesis of a library of vancomycin monosaccharides **36**. a) TBSOTf (60 equiv), 2,6-lut. (120 equiv), CH_2Cl_2/DMF 10:1, 23 °C, sonication, 8 h; b) alloc-Cl (5.0 equiv), $NaHCO_3$ (10.0 equiv), 1,4-dioxane/H_2O 3:1, 23 °C, 3 h, 60 % over two steps; c) **14** (8.0 equiv), $CsHCO_3$ (5.0 equiv), DMF, 23 °C (vacuum), 0.5 h, 50 °C, 5 h, 86 %; d) TFA/Me_2S/CH_2Cl_2 1:1:1, 23 °C, 3 h, >95 %; e) trichloroacetimidate **33** (5.0 equiv), $BF_3 \cdot Et_2O$ (7.5 equiv), $-40 \rightarrow 0$ °C, CH_2Cl_2, 12 h, >90 %; f) Et_3P (5.0 equiv), THF/H_2O 10:1, 23 °C, 4 h; g) R^2COCl (5.0 equiv), Et_3N (10.0 equiv), CH_2Cl_2, 8 h, >85 % (for two steps); h) H_2O_2, THF, 23 °C, 48 h; i) K_2CO_3 (10.0 equiv), MeOH, 23 °C, 6 h; j) CsF (5.0 equiv), DMF, 23 °C, 15 h; k) $[Pd(PPh_3)_4]$ (0.25 equiv), nBu$_3$SnH (10.0 equiv), DMF, 23 °C, 1 h (30 % for three steps). alloc = allyloxycarbonyl, see Figure 6 for the respective trichloroacetimidates **33**.

amide). A cleavage/deprotection sequence similar to that developed for the vancomycin semisynthesis, as summarized in Scheme 6, provided an initial library of vancomycin analogues for biological evaluation.

Table 1 includes the structures of the synthesized compounds along with MIC values against vancomycin-susceptible strains, vancomycin-intermediate resistant strains, and a vancomycin-resistant strain. The monosaccharide vancomycin derivatives were found to be uniformly less active than the parent vancomycin against all strains examined. The location of the amino group appears to be important as evidenced by the fact that compounds **36a** and **36b** (amine at the C-6 position of glucose) are at least two-fold more active than compound **36c** (amine at the C-3 position of glucose). Also, these results show that incorporation of a moderate degree of lipophilicity (compounds **36d** and **36e**) leads to a further

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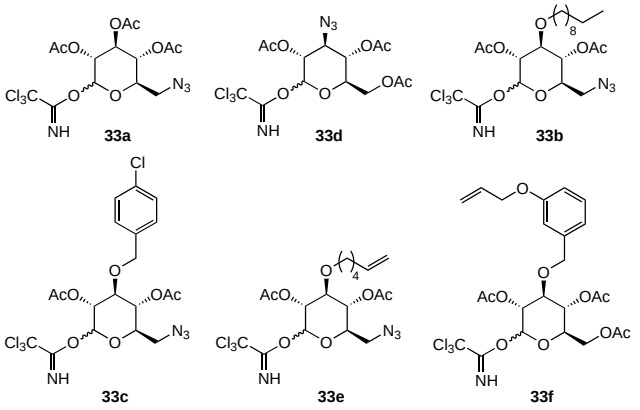


Figure 6. Trichloroacetimidates **33** used for the generation of vancomycin-derived monosaccharides.

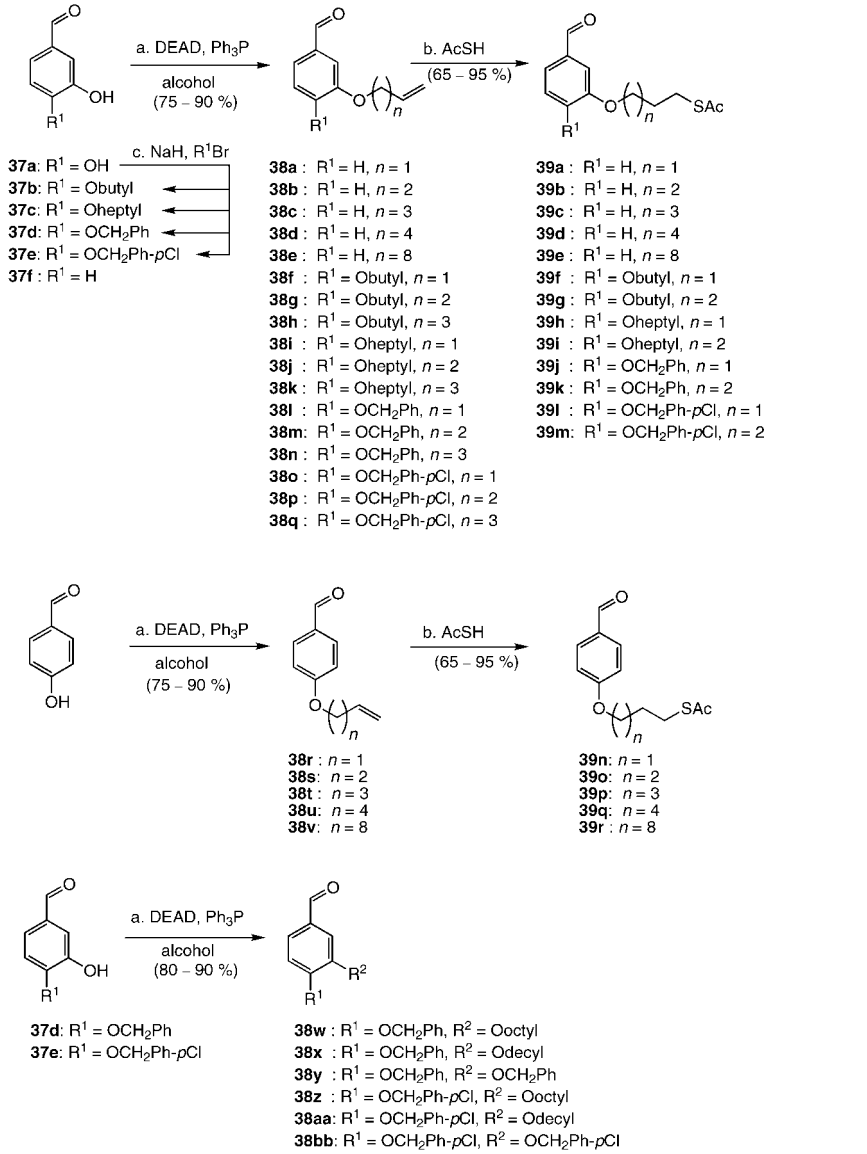
restoration of activity; however, too much lipophilicity has deleterious effects on antibacterial activity as demonstrated by compound **36 f**. The conclusion from this initial study was that retaining both sugar moieties on vancomcyin was a more desirable feature for the eventual development of highly potent vancomycin analogues.

Olefinic and thioacetate vancomycin analogues: Having recognized the importance of the vancosamine moiety for antibacterial activity we proceeded to design and synthesize a new series of vancomycin analogues with the intact skeleton of the molecule in place. Since regioselective derivatization of either of vancomycin's two amino groups had already been demonstrated, initial strategies toward such compounds proceeded through intermediates derived via such chemical manipulation. Interestingly, the antibacterial activity of some of these newly synthesized monomeric vancomycin derivatives rivaled the action of some of the most effective, previously known, antibacterial agents against vancomycin-resistant strains as will be discussed below.

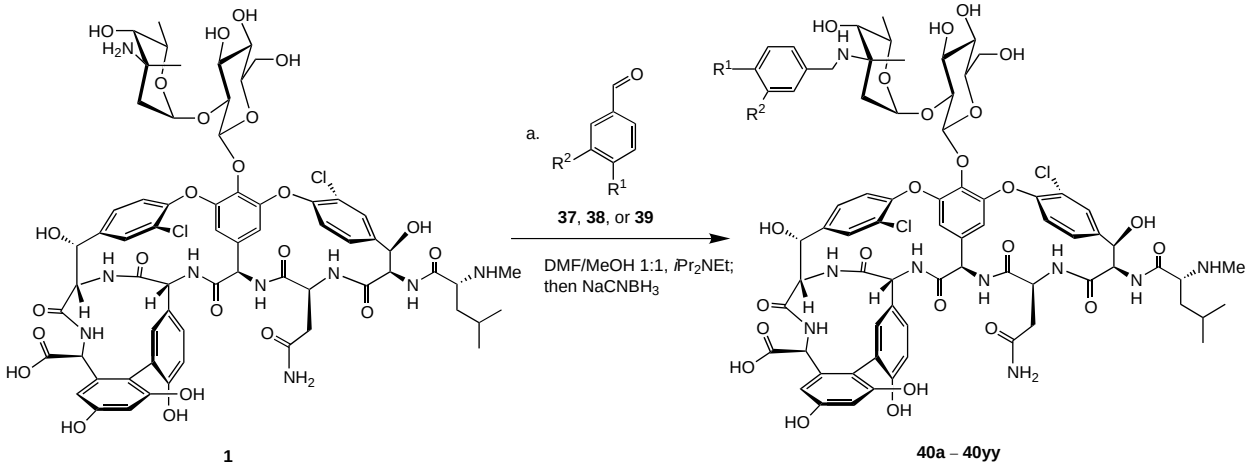
Construction of these analogues began with the synthesis of the requisite benzaldehyde derivatives (**37**–**39**, see Scheme 7) from the appropriate phenols by initial Mitsunobu reaction followed by a radical-based regioselective thioacetate addition to the terminal double bond.

Scheme 8 summarizes the synthesis of the targeted compounds in which regioselective reductive amination at the vancosamine site was the key step. Reaction of vancomycin with aldehydes **37**, **38**, or **39** in the presence of $i\mathrm{Pr_2NEt}$ followed by addition of $NaCNBH_3$ at 65 °C led to compounds **40 a**–**yy**. The presence of $i\mathrm{Pr_2NEt}$ was found, in our experience, to be essential for ensuring smooth conversion and high regioselectivity. As depicted in Figure 7, the regioselectivity of the reaction was evident from mass spectroscopic fragmentation and ^{1}H NMR analysis of the products **40** obtained.

Compounds synthesized in this manner were evaluated for their antibacterial activity against a variety of vancomycin-



Scheme 7. Preparation of substituted benzaldehydes **37**–**39** used in the preparation of vancomycin derivatives. a) DEAD (1.5 equiv), Ph_3P (1.5 equiv), alcohol (1.5 equiv), THF, 23 °C, 4 h; b) AcSH (2.0 equiv), AIBN (0.2 equiv), benzene, 85 °C, 2 h; c) NaH (1.0 equiv), R^1Br (1.0 equiv), DMF, 0 → 23 °C, 12 h. AIBN = 2,2′-azobisisobutyronitrile, alcohol = allyl alcohol or 3-buten-1-ol or 4-penten-1-ol or 5-hexen-1-ol or 9-decen-1-ol or 1-hexanol or 1-octanol or benzyl alcohol or *p*-chlorobenzyl alcohol, R^1Br = butyl bromide, heptyl bromide, benzyl bromide, *p*-chlorobenzyl bromide.



Scheme 8. Regioselective reductive alkylation of vancomycin (**1**) with benzaldehyde derivatives **37**–**39**. a) **37**, **38**, or **39** (1.1 equiv), iPr$_2$NEt (1.2 equiv), DMF/MeOH 1:1, 65 °C, 2 h; then NaCNBH$_3$ (2.0 equiv), 65 °C, 2 h. See Tables 2, 3, and 4 for definitions of R^1 and R^2.

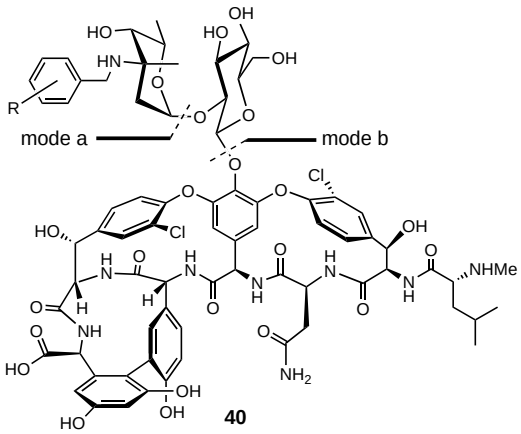


Figure 7. Molecular fragmentation of alkylated vancomycins **40** during mass spectrometric analysis. Both modes of fragmentation (a and b) are diagnostic for determining the site of reductive amination (vancosamine or amino acid 1).

susceptible, vancomycin-intermediate resistant, and vancomycin-resistant bacteria, and these data are summarized in Table 2 and Table 3, respectively. Most interestingly, several of the compounds tested exhibited good activity against VRE (strain L4001). Specifically, olefins **40d** and **40i** (Table 2), showed an MIC value of 8 μg mL^{-1} against L4001 and olefins **40h** and **40k**–**p** demonstrated potencies in the range of 1 to 2 μg mL^{-1} against this strain. Similarly, the lipophilic thioacetates **40dd** and **40kk**–**oo** (Table 3) exhibited good antibacterial activity with MIC values ranging from 2–4 μg mL^{-1}. Perhaps, the lower potencies of the thioacetates as compared to their olefinic counterparts are due to their more polar terminus, which renders them less capable of anchoring into the bacterium's membrane. Interestingly, the chlorobenzyl thioacetate derivatives **40pp** and **40qq** were found to be twofold more active than the corresponding benzyl derivatives **40nn** and **40oo**. It is tempting to speculate that this observation is a manifestation of an additional localizing effect by the chlorine atom on the bacterium's cell wall as a similar effect has been postulated in attempting to rationalize the remarkable activity of Ly333328.[30] Further results and analysis are, however, required before final judgment as to the cause of this effect.[31] In order to determine the antibacterial spectrum of activity of these lipophilic vancomycin derivatives we screened a select number of compounds against a larger set of vancomycin-resistant strains. The collected data are summarized in Table 4. Interestingly, while the moderately lypophilic compounds **40ii**, **40dd**, **40ss**, **40vv**, and **40ww** exhibited good activity against a range of vancomycin-resistant bacteria, the much more lipophilic compounds **40xx** and **40yy** showed almost no activity. These observations are consistent with previously reported results[15] suggesting that too much lipophilicity is detrimental to the antibacterial activity.

Amino acid core modified vancomycin derivatives: A small number of N-terminus modified vancomycin analogues were also synthesized and tested as shown in Table 2 (**40q**–**y**). While none of these compounds were as active as vancomycin itself against the strains examined, some of them exhibited significant activity against a number of strains. This phenomenon most likely reflects the diminished, but not extinct, ability of these compounds to bind to their target[32] within the bacterial cell-wall. In order to probe the effect of such substitutions further, we proceeded to apply solid-phase chemistry to construct an expanded library of vancomycin with various amino acids attached at the N-terminus of the molecule.

The strategy for the synthesis of the vancomycin monomers described above is depicted in Scheme 9. Thus, selective Boc protection of vancomycin (**1**) on the N-terminus followed by reductive alkylation under standard conditions (1.1 equiv **39e** or **40e**, 1.4 equiv iPr$_2$NEt; then NaCNBH$_3$, 65 °C) cleanly afforded **42a** or **42b**, respectively. Boc protection facilitated the large-scale procurement of material as it allowed the reductive alkylation to be driven to completion with absolute regioselectivity. Removal of the Boc group with dilute TFA followed by Edman degradation[33] gave vancomycin hexapeptide **40x** or **44**. The preceding sequence could be conducted with no other purification necessary other than

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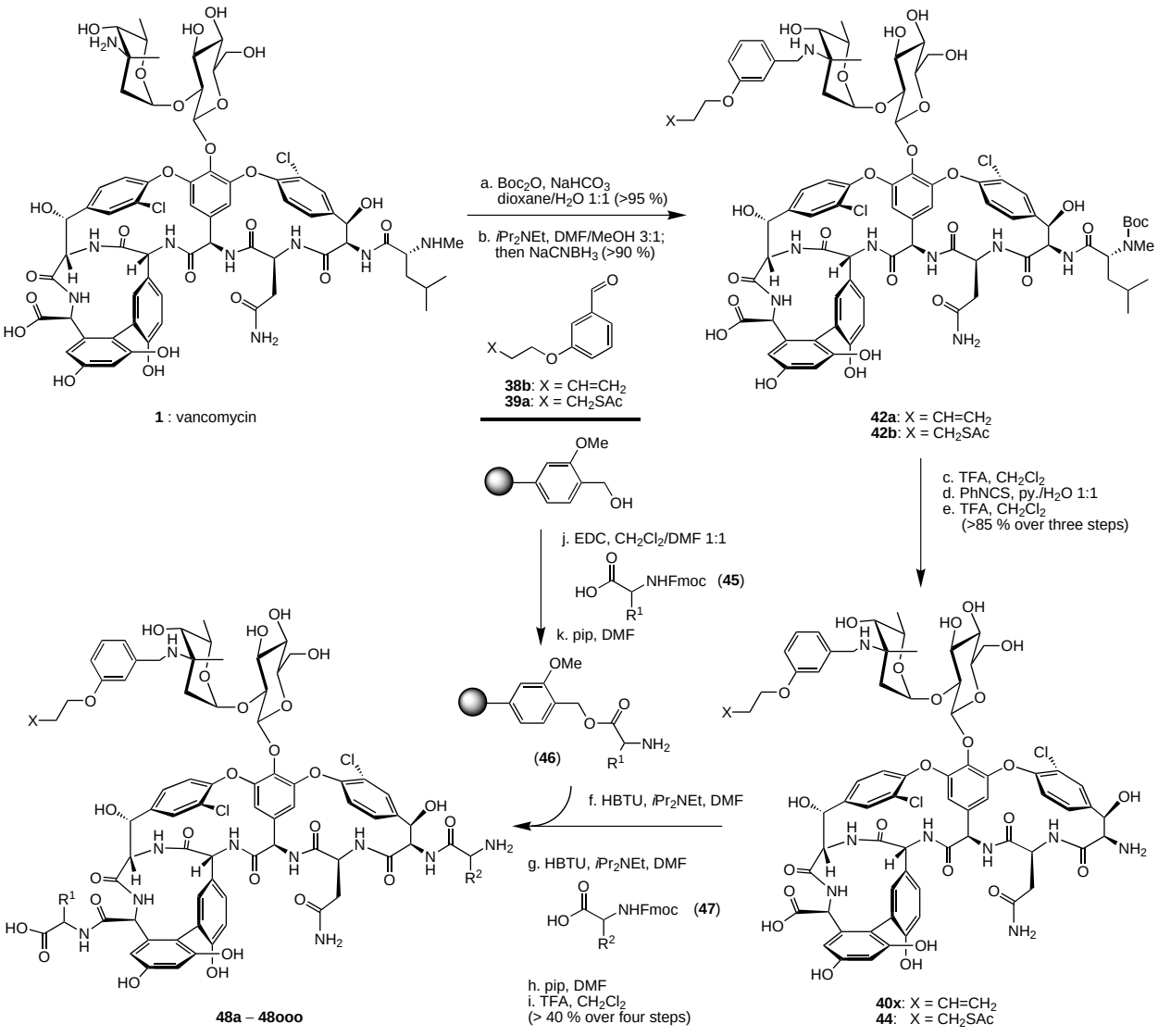

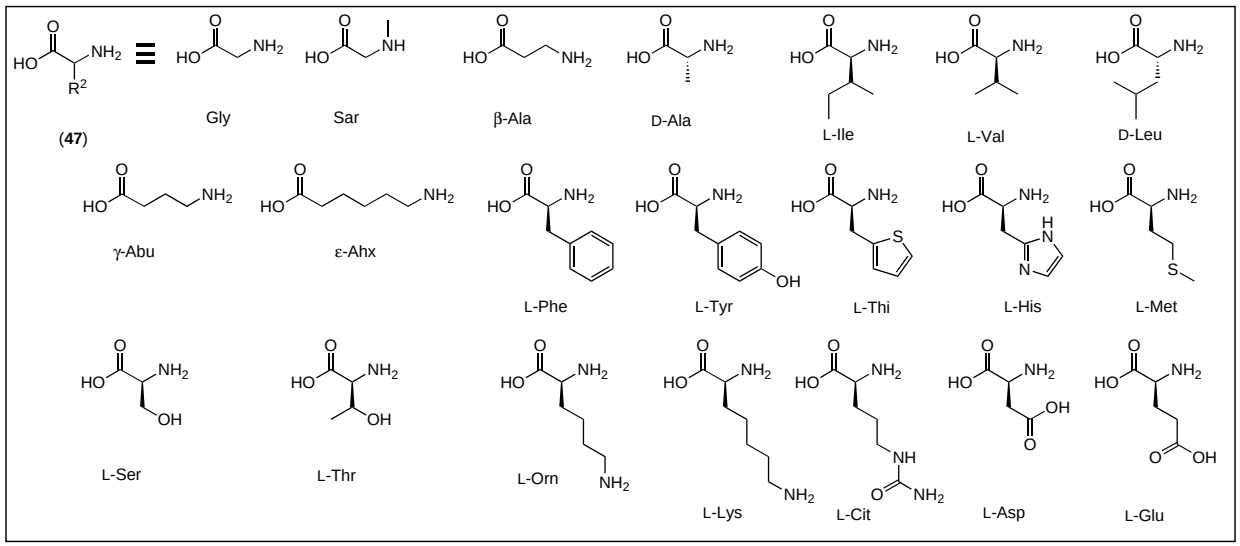

Scheme 9. Solid-phase synthesis of vancomycin analogues **48a**–**48ooo**. a) Boc_2O (1.2 equiv), $NaHCO_3$ (2.0 equiv), dioxane/H_2O 1:1, 23 °C, 4 h; b) **39e** or **40e** (2.0 equiv), iPr_2NEt (2.5 equiv), $NaCNBH_3$ (2.2 equiv), 65 °C, 20 h; c) 10% TFA in CH_2Cl_2, 23 °C, 1 h, 90%; d) PhN=C=S (1.2 equiv), pyridine/H_2O 1:1, 23 °C, 2 h, 100%; e) 10% TFA in CH_2Cl_2, 23 °C, 2 h, 75%; f) iPr_2NEt (6.0 equiv), HBTU (3.0 equiv), DMF, 23 °C, 1 h; g) amino acid Fmoc-derivative (3.0 equiv), iPr_2NEt (4.0 equiv), HBTU (2.0 equiv), DMF, 23 °C, 2 h; h) 5% piperidine in DMF, 30 min, 23 °C; i) 5% TFA in CH_2Cl_2, 2 h, 23 °C; j) EDC (3 equiv), **45** (2.5 equiv), DMF/CH_2Cl_2 (1:1), 23 °C, 4 h; k) 5% piperidine in DMF, 23 °C, 1 h. EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HBTU = *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, pip = piperidine, py = pyridine.

filtration. In further experiments and in order to expedite the synthesis of several monomers, the vancomycin scaffold was loaded onto a solid support by a method similar to that used by Griffin.[34] Thus, treatment of hexapeptide **40x** or **44** with polymer-bound amino acid **46** for one hour in the presence of HBTU gave a polymer-bound heptapeptide (Scheme 9). Coupling of Fmoc-protected amino acids to the polymer-bound heptapeptide proceeded rapidly in the presence of HBTU leading to an octapeptide which was deprotected and cleaved from the solid support as follows: i) exposure to piperidine; and ii) treatment with dilute TFA. The amino acid building blocks shown in Scheme 9 were utilized in this sequence to produce a small library of analogues which was screened against a range of vancomycin-susceptible, vancomycin-intermediate resistant and vancomycin-resistant strains. Table 5 summarizes some of the results from the antibacterial activity assays for the most active compounds synthesized in Scheme 9. The remaining compounds showed little, if any, activity against the strains examined, confirming the low profitability of this substitution pattern.[35]

Conclusion

In conclusion, we have accomplished the solid-phase semisynthesis of vancomycin (**1**) and in the process developed a selenium-based safety catch linker which may enjoy wider applicability to the solid-phase manipulation of polyfunctional natural products and other molecules of medicinal interest. Using the methods developed, we designed and synthesized several vancomycin libraries with molecular diversity at the sugar moieties, the amino acid 1 site, and the C-terminus. Biological evaluation of these analogues, revealed several highly potent compounds effective against vancomycin-resistant strains. Among them were a few which rival the most active agents known in this series. Most importantly, this work set the stage for the next phase of the program which aimed at producing covalently linked dimeric vancomycin constructs, some of which proved to be extremely potent against vancomycin-resistant bacteria. The following article describes these investigations.

Experimental Section

General: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF), toluene and diethyl ether were distilled from sodium/benzophenone, and methylene chloride (CH_2Cl_2) from calcium hydride. Anhydrous solvents were also obtained by passing them through commercially available alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at highest available commercial quality and used without further purification unless otherwise stated. NMR spectra were recorded on Bruker DRX-600, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Semipreparative HPLC was performed on either a VYDAC C18, 10 mm × 250 mm, column with flow rate 3.5 mL min^{-1}, 0 → 100% CH_3CN in H_2O over 20 min or on VYDAC C18, 25 mm × 250 mm, column with flow rate 6.5 mL min^{-1}, 0 → 100% CH_3CN in H_2O over 30 min. High resolution mass spectra were obtained by MALDI on a VG AZB ZSE spectrometer. LCMS was performed on a Hewlett–Packard 1100 series system.

***N,N′*-Di-Cbz-nona-TBS-vancomycin (4)**: TBSOTf (47.6 mL, 207 mmol) was added dropwise to a solution of vancomycin·HCl (2.00 g, 1.35 mmol) and 2,6-lutidine (18.8 mL, 161 mmol) in CH_2Cl_2/DMF (10:1, 13.3 mL) at 0 °C. The reaction mixture was sonicated for 8 h keeping the temperature below 35 °C. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ (200 mL) and the resulting mixture was stirred at 25 °C for 12 h. The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 150 mL). The combined organic layers were dried ($MgSO_4$), concentrated on a rotary evaporator and the residue obtained was purified by flash column chromatography (silica gel, 1 → 8% MeOH in CH_2Cl_2) to afford nona-TBS-vancomycin as a white foam (2.22 g, 65%). A solution of this compound (4.00 g, 1.62 mmol, 1.0 equiv) in dioxane/H_2O (10:1, 36 mL) was treated sequentially with solid $NaHCO_3$ (1.36 g, 16.0 mmol, 10.0 equiv) and CbzCl (1.32 g, 8.08 mmol, 5.0 equiv) at 0 °C. After stirring for 3 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and 4-DMAP (196 mg, 1.62 mmol, 1.0 equiv). The mixture was stirred for 6 h at ambient temperature and then extracted with Et_2O (3 × 120 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 0 → 4% MeOH in CH_2Cl_2) to provide *N,N′*-di-Cbz-nona-TBS-vancomycin (**4**) (3.54 g, 80%) as a white foam. **4**: $R_f = 0.36$ (silica gel, 5% MeOH in CH_2Cl_2); ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.65$ (d, $J = 1.5$ Hz, 1H), 7.52 (dd, $J = 7.0$, 1.5 Hz, 1H), 7.36–7.20 (m, 15H), 7.06 (d, $J = 1.5$ Hz, 1H), 6.99 (dd, $J = 7.0$, 1.5 Hz, 1H), 7.04 (s, 1H), 6.77 (d, $J = 8.5$ Hz, 1H), 6.57 (d, $J = 1.0$ Hz, 1H), 6.39 (d, $J = 2.0$ Hz, 1H), 6.06 (d, $J = 4.0$ Hz, 1H), 5.77 (s, 1H), 5.75 (s, 1H), 5.61 (s, 1H), 5.42 (d, $J = 3.0$ Hz, 1H), 5.33 (s, 1H), 5.13 (br d, $J = 1.0$ Hz, 1H), 5.00 (d, $J = 16.5$ Hz, 1H, Cbz), 4.92 (d, $J = 16.5$ Hz, 1H, Cbz), 4.88 (s, 1H), 4.86–4.83 (m, 1H), 4.71–4.68 (m, 1H), 4.61 (s, 1H), 4.58 (s, 2H), 4.47 (q, $J = 7.0$ Hz, 1H), 4.27 (t, $J = 1.0$ Hz, 1H), 4.22 (d, $J = 2.0$ Hz, 1H), 4.13–4.07 (m, 2H), 4.02 (d, $J = 10.0$ Hz, 1H), 3.94–3.91 (m, 2H), 3.60 (s, 1H), 2.91 (s, 3H), 2.46–2.38 (m, 2H), 1.96 (dd, $J = 10.0$, 4.0 Hz, 1H), 1.83–1.80 (m, 2H), 1.59 (s, 3H), 1.58–1.47 (m, 2H), 1.03 (d, $J = 6.5$ Hz, 3H), 1.01 (s, 9H), 0.93 (s, 9H), 0.96–0.92 (m, 6H), 0.90 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.84 (s, 9H), 0.73 (s, 9H), 0.61 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), 0.18 (s, 3H), 0.16 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 6H), 0.06 (s, 3H), 0.05 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), −0.02 (s, 3H), −0.03 (s, 3H), −0.09 (s, 3H); HRMS: calcd for $C_{137}H_{215}Cl_2N_9O_{28}Si_9Cs$ $[M+Cs]^+$: 2889.2032, found 2889.2237.

Preparation of resin 14: $LiBH_4$ (1.5 equiv) was added at 0 °C to a stirred suspension of resin **13** (5.0 g, 1.0 equiv) in THF (60 mL). After 30 min the resin had completely decolorized. After removal of the supernatant and washing of the resin with THF (150 mL) the resin was re-suspended in THF/DMF (1:1, 50 mL). To this suspension was added at 23 °C, 1,3-diiodopropane (4.0 equiv) and the suspension gently stirred for 5 h. Filtration of the reaction mixture and washing of the resin with CH_2Cl_2 (200 mL), MeOH (200 mL), and Et_2O (200 mL) provided resin **14**.

Polymer-bound protected vancomycin 23: Protected vancomycin carboxylic acid **4** (3.20 g, 1.17 mmol, 1.0 equiv) was dissolved in DMF (80 mL) and $CsHCO_3$ (1.13 g, 5.85 mmol, 5.0 equiv) and flame-dried 4 Å MS (1.0 g) were added. The reaction mixture was stirred under reduced pressure (vacuum pump) for 30 min after which time the resin (**14**) (6.00 g, 9.0 mmol, 7.7 equiv) was added. The reaction mixture was stirred at 50 °C for 5 h, then filtered and washed with Et_2O (400 mL). The resin was dried to a constant weight of 8.71 g (89% yield based on mass gain). The calculated loading of this resin was 0.119 mmol g^{-1}.

Polymer-bound vancomycin aglycon 24

Hydrolysis of disaccharide from resin 23: The resin **23** (8.49 g, 1.01 mmol) was suspended in CH_2Cl_2 (30 mL) and Me_2S (30 mL) and then treated with TFA (30 mL) and stirred gently for 3 h (the reaction mixture turns deep red). The reaction mixture was then diluted with Et_2O (100 mL), filtered, washed (CH_2Cl_2 2 × 200 mL, MeOH 2 × 200 mL, Et_2O 2 × 200 mL) and dried to a constant weight of 7.51 g. A small portion of the resin was cleaved and the product obtained was analyzed **24**: ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.69$ (br s, 2H), 7.54 (dd, $J = 8.0$, 1.0 Hz, 1H), 7.42 (s, 1H), 7.35–7.30 (m, 6H), 7.12 (d, $J = 2.0$ Hz, 1H), 7.01 (dd, $J = 8.5$, 2.0 Hz, 1H), 6.79 (d, $J = 8.5$ Hz, 1H), 6.78–5.85 (m, 1H), 6.41 (d, $J = 2.0$ Hz, 1H), 6.38 (d, $J =$

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2.0 Hz, 1H), 5.92 (ddt, $J = 16.0, 8.0, 6.5$ Hz, 1H), 5.68 (s, 1H), 5.48 (m, 1H), 5.36 (s, 2H), 5.35 (ddt, $J = 16.0, 1.5, 1.5$ Hz, 1H), 5.22 (ddt, $J = 8.0, 1.5, 1.5$ Hz, 1H), 5.22–5.17 (m, 2H), 4.96 (brs, 2H), 4.90–4.83 (m, 1H), 4.77–4.70 (m, 1H), 4.72 (dddd, $J = 10.0, 6.5, 1.5, 1.5$ Hz, 1H), 4.61 (s, 1H), 4.72 (dddd, $J = 10.0, 6.5, 1.5, 1.5$ Hz, 1H), 4.11 (s, 1H), 2.93 (s, 3H, NCH_3), 2.45–2.39 (m, 2H), 1.84–1.81 (m, 1H), 1.53–1.45 (m, 2H), 1.01 (s, 9H), 0.94 (s, 9H), 0.93–0.90 (m, 6H), 0.86 (s, 9H), 0.75 (s, 9H), 0.64 (s, 9H), 0.23 (s, 6H), 0.18 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.02 (s, 3H), −0.09 (s, 3H); MS (ES): calcd for $C_{94}H_{132}Cl_2N_8O_{19}Si_5$ $[M+H]^+$: 1889.1, found 1889.1.

Vancomycin monosaccharide 26

Glycosidation of polymer-bound phenol 24: Glucose imidate **25**[20a] (915 mg, 1.51 mmol) was azeotroped with benzene (3 × 10 mL) and then dried under high vacuum for 1 h. The imidate was then transferred as a CH_2Cl_2 (15 mL) solution to a flask containing resin **24** (2.00 g, 0.252 mmol) and flame-dried 4 Å MS (1.0 g). This mixture was stirred at ambient temperature for 2 h, then cooled to −40 °C and $BF_3 \cdot Et_2O$ (330 μL, 2.26 mmol) was added dropwise. The reaction mixture was allowed to warm up to 0 °C over the course of 12 h. The reaction mixture was cooled back to −40 °C and quenched with Et_3N (0.64 mL, 4.56 mmol, 2.0 equiv relative to $BF_3 \cdot Et_2O$). The resin was filtered and washed (MeOH 2 × 20 mL and CH_2Cl_2 2 × 20 mL). A small portion of this resin was cleaved and the product obtained was analyzed **26**: $R_f = 0.33$ (silica gel, 5% MeOH in CH_2Cl_2); ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.64$ (brs, 2H), 7.39–7.24 (m, 8H), 7.06 (m, 1H), 7.01 (dt, $J = 8.5, 2.0$ Hz, 1H), 6.79 (d, $J = 8.5$ Hz, 1H), 6.78–5.85 (m, 1H), 6.42 (d, $J = 2.0$ Hz, 1H), 6.40 (d, $J = 2.0$ Hz, 1H), 5.92 (m, 2H), 5.72 (d, $J = 7.0$ Hz, 1H), 5.52–5.44 (m, 3H), 5.40 (s, 2H), 5.35 (m, 2H), 5.33–5.26 (m, 3H), 5.22 (m, 2H), 5.23–5.16 (m, 2H), 5.05–5.02 (m, 1H), 4.96 (brs, 2H), 4.93–4.92 (m, 1H), 4.89–4.83 (m, 1H), 4.77–4.70 (m, 1H), 4.72–4.58 (m, 6H), 4.61 (s, 1H), 4.43 (m, 1H), 4.19 (m, 1H), 4.10 (s, 1H), 3.92–3.74 (m, 2H), 3.62 (m, 1H), 2.94 (s, 3H), 2.45–2.39 (m, 2H), 2.01 (s, 6H), 1.84–1.81 (m, 1H), 1.53–1.45 (m, 2H), 1.29 (s, 9H), 1.11 (s, 9H), 0.93–0.90 (m, 6H), 0.88 (s, 9H,), 0.77 (s, 9H), 0.61 (s, 9H), 0.25 (s, 6H), 0.14 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.02 (s, 3H), −0.08 (s, 3H), −0.10 (s, 3H), −0.14 (s, 3H); MS (ES): calcd for $C_{114}H_{164}Cl_2N_8O_{28}Si_6$ $[M+H]^+$: 2334.2, found 2334.3.

Vancomycin monosaccharide alcohol 27

Removal of the alloc group from 26: Resin **26** (1.82 g, 0.215 mmol, 1.0 equiv) was suspended in CH_2Cl_2 (25 mL) at 23 °C and treated sequentially with $[Pd(PPh_3)_4]$ (21 mg, 21 μmol, 0.1 equiv) and n-Bu_3SnH (623 mg, 2.15 mmol, 10 equiv). The reaction mixture was stirred for 2 h at 23 °C after which time the resin was filtered and washed (CH_2Cl_2 2 × 50 mL, MeOH 2 × 50 mL, Et_2O 2 × 20 mL). A small amount of this resin was cleaved and the product obtained was analyzed **27**: ^{1}H NMR (600 MHz, CD_3OD, 330 K): $\delta = 7.59$ (brs, 2H), 7.54 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.39–7.30 (m, 7H), 7.14 (d, $J = 2.0$ Hz, 1H), 6.98 (dd, $J = 8.5, 2.0$ Hz, 1H), 6.78 (d, $J = 8.5$ Hz, 1H), 6.76–5.84 (m, 1H), 6.42 (d, $J = 2.0$ Hz, 1H), 6.39 (d, $J = 2.0$ Hz, 1H), 5.92 (ddt, $J = 16.0, 8.0, 6.5$ Hz, 1H), 5.68 (s, 1H), 5.47 (m, 1H), 5.34 (s, 2H), 5.35 (m, 1H), 5.30 (m, 1H), 5.21 (m, 1H), 5.22–5.17 (m, 2H, CH_2-Cbz), 4.96 (brs, 2H), 4.90–4.83 (m, 1H), 4.77–4.70 (m, 1H), 4.72 (m, 1H), 4.61 (s, 1H), 4.72 (m, 1H), 4.29–4.18 (m, 1H), 4.11 (s, 1H), 4.09 (m, 1H), 3.96–3.92 (m, 1H), 3.80–3.75 (m, 1H), 3.58 (dd, $J = 11.0, 3.5$ Hz, 1H), 2.93 (s, 3H), 2.55–2.40 (m, 2H), 2.03 (s, 3H), 2.00 (s, 3H), 1.78–1.75 (m, 1H), 1.53–1.49 (m, 2H), 1.01 (s, 9H), 0.94 (s, 9H), 0.93–0.91 (m, 6H), 0.89 (s, 9H), 0.77 (s, 9H), 0.73 (s, 9H), 0.63 (s, 9H), 0.23 (s, 6H), 0.18 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), −0.08 (s, 3H), −0.09 (s, 3H); MS (ES): calcd for $C_{110}H_{160}Cl_2N_8O_{26}Si_6$ $[M+H]^+$: 2247.6, found 2247.5.

Fully protected polymer-bound vancomycin 29

Second glycosidation: Freshly prepared vancosamine fluoride **28**[20] (0.367 mmol, 6.0 equiv) was azeotroped with benzene (3 × 10 mL) and then dried under high vacuum for 1 h. The glycosyl fluoride was then transferred as a CH_2Cl_2 (5 mL) solution to a flask containing resin **27** (51 mg, 61.2 μmol) and flame-dried 4 Å MS (0.5 g). The mixture was stirred at ambient temperature for 2 h, then cooled to −40 °C and $BF_3 \cdot Et_2O$ (80 μL, 0.550 mmol) was added dropwise. The reaction mixture was allowed to warm up to 0 °C over the course of 4 h. The reaction mixture was cooled back to −40 °C and quenched with Et_3N (0.152 mL, 1.10 mmol, 2.0 equiv relative to $BF_3 \cdot Et_2O$). The resin was filtered, washed (CH_2Cl_2 2 × 50 mL, MeOH 2 × 50 mL), a small amount was cleaved, and the product obtained was analyzed **29**: ^{1}H NMR (600 MHz, CD_3COD, 330 K): $\delta = 7.65–7.45$ (m, 3H), 7.40–7.20 (m, 12H), 7.10–7.08 (m, 2H), 7.03 (m, 2H), 6.80 (d, $J = 8.5$ Hz, 1H), 6.78 (d, $J = 8.5$ Hz, 1H), 6.44 (d, $J = 2.0$ Hz, 1H), 6.40 (s, 1H), 5.91 (m, 1H), 5.83–5.78 (m, 2H), 5.64–5.45 (m, 2H), 5.44–5.28 (m, 5H), 5.26–5.10 (m, 5H), 4.90 (q, $J = 12.5$ Hz, 2H), 4.64 (m, 2H), 4.18–4.07 (m, 2H), 3.85–3.80 (m, 2H), 3.64 (m, 1H), 2.94 (s, 3H), 2.48 (m, 2H), 2.03 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 2.05–1.98 (m, 2H), 1.55 (brs, 3H), 1.29 (s, 3H), 1.09 (m, 3H), 1.02 (s, 9H), 0.97 (s, 9H), 0.93 (m, 6H), 0.88 (s, 9H), 0.82 (s, 9H), 0.79 (s, 9H), 0.71 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H), 0.19 (s, 3H), 0.18 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.10 (m, 9H), 0.04 (s, 3H), 0.03 (s, 3H), −0.06 (s, 3H), −0.08 (s, 3H); MS (ES): calcd for $C_{127}H_{181}Cl_2N_9O_{31}Si_6$ $[M+Na]^+$: 2592.9, found 2592.6.

Fully protected vancomycin 5

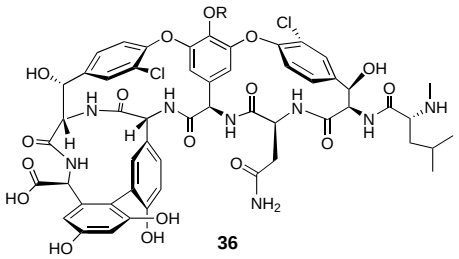
Cleavage from resin 29: Resin **29** (300 mg, 34.5 μmol of vancomycin, 0.24 mmol of Se) was suspended in THF (4 mL) and treated with H_2O_2 (30% in water, 48 μL, 0.48 mmol, 2.0 equiv) and stirred for 2 h after which time, Me_2S (111 μL, 1.76 mmol, 4.0 equiv relative to H_2O_2) was added to the reaction mixture which was stirred for an additional 48 h. The reaction mixture was filtered, concentrated, and passed through a short plug of silica gel (eluting with CH_2Cl_2, then 10% MeOH in CH_2Cl_2) to recover **5** as a single product (54.1 mg, 80%).

Deprotection of 5 to give vancomycin (1) via intermedite 30

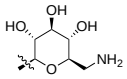
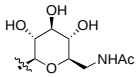
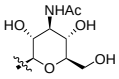
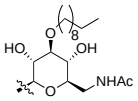
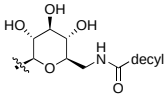
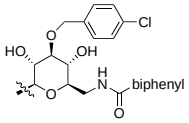
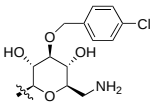
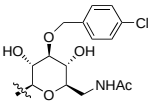
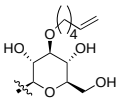
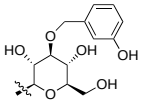
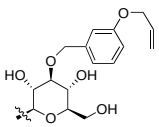
Deacetylation and desilylation: Fully protected vancomycin derivative **5** (48 mg, 18.7 μmol, 1.0 equiv) was dissolved in MeOH (5 mL) and treated with solid K_2CO_3 (5.2 mg, 37.4 μmol, 2.0 equiv) and stirred at room temperature for 6 h, at which point TLC analysis of the reaction mixture indicated complete disappearance of the starting material. The crude reaction mixture was filtered through Celite and concentrated. The crude residue thus obtained was dissolved in wet DMF (0.5 mL), and solid $NaHCO_3$ (30 mg, 0.36 mmol, 20 equiv) and CsF (30 mg, 0.197 mmol, 12 equiv) were added. The resulting heterogeneous mixture was stirred vigorously for 15 h. The crude reaction mixture was purified directly by HPLC to give vancomycin ester derivative **30** (20.4 mg, 62%) as a white solid: **30**: HPLC: $t_R = 9.8$ min (LiChrospher C18, 4 mm × 250 mm, flow rate = 1.0 mL min^{-1}, 5 → 100% CH_3CN in H_2O (0.1% TFA) over 15 min); **30**: ^{1}H NMR (500 MHz, CD_3COD, 330 K): $\delta = 7.66$ (brs, 1H), 7.56 (d, $J = 2.0$ Hz, 1H), 7.55 (d, $J = 2.0$ Hz, 1H), 7.44 (s, 1H), 7.40–7.29 (m, 12H), 6.13 (brd, $J = 9.0$ Hz, 1H), 7.08 (d, $J = 1.5$ Hz, 1H), 7.01 (dd, $J = 8.5, 2.5$ Hz, 1H), 6.83 (d, $J = 6.5$ Hz, 1H), 6.47 (d, $J = 2.0$ Hz, 1H), 6.32 (d, $J = 2.0$ Hz, 1H), 5.96 (ddt, $J = 16.0, 10.0, 6.5$ Hz, 1H), 5.75 (brs, 2H), 5.47 (d, $J = 2.5$ Hz, 1H), 5.46 (s, 1H), 5.39 (ddt, $J = 16.0, 1.5, 1.5$ Hz, 1H), 5.37 (s, 1H), 5.36 (s, 1H), 5.34 (s, 1H), 5.22 (ddt, $J = 10.0, 1.5, 1.5$ Hz, H), 5.22–5.17 (m, 2H), 5.01 (d, $J = 6.0$ Hz, 1H), 4.92–4.86 (m, 2H), 4.85 (s, 2H), 4.74 (m, 2H), 4.65 (s, 1H), 4.21 (s, 1H), 3.87 (d, $J = 9.0$ Hz, 1H), 3.84 (dd, $J = 10.5, 2.0$ Hz, 1H), 3.77 (dd, $J = 10.5, 4.5$ Hz, 1H), 3.69 (brt, $J = 8.0$ Hz, 1H), 3.56 (t, $J = 9.0$ Hz, 1H), 3.55 (q, $J = 8.0$ Hz, 1H), 3.43 (s, 1H), 2.94 (s, 3H), 2.38 (dd, $J = 10.5, 5.5$ Hz, 1H), 2.19 (d, $J = 13.0$ Hz, 1H), 1.92 (dd, $J = 10.5, 4.0$ Hz, 1H), 1.74–1.68 (m, 1H), 1.61 (d, $J = 8.0$ Hz, 1H), 1.53 (s, 3H), 1.21 (d, $J = 6.5$ Hz, 3H), 1.17 (d, $J = 6.5$ Hz, 3H), 0.90 (brd, $J = 6.5$ Hz, 3H), 0.89 (brd, $J = 6.5$ Hz, 3H); MS (ES): calcd for $C_{85}H_{91}Cl_2N_9O_{28}Na$ $[M+Na]^+$: 1780, found 1780.

Removal of the allyl group: A fresh solution of $[Pd(PPh_3)_4]$ (1.0 mM in DMF, 176 μL, 0.176 μmol, 0.1 equiv) followed by n-Bu_3SnH (2.5 mg, 8.8 μmol, 5.0 equiv) was added at room temperature to a solution of the above allyl ester (**30**, 3.1 mg, 1.76 μmol, 1.0 equiv) in DMF (100 μL). The reaction mixture was stirred vigorously for 30 min after which time HPLC analysis of the reaction mixture indicated complete deprotection. The crude reaction mixture was injected directly into the HPLC instrument to recover 2.8 mg (92% isolated) of product as a white solid. HPLC: $t_R = 6.1$ min (LiChrospher C18, 4 mm × 250 mm, low rate = 1.0 mL min^{-1}, 5 → 100% CH_3CN in H_2O (0.1% TFA) over 15 min); ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.68$ (brs, 1H), 7.53 (d, $J = 7.0$ Hz, 1H), 7.43 (brs, 1H), 7.40–7.29 (m, 7H), 7.14 (t, $J = 7.0$ Hz, 2H), 7.04 (brs, 1H), 6.98 (dd, $J = 9.0, 1.0$ Hz, 1H), 6.83 (d, $J = 8.5$ Hz, 1H), 6.63 (d, $J = 1.5$ Hz, 1H), 6.43 (d, $J = 1.5$ Hz, 1H), 5.75 (brs, 2H), 5.46 (d, $J = 2.5$ Hz, 1H), 5.39 (s, 1H), 5.36 (brs, 2H), 5.23 (brs, 1H), 5.01 (s, 1H), 4.92–4.81 (m, 3H), 4.70 (s, 1H), 4.67 (s, 1H), 4.14 (s, 1H), 3.89–3.82 (m, 2H), 3.77 (dd, $J = 10.5, 4.5$ Hz, 1H), 3.69 (brt, $J = 8.0$ Hz, 1H), 3.56 (t, $J = 9.0$ Hz, 1H), 3.55 (q, $J = 8.0$ Hz, 1H), 3.43 (s, 1H), 2.94 (s, 3H), 2.39 (dd, $J = 10.5, 5.5$ Hz, 1H), 2.21 (m, 1H), 1.74–1.68 (m, 2H), 1.63 (m, 1H), 1.53 (s, 3H), 1.22 (d, $J = 6.5$ Hz, 3H), 1.17 (d, $J =$

Table 1. Antibacterial activity (MIC: $\mu g\,mL^{-1}$) of vancomycin-derived monosaccharides (**36a–k**) against vancomycin-susceptible, vancomycin-intermediate resistant, and vancomycin-resistant bacteria.



36

Compound	R	Sa8250[a]	Sp670[a]	27266[b]	4002[b]	27261[b]	48N[c]	25701[c]	LO3[c]	133[c]	MU50[d]	4001[e]
	ampicillin	0.4	3.13	3.13	3.13	3.13	50	25	25	<0.2	12.5	50
	tetracycline	3.13	50	100	100	50	>100	25	<0.2	<0.2	25	50
1	**vancomycin**	0.5	0.25	2	0.5	2	1	1	0.5	0.25	4	>16
36a		4	2	8	4	8	4	8	2	4	8	>16
36b		4	2	8	4	8	4	4	4	4	8	>16
36c		8	8	>16	16	>16	16	>16	16	16	16	>16
36d		0.25	0.125	0.5	0.25	0.25	>16	>16	>16	>16	>16	16
36e		4	2	4	4	4	2	4	4	2	4	>16
36f		>16	16	>16	16	16	>16	>16	16	16	16	16
36g		4	2	8	8	8	8	16	4	4	4	>16
36h		4	4	8	4	4	4	8	4	8	8	>16
36i		4	4	8	8	8	4	4	4	4	8	>16
36j		8	8	16	16	16	8	16	8	8	16	>16
36k		>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16

[a] Vancomycin-susceptible strains of *Streptooccus pneumoniae*. [b] Vancomycin-susceptible strains of *Enterococcus faecalis*. [c] Vancomycin-susceptible strains of *Staphylococcus aureus*. [d] Vancomycin-intermediate resistant *Staphylococcus aureus*. [e] Vancomycin-resistant (van A) *Enterococcus faecium*.

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6.5 Hz, 3H), 0.94 (br d, $J = 6.5$ Hz, 3H), 0.90 (br d, $J = 6.5$ Hz, 3H); MS (ES): calcd for $C_{82}H_{87}Cl_2N_9O_{28}$ $[M+H]^+$: 1717.4, found 1717.5.

Removal of the Cbz group: To a solution of the resulting di-Cbz-vancomycin derivative (2.1 mg, 1.22 μmol, 1.0 equiv) in H_2O/MeOH (1:1, 200 μL) under an argon atmosphere was added 10% Pd/C (≈0.5 mg, ≈0.5 equiv) followed by NH_4HCO_2 (2.0 mg, 31 μmol, 26 equiv) and the reaction mixture was stirred at room temperature for 2 h after which time HPLC analysis indicated complete and clean conversion to vancomycin. The reaction mixture was filtered through a 20 μm syringe fritt and the fritt was washed with H_2O/MeOH/AcOH (1:1:1, 2 × 0.2 mL). The combined filtrates were diluted with acetone (2 mL) and centrifuged at 15000 rpm to obtain a white solid. Purification of this material by HPLC afforded 1.5 mg of vancomycin (**1**) (85%) which was identical to authentic material (^{1}H NMR, HPLC, HRMS). **1**: HPLC: $t_R = 4.9$ min (LiChrospher C18, 4 mm × 250 mm, flow rate = 1.0 mL min^{-1}, 5 → 100% CH_3CN in H_2O (0.1% TFA) over 15 min); ^{1}H NMR (600 MHz, D_2O, 330 K): $\delta = 8.03$ (s, 1H), 7.96 (s, 1H), 7.91–7.88 (m, 2H), 7.79–7.78 (m, 2H), 7.42 (s, 1H), 7.34–7.32 (m, 1H), 7.28 (s, 1H), 6.91 (s, 1H), 6.82 (s, 1H), 6.14 (br s, 1H), 6.06 (br s, 1H), 5.86 (s, 1H), 5.82 (d, $J = 6.5$ Hz, 1H), 5.75 (d, $J = 4.0$ Hz, 1H), 5.71 (s, 1H), 5.67 (s, 1H), 5.23 (br s, 1H), 5.17 (q, $J = 6.6$ Hz, 1H), 5.03–5.00 (m, 2H), 4.55 (s, 1H), 4.41 (t, $J = 7.4$ Hz, 1H), 4.18–4.16 (m, 1H), 4.14–4.07 (m, 1H), 3.94 (t, $J = 8.8$ Hz, 1H), 3.87–3.84 (m, 1H), 3.78 (s, 1H), 3.40–3.39 (m, 1H), 3.15–3.14 (m, 1H), 3.11 (s, 1H), 2.72–2.70 (m, 1H), 2.42–2.40 (m, 1H), 2.38–2.34 (m, 1H), 2.16–2.13 (m, 1H), 2.06–2.02 (m, 1H), 1.99–1.94 (m, 1H), 1.76 (s, 3H), 1.49 (d, $J = 6.6$ Hz, 3H), 1.24 (d, $J = 6.5$ Hz, 3H), 1.20 (d, $J = 6.5$ Hz, 3H); HRMS (MALDI): calcd for $C_{66}H_{75}Cl_2N_9O_{24}Na$ $[M+Na]^+$: 1470.4200, found 1470.4231.

General procedure for the synthesis of vancomycin monosaccharides analogues: The preparation of these compounds proceeded in a similar manner to the solid-phase semisynthesis of vancomycin. Conversion of compounds **34** to **35** is detailed below.

Conversion of compounds 34 to 35: Resin **34** (200 mg) was suspended in THF (2 mL) and H_2O (2 mL) was added. To this suspension, at 23 °C, was added Et_3P (5.0 equiv) and the mixture was stirred for 4 h. The resin was filtered and washed (CH_2Cl_2 2 × 20 mL, MeOH 2 × 20 mL, Et_2O 2 × 20 mL) and then re-suspended in CH_2Cl_2 (20 mL) at 23 °C and Et_3N (10.0 equiv) followed by the appropriate acid chloride (5.0 equiv) were added. After 8 h of stirring the resin was filtered off and washed (CH_2Cl_2 2 × 20 mL, MeOH 2 × 20 mL, Et_2O 2 × 20 mL). Product was cleaved from the resin and globally deprotected as described above for the conversion of **5** to **1** to yield **36a–k** (analytical HPLC: LiChrospher C18, 6 mm × 250 mm, flow rate 1.0 mL min^{-1}, 0 → 100% CH_3CN (0.05% TFA) in H_2O (0.05% TFA) over 10 min).

36a: $t_R = 5.1$ min; LCMS (ES): calcd for $C_{59}H_{63}Cl_2N_9O_{21}$ $[M+H]^+$: 1306.1, found 1306.1.

36b: $t_R = 5.5$ min; LCMS (ES): calcd for $C_{61}H_{65}Cl_2N_9O_{22}$ $[M+H]^+$: 1348.1, found 1348.4.

36c: $t_R = 5.9$ min; LCMS (ES): calcd for $C_{61}H_{65}Cl_2N_9O_{22}$ $[M+H]^+$: 1348.2, found 1348.2.

36d: $t_R = 6.5$ min; LCMS (ES): calcd for $C_{71}H_{85}Cl_2N_9O_{22}$ $[M+H]^+$: 1488.4, found 1488.4.

36e: $t_R = 7.7$ min; LCMS (ES): calcd for $C_{71}H_{85}Cl_2N_9O_{22}$ $[M+H]^+$: 1488.4, found 1488.4.

36f: $t_R = 7.6$ min; LCMS (ES): calcd for $C_{79}H_{76}Cl_3N_9O_{22}$ $[M+H]^+$: 1610.8, found 1610.3.

36g: $t_R = 5.8$ min; LCMS (ES): calcd for $C_{66}H_{68}Cl_3N_9O_{22}$ $[M+H]^+$: 1430.6, found 1430.6.

36h: $t_R = 6.8$ min; LCMS (ES): calcd for $C_{68}H_{70}Cl_3N_9O_{22}$ $[M+H]^+$: 1472.6, found 1472.5.

36i: $t_R = 6.2$ min; LCMS (ES): calcd for $C_{65}H_{72}Cl_2N_8O_{22}$ $[M+H]^+$: 1388.2, found 1388.2.

36j: $t_R = 6.1$ min; LCMS (ES): calcd for $C_{66}H_{68}Cl_2N_8O_{23}$ $[M+H]^+$: 1412.2, found 1412.2.

36k: $t_R = 6.7$ min; LCMS (ES): calcd for $C_{69}H_{72}Cl_2N_8O_{23}$ $[M+H]^+$: 1453.3, found 1453.3.

Preparation of substituted phenols 37b–e: NaH (694 mg, 1.0 equiv, 60% suspension) was added to a solution of 3,4-dihydroxybenzaldehyde (**37a**, 2.50 g, 18.1 mmol, 1.0 equiv) in DMF (25 mL, 0.7 M) cooled to 0 °C. The reaction mixture was allowed to stir for 10 min whereupon the appropriate benzyl or alkyl bromide was added (1.0 equiv). After warming to 23 °C with stirring over a period of 12–18 h, the reaction was quenched with 10% aq HCl and extracted with EtOAc (200 mL). After concentration, the crude residue was purified by flash column chromatography (silica gel, mixtures of EtOAc and hexanes) to give the desired phenol (**37b–e**).

37b: $R_f = 0.43$ (40% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3409$, 1681, 1606, 1508, 1277, 1123, 804 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1H), 7.51 (d, $J = 1.8$ Hz, 1H), 7.49–7.47 (m, 1H), 7.02 (d, $J = 8.0$ Hz, 1H), 5.93 (s, 1H), 4.21 (t, $J = 6.2$ Hz, 2H), 1.93–1.90 (m, 2H), 1.60–1.56 (m, 2H), 1.06 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.4$, 151.7, 146.6, 130.8, 124.9, 114.4, 111.2, 69.3, 31.4, 19.5, 14.1; HRMS: calcd for $C_{11}H_{14}O_3$ $[M+Na]^+$: 217.0835, found 217.0839.

37c: $R_f = 0.56$ (40% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3223$, 1674, 1606, 1581, 1507, 1465, 1265, 1248, 1124, 802 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1H), 7.51 (d, $J = 1.9$ Hz, 1H), 7.49–7.47 (m, 1H), 7.02 (d, $J = 8.1$ Hz, 1H), 5.89 (s, 1H), 4.20 (t, $J = 6.6$ Hz, 2H), 1.94–1.90 (m, 2H), 1.56–1.52 (m, 2H), 1.46–1.38 (m, 6H), 0.97 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.4$, 151.6, 146.6, 130.8, 124.8, 114.4, 111.2, 69.7, 32.1, 29.4, 29.3, 26.2, 22.9, 14.4; HRMS: calcd for $C_{14}H_{20}O_3$ $[M+Na]^+$: 259.2960, found 259.2962.

37d: $R_f = 0.34$ (50% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3242$, 1675, 1604, 1510, 1456, 1281, 1117, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 9.80 (s, 1H), 7.45–7.38 (m, 7H), 7.03 (d, $J = 8.5$ Hz, 1H), 6.04 (s, 1H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 191.1$, 151.1, 146.3, 135.2, 130.7, 128.8, 127.8, 124.4, 99.9, 71.2; HRMS: calcd for $C_{14}H_{12}O_3$ $[M+Na]^+$: 251.0678, found 251.0683.

37e: $R_f = 0.34$ (50% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3372$, 1678, 1606, 1545, 1579, 1277, 1124, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 9.82 (s, 1H), 7.45–7.26 (m, 6H), 7.00 (d, $J = 8.1$ Hz, 1H), 5.89 (s, 1H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 191.0$, 150.6, 146.2, 134.7, 133.6, 130.9, 129.2, 129.1, 124.3, 114.5, 111.5, 70.4; HRMS: calcd for $C_{14}H_{11}ClO_3$ $[M+Na]^+$: 285.0289, found 285.0283.

General procedure for the conversion of phenols 37 to olefins 38: The appropriate olefinic alcohol (1.5 equiv), triphenylphosphine (1.5 equiv) and diethyl azodicarboxylate (1.5 equiv) were added to a solution of phenol **37** (1.0 equiv) in THF (0.5 M) at 23 °C. The mixture was stirred for 5 h at ambient temperature and then concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc/hexanes mixtures) to give the desired olefin **38**.

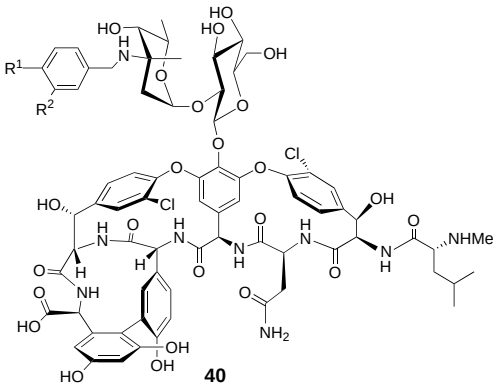
38a: $R_f = 0.36$ (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1698$, 1595, 1263, 990, 929, 787 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.98$ (s, 1H), 7.53–7.46 (m, 3H), 7.30–7.25 (m, 1H), 6.16–6.11 (m, 1H), 5.55 (dd, $J = 3.5$, 19.3 Hz, 1H), 5.41 (dd, $J = 3.5$, 19.3 Hz, 1H), 4.67–4.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 192.4$, 159.5, 138.2, 133.0, 130.4, 123.9, 122.4, 18.4, 113.5, 69.7; HRMS: calcd for $C_{10}H_{10}O_2$ $[M+Na]^+$: 185.0573, found 185.0579.

38b: $R_f = 0.45$ (15% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1697$, 1597, 1487, 1451, 1263, 1146, 1039, 919 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 10.0 (s, 1H), 7.49–7.44 (m, 3H), 7.23–7.21 (m, 1H), 6.00–5.94 (m, 1H), 5.55 (dd, $J = 3.5$, 19.3 Hz, 1H), 5.41 (dd, $J = 3.5$, 19.3 Hz, 1H), 4.13–4.11 (m, 2H), 2.64–2.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 192.5$, 159.8, 138.1, 134.5, 130.4, 123.8, 117.7, 67.8, 33.8; HRMS: calcd for $C_{11}H_{12}O_2$ $[M+Na]^+$: 199.0729, found 199.0721.

38c: $R_f = 0.48$ (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1697$, 1597, 1488, 1391, 1263, 1148 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.0$ (s, 1H), 7.54–7.51 (m, 2H), 7.46–7.45 (m, 1H), 7.26–7.22 (m, 1H), 5.96–5.86 (m, 1H), 5.15–5.11 (m, 1H), 5.09–5.06 (m, 1H), 4.08 (t, $J = 7.0$ Hz, 2H), 2.31 (q, $J = 7.0$ Hz, 2H), 2.00–1.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 192.5, 160.0, 138.2, 137.9, 130.4, 123.7, 122.2, 116.9, 113.2, 37.8, 30.4, 28.7; HRMS: calcd for $C_{12}H_{14}O_2$ $[M+Na]^+$: 213.0886, found 213.0890.

38d: $R_f = 0.77$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1697.5$, 1592.4, 1447.0, 1261.7, 1042.1, 912.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 10.0 (s, 1H), 7.52–7.50 (m, 2H), 7.25–7.24 (m, 1H), 5.93–5.86 (m, 1H), 5.12 (d, $J = 17.5$ Hz, 1H), 5.06 (d, $J = 10.3$ Hz, 1H), 4.10 (t, $J = 6.6$ Hz, 2H), 2.29–2.19 (m, 2H), 1.93–1.87 (m, 2H), 1.69–1.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 199.9$, 160.0, 138.7, 138.1, 130.4, 123.7, 122.3, 115.2, 113.1, 68.4, 33.7, 28.9, 25.6; HRMS: calcd for $C_{13}H_{16}O_2$ $[M+Na]^+$: 227.2537, found 227.2540.

Table 2. Antibacterial activity (MIC: $\mu g\,mL^{-1}$) of vancomycin-derived olefins (**40a–y**) against vancomycin-susceptible, vancomycin-intermediate resistant, and vancomycin-resistant bacteria.



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Compound	R	R^2	R^3	Sa8250[a]	Sp670[a]	27266[b]	4002[b]	27261[b]	48N[c]	25701[c]	LO3[c]	133[c]	MU50[d]	4001[e]
1		**vancomycin**		0.5	0.25	2	0.5	2	1	1	0.5	0.25	4	>16
40a		H	D-NMeLeu	0.06	<0.03	0.125	<0.03	0.25	0.25	0.06	0.125	0.06	0.5	16
40b		H	D-NMeLeu	0.06	0.06	0.25	0.13	0.25	0.25	1	0.125	0.06	0.5	16
40c		H	D-NMeLeu	<0.03	<0.03	0.125	0.06	0.25	0.125	0.125	<0.03	<0.03	0.5	16
40d		H	D-NMeLeu	0.25	0.25	2	0.5	1	8	8	0.06	4	4	8
40e	H		D-NMeLeu	0.25	0.25	0.5	0.25	1	0.5	0.25	0.5	0.25	1	>16
40f	H		D-NMeLeu	0.125	0.06	0.5	0.13	0.5	1	0.25	0.125	0.06	0.5	>16
40g	H		D-NMeLeu	<0.03	<0.03	0.125	0.06	0.25	0.125	0.125	<0.03	<0.03	0.5	16
40h	H		D-NMeLeu	<0.03	<0.03	0.5	0.06	0.25	2	1	0.125	0.25	0.5	2
40i			D-NMeLeu	0.125	0.06	0.25	0.125	0.25	0.125	0.125	0.125	2	0.25	8
40j			D-NMeLeu	1	1	2	2	2	2	2	2	2	4	16
40k			D-NMeLeu	0.06	<0.03	0.5	0.25	0.5	1	1	1	1	1	2
40l			D-NMeLeu	0.125	0.06	2	0.5	2	2	2	2	8	2	2
40m			D-NMeLeu	0.06	0.06	0.125	0.125	0.25	0.125	0.125	0.125	0.5	0.25	2
40n			D-NMeLeu	0.125	0.06	0.25	0.125	0.25	1	0.5	0.25	4	1	2
40o			D-NMeLeu	0.25	0.06	0.25	0.06	0.25	0.25	0.25	0.25	0.25	0.5	1
40p			D-NMeLeu	0.125	0.06	1	0.25	0.5	1	1	1	4	1	2
40q	H		L-Asn	4	8	>16	16	>16	>16	16	16	8	>16	>16
40r	H		L-Asn	1	2	4	4	4	4	>16	16	2	8	16
40s	H		β-Ala	1	2	8	4	8	4	16	8	4	8	>16
40t	H		β-Ala	1	2	4	4	4	4	8	16	1	4	>16
40u	H		γ-Abu	8	4	16	4	16	4	4	4	4	8	>16
40v	H		L-Phe	2	4	8	4	8	4	16	16	>16	8	>16
40w	H		L-Arg	4	4	16	16	16	8	16	16	2	8	>16
40x	H		H	2	2	16	8	16	4	8	4	4	16	>16
40y	H		H	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16

[a] Vancomycin susceptible strains of *Streptococcus pneumoniae*. [b] Vancomycin susceptible strains of *Enterococcus faecalis*. [c] Vancomycin susceptible strains of *Staphylococcus aureus*. [d] Vancomycin-intermediate resistant *Staphylococcus aureus*. [e] Vancomycin-resistant (van A) *Enterococcus faecium*.

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38e: $R_f = 0.67$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1698, 1597, 1487, 1451, 1386, 1263, 1147, 1040\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 10.0 (s, 1H), 7.52–7.48 (m, 2H), 7.45 (d, $J = 2.71$ Hz, 1H), 7.26–7.22 (m, 1H), 5.91–5.83 (m, 1H), 5.08–5.07 (m, 1H), 5.01–5.00 (m, 1H), 4.08 (t, $J = 6.5$ Hz, 2H), 2.09–2.08 (m, 2H), 1.92–1.84 (m, 2H), 1.55–1.48 (m, 2H), 1.41–1.26 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 192.5, 160.1, 139.5, 138.2, 130.3, 123.6, 122.3, 114.5, 113.1, 68.7, 34.1, 29.7, 29.5, 29.4, 29.4, 29.3$ 26.3; HRMS: calcd for $C_{17}H_{24}O_2$ $[M+Na]^+$: 283.1668, found 283.1675.

38f: $R_f = 0.5$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1687, 1591, 1510, 1435, 1268, 1132, 1027\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1H), 7.51 (dd, $J = 1.9$, 8.0 Hz, 1H), 7.48 (d, $J = 1.9$ Hz, 1H), 7.02 (d, $J =$ 8.0 Hz, 1H), 5.95–5.88 (m, 1H), 5.55 (dd, $J = 3.5$, 19.3 Hz, 1H), 5.41 (dd, $J = 3.5$, 19.3 Hz, 1H), 4.15–4.11 (m, 4H), 2.73–2.67 (m, 2H), 1.99–1.89 (m, 2H), 1.62–1.53 (m, 2H), 1.07 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.3, 155.1, 149.6, 134.5, 130.2, 127.1, 117.6, 112.3, 111.8, 69.2,$ 68.8, 33.9, 31.4, 19.5, 14.2; HRMS: calcd for $C_{14}H_{18}O_3$ $[M+Na]^+$: 257.1148, found 257.1152.

38g: $R_f = 0.64$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1687, 1590, 1508, 1435, 1268, 1132, 1021\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1H), 7.51 (dd, $J = 1.9$, 8.0 Hz, 1H), 7.48 (d, $J = 1.9$ Hz, 1H), 7.02 (d, $J =$ 8.0 Hz, 1H), 5.95–5.88 (m, 1H), 5.55 (dd, $J = 3.5$, 19.0 Hz, 1H), 5.41 (dd, $J = 3.5$, 19.0 Hz, 1H), 4.15–4.11 (m, 4H), 2.34–2.30 (m, 2H), 2.02–1.98 (m, 2H), 1.93–1.87 (m, 2H), 1.62–1.49 (m, 2H), 1.05 (t, $J = 7.7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.2, 155.1, 149.7, 138.1, 130.2, 127.0,$ 115.6, 112.1, 111.5, 69.1, 68.7, 31.4, 30.4, 28.7, 19.5, 14.2; HRMS: calcd for $C_{15}H_{20}O_3$ $[M+Na]^+$: 271.1304, found 271.1300.

38h: $R_f = 0.58$ (30% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1687, 1589, 1435, 1266, 1131\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.82$ (s, 1H), 7.51–7.45 (m, 2H), 7.01 (d, $J = 8.1$ Hz, 1H), 5.96–5.76 (m, 1H), 5.24–5.06 (m, 2H), 4.18–4.10 (m, 4H), 2.32 (q, $J = 6.8$ Hz, 2H), 2.02–1.99 (m, 2H), 1.95–1.88 (m, 2H), 1.60–1.51 (m, 2H), 1.05 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 191.2, 155.1, 149.7, 138.1, 130.2, 127.0, 115.6, 112.3,$ 112.1, 111.5, 111.2, 69.2, 31.4, 30.5, 30.4, 28.7, 19.6, 14.2; HRMS: calcd for $C_{16}H_{22}O_3$ $[M+Na]^+$: 285.1461, found 285.1462.

38i: $R_f = 0.73$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1691, 1591, 1508, 1435, 1268, 1132, 808\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.92$ (s, 1H), 7.51 (dd, $J = 1.9$, 8.0 Hz, 2H), 7.48 (d, $J = 1.9$ Hz, 1H), 7.02 (d, $J =$ 8.0 Hz, 1H), 5.98–5.90 (m, 1H), 5.55 (dd, $J = 3.5$, 19.0 Hz, 1H), 5.41 (dd, $J = 3.5$, 19.0 Hz, 1H), 4.14 (q, $J = 5.1$ Hz, 4H), 2.34 (q, $J = 7.0$ Hz, 2H), 2.04–1.99 (m, 2H), 1.96–1.90 (m, 2H), 1.58–1.52 (m, 2H), 1.50–1.41 (m, 2H), 1.38–1.37 (m, 4H), 0.96 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.3, 155.1, 149.7, 138.1, 130.2, 127.0, 115.6, 112.1, 111.5, 69.5,$ 68.7, 32.1, 30.4, 29.3, 28.7, 26.3, 22.9, 14.4; HRMS: calcd for $C_{17}H_{24}O_3$ $[M+Na]^+$: 299.1617, found 299.1612.

38j: $R_f = 0.57$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1688, 1590, 1510, 1268, 1132\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1H), 7.51–7.48 (m, 2H), 7.03 (d, $J = 8.1$ Hz, 1H), 6.03–5.95 (m, 1H), 5.25 (d, $J =$ 17.2 Hz, 1H), 5.19 (d, $J = 10.3$ Hz, 1H), 4.13–3.97 (m, 2H), 2.69–2.65 (m, 2H), 1.95–1.90 (m, 2H), 1.57–1.55 (m, 2H), 1.46–1.38 (m, 7H), 0.98–0.95 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.3, 155.1, 149.5, 134.5, 130.2,$ 127.1, 117.6, 112.2, 111.8, 69.5, 68.7, 33.9, 32.1, 29.3, 26.2, 22.9, 14.4; HRMS: calcd for $C_{18}H_{26}O_3$ $[M+Na]^+$: 313.1774, found 313.1778.

38k: $R_f = 0.61$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1691, 1591, 1508, 1466, 1435, 1288, 1132\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.98$ (s, 1H), 7.50–7.46 (m, 2H), 7.02 (d, $J = 8.1$ Hz, 1H), 5.98–5.90 (m, 1H), 5.18–5.05 (m, 2H), 4.16–4.12 (m, 4H), 2.33 (q, $J = 8.0$ Hz, 2H), 2.06–1.97 (m, 2H), 1.96–1.90 (m, 2H), 1.58–1.52 (m, 2H), 1.50–1.35 (m, 6H), 0.96 (t, $J =$ 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.3, 155.1, 149.7, 138.1,$ 130.2, 127.0, 115.6, 112.1, 111.5, 69.5, 68.7, 32.1, 30.4, 29.3, 28.7, 26.3, 22.9, 14.1; HRMS: calcd for $C_{19}H_{28}O_3$ $[M+Na]^+$: 327.1930, found 327.1932.

38l: $R_f = 0.61$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1686, 1589, 1507, 1434.8, 1266, 1131, 1015\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1H), 7.53–7.40 (m, 7H), 7.09 (d, $J = 8.1$ Hz, 1H), 6.20–6.13 (m, 1H), 5.53 (d, $J = 17.2$ Hz, 1H), 5.39 (d, $J = 10.6$ Hz, 1H), 5.32 (s, 2H), 4.76 (d, $J =$ 5.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.2, 154.4, 149.4, 136.6,$ 133.1, 130.7, 129.0, 128.5, 127.4, 126.9, 118.4, 113.3, 112.1, 71.2, 70.1; HRMS: calcd for $C_{17}H_{16}O_3$ $[M+Na]^+$: 291.0991, found 291.0988.

38m: $R_f = 0.48$ (30% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1686, 1588, 1507, 1435, 1268, 1130, 1019\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.83$ (s, 1H), 7.38–7.26 (m, 7H), 7.00 (d, $J = 8.2$ Hz, 1H), 5.96–5.88 (m, 1H), 5.18–5.12 (m, 4H), 4.14 (t, $J = 6.7$ Hz, 2H), 2.63 (t, $J = 6.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 190.9, 153.9, 149.4, 136.2, 134.1, 130.4, 128.6, 128.0,$ 126.9, 126.5, 117.3, 112.9, 111.1, 70.7, 68.2, 33.5; HRMS: calcd for $C_{18}H_{18}O_3$ $[M+Na]^+$: 305.1148, found 305.1146.

38n: $R_f = 0.3$ (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1693, 1600, 1575, 1508, 1256, 1161, 832\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1H), 7.90 (d, $J = 9.5$ Hz, 2H), 7.05 (d, $J = 9.5$ Hz, 2H), 5.98–5.91 (m, 1H), 5.51–5.48 (m, 1H), 5.40–5.37 (m, 1H), 4.69–4.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.2, 164.0, 132.7, 130.4, 118.7, 115.4, 69.3$; HRMS: calcd for $C_{19}H_{20}O_3$ $[M+Na]^+$: 319.3491, found 319.3498.

38o: $R_f = 0.28$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1686, 1589, 1502, 1433, 1267, 1132, 1011, 809\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 9.91 (s, 1H), 7.51–7.42 (m, 6H), 7.05 (d, $J = 8.05$, 1H), 6.20–6.12 (m, 1H), 5.52 (d, $J = 18.7$ Hz, 1H), 5.39 (d, $J = 9.2$ Hz, 1H), 5.27 (s, 2H), 4.75–4.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.1, 154.0, 149.4, 135.1, 134.3,$ 133.0, 130.9, 129.2, 128.8, 126.8, 118.5, 113.3, 112.0, 70.5, 70.1; HRMS: calcd for $C_{17}H_{15}ClO_3$ $[M+Na]^+$: 325.0602, found 325.0608.

38p: $R_f = 0.18$ (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1686, 1589, 1507, 1434, 1388, 1267, 1130, 1012\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 10.0 (s, 1H), 7.53–7.40 (m, 6H), 7.05 (d, $J = 8.1$ Hz, 1H), 6.03–5.95 (m, 1H), 5.29–5.15 (m, 4H), 4.19 (t, $J = 7.5$ Hz, 2H), 2.70–2.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.2, 154.0, 149.9, 135.2, 134.5, 134.2,$ 131.0, 129.3, 128.8, 126.7, 117.7, 113.5, 111.6, 71.4, 68.6, 33.9; HRMS: calcd for $C_{18}H_{17}ClO_3$ $[M+Na]^+$: 339.0758, found 339.0760.

38q: $R_f = 0.18$ (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1686, 1589, 1508, 1434, 1388, 1266, 1130, 1012\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 9.89 (s, 1H), 7.49–7.40 (m, 8H), 7.04 (d, $J = 8.1$ Hz, 1H), 5.22 (s, 2H), 5.13 (d, $J = 17.2$ Hz, 1H), 5.08 (d, $J = 10.2$ Hz, 1H), 4.15 (t, $J = 6.2$ Hz, 2H), 2.34 (q, $J = 6.9$ Hz, 2H), 2.05–1.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 191.2, 154.0, 150.0, 138.0, 135.2, 134.2, 131.0, 129.2, 128.8, 128.7, 126.6, 115.7, 113.3, 111.4, 70.4, 68.6, 30.5, 28.7; HRMS: calcd for $C_{19}H_{19}ClO_3$ $[M+Na]^+$: 353.0915, found 353.0912.

38r: $R_f = 0.4$ (15% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1690, 1599, 1506, 1425, 1310, 1256, 1160\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.87$ (s, 1H), 7.80 (d, $J = 9.0$ Hz, 2H), 7.01 (d, $J = 9.0$ Hz, 2H), 6.09–5.99 (m, 1H), 5.40 (d, $J = 17.0$ Hz, 1H), 5.32 (d, $J = 11.0$ Hz, 1H), 4.66 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 191.9, 164.5, 133.0, 1327.7, 130.7, 119.0,$ 114.9, 69.4; HRMS: calcd for $C_{10}H_{10}O_2$ $[M+Na]^+$: 185.0573, found 185.0576.

38s: $R_f = 0.4$ (15% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1695, 1600, 1575, 1508, 1256, 1159, 832\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1H), 7.90 (d, $J = 9.5$ Hz, 2H), 7.05 (d, $J = 9.5$ Hz, 2H), 5.98–5.91 (m, 1H), 5.28–5.16 (m, 2H), 4.15–4.09 (m, 2H), 2.60–2.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.2, 164.3, 134.3, 132.2, 130.2, 117.8, 115.0, 67.9,$ 33.7; HRMS: calcd for $C_{11}H_{12}O_2$ $[M+Na]^+$: 199.0729, found 199.0734.

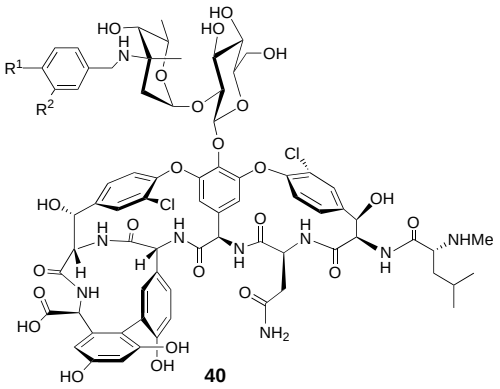
38t: $R_f = 0.42$ (15% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1696, 1601, 1575, 1256, 1159, 832\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.90$ (s, 1H), 7.90 (d, $J = 9.5$ Hz, 2H), 7.05 (d, $J = 9.5$ Hz, 2H), 5.88–5.79 (m, 1H), 5.08–4.99 (m, 2H), 4.06 (t, $J = 6.5$ Hz, 2H), 2.29–2.25 (m, 2H), 1.97–1.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.1, 164.5, 137.8, 132.3, 130.4,$ 115.8, 115.0, 68.1, 30.4, 28.5; HRMS: calcd for $C_{12}H_{14}O_2$ $[M+Na]^+$: 213.0806, found 213.0799.

38u: $R_f = 0.41$ (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1696, 1601, 1575, 1256, 1159\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 10.0$ (s, 1H), 7.90 (d, $J = 9.5$ Hz, 2H), 7.05 (d, $J = 9.5$ Hz, 2H), 5.88–5.79 (m, 1H), 5.08–4.99 (m, 2H), 4.04 (t, $J = 6.4$ Hz, 2H), 2.16–2.12 (m, 2H), 1.86–1.80 (m, 2H), 1.62–1.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.0, 164.5, 138.7,$ 132.4, 130.2, 115.2, 115.1, 68.1, 33.7, 28.9, 25.6; HRMS: calcd for $C_{13}H_{13}O_2$ $[M+Na]^+$: 227.1043, found 227.1048.

38v: $R_f = 0.5$ (15% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2926, 1695, 1601, 1575, 1509, 1257, 1158\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.97$ (s, 1H), 7.89 (d, $J = 10.0$ Hz, 2H), 7.06 (d, $J = 10.0$ Hz, 2H), 5.91–5.83 (m, 1H), 5.08–5.07 (m, 1H), 5.01–5.00 (m, 1H), 4.08 (t, $J = 6.5$ Hz, 2H), 2.09–2.08 (m, 2H), 1.92–1.84 (m, 2H), 1.55–1.48 (m, 2H), 1.41–1.26 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.1, 164.6, 139.4, 132.3, 130.1, 115.1,$ 114.5, 68.7, 34.1, 29.9, 29.7, 29.6, 29.4, 29.2, 26.3; HRMS: calcd for $C_{17}H_{24}O_2$ $[M+Na]^+$: 283.1668, found 283.1660.

38w: $R_f = 0.30$ (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2926, 2856, 1687, 1588, 1508, 1436, 1389, 1268, 1131, 1018\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.82$ (s, 1H), 7.45–7.32 (m, 7H), 6.98 (d, $J = 8.2$ Hz, 1H), 5.23

Table 3. Antibacterial activity (MIC: $\mu g\,mL^{-1}$) of vancomycin-derived thioacetate (**40z–qq**) against vancomycin-susceptible, vancomycin-intermediate resistant, and vancomycin-resistant bacteria.



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Compound	R^1	R^2	Sa8250[a]	Sp670[a]	27266[b]	4002[b]	27261[b]	48N[c]	25701[c]	LO3[c]	133[c]	MU50[d]	4001[e]
1	**vancomycin**		0.5	0.25	2	0.5	2	1	1	0.5	0.25	4	>16
40z	O(CH2)2SAc	H	0.5	0.25	0.5	0.5	1	0.5	0.5	0.5	0.25	2	>16
40aa	O(CH2)3SAc	H	0.5	0.25	0.125	0.125	0.25	0.125	0.25	0.06	<0.03	0.5	16
40bb	O(CH2)4SAc	H	0.5	0.5	0.125	0.125	0.25	0.125	0.125	0.06	<0.03	0.5	16
40cc	O(CH2)5SAc	H	0.5	0.5	0.125	0.125	0.125	0.125	0.125	0.125	<0.03	0.5	16
40dd	O(CH2)7SAc	H	0.5	0.5	2	1	1	4	4	4	2	8	4
40ee	H	O(CH2)2SAc	0.5	0.25	1	0.5	1	0.5	0.5	0.5	0.25	2	>16
40ff	H	O(CH2)3SAc	0.5	0.25	0.25	0.25	0.5	0.25	0.25	0.125	0.06	1	>16
40gg	H	O(CH2)4SAc	0.5	0.25	0.125	0.25	0.25	0.25	0.125	0.125	<0.03	1	>16
40hh	H	O(CH2)5SAc	0.5	0.25	0.125	0.125	0.125	0.125	0.125	0.06	<0.03	0.5	16
40ii	H	O(CH2)7SAc	1	0.5	4	2	2	8	8	8	4	8	8
40jj	O(CH2)4CH3	O(CH2)2SAc	0.5	0.25	0.25	0.25	0.5	0.25	0.25	0.25	4	0.5	8
40kk	O(CH2)4CH3	O(CH2)3SAc	0.125	0.06	0.25	0.06	0.25	0.25	0.125	0.125	0.125	0.5	2
40ll	O(CH2)6CH3	O(CH2)2SAc	0.125	0.06	2	0.5	1	2	2	1	2	2	2
40mm	O(CH2)6CH3	O(CH2)3SAc	1	0.5	2	0.5	2	8	2	4	8	4	4
40nn	OPh	O(CH2)2SAc	1	1	0.5	0.25	0.5	0.5	0.5	0.5	1	1	4
40oo	OPh	O(CH2)3SAc	2	0.25	0.25	0.25	0.5	1	0.5	0.5	0.5	1	4
40pp	OPh*p*Cl	O(CH2)2SAc	0.5	0.5	0.5	0.25	0.5	0.5	0.5	0.25	1	1	2
40qq	OPh*p*Cl	O(CH2)3SAc	0.25	0.125	0.5	0.25	0.5	1	1	1	0.5	1	2

[a] Vancomycin-susceptible strains of *Streptococcus pneumoniae*. [b] Vancomycin-susceptible strains of *Enterococcus faecalis*. [c] Vancomycin-susceptible strains of *Staphylococcus aureus*. [d] Vancomycin-intermediate resistant *Staphylococcus aureus*. [e] Vancomycin-resistant (van A) *Enterococcus faecium*.

(s, 2H), 4.08 (t, $J=6.7$ Hz, 2H), 1.88–1.84 (m, 2H), 1.51–1.47 (m, 2H), 1.33–1.29 (m, 8H), 0.89–0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 191.0, 153.9, 149.6, 136.3, 130.3, 128.6, 128.0, 126.9, 126.3, 112.8, 110.8, 70.7, 69.0, 31.7, 29.3, 29.2, 29.0, 26.0, 22.6, 14.1; HRMS: calcd for $C_{22}H_{28}O_3$ $[M+Na]^+$: 363.1930, found 363.1935.

38x: $R_f=0.33$ (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}=2924$, 2854, 1688, 1588, 1508, 1436, 1389, 1268, 1131, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.82$ (s, 1H), 7.45–7.32 (m, 7H), 6.99 (d, $J=8.0$ Hz, 1H), 5.23 (s, 2H), 4.08 (t, $J=6.7$ Hz, 2H), 1.89–1.82 (m, 2H), 1.50–1.47 (m, 2H), 1.36–1.26 (m, 12H), 0.88 (t, $J=6.72$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=191.0$, 153.9, 149.6, 136.3, 130.3, 128.6, 128.0, 126.9, 126.9, 126.3, 112.8, 110.8, 70.7, 69.0, 31.8, 29.6, 29.5, 29.3, 29.0, 26.0, 22.6, 14.1; HRMS: calcd for $C_{24}H_{32}O_3$ $[M+Na]^+$: 391.2243, found 391.2239.

38y: $R_f=0.16$ (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}=1685$, 1588, 1507, 1434, 1434, 1387, 1269, 1129 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 9.81 (s, 1H), 7.50–7.36 (m, 12H), 7.01 (d, $J=8.1$ Hz, 1H), 5.26 (s, 2H), 5.22 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=190.8$, 154.2, 149.1, 136.5, 136.2, 130.2, 128.6, 128.5, 128.1, 128.0, 127.3, 127.0, 126.7, 113.0, 112.2, 70.9, 70.7; HRMS: calcd for $C_{21}H_{18}O_3$ $[M+Na]^+$: 341.1148, found 341.1156.

38z: $R_f=0.35$ (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}=2924$, 2854, 1686, 1586, 1509, 1270, 1126 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.83$ (s, 1H), 7.42–7.35 (m, 6H), 6.96 (d, $J=8.0$ Hz, 1H), 5.18 (s, 2H), 4.07 (t, $J=$

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6.4 Hz, 2H), 1.88–1.83 (m, 2H), 1.49–1.46 (m, 2H), 1.34–1.28 (m, 10H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 153.5, 149.7, 134.8, 133.8, 130.5, 128.7, 128.3, 126.2, 112.8, 110.8, 70.0, 69.0, 31.7, 29.3, 29.2, 29.0, 26.0, 22.6, 14.1; HRMS: calcd for $C_{23}H_{29}ClO_3$ $[M+Na]^+$: 411.1697, found 411.1691.

38aa: R_f = 0.36 (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 2921, 2850, 1684, 1585, 1508, 1462, 1270, 1234, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1H), 7.41–7.32 (m, 6H), 6.95 (d, J = 8.2 Hz, 1H), 5.19 (s, 2H), 4.06 (t, J = 6.2 Hz, 2H), 1.86–1.82 (m, 2H), 1.49–1.43 (m, 2H), 1.35–1.27 (m, 14H), 0.87 (t, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 153.5, 149.7, 134.8, 133.8, 130.5, 128.7, 128.3, 126.2, 112.8, 110.8, 69.9, 69.0, 31.8, 29.6, 29.6, 29.5, 29.3, 29.0, 26.0, 22.6, 14.1; HRMS: calcd for $C_{25}H_{33}ClO_3$$[M+Na]^+$: 439.2010, found 439.2016.

38bb: R_f = 0.08 (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1686, 1590, 1506, 1435, 1269, 1130, 1012, 809 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 1H), 7.46–7.26 (m, 10H), 7.00 (d, J = 8.2 Hz, 1H), 5.19 (s, 2H), 5.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7, 153.8, 148.9, 134.9, 134.5, 134.0, 133.8, 130.4, 128.8, 128.7, 128.6, 128.4, 126.9, 112.9, 112.0, 70.0; HRMS: calcd for $C_{21}H_{16}Cl_2O_3$ $[M+Na]^+$: 409.0364, found 409.0364.

Preparation of thioacetates 39 from olefins 38: Thioacetic acid (2.0 equiv) followed by AIBN (0.2 equiv) was added to a solution of olefinic aldehyde, **38**, (1.0 equiv) in benzene (0.1M). The reaction mixture was heated to reflux and stirred for 1.5 h. After cooling, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, EtOAc/hexanes mixtures) to give the desired thioacetate **39**.

39a: R_f = 0.44 (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1695, 1592, 1260, 1137, 1038, 955 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.0 (s, 1H), 7.54–7.51 (m, 2H), 7.46–7.45 (m, 1H), 7.26–7.22 (m, 1H), 4.14 (t, J = 6.3 Hz, 2H), 3.01 (t, J = 6.3 Hz, 2H), 2.40 (s, 3H), 2.17–2.13 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.0, 193.0, 160.3, 138.5, 130.9, 124.5, 123.2, 113.9, 68.5, 31.1, 30.6, 26.8; HRMS: calcd for $C_{12}H_{14}O_3S$ $[M+Na]^+$: 261.0556, found 261.0559.

39b: R_f = 0.43 (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1696, 1594, 1487, 1450, 1263, 1134, 789 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.0 (s, 1H), 7.54–7.51 (m, 2H), 7.46–7.45 (m, 1H), 7.26–7.22 (m, 1H), 4.14 (t, J = 6.3 Hz, 2H), 3.01 (t, J = 6.3 Hz, 2H), 2.40 (s, 3H), 1.97–1.92 (m, 2H), 1.97–1.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.2, 192.5, 159.8, 138.1, 130.4, 123.8, 122.3, 113.1, 67.9, 31.0, 29.1, 28.5, 26.6; HRMS: calcd for $C_{13}H_{16}O_3S$ $[M+Na]^+$: 275.0712, found 275.0719.

39c: R_f = 0.2 (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1695, 1596, 1488, 1263, 1137, 951 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.0 (s, 1H), 7.54–7.51 (m, 2H), 7.46–7.45 (m, 1H), 7.26–7.22 (m, 1H), 4.09 (t, J = 6.9 Hz, 2H), 2.98 (t, J = 6.9 Hz, 2H), 2.40 (s, 3H), 1.93–1.87 (m, 2H), 1.76–1.72 (m, 2H), 1.66–1.61 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3, 192.5, 160.0, 138.2, 130.4, 123.7, 122.3, 113.1, 68.3, 31.0, 29.7, 29.3, 29.0, 25.6; HRMS: calcd for $C_{14}H_{18}O_3S$ $[M+Na]^+$: 289.0869, found 289.0873.

39d: R_f = 0.3 (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1695, 1596, 1488, 1263, 1137, 951 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.97 (s, 1H), 7.45–7.44 (m, 2H), 7.39–7.38 (m, 1H), 7.18–7.14 (m, 1H), 4.01 (t, J = 6.6 Hz, 2H), 2.89 (t, J = 6.6 Hz, 2H), 2.31 (s, 3H), 1.84–1.79 (m, 2H), 1.65–1.54 (m, 4H), 1.51–1.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.1, 192.4, 160.0, 138.1, 130.3, 128.6, 123.5, 122.1, 113.2, 68.4, 30.9, 29.8, 29.4, 29.3, 28.8, 25.9, 25.4; HRMS: calcd for $C_{15}H_{20}O_3S$ $[M+Na]^+$: 303.1025, found 303.1018.

39e: R_f = 0.37 (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1695, 1595, 1451, 1262, 1138, 1039, 953 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.0 (s, 1H), 7.52–7.48 (m, 2H), 7.45 (d, J = 2.7 Hz, 1H), 7.26–7.22 (m, 1H), 4.08 (t, J = 6.5 Hz, 2H), 2.93 (t, J = 7.36 Hz, 2H), 2.39 (s, 3H), 1.89–1.85 (m, 2H), 1.66–1.61 (m, 2H), 1.55–1.53 (m, 2H), 1.43–1.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.4, 192.6, 160.1, 138.1, 130.9, 123.7, 122.3, 113.1, 68.6, 31.0, 29.9. 29.8, 29.7, 29.6, 29.5, 29.5, 29.4, 29.1, 26.3; HRMS: calcd for $C_{19}H_{28}O_3S$ $[M+Na]^+$: 359.1651, found 359.1649.

39f: R_f = 0.31 (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1692, 1592, 1509, 1434, 1268, 1132 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.89 (s, 1H), 7.50 (dd, J = 1.9, 8.1 Hz, 1H), 7.46 (d, J = 1.85 Hz, 1H), 7.02 (d, J = 8.1 Hz), 4.17–4.13 (m, 4H), 3.14 (t, J = 7.0 Hz, 2H), 2.40 (s, 3H), 2.20–2.15 (m, 2H), 1.96–1.88 (m, 2H), 1.60–1.54 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.9, 191.2, 155.1, 149.4, 130.2, 127.2, 119.4, 112.2, 69.2, 67.8, 31.4, 29.5, 26.1, 25.5, 19.6, 14.2; HRMS: calcd for $C_{16}H_{22}O_4S$ $[M+Na]^+$: 333.1131, found 333.1140.

39g: R_f = 0.20 (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1691, 1589, 1509, 1435, 1268, 1132, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.87 (s, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.42 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 4.12 (m, 4H), 3.01 (t, J = 7.4 Hz, 2H), 2.40 (s, 3H), 1.98–1.94 (m, 2H), 1.93–1.81 (m, 4H), 1.60–1.52 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.1, 191.1, 155.1, 149.5, 130.2, 127.1, 119.4, 112.1, 111.5, 69.1, 68.9, 31.4, 29.5, 26.1, 25.5, 19.6, 14.2; HRMS: calcd for $C_{17}H_{24}O_4S$ $[M+Na]^+$: 347.1287, found 347.1292.

39h: R_f = 0.58 (30% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 2928, 1691, 1588, 1510, 1268, 1132, 1014 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.90 (s, 1H), 7.50–7.45 (m, 2H), 7.02 (d, J = 8.5 Hz, 1H), 4.16–4.10 (m, 4H), 2.97 (t, J = 7.4 Hz, 2H), 2.39 (s, 3H), 1.96–1.90 (m, 4H), 1.79–1.72 (m, 2H), 1.65–1.63 (m, 2H), 1.56–1.52 (m, 2H), 1.43–1.37 (m, 6H), 0.96 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.2, 191.3, 155.0, 149.6, 130.2, 127.0, 112.1, 111.4, 69.5, 69.2, 32.1, 31.0, 29.6, 29.3, 28.9, 26.9, 25.7, 22.9, 14.4; HRMS: calcd for $C_{19}H_{28}O_4S$ $[M+Na]^+$: 375.1200, found 375.1201.

39i: R_f = 0.51 (30% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 2928, 1686, 1588, 1509, 1268, 1131 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1H), 7.43–7.37 (m, 2H), 6.94 (d, J = 8.2 Hz, 1H), 4.06 (t, J = 6.1 Hz, 2H), 2.97 (t, J = 6.1 Hz, 2H), 2.30 (s, 3H), 1.93–1.77 (m, 8H), 1.48–1.30 (m, 8H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195. 0, 190.9, 154.6, 149.1, 129.7, 126.7, 111.6, 110.9, 69.0, 68.4, 31.7, 30.6, 28.9, 28.8, 28.7, 28.0, 26.3, 25.8, 22.5, 14.0; HRMS: calcd for $C_{20}H_{30}O_4S$ $[M+Na]^+$: 389.1757, found 389.1759.

39j: R_f = 0.50 (30% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1686, 1587, 1506, 1435, 1267, 1132, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.91 (s, 1H), 7.53–7.47 (m, 7H), 7.08 (d, J = 8.0 Hz, 1H), 5.23 (s, 2H), 4.22 (t, J = 6.3 Hz, 2H), 3.17 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H), 2.23–2.20 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.0, 191.2, 154.4, 149.7, 136.6, 130.7, 129.0, 128.5, 127.4, 113.3, 111.8, 71.2, 67.8, 31.0, 29.5, 26.2; HRMS: calcd for $C_{19}H_{20}O_4S$ $[M+H]^+$: 344.1082, found 344.1081.

39k: R_f = 0.34 (30% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1687, 1588, 1508, 1436, 1268, 1131 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1H), 7.44–7.32 (m, 7H), 6.99 (d, J = 7.9 Hz, 1H), 5.21 (s, 2H), 4.09 (t, J = 6.5 Hz, 2H), 2.96 (t, J = 6.5 Hz, 2H), 2.32 (s, 3H), 1.94–1.91 (m, 2H), 1.80–1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.8, 290.9, 153.9, 149.4, 136.2, 130.0, 128.6, 128.0, 127.0, 126.5, 112.7, 111.0, 70.7, 68.4, 30.6, 28.7, 28.0, 26.3; HRMS: calcd for $C_{20}H_{22}O_4S$ $[M+Na]^+$: 358.1239, found 358.1237.

39l: R_f = 0.38 (30% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1692, 1591, 1508, 1435, 1267, 1012, 811 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.90 (s, 1H), 7.49–7.39 (m, 6H), 7.05 (d, J = 7.9 Hz, 1H), 5.27 (s, 2H), 4.18 (t, J = 11.8 Hz, 2H), 3.14 (t, J = 9.7 Hz, 2H), 2.40 (s, 3H), 2.24–2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.2, 191.2, 154.1, 149.7, 135.1, 134.3, 130.9, 129.2, 128.8, 126.9, 113.3, 111.7, 70.4, 67.8, 31.0, 29.5, 26.2; HRMS: calcd for $C_{19}H_{19}O_4ClS$ $[M+Na]^+$: 401.0585, found 401.0589.

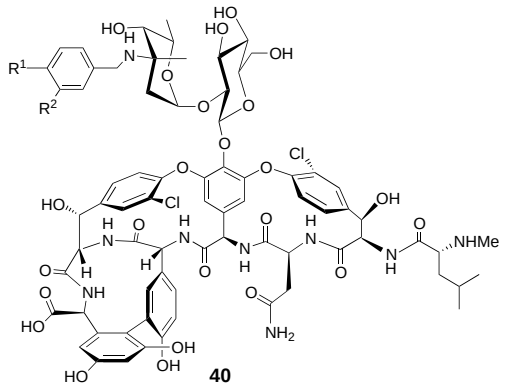
39m: R_f = 0.42 (30% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1686, 1589, 1508, 1435, 1267, 1132, 1011, 811 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.90 (s, 1H), 7.51–7.44 (m, 6H), 7.05 (d, J = 7.9 Hz, 1H), 5.28 (s, 2H), 4.15 (t, J = 6.2 Hz, 2H), 3.05 (t, J = 6.6 Hz, 2H), 2.40 (s, 3H), 2.03–1.96 (m, 2H), 1.92–1.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.1, 191.2, 154.0, 149.9, 135.1, 134.3, 130.9 129.2, 128.8, 128.7, 126.7, 113.2, 111.5, 70.4, 68.8, 31.0, 29.1, 28.5, 26.8; HRMS: calcd for $C_{20}H_{21}ClO_4S$ $[M+Na]^+$: 415.0741, found 415.0749.

39n: R_f = 0.27 (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1693, 1600, 1577, 1510, 1254, 1160, 1029, 956, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.0 (s, 1H), 7.90 (d, J = 9.5 Hz, 2H), 7.05 (d, J = 9.5 Hz, 2H), 4.10 (t, J = 6.4 Hz, 2H), 3.01 (t, J = 6.3 Hz, 2H), 2.40 (s, 3H), 2.17–2.13 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3, 191.2, 164.1, 132.4, 130.2, 119.5, 115.1, 68.4, 31.5, 29.8, 26.0; HRMS: calcd for $C_{12}H_{14}O_3S$ $[M+Na]^+$: 261.0556, found 261.0547.

39o: R_f = 0.39 (20% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1695, 1600, 1575, 1509, 1258, 1159 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.0 (s, 1H), 7.90 (d, J = 9.5 Hz, 2H), 7.05 (d, J = 9.5 Hz, 2H), 4.10 (t, J = 6.4 Hz, 2H), 2.97 (t, J = 7.2 Hz, 2H), 2.36 (s, 3H), 1.93–1.87 (m, 2H), 1.75–1.70 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3, 191.2, 164.1, 132.4, 130.2, 119.5, 115.1, 68.4, 31.0, 29.7, 29.2, 25.6; HRMS: calcd for $C_{13}H_{16}O_3S$ $[M+Na]^+$: 275.0712, found 275.0717.

39p: R_f = 0.26 (15% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 1695, 1600, 1509, 1257, 1159, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.0 (s, 1H), 7.90 (d, J = 9.5 Hz, 2H), 7.05 (d, J = 9.5 Hz, 2H), 4.10 (t, J = 7.0 Hz, 2H),

Table 4. Antibacterial activity (MIC: $\mu g\,mL^{-1}$) of monomeric vancomycin derivatives against vancomycin-susceptible, vancomycin-intermediate resistant, and vancomycin-resistant bacteria.



40

Compound	R^1	R^2	MU50[a]	133[a]	4002[b]	1528[c]	2689[c]	2741[c]	2781[c]	2805[c]	4001[d]	1669[e]	2671[e]	2823[e]	1803[f]	1924[f]	1944[f]
	tetracycline		50	0.2	50	100	100	>100	50	50	50	100	50	25	>100	25	50
1	**vancomycin**		3.13	0.39	0.39	>100	50	>100	100	25	>100	100	50	100	50	25	50
40gg	H	O(CH2)4SAc	8	2	2	1	1	2	2	2	2	0.5	1	1	1	0.125	1
40dd	O(CH2)9SAc	H	4	2	0.5	2	4	4	4	4	8	1	2	2	0.5	0.125	2
40ii	H	O(CH2)9SAc	0.5	4	4	2	8	8	4	8	8	1	1	4	1	0.06	1
40rr	OPh	OH	0.25	0.125	0.25	2	16	0.5	4	2	8	8	4	1	1	1	4
40ss	OPh	OPh	0.5	0.5	0.25	1	2	0.125	2	0.5	4	2	2	1	0.5	0.25	2
40tt	OPh	O(CH2)6	8	8	2	8	8	4	8	16	8	4	8	2	2	1	4
40uu	OPh	O(CH2)8	>16	>16	16	>16	>16	>16	>16	>16	>16	>16	>16	>16	16	16	16
40vv	OPh*p*Cl	OH	0.25	0.25	0.125	0.25	2	0.125	2	0.25	4	2	0.5	0.5	0.25	0.5	1
40ww	OPh*p*Cl	OPh*p*Cl	2	4	1	4	4	4	4	4	4	2	4	1	1	0.5	2
40xx	OPh*p*Cl	O(CH2)6	>16	>16	16	>16	>16	>16	>16	>16	>16	>16	>16	>16	16	8	16
40yy	OPh*p*Cl	O(CH2)8	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16

[a] Vancomycin-intermediate resistant *Staphylococcus aureus.* [b] Vancomycin-susceptible *Enterococcus faecalis.* [c] Vancomycin-resistant (van A) *Enterococcus faecalis.* [d] Vancomycin-resistant (van A) *Enterococcus faecium*. [e] Vancomycin-resistant (van A) and Synercid-resistant (sat G) *Enterococcus faecium*. [f] Vancomycin-resistant (van A) and Synercid-resistant (sat A) *Enterococcus faecium*.

2.98 (t, $J = 6.9$ Hz, 2H), 2.39 (s, 3H), 1.92–1.87 (m, 2H), 1.75–1.69 (m, 2H), 1.65–1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 196.2$, 191.1, 164.5, 132.3, 130.2, 119.4, 115.1, 68.4, 31.0, 29.6, 29.2, 25.5; HRMS: calcd for $C_{14}H_{18}O_3S$ $[M+Na]^+$: 289.0869, found 289.0868.

39q: $R_f = 0.25$ (15% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1695$, 1600, 1510, 1257, 1159, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.96$ (s, 1H), 7.90 (d, $J = 9.5$ Hz, 2H), 7.05 (d, $J = 9.5$ Hz, 2H), 4.10 (t, $J = 7.0$ Hz, 2H), 2.98 (t, $J = 7.1$ Hz, 2H), 2.38 (s, 3H), 1.91–1.85 (m, 2H), 1.72–1.66 (m, 2H), 1.59–1.49 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 196.2$, 191.1, 164.5, 132.3, 130.2, 115.1, 68.5, 31.0, 29.8, 29.3, 28.8, 25.9, 25.5; HRMS: calcd for $C_{15}H_{20}O_3S$ $[M+Na]^+$: 303.1025, found 303.1030.

39r: $R_f = 0.34$ (10% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 1683$, 1601, 1257, 1159, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.97$ (s, 1H), 7.89 (d, $J = 10.0$ Hz, 2H), 7.06 (d, $J = 10.0$ Hz, 2H), 4.08 (t, $J = 6.5$ Hz, 2H), 2.93 (t, $J = 7.4$ Hz, 2H), 2.39 (s, 3H), 1.89–1.85 (m, 2H), 1.66–1.61 (m, 2H), 1.55–1.53 (m, 2H), 1.43–1.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 196.4, 192.5, 164.6, 132.4, 130.1, 115.1, 68.6, 31.0, 29.9, 29.7, 29.6, 29.5, 29.4, 29.1, 26.3, 25.5; HRMS: calcd for $C_{19}H_{28}O_3S$ $[M+Na]^+$: 359.1651, found 359.1652.

General procedure for the reductive alkylation of vancomycin: DIEA (15.0 µL, 1.2 equiv, 82.7 µmol) was added to a solution of vancomycin (**1**, 100.0 mg, 1.0 equiv, 69.0 µmol) in DMF/MeOH (1:1, 0.01M) and the appropriate aldehyde (**37**, **38**, or **39**, ≈18.0 mg, 1.3 equiv, 89.6 µmol). The solution was heated at 65 °C for 2 h and then allowed to cool to room temperature prior to addition of $NaCNBH_3$ (8.6 mg, 2.0 equiv, 138.0 µmol). The reaction mixture was then stirred at 65 °C for an additional 2 h and allowed to cool to ambient temperature overnight (12–18 h). Purification by preparative reverse-phase HPLC (VYDAC C18, 25 mm × 250 mm, flow rate 6.5 mL min^{-1}, 0 → 100% CH_3CN (0.1% TFA) in H_2O over 30 min) gave the desired compounds **40** (analytical HPLC data given below for LiChrospher C18, 6 mm × 250 mm, flow rate 1.0 mL min^{-1}, 0 → 100% CH_3CN (0.05% TFA) in H_2O (0.05% TFA) over 10 min for **40a–qq**, over 8 min for **40rr–yy**.).

40a: $t_R = 7.0$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.92$ (d, $J =$ 9.0 Hz, 2H), 7.76 (d, $J = 15.0$ Hz, 2H), 7.66 (d, $J = 9.5$ Hz, 1H), 7.48 (br, 1H), 7.22 (d, $J = 8.5$ Hz, 1H), 7.11 (s, 1H), 7.05 (d, $J = 9.5$ Hz, 2H), 6.78 (br s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (br s, 2H), 5.98–5.91 (m, 1H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.28–5.10 (m, 2H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20–3.88 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.60–2.59 (m, 2H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.77 (s, 3H), 1.36 (m, 2H), 1.25 (d, $J = 6.25$ Hz, 3H), 1.00–0.97 (m, 6H); LCMS (ES): calcd for $C_{78}H_{89}Cl_2N_9O_{25}$ $[M+H]^+$: 1623.5, found 1623.5.

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40b: $t_R = 7.2$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.80$ (d, $J =$ 9.2 Hz, 2H), 7.80 (s, 1H), 7.73 (d, $J = 13.0$ Hz, 2H), 7.60 (d, $J = 10.0$ Hz, 1H), 7.48 (br, 1H), 7.24 (d, $J = 8.5$ Hz, 1H), 7.11 (s, 1H), 7.06 (d, $J = 10.0$ Hz, 2H), 6.80 (s, 2H), 6.65 (s, 1H), 6.50 (d, $J = 2.5$ Hz, 1H), 6.08 (s, 2H), 5.88–5.79 (m, 1H), 5.63–5.57 (m, 2H), 5.47 (d, $J = 15.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.08–4.99 (m, 2H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.06–3.88 (m, 6H), 3.72 (d, $J =$ 8.0 Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.29–2.25 (m, 2H), 2.15 (m, 2H), 2.01–1.91 (m, 3H), 1.78 (s, 3H), 1.36 (m, 2H), 1.25 (d, $J =$ 6.25 Hz, 3H), 1.04–1.00 (m, 6H); LCMS (ES): calcd for $C_{79}H_{91}Cl_2N_9O_{25}$ $[M+H]^+$: 1637.5, found 1637.5.

40c: $t_R = 7.3$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.91$ (d, $J =$ 9.8 Hz, 2H), 7.68 (d, $J = 13.0$ Hz, 2H), 7.66 (d, $J = 9.5$ Hz, 1H), 7.58 (br s, 1H), 7.24 (d, $J = 8.6$ Hz, 1H), 7.11 (s, 1H), 7.10 (d, $J = 10.0$ Hz, 2H), 6.8 (s, 2H), 6.62 (s, 1H), 6.50 (d, $J = 2.5$ Hz, 1H), 6.10 (s, 2H), 5.88–5.79 (m, 1H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.56 (d, $J = 4.5$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.08–4.99 (m, 2H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.04–3.88 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.16–2.12 (m, 4H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.86–1.74 (m, 5H), 1.62–1.56 (m, 2H), 1.36 (m, 2H), 1.25 (d, $J = 6.25$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 5.85$ Hz, 3H); LCMS (ES): calcd for $C_{80}H_{93}Cl_2N_9O_{25}$ $[M+H]^+$: 1651.5, found 1651.4.

40d: $t_R = 9.0$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.92$ (d, $J =$ 9.0 Hz, 2H), 7.80 (s, 1H), 7.75 (d, $J = 13.0$ Hz, 2H), 7.48 (br, 1H), 7.20 (d, $J = 8.2$ Hz, 1H), 7.11 (s, 1H), 7.05 (d, $J = 9.9$ Hz, 2H), 6.80 (s, 2H), 6.63 (s, 1H), 6.50 (d, $J = 2.5$ Hz, 1H), 6.08 (br s, 2H), 5.91–5.83 (m, 1H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.47–5.35 (m, 3H), 5.08–5.07 (m, 1H), 5.01–5.00 (m, 1H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.08–3.88 (m, 6H), 3.72 (d, $J =$ 8.0 Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.15–2.01 (m, 5H), 1.92–1.74 (m, 5H), 1.41–1.36 (m, 10H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 5.8$ Hz, 3H); LCMS (ES): calcd for $C_{83}H_{99}Cl_2N_9O_{25}$ $[M+H]^+$: 1693.7, found 1693.8.

40e: $t_R = 7.1$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.78$ (s, 1H), 7.76 (d, $J = 15.0$ Hz, 2H), 7.66 (d, $J = 9.5$ Hz, 1H), 7.49–7.44 (m, 4H), 7.23–7.21 (m, 2H), 7.11 (s, 1H), 6.80 (s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08–5.94 (m, 3H), 5.65–5.55 (m, 3H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46–5.35 (m, 3H), 5.35 (d, $J = 3.9$ Hz, 1H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.13–4.10 (m, 2H), 4.04–3.88 (m, 4H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.64–2.60 (m, 2H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.77 (m, 3H), 1.36 (m, 2H), 1.25 (d, $J = 6.25$ Hz, 3H), 1.04–0.98 (m, 6H); LCMS (ES): calcd for $C_{78}H_{89}Cl_2N_9O_{25}$ $[M+H]^+$: 1623.5, found 1623.5.

40f: $t_R = 7.2$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.78–7.75$ (s, 1H), 7.73 (d, $J = 17.0$ Hz, 2H), 7.60 (d, $J = 9.0$ Hz, 1H), 7.54–7.45 (m, 4H), 7.26–7.22 (d, $J = 8.5$ Hz, 2H), 7.11 (s, 1H), 6.78 (br s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 5.96–5.86 (m, 1H), 5.66 (d, $J = 8.0$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.15–5.06 (m, 2H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J =$ 8.8 Hz, 1H), 4.20 (s, 1H), 4.08–3.88 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.20 (m, 4H), 2.01–1.95 (m, 3H), 1.76 (s, 3H), 1.36 (m, 2H), 1.25 (d, $J = 6.25$ Hz, 3H), 1.02–1.00 (m, 6H); LCMS (ES): calcd for $C_{79}H_{91}Cl_2N_9O_{25}$ $[M+H]^+$: 1637.5, found 1637.4.

40g: $t_R = 7.5$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.80$ (s, 1H), 7.73 (d, $J = 13.5$ Hz, 2H), 7.63 (d, $J = 10.0$ Hz, 1H), 7.52–7.45 (m, 4H), 7.24–7.22 (m, 2H), 7.11 (s, 1H), 6.78 (s, 2H), 6.62 (s, 1H), 6.50 (d, $J =$ 2.5 Hz, 1H), 6.00–5.90 (m, 3H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J =$ 4.4 Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.12–5.06 (m, 2H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J =$ 8.8 Hz, 1H), 4.20 (s, 1H), 4.10–3.88 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.30–2.15 (m, 4H), 2.00–1.90 (m, 3H), 1.80–1.74 (m, 3H), 1.70–1.64 (m, 5H), 1.36 (m, 2H), 1.25 (d, $J = 6.25$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 5.85$ Hz, 3H); LCMS (ES): calcd for $C_{80}H_{93}Cl_2N_9O_{25}$ $[M+H]^+$: 1651.6, found 1651.6.

40h: $t_R = 9.4$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.85$ (s, 1H), 7.73 (d, $J = 15.5$ Hz, 2H), 7.68 (d, $J = 9.0$ Hz, 1H), 7.52–7.48 (m, 4H), 7.26–7.22 (m, 2H), 7.11 (s, 1H), 6.83 (s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (br s, 2H), 5.91–5.83 (m, 1H), 5.60–5.45 (m, 4H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.28–5.10 (m, 2H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.08–3.88 (m, 6H), 3.72 (d, $J =$ 8.0 Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.15–2.01 (m, 5H), 1.92–1.70 (m, 11H), 1.55–1.48 (m, 2H), 1.41–1.25 (m, 12H), 1.03–0.99 (m, 6H); LCMS (ES): calcd for $C_{83}H_{99}Cl_2N_9O_{25}$ $[M+H]^+$: 1693.7, found 1693.8.

40i: $t_R = 8.5$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.76–7.72$ (m, 2H), 7.66 (d, $J = 9.5$ Hz, 1H), 7.50–7.47 (m, 3H), 7.22 (d, $J = 8.45$ Hz, 1H), 7.11 (s, 1H), 7.02–7.00 (m, 1H), 6.80 (s, 2H), 6.62 (s, 1H), 6.49 (d, $J =$ 2.2 Hz, 1H), 6.08 (br s, 2H), 5.95–5.88 (m, H), 5.65–5.57 (m, 2H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46–5.42 (m, 3H), 5.35 (d, $J = 3.9$ Hz, 1H), 4.90 (q, $J =$ 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20–3.88 (m, 9H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.73–2.67 (m, 2H), 2.15 (m, 2H), 2.01–1.85 (m, 3H), 1.77 (s, 3H), 1.62–1.53 (m, 2H), 1.36 (m, 2H), 1.25 (d, $J = 6.25$ Hz, 3H), 1.05–0.99 (m, 9H); LCMS (ES): calcd for $C_{81}H_{95}Cl_2N_9O_{26}$ $[M+H]^+$: 1682.6, found 1682.6.

40j: $t_R = 8.8$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.82$ (s, 1H), 7.77 (d, $J = 13.7$ Hz, 2H), 7.69 (d, $J = 9.3$ Hz, 1H), 7.50–7.48 (m, 3H), 7.25 (d, $J = 8.70$ Hz, 1H), 7.13 (s, 1H), 7.02–7.00 (m, 1H), 6.78 (br s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (br s, 2H), 5.95–5.88 (m, 1H), 5.65–5.57 (m, 2H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46–5.42 (m, 3H), 5.35 (d, $J = 3.9$ Hz, 1H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20–4.11 (m, 5H), 4.04–3.88 (m, 4H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.34–2.30 (m, 2H), 2.15 (m, 2H), 2.03–1.99 (m, 2H), 1.80–1.74 (m, 6H), 1.62–1.49 (m, 2H), 1.36 (m, 2H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.05–1.00 (m, 9H); LCMS (ES): calcd for $C_{82}H_{97}Cl_2N_9O_{26}$ $[M+H]^+$: 1696.0, found 1696.0.

40k: $t_R = 9.8$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.76$ (s, 1H), 7.73 (d, $J = 15.0$ Hz, 2H), 7.64 (d, $J = 9.4$ Hz, 1H), 7.51–7.48 (m, 3H), 7.22 (d, $J = 8.5$ Hz, 1H), 7.11–7.05 (m, 2H), 6.76 (s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.05–5.97 (m, 3H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J =$ 4.4 Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.30–5.20 (m, 3H), 4.90 (q, $J =$ 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20–3.75 (m, 8H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.70–2.66 (m, 2H), 2.00–1.90 (m, 6H), 1.83–1.77 (m, 3H), 1.73–1.33 (m, 12H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.03–0.95 (m, 9H); LCMS (ES): calcd for $C_{84}H_{101}Cl_2N_9O_{26}$ $[M+H]^+$: 1724.6, found 1724.7.

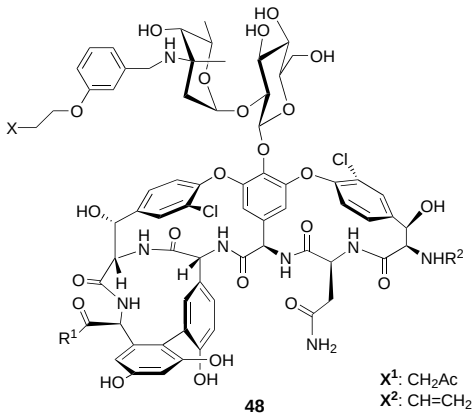
40l: $t_R = 10.1$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.82$ (s, 1H), 7.73 (d, $J = 15.3$ Hz, 2H), 7.63 (d, $J = 9.3$ Hz, 1H), 7.51–7.48 (m, 4H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.13 (s, 1H), 7.08 (d, $J = 8.0$ Hz, 1H), 6.80 (s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (br s, 2H), 5.98–5.90 (m, 1H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58–5.52 (m, 2H), 5.46–5.41 (m, 3H), 5.35 (d, $J = 3.9$ Hz, 1H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20–4.13 (m, 5H), 4.04–3.88 (m, 4H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.37–2.34 (m, 2H), 2.15 (m, 2H), 2.04–1.98 (m, 3H), 1.96–1.90 (m, 2H), 1.77 (m, 3H), 1.58–1.52 (m, 2H), 1.50–1.36 (m, 4H), 1.38–1.26 (m, 7H), 1.25 (d, $J = 6.25$ Hz, 3H), 1.04–0.95 (m, 9H); LCMS (ES): calcd for $C_{85}H_{103}Cl_2N_9O_{26}$ $[M+H]^+$: 1738.6, found 1738.6.

40m: $t_R = 7.4$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.76$ (d, $J =$ 15.0 Hz, 2H), 7.63 (d, $J = 10.0$ Hz, 1H), 7.50–7.47 (m, 3H), 7.38–7.23 (m, 6H), 7.12 (s, 1H), 7.05 (m, 2H), 6.78 (br s, 2H), 6.62 (s, 1H), 6.49 (d, $J =$ 2.2 Hz, 1H), 6.20–6.15 (m, 1H), 6.08 (br s, 2H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58–5.48 (m, 4H), 5.41–5.35 (m, 2H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.77 (s, 2H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.16–3.88 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01–2.94 (m, 3H), 2.29–2.20 (m, 4H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.77 (s, 3H), 1.36 (m, 2H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.05–1.01 (m, 6H); LCMS (ES): calcd for $C_{85}H_{95}Cl_2N_9O_{26}$ $[M+H]^+$: 1730.6, found 1731.0.

40n: $t_R = 7.1$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.79$ (s, 1H), 7.73 (d, $J = 14.7$ Hz, 2H), 7.62 (d, $J = 9.0$ Hz, 1H), 7.46–7.23 (m, 9H), 7.11 (s, 1H), 6.80 (br s, 2H), 7.00 (d, $J = 8.0$ Hz, 1H), 6.64 (s, 1H), 6.49 (d, $J =$ 2.2 Hz, 1H), 6.08 (br s, 2H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.96–5.88 (m, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.18–5.14 (m, 4H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.14–3.88 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.63–2.60 (m, 2H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.80–1.72 (m, 6H), 1.36 (m, 2H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 5.8$ Hz, 3H); LCMS (ES): calcd for $C_{84}H_{93}Cl_2N_9O_{26}$ $[M+H]^+$: 1716.6, found 1716.3.

40o: $t_R = 7.7$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K); 7.90–7.80 (m, 3H), 7.68 (d, $J = 9.3$ Hz, 1H), 7.48 (br, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.10–7.05 (m, 3H), 6.80 (s, 2H), 6.61 (s, 1H), 6.50 (d, $J = 2.4$ Hz, 1H), 6.10 (br s, 2H),

Table 5. Antibacterial activity (MIC: $\mu g\,mL^{-1}$) of amino acid 1 modified vancomycin derivatives against vancomycin-susceptible, vancomycin-intermediate resistant, and vancomycin-resistant bacteria.



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Compound	R^1	R^2	X	MU50[a]	133[a]	4002[b]	1528[c]	2689[c]	2741[c]	2781[c]	2805[c]	4001[d]	1669[e]	2671[e]	2823[e]	1803[f]	1924[f]	1944[f]
1	**vancomycin**			3.13	0.39	0.39	>100	50	>100	100	25	>100	100	50	100	50	25	50
48a	Gly	H	X^1	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
48c	Gly	L-Ala	X^1	8	2	4	8	>16	4	>16	8	>16	>16	16	16	8	16	>16
48g	Gly	ε-Ahx	X^1	16	4	4	8	>16	8	>16	>16	>16	>16	>16	>16	16	>16	16
48i	Gly	L-Val	X^1	8	4	4	8	>16	4	>16	8	>16	>16	>16	16	16	16	>16
48k	Gly	L-Leu	X^1	8	4	4	16	>16	4	>16	16	>16	>16	16	16	8	16	>16
48l	Gly	L-Ser	X^1	16	4	4	>16	>16	16	>16	>16	>16	>16	>16	>16	16	>16	16
48s	Gly	L-Lys	X^1	8	2	4	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
48w	Gly	H	X^2	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
48x	Gly	L-Val	X^2	2	1	2	8	>16	2	16	8	8	8	8	8	8	8	8
48z	Gly	L-Cha	X^2	8	4	4	16	>16	16	16	16	16	16	16	8	16	8	8
48ee	Gly	L-Lys	X^2	4	1	4	>16	>16	>16	>16	>16	16	>16	>16	16	16	16	16
48ff	L-Val	H	X^2	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
48gg	L-Val	L-Val	X^2	8	4	4	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
48ww	L-Phe	L-Lys	X^2	8	4	4	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16	>16
48ddd	L-Glu	L-Thi[g]	X^2	4	1	2	16	>16	4	>16	16	>16	>16	>16	>16	16	16	>16
48hhh	L-Lys	L-Val	X^2	8	1	2	>16	>16	8	>16	>16	16	16	16	16	8	8	8
48ooo	L-Lys	L-Lys	X^2	16	1	4	>16	>16	>16	>16	>16	16	>16	>16	16	16	16	16

[a] Vancomycin-intermediate resistant *Staphylococcus aureus.* [b] Vancomycin-susceptible *Enterococcus faecalis.* [c] Vancomycin-resistant (van A) *Enterococcus faecalis.* [d] Vancomycin-resistant (van A) *Enterococcus faecium*. [e] Vancomycin-resistant (van A) and Synercid-resistant (sat G) *Enterococcus faecium*. [f] Vancomycin-resistant (van A) and Synercid-resistant (sat A) *Enterococcus faecium*. [g] Thi is β-(2-thienyl)alanine.

5.88 – 5.70 (m, 2H), 5.60 (d, $J = 5.0$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.05 – 4.90 (m, 3H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.04 – 3.88 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.05 – 3.00 (m, 1H), 2.15 – 2.10 (m, 4H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.83 – 1.74 (m, 5H), 1.64 – 1.59 (m, 5H), 1.36 (m, 2H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 5.8$ Hz, 3H); LCMS (ES): calcd for $C_{85}H_{94}Cl_3N_9O_{26}$ $[M+H]^+$: 1765.0, found 1766.0.

40p: $t_R = 7.6$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.80$ (s, 1H), 7.75 (d, $J = 13.0$ Hz, 2H), 7.62 (d, $J = 10.0$ Hz, 1H), 7.51 – 7.39 (m, 7H), 7.25 (d, $J = 8.6$ Hz, 1H), 7.13 (s, 1H), 7.05 – 7.04 (m, 1H), 6.72 (s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 – 5.97 (m, 3H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 – 5.27 (m, 5H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 – 4.18 (m, 3H), 4.04 – 3.88 (m, 4H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.70 – 2.68 (m, 2H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.77 (s, 3H), 1.36 (m, 2H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.03 – 1.00 (m, 6H); LCMS (ES): calcd for $C_{84}H_{92}Cl_2N_9O_{26}$ $[M+H]^+$: 1751.9, found 1752.0.

40z: $t_R = 6.9$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.90$ (d, $J = 9.5$ Hz, 2H), 7.74 – 7.67 (m, 4H), 7.48 (br, 1H), 7.22 (d, $J = 8.5$ Hz, 1H), 7.11 (s, 1H), 7.05 (d, $J = 9.4$ Hz, 2H), 6.78 (brs, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (brs, 2H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.10 – 3.88 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.05 – 3.01 (m, 3H), 2.40 (s, 3H), 2.17 – 2.13 (m, 4H), 2.03 – 2.00 (m, 1H), 1.79 (s, 3H), 1.36 (m, 2H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.02 – 0.98 (m, 6H); LCMS (ES): calcd for $C_{78}H_{89}Cl_2N_9O_{26}S$ $[M+H]^+$: 1671.6, found 1671.6.

40aa: $t_R = 7.1$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.89$ (d, $J = 9.3$ Hz, 2H), 7.78 – 7.76 (m, 3H), 7.70 (d, $J = 9.6$ Hz, 1H), 7.48 (br, 1H), 7.24 (d, $J = 8.50$ Hz, 1H), 7.11 – 7.05 (m, 3H), 6.80 (s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (brs, 2H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.10 – 3.88 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.05 – 3.01 (m, 3H), 2.40 (s, 3H), 2.17 – 2.13 (m, 4H), 2.01 – 1.87 (m, 3H), 1.80 – 1.70 (m, 8H),

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1.65–1.59 (m, 2H), 1.36 (m, 2H), 1.25 (d, J = 6.25 Hz, 3H), 1.03–1.00 (m, 6H); LCMS (ES): calcd for $C_{79}H_{91}Cl_2N_9O_{26}S$ $[M+H]^+$: 1685.6, found 1685.6.

40bb: t_R = 7.2 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.90–7.80 (m, 3H), 7.75 (d, J = 13.5 Hz, 2H), 7.67 (d, J = 9.6 Hz, 1H), 7.48 (br, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.10–7.07 (m, 3H), 6.78 (brs, 2H), 6.62 (s, 1H), 6.50 (d, J = 2.3 Hz, 1H), 6.10 (s, 2H), 5.65 (d, J = 7.7 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 4.10–3.90 (m, 6H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.05–2.95 (m, 3H), 2.38 (s, 3H), 2.15 (m, 2H), 2.05–1.87 (m, 3H), 1.64–1.48 (m, 7H), 1.36 (m, 2H), 1.25 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 5.8 Hz, 3H), 1.02 (d, J = 5.8 Hz, 3H); LCMS (ES): calcd for $C_{80}H_{93}Cl_2N_9O_{26}S$ $[M+H]^+$: 1699.6, found 1699.6.

40cc: t_R = 7.4 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.90 (d, J = 9.2 Hz, 2H), 7.78 (s, 1H), 7.76 (d, J = 15.0 Hz, 2H), 7.66 (d, J = 9.5 Hz, 1H), 7.48 (br, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.11 (s, 1H), 7.05 (d, J = 9.4 Hz, 2H), 6.78 (brs, 2H), 6.62 (s, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.08 (brs, 2H), 5.65 (d, J = 7.7 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 4.10–3.88 (m, 6H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.01–2.98 (m, 3H), 2.38 (s, 3H), 2.15 (m, 2H), 2.01 (d, J = 13.5 Hz, 1H), 1.91–1.74 (m, 5H), 1.72–1.66 (m, 2H), 1.59–1.49 (m, 4H), 1.36 (m, 2H), 1.25 (d, J = 6.3 Hz, 3H), 1.02–0.98 (m, 6H); LCMS (ES): calcd for $C_{81}H_{95}Cl_2N_9O_{26}S$ $[M+H]^+$: 1713.6, found 1713.6.

40dd: t_R = 8.9 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.90 (d, J = 10.0 Hz, 2H), 7.78 (s, 1H), 7.76 (d, J = 15.0 Hz, 2H), 7.66 (d, J = 9.5 Hz, 1H), 7.48 (br, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.11 (s, 1H), 7.05 (d, J = 9.7 Hz, 2H), 6.78 (brs, 2H), 6.62 (s, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.08 (brs, 2H), 5.65 (d, J = 7.7 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 4.12–3.88 (m, 6H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.01–2.95 (m, 3H), 2.38 (s, 3H), 2.15 (m, 2H), 2.01 (d, J = 13.5 Hz, 1H), 1.89–1.74 (m, 5H), 1.66–1.61 (m, 2H), 1.55–1.53 (m, 2H), 1.43–1.34 (m, 12H), 1.25 (d, J = 6.3 Hz, 3H), 1.04–1.00 (m, 6H); LCMS (ES): calcd for $C_{85}H_{103}Cl_2N_9O_{26}S$ $[M+H]^+$: 1769.7, found 1769.7.

40ee: t_R = 7.0 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.90 (s, 1H), 7.75 (d, J = 13.5 Hz, 2H), 7.66 (d, J = 9.5 Hz, 1H), 7.54–7.45 (m, 4H), 7.26–7.22 (m, 2H), 7.11 (s, 1H), 6.78 (brs, 2H), 6.63 (s, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.08 (brs, 2H), 5.67 (d, J = 7.6 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 4.14 (t, J = 6.3 Hz, 2H), 4.04–3.88 (m, 4H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.03–3.01 (m, 3H), 2.40 (s, 3H), 2.17–2.13 (m, 4H), 2.01 (d, J = 13.5 Hz, 1H), 1.80–1.74 (m, 6H), 1.36 (m, 2H), 1.25 (d, J = 6.3 Hz, 3H), 1.03–0.99 (m, 6H); LCMS (ES): calcd for $C_{78}H_{89}Cl_2N_9O_{26}S$ $[M+H]^+$: 1671.6, found 1671.6.

40ff: t_R = 7.2 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.77–7.75 (m, 1H), 7.75 (d, J = 15.3 Hz, 2H), 7.63 (d, J = 9.3 Hz, 1H), 7.54–7.45 (m, 4H), 7.25–7.22 (m, 2H), 7.11 (s, 1H), 6.78 (brs, 2H), 6.62 (s, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.08 (brs, 2H), 5.62 (d, J = 7.8 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 4.14 (t, J = 6.2 Hz, 2H), 4.04–3.88 (m, 4H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.04–3.00 (m, 3H), 2.39 (s, 3H), 2.15 (m, 2H), 2.01–1.92 (m, 3H), 1.78 (s, 3H), 1.36 (m, 2H), 1.25 (d, J = 6.2 Hz, 3H), 1.02–0.99 (m, 6H); LCMS (ES): calcd for $C_{79}H_{91}Cl_2N_9O_{26}S$ $[M+H]^+$: 1685.6, found 1685.6.

40gg: t_R = 7.8 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.80–7.75 (m, 3H), 7.68 (d, J = 10.0 Hz, 1H), 7.54–7.48 (m, 4H), 7.26–7.22 (m, 2H), 7.11 (s, 1H), 6.65 (s, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.08 (brs, 2H), 5.63 (d, J = 7.5 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 4.14 (t, J = 6.3 Hz, 2H), 4.08–3.88 (m, 6H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.05–3.01 (m, 3H), 2.40 (s, 3H), 2.15 (m, 2H), 2.01–1.92 (m, 7H), 1.77 (s, 3H), 1.66–1.62 (m, 2H), 1.36 (m, 2H), 1.25 (d, J = 6.2 Hz, 3H), 1.04 (d, J = 5.8 Hz, 3H), 1.02 (d, J = 5.8 Hz, 3H); LCMS (ES): calcd for $C_{80}H_{93}Cl_2N_9O_{26}S$ $[M+H]^+$: 1699.6, found 1699.7.

40hh: t_R = 7.7 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.80 (s, 1H), 7.73 (d, J = 14.5 Hz, 2H), 7.66 (d, J = 9.5 Hz, 1H), 7.55–7.44 (m, 3H), 7.40–7.10 (m, 4H), 6.78 (s, 2H), 6.62 (s, 1H), 6.50 (d, J = 2.5 Hz, 1H), 6.08 (brs, 2H), 5.65 (d, J = 7.7 Hz, 1H), 5.59 (d, J = 4.3 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 4.03–3.88 (m, 6H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.01–2.90 (m, 3H), 2.30 (s, 3H), 2.15 (m, 2H), 2.01 (d, J = 13.5 Hz, 1H), 1.85–1.75 (m, 5H), 1.65–1.55 (m, 5H), 1.52–1.40 (m, 2H), 1.36 (m, 2H), 1.25 (d, J = 6.25 Hz, 3H), 1.04 (d, J = 5.8 Hz, 3H), 1.02 (d, J = 5.85 Hz, 3H); LCMS (ES): calcd for $C_{81}H_{95}Cl_2N_9O_{26}S$ $[M+H]^+$: 1713.6, found 1713.6.

40ii: t_R = 9.2 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.82 (s, 1H), 7.75 (d, J = 15.5 Hz, 2H), 7.63 (d, J = 9.6 Hz, 1H), 7.52–7.48 (m, 4H), 7.26–7.22 (m, 2H), 7.11 (s, 1H), 6.78 (s, 2H), 6.62 (s, 1H), 6.50 (d, J = 2.2 Hz, 1H), 6.08 (brs, 2H), 5.67 (d, J = 8.0 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 4.08–3.88 (m, 6H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.01–2.93 (m, 3H), 2.39 (s, 3H), 2.15 (m, 2H), 2.01 (d, J = 13.5 Hz, 1H), 1.89–1.74 (m, 8H), 1.66–1.61 (m, 2H), 1.55–1.53 (m, 2H), 1.43–1.34 (m, 12H), 1.36 (m, 2H), 1.25 (d, J = 6.25 Hz, 3H), 1.04–1.00 (m, 6H); LCMS (ES): calcd for $C_{85}H_{103}Cl_2N_9O_{26}S$ $[M+H]^+$: 1769.7, found 1769.7.

40jj: t_R = 7.2 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.78 (s, 1H), 7.76 (d, J = 15.0 Hz, 2H), 7.66 (d, J = 9.5 Hz, 1H), 7.50–7.46 (m, 3H), 7.22 (d, J = 8.5 Hz, 1H), 7.11 (s, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.78 (brs, 2H), 6.62 (s, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.08 (s, 2H), 5.65 (d, J = 7.7 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20–4.13 (m, 5H), 4.04–3.88 (m, 4H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.14 (t, J = 7.0 Hz, 2H), 3.01 (d, J = 14.6 Hz, 1H), 2.40 (s, 3H), 2.20–2.15 (m, 4H), 2.01 (d, J = 13.5 Hz, 1H), 1.96–1.88 (m, 2H), 1.79 (m, 3H), 1.60–1.54 (m, 2H), 1.36 (m, 2H), 1.25 (d, J = 6.3 Hz, 3H), 1.05–1.00 (m, 9H); LCMS (ES): calcd for $C_{82}H_{97}Cl_2N_9O_{27}S$ $[M+H]^+$: 1743.6, found 1743.6.

40kk: t_R = 7.4 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.80 (s, 1H), 7.75 (d, J = 14.7 Hz, 2H), 7.63 (d, J = 9.8 Hz, 1H), 7.48–7.47 (m, 2H), 7.42 (s, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.11 (s, 1H), 7.00 (d, J = 7.9 Hz, 2H), 6.62 (s, 1H), 6.49 (d, J = 2.2 Hz, 1H), 5.66 (d, J = 7.8 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 4.12–4.10 (m, 2H), 4.04–3.88 (m, 4H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.05–3.01 (m, 3H), 2.40 (s, 3H), 2.15 (m, 2H), 2.01 (d, J = 13.5 Hz, 1H), 1.80–1.74 (m, 10H), 1.60–1.52 (m, 4H), 1.36 (m, 2H), 1.25 (d, J = 6.2 Hz, 3H), 1.04–0.98 (m, 9H); LCMS (ES): calcd for $C_{83}H_{99}Cl_2N_9O_{27}S$ $[M+H]^+$: 1757.9, found 1758.0.

40ll: t_R = 8.1 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.90 (s, 1H), 7.76 (d, J = 15.0 Hz, 2H), 7.65 (d, J = 9.3 Hz, 1H), 7.50–7.44 (m, 3H), 7.22 (d, J = 8.4 Hz, 1H), 7.11 (s, 1H), 7.00–6.92 (m, 3H), 6.62 (s, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.08 (brs, 2H), 5.67 (d, J = 7.2 Hz, 1H), 5.59 (d, J = 4.5 Hz, 1H), 5.46 (d, J = 14.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20–4.10 (m, 5H), 4.04–3.88 (m, 4H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.02–2.91 (m, 3H), 2.37 (s, 3H), 2.15 (m, 2H), 2.00–1.75 (m, 10H), 1.65–1.50 (m, 7H), 1.44–1.20 (m, 11H), 1.05–1.00 (m, 9H); LCMS (ES): calcd for $C_{85}H_{103}Cl_2N_9O_{27}S$ $[M+H]^+$: 1785.7, found 1785.6.

40mm: t_R = 8.4 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.81 (s, 1H), 7.76 (d, J = 15.2 Hz, 2H), 7.76 (d, J = 9.6 Hz, 1H), 7.50–7.40 (m, 3H), 7.22 (d, J = 8.5 Hz, 1H), 7.11 (s, 1H), 6.94–6.90 (m, 1H), 6.78 (brs, 2H), 6.62 (s, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.08 (brs, 2H), 5.63–5.55 (m, 2H), 5.45 (d, J = 13.0 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.20 (s, 1H), 4.05–3.90 (m, 6H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.05–2.90 (m, 3H), 2.73 (s, 3H), 2.15 (m, 2H), 2.01 (d, J = 13.5 Hz, 1H), 1.80–1.74 (m, 3H), 1.65–1.20 (m, 18H), 1.05–1.00 (m, 9H); LCMS (ES): calcd for $C_{86}H_{105}Cl_2N_9O_{27}S$ $[M+H]^+$: 1799.7, found 1799.7.

40nn: t_R = 8.6 min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): δ = 7.78–7.73 (m, 2H), 7.53–7.48 (m, 8H), 7.22 (d, J = 8.5 Hz, 1H), 7.11–7.08 (m, 2H), 6.78 (brs, 2H), 6.62 (s, 1H), 6.49 (d, J = 2.2 Hz, 1H), 6.08 (brs, 2H), 5.60–5.58 (m, 2H), 5.47 (d, J = 14.1 Hz, 2H), 5.35 (d, J = 3.9 Hz, 1H), 4.90 (q, J = 6.6 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.22–4.20 (m, 3H), 4.04–3.88 (m, 4H), 3.72 (d, J = 8.0 Hz, 2H), 3.49 (m, 1H), 3.17–3.15 (m, 2H), 3.01 (d, J = 14.6 Hz, 1H), 2.40 (s, 3H), 2.23–2.15 (m, 4H), 2.01 (d, J = 13.5 Hz, 1H), 1.77 (s, 3H), 1.36 (m, 2H), 1.25 (d, J = 6.3 Hz,

3H), 1.04–1.02 (m, 6H); LCMS (ES): calcd for $C_{85}H_{95}Cl_2N_9O_{27}S$ $[M+H]^+$: 1778.7, found 1778.7.

40oo: $t_R = 8.8$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.79$ (s, 1H), 7.76 (d, $J = 15.1$ Hz, 2H), 7.63 (d, $J = 9.7$ Hz, 1H), 7.50–7.32 (m, 8H), 7.20–6.95 (m, 3H), 6.78 (br s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (br s, 2H), 5.67 (d, $J = 7.9$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.37–5.25 (m, 3H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20–3.90 (m, 7H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.00–2.95 (m, 3H), 2.36 (s, 3H), 2.15 (m, 2H), 2.03–1.74 (m, 7H), 1.64 (s, 3H), 1.36 (m, 2H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 5.8$ Hz, 3H); LCMS (ES): calcd for $C_{86}H_{97}Cl_2N_9O_{27}S$ $[M+H]^+$: 1792.3, found 1792.3.

40pp: $t_R = 7.7$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.76$ (d, $J = 15.0$ Hz, 2H), 7.68 (d, $J = 9.5$ Hz, 1H), 7.50–7.45 (m, 5H), 7.22 (d, $J = 8.45$ Hz, 1H), 7.11 (s, 1H), 7.02 (d, $J = 8.0$ Hz, 1H), 6.78 (br s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (s, 2H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20–4.10 (m, 5H), 4.04–3.88 (m, 4H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01–2.97 (m, 3H), 2.39 (s, 3H), 2.15 (m, 2H), 2.01–1.90 (m, 5H), 1.80–1.74 (m, 5H), 1.65–1.63 (m, 2H), 1.56–1.37 (m, 5H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.04–0.96 (m, 9H); LCMS (ES): calcd for $C_{85}H_{94}Cl_3N_9O_{27}S$ $[M+H]^+$: 1813.1, found 1813.8.

40qq: $t_R = 7.8$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.78$ (s, 1H), 7.76 (d, $J = 15.0$ Hz, 2H), 7.66 (d, $J = 9.5$ Hz, 1H), 7.51–7.44 (m, 5H), 7.22 (d, $J = 8.5$ Hz, 1H), 7.11 (s, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 6.78 (br s, 2H), 6.62 (s, 1H), 6.50 (d, $J = 2.5$ Hz, 1H), 6.08 (br s, 2H), 5.67 (d, $J = 7.9$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35–5.28 (m, 3H), (d, $J = 3.9$ Hz, 1H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20–4.15 (m, 3H), 4.04–3.88 (m, 4H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49–3.45 (m, 1H), 3.05–3.01 (m, 3H), 2.40 (s, 3H), 2.15 (m, 2H), 2.03–1.96 (d, $J = 13.5$ Hz, 3H), 1.92–1.74 (m, 5H), 1.36 (m, 2H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.04–1.02 (m, 6H); LCMS (ES): calcd for $C_{86}H_{96}Cl_3N_9O_{27}S$ $[M+H]^+$: 1826.1, found 1826.2.

40rr: $t_R = 6.6$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.78$ (s, 1H), 7.76 (d, $J = 15.0$ Hz, 2H), 7.66 (d, $J = 9.5$ Hz, 1H), 7.50–7.38 (m, 8H), 7.22 (d, $J = 8.4$ Hz, 1H), 7.11 (s, 1H), 7.03–6.78 (m, 3H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.10–6.04 (m, 3H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.20 (s, 2H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.04–3.88 (m, 4H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.80–1.74 (m, 3H), 1.64 (s, 3H), 1.36 (m, 2H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 5.8$ Hz, 3H); LCMS (ES): calcd for $C_{80}H_{87}Cl_2N_9O_{26}$ $[M+H]^+$: 1661.5, found 1661.5.

40ss: $t_R = 7.7$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.77$ (s, 1H), 7.75 (d, $J = 14.5$ Hz, 2H), 7.66 (d, $J = 9.6$ Hz, 1H), 7.50–7.20 (m, 14H), 7.11 (s, 1H), 7.01–6.78 (m, 3H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (br s, 2H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35–5.26 (m, 5H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.04–3.88 (m, 4H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.80–1.74 (m, 3H), 1.36 (m, 2H), 1.25 (d, $J = 6.3$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 5.8$ Hz, 3H); LCMS (ES): calcd for $C_{87}H_{93}Cl_2N_9O_{26}$ $[M+H]^+$: 1752.6, found 1752.6.

40tt: $t_R = 8.5$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.80$ (s, 1H), 7.73 (d, $J = 14.9$ Hz, 2H), 7.67 (d, $J = 9.4$ Hz, 1H), 7.50–7.32 (m, 5H), 7.23 (d, $J = 8.5$ Hz, 1H), 7.11 (s, 1H), 6.96–6.86 (m, 3H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (br s, 2H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35–5.32 (m, 3H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.10–3.92 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.85–1.70 (m, 8H), 1.51–1.45 (m, 2H), 1.35–1.25 (m, 13H), 1.00–0.86 (m, 9H); LCMS (ES): calcd for $C_{88}H_{103}Cl_2N_9O_{26}$ $[M+H]^+$: 1774.7, found 1774.7.

40uu: $t_R = 9.4$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.82$ (s, 1H), 7.76 (d, $J = 15.0$ Hz, 2H), 7.67 (d, $J = 9.7$ Hz, 1H), 7.49–7.30 (m, 8H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.05–7.00 (m, 2H), 6.80 (br s, 2H), 6.63 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.01 (s, 2H), 5.65 (d, $J = 7.5$ Hz, 1H), 5.59 (d, $J = 4.5$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.33–5.23 (m, 3H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.07–3.81 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.83–1.75 (m, 8H), 1.50–1.45 (m, 2H), 1.36–1.00 (m, 23H); LCMS (ES): calcd for $C_{90}H_{107}Cl_2N_9O_{26}$ $[M+H]^+$: 1802.7, found 1802.7.

40vv: $t_R = 7.0$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.78$ (s, 1H), 7.76 (d, $J = 15.0$ Hz, 2H), 7.66 (d, $J = 9.5$ Hz, 1H), 7.45–7.20 (m, 8H), 7.08–7.00 (m, 2H), 6.78 (br s, 2H), 6.62 (s, 1H), 6.49 (d, $J = 2.2$ Hz, 1H), 6.08 (br s, 2H), 5.89 (m, 5H), 5.65 (d, $J = 8.0$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.16 (s, 2H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.04–3.88 (m, 4H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.78–1.70 (m, 6H), 1.36 (m, 2H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 5.8$ Hz, 3H); LCMS (ES): calcd for $C_{80}H_{86}Cl_3N_9O_{26}$ $[M+H]^+$: 1696.9, found 1696.8.

40ww: $t_R = 8.0$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.77$ (d, $J = 14.7$ Hz, 2H), 7.67 (d, $J = 9.5$ Hz, 1H), 7.51–7.26 (m, 12H), 7.11 (s, 1H), 7.00–6.9 (m, 3H), 6.62 (s, 1H), 6.51 (d, $J = 2.5$ Hz, 1H), 6.10 (s, 1H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.21–5.16 (m, 4H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.04–3.88 (m, 4H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.80–1.74 (m, 3H), 1.64 (s, 3H), 1.36 (m, 2H), 1.25 (d, $J = 6.25$ Hz, 3H), 1.04 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 5.85$ Hz, 3H); LCMS (ES): calcd for $C_{87}H_{91}Cl_4N_9O_{26}$ $[M+H]^+$: 1821.5, found 1822.0.

40xx: $t_R = 9.2$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.78–7.74$ (m, 3H), 7.66 (d, $J = 9.5$ Hz, 1H), 7.44–7.12 (m, 9H), 6.92–6.78 (m, 2H), 6.60 (s, 1H), 6.50 (d, $J = 2.0$ Hz, 1H), 6.05 (s, 2H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.20–4.90 (m, 2H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.08–3.89 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.15 (m, 2H), 1.96–1.70 (m, 9H), 1.50–1.39 (m, 4H), 1.34–1.20 (m, 10H), 1.05–0.90 (m, 9H); LCMS (ES): calcd for $C_{88}H_{102}Cl_3N_9O_{26}$ $[M+H]^+$: 1809.1, found 1809.2.

40yy: $t_R = 9.8$ min; ^{1}H NMR (500 MHz, CD_3OD, 330 K): $\delta = 7.76$ (d, $J = 15.0$ Hz, 2H), 7.65 (d, $J = 9.8$ Hz, 1H), 7.42–7.22 (m, 8H), 7.02–6.82 (m, 4H), 6.60–6.50 (m, 3H), 6.14 (s, 2H), 5.65 (d, $J = 7.7$ Hz, 1H), 5.58 (d, $J = 4.4$ Hz, 1H), 5.46 (d, $J = 14.0$ Hz, 2H), 5.35 (d, $J = 3.9$ Hz, 1H), 5.22 (s, 2H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 4.36 (d, $J = 8.8$ Hz, 1H), 4.20 (s, 1H), 4.08–3.88 (m, 6H), 3.72 (d, $J = 8.0$ Hz, 2H), 3.49 (m, 1H), 3.01 (d, $J = 14.6$ Hz, 1H), 2.15 (m, 2H), 2.01 (d, $J = 13.5$ Hz, 1H), 1.81–1.70 (m, 8H), 1.50–1.20 (m, 21H), 1.09–0.80 (m, 9H); LCMS (ES): calcd for $C_{90}H_{106}Cl_3N_9O_{26}$ $[M+H]^+$: 1836.2, found 1835.9.

Preparation of Boc-protected 42a and 42b: $NaHCO_3$ (430.0 mg, 1.5 equiv, 5.3 mmol) and Boc_2O (1.6 g, 2.2 equiv, 7.7 mmol) were was added at 0 °C to a solution of vancomycin (**1**, 5.0 g, 1.0 equiv, 3.5 mmol) in 1,4-dioxane/H_2O (1:1, 60.0 mL, 0.06 M). After stirring for 4 h at 0 °C, acetone (500 mL) was added to precipitate the desired product. After filtration, the residue was dissolved in MeOH/DMF (1:1, 50 mL) and precipitated by the addition of acetone (500 mL). A portion of the isolated precipitate (1.0 g, 1.0 equiv, 0.6 mmol) was dissolved in DMF/MeOH (4:1, 25 mL) and the appropriate aldehyde (**39e** or **40e**) was added (≈250 mg, 2.0 equiv, 1.2 mmol) followed by *i*Pr_2NEt (460 μL, 4.0 equiv, 2.4 mmol) and $NaCNBH_3$ (160.0 mg, 4.0 equiv, 2.4 mmol). The mixture was warmed to 65 °C and stirred for 20 h. After cooling of the reaction mixture, Et_2O (200 mL) was added to precipitate the product (**42a** or **42b**; HPLC data: LiChrospher C18, 6 mm × 250 mm, flow rate = 1.0 mL min^{-1}, 0 → 100% CH_3CN (0.05% TFA) in H_2O (0.05% TFA) over 10 min) which was then collected by filtration and used without further purification.

42a: $t_R = 8.5$ min; LCMS (ES): calcd for $C_{77}H_{87}Cl_2N_9O_{25}$ $[M+H]^+$: 1610.5, found 1610.5.

42b: $t_R = 9.0$ min; LCMS (ES): calcd for $C_{78}H_{89}Cl_2N_9O_{26}S$ $[M+H]^+$: 1672.6, found 1672.6.

General procedure for the conversion of 42a and 42b to 40x and 44: TFA (10 mL) was added dropwise at ambient temperature to a vigorously stirred suspension of Boc-protected vancomycin derivative (**42a** or **42b**, 2.0 g, ≈1.1 mmol) in CH_2Cl_2 (90 mL). After stirring for 1 h, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in MeOH (40 mL). Et_2O (250 mL) was then added to precipitate the desired product. A portion of this product (1.00 g, 1.0 equiv, ≈0.68 mmol) was

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dissolved in pyridine/H_2O (1:1, 22 mL, 0.03 M) and phenylthioisocyanate (82.5 μL, 1.5 equiv, 1.03 mmol) was added. After stirring for 4 h at ambient temperature, Et_2O (250 mL) was added to precipitation the desired thiourea which was isolated by filtration. To a suspension of the intermediate thiourea in CH_2Cl_2 (50 mL) was added of TFA (2.5 mL) dropwise. After 2 h, MeOH (100 mL) was added and the solution was carefully evaporated to dryness without heating. Dissolution of the residue in MeOH (25 mL) and precipitation with Et_2O (200 mL) followed by filtration gave the pure hexapeptide. HPLC data: LiChrospher C18, 6 mm × 250 mm, flow rate = 1.0 mL min^{-1}, 0 → 100 % CH_3CN (0.05 % TFA) in H_2O (0.05 % TFA) over 10 min.

40x: t_R = 6.9 min; LCMS (ES): calcd for $C_{70}H_{74}Cl_2N_8O_{24}$ $[M+H]^+$: 1483.2, found 1483.2.

44: t_R = 6.8 min; LCMS (ES): calcd for $C_{71}H_{76}Cl_2N_8O_{25}S$ $[M+H]^+$: 1545.3, found 1545.3.

40y (Table 2, prepared in a similar manner as above): t_R = 7.2 min; LCMS (ES): calcd for $C_{72}H_{78}Cl_2N_8O_{24}$ $[M+H]^+$: 1511.3, found 1511.4.

Preparation of compounds 40q–w (Table 2) Acylation of the hexapeptide (40x or 40y): *i*Pr_2NEt (7.0 μL, 3.0 equiv, 40.0 μmol) followed by HBTU (7.7 mg, 1.5 equiv, 20.0 μmol) were added room tempeature to a solution of the hexapeptide **40x** or **40y** (20.0 mg, 1.0 equiv, ≈13.3 μmol) in DMF (660 μL, 0.02 M) and the appropriate Fmoc-protected amino acid (Scheme 6, ≈6.6 mg, 1.5 equiv, 20.0 μmol). After stirring for 2 h, Et_2O (15 mL) was added to precipitate the product. After filtration, dissolution of the residue in MeOH/DMF (1:1, 2.0 mL) followed by precipitation with Et_2O (10 mL) gave the desired Fmoc-protected heptapeptide. Dissolution of this compound in 5 % piperidine in DMF (600 μL, 0.02 M) gave, after 30 min, the desired heptapeptide **40q** or **40y** which was precipitated by addition of Et_2O (10 mL) and purified by preparative HPLC (VYDAC C18, 25 mm × 250 mm, flow rate 6.5 mL min^{-1}, 0 → 100 % CH_3CN (0.01 % TFA) in H_2O over 30 min). Analytical HPLC data given below for LiChrospher C18, 6 mm × 250 mm, flow rate = 1.0 mL min^{-1}, 0 → 100 % CH_3CN (0.05 % TFA) in H_2O (0.05 % TFA) over 8 min.

40q: t_R = 6.6 min; LCMS (ES): calcd for $C_{74}H_{80}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1597.3, found 1597.4.

40r: t_R = 7.2 min; LCMS (ES): calcd for $C_{76}H_{84}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1625.4, found 1625.6.

40s: t_R = 6.4 min; LCMS (ES): calcd for $C_{73}H_{79}Cl_2N_9O_{25}$ $[M+H]^+$: 1554.3, found 1554.2.

40t: t_R = 7.0 min; LCMS (ES): calcd for $C_{75}H_{83}Cl_2N_9O_{25}$ $[M+H]^+$: 1582.4, found 1582.4.

40u: t_R = 6.5 min; LCMS (ES): calcd for $C_{74}H_{81}Cl_2N_9O_{25}$ $[M+H]^+$: 1568.3, found 1568.3.

40v: t_R = 6.8 min; LCMS (ES): calcd for $C_{79}H_{83}Cl_2N_9O_{25}$ $[M+H]^+$: 1630.4, found 1630.4.

40w: t_R = 7.00 min; LCMS (ES): calcd for $C_{83}H_{99}Cl_2N_{13}O_{26}$ $[M+H]^+$: 1766.6, found 1766.5.

General procedure for the solid phase synthesis of analogues 48a–48ooo (Scheme 9): A solution of vancomycin-derived olefin **40x** or thioacetate **44** (≈260 mg, 2.0 equiv, 0.18 mmol) in DMF (10.0 mL) was added to a suspension of the appropriate resin-bound amino acid (**46**, 250.0 mg) followed by the addition of *i*Pr_2NEt (62.0 mL, 4.0 equiv, 0.35 mmol) and HBTU (66.0 mg, 2.0 equiv, 0.18 mmol). The reaction mixture was shaken at room temperature for 1 h, the resin was collected by filtration and washed, sequentially, with DMF (10 mL), MeOH (10 mL) and CH_2Cl_2 (10 mL). A portion (25 mg) of the vancomycin-loaded resin thus obtained was mixed with the appropriate Fmoc-protected amino acid **47**, (Scheme 9, ≈5 mg, 2.0 equiv, 14.0 μmol) and suspended in DMF (1.0 mL). To this suspension was added *i*Pr_2NEt (5.0 μL, 4.0 equiv, 28.0 μmol) at ambient temperature, followed by HBTU (5.3 mg, 2.0 equiv, 14.0 μmol). The suspension was shaken for 2 h before the resin was collected and washed as described above. After re-suspension of the resin in 2 % piperidine in DMF (1 mL) and shaking for 1 h at room temperature to remove the Fmoc protecting group, the resin was collected and washed as above. To cleave the vancomycin derivative from the resin, a suspension of the resin in CH_2Cl_2 containing 2.5 % TFA (1.5 mL) was stirred for 1.5 h at ambient temperature. The resin was filtered, washed with MeOH (10 mL), and the combined washings were concentrated to afford vancomycin analogue **48** in essentially pure form. Analytical HPLC data given below for LiChrospher C18, 6 mm × 250 mm, flow rate 1.0 mL min^{-1}, 0 → 100 % CH_3CN (0.05 % TFA) in H_2O (0.05 % TFA) over 10 min.

48a: t_R = 7.4 min; LCMS (ES): calcd for $C_{73}H_{79}Cl_2N_9O_{26}S$ $[M+H]^+$: 1601.4, found 1600.9.

48b: t_R = 7.4 min; LCMS (ES): calcd for $C_{75}H_{82}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1659.5, found 1659.6.

48c: t_R = 7.2 min; LCMS (ES): calcd for $C_{76}H_{84}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1673.5, found 1673.2.

48d: t_R = 7.3 min; LCMS (ES): calcd for $C_{76}H_{84}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1673.5, found 1673.5.

48e: t_R = 7.3 min; LCMS (ES): calcd for $C_{76}H_{84}Cl_2N_1O_{27}S$ $[M+H]^+$: 1673.5, found 1673.5.

48f: t_R = 7.2 min; LCMS (ES): calcd for $C_{77}H_{86}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1687.5, found 1687.5.

48g: t_R = 7.4 min; LCMS (ES): calcd for $C_{79}H_{90}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1714.6, found 1715.0.

48h: t_R = 7.6 min; LCMS (ES): calcd for $C_{79}H_{90}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1715.5, found 1715.6.

48i: t_R = 7.3 min; LCMS (ES): calcd for $C_{78}H_{88}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1701.6, found 1701.5.

48j: t_R = 8.1 min; LCMS (ES): calcd for $C_{82}H_{94}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1755.7, found 1755.6.

48k: t_R = 7.4 min; LCMS (ES): calcd for $C_{79}H_{90}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1715.5, found 1715.5.

48l: t_R = 7.3 min; LCMS (ES): calcd for $C_{76}H_{84}Cl_2N_{10}O_{28}S$ $[M+H]^+$: 1689.5, found 1689.5.

48m: t_R = 7.4 min; LCMS (ES): calcd for $C_{77}H_{86}Cl_2N_{10}O_{28}S$ $[M+H]^+$: 1703.5, found 1703.6.

48n: t_R = 7.6 min; LCMS (ES): calcd for $C_{78}H_{88}Cl_2N_{10}O_{27}S_2$ $[M+H]^+$: 1733.6, found 1733.6.

48o: t_R = 7.7 min; LCMS (ES): calcd for $C_{82}H_{88}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1749.6, found 1749.6.

48p: t_R = 7.5 min; LCMS (ES): calcd for $C_{82}H_{80}Cl_2N_{10}O_{28}S$ $[M+H]^+$: 1765.6, found 1764.9.

48q: t_R = 7.6 min; LCMS (ES): calcd for $C_{80}H_{86}Cl_2N_{10}O_{27}S$ $[M+H]^+$: 1755.6, found 1755.6.

48r: t_R = 7.7 min; LCMS (ES): calcd for $C_{78}H_{89}Cl_2N_{11}O_{27}S$ $[M+H]^+$: 1715.5, found 1715.5.

48s: t_R = 7.3 min; LCMS (ES): calcd for $C_{79}H_{91}Cl_2N_{11}O_{27}S$ $[M+H]^+$: 1730.6, found 1730.5.

48t: t_R = 7.2 min; LCMS (ES): calcd for $C_{79}H_{90}Cl_2N_{12}O_{28}$ $[M+H]^+$: 1759.6, found 1759.6.

48u: t_R = 7.5 min; LCMS (ES): calcd for $C_{81}H_{92}Cl_2N_{10}O_{29}S$ $[M+H]^+$: 1772.6, found 1771.9.

48v: t_R = 7.6 min; LCMS (ES): calcd for $C_{82}H_{94}Cl_2N_{10}O_{29}S$ $[M+H]^+$: 1787.6, found 1787.6.

48x: t_R = 7.3 min; LCMS (ES): calcd for $C_{77}H_{86}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1638.5, found 1638.5.

48y: t_R = 7.6 min; LCMS (ES): calcd for $C_{78}H_{88}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1653.5, found 1653.4.

48z: t_R = 8.0 min; LCMS (ES): calcd for $C_{81}H_{92}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1693.5, found 1693.5.

48aa: t_R = 7.5 min; LCMS (ES): calcd for $C_{77}H_{86}Cl_2N_{10}O_{26}S$ $[M+H]^+$: 1671.5, found 1671.5.

48bb: t_R = 7.2 min; LCMS (ES): calcd for $C_{75}H_{82}Cl_2N_{10}O_{27}$ $[M+H]^+$: 1627.4, found 1627.5.

48cc: t_R = 7.6 min; LCMS (ES): calcd for $C_{79}H_{84}Cl_2N_{10}O_{26}S$ $[M+H]^+$: 1693.5, found 1693.5.

48dd: t_R = 7.7 min; LCMS (ES): calcd for $C_{81}H_{86}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1687.5, found 1687.5.

48ee: t_R = 7.3 min; LCMS (ES): calcd for $C_{78}H_{89}Cl_2N_{11}O_{26}$ $[M+H]^+$: 1668.5, found 1668.5.

48ff: t_R = 7.5 min; LCMS (ES): calcd for $C_{75}H_{83}Cl_2N_9O_{25}$ $[M+H]^+$: 1582.4, found 1582.4.

48gg: $t_R = 7.8$ min; LCMS (ES): calcd for $C_{80}H_{92}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1681.5, found 1681.5.

48hh: $t_R = 8.3$ min; LCMS (ES): calcd for $C_{81}H_{94}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1694.6, found 1694.6.

48ii: $t_R = 8.3$ min; LCMS (ES): calcd for $C_{84}H_{98}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1735.6, found 1735.5.

48jj: $t_R = 7.8$ min; LCMS (ES): calcd for $C_{80}H_{92}Cl_2N_{10}O_{26}S[M+H]^+$: 1713.6, found 1716.6.

48kk: $t_R = 7.6$ min; LCMS (ES): calcd for $C_{78}H_{88}Cl_2N_{10}O_{27}$ $[M+H]^+$: 1669.5, found 1669.5.

48ll: $t_R = 8.0$ min; LCMS (ES): calcd for $C_{82}H_{90}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1735.6, found 1735.6.

48mm: $t_R = 8.1$ min; LCMS (EI):calcd for $C_{84}H_{92}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1729.5, found 1729.5.

48nn: $t_R = 7.7$ min; LCMS (ES): calcd for $C_{81}H_{95}Cl_2N_{11}O_{26}$ $[M+H]^+$: 1710.6, found 1710.6.

48oo: $t_R = 7.9$ min; LCMS (ES): calcd for $C_{79}H_{83}Cl_2N_9O_{25}$ $[M+H]^+$: 1630.4, found 1630.6.

48pp: $t_R = 8.1$ min; LCMS (ES): calcd for $C_{84}H_{92}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1729.6, found 1729.7.

48qq: $t_R = 8.0$ min; LCMS (ES): calcd for $C_{85}H_{94}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1742.6, found 1742.6

48rr: $t_R = 8.7$ min; LCMS (ES): calcd for $C_{88}H_{98}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1783.6, found 1783.6.

48ss: $t_R = 8.3$ min; LCMS (ES): calcd for $C_{84}H_{92}Cl_2N_{10}O_{26}S$ $[M+H]^+$: 1761.6, found 1761.6.

48tt: $t_R = 8.0$ min; LCMS (ES): calcd for $C_{78}H_{86}Cl_2N_{10}O_{29}$ $[M+H]^+$: 1699.4, found 1699.5.

48uu: $t_R = 8.3$ min; LCMS (ES): calcd for $C_{86}H_{90}Cl_2N_{10}O_{26}S[M+H]^+$: 1783.7, found 1783.7.

48vv: $t_R = 8.3$ min; LCMS (ES): calcd for $C_{88}H_{92}Cl_2N_{10}O_{26}$ $[M+H]^+$: 1777.6, found 1777.6.

48ww: $t_R = 8.1$ min; LCMS (ES): calcd for $C_{85}H_{95}Cl_2N_{11}O_{26}$ $[M+H]^+$: 1758.6, found 1758.6.

48xx: $t_R = 7.0$ min; LCMS (ES): calcd for $C_{75}H_{81}Cl_2N_9O_{27}$ $[M+H]^+$: 1612.4, found 1612.3.

48yy: $t_R = 7.4$ min; LCMS (ES): calcd for $C_{80}H_{90}Cl_2N_{10}O_{28}$ $[M+H]^+$: 1711.5, found 1711.5.

48zz: $t_R = 7.6$ min; LCMS (ES): calcd for $C_{81}H_{92}Cl_2N_{10}O_{28}$ $[M+H]^+$: 1725.5, found 1725.5.

48aaa: $t_R = 8.0$ min; LCMS (ES): calcd for $C_{84}H_{96}Cl_2N_{10}O_{28}$ $[M+H]^+$: 1765.6, found 1765.6.

48bbb: $t_R = 7.6$ min; LCMS (ES): calcd for $C_{80}H_{90}Cl_2N_{10}O_{28}S$ $[M+H]^+$: 1743.5, found 1743.5.

48ccc: $t_R = 7.3$ min; LCMS (ES): calcd for $C_{78}H_{86}Cl_2N_{10}O_{29}$ $[M+H]^+$: 1699.4, found 1699.4.

48ddd: $t_R = 6.9$ min; LCMS (ES): calcd for $C_{82}H_{88}Cl_2N_{10}O_{28}$ $[M+H]^+$: 1765.5, foud 1765.5.

48eee: $t_R = 7.7$ min; LCMS (ES): calcd for $C_{84}H_{90}Cl_2N_{10}O_{28}$ $[M+H]^+$: 1758.5, found 1785.5.

48fff: $t_R = 7.3$ min; LCMS (ES): calcd for $C_{81}H_{93}Cl_2N_{11}O_{28}$ $[M+H]^+$: 1740.5, found 1740.5.

48ggg: $t_R = 7.0$ min; LCMS (ES): calcd for $C_{76}H_{86}Cl_2N_{10}O_{25}$ $[M+H]^+$: 1611.5, found 1611.6.

48hhh: $t_R = 7.3$ min; LCMS (ES): calcd for $C_{81}H_{95}Cl_2N_{11}O_{26}$ $[M+H]^+$: 1710.6, found 1710.6.

48iii: $t_R = 7.6$ min; LCMS (ES): calcd for $C_{82}H_{97}Cl_2N_{11}O_{26}$ $[M+H]^+$: 1723.6, found 1723.6.

48jjj: $t_R = 8.1$ min; LCMS (ES): calcd for $C_{85}H_{101}Cl_2N_{11}O_{26}$ $[M+H]^+$: 1764.6, found 1764.5.

48kkk: $t_R = 7.6$ min; LCMS (ES): calcd for $C_{81}H_{95}Cl_2N_{11}O_{26}S$ $[M+H]^+$: 1742.6, found 1742.6.

48lll: $t_R = 7.2$ min; LCMS (ES): calcd for $C_{79}H_{91}Cl_2N_{11}O_{27}$ $[M+H]^+$: 1698.5, found 1698.5.

48mmm: $t_R = 7.6$ min; LCMS (ES): calcd for $C_{83}H_{93}Cl_2N_{11}O_{26}S$ $[M+H]^+$: 1764.7, found 1764.7.

48nnn: $t_R = 7.7$ min; LCMS (ES): calcd for $C_{85}H_{95}Cl_2N_{11}O_{26}$ $[M+H]^+$: 1758.6, found 1758.6.

48ooo: $t_R = 6.9$ min; LCMS (ES): calcd for $C_{82}H_{98}Cl_2N_{12}O_{26}$ $[M+H]^+$: 1739.6, found 1739.6.

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