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Discovery of a Novel Series of Semisynthetic Vancomycin Derivatives Effective against Vancomycin-Resistant Bacteria

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Novel semisynthetic vancomycin derivatives with antibacterial activity against vancomycin-resistant *S. aureus* (VRSA) were prepared. Replacement of Cl groups of vancomycin by Suzuki−Miyaura cross-coupling reaction, which gave the title compounds, is described for the first time. Introduction of a carbon substituent at the amino acid residue 2 of vancomycin led to an enhancement of antibacterial activity against vancomycin-resistant strains, whereas the additional introduction at the amino acid residue 6 resulted in a reduction in activity even against vancomycin-susceptible strains.

Introduction

The emergence of vancomycin-resistant enterococci (VRE[a]) and *Staphylococcus aureus* (VRSA)[1−3] is a serious concern in hospitals because vancomycin is the drug of last resort for the treatment of nosocomial infections by methicillin-resistant *Staphylococcus aureus* (MRSA). To this end, extensive studies have been conducted on novel semisynthetic glycopeptides antibiotics with efficacy against VRE and VRSA.[4−7] The most notable are the successes of telavancin (approved by FDA for treatment of complicated skin and skin structure infections in 2009)[8,9] and oritavancin.[10] A common and unique feature of these vancomycin derivatives is the N-alkyl modification at the vancosamine sugar moiety. Vancomycin exhibits antibacterial activities against Gram-positive bacteria by binding to a bacterial cell wall intermediate. The alkylation results in the additional antibacterial mechanism, which disrupts the functional integrity of the bacterial membrane even of vancomycin-resistant strains.[11]

Vancomycin (**1**) is a complex and polyfunctionalized compound, and chemoselective reactions have played an indispensable role in the medicinal chemistry of vancomycin (Figure 1). In addition to the above-mentioned N-alkylation of vancosamine,[12] amidation of C-terminal (residue 7), Mannich-type aminomethylation (residue 7),[13] and Edman degradation of the N-terminal residue (residue 1)[14,15] followed by reacylation[15] were employed. Modification of vancomycin by multistep synthesis still requires significant challenges,[16] and thus, the current medicinal chemistry of vancomycin has relied solely on these limited numbers of classical transformations.

Recent progress in transition metal catalysts has enabled the selective modification of functional groups that were previously regarded as inert.[17] The impressive progress over the past decade and the need for a potent antibacterial has prompted us to explore a novel series of vancomycin derivatives. Because the amino acid residues 2 and 6 have aryl chloride substructures, we decided to explore the modification of vancomycin by Suzuki−Miyaura cross-coupling with highly active palladium catalysts. Considering the low solubility of vancomycin in organic media, a water-soluble catalyst recently developed by Buchwald was selected for this study.[18] The catalyst had been shown to be effective for the Suzuki−Miyaura cross-coupling of simple aryl chlorides and arylboronic acids in water at temperatures ranging from room temperature to 150 °C; however, to the best of our knowledge, the potential of the reaction for modification of complex natural products has not been examined.

Results and Discussion

Cross-coupling of vancomycin and phenylboronic acid was conducted with $Pd(OAc)_2$, Buchwald's water-soluble

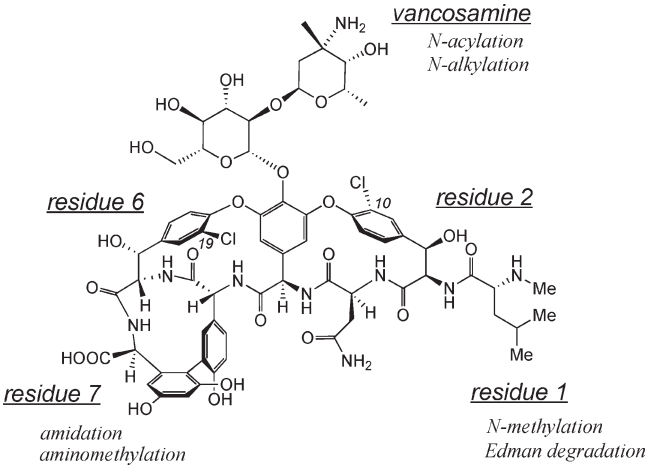

Figure 1. Methods available for selective modification of vancomycin (**1**).

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[a] Abbreviations: VRE, vancomycin-resistant enterococci; VRSA, vancomycin-resistant *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; WSPL, water-soluble phosphine ligand; MIC, minimum inhibitory concentration.

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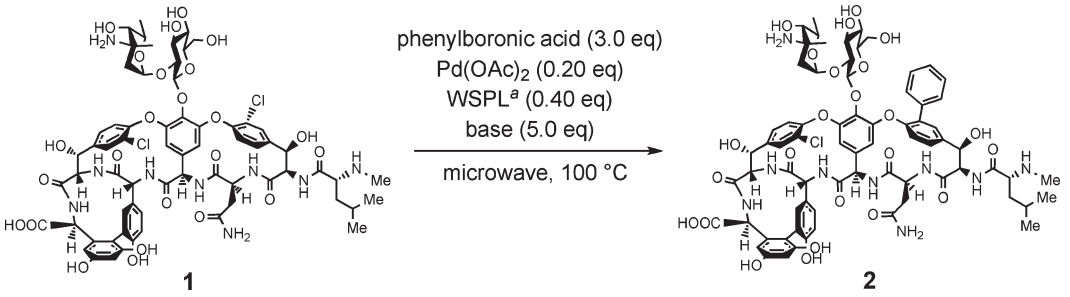
Table 1. Survey of Reaction Conditions for Suzuki−Miyaura Cross-Coupling



entry	solvent	base	time	product (%)[b]	recovered SM (%)[b]
1	H_2O	NaOAc	30 min	13	30
2	H_2O/CH_3CN (3/1)	NaOAc	30 min	22	28
3	H_2O/CH_3CN (3/1)	K_2CO_3	15 min	20	0
4	H_2O	K_3PO_4	5 min	14	12
5[c]	H_2O	K_2CO_3	5.5 h	25	27

[a] Sodium 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl-3′-sulfonate. [b] Yields were calculated from HPLC peak areas using naproxen as the internal standard. [c] The reaction was performed at 60 °C with conventional heating.

phosphine ligand (WSPL),[18] and NaOAc as a base. The reaction did not proceed at room temperature and thus was investigated at 100 °C under microwave irradiation (Table 1). Analysis of the crude reaction mixture revealed the formation of the desired product albeit in low yield (13%, entry 1). The use of CH_3CN as a cosolvent made the reaction mixture homogeneous and improved the yield up to 22% (entry 2). Other bases (K_2CO_3, K_3PO_4) were also examined (entries 3 and 4), but they did not significantly improve the product yield. The reaction without microwave irradiation at 60 °C (solvent H_2O, base K_2CO_3, 5.5 h, entry 5) gave the product in 25% yield.

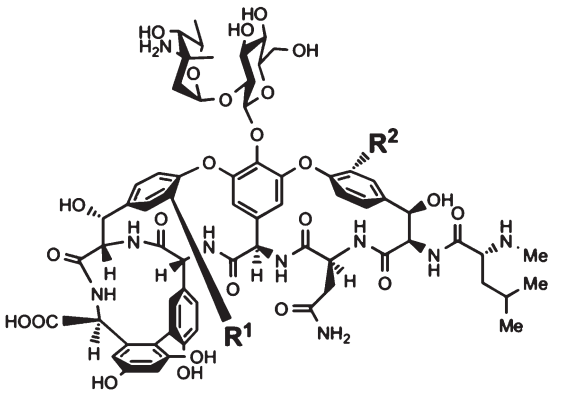
The product **2** was then purified by repeated chromatography. Analysis of the isolated coupling product by mass spectrometry indicated that a phenyl group substituted only one of the two chlorides. To determine the site of modification, two-dimensional NMR experiments (COSY, NOESY, HMBC) were carried out to prove the modification at the amino acid residue 2 (Figures S1−S6 of Supporting Information). This regioselectivity of Suzuki−Miyaura cross-coupling is in agreement with the selectivity observed in monodechlorination of vancomycin by Pd-catalyzed hydrogenation.[19] The selectivity can be rationalized because vancomycin has the chlorine of the residue 2 on the less-hindered backside of the molecule. By use of 4- and 2-methoxyphenylboronic acids, the corresponding monosubstituted derivatives **3** and **4** were obtained (Table 2).

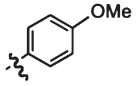
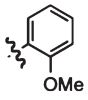
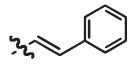
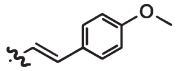
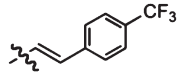
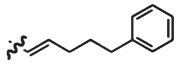
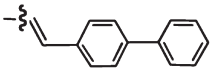
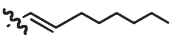
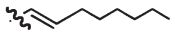
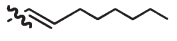
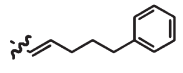
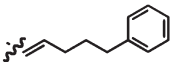
Because of the low efficacy of the coupling reaction with arylboronic acids, we turned our attention to the use of alkenylboronic acids. However, despite the recent achievements in the research area, the cross-coupling of aryl *chlorides* with *alkenyl*boronic acids remains quite challenging.[20,21] The reaction with Buchwald's phosphine ligands[18,20] has not been reported to date. Thus, we were delighted to find that the reaction with octenylboronic acid proceeded smoothly and gave monooctenyl-substituted compound **8** in 42% yield (25% isolated yield, Scheme 1). It is noteworthy that the product **13** substituted at both of the aryl chloride moieties was also obtained in 30% yield. Because the disubstitution was not observed with arylboronic acids, the result indicates the higher reactivity of alkenylboronic acid in the coupling process. A series of mono- and disubstituted derivatives were likewise prepared (Table 2).

Antibacterial activities of monosubstituted derivatives (**2**−**10**) are shown in Table 3. Compounds are listed in the order of approximate size of substitutions. Aryl substitutions did not alter the antibacterial profile of parent vancomycin; however, styryl substitutions (compounds **5** and **6**) exhibited significant effects on VRSA. Since VRSA is generally more pathogenic than VRE, the observed activity of styryl-substituted vancomycin is important. As the size of substituents became larger, the activity against VRSA was lost, and remarkable antibacterial effects against VREs of VanB-phenotype were observed (compounds **7** and **10**). Since this series of derivatives was prepared for the first time, the mechanism of action is currently unknown. Because the alkyl modifications at the vancosamine moiety have been shown to add a novel antibacterial mechanism of action such as a disruption of bacterial membrane integrity or direct interaction with transglycosylase,[22,23] we are interested in determining whether our derivatives having modifications at different sites could acquire these new antibacterial mechanisms. It is also possible that there is another type of antibacterial mechanism resulting in the observed activities against VRSA or VREs. This possibility is a topic of our continuing study. We recently developed a new semiquantitative in vitro assay on the cell wall synthesis of VRSA, in which cell membrane particles of *S. aureus* were used as a crude enzyme mixture,[24] and a cell wall intermediate of VRE/VRSA was used as the substrate of peptidoglycan synthesis.[25] This assay would allow us to evaluate the inhibitory effect of these monosubstituted derivatives and may provide insight into their antibacterial mechanism against vancomycin-resistant strains.

The activities of disubstituted derivatives were then evaluated (Table 4, compounds **11**−**14**). Unfortunately, none of the disubstituted series showed activity against VRSA or VRE. It is interesting, however, that most of these derivatives also lost activity against vancomycin-*susceptible* strains. Only compound **11** with a small substituent at residue 6 retained antibacterial activity against the susceptible strains. When the R^1 substituent (Table 2) at residue 6 was replaced with the larger octenyl group (compound **13**), the activities against *vancomycin-susceptible* strains were reduced.

Table 2. Structures of Vancomycin Derivatives



compounds	R^1	R^2
1	Cl	Cl
2	Cl	
3	Cl	
4	Cl	
5	Cl	
6	Cl	
7	Cl	
8	Cl	
9	Cl	
10	Cl	
11		
12		
13		
14		

Vancomycin is known to inhibit cell wall biosynthesis of Gram-positive bacteria by binding to the C-terminal L-Lys-D-Ala-D-Ala motif present in cell wall precursors of susceptible strains. Nitanai et al. recently disclosed the crystal structure of vancomycin complexed with diacetyl-Lys-D-Ala-D-Ala (Figure 2).[26] Because the substituent at the amino acid residue 6 is on the front side of the molecule, we assumed that the reduced potency of the disubstituted derivatives was due to the steric interference of D-Ala-D-Ala binding by the substituent. To this end, the affinities of vancomycin, **8** (monosubstituted), and **13** (disubstituted) with the D-Ala-D-Ala motif were measured using surface plasmon resonance spectroscopy. Compound **13** did display weaker affinity for D-Ala-D-Ala dipeptide (K_D = 11.6 μM) than the former two (K_D = 3.39 and 3.77 μM, respectively), and the trend is compatible with the results of antibacterial tests. These findings support the above idea that an unfavorable steric interaction between the installed substituent and the dipeptidic terminal reduced the antibacterial activity of the disubstituted derivatives.

Conclusion

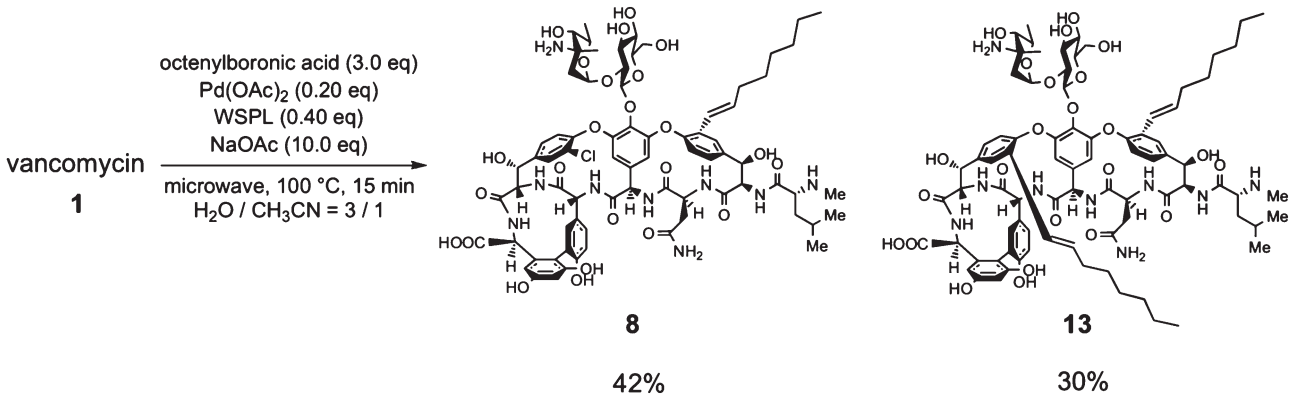
Novel methodology for the modification of vancomycin's carbon framework was developed using Suzuki−Miyaura cross-coupling. By taking advantage of the commercial availability of various boronic acids, this method should become indispensable in the medicinal chemistry of vancomycin-class glycopeptides. Moreover, this methodology does not require protection of functional groups. Evaluation of antibacterial potency revealed that substitutions in the amino acid residue 2 of vancomycin exhibited significant antibacterial activity against VRSA and VRE. These novel semisynthetic vancomycin derivatives should be explored further for the treatment of infections by glycopeptides-resistant bacteria.

Experimental Section

General Procedures. All reagents were commercially available and used without further purification. Microwave irradiations were performed using Discover (CEM). All reactions were carried out under an argon atmosphere. Column chromatography was carried out on ULTRA PACK ODS columns (YAMAZEN CORPORATION). HPLC analysis was performed on a Cosmosil HG (C_{18}, diameter = 4.6 mm, length = 150 mm) with UV detector monitoring at 280 nm, at a flow rate of 1 mL/min, and with a gradient from 15:85 to 100:0 CH_3CN (0.1% TFA)/H_2O (0.1% TFA) or from 6:94 to 40:60 CH_3CN (0.1% TFA)/H_2O (0.1% TFA) over 10 min. HPLC showed that the purities of all the final products were greater than 95% except in the cases of **4** (93%), **8** (94%), **10** (85%), and **13** (92%). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA-600 instrument. FAB-MS spectra were measured with a JEOL LMS-700 using 3-nitrobenzyl alcohol and glycerol as a matrix.

10-Dechloro-10-phenyl Vancomycin (2). In a flask equipped with a condenser, argon gas was bubbled through H_2O (9 mL) for 2 min. Vancomycin−HCl (1.00 g, 0.674 mmol), phenylboronic acid (73.9 mg, 0.606 mmol, 3.0 equiv), sodium 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl-3′-sulfonate (41.4 mg, 0.0808 mmol, 0.40 equiv), K_2CO_3 (140 mg, 1.01 mmol, 5.0 equiv), and $Pd(OAc)_2$ (9.1 mg, 0.0405 mmol, 0.20 equiv) were stirred at 60 °C for 5.5 h. The resulting solution was cooled to room temperature and acidified with 1 M aqueous HCl to pH 5. The mixture was purified by ODS column chromatography (CH_3OH/H_2O containing 0.1% TFA). The fractions containing product **2** were combined and concentrated under reduced pressure. The resulting solution was added dropwise to AcOEt (800 mL), and the solid formed was collected by filteration (Millipore, pore size 1.0 μm, JAWP047) and dried under reduced pressure to yield a white solid **2** (54.0 mg, 18%). HRMS (FAB) calcd for $C_{72}H_{81}ClN_9O_{24}$ $[M + H]^+$ m/z 1490.5083, found m/z 1490.5079.

Scheme 1. Coupling Reaction with a Alkenylboronic Acid[a]



[a] Yields were calculated from HPLC peak areas using naproxen as the internal standard.

Table 3. MICs (μg/mL) of Vancomycin **1** and Its Monosubstituted Derivatives (**2**−**10**)

	S. aureus			*E. faecium*			*E. faecalis*		
	susceptible		resistant	susceptible	resistant		susceptible	resistant	
compd	RN4220	SR3637 (H-MRSA)	VRS-2 (vanA)	SR16972	SR7940 (vanA)	SR23598 (vanB)	SR1004	SR7914 (vanA)	SR23630 (vanB)
1	1	1	> 64	1	> 64	> 64	2	> 64	64
2	4	4	64	2	> 64	> 64	4	> 64	64
3	4	4	> 64	2	> 64	> 64	4	> 64	> 64
4	4	8	64	4	> 64	> 64	8	> 64	> 64
5	1	2	16	1	> 64	> 64	1	> 64	64
6	1	2	16	1	> 64	> 64	1	> 64	32
7	1	2	64	1	> 64	32	1	64	2
8	1	2	> 64	2	> 64	> 64	2	> 64	> 64
9	1	2	> 64	2	> 64	> 64	1	> 64	> 64
10	0.25	0.5	> 64	0.25	64	0.5	0.25	32	2

Table 4. MICs (μg/mL) of Dialkenyl-Substituted Derivatives (**11**−**14**)

	S. aureus			*E. faecium*			*E. faecalis*		
	susceptible		resistant	susceptible	resistant		susceptible	resistant	
compd	RN4220	SR3637 (H-MRSA)	VRS-2 (vanA)	SR16972	SR7940 (vanA)	SR23598 (vanB)	SR1004	SR7914 (vanA)	SR23630 (vanB)
11	1	2	64	1	> 64	> 64	2	> 64	> 64
12	32	64	> 64	32	> 64	> 64	32	> 64	> 64
13	32	64	> 64	32	> 64	> 64	32	> 64	> 64
14	32	64	> 64	32	> 64	> 64	32	> 64	> 64

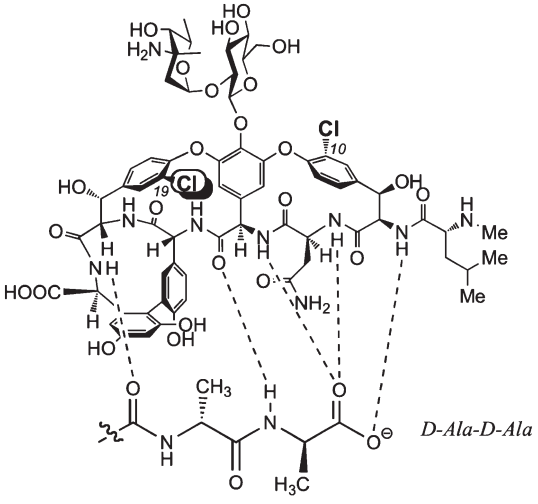


Figure 2. Orientation of the 19-Cl group in complex of vancomycin and D-Ala-D-Ala motif.[26]

10-Dechloro-10-(4-methoxyphenyl) Vancomycin (3). In a flask equipped with a condenser, argon gas was bubbled through H_2O (30 mL) for 2 min. Vancomycin−HCl (1.00 g, 0.674 mmol), *p*-methoxyphenylboronic acid (306 mg, 2.02 mmol, 3.0 equiv), sodium 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl-3′-sulfonate (114.2 mg, 0.270 mmol, 0.40 equiv), and K_2CO_3 (464 mg, 3.36 mmol, 5.0 equiv) were added, and argon gas was bubbled through the solution for another 2 min. $Pd(OAc)_2$ (30.2 mg, 0.135 mmol, 0.20 equiv) was then added to the solution and stirred at 60 °C for 2.5 h. The resulting solution was cooled to room temperature and acidified with 1 M aqueous HCl to pH 5. The mixture was filtered (Millipore, pore size 1.0 μm, JAWP047, washed with 2:3 CH_3CN/H_2O, 50 mL), and the filtrate was mixed with ethanol and concentrated under reduced pressure. The residue was purified by ODS column chromatography (CH_3OH/5 mM aqueous HCl). The fractions containing product **3** were combined and concentrated under reduced pressure to remove the methanol. The concentrated solution was treated with poly-4-vinylpyridine resin to remove excess acid. The aqueous solution was lyophilized to yield **3** as a white powder (18.5 mg, 2%). MS (FAB) calcd for $C_{73}H_{83}ClN_9O_{25}$

$[M + H]^+$ *m/z* 1520, found *m/z* 1520; ^{1}H NMR (600 MHz, 10% D_2O in DMSO) δ 8.60 (br s, 1 H), 8.57 (br s, 1 H), 7.82 (s, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 7.47 (d, J = 8.4 Hz, 2 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.31 (br s, 1 H), 7.25 (d, J = 8.4 Hz, 1 H), 7.15 (s, 1 H), 7.01 (d, J = 8.4 Hz, 1 H), 6.99 (d, J = 8.4 Hz, 2 H), 6.77 (d, J = 9.0 Hz, 1 H), 6.74 (d, J = 9.0 Hz, 1 H), 6.43 (d, J = 1.8 Hz, 1 H), 6.26 (d, J = 1.8 Hz, 1 H), 5.68 (br s, 1 H), 5.60 (br d, J = 6.6 Hz, 1 H), 5.35 (br d, J = 9.0 Hz, 1 H), 5.33 (m, 1 H), 5.27 (br s, 1 H), 5.13 (br s, 1 H), 5.08 (br s, 1 H), 5.02 (s, 1 H), 4.62 (d, J = 6.6 Hz, 1 H), 4.54 (br s, 1 H), 4.44 (d, J = 5.4 Hz, 1 H), 4.44 (m, 1 H), 4.17 (br s, 1 H), 3.93 (m, 1 H), 3.78 (3 H overlapped with solvent signal), 3.68 (br d, J = 9.6 Hz, 1 H), 3.61 (br d, J = 9.6 Hz, 1 H), 3.58 (dd, J = 9.0, 9.0 Hz, 1 H), 3.47 (dd, J = 9.0, 9.0 Hz, 1 H), 3.38 (dd, J = 9.0, 9.0 Hz, 1 H), 3.26 (br d, J = 9.6 Hz, 1 H), 3.20 (br s, 1 H), 2.69 (s, 3 H), 2.42 (br s, 1 H), 2.20 (br d, J = 11.4 Hz, 1 H), 1.93 (br d, J = 12.6 Hz, 1 H), 1.77 (d, J = 12.6 Hz, 1 H), 1.71 (m, 1 H), 1.60 (m, 2H), 1.34 (s, 3 H), 1.08 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.0 Hz, 3 H), 0.85 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (125 MHz, 10% D_2O in DMSO) δ 172.4, 171.0, 170.4, 169.1 (2 C), 167.9, 167.8, 166.8, 158.8, 157.0, 156.3, 154.9, 152.8, 152.0, 150.7, 148.0, 142.2, 137.6, 135.8, 135.4, 135.1, 134.0, 132.0, 130.0 (2 C), 129.0, 128.6, 127.5 (2 C), 127.0, 126.4 (2 C), 125.6, 123.4, 123.3, 121.4, 117.9, 116.1, 113.8 (2 C), 109.2, 105.5, 104.0, 102.1, 100.7, 96.7, 78.2, 76.8, 76.7, 71.2 (2 C), 70.4, 69.3, 63.0, 61.6, 60.3, 59.5, 58.9, 56.5, 54.9, 54.5, 53.7, 53.3, 50.6, 39 (overlapped with solvent signal), 37.2, 32.9, 31.0, 23.6, 22.4 (2 C), 22.1, 16.7.

10-Dechloro-10-(2-methoxyphenyl) Vancomycin (4). Compound **4** (5%, white solid) was prepared using the procedure described for the synthesis of **3** except for the reaction period of 2 h with 2-methoxyphenylboronic acid. MS (FAB) calcd for $C_{73}H_{83}ClN_9O_{25}$ $[M + H]^+$ *m/z* 1520, found *m/z* 1520.

10-Dechloro-10-(*trans*-2-phenylvinyl) Vancomycin (5). Argon gas was bubbled through a mixture of vancomycin−HCl (50.0 mg, 33.7 μmol), NaOAc (27.6 mg, 337 μmol, 10 equiv), $Pd(OAc)_2$ (1.5 mg, 6.7 μmol, 0.20 equiv), and sodium 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl-3′-sulfonate (6.9 mg, 13.5 μmol, 0.40 equiv) in a mixed solution of CH_3CN and H_2O (3/1, 1.5 mL) for 1 min. Then *trans*-2-phenylvinylboronic acid (14.9 mg, 101 μmol, 3.0 equiv) was added to the mixture. The reaction vessel was sealed and heated by microwave irradiation at 100 °C for 15 min. The resulting solution was cooled to room temperature and acidified to pH 5 with 1 M aqueous HCl. A total of 250 mg (50 mg × 5, 168 μmol) of vancomycin−HCl was treated in this manner, and the resulting reaction mixtures were combined. The mixture was added dropwise to AcOEt (800 mL) to give a gray solid. The solid was collected by filtration (Millipore, pore size 1.0 um, JAWP047) and was purified by ODS column chromatography (CH_3OH/H_2O containing 0.1% TFA). The fractions containing product **5** were combined and concentrated under reduced pressure. The resulting solution was added dropwise to AcOEt (800 mL), and the resulting solid was collected by filtration (Millipore, pore size 1.0 μm, JAWP). The solid was dried under reduced pressure to yield a white powder **5** (32.0 mg, 13%). HRMS (FAB) calcd for $C_{74}H_{83}ClN_9O_{24}$ $[M + H]^+$ *m/z* 1516.5240, found *m/z* 1516.5239.

10-Dechloro-10-[*trans*-2-(4-methoxyphenyl)vinyl] Vancomycin (6). Compound **6** (6%, white solid) was prepared using the procedure described for the synthesis of **5** except for the reaction period of 30 min with *trans*-2-(4-methoxyphenyl)vinylboronic acid. HRMS (FAB) calcd for $C_{75}H_{85}ClN_9O_{25}$ $[M + H]^+$ *m/z* 1546.5345, found *m/z* 1546.5338.

10-Dechloro-10-{*trans*-2-[4-(trifluoromethyl)phenyl]vinyl} Vancomycin (7). Compound **7** (12%, white solid) was prepared using the procedure described for the synthesis of **5** except for using *trans*-2-[4-(trifluoromethyl)phenyl]vinylboronic acid. HRMS (FAB) calcd for $C_{75}H_{82}ClF_3N_9O_{24}$ $[M + H]^+$ *m/z* 1584.5113, found *m/z* 1584.5105.

10-Dechloro-10-(*trans*-oct-1-en-1-yl) Vancomycin (8). Compound **8** (25%, white solid) was prepared using the procedure described for the synthesis of **5** except for using 1-octen-1-ylboronic acid. HRMS (FAB) calcd for $C_{74}H_{91}ClN_9O_{24}$ $[M + H]^+$ *m/z* 1524.5866, found *m/z* 1524.5870.

10-Dechloro-10-(*trans*-5-phenylpent-1-en-1-yl) Vancomycin (9). Compound **9** (24%, white solid) was prepared using the procedure described for the synthesis of **5** except for the reaction period of 20 min with 5-phenylpent-1-en-1-ylboronic acid. HRMS (FAB) calcd for $C_{77}H_{89}ClN_9O_{24}$ $[M + H]^+$ *m/z* 1558.5709, found *m/z* 1558.5706.

10-Dechloro-10-*trans*-[2-(biphenyl-4-yl)vinyl] Vancomycin (10). Compound **10** (7%, white solid) was prepared using the procedure described for the synthesis of **5** except for the reaction period of 10 min with *trans*-[2-(biphenyl-4-yl)vinyl]boronic acid. HRMS (FAB) calcd for $C_{80}H_{87}ClN_9O_{24}$ $[M + H]^+$ *m/z* 1592.5553, found *m/z* 1592.5568.

10,19-Didechloro-10,19-di-(*trans*-prop-1-en-1-yl) Vancomycin (11). Compound **11** (31%, white solid) was prepared using the procedure described for the synthesis of **5** except that the reaction was conducted using K_2CO_3 as a base and prop-1-en-1-ylboronic acid (10 equiv) at 80 °C for 30 min. HRMS (FAB) calcd for $C_{72}H_{86}N_9O_{24}$ $[M + H]^+$ *m/z* 1460.5786, found *m/z* 1460.5791.

10,19-Didechloro-10-(*trans*-prop-1-en-1-yl)-19-(*trans*-oct-1-en-1-yl) Vancomycin (12). Compound **12** (2% in two steps, white solid) was prepared in two steps using the procedure described for the synthesis of **5**. In the first step, a propenyl substituent was introduced at position 10 using *trans*-prop-1-en-1-ylboronic acid (3 equiv). After purification, an octenyl substituent was then introduced at position 19 using *trans*-oct-1-en-1-ylboronic acid (3 equiv). HRMS (FAB) calcd for $C_{77}H_{96}N_9O_{24}$ $[M + H]^+$ *m/z* 1530.6568, found *m/z* 1530.6573.

10,19-Didechloro-10,19-di-(*trans*-oct-1-en-1-yl) Vancomycin (13). Compound **13** (13%, white solid) was prepared using the procedure as described for the synthesis of **5** except for the reaction period of 30 min with *trans*-oct-1-en-1-ylboronic acid (5 equiv). HRMS (FAB) calcd for $C_{82}H_{106}N_9O_{24}$ $[M + H]^+$ *m/z* 1600.7351, found *m/z* 1600.7350.

10,19-Didechloro-10,19-di-(5-phenylpent-1-en-1-yl) Vancomycin (14). Compound **14** (6%, white solid) was prepared using the procedure as described for the synthesis of **5** except for the reaction period of 20 min with 5-phenylpent-1-en-1-ylboronic acid. HRMS (FAB) calcd for $C_{88}H_{102}N_9O_{24}$ $[M + H]^+$ *m/z* 1668.7038, found *m/z* 1668.7046.

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Supporting Information Available: Details of SPR experiments; ^{1}H, ^{13}C NMR data and two-dimensional NMR spectra (COSY, NOESY, HMBC) of compound **3**,; ^{1}H NMR spectra of compounds **2**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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