



## A stepwise dechlorination/cross-coupling strategy to diversify the vancomycin 'in-chloride'



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### ABSTRACT

In an effort to rapidly access vancomycin analogues bearing diverse functionality at the 6<sub>c</sub>-Cl (the 'in-chloride') position, a two-step dechlorination/cross-coupling protocol was developed. Conditions for efficient cross-coupling of the relatively unreactive 6<sub>c</sub>-Cl group were found that ensure high conversion with minimal product decomposition. A set of 2<sub>c</sub>-dechloro-6<sub>c</sub>-functionalized vancomycin derivatives was prepared, and antibiotic activities of the compounds were evaluated against a panel of vancomycin-resistant and vancomycin-susceptible strains. Results from biological testing further underscore the steric sensitivity of vancomycin's binding pocket.

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Glycopeptide natural product antibiotics, vancomycin (**1**) in particular, have seen widespread use and extensive study over the past half century.<sup>1,2</sup> The glycopeptide antibiotics inhibit cell wall biosynthesis by coordinating the D-Ala-D-Ala peptide termini of peptidoglycan precursors, disrupting peptidoglycan cross-linking.<sup>3,4</sup> Strong binding to D-Ala-D-Ala results from a network of five hydrogen bonds along with hydrophobic interactions within the glycopeptide binding pocket (Fig. 1).<sup>5–10</sup> For a period after its discovery, vancomycin was considered the 'antibiotic of last resort;' however, clinical resistance was first observed in the 1980s and has become increasingly prevalent since then.<sup>11–14</sup> In an effort to combat resistant infections and better understand resistance mechanisms, synthetic chemists have generated a diverse range of vancomycin analogues through both semisynthesis<sup>15</sup> and total synthesis.<sup>16,17</sup>

The 6<sub>c</sub>-Cl group (the 'in-chloride'), located in vancomycin's binding pocket, has inspired revealing studies over the past three decades. Harris and co-workers reported a method to prepare dechlorinated vancomycin derivatives via palladium-catalyzed hydrogenation and found 2<sub>c</sub>-Cl, oriented toward the convex face of the molecule, to be significantly more reactive than the in-chloride group.<sup>15a</sup> The authors prepared 2<sub>c</sub>-dechlorovancomycin (**2**) with 2<sub>c</sub>,6<sub>c</sub>-didechlorovancomycin (**3**) observed as the product of overreaction. More recently, Arimoto and co-workers utilized Suzuki–Miyaura (SM) coupling to access a library of 2<sub>c</sub>-functionalized and 2<sub>c</sub>,6<sub>c</sub>-difunctionalized vancomycin analogues, again observing substantially higher reactivity at 2<sub>c</sub>-Cl relative to

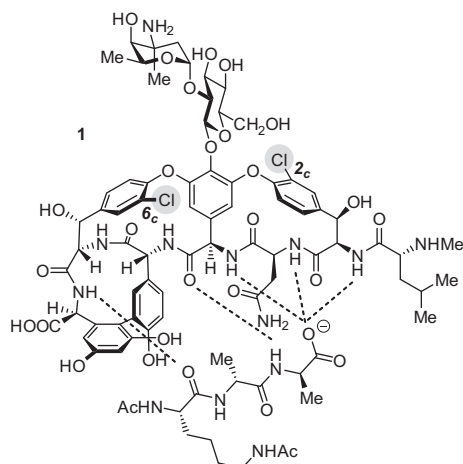
6<sub>c</sub>-Cl.<sup>15k</sup> Boger also reported an elegant 2<sub>c</sub>-borylation protocol that allowed unique access to organometallic substitution reactions at the 2<sub>c</sub>-position.<sup>15l</sup> Moreover, although a synthesis of 6<sub>c</sub>-dechlorovancomycin has not yet been reported, Boger and co-worker recently prepared the aglycone of 6<sub>c</sub>-dechlorovancomycin, enabling binding studies and antibiotic measurements.<sup>15m</sup>

In recent years, our group has become interested in discovering approaches for the site-selective modification of vancomycin, and a single-step and site-selective synthesis of 6<sub>c</sub>-functionalized vancomycin has emerged as a goal.<sup>18</sup> Toward this goal, we sought to better understand the reactivity of vancomycin's 6<sub>c</sub>-Cl position absent the competing, more favorable, reaction at 2<sub>c</sub>-Cl under SM coupling conditions. We identified **2** as a suitable substrate for such studies, and a modified method based on that of Harris et al. was found to furnish **2** with minimal overreaction to **3** (Scheme 1).<sup>19</sup> Furthermore, we anticipated that products resulting from such reactivity studies could possess increased biological activity and inspire future research efforts toward 6<sub>c</sub>-Cl modification. Herein, we report a stepwise dechlorination/cross-coupling strategy to access 2<sub>c</sub>-dechloro-6<sub>c</sub>-functionalized vancomycin derivatives and antibiotic evaluation of novel reaction products featuring diverse functionality at the in-chloride position.

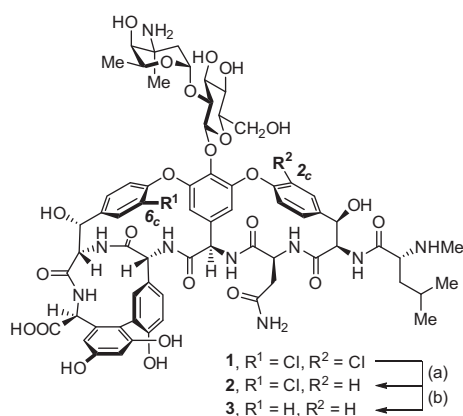
Due to the substrate's unique combination of reactivity, stability, and solubility properties, unusual challenges in the SM cross-coupling of **2** were encountered during reaction optimization. We found that aqueous conditions were required for substrate solubility, but that rapid decomposition of boronic acid coupling partners in water limited conversion.<sup>20–23</sup> Additionally, product decomposition was unavoidable as a function of long reaction times; excess

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**Figure 1.** Schematic representation of model ligand *N,N'*-Ac<sub>2</sub>-L-Lys-D-Ala-D-Ala bound to vancomycin.



**Scheme 1.** Stepwise dechlorination of vancomycin (**1**). Reagents and conditions: (a) 10% Pd/C, H<sub>2</sub> (1 atm), H<sub>2</sub>O, rt, 3 h, 23%; (b) 10% Pd/C, H<sub>2</sub> (4 atm), H<sub>2</sub>O, rt, 24 h, 75%.

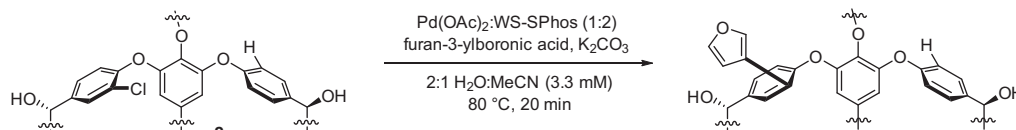
base (relative to boronic acid) was also found to accelerate this decomposition under the reaction conditions.<sup>24</sup> The byproduct resulting from product decomposition was not identified; however, LCMS analysis revealed an identical isotope pattern to that of the product (see [Supporting information](#) for more detail). Minimizing both types of decomposition (decomposition of boronic

acid and decomposition of product) was found to be critical for efficient SM coupling of **2**.

We began reaction optimization by investigating conditions utilizing high catalyst loading along with dropwise addition of a boronic acid/K<sub>2</sub>CO<sub>3</sub> solution over a short reaction time ([Table 1](#), entry 1). Longer reaction times led to increased byproduct formation and lower product yield (entry 2); yet, fewer equivalents of boronic acid and base led to decreased byproduct formation and higher product yield (entry 3). We expected that dropwise addition of a boronic acid/K<sub>2</sub>CO<sub>3</sub> solution would help avoid boronic acid decomposition and enable higher conversion; however, we observed nearly identical conversion upon switching to a 'dump-and-stir' protocol (entry 4; longer dropwise additions were not examined due to significant byproduct formation over longer reaction times). Next, we investigated conditions employing an excess of boronic acid relative to K<sub>2</sub>CO<sub>3</sub> to further suppress base-promoted product decomposition, and a slight increase in product yield was, indeed, observed (entry 5). Lower catalyst loading was also examined but afforded decreased yield due to low conversion, presumably because the slower coupling was unable to outcompete rapid boronic acid decomposition (entries 6 and 7). Ultimately, the conditions in entry 5 were best able to minimize decomposition of both boronic acid and product, leading to the highest product yield.

Once optimized SM reaction conditions were identified, a small library of 2<sub>c</sub>-dechloro-6<sub>c</sub>-functionalized vancomycin derivatives was prepared ([Table 2](#)). The antibiotic activities of vancomycin (**1**) and vancomycin derivatives **2–10** were then measured against vancomycin-sensitive *Staphylococcus aureus* and *Enterococcus faecalis* strains and vancomycin-resistant strains of *E. faecalis* (VanA and VanB) using a standard microtiter plate-based antimicrobial assay ([Table 3](#)).<sup>25</sup> In every case, **2** exhibited an approximately four-fold reduced activity compared to **1** (entries 1 and 2), and the activity of **3** was reduced approximately eight-fold relative to **1** (entries 1 and 3). These findings are consistent with those of Boger and co-worker, who measured similar reductions in activity against a vancomycin-sensitive strain of *S. aureus* for dechlorinated vancomycin aglycone derivatives relative to vancomycin aglycone.<sup>15l,m</sup> In these prior studies, comparative binding of model cell wall ligands to **1–3**<sup>15a</sup> as well as dechlorovancomycin aglycone derivatives<sup>15l,m</sup> suggested that the reduced antibiotic activity results from reduced binding efficiency between dechlorovancomycin analogues and cell wall precursors. The studies also indicate that decreases in binding affinity arising from dechlorination at 2<sub>c</sub>-Cl and 6<sub>c</sub>-Cl are additive in the case of 2<sub>c</sub>,6<sub>c</sub>-didechlorovancomycin analogues. Accordingly, the antibiotic activity of **2** is expected to be the most reliable

**Table 1**  
Representative optimization studies for the SM coupling of **2**<sup>a</sup>



Entry	Catalyst (%)	Boronic acid (equiv)	K <sub>2</sub> CO <sub>3</sub> (equiv)	Boronic acid/K <sub>2</sub> CO <sub>3</sub> addition time (min)	Starting material (%)	Product (%)	Byproduct (%)
1	50	10	10	20	13	77	10
2 <sup>b</sup>	50	10	10	20	9	57	34
3	50	5	5	20	15	81	4
4	50	5	5	0	14	81	5
5	50	5	4	0	14	83	3
6	25	5	5	20	31	64	4
7 <sup>b</sup>	25	5	5	20	27	51	22

<sup>a</sup> Yields represented by uncorrected HPLC integrations at 280 nm.

<sup>b</sup> Reaction time = 60 min.

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