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Catalytic Site-Selective Thiocarbonylations and Deoxygenations of Vancomycin Reveal Hydroxyl-Dependent Conformational Effects

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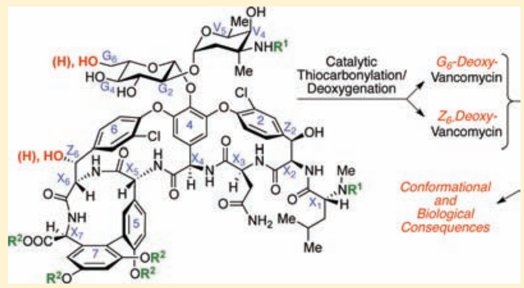
Supporting Information

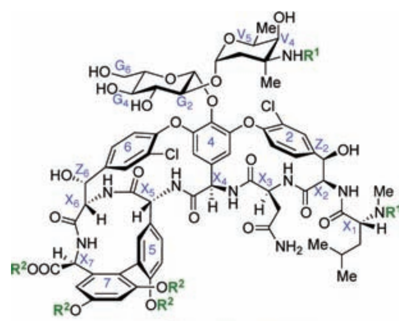
ABSTRACT: We have examined peptide-based catalysts for the site-selective thiocarbonylation of a protected form of vancomycin. Several catalysts were identified that either enhanced or altered the inherent selectivity profile exhibited by the substrate. Two catalysts, one identified through screening and another through rational design, were demonstrated to be effective on 0.50-g scale. Deoxygenations led ultimately to two new deoxy-vancomycin derivatives, and surprising conformational consequences of deoxygenation were revealed for one of the new compounds. These effects were mirrored in the biological activities of the new analogues and support a structural role for certain hydroxyls in the native structure.



INTRODUCTION

The selective alteration of complex, biologically active natural products is a long-standing objective for chemists. The allure of catalytic modification stems from the potential for one- or two-step access to new, complex analogues that might provide improved pharmacological properties. This potential is particularly significant when the natural products are readily accessible by fermentation. The identification of catalysts, whether they are enzymes or synthetic catalysts, for selective diversification of complex scaffolds represents a significant chemical challenge. Our laboratory has been pursuing this goal with peptide-based catalysts. To date we have identified catalysts for the selective derivatization of polyols, including selective acylations of simple sugars[1] as well as erythromycin and apoptolidin.[2]

Site-selective deoxygenation has become an increasing focus of our attention, given the appeal of interrogation of the structure−activity relationships (SAR) that might be associated with individual hydroxyl groups within a polyol. Hydroxyl groups have been implicated in drug specificity, toxicity, potency, and bioavailability.[3] Furthermore, hydroxyls may be targeted by drug-resistant organisms as sites of acylation or phosphorylation for "deactivation" of the drug.[4] Recent studies from our group demonstrated the chemical capacity to remove oxygen atoms in this sense in the context of simple sugars[5] and, more recently, in erythromycin A.[6] We have now turned our attention to the significantly more complex glycopeptide antibiotics, including vancomycin (**1**; Figure 1). These studies have culminated in strikingly selective catalysts for modification of a minimally protected form of **1**. Moreover, these studies have revealed structural control elements within **1** that were unexpected. In light of other observations in our laboratory, we believe that site-selective catalysts may provide a general tool for studying not only (a) selectivity issues in catalysis and (b) SAR associated with individual hydroxyl groups, but also (c) the possible biosynthetic significance of individual functional groups, the deletion of which can cause significant perturbation of a natural product's native structure.



$R^1 = R^2 = H$ (vancomycin, **1**)
R^1 = Alloc, R^2 = Allyl (protected vancomycin, **2**)

Figure 1. Structure of vancomycin and its protected form, **2**.

Vancomycin represents an important, complex scaffold that plays a significant role in the treatment of infectious disease. Analogues of vancomycin have been accessed through total synthesis,[7] enzymatic derivatization,[8] and biosynthetic engineering.[9] Semisynthesis of vancomycin analogues has been examined by many groups and, indeed, has led to important, biologically active analogues.[10] To our knowledge, systematic studies of hydroxyl group deletions have not been reported for **1**. We thus describe studies of this type and report catalyst-dependent syntheses of two previously unknown deoxy-vancomycins,[11] their biological activity profiles, and intriguingly, unexpected aspects of their structure.

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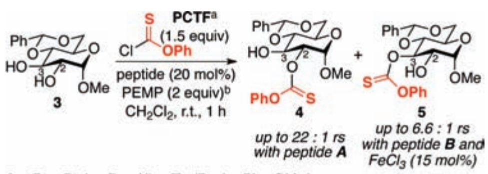
■ RESULTS AND DISCUSSION

Our studies began with the examination of catalyst-dependent thiocarbonylation of vancomycin as a prelude to deoxygenation through the venerable Barton–McCombie method.[12] Previous studies from our laboratory had shown that peptide-dependent regioselectivity was possible in the selective manipulation of simple sugar derivatives.[5a] As noted in Figure 2, regioselective



A = Boc-Pmh-DPro-Aib-DTrp(Boc)-DPhe-OMe[c]
B = Boc-Pmh-Thr(Ot-Bu)-DVal-His(Trt)-Phe-DVal-Thr(Ot-Bu)-Ile-OMe

[a] PCTF = O-phenyl chlorothionoformate. [b] PEMP = 1,2,2,6,6-pentamethylpiperidine. [c] Pmh = π-methylhistidine; Aib = α-amino-iso-butyric acid.

Figure 2. Peptide-catalyzed thiocarbonylation of diol **3**.

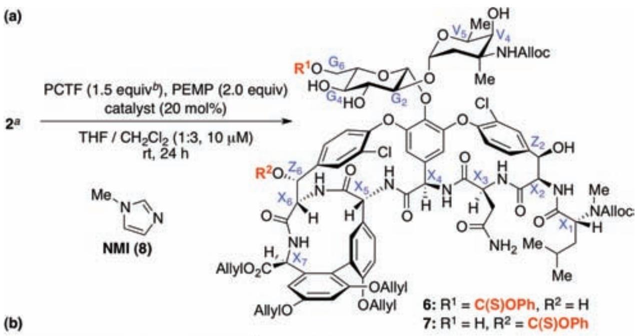
thiocarbonylation of **3** could be achieved such that **4** or **5** could be efficiently accessed in a catalyst and condition-dependent fashion. Conventional deoxygenation of these compounds led to the corresponding deoxy-sugars. Extrapolation of these findings to vancomycin was then addressed. In order to apply this method directly, we elected to initially pursue the selective modification of a readily available vancomycin derivative.[13] The known alloc- and allyl-protected vancomycin derivative **2** (Figure 1, above) proved readily amenable to study. Vancomycin derivative **2** retains six hydroxyl groups, relative to the nine of **1**, reducing the site-selectivity challenge somewhat. Compound **2** also exhibits excellent solubility properties in the organic solvents where the peptide-catalyzed thiocarbonylation chemistry developed to date works best.

Vancomycin itself is readily available by fermentation,[14] and we prepared its protected analogue **2** on a 30-g scale. We were then pleased to find that the conditions we had developed for the selective thiocarbonylation of simple sugars proved quite portable to the study of selective modification of **2**. Figure 3 shows the results of our initial study. These conditions provided a negligible background reaction in the absence of a catalyst (entry 1). However, the achiral control catalyst N-methylimidazole (NMI, **8**) did result in modest rate acceleration, yielding moderate conversion to a major and a minor product, each of which we were able to isolate from the reaction mixture.

The structures of the thionocarbonate products were identified by NMR spectroscopy (Figure 4). Using an edited HSQC experiment, we were able to observe clear changes in the chemical shifts of modified sites, relative to the spectrum recorded for **2** (Figure 4a). The faster-eluting peak was assigned as the G_6-thionocarbonate (**6**), while the slower-eluting peak was assigned as the Z_6-thionocarbonate (**7**). In Figure 4b, we see a large change in the G_6-methylene and smaller changes in the G_5- and G_4-methines. Likewise, in Figure 4c, we see a large change in the Z_6-methine as well as smaller changes in the X_6- and X_5-methines.[15]

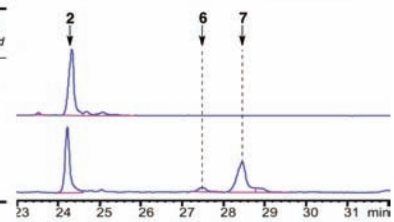
Having established a sense of the inherent reactivity, we evaluated peptide-based catalysts for perturbations in the product ratio. We initiated two approaches to catalyst discovery: one in which we would screen libraries of peptides, and one in which we would design peptides based on the natural binding site of vancomycin. Upon pursuing the first

(a)



(b)

Entry	Catalyst	HPLC Conv.[c]	6 : 7 Ratio[d]
1	none	no reaction	N/A
2	NMI (8)	49%	1 : 5



[a] Starting with 50 mg (28 μmol) of **2**. [b] Added by syringe pump over 10 h. [c] Uncorrected ratio of product peaks to substrate peak observed by HPLC at 285 nm. [d] Uncorrected ratio of peaks observed by HPLC at 285 nm.

Figure 3. Background and achiral catalyst control reactions of **2** under the optimized conditions. (a) The reaction of **2** under the optimized thiocarbonylation conditions. (b) Tabulated and raw HPLC data revealing the product distributions observed when N-methylimidazole (NMI, **8**) is employed as a catalyst.

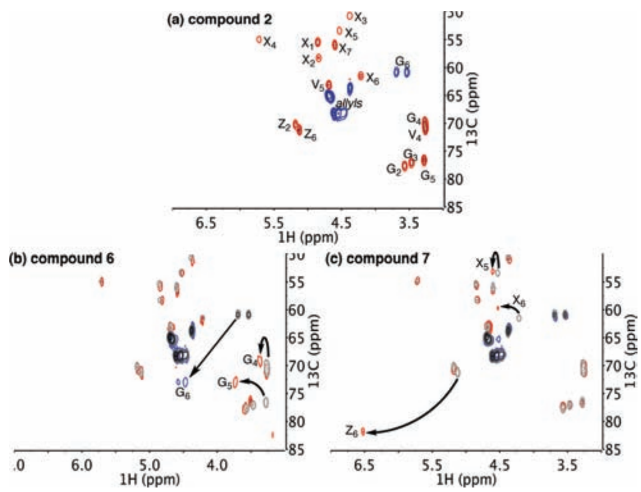
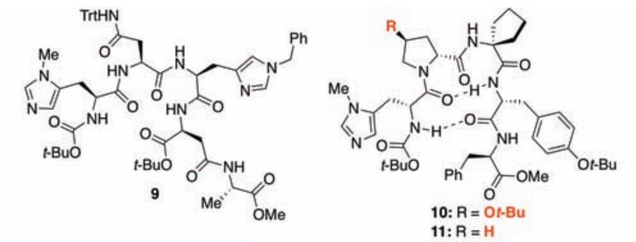
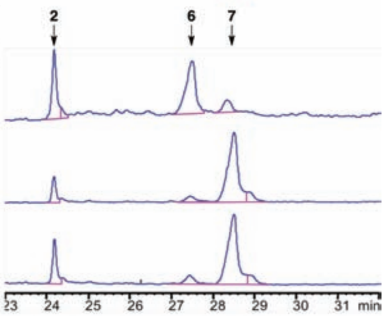


Figure 4. $^1H-^{13}C$ correlation with DEPT; methyls and methines shown in red, methylenes shown in blue. (a) Partial HSQC spectrum of **2**. (b) Partial HSQC spectrum of **6** with **2** overlaid in gray. (c) Partial HSQC spectrum of **7** with **2** overlaid in gray. HSQC = heteronuclear single-quantum correlation. DEPT = distortionless enhancement by polarization transfer.

approach, one of our initial catalyst screens examined a library (25 members) of previously synthesized catalysts from historical projects focused on enantioselective or regioselective reactions of alcohols and amides.[2c,16] Strikingly, from this small test library, we found two catalysts, peptide **9** and peptide **10**, that could either reverse or enhance the product selectivity observed with NMI (Figure 5). Peptide **9** and the enantiomer of **10** have been reported previously for the enantioselective phosphorylation of tribenzyl-*myo*-inositol.[17] Peptide **9** provided a clear reversal in selectivity, in comparison to the selectivity exhibited by NMI, to give primarily the G_6-thionocarbonate



Entry[a]	Catalyst	HPLC Conv.[b]	6 : 7 Ratio[c]
1	9	64%	5 : 1
2	10	88%	1 : 9
3	11	80%	1 : 7



[a] Starting with 50 mg (28 μmol) of **2** using the conditions from Figure 3. [b] Uncorrected ratio of product peaks to substrate peak observed by HPLC at 285 nm. [c] Uncorrected ratio of peaks observed by HPLC at 285 nm.

Figure 5. Tabulated and raw HPLC data revealing the product distributions observed when catalysts **9**, **10**, and **11** were employed as catalysts for the derivatization of **2**.

(entry 1). Catalyst **10**, on the other hand, enhanced the Z_6-selectivity afforded by NMI (entry 2). Moreover, both catalysts were significantly more active than NMI. Peptide **11**, which differs from **10** by substituting the expensive DHyp(O*t*-Bu) amino acid with DPro, showed similar Z_6-selectivity (entry 3). While it is presently unclear exactly how these peptides interact with **2**, one can imagine various hydrogen-bonding schemes that could lead to the site selectivity observed.

On the other hand, the interaction between vancomycin and peptides that mimic its native binding site (the Lys-DAla-DAla terminus of the Gram-positive bacterial peptidoglycan) is well-known and has been observed in X-ray crystallographic (Figure 6a)[18] and NMR studies.[19] We hypothesized that this motif could enhance our ability to control the site of thiocarbonylation with judicious localization of the catalytic alkylimidazole moiety.[20] We thus designed several catalysts based on incorporation of the catalytic histidine residue, Pmh (π-methylhistidine) in the D-form, as illustrated in Figure 6b. In particular, we assessed the catalyst scaffold based on Lys-DAla-DPmh. Our concept was that we might further enhance the targeting of the glucosyl residue by this strategy.

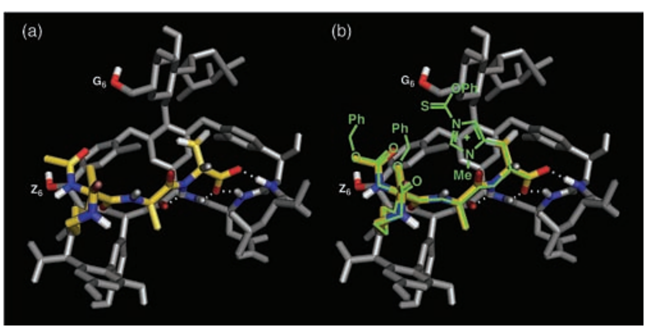
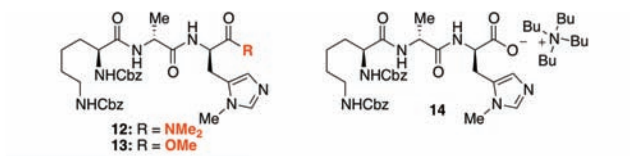
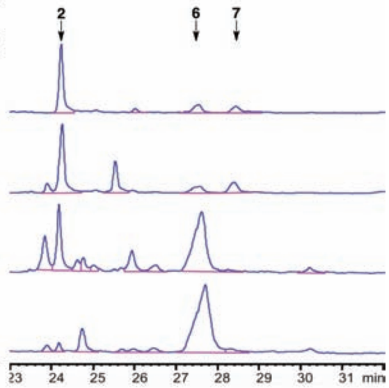


Figure 6. (a) X-ray crystal structure of Ac-Lys(Ac)-DAla-DAla-O⁻ (yellow) bound to vancomycin (gray). (b) Proposed model for delivery of phenyloxythiocarbonyl to the G_6-hydroxyl by Cbz-Lys(Cbz)-DAla-DPmh-O⁻ (green). *X-ray structure adapted from ref 18, PDB 1FVM.*

We were initially concerned that the affinity of **2** for catalysts based on the Lys-DAla-DAla motif might be too high to allow for catalyst turnover. Thus, we examined these catalysts with a full (100 mol %) loading (Figure 7). Despite the increase in



Entry[a]	Catalyst	HPLC Conv.[b]	6 : 7 Ratio[c]
1	12 (100 mol%)	20%	1 : 1.3
2	13 (100 mol%)	32%	1 : 1.3
3	14 (100 mol%)	69%	47 : 1
4	14 (20 mol%)	97%	27 : 1



[a] Starting with 25 mg (14 μmol) of **2** using the conditions in Figure 3. [b] Uncorrected ratio of product peaks to substrate peak observed by HPLC at 285 nm. [c] Uncorrected ratio of peaks observed by HPLC at 285 nm.

Figure 7. Tabulated and raw HPLC data revealing the product distributions observed when Lys-DAla-DPmh catalysts **12**–**14** were employed as catalysts for the derivatization of **2**.

catalyst loading, the first two peptides we examined, with amide and ester functionality at the C-terminal position (e.g., **12** and **13**, entries 1–2), showed low conversions. In addition, the slight selectivity that was observed favored the Z_6-position, contrary to our hypothesis (Figure 6b). However, maintaining the C-terminal carboxylate that is critical to the biological binding of vancomycin to the Lys-DAla-DAla motif proved decisive. Thus, the organic soluble tetrabutylammonium salt **14** led to a dramatic increase in reactivity. Furthermore, selectivity for the G_6-thionocarbonate proved to be very high (entry 3). Also of significant note, the reaction is very efficient with a 20 mol % catalyst loading (entry 4). Indeed, we found the reaction proceeded to higher conversion while maintaining excellent selectivity, allaying concerns about a possible lack of catalyst turnover.[21] Importantly, control experiments revealed that tetrabutylammonium chloride is not a catalyst for the reaction. A combination of equimolar tetrabutylammonium chloride and NMI provided results that were essentially indistinguishable from those observed with NMI alone. Moreover, reactions catalyzed by peptide **14**, performed in the presence of Cbz-Lys(Cbz)-DAla-DAla/NBu_4 as a putative competitive inhibitor resulted in lower levels of conversion and selectivity.[22]

With selective catalysts **11** and **14** in hand, we wished to assess their performance on a significant scale. These experiments would set the stage for deoxygenation and deprotection experiments. We were pleased to find that the reactions proceeded with equivalent or better efficiency when conducted on 0.50-g scale, as shown in Figure 8. While the results for catalyst **14** were almost identical to the smaller-scale

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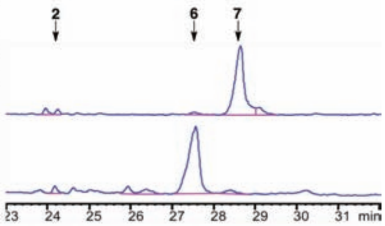
reaction, we observed a significant improvement in conversion and selectivity for catalyst **11**.

Entry[a]	Catalyst	HPLC Conv.[b]	6 : 7 Ratio[c]
1	11	89%[d]	1 : 21[d]
2	14	95%[e]	24 : 1[e]



[a]Starting with 0.50 g (0.28 mmol) of **2** using the conditions in Figure 3. [b]Uncorrected ratio of product peaks to substrate peak observed by HPLC at 285 nm. [c]Uncorrected ratio of peaks observed by HPLC at 285 nm. [d]Averaged values from four reactions. [e]Averaged values from two reactions.

Figure 8. Tabulated and raw HPLC data revealing the product distributions observed when catalysts **11** and **14** were employed as catalysts for the derivatization of **2** on half-gram scale.

We then turned our attention to deoxygenation and deprotection. We expected that the G_6- (**6**) and Z_6-thionocarbonate (**7**) might require different conditions for radical deoxygenation since **6** is a primary thionocarbonate while **7** is benzylic. Under traditional Barton−McCombie conditions,[12] we observed complete reaction of the primary G_6-thionocarbonate at 80 °C, whereas the reduction of the benzylic Z_6-thionocarbonate proceeded at 70 °C (Figure 9). Deoxygenation of **7** was also performed at room temperature using BEt_3/air as the radical initiator.[23,24] Allyl- and alloc-removal from the protected deoxy-vancomycins proceeded smoothly under conditions similar to those in the literature.[13b,25] Notably, $HSnBu_3$ could be substituted with $PhSiH_3$ without loss of reaction efficiency. Thus, compounds **15** (G_6-deoxy-vancomycin) and **16** (Z_6-deoxy-vancomycin) were obtained, each in five efficient steps from **1**.

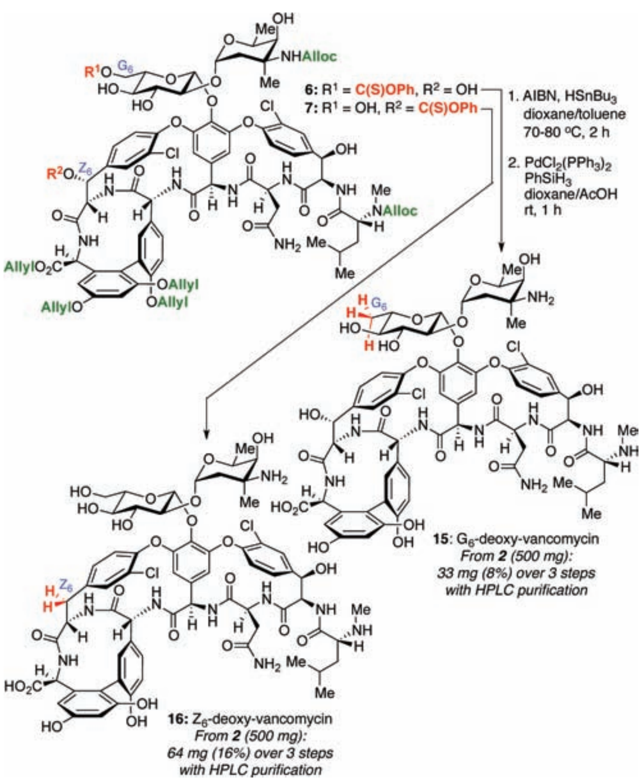


Figure 9. Deoxygenation and deprotection of thionocarbonates **6** and **7** to yield the corresponding deoxy-vancomycins **15** and **16**.

Preparative HPLC purification of deoxy-vancomycins **15** and **16** provided access to high-purity samples for structural characterization and biological evaluation. G_6-Deoxy-vancomycin (**15**), perhaps unsurprisingly, revealed close analogy to vancomycin structurally. As shown in Figure 10a, samples could

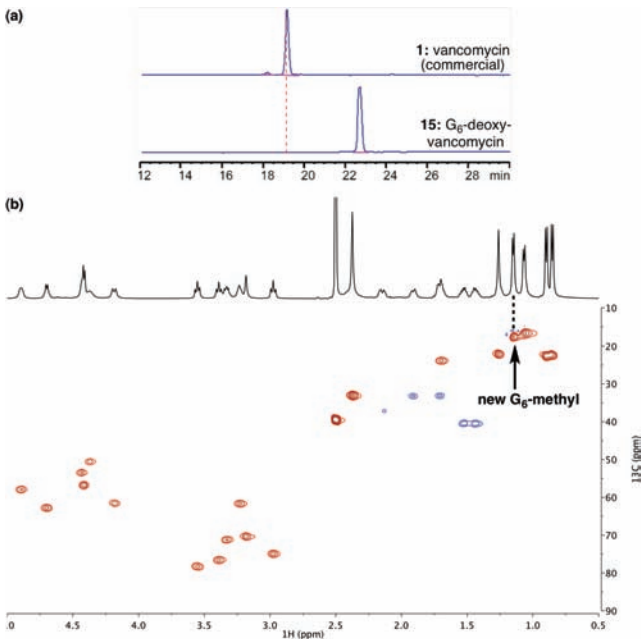


Figure 10. (a) HPLC trace of **15** after purification. (b) Partial HSQC spectrum of **15**.

be obtained in significant quantity and in high purity. NMR analysis, exemplified by the HSQC spectrum in Figure 10b, revealed a highly homogeneous structure, for which analogy to the spectra of **1** itself was excellent.[15]

Z_6-Deoxy-vancomycin (**16**) presented surprising differences from **1** and **15**. HPLC purification and LC/MS analysis of **16** consistently revealed the presence of two peaks (Figure 11a) of equivalent mass. Moreover, isolation of the fast-eluting peak and reinjection for HPLC analysis revealed the same doubling of the peaks. Isolation and reinjection of the slow-eluting peak produced an identical HPLC trace. These observations led us to conclude that the Z_6-deoxy-vancomycin (**16**) exists at room temperature as a conformationally mobile species of at least two interconverting states, in stark contrast to either **1** or **15**. The conformational heterogeneity was supported by NMR studies, which revealed doubling of cross-peaks in the aromatic and α-CH regions of the HSQC spectrum (e.g., Figure 11b).

The exact nature of the conformational equilibrium exhibited by **16** is difficult to establish unambiguously. We have considered several possibilities. Our first proposal, stimulated by conformational studies of synthetic vancomycin fragments in the literature,[26] was that of possible atropisomerism about the chloroarene ring-6 of **16** (Figure 12a). However, when **16** was subjected to dechlorination conditions (Pd/C, H_4N_2, NH_4OH, $MeOH/H_2O$),[27] the HPLC trace exhibited by didechloro-Z_6-deoxy-vancomycin **17** retains its apparent conformational heterogeneity (Figure 12b).

There are at least three other possibilities that one can consider for the observed conformational equilibrium: (a) a *cis*-

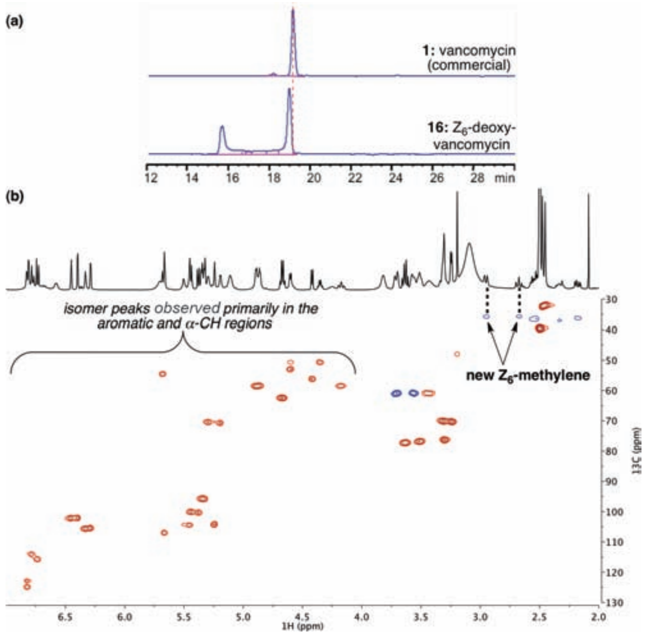


Figure 11. (a) HPLC trace of **16** after purification. (b) Partial HSQC spectrum of **16**.

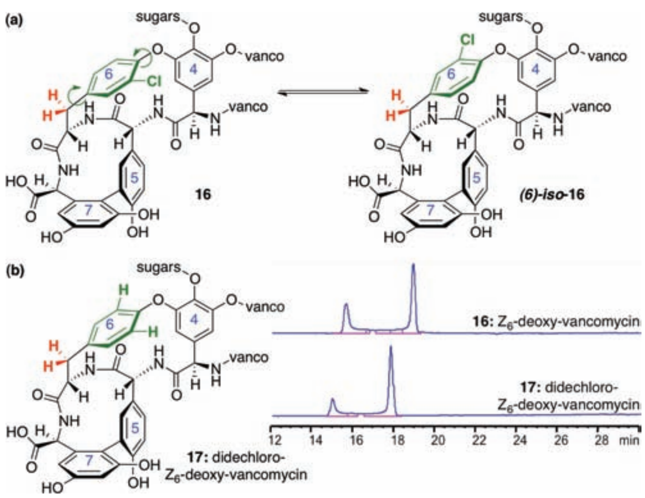


Figure 12. (a) Proposed atropisomers about the chloroarene ring-6 of **16**. (b) HPLC analysis of didechloro-Z_6-deoxy-vancomycin (**17**).

amide/*trans*-amide isomerization about the C_5–W_6 amide bond (Figure 13a);[28] (b) medium ring isomerization associated with the allylic strain conformers induced by the C_6–W_7 amide bond (Figure 13b);[29] and (c) atropisomerization about the biaryl moiety of the 5- and 7-arenes (not shown).[30] Of course, these issues could also operate simultaneously and synergistically. What is remarkable about this observation of conformational heterogeneity exhibited by **16** is that our catalytic studies have unveiled conformational programming induced by the Z_6-hydroxyl in native vancomycin. *Thus, its presence is not associated with a simple SAR but carries with it significant conformational consequences.* Our current assessment of the role of the hydroxyl is that it may form a hydrogen bond with the C_6-amide carbonyl, stabilizing the peptidoglycan-binding conformation, as illustrated in Figure 13c (the O_{C_6}–O_{Z_6} distance is 3.2 Å in the X-ray structure of vancomycin complexed with Ac-Lys(Ac)-DAla-DAla).[18] We also note in passing that this structural

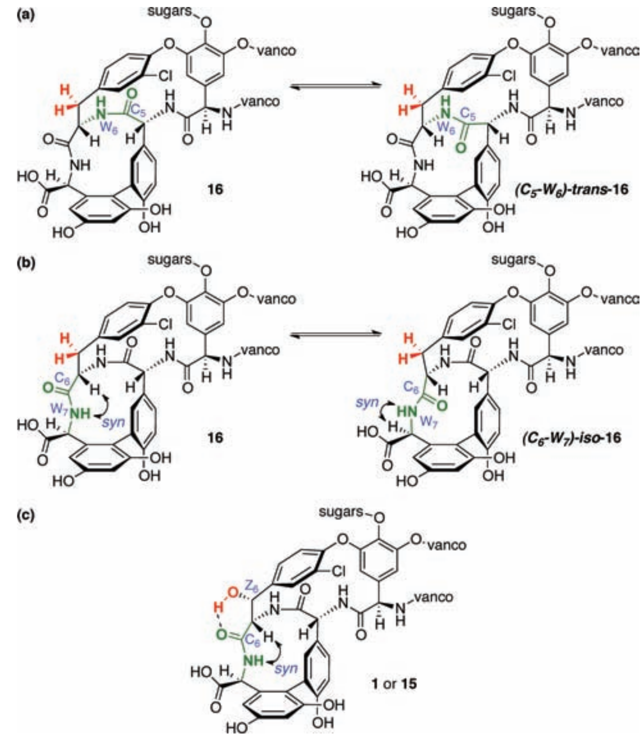


Figure 13. (a) *cis/trans*-Isomerization of the C_5–W_6 amide bond. (b) *syn/anti*-Conformational change within the (5-6-7)-macrocycle about the C_6–W_7 amide. (c) A proposed hydrogen bond that may rigidify the *syn/anti*-isomer shown.

programming of native natural product conformations has surfaced in our previous studies of catalytic polyol modification, with analogous structural reorganizations of erythromycin upon site-selective acylation of individual hydroxyl groups.[2c,31]

Of note, the conformational mobility of the Z_6-deoxy-vancomycin **16** appears to have biological consequences. The minimum inhibitory concentrations (MICs) exhibited by **1** and the new compounds were measured as an indicator of antibiotic activity (Table 1). Interestingly, G_6-deoxy-vancomycin (**15**)

Table 1. MIC Values for Deoxy-vancomycins 15 and 16 against Selected Bacterial Strains

entry	cmpd	MSSA[a,b]	MRSA[c]	VSE[d]	VRE (VanB)[e]	VRE (VanA)[f]
1	**1**	0.5	1	2	16	>64
2	**15**	0.5	1	2	16	>64
3	**16**	2	4	8	>64	>64

[a]MIC values reported in μg/mL. [b]MSSA = methicillin-susceptible *Staphylococcus aureus*, ATCC 29213. [c]MRSA = methicillin-resistant *S. aureus*, ATCC 43300. [d]VSE = vancomycin-susceptible enterococci, ATCC 29212. [e]VRE = vancomycin-resistant enterococci, ATCC 51299. [f]MMX 486. See Supporting Information for additional details.

showed identical activity against all tested bacterial strains. Z_6-Deoxy-vancomycin (**16**), however, proved to be consistently less active; this result likely reflects the conformational heterogeneity and the differential activity (high and low) associated with each interconverting structure.[32]

■ CONCLUSIONS

In summary, we have discovered site-selective catalysts that allow hydroxyl group-selective thiocarbonylation of a minimally protected version of **1**. These catalysts ultimately allowed

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preparation of two deoxy-vancomycins that differ from **1** only in that a singular oxygen atom is missing from either **15** or **16**. We have shown that two methods of catalyst discovery, library screening and binding site-based design, are both viable strategies to selective modification of natural product derivatives. The prospects for generalizing this catalytic approach seem encouraging, given the substantially divergent site-selectivity exhibited by catalysts **11** and **14**. The observation of near total conformational homology between **1** and **15** is mirrored in their essentially indistinguishable biological profiles. On the other hand, the removal of the O-atom from the Z_6-position of **1** revealed a pronounced conformational role for the Z_6-hydroxyl group. The biological effects of reducing the inherent rigidity of **1** manifest in the attenuated activity of **16** in the MIC assays. Perhaps most notable, however, is the capacity of site-selective catalysis to unveil conformational programming in complex structures, perhaps encoded by biosynthesis,[33] which we will now look for in systematic ways.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures and characterization data for all of the experiments described in the manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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