Target-Accelerated Combinatorial Synthesis and Discovery of Highly Potent Antibiotics Effective Against Vancomycin-Resistant Bacteria**

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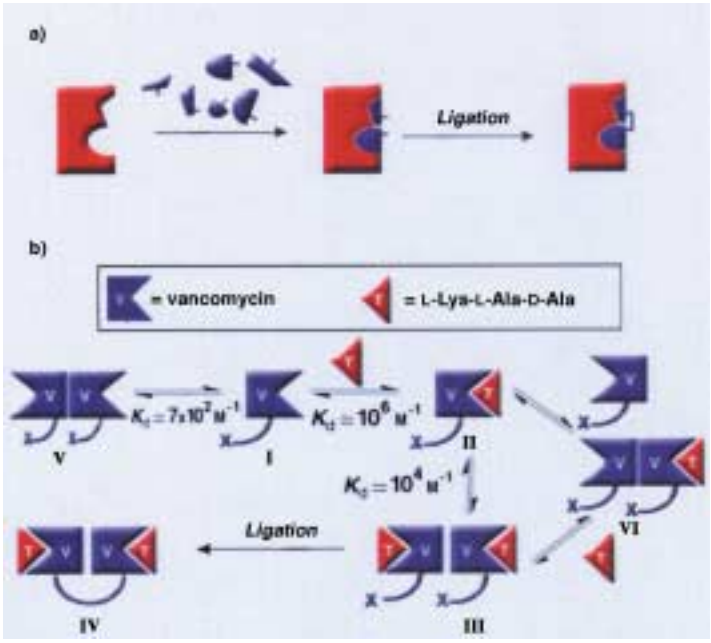
In the past decade combinatorial chemistry has evolved into a powerful tool for chemical biology and the drug discovery process.[1] The complete sequencing of the human genome will inevitably increase the demand for libraries of small organic molecules and create a strong evolutionary pressure on methods to rapidly generate such molecules. Lehn and co-workers have recently proposed and demonstrated[2, 3] the feasibility of "dynamic target-driven combinatorial synthesis" wherein the building blocks of a combinatorial library are allowed to assemble and react in the presence of a target (Scheme 1 a). This synthetic approach should, thus, selectively deliver the product with the highest affinity for the target out of a virtual library of all possible reaction products.[4] In a related approach, Fesik and co-workers have developed a technique whereby the building blocks of potential combinatorial libraries are screened for binding to their target by NMR spectroscopy.[5] The building blocks with the highest affinity for the target are then covalently tethered in a separate experiment. More recently, Ellman and co-workers reported a similar approach in which an initial combinatorial library was screened for binding to a target by an enzyme-linked immunosorbent assay (ELISA) in order to narrow down the selection of building blocks[6] for eventual, separately performed, covalent tethering. Herein we report the application of direct target-accelerated combinatorial synthesis (TACS) of vancomycin dimers for the identification of ligands with the highest affinity for vancomycin's receptor, D-Ala-D-Ala. Among the dimers synthesized are a number possessing potent activities against vancomycin-resistant *enterococci* (VRE) and vancomycin intermediate susceptible *Staphylococcus aureus* (VISA) that rival or exceed the most active compounds known today[7] for these bacterial strains.



Scheme 1. a) Schematic representation of target-accelerated combinatorial synthesis. A target (red shape) is incubated with a library of building blocks (blue shapes). The building blocks that show affinity for the target will assemble onto the target. Upon a ligation reaction, the selectively preorganized assembly will ligate preferentially. b) Schematic representation of dynamic target-accelerated combinatorial synthesis of vancomycin dimers. A library of vancomycin analogues (**V**, blue shape) are incubated with their target, Ac_2-L-Lys-D-Ala-D-Ala (**T**, red shape). Since the formation constant of the vancomycin dimer ($K_d \approx 7 \times 10^2\,M^{-1}$) is greater in the presence of its target ($K_d \approx 10^4\,M^{-1}$), it is expected that the target-bound dimeric assembly (**III**) should ligate faster than its nontarget-bound counterpart (**V**).

Vancomycin (**1**, Scheme 2 a),[8, 9] a prominent member of the glycopeptide class of antibiotics, has been used clinically for the past 40 years to treat infections caused by Gram-positive bacteria. Its renowned action against methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria has made it an antibiotic of last resort. However, the emergence of vancomycin-resistant *enterococci* (VRE)[10] and, more recently, vancomycin intermediate susceptible *Staphylococcus aureus* (VISA)[11] are raising serious health concerns and has prompted renewed and vigorous research activities targeting modified vancomycin analogues with restored activity against VRE or VISA.[12, 13] Vancomycin's antibacterial activity arises from its ability to inhibit peptidoglycan biosynthesis within the bacterial cell wall. Specifically, vancomycin binds to the terminal Lys-D-Ala-D-Ala fragment of the growing peptidoglycan biosynthetic precursor through an intricate network of five hydrogen bonds (Scheme 2 a),[14] thereby inhibiting cell-wall growth and cross-linking. While the resistance mechanism of VISA is not yet understood in detail,[15, 16] the molecular mechanism of VRE (types A and B) defense against vancomycin relies on a modified peptidoglycan biosynthesis in which the terminal D-Ala residue is substituted

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[**] We thank Dr. Gary Siuzdak for mass spectrometric assistance and Prof. Dr. Gunter Benz and Drs. Rudolf Hanko and Joachim Krueger of Bayer AG for helpful discussions. This work was financially supported by the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, and Bayer AG, as well as by fellowships from the Division of Organic Chemistry of the American Chemical Society (sponsored by Hoescht Marion Roussel, to R.H.) and the George Hewitt Foundation (to N.W.).

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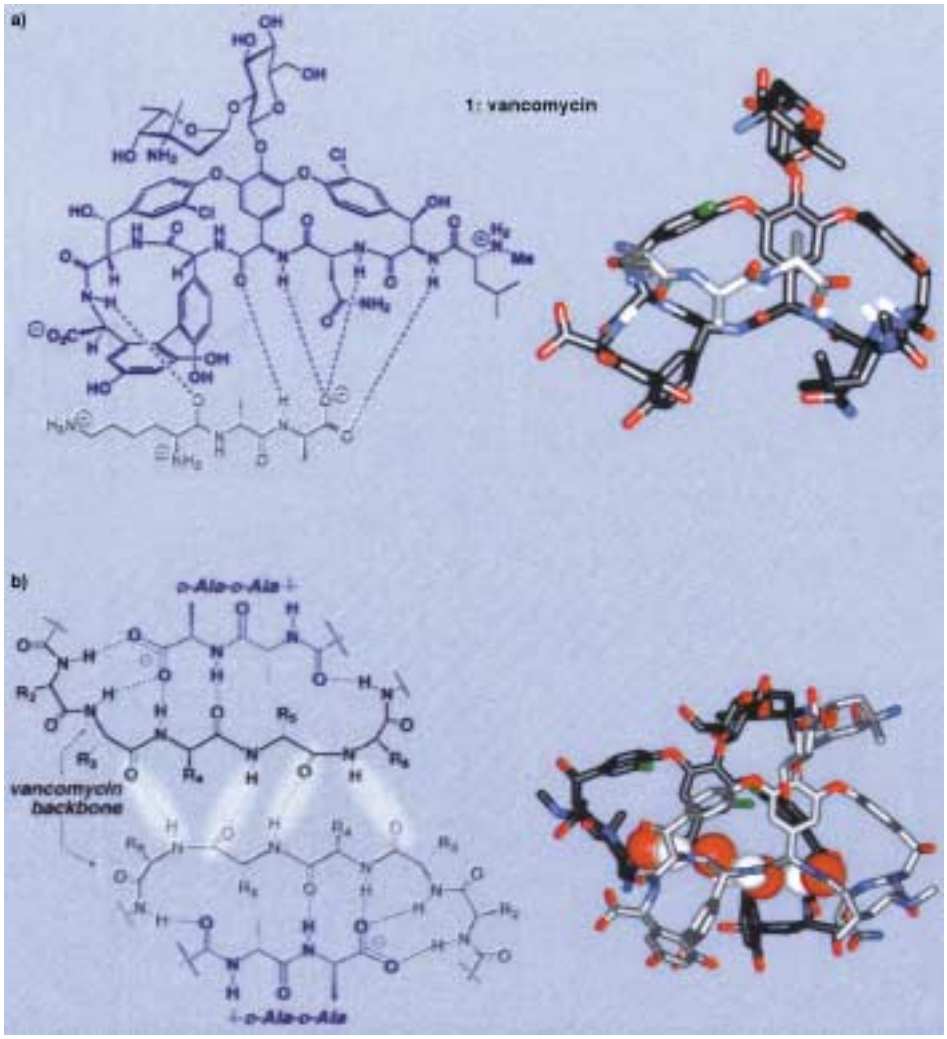

Scheme 2. a) Hydrogen-bond network between vancomycin (dark structure) and the L-Lys-D-Ala-D-Ala tripeptide (light structure) as a ChemDraw (left) and as a wire-frame model (right). b) Hydrogen-bonding network of the vancomycin back-to-back dimer as a ChemDraw (left) and as a wire-frame model (right, one vancomycin molecule is shown in light gray whereas the other is shown in black) with the hydrogen bonds in the latter highlighted by space-filling atoms (oxygen = red; hydrogen = white).[18]

by a D-Lac moiety.[17] This substitution results in the loss of one hydrogen bond with the consequence that the reduced affinity of vancomycin for D-Ala-D-Lac is no longer sufficient to inhibit the peptidoglycan biosynthesis.

A number of glycopeptide antibiotics form dimers[18, 19] and, significantly, their propensity to dimerize has been correlated to their biological activity.[20] Vancomycin has been shown to form a weak back-to-back dimer with a dimerization constant[21] of approximately $7 \times 10^2\,\text{M}^{-1}$. In addition to the benefit of multivalency,[22] an important feature of this back-to-back dimerization is the strengthening of the hydrogen-bonding interaction between the vancomycin framework and its target (Scheme 2b). Thus, back-to-back dimerization is mediated by a network of hydrogen bonds which involve the same amide linkages as those involved in binding to the D-Ala-D-Ala moiety. The net result of this cooperative, back-to-back binding is that the dimer has greater affinity for its target than the monomer; likewise, vancomycin bound to its target has a greater dimerization constant (ca. $10^4\,\text{M}^{-1}$) than vancomycin alone.[23] Griffin and coworkers have prepared covalent dimers[24] linked through the C-terminus of vancomycin which exhibit moderate activity against VRE. Interestingly, the biological activity of these dimers varied significantly with the nature of the tether. Several other covalent vancomycin dimers,[25–27] a trimer,[28] and a polymer[29] have also been reported. Most recently, surface plasmon resonance was used to investigate the self-association of several covalent vancomycin dimers. The study indicated that the biological activity of such covalent dimers is correlated to their ability to self-assemble (that is, to adopt the back-to-back conformation).[30]

On the basis of the structure of the back-to-back dimer (Scheme 2b) we reasoned that the most appropriate means by which to form such a stable dimer would be to construct a bridge across the saccharide domains of two vancomycin molecules. However, selecting the appropriate tether so as to permit the full cooperation of the two monomers in forming the desired back-to-back arrangement was the more demanding challenge. We postulated that a dynamic target-accelerated combinatorial synthesis of such a dimer (Scheme 1b) would be particularly attractive for the case of vancomycin dimers (Scheme 1b), with the ones with the strongest affinity for the target being favored. As such, a library of vancomycin analogues (monomers) would be allowed to self-assemble in the presence of their target while a latent reactive functionality could later be utilized to covalently dimerize the product of the most stable and longest-lived supramolecular assembly.[31] Since the vancomycin template has a higher formation constant for the dimer when bound to its target, we hypothesized that the selection should function for both the adequacy of the tether and the binding affinity of the vancomycin analogue to its target. Such a strategy would also enable the formation of covalent hetero-vancomycin dimers.[32] The final task was to choose an appropriate ligation method which could operate efficiently at biologically relevant temperatures and in aqueous media, be compatible with vancomycin's polyfunctional structure, and, most importantly, operate reversibly so as to allow equilibration. Towards this end we selected two processes, the olefin metathesis reac-

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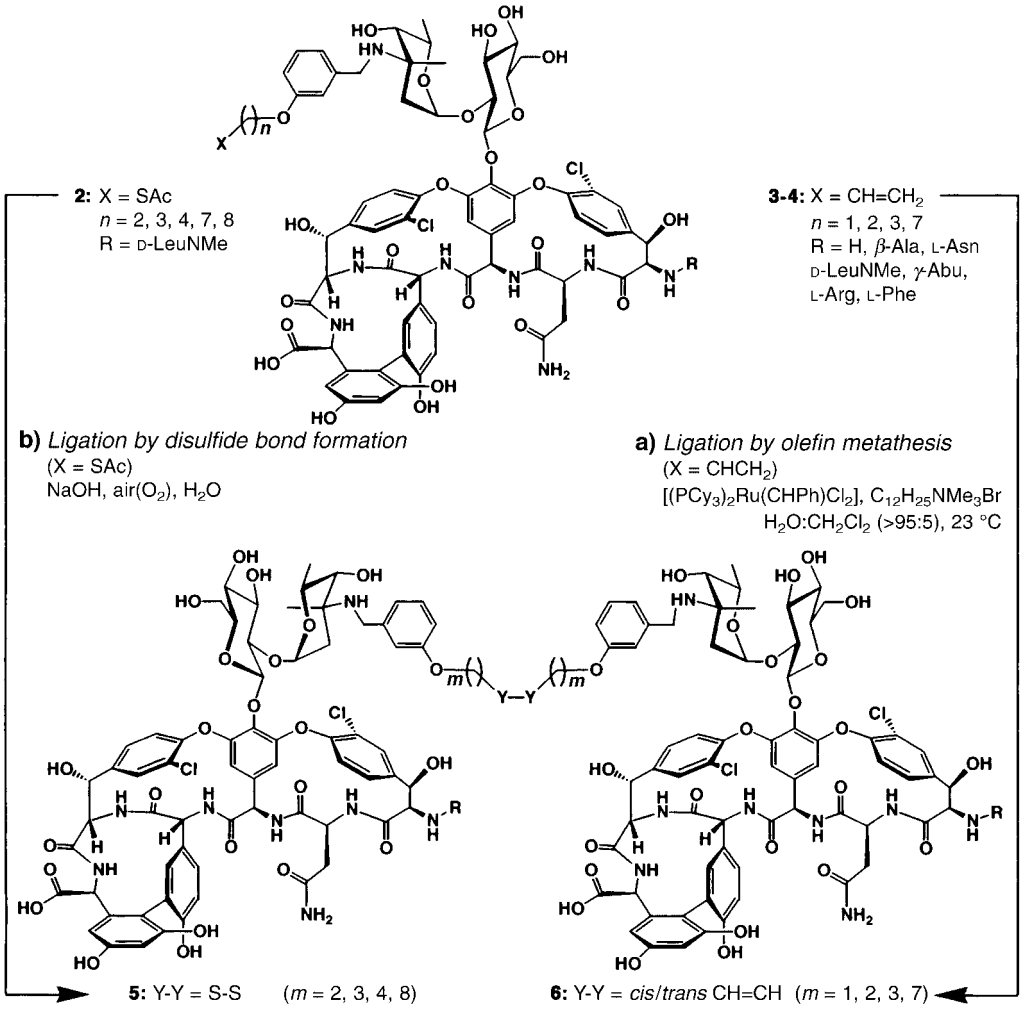
tion[33] and the formation of a disulfide bond, which could meet these stringent requirements.

We employed both solid- and solution-phase combinatorial chemistry (see Supporting Information) to synthesize the required substrates for the target-accelerated dimerization studies. All synthesized vancomycin libraries were then subjected to biological screening for antibacterial properties, and a representative set of the library members were chosen for the proposed dimerization studies.

As an initial experiment to validate the target-accelerated dimerization hypothesis we subjected vancomycin derivatives **2** and **3** to disulfide formation and to olefin metathesis, respectively, in both the absence and presence of vancomycin's targets Ac-D-Ala-D-Ala and Ac_2-L-Lys-D-Ala-D-Ala for which vancomycin has the greatest affinity (Scheme 3). To achieve olefin metathesis, $[(PCy_3)_2Ru(CHPh)Cl_2]$ was used as a catalyst in conjunction with the phase-transfer catalyst $C_{12}H_{25}NMe_3Br$, with the reactions carried out in water at 23 °C. The reactions proceeded at reasonable rates under these conditions and were conveniently monitored by both HPLC and mass spectrometry. A significant rate acceleration for this reaction was observed in the presence of either ligand relative to the control experiment as measured by product formation by HPLC (Figure 1). As expected, Ac_2-L-Lys-D-Ala-D-Ala induced the highest rate acceleration by virtue of its higher affinity for vancomycin. The positive correlation between the observed target-induced rate acceleration and the target binding affinity to vancomycin is in accord with the postulated target-induced rate-acceleration mechanism. Likewise, the series of vancomycin thioacetate analogues **2** were saponified with NaOH and induced to dimerize by air oxidation in aqueous solution at ambient temperature in the absence and presence of Ac_2-L-Lys-D-Ala-D-Ala. Again, a strong target-induced rate acceleration was observed in the presence of these vancomycin targets (data not shown).

Having established the validity of the target-accelerated synthesis of vancomycin dimers from individual monomers,



Scheme 3. Dimerization of monomeric vancomycin thioacetates (**2**) and vancomycin derivatives with terminal olefins (**3**, **4**) to form disulfides (**5**) and olefinic dimers (**6**), respectively. Reagents and conditions: a) $[(PCy_3)_2Ru(CHPh)Cl_2]$ (0.2 equiv), $C_{12}H_{25}NMe_3Br$ (2.2 equiv), H_2O:CH_2Cl_2 (>95:5), 23 °C; b) NaOH (10.0 equiv), H_2O, 23 °C. Individual compounds (homo-dimers) were most conveniently prepared as single compounds from the corresponding monomers and were isolated in pure form by HPLC. Isolated compounds were characterized by NMR spectroscopy and mass spectrometry. In this report, we use the convention **xx-(R)C_n** to designate library members with the following designations: **xx** = compound number; **(R)** = the first amino acid residue; **C_n** = number of carbon atoms between the phenolic oxygen atom and the dimerization moiety X. Thus, **3-(LeuNMe)C_4** designates a monomer and **6-(LeuNMe)C_4-(LeuNMe)C_4** designates its corresponding dimer. Cy = cyclohexyl.

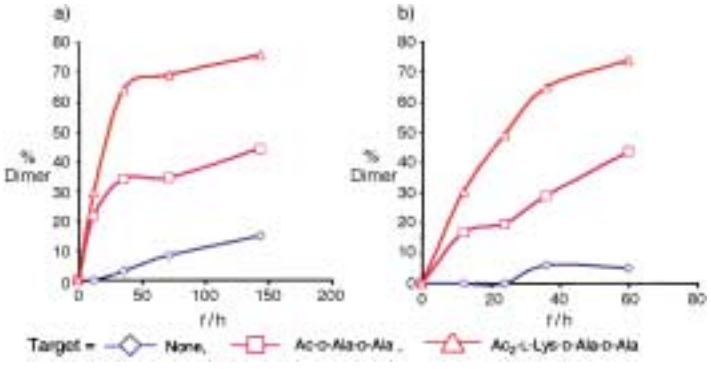


Figure 1. Proof of principle of target-accelerated synthesis of covalently linked vancomycin dimers through the olefin metathesis reaction in the absence and in the presence of the target. Formation of a) **6-(LeuNMe)C_2-(LeuNMe)C_2** and b) **6-(LeuNMe)C_4-(LeuNMe)C_4**. Reagents and conditions: vancomycin analogue (550 μM), $C_{12}H_{25}NMe_3Br$ (2.75 mM), target (110 μM), $[(PCy_3)_2Ru(CHPh)Cl_2]$ (110 μM), H_2O:CH_2Cl_2 (>95:5), 23 °C (see Scheme 3 for reaction and structures).

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we then investigated a combinatorial version of this reaction. Therefore, three vancomycin analogues **3-(LeuNMe)C_2**, **3-(LeuNMe)C_3**, and **3-(LeuNMe)C_4** (see Scheme 3 and Supporting Information) bearing tethers of differing length were mixed and subjected to target-accelerated covalent dimerization under combinatorial conditions. In the absence of the target, the expected statistical mixture (1:2:3:2:1; two permutations are degenerate) of all possible (six) dimers (**6-(LeuNMe)C_2-(LeuNMe)C_2**, **6-(LeuNMe)C_2-(LeuNMe)C_3**, **6-(LeuNMe)C_2-(LeuNMe)C_4**, **6-(LeuNMe)C_3-(LeuNMe)C_3**, **6-(LeuNMe)C_3-(LeuNMe)C_4**, and **6-(LeuNMe)C_4-(LeuNMe)C_4**) was observed, whereas in the presence of the target (Ac_2-L-Lys-D-Ala-D-Ala) a clear bias for dimers with shorter tethers was observed ($n = 1$ and 2; Figure 2). The individual olefinic dimers (homodimers only) were tested for their biological activity and a good agreement between the target-induced rate acceleration and their potency was observed (Figure 3a). The same correlation between length and activity was also observed for the disulfide dimers (Figure 3b). Most significantly, dimers from both the olefinic and the disulfide categories with optimal tether length (16–18 atoms between the two nitrogen atoms) exhibited strong activities, particularly against VRE. In comparing the results for these two sets of compounds it is noteworthy recalling that olefinic bonds have been used as disulfide bond mimics. As a consequence of the expected superiority of the olefinic compounds over their disulfide counterparts as potential drug candidates, because of their greater metabolic stability, we focused the remainder of our studies on the mediation of the dimerization process by olefin metathesis.

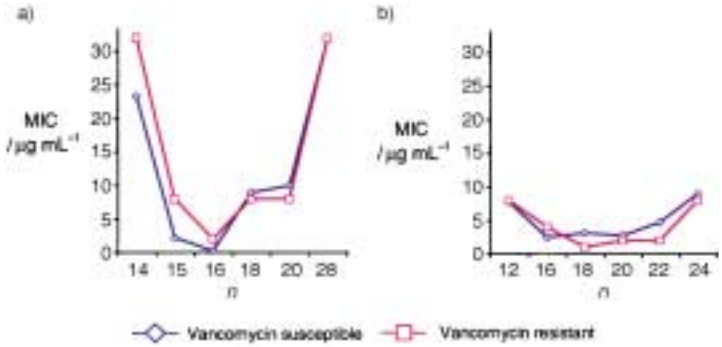

Figure 3. Correlation between the tether length n and antibacterial activity of vancomycin dimers. The number corresponding to the tether length represents the total number of atoms between the two nitrogen atoms of the olefinic (a) and disulfide dimers (b). The data for the vancomycin-susceptible bacteria represent the average of nine vancomycin-susceptible strains (*Streptococcus pneumoniae* (Sa8250 and Sp670), *Enterococcus faecalis* (27266, 4002, 27261), *Staphylococcus aureus* (48N, 25701, LO3, 133); see Scheme 3 for structures).

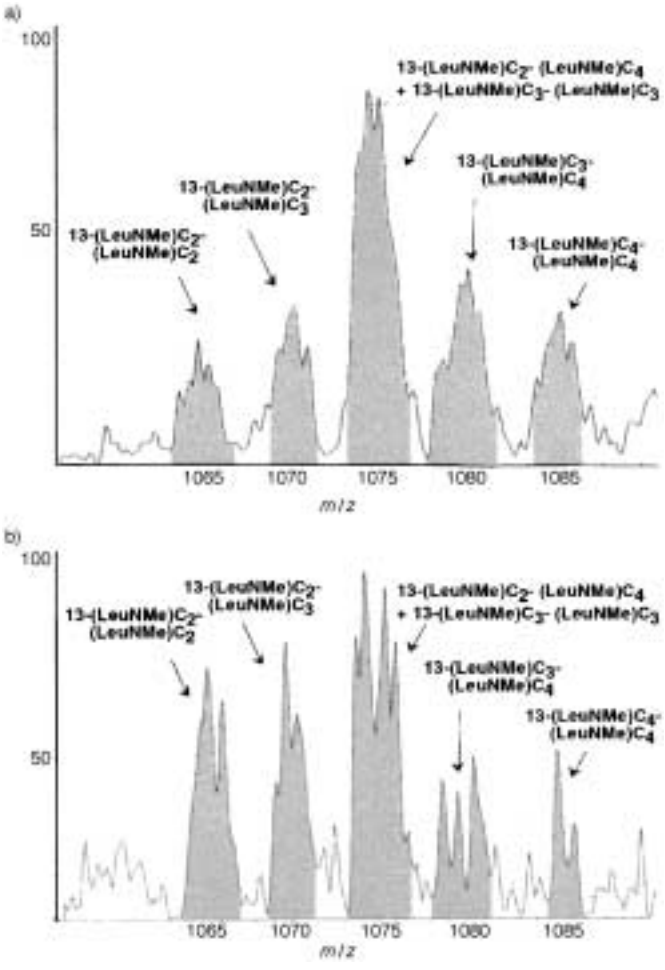

Figure 2. Mass spectrometric analysis of the vancomycin dimer mixture formed from **3-(LeuNMe)C_2**, **3-(LeuNMe)C_3**, and **3-(LeuNMe)C_4** (see Supporting Information). In the absence (a) of the target a statistical mixture (1:2:3:2:1) of products is observed whereas in the presence (b) of the target (Ac_2-L-Lys-D-Ala-D-Ala) shorter tethered dimers (**6-(LeuNMe)C_2-(LeuNMe)C_2** and **6-(LeuNMe)C_2-(LeuNMe)C_3**) are formed preferentially (see Scheme 3 for structures).

With the optimum length of the tethering bridge established, we then turned our attention to the influence of the binding affinity between the target (Ac_2-L-Lys-D-Ala-D-Ala) and the ligand (vancomycin residue) on the rate of dimerization. A convenient and potentially productive way of modulating this affinity is to vary the first amino acid residue of vancomycin (see Supporting Information). Thus, a combination of two vancomycin analogues (**3-(LeuNMe)C_2** and **4-(β-ala)C_2**; for definitions of abbreviations, see the legend in Scheme 3) were treated under the above-described olefin metathesis conditions in both the absence and presence of their target (Ac_2-L-Lys-D-Ala-D-Ala; see Supporting Information). Interestingly, in the absence of the target, the homodimer of the β-Ala-substituted vancomycin (**6-(β-Ala)C_2-(β-Ala)C_2**) was formed preferentially over the vancomycin homo-dimer (**6-(LeuNMe)C_2-(LeuNMe)C_2**; Figure 4a). This result may be attributed to a higher tendency of the β-Ala-substituted vancomycin monomer to dimerize in the absence of the target. In the presence of the target, however, the vancomycin homo-dimer **6-(LeuNMe)C_2-(LeuNMe)C_2** was formed preferentially as expected (Figure 4b). The results of this experiment are again consistent with the biological activities exhibited by these compounds (Table 1), and that the stronger affinity for the target translates into higher dimerization rates by monomer selection. The observed enhancement results also demonstrate that the background reaction is relatively inconsequential.

Having established that the target-accelerated dimerization of vancomycin analogues selects for both the adequecy of the tether and the affinity for the target, we performed an eight-

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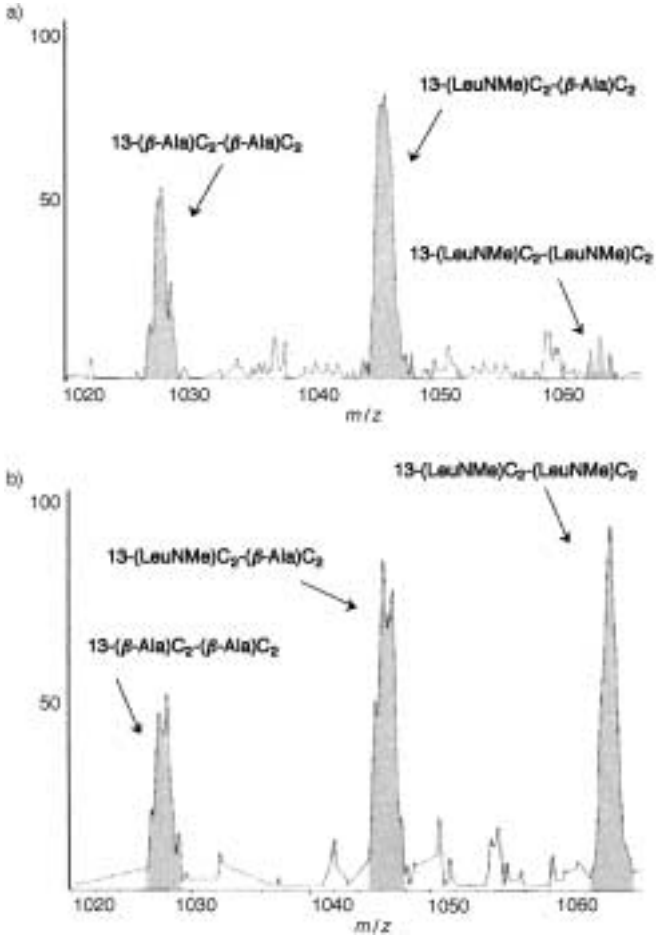

Figure 4. Mass spectrometric analysis of the vancomycin dimer mixture formed from **3-(LeuNMe)C_2** and **4-(β-Ala)C_2**. Note that in the absence of the target (a), the dimer containing D-LeuNMe (**6-(LeuNMe)C_2-(LeuNMe)C_2**) is formed at a slower rate than the ones containing β-Ala. In the presence (b) of the target (Ac_2-L-Lys-D-Ala-D-Ala) the dimers containing D-LeuNMe (**6-(LeuNMe)C_2-(LeuNMe)C_2**) rather than β-Ala are formed preferentially.

component (**3-(LeuNMe)C_2**, **3-(LeuNMe)C_4**, **4-(β-Ala)C_2**, **4-(β-Ala)C_4**, **4-(Asn)C_2**, **4-(Asn)C_4**, **4-(H)C_2**, **4-(H)C_4**) target-accelerated (Ac_2-L-Lys-D-Ala-D-Ala) combinatorial synthesis experiment employing the olefin metathesis reaction (Figure 5). Thirty-six library members were expected, but only thirty could be observed separately by mass spectrometry as a consequence of the degeneracy of six of the dimers. The vertical bars in Figure 5 reflect the observed relative abundance of each of the thirty distinct (with regard to their mass) vancomycin dimers after adjustment to account for the expected statistical occurrence (average values for three experiments). The eleven compounds indicated by letters (a – j; all homo-dimers, except for d) were individually synthesized from their respective monomers through separate reactions and purified by HPLC for biological evaluation. Figure 6 and Table 1 show a selection of the antibacterial activities of these discrete compounds (a – j) against a number of vancomycin-susceptible and vancomycin-resistant bacterial strains. Gratifyingly, the target-accelerated dimerization experiments predicted quite reliably the overall trend of the observed biological activity of the library members, with only relatively small deviations. The identification and correct ranking of compounds a: **6-(LeuNMe)C_2-(LeuNMe)C_2**, b: **6-(LeuNMe)C_2-(β-Ala)C_2**, and c: **6-(LeuNMe)C_2-(LeuNMe)C_4** as highly potent antibacterial agents effective against both vancomycin-susceptible and vancomycin-resistant strains is highly significant. Since six out of the seven most abundant compounds contain LeuNMe, the results also underscore the importance of the natural first amino acid residue (LeuNMe) for strong binding and presumed (observed in some cases) biological activity. Table 1 lists further examples of highly potent vancomycin dimers from the disulfide family.

In conclusion, we have demonstrated the power of the target-accelerated combinatorial synthesis concept and applied it to the discovery of a number of highly potent antibiotics active against both vancomycin-susceptible and

Table 1. Antibacterial activity (MIC: $\mu g\,mL^{-1}$) of selected vancomycin dimers against vancomycin susceptible strains, a vancomycin intermediate resistant strain, and a vancomycin-resistant strain.

[Rank]Compound	Strain						
	Sa8250[a]	Sp670[a]	27266[a]	L4002[a]	48Na[a]	Mu50[b]	L4001[c]
tetracycline	3.13	50	100	100	> 100	50	50
vancomycin	0.4	0.4	3.13	0.8	0.8	3.1	> 100
olefinic dimers							
[a] **6-(LeuNMe)C_2-(LeuNMe)C_2**	< 0.03	< 0.03	0.125	0.25	0.25	1	2
[b] **6-(LeuNMe)C_2-(β-Ala)C_2**	< 0.03	0.125	0.25	0.25	1	4	8
[c] **6-(LeuNMe)C_3-(LeuNMe)C_3**	< 0.03	< 0.03	1	1	4	8	4
[d] **6-(β-Ala)C_4-(β-Ala)C_4**	1	0.5	4	2	2	4	8
[e] **6-(LeuNMe)C_4-(LeuNMe)C_4**	4	8	> 16	16	16	> 16	> 16
[f] **6-(β-Ala)C_2-(β-Ala)C_2**	0.25	0.25	1	0.25	2	4	> 16
[g] **6-(Asn)C_4-(Asn)C_4**	4	8	16	8	16	> 16	> 16
[h] **6-(H)C_2-(H)C_2**	2	4	16	16	> 16	> 16	> 16
[i] **6-(Asn)C_2-(Asn)C_2**	8	> 16	> 16	> 16	> 16	> 16	> 16
[j] **6-(H)C_4-(H)C_4**	8	4	16	8	16	> 16	> 16
disulfide dimers							
5-(LeuNMe)C_2-(LeuNMe)C_2	< 0.03	< 0.03	1	1	8	8	1
5-(LeuNMe)C_2-(LeuNMe)C_2	< 0.03	< 0.03	2	1	4	8	2
5-(LeuNMe)C_3-(LeuNMe)C_3	0.125	0.06	4	2	8	8	2

[a] Vancomycin-susceptible strains (Sa8250 and Sp670 are *Streptococcus pneumoniae* strains; 27266 and L4002 are *Enterococcus faecalis* strains; 48N is a multiresistant *Staphylococcus aureus* strain (MRSA)). [b] Vancomycin intermediate resistant strain (MU50 is a *Staphylococcus aureus* strain). [c] Vancomycin-resistant strain (L4001 is a *Enterococcus faecium* strain).

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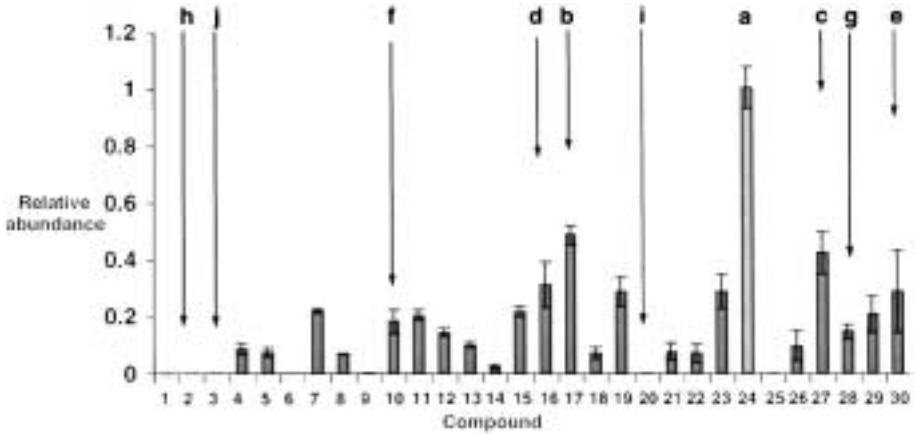

Figure 5. Target-accelerated combinatorial synthesis of a 36-member library of vancomycin dimers. The vertical bars represent the relative abundance of the vancomycin dimers relative to that of **6-(LeuNMe)C_2-(LeuNMe)C_2** (a) after the appropriate statistical adjustment. The error bars represent the range over three experiments. Compounds are labeled as follows: 1: **6-(H)C_2-(H)C_2**, 2: **6-(H)C_2-(H)C_4**, 3: **6-(H)C_4-(H)C_4**, 4: **6-(H)C_2-(*β*-Ala)C_2**, 5: **6-(*β*-Ala)C_2-(H)C_4**, 6: **6-(H)C_2-(Asn)C_2**, 7: **6-(H)C_2-(LeuNMe)C_2**, 8: **6-(H)C_4-(*β*-Ala)C_4**, 9: **6-(Asn)C_2-(H)C_4**, 10: **6-(*β*-Ala)C_2-(*β*-Ala)C_2**, 11: **6-(LeuNMe)C_2-(H)C_4**, 12: **6-(*β*-Ala)C_2-(*β*-Ala)C_4**, 13: **6-(Asn)C_4-(H)C_4**, 14: **6-(*β*-Ala)C_2-(Asn)C_2**, 15: **6-(LeuNMe)C_4-(H)C_4**, 16: **6-(*β*-Ala)C_4-(*β*-Ala)C_4**, 17: **6-(LeuNMe)C_2-(*β*-Ala)C_2**, 18: **6-(*β*-Ala)C_2-(Asn)C_4**, 19: **6-(*β*-Ala)C_2-(LeuNMe)C_4**, 20: **6-(Asn)C_2-(Asn)C_2**, 21: **6-(Asn)C_2-(*β*-Ala)C_4**, 22: **6-(LeuNMe)C_2-(Asn)C_2**, 23: **6-(*β*-Ala)C_4-(LeuNMe)C_4**, 24: **6-(LeuNMe)C_2-(LeuNMe)C_2**, 25: **6-(Asn)C_2-(Asn)C_4**, 26: **6-(Asn)C_2-(LeuNMe)C_4**, 27: **6-(LeuNMe)C_2-(LeuNMe)C_4**, 28: **6-(Asn)C_4-(Asn)C_4**, 29: **6-(Asn)C_4-(LeuNMe)C_4**, and 30: **6-(LeuNMe)C_4-(LeuNMe)C_4** (see Scheme 3 for structures).

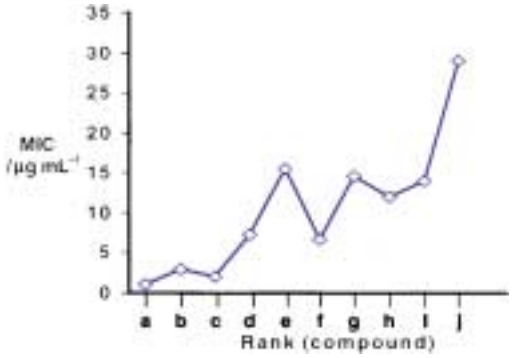

Figure 6. Correlation of the relative abundance of vancomycin dimers (a – j, Figure 5 and Table 1) with antibacterial activity (minimum inhibition concentration MIC, average of values against the nine vancomycin susceptible strains listed in Figure 3).

vancomycin-resistant bacteria (VRE or VISA). A strong correlation between rate enhancement and antibiotic activity has confirmed the usefulness of this strategy in predicting biological properties at a pre-screening stage. While the acute need for new antibiotics dictates further development of these compounds, the described combinatorial synthesis strategy may be applied to other biological targets.

Received: August 7, 2000 [Z15590]

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