Pergamon

Bioorganic & Medicinal Chemistry, Vol. 4, No. 1, pp. 43–48, 1996

0968-0896/96 $15.00 + 0.00

0968-0896(95)00161-1

Synthesis and In Vitro Antibacterial Activity of Spermidine-Based Mixed Catechol- and Hydroxamate-Containing Siderophore–Vancomycin Conjugates

Manuka Ghosh and Marvin J. Miller*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46556, U.S.A.

Abstract—The first antibiotic conjugates of vancomycin (**1**) and siderophore analogues containing spermidine-based catechol ligands (conjugate **11**) as well as mixed catechol and hydroxamate ligands (conjugate **13**) are described. The design of the conjugates was based on the earlier observation that conjugation of siderophore components to β-lactam antibiotics induced active iron transport-mediated drug delivery. The novel conjugates (**11** and **13**) were synthesized by selective acylation of the primary amino group of **1**. Preliminary biological studies indicated that siderophore modified vancomycins lost some activity (4- to 16-fold) against Gram-positive bacteria relative to vancomycin itself, and were generally similar to vancomycin in activity against Gram-negative bacteria under iron-sufficient conditions. However, under iron-depleted conditions which mimic human serum, conjugate **11** displayed enhanced antibacterial activity against an antibiotic hypersensitive strain of *Pseudomonas aeruginosa*.

Introduction

Vancomycin (**1**), an important member of the glycopeptide antibiotic family, has found wide clinical application over the last four decades, and currently is the only effective therapeutic agent for the treatment of infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) or other Gram-positive bacteria in patients allergic to β-lactam antibiotics.[1] Although most Gram-positive organisms are susceptible to vancomycin, Gram-negative organisms are resistant. The therapeutic efficacy of vancomycin has been attributed to its ability to inhibit cell wall biosynthesis through specific hydrogen bonding and electrostatic interactions between the *N*-acyl-D-Ala-D-Ala terminal sequence of the bacterial cell-wall peptide and the bicyclic heptapeptide core of vancomycin, a beautiful example of molecular recognition.[2] However, the emergence of vancomycin-resistant strains of enterococci, that are endemic in hospitals and are capable of sharing DNA information with staphylococci, has posed a grave concern to the health care system.[3]

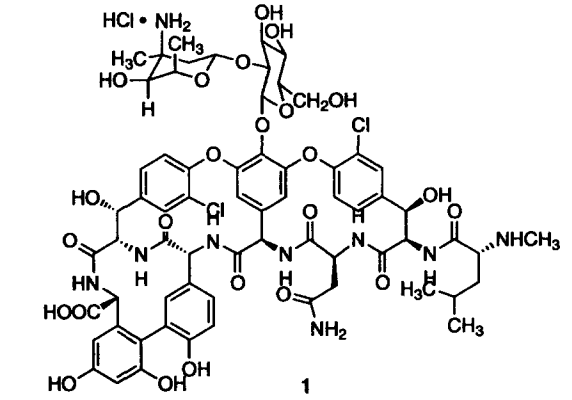
We have recently demonstrated[4] facilitated microbial assimilation of β-lactam antibiotics (e.g., Lorabid®) through conjugation with components of siderophores, natural iron chelators utilized by many microbes for sequestering and ingesting physiologically essential iron,[5] during development of processes for active transport of antibiotics into microbes. Conjugates containing catechol and hydroxamate components of siderophores were found to use different microbial receptors and transport systems, while mixed-ligand conjugates, such as **2**, were able to use multiple siderophore recognition processes to initiate active transport through the outer membrane of various microbes studied. These results prompted us to consider the synthesis of related conjugates of vancomycin with the anticipation that siderophore modification might extend activity of the antibiotic toward Gram-negative bacteria, while retaining potency against Gram-positive organisms. Herein, we report the synthesis and antibacterial activity of the first siderophore–vancomycin conjugates, obtained from selective acylation of the primary amino group of **1** with protected catechol (**3**) and mixed-ligand (**4**) siderophore components.

Results and Discussion

Point of attachment of vancomycin to protected siderophore components 3 and 4

Despite several unsuccessful attempts[6] towards the total synthesis of vancomycin (**1**), systematic synthetic modification is still the most productive approach to the development of an understanding of the molecular recognition phenomena associated with this and other members of this family. Vancomycin contains a central core heptapeptide, five aromatic amino acids and two aliphatic amino acids including *N*-methyl leucine as the N-terminal residue.[7] The phenolic hydroxyl group of one of the aromatic amino acids carries an amino sugar-containing disaccharide, an α-L-vancosaminyl-β-D-glucose. Several potential points of attachment exist within this functionally rich molecule. Although the sugar components of vancomycin recently have been shown to be important for promoting what may

be physiologically important dimerization,[1c] improved activity of some glycopeptide antibiotics containing long chain aliphatic acyl residues on the amino sugars have been observed.[8] The synthesis and antibacterial activity of *N*-acyl vancomycins have also been reported.[9] However, the *N*-methyl leucine unit has been shown to be very important for binding to the bacterial cell wall.[2] Thus, considering these precedents and the ease of synthetic manipulation with the carboxylate linker of the siderophore components (**3** and **4**), a selective acylation of the primary amino group of vancomycin was sought.



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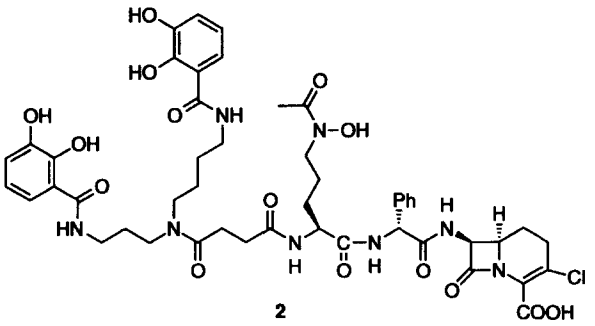

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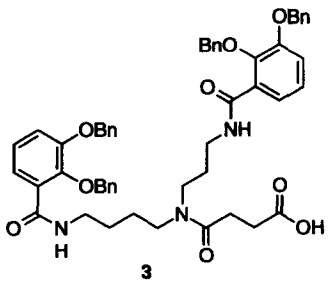

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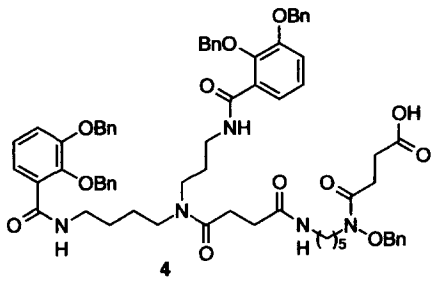
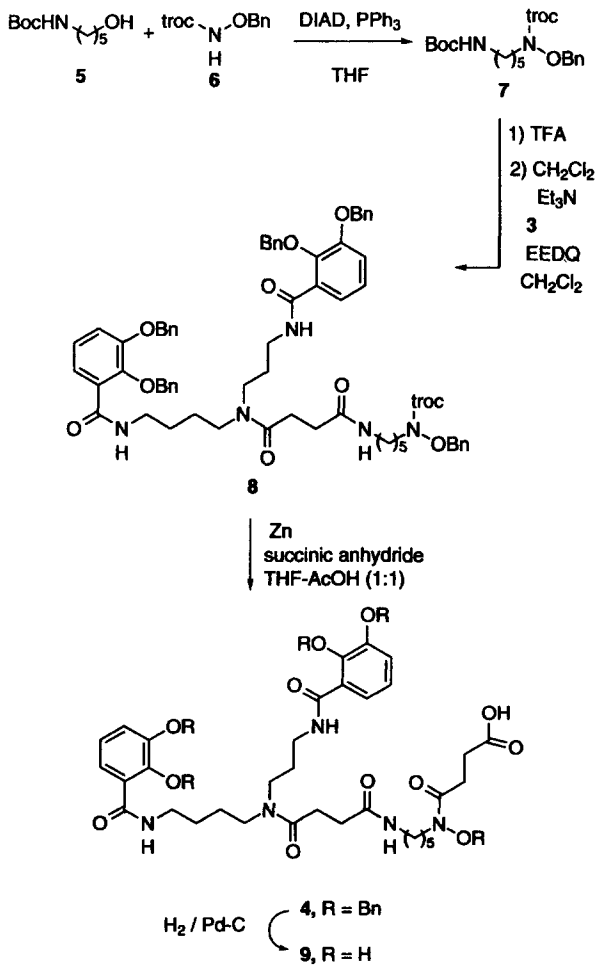


4

Syntheses of conjugates

Forms of the bis-catechol-containing spermidine derivative **3**, suitable for direct conjugation with vancomycin have been described earlier.[10] Syntheses of the partially protected (**4**) and deprotected (**9**) forms of the mixed-ligand iron chelator for conjugation to vancomycin are summarized in Scheme 1. The protected hydroxamate component **7** was prepared by coupling Boc-protected aminopentanol **5** with troc-*O*-benzylhydroxylamine **6** under Mitsunobu conditions.[11] Brief exposure of **7** to TFA at room temperature, followed by neutralization with Et_3N, provided the corresponding free amine, which was treated in situ with acid **3** and EEDQ to furnish coupled product **8** in 89% yield. Reductive removal of the Troc group and acylation of **8** were carried out simultaneously by using Zn and succinic anhydride in a mixed solvent system (THF:AcOH, 1:1) at room temperature for 10 h[12] to afford compound **4** in 92% yield. Hydrogenolytic removal of the benzyl protective groups of **4** over 10% Pd–C in 9:1 MeOH:H_2O provided the fully deprotected mixed siderophore analogue **9**, in 96% yield.

For the synthesis of conjugate **11**, a THF solution of the preformed *N*-hydroxysuccinimide active ester of



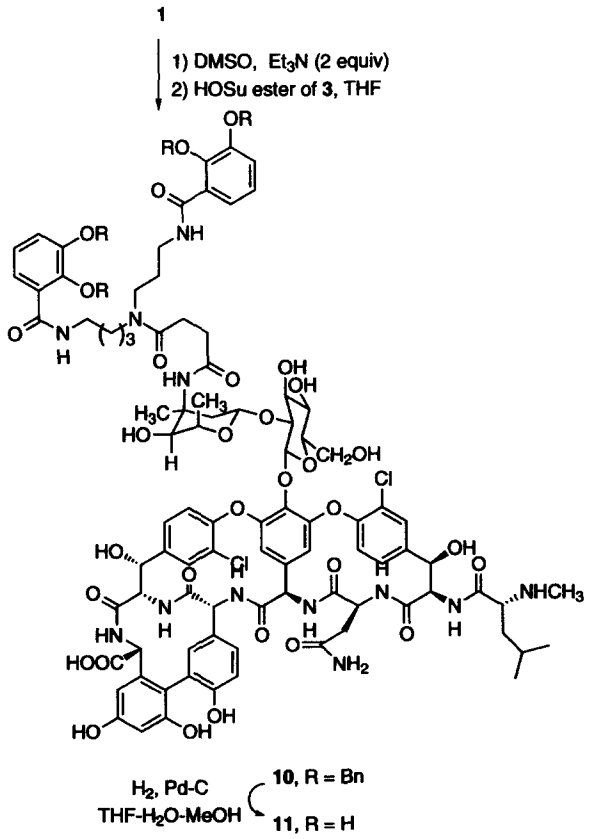
Scheme 1.

compound **3** was treated with vancomycin in DMSO (Scheme 2). After stirring overnight, the reaction mixture was lyophilized, and the residue was purified by extractive workup. The purity of compound **10** was verified by reverse-phase HPLC. There was no corresponding peak for unreacted vancomycin. The benzyl protective groups of compound **10** were removed by hydrogenolysis over 10% Pd–C to obtain fully deprotected conjugate **11** as a solid in 88% yield. The purity of conjugate **11** also was verified by reverse phase HPLC. The position of attachment of the siderophore component to vancomycin was determined by mass spectral analysis of **11** and comparison with related analyses of modified vancomycins in the literature.[8,13] Fast atom bombardment mass spectral (FABMS) analysis of the *N*-acyl vancomycin proved to be most useful for the structural assignment of the conjugated vancomycins. Thus, if derivatization occurred at the primary amine, two fragmentations at 1305 (desvancosamine vancomycin plus H) and at 1143 (aglucovancomycin plus H) would be apparent. On the other hand, if conjugation had taken place at the secondary amine, two peaks corresponding to 1305 plus siderophore and 1143 plus siderophore would be detected. FABMS of conjugate **11** showed only one characteristic fragment ion at 1305 with the expected peak at 1948 (MH^+), which clearly indicated that acylation had occurred at the primary amine, as desired.

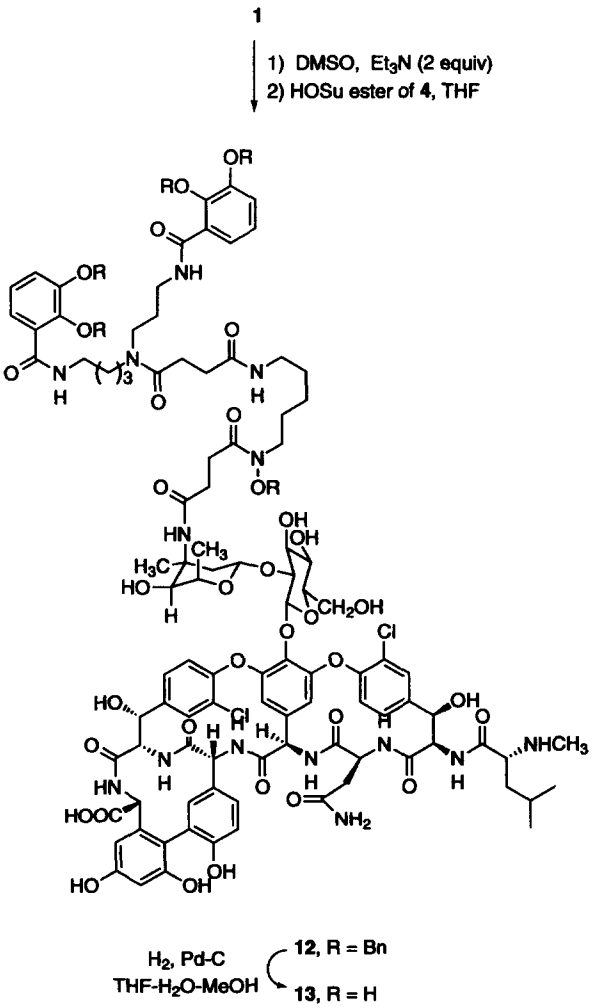
Following a similar reaction sequence (Scheme 3), compound **4** also was treated with vancomycin to obtain coupled product **12** in 60% yield as a solid. Purity and structural integrity of the compound was confirmed by HPLC, ^1H NMR, and FABMS, as before. Hydrogenolytic removal of the benzyl protective groups of **12** then provided desired conjugate **13** in 90% yield. Conjugate **13** showed two characteristic fragments corresponding to desvancosamine vancomycin plus H (1305) and aglucovancomycin plus H (1143), again confirming selective acylation of the primary amine of vancomycin.

Biological results

Conjugates **11** and **13** were screened for their antibacterial activity by using the broth-microdilution method with an inoculum of 10^5 bacteria per mL. Conjugates were tested in Mueller–Hinton broth, under iron-depleted as well as iron-sufficient conditions on a broad spectrum of Gram-negative and Gram-positive strains (Table 1). Representative Gram-negative strains included wild-type *Escherichia coli* (EC14), wild-type *Pseudomonas aeruginosa* (X620), and an antibiotic hypersensitive strain (X621) of *P. aeruginosa*. The Gram-positive strains studied included



Scheme 2.



Scheme 3.

Table 1. Comparison of representative MIC values of **11**, **13** and vancomycin in Mueller–Hinton broth under iron-sufficient and iron-depleted [MH(−Fe)] conditions

Isolate	**11**		**13**		Vancomycin	
	MH broth	MH (−Fe)	MH broth	MH (−Fe)	MH broth	MH (−Fe)
E coli X580	>128	128	32	128	32–64	32
E. coli EC14	>128	>128	>128	>128	>128	>128
P. aeruginosa X620	>128	>128	>128	>128	>128	>128
P. aeruginosa X621	>128	32	>128	>128	>128	>128
S. aureus X1.1	32	32	8	8	1–4	0.5–4
M. luteus	16	32	16	16	2–4	1–4

a penicillin-sensitive and a methicillin-resistant *Staphylococcus aureus*, and a *Micrococcus luteus*, a nonpathogenic test strain.

Biological studies indicated that siderophore modified vancomycins lost some activity (4- to 16-fold) against Gram-positive bacteria relative to vancomycin itself, and, similar to vancomycin, were generally inactive against Gram-negative bacteria under iron-sufficient conditions. In this respect, the siderophore conjugates appear to be similar to other acylated vancomycins.[8] However, under iron-depleted conditions which mimic human serum, and render microbes especially dependent on siderophores for sequestering iron,[14] conjugate **11** displayed enhanced (4- to 8-fold) antibacterial activity against an antibiotic, hypersensitive strain of *P. aeruginosa* compared to vancomycin itself. This interesting result suggests the potential for species selective drug development based on siderophore conjugation.

Experimental

General Methods

Solvents used were dried and purified by standard methods.[15] The term 'dried' refers to the drying of an organic layer over anhydrous magnesium or sodium sulfate. All reactions were performed under a nitrogen atmosphere. ^{1}H NMR spectra were recorded on a General Electric GN-300 (300 MHz), Varian VXR 500-S (500 MHz), or a Varian unity plus 600 (600 MHz) spectrometer in $CDCl_3$ or DMSO-d_6. Reverse phase HPLC employed Alltech C-18 columns (5 μ, 25 cm × 4.6 mm i.d.) integrated with an ISCO HPLC system consisting of pump (Model 2350), gradient programmer (Model 2360), and ISCO UV detector (254 nm, Model 1840). A flow rate of 1.4 mL/min was used with a gradient program which used two solvent solutions—A (H_2O containing 0.2% TFA) and B (CH_3CN containing 0.2% TFA). The gradient program was 0% B for 3 min from the start of the program, linear step 14% B for 10 min, linear step 50% B for 5 min, linear step 100% B for 5 min and linear step 100% A for 3 min (program 1). A second gradient program consisted of 14% B for 10 min from the start of the program, linear step 50% B for 10 min, linear step 100% A for 5 min, linear step 14% B for 4 min (program 2).

Protected bis catechol monohydroxamate 8. Compound **7**[16] (140 mg, 0.29 mmol) was dissolved in TFA (2 mL) and stirred for 5 min at room temperature. The TFA was removed by azeotropic evaporation with toluene. The resulting TFA salt was dissolved in anhydrous CH_2Cl_2 (2.0 mL), then compound **3** (254 mg, 0.29 mmol) and EEDQ (142 mg, 0.58 mmol) were added to the solution, followed by Et_3N (60 μL, 0.43 mmol). The reaction mixture was stirred overnight at room temperature under nitrogen. The solvent was evaporated, and the residue dissolved in EtOAc. The EtOAc solution was washed with 0.5 N HCl, H_2O, brine, dried, filtered and concentrated. Radial silica gel chromatography of the residue eluting with MeOH:$CHCl_3$ (1:9) afforded compound **8** (320 mg, 89%) as an oil: IR (neat) 1700–1735 (br), 1620–1660 (br), 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18–1.68 (m, 12H), 2.35–2.61 (m, 4H), 3.02–3.32 (m, 10H), 3.42–3.52 (m, 2H), 4.81 (s, 2H), 4.91 (d, J=1.8 Hz, 2H), 5.01–5.17 (m, 8H), 6.05–6.2 (m, 1H), 7.09–7.16 (m, 4H), 7.26–7.52 (m, 25H), 7.62–7.74 (m, 2H), 7.91–8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 172.14, 172.1, 171.52, 171.21, 165.12, 164.91, 164.84, 151.54, 151.48, 146.62, 146.48, 136.44, 136.29, 136.25, 136.20, 134.69, 129.27, 128.52, 128.47, 128.31, 128.05, 127.99, 127.41, 124.2, 123.07, 123.00, 122.85, 116.96, 116.81, 116.68, 116.54, 76.42, 76.32, 76.25, 76.16, 76.00, 74.9, 71.10, 49.34, 47.12, 45.33, 45.17, 43.09, 39.10, 39.01, 38.76, 36.86, 31.51, 28.96, 28.54, 27.42, 26.62, 26.51, 26.42, 25.86, 24.84, 23.71; Anal. calcd for $C_{68}H_{74}Cl_3N_5O_{11}$: C, 65.67; H, 6.45; N, 5.6. Found: C, 65.31; H, 6.54; N, 5.49.

Succinylated protected bis catechol monohydroxamate 4. To a solution of compound **8** (300 mg, 0.24 mmol) in THF:AcOH (1:1, 5 mL) was added succinic anhydride (240 mg, 2.41 mmol) and freshly activated zinc dust (157 mg, 2.41 mmol). The reaction mixture was vigorously stirred at room temperature for 10 h, filtered, and the solvent removed under reduced pressure. The residue was diluted with EtOAc, and the organic layer was washed with H_2O, brine, dried, filtered and concentrated. The crude compound was purified by silica gel chromatography eluting with $CHCl_3$:*i*-PrOH:AcOH (90:10:1) as the eluent to

afford compound **4** (260 mg, 92%) as a sticky oil: IR (neat) 1710–1740 (br), 1610–1670 (br), 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15–1.70 (m, 12H), 2.45–2.66 (m, 8H), 3.05–3.29 (m, 10H), 3.66–3.77 (m, 2H), 4.80 (d, $J=1.5$ Hz, 2H), 5.05–5.11 (m, 4H), 5.12–5.17 (m, 4H), 6.87 (t, $J=4.8$ Hz, 1H), 6.94 (t, $J=4.8$ Hz, 1H), 7.07–7.74 (m, 2H), 7.90–8.04 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 175.08, 175.06, 173.64, 172.54, 172.47, 172.39, 172.29, 165.32, 165.07, 165.99, 151.53, 151.48, 146.67, 146.60, 146.53, 136.35, 136.30, 136.23, 134.32, 129.08, 128.78, 128.59, 128.52, 128.03, 127.66, 127.47, 127.23, 124.28, 124.14, 123.01, 122.91, 122.81, 116.91, 116.77, 116.64, 77.20, 76.32, 76.27, 76.22, 76.14, 75.92, 71.05, 51.6, 47.51, 45.66, 45.47, 43.55, 39.24, 39.01, 38.86, 36.93, 31.54, 28.74, 28.39, 28.15, 27.97, 27.26, 26.55, 26.53, 26.46, 26.6, 25.88, 24.69, 23.34; FABMS calcd for $C_{69}H_{78}N_5O_{12}$ 1168.5 (MH^+), found 1168; anal. calcd for $C_{69}H_{77}N_5O_{12}$: C, 70.92; H, 6.65; N, 6.0. Found: C, 71.31; H,.41; N, 5.50.

Succinylated mixed ligand iron chelator 9. To a solution of compound **4** (120 mg, 0.102 mmol) in 90% MeOH (aqueous, 5 mL, spectra grade) was added 10% Pd–C (24 mg, 20% w/w). The resulting suspension was placed under a hydrogen atmosphere (balloon) for 6 h. TLC indicated that the reaction was complete. The reaction mixture was filtered through Celite and the volatiles were removed to afford compound **9** (70 mg, 96%) as a gummy liquid: $FeCl_3$ test positive (purple color); IR (neat) 3200–3400 (br), 1700–1720 (br), 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21–2.00 (m, 12H), 2.42–2.79 (m, 8H), 3.10 (t, $J=6.6$ Hz, 2H), 3.51–3.9 (m, 10H), 6.69 (t, $J=7.65$ Hz, 2H), 6.92 (d, $J=7.65$ Hz, 2H), 6.92 (d, $J=7.8$ Hz, 2H), 7.2 (d, $J=7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 177.19, 174.58, 174.32, 174.29, 173.67, 173.44, 171.52, 171.39, 171.34, 171.26, 150.53, 150.31, 150.19, 150.09, 147.13, 119.49, 118.55, 118.50, 118.37, 116.56, 116.41, 44.21, 43.37, 40.20, 39.93, 39.74, 37.87, 37.93, 31.84, 30.73, 30.17, 29.96, 29.75, 29.43, 29.20, 28.44, 28.27, 27.51, 27.14, 26.87, 25.89, 25.78, 24.70, 20.23; FABMS calcd for $C_{34}H_{48}N_5O_{12}$ 718.3 (MH^+), found 718.

Protected bis catechol conjugate 10. To a solution of vancomycin·HCl salt (**1**, 0.118 mg, 0.079 mmol) in dry DMSO (2 mL) was added Et_3N (22 μL, 0.159 mmol) to neutralize the salt. To the resulting solution of free amine was added a solution of the active ester of compound **3** [obtained after overnight stirring compound **3** (0.07 g, 0.079 mmol), DCC (0.018 g, 0.087 mmol) and NHS (0.01 g, 0.087 mmol) in dry THF (3 mL)] and stirred overnight at room temperature under nitrogen. After filtering to remove precipitated DCU, the reaction mixture was diluted with deionized, distilled water. The pH of the solution was adjusted to 3 with 1 N HCl, and the aqueous solution was lyophilized. The solid residue was resuspended in water, filtered, to remove unreacted vancomycin and residual DCU. The new solid residue was triturated with distilled EtOAc to remove any unreacted acid (**3**). The resulting solid was dissolved in H_2O:THF (1:1) and passed through a C_{18} maxi cleaner filtering bed, and the filtrate was lyophilized to afford **10** (100 mg, 65%): mp 155–160 °C (dec); retention time 8 min (program 1); ^1H NMR (DMSO-d_6, 500 MHz) δ showed characteristic resonances for vancomycin including a clear dd for the methyl protons of the isobutyl group of leucine at δ 0.88 ($J=23.0$, 6.5 Hz) as well as new singlets at δ 5.02 and 5.19 (benzylic CH_2) and multiplets at δ 7.00–8.30 (aromatic H, and NH). The enhanced multiplicity at δ 1.10–1.80 (CH_2) due to the presence of the siderophore component was also clearly visible; FABMS calcd for $C_{119}H_{129}N_{12}O_{32}Cl_2$ (MH^+) 2307.8, found 2308.

Bis catechol conjugate 11. To a suspension of **10** (0.03 g, 0.013 mmol) in THF:H_2O:MeOH, 1:2:2, was added 10% Pd–C (30 mg). This mixture was exposed to hydrogen at atmospheric pressure for 24 h. The catalyst was removed by filtration. The organic solvents from the filtrate were evaporated under reduced pressure and the residual aqueous solution was lyopholized to afford **11** (22 mg, 88%) as an off-white solid; mp 172–176 °C (dec); $FeCl_3$ positive (purple); retention time 12 min (program 6); ^1H NMR (DMSO-d_6, 500 MHz) showed a dd at δ 0.88 ($J=23.0$, 6.5 Hz) and clear disappearance of resonances at δ 5.02 and 5.19 (benzylic CH_2) as well as decreased multiplicity in the aromatic region (δ 7.00–8.30); FABMS calcd for $C_{91}H_{105}N_{12}O_{32}Cl_2$ (MH^+) 1947.6, found 1947.6. Conjugate **11** also gave a fragment ion at 1305.5, which corresponds to desvancosamine vancomycin plus H.

Protected mixed ligand conjugate 12. Protected conjugate **12** was obtained from **4** as a solid in 60% yield in the same manner as **10** was obtained from **3**; mp 165–176 °C (dec). As before, ^1H NMR (DMSO-d_6, 500 MHz) showed a dd at δ 0.88 ($J=23.5$, 6.45 Hz), additional singlets at δ 5.02 and 5.20 (benzylic CH_2) and multiplets at δ 7.00–8.30 (aromatic H); FABMS calcd for $C_{135}H_{151}N_{14}O_{35}Cl_2$ (MH^+) 2597.9, found 2598.

Mixed ligand conjugate 13. Hydrogenation of **12** was carried out using the same conditions as for the conversion of **10** to **11** to furnish **13** in 90% yield as a white solid; mp 185–191 °C (dec); $FeCl_3$ positive (purple); ^1H NMR (DMSO-d_6, 600 MHz) showed a dd at δ 0.88 ($J=25.8$, 6.6 Hz) and clear disappearance of resonances at δ 5.02 and 5.20 (benzylic CH_2) as well as decreased multiplicity in the aromatic region (δ 7.00–8.30); FABMS calcd for $C_{100}H_{120}N_{14}O_{35}Cl_2$ (MH^+) 2146.7, found 2147 as well as fragment ions at 1305.5 and 1143 corresponding to desvancosamine vancomycin plus H and aglucovancomycin plus H, respectively.

Acknowledgments

We gratefully acknowledge the National Institutes of Health for financial support of this work, and the Lizzadro Magnetic Resonance Research Center at Notre Dame for NMR facilities. A gift of vancomycin from Eli Lilly and Co., Indianapolis, IN, and biological

testing at Eli Lilly and Co. as well as helpful suggestions from Dr Thalia Nicas (Lilly) were sincerely appreciated.

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(*Received in U.S.A.* 14 *August* 1995; *accepted* 26 *September* 1995)