HHS Public Access

Author manuscript

*Chem Rev*. Author manuscript; available in PMC 2018 September 27.

Published in final edited form as:

*Chem Rev*. 2017 September 27; 117(18): 11952–11993. doi:10.1021/acs.chemrev.6b00820.

# Total Syntheses of Vancomycin Related Glycopeptide Antibiotics and Key Analogues

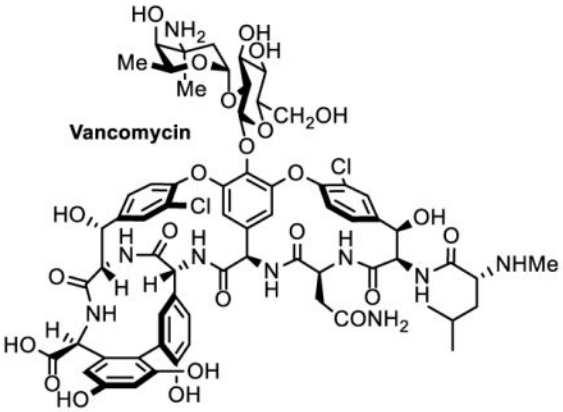
**Akinori Okano**, **Nicholas A. Isley**, and **Dale L. Boger***

Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

## Abstract

A review of efforts that have provided total syntheses of vancomycin and related glycopeptide antibiotics, their agylcons, and key analogues is provided. It is a tribute to developments in organic chemistry and the field of organic synthesis that not only can molecules of this complexity be prepared today by total synthesis, but that such efforts can be extended to the preparation of previously inaccessible key analogues that contain deep-seated structural changes. With the increasing prevalence of acquired bacterial resistance to existing classes of antibiotics and with the emergence of vancomycin resistant pathogens (VRSA and VRE), the studies pave the way for the examination of synthetic analogues rationally designed to not only overcome vancomycin resistance, but to provide the foundation for the development of even more powerful and durable antibiotics.

## Graphical abstract




### Keywords

Vancomycin; Orienticin C; Teicoplanin; and Ristocetin A; Enzymatic Glycosylation; Glycopeptide Antibiotics; Vancomycin Analogues; Complestatin; Chloropeptin

*Corresponding Author: boger@scripps.edu.

The authors declare no competing financial interest.

## 1. Introduction

An important development in the field of glycopeptide antibiotics occurred in the late 1990s when three groups independently achieved the total synthesis of vancomycin. Given the sheer structural complexity of the natural product, this series of synthetic accomplishments was remarkable and at the frontiers of the field of organic synthesis at that time. With reports of the rapid increase in resistant bacterial strains by health officials, this effort was driven not only by the challenge of developing an effective route to the complex natural product, but also to pave the way for biological interrogation of previously inaccessible synthetic analogues. Herein, we review only work completing total syntheses of members of the vancomycin related glycopeptide antibiotics, their aglycons, and synthetic analogues. Work on their semisynthetic modifications[1,2] and methodological studies are not reviewed as they have been covered elsewhere.

The glycopeptide antibiotics are currently among the leading members of the clinically important natural products discovered through the isolation of bacterial metabolites. They possess a broad spectrum of antibacterial activity against Gram-positive pathogens with manageable side-effects. Since their clinical introduction, the glycopeptide antibiotics vancomycin (**1**) and teicoplanin (**6**) have become the drugs of ‘last resort’ when resistant bacterial infections are encountered (Figure 1). With the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin (**1**) has been widely used in the clinic as the ‘go to’ treatment.[3,4] Originally restricted to hospitals, today more than 60% of both ICU (intensive care unit) and community acquired *S. aureus* infections are MRSA,[5,6] and are responsible for upwards of 12,000 deaths in the United States in 2011 alone.[7] Moreover, infectious diseases (e.g. influenza and pneumonia), complicated by additional bacterial infections often requiring treatment with vancomycin, are ranked among the leading causes of death in the U.S.. The glycopeptide antibiotics are also recommended for use with patients allergic to β-lactam antibiotics, undergoing cancer chemotherapy or ongoing dialysis therapy.[8] Consequently, the importance and clinical use of vancomycin continues to steadily increase since its introduction 60 years ago.[9] As vancomycin resistant bacteria have been observed in the clinic in both enterococci (VRE, 1987)[10] and *S. aureus* (VRSA, 2002)[11–17] and as the prevalence of antibiotic resistant pathogens has increased, discovery of the next generation durable antibiotics capable of addressing such bacterial infections has become an increasely urgent problem.[18]

Since the establishment of the structures of glycopeptide antibiotics, extensive synthetic efforts have been made through both semisynthetic and total synthesis means. These studies have laid the foundation for ongoing structure–function studies of the antibiotics, aiding in the definition of their mechanism(s) of action. They have also elucidated unanticipated new roles for added non-naturally occurring functionality that have led to the discovery of improved or rationally designed glycopeptide antibiotics.

This review summarizes the total synthesis of the vancomycin related glycopeptide antibiotics, along with occasional discussions of their use in key studies to define specific mechanisms of action responsible for their continued effective clinical use for decades. Lastly, a summary of recent total synthesis efforts aimed at the redesign of vancomycin

through rational structural modifications to address vancomycin resistant bacterial infections is provided.

## 2. Glycopeptide Antibiotic Background

### 2.1 Structure: Isolation and Characterization

Vancomycin was isolated in the early 1950s at Eli Lilly and disclosed in 1956, and other glycopeptide antibiotics within this family followed.[19] Even though vancomycin was approved for clinical use in 1958, its structure was established only 25 years later. Early chemical degradation studies,[20–22] followed by the subsequent seminal NMR studies of Williams,[23] and a pioneering X-ray crystal structure by Sheldrick of the degradation product CDP-1[24] provided an initial structure. This was followed by iterative corrections to the assigned structure that resulted from an unrecognized atropisomer isomerization[25] and an asparagine to isoaspartate rearrangement[26,27] under conditions of deglycosylation and provide a rich history to the full structural assignment of vancomycin by Harris that appeared in 1982.[26] This was followed by full structural assignments for ristocetin, teicoplanin and a series glycopeptide antibiotics. The comprehensive reviews of Perkins,[28] Williams,[29,30] Nicolaou,[31] Courvalin,[32,33] Walsh[34,35] and Kahne[36] and others[37–39] provide tabular accounts of the known glycopeptide antibiotics, a summary of the structure elucidation studies, and discussions of their biosynthesis, mechanism of action, and mechanisms of resistance.

The complex structures, the strained cyclic peptide subunits that contain biaryl and diaryl ether linkages interwoven into the intricate bi-, tri- and tetracyclic heptapeptide frameworks of their underlying rigid structures, the varied glycosylation patterns, and the unusual centers of axial or planar chirality (atropisomers) of the glycopeptide antibiotics present formidable synthetic challenges that were addressed in the efforts summarized herein.

### 2.2 Mechanism of Action

The seminal studies that defined the mechanism of action of the glycopeptide antibiotics include: (1) the initial Strominger demonstration that they inhibit bacterial cell wall biosynthesis,[40] (2) the insightful and comprehensive studies of Perkins that established antibiotic binding to the D-Ala-D-Ala terminus of precursor peptidoglycans,[28,41,42] (3) the pioneering NMR studies of Williams that defined the structures of antibiotic bound complexes with model D-Ala-D-Ala ligands,[43] (4) the later confirmation of the structures and their complexes by X-ray crystallographic studies conducted by Sheldrick[44] and (5) the beautiful studies of Walsh–Courvalin[45] that unraveled the molecular mechanism of vancomycin resistance. Each of these developments constitute rich chapters in our understanding of the glycopeptide antibiotics today.

The glycopeptides antibiotics are unusual in that they do not target a specific protein or nucleic acid within bacteria like most other antibiotic classes (e.g. β-lactams), but instead they bind the peptidoglycan precursors necessary for construction of the cell wall. The binding to D-Ala-D-Ala sequesters a substrate for the enzyme-catalyzed bacterial cell wall cross-linking reaction (transpeptidase) and impacts the transglycosylase catalyzed

incorporation of lipid intermediate II into the polysaccharide cell wall backbone (Figure 2). It is difficult for bacteria to make single genetic alterations that result in resistant conferring changes within these precursors, thus allowing the glycopeptide antibiotics to remain effective for nearly 60 years.[9]

In fact, the only clinically significant resistance to the glycopeptide antibiotics, which first emerged in enterococci in 1987 (VanA and VanB VRE),[10] was not independently evolved by pathogenic bacteria. Rather, it was co-opted from nonpathogenic vancomycin producing organisms that use this intricate mechanism of resistance to protect themselves while producing the glycopeptide antibiotic.[46] In short, it entails detection of a glycopeptide challenge and an orchestrated response that results in late stage remodeling of the peptidoglycan precursor N-terminus from D-Ala-D-Ala to D-Ala-D-Lac.[45,47] This change, which represents a single atom exchange in the precursors, reduces glycopeptide antibiotic binding 1000-fold, rendering them ineffective.[48]

Thus, extension of the efforts on the total synthesis of the glycopeptide antibiotics to the preparation of analogues that contain compensatory single atom exchanges have been disclosed, which now exhibit dual D-Ala-D-Ala/D-Ala-D-Lac binding and activity against both vancomycin sensitive and resistant organisms. These efforts, along with peripheral modifications to the glycopeptide antibiotics that introduce additional mechanisms of action, are summarized in Section 7. These studies have provided extraordinarily potent analogues that display especially durable antimicrobial activity.

## 3. Total Synthesis of Orienticin C Aglycon

### 3.1 Evans Synthesis

In route to the development of a total synthesis of vancomycin itself, Evans reported the total synthesis of the orienticin C aglycon.[49,50] This natural product aglycon is nearly identical to that found in vancomycin, lacking only the C and E ring aryl chlorides on the aglycon.[51] This difference removes the challenge of controlling two of the three centers of axial or planar (atropisomer) chirality found in vancomycin, but addresses the key bonds formed in assembling the core structure. Moreover, the late stage intermediates prepared in these efforts conceivably could be used to also prepare the vancomycin aglycon.

Key highlights of the route include two biomimetic oxidative cyclization reactions of an acyclic tetrapeptide containing the ABCD rings,[52–58] a late stage thermal equilibration about the AB biaryl center of axial chirality to access the natural atropisomer, along with a final stage $S_NAr$ diaryl ether macrocyclization reaction for DE ring closure (Figure 3).[59,60] They additionally utilized the powerful Evans chiral oxazolidone-based imide enolate functionalization reactions and aldol methodology to obtain the unnatural amino acid subunits with high enantio- and diastereoselectivity.[61–64] For details on the preparation of the individual unnatural amino acid subunits (e.g. Rings A–E, **7**–**12**), the reader is referred to their original reports.[49,50]

Beginning with the acyclic tetrapeptide **13**, thallium(III) nitrate-promoted formation of the CD macrocycle with formation of the diaryl ether was accomplished through a modified

Yamamura oxidative cyclization[55–58] of the CD ring system with subsequent in situ reduction of an intermediate *p*-quinol (Scheme 1). The free phenol of the E ring was protected as an acid-stable mesylate, which increased the oxidation potential of ring D rendering it unreactive toward the conditions of a subsequent $VOF_3$-mediated oxidative biaryl coupling.[53,54] Protecting group exchange at the N-terminus, from *N*-Boc to trifluoroacetamide, afforded **14** in 46% overall yield from **13**. A second key macrocyclization with formation of the AB ring system was accomplished by oxidative biaryl coupling of **14** mediated by $VOF_3$ to yield the unnatural atropisomer[53,54] **15** of the bicyclic tetrapeptide that by design also cleaved the B ring benzyl ether. Notably, the unnatural AB atropisomer in **15**, as well as in the isolated AB ring system, adopts a conformation that bears a central *trans* amide. Conversion of this released phenol to a triflate and its reductive cleavage[65] was conducted to remove the extraneous B ring phenol originally needed for biaryl coupling and that served to control the cyclization atropodiastereoselectivity. This latter reaction also unexpectedly debrominated the D ring, necessitating re-halogenation in a subsequent step. Next, global demethylation enlisting $AlBr_3$–NaI (vs $AlCl_3$, $ClCH_2CH_2Cl$) yielded **16** in 88% yield. The natural atropisomer **17** was obtained by thermal atropisomerization of **16** in MeOH (55 °C) over two days, at which time no starting unnatural atropisomer **16** was observed by $^1H$ NMR analysis. The stability of the precursor methyl ether towards atropisomerization as well as the thermodynamic preference for the (*P*)-atropisomer of the AB ring system and its preferential adoption of the central *cis* amide were defined both with **16**/**17** as well as with the isolated AB ring system.[49,50,53,54] Exhaustive benzylation of the three phenols, reductive removal of the trifluoroacetamide with $NaBH_4$, mesylate cleavage with methyl magnesium chloride, and Boc protection of the N-terminus amine, followed by regioselective iodination of the D ring with NIS afforded **18** in 57% overall yield from **17**. Lastly, the ring D free phenol was protected as its allyl ether (85%), and the missing D ring phenol required for down-stream macrocyclization was installed via lithium–halogen exchange, trapping the resulting anion with triethyl borate followed by oxidation (**19**, 53%).

After Boc deprotection, EDCI-promoted peptide coupling of **21** with the tripeptide **22**[52] assembled the heptapeptide framework that contains the E ring in a reaction where competitive epimerization has consistently challenged most other efforts (Scheme 2). The final DE macrocycle was closed in a $S_NAr$ reaction upon treatment with CsF in DMSO at room temperature, which provided the product both in high yield (90%) and with a kinetic diastereoselection of 7:1 in favor of the natural atropisomer **23**. Although this planar chirality was removed in subsequent steps for orienticin C, this result demonstrated that, unlike the isolated ring system,[60] the DE ring system could be closed atropodiastereoselectively when attached to the intact ABCD ring system. This had important implications for subsequent work on the total synthesis of vancomycin. Reduction of the nitro group with Zn and acetic acid followed by formation and in situ reductive removal of the diazonium salt yielded **24**.[66] Notably, initial extensive efforts to implement a third biomimetic inspired oxidative cyclization reaction for closure of the DE ring system with formation of the diaryl ether, enlisting modifications of the Yamamura protocols, provided more modest results (ca. 20% yield). This led Evans to adopt the $S_NAr$ macrocyclization reaction introduced and developed by Boger[60] and Beugelmans.[67]

Next, the *N*-methylamide, which served admirably to prevent C-terminus epimerization throughout the total synthesis, was selectively nitrosated with dinitrogen tetraoxide ($N_2O_4$).[68,69] This nitrosated amide could be cleaved under mild conditions with LiOOH, unmasking the C-terminus carboxylic acid. The final three steps entailed palladium-catalyzed deallylation, hydrogenolysis removal of the aryl chlorides as well as the benzyl and Ddm groups, and Boc deprotection of the N-terminus amine to afford the orienticin C aglycon (**27**).

## 4. Total Synthesis of Vancomycin

### 4.1 Total Synthesis of Vancomycin Aglycon

Vancomycin is a rigid tricyclic heptapeptide with three macrocyclic ring systems embedded in the framework, one possessing axial chirality and two containing elements of planar chirality. The central phenol of the aglycon is attached to a disaccharide, consisting of glucose and vancosamine. Given the complexity of vancomycin, the development of synthetic strategies to construct its skeleton attracted many groups, three of which reported total syntheses in 1998–1999: David A. Evans, K. C. Nicolaou, and Dale L. Boger. This transpired roughly 45 years after its isolation, 40 years after its introduction into the clinic, and nearly 25 years after its structure determination. Within this section, the three separate reports are discussed and key differences in their strategies are outlined.

**4.1.1 Evans Synthesis—**The Evans total synthesis of the vancomycin aglycon[70,71] was based largely on their previous work with orienticin C. The same key disconnections were envisioned apart from the disconnection of the CD ring system (Figure 4). Here, the C–O bond of the C ring was broken rather than to the D ring C–O bond and its synthetic formation now relied on a $S_NAr$ diaryl ether bond formation[60] rather than a biomimetic inspired oxidative cyclization. Major differences are also found within the synthesis of the ABCD system where the AB macrocycle was formed first at the tripeptide stage, followed by the coupling addition of the D ring and construction of the CD macrocycle. This contrasts the efforts on orienticin C,[49,50] where the ABCD acyclic tetrapeptide was prepared before sequentially closing the macrocycles in the reverse order, forming the CD ring macrocycle prior to formation of the AB ring system. Thus, the overarching strategy adopted for the total synthesis of the vancomycin aglycon entailed a macrocyclization order in which the AB, CD and DE ring systems were sequentially introduced and relied on empirically defined substrate control of the kinetic atropodiastereoselectivity of the three key macrocyclization reactions. As with orienticin C, the C-terminus carboxylic acid was masked as a *N*-methylamide to prevent epimerization at this base-sensitive center.

After Boc deprotection of the ring A precursor **29**, attachment of the C ring was achieved by EDCI-promoted amide coupling and afforded **31** in 72% yield (Scheme 3). The B ring (**30**) was attached to the AC fragment with EDCI, after a base-mediated ring opening of the oxazolidinone and Boc deprotection of the N-terminus amine of **31**. After a protecting group exchange at the N-terminus amine (trifluoroacetamide for *N*-Boc), the 12-membered AB macrocycle **34** was formed, using $VOF_3$ to mediate an oxidative biaryl coupling of **33** that selectively formed the unnatural atropisomer (>95:5). The N-terminus amine of **34** was

deprotected with $NaHCO_3$, and the D ring **35** was subsequently attached with HATU–HOAt in 65% yield. Silyl ether cleavage of the TBS protected D ring phenol was achieved with HF–pyridine to provide **36** in 85% yield. It is noteworthy that the triphenolic D ring was orthogonally protected as the *O*-allyl, *O*-TBS, and *O*-Ms derivatives avoiding problematic debromination experienced in the total synthesis of orienticin C. The CD ring system and its 16-membered diaryl ether **37** were formed in a base promoted, room temperature $S_NAr$ reaction[60] between the D ring phenol with the C ring *o*-nitrofluoroarene in which the atropodiastereoselectivity favored the natural atropisomer disposition of the chloro substituent in a 5:1 ratio. Remarkably, the cyclization could be achieved even without added base at a reasonable rate simply upon dissolution in polar, aprotic solvents (e.g. NMP). Both this more reactive chloro substituted C ring precursor **28** as well as the corresponding dechloro substrate were examined. The ring closure of the initially examined unsubstituted (dechloro) precursor provided a 10:1 atropodiastereoselectivity favoring the unnatural disposition of the nitro substituent. That led to the examination of the chloro substituted substrate **36** where the nitro group stereochemical disposition still dominated and the adoption of a strategy in which the activating nitro group was reductively removed rather than additionally serving as a precursor for the chloro substituent. Conversion of the B ring phenol to a triflate **37**, nitro group reduction, and aniline diazotization/reduction[66] followed by a Pd-catalyzed hydrogenolysis of the aryl triflate[65] and allyl ether cleavage yielded **38** in 77% over three steps.

Before equilibrating the AB ring system to the natural atropisomer, the D ring phenol was converted to a pivalate ester and the N-terminus amine was deprotected and converted to the trifluoroacetamide. Lastly, global demethylation of the A and B ring methyl ethers with $AlBr_3$–EtSH yielded **41**. Upon warming the bicyclic tetrapeptide **41** in MeOH (55 °C), clean atropisomerization to the natural *P*-configuration was achieved, providing **42** in 54% yield (in 96 h) from **40**.[53,54]

In preparation for the final peptide coupling, the three phenols were converted to their benzyl ethers, the pivalate group was removed and the resulting phenol re-protected as an allyl ether, and both the mesylate and trifluoroacetamide protecting groups were removed, yielding **43** in 65% over 5 steps.

The final peptide coupling brought together the ABCD tetrapeptide **43** and the acyclic tripeptide **44** and was conducted with EDCI, remarkably without detectable epimerization (Scheme 4). The final macrocyclization of the 16-membered DE ring system was accomplished with a second room temperature $S_NAr$ reaction for diaryl ether formation, using CsF (DMSO) and providing selective formation of the natural *P* atropisomer **45** (5:1 ratio) in high yield (95%).[59,60,67] After subsequent reduction of the nitro group to the aniline, the diastereomers could be separated by column chromatography. The appropriately functionalized E ring **46** was formed through a Sandmeyer substitution reaction upon CuCl and $CuCl_2$ treatment of the aniline-derived diazonium tetrafluoroborate salt.[72–74] Next, the masked C-terminus *N*-methylamide was nitrosated with dinitrogen tetraoxide ($N_2O_4$) and subsequently hydrolyzed with LiOOH in 68% yield.[68] Despite the potential nitrosation at other amide sites, the documented steric effects of such a competitive reaction with amides were defined,[68,69] aiding in the designed and implemented selectivity first explored in the

total synthesis of the orienticin aglycon.[49,50] Allyl ether cleavage followed by hydrogenolysis cleavage of the benzyl ethers, using transfer hydrogenation conditions (Pd/C and 1,4-cyclohexadiene) to avoid dechlorination, afforded **49**.[75] The final step in the conversion to vancomycin aglycon (**50**) was achieved by acid-catalyzed N-terminus Boc and asparagine residue Ddm removal (83%).

The total synthesis of eremomycin aglycon was also disclosed in these efforts although no details were reported.[70,71] In these efforts, the nitro group of the predominant unnatural atropisomer derived from cyclization of the unsubstituted (dechloro) substrate related to **36** was removed and carried through an analogous synthesis to provide the eremomycin aglycon.

**4.1.2 Nicolaou Synthesis—**Concurrent with the Evans report, Nicolaou published three back-to-back papers[76–78] describing work culminating in a total synthesis of vancomycin aglycon (Figure 5 for retrosynthetic analysis). All three total syntheses are based on formation of the linking diaryl ethers in the key CD and DE ring system macrocyclization reactions, and Nicolaou developed a new reaction for this bond construction. Through a triazene appended to the D ring with *o,o*'-dibromo substitution, copper bromide successfully promoted a metal-activated $S_NAr$ reaction for both CD and DE diaryl ether formation.[79] An additional difference from the Evans approach was the use of the Sharpless asymmetric dihydroxylation[80] reaction to access the individual subunits with the required absolute stereochemistry in the A, D and E rings, along with use of a Sharpless asymmetric aminohydroxylation[81] reaction for asymmetric synthesis of the the C ring subunit. Details on the design and development of the methodology involved in the approach can be found in a full account of this work.[82–84]

The chiral benzooxaborolol **54** was coupled with the B ring aryl iodide **55** under Suzuki cross-coupling reaction conditions to obtain **58** with modest atropodiastereoselectivity (2:1), favoring the desired atropisomer (Scheme 5). A Mitsunobu reaction was used for the introduction of an azido group with stereochemical inversion to provide (*S*)-**59** in high yield. Attachment of the C ring **51** mediated by EDCI was achieved in 85% yield after hydrolysis of the precursor methyl ester. After *N*-Boc deprotection to afford **61** in 90% yield, the central amino acid **52** was coupled to the tripeptide **61** with EDCI to obtain the tetrapeptide **62** in good yield. Copper bromide activated formation of the 16-membered diaryl ether through triazene chelation and promoted the $S_NAr$ reaction (MeCN, reflux, 20 min) to provide **63** as a separable 1:1 mixture of atropisomers in a combined yield of 60%.[79] With the monocyclic tetrapeptide in hand, the TBS ether was cleaved with $Bu_4NF$ (80%), the azido group was reduced with triethylphosphine (71%), and the ethyl ester was hydrolyzed with LiOH (68%). The resulting free amine and carboxylic acid were coupled in a macrolactamization reaction mediated by FDPP (71%), affording the bicyclic ABCD ring system.[85,86] Lastly, the ABCD vancomycin ring system **64** was prepared for subsequent peptide attachment by TBS protection of the β-hydroxy group and Boc deprotection of the N-terminus amine, providing the bicyclic tetrapeptide **66**.

After obtaining **53** in high enantio- and diastereopurity in a 4-step synthetic sequence, **53** was coupled with *N*-Boc-*N*-methylleucine (**57**, EDCI–HOBt) and was followed by ethyl

ester hydrolysis with lithium hydroxide to afford **67** (Scheme 6). Next, attachment of the Ddm-protected asparagine methyl ester (EDCI–HOAt) gave the tripeptide in 82% yield. Subsequent TBS protection of the free alcohol and cleavage of the benzyl ether yielded **68** in 80% (2 steps). The desired E ring tripeptide was obtained after phenol *o*-chlorination with sulfuryl chloride and hydrolysis of the methyl ester, affording **69** for peptide coupling with the ABCD ring system.

The heptapeptide backbone was assembled by coupling **66** and **69** (EDCI–HOAt). Final ring closure mediated by copper bromide provided the 16-membered DE ring system **70** in 74% (MeCN, reflux, 2 h) as a 1:3 mixture of atropisomers, providing predominantly the undesired isomer (Scheme 7). Following protocols disclosed in and central to the efforts of Boger,[72–74,87] the major undesired isomer was re-equilibrated to a 1:1 mixture of DE ring system atropisomers in 1,2-dichlorobenzene under thermal conditions that do not impact the AB or CD atropisomer stereochemistry. Repeating this re-equilibration of the unnatural atropisomer led to a >90% recycled and recovered yield. The next challenge was the conversion of the triazene group to the corresponding phenol. Although the initial report by Nicolaou successfully achieved this transformation,[78] the conditions presented in Scheme 7 represent an improved route disclosed shortly thereafter.[84] Conversion of the triazene to the aryl iodide (NaI, $I_2$, and TMSCl) was followed by formation of the corresponding aryl Grignard reagent, its trap with $B(OMe)_3$ and subsequent oxidation to provide **72** in 32% yield from **71**.

The final stages of the total synthesis involved reductive cleavage of the C-terminus benzyl ether (94%), methylation of the D ring free phenol (94%), and stepwise oxidation of the primary alcohol to the corresponding carboxylic acid.[88,89] Carboxylic acid esterification with diazomethane (84%), and TBS ether deprotection followed by global deprotection (62%) with $AlBr_3$–EtSH provided vancomycin aglycon (**50**).

**4.1.3 Boger Synthesis—**Shortly after the first two reports of the total synthesis of the vancomycin aglycon, Boger disclosed a complementary convergent strategy.[87,90] In efforts leading up to the total synthesis, Boger established that the CD and DE ring systems were most effectively closed through formation of the diaryl ether linkage,[91] and explored,[92–94] implemented,[60,72–74] and improved[95] methodology to be used for ring closure of the CD and DE ring systems. An effective macrolactamization for closure of the 12-membered biaryl AB ring system was also disclosed by Boger, defining subtle features key to its unusual success, and an indirect strategy for controlling the three stereochemical elements of atropisomerism.[72–74,95–98] Thus, two $S_NAr$ macrocyclizations of the 16-membered diaryl ethers, enlisting phenol nucleophilic substitution reactions of an *o*-nitrofluoroaromatic, were used for sequential CD and DE ring formations.[60,72–74] A key macrolactamization reaction was employed for cyclization of the AB ring system, and the defined order of CD, AB and DE ring closures permitted selective thermal atropisomerism of the newly formed ring systems or their intermediate precursors (Figure 6). In addition to any diastereoselection that was achieved in the ring closures, this order permitted the recycling of any undesired atropisomer for each ring system and provided predictable control of the stereochemistry, dependably funneling all synthetic material into the one of eight atropodiastereomers found in the natural product. Key to recognition of this order was the establishment of the disparate

thermodynamic parameters of atropisomerism: DE ring system $E_a$ = 18.7 kcal/mol, 1:1 natural-*P:M* < AB biaryl precursor[90] $E_a$ = 25.1 kcal/mol, 3:1 natural-*P:M* < CD ring system $E_a$ = 30.4 kcal/mol, 1:1.1 natural-*P:M* (Figure 6).[72,95–97] Prior to these studies, the assumption was that the barrier to isomerization of either the CD or DE ring system atropisomers was too large to permit their observation.[25]

Similarly, the preference for a *cis* amide bond in the natural atropisomer of the isolated 12-membered AB ring system was defined. Prior to this work, the assumption was that the surrounding CD ring system in vancomycin induced adoption of this *cis* amide. Given this redefined intrinsic preference, it is now thought that it is the rigid AB ring system that dominates the conformational properties of the surrounding CD ring system. In contrast, the isolated or imbedded unnatural AB atropisomer adopts a conformation that bears a central *trans* amide.

Unlike the Evans synthesis in which the AB, CD, and DE ring systems were sequentially assembled, but like that of Nicolaou, the order of ring closures entailed CD, AB, and DE macrocyclizations. Two aromatic nucleophilic substitution reactions were used for formation of the CD and DE ring system diaryl ethers,[60,72–74] and a distinguishing macrolactamization reaction was used to close the AB ring system. Unlike the Nicolaou approach, the stage at which the axial chirality of AB ring system was introduced permitted adjustment of atropisomer stereochemistry within both the CD and AB ring systems.

The absolute stereochemistry within each unnatural amino acid subunit was installed with use of the Sharpless asymmetric aminohydroxylation reaction (phenylglycine rings A, B and D[99]), or a diastereoselective Schöllkopf aldol-like addition reaction (β-hydroxylphenylalanine rings C and E) (Figure 7). Improvements in the synthesis of the E ring β-hydroxylphenylalanine, enlisting an asymmetric aldol reaction of a glycine imine bearing an α-hydroxypinanone chiral auxiliary, was also later disclosed.[100] For details on the synthesis of each subunit, the reader is directed to the original reports.[90]

Peptide coupling of **76** with **80** (EDCI–HOBt) afforded the dipeptide **83** in 81% yield (Scheme 8). Boc deprotection of **83** with TBSOTf proceeded in 99% yield and coupling with **77** afforded **85**. Using improved reaction conditions discussed in Section 7.1, treatment of **85** with $K_2CO_3$–$CaCO_3$ closed the 16-membered macrocycle (85%) in a key $S_NAr$ reaction that proceed with little atropodiastereoselectivity (1:1.1, natural-*P:M*). In this reaction, the added $CaCO_3$ served to scavenge the liberated fluoride as insoluble $CaF_2$, preventing inadvertent silyl ether deprotection and competitive retro aldol cleavage of intact CD ring system. The isolated unnatural *M* atropisomer was converted to the natural *P* atropisomer upon heating at 140 °C in a solution of *o*-dichlorobenzene.[95] Although this equilibration provides in a 1:1 mixture of *M* and *P* atropisomers, each atropisomer can be isolated and (*M*)-**86** recycled through this procedure, funneling all material into the total synthesis. Conversion of the aryl nitro group to the corresponding chloride, achieved by nitro group reduction, aniline diazotization, and Sandmeyer substitution, afforded **88** in 89% yield.[95] The barrier for atropisomer interconversion of the newly installed chloride is higher than that of the aryl nitro intermediate **87**, further enhancing its stability toward a later atropisomer equilibration. A Suzuki reaction introduced the A ring (88%) and enlisted a

powerful ligand-catalyst combination ($Pd_2(dba)_3$ and ($o$-tolyl)$_3$P) to promote an otherwise challenging coupling of a hindered, electron-rich aryl bromide with an especially hindered aryl boronic acid.[101] The kinetic atropodiastereoselectivity was modest (1:1.3 *P:M*), but thermal equilibration converted the material to a mixture preferentially favoring natural (*P*)-**89** (3:1, *P:M*). Separation of the biaryl atropisomers and thermal re-equilibration and recycling of unnatural (*M*)-**90** ($E_a$ = 25.1 kcal/mol) under conditions that do not impact the preinstalled CD ring system atropisomers ($E_a$ = 30.4 kcal/mol) funneled all material into the synthesis of **50**. Removal of the TBS group (87%) facilitated subsequent hydrolysis of the methyl ester to the carboxylic acid (99%), and Cbz cleavage (99%) afforded **93**. Lastly, to complete the ABCD ring system, a key macrolactamization was used to form the second macrocycle **94** (EDCI) in 62% yield. The C-terminus carboxylic acid was carried through this sequence as a MEM-protected hydroxymethyl group. This not only avoided inadvertent epimerization throughout the synthesis, but it also improved the macrolactamization reaction, which proceeded at both a faster rate and in higher yields than the corresponding methyl ester.

After Boc deprotection of the N-terminus amine, tripeptide **96** was coupled to residue 4 with EDCI–HOAt in 61% from **94** (Scheme 9). The final 16-membered macrocycle was formed in a room temperature nucleophilic aromatic substitution reaction promoted by CsF (DMSO), closing the ring with a kinetic atropodiastereoselectivity (8:1) favoring the natural *P*-isomer **97**. Conversion of the nitro group to the corresponding aryl chloride afforded **98** in 60% yield from **97**. Bis-TBS protection of the secondary alcohols under neutral conditions was conducted with use of *N*-TBS-*N*-methyl-trifluoroacetamide to avoid retro-aldol cleavage of the CD and DE ring systems. Cleavage of the MEM ether with *B*-bromocatecholborane (BCB), followed by stepwise Dess–Martin and Pinnick oxidation of the released primary alcohol and esterification of the carboxylic acid provided the methyl ester **101.** Finally, stepwise nitrile hydration ($H_2O_2$, $K_2CO_3$, 85%), TBS ether cleavage under conditions that avoid competitive retro-aldol reaction of the released secondary alcohols ($Bu_4NF$–HOAt, 81%), and global deprotection of the remaining four methyl ethers, the methyl ester, and N-terminus Boc group with $AlBr_3$–EtSH (50%) in a single step afforded the vancomycin aglycon (**50**).

### 4.2 Carbohydrate Introduction

Carbohydrate introduction on the vancomycin aglycon has been accomplished by two complementary approaches: (1) chemical glycosylation[102–107]; and (2) *in vitro* enzymatic glycosylation.[108–115] An advantage of the chemical strategy is the broad substrate scope that allows use of a variety of modified carbohydrate coupling partners compared to the enzymatic glycosylation. The enzymatic reaction has the advantage that it is not necessary to protect nucleophilic functionalities in either the aglycon or the sugar, directly provides vancomycin in two steps from the fully deprotected aglycon, and avoids the chemoselectivity issues of the non-enzymatic means. The stable expression of the recombinate enzymes and the commericial or synthetic availability of the UDP-based cosubstrates today make the enzymatic glycosylation as scalable as the chemical glycosylation. Over the past few decades, base and acid promoted chemical glycosylation methods for selective glycosyl bond formation have been developed. However, base-

mediated $S_N2$ substitution of an anomeric halide is not suitable for use with vancomycin and related derivative due to competitive aglycon epimerization. The use of an acid-promoted glycosylation eliminates such issues.

### 4.2.1 Chemical Glycosylation

**4.2.1.1 Kahne Synthesis:** Kahne developed an approach in which activated glycosyl donors are sequentially coupled with the protected aglycon **104** via the acid promoted glycosylation strategy.[102–104] A C2 ester functional group was used to assist in the selective formation of β-glycosyl bond with neighboring group stabilization of the oxonium ion intermediate **105** and for stereochemical control of the anomeric nucleophilic substitution with an oxygen nucleophile (Figure 8).[116]

Initial model studies with substrates bearing conventional leaving groups such as acetate did not provide promising results. To overcome this issue, Kahne pursued the use of sulfoxide derivative **108** which could be activated under milder reaction conditions (Scheme 10).[117–119] The sterically hindered base 2,3-di-*tert*-butyl-4-methylpyridine (DTBMP) was used to suppress formation of undesired orthoester by enhancing the nucleophilicity of the phenol.[120] Addition of $BF_3{\cdot}OEt_2$ minimized formation of the orthoester by promoting its rearrangement to the glycoside **110**,[121] and it also helped suppress $Tf_2O$-mediated dehydration of the vancomycin-derived residue 3 carboxamide. Further improvement was made by use of a C2 azidobutyrate introduced by Kusumoto[122] in place of a conventional acyl protecting group such as acetyl (56%) and pivaloyl (50%). Notably, the 4-azidobutyryl group can be selectively removed under neutral reaction conditions by treatment with $PPh_3$ (64%), unlike acyl group removal.

With protocols for the coupling established, glycosylation of the vancomycin aglycon was examined (Scheme 11).[103] The protected aglycon **113** was prepared from vancomycin aglycon using a 6-step protocol. This sequence includes alloc protection of the N-terminus amine (40%), temporary protection of the residue 4 phenol as a PMB ether (70%), global allylation of the C-terminus carboxylic acid and remaining three phenols (60%), acetylation of the secondary alcohols, and cleavage of the PMB ether under acidic conditions (95%). The first glycosylation with **114** afforded the intermediate compound and was followed by removal of the azidobutyrate with $PPh_3$ to afford the protected pseudoaglycon **115** in 13% over 2 steps. Unlike the first glycosylation, the second glycosylation reaction with the vancosamine sulfoxide derivative **116** provided the disaccharide without addition of DTBMP (60%). Finally, global deprotection with removal of acetyl groups (63%) followed by the allyl and alloc groups with $PdCl_2(PPh_3)_4$–$Bu_3SnH$ (78%) afforded vancomycin (**1**).

**4.2.1.2 Nicolaou Synthesis:** Nicolaou pursued two chemical glycosylation strategies: (1) single step direct introduction of the disaccharide **117**, and (2) sequential glycosylation with two functionalized sugar coupling partners (**118** and **119**), as shown in Scheme 12.[106,107]

The protected glycosylation precursor **120** was prepared from vancomycin aglycon (**50**) in 4 steps (Scheme 13). The protection sequence relied on a global TBS protection with excess TBSOTf and 2,6-lutidine (72%) followed by methyl ester formation of the C-terminus carboxylic acid (92%), N-terminus free amine protection with a Cbz group (91%), and

selective cleavage of the central residue TBS ether with KF–$Al_2O_3$ (60%).[123] The direct coupling of the disaccharide **117** with the aglycon **120** occurred stereoselectively upon treatment with $BF_3{\cdot}OEt_2$ without the addition of base to afford the fully protected vancomycin **121** solely as the β-isomer (70%). This outstanding stereoselectivity was rationalized as arising from steric interactions between the aglycon and the disaccharide, favoring equatorial disposition of the large aglycon. In the final deprotection steps of **121**, E ring dechlorination occurred under the conditions required to cleave four benzyl ethers and two Cbz groups ($H_2$, Pd/C), and was not satisfactorily avoided even after optimization of the reaction conditions or by use of other methods. In contrast, the stepwise glycosylation was successfully implemented. The first glycosylation with the alloc-protected glycosyl donor **125** proceeded smoothly affording the protected pseudoaglycon **126** in good yield (82%) accompanied by a minor side product thought to be the α-anomer.[124,125] Subsequent removal of the alloc group with $Pd(PPh_3)_4$–$Bu_3SnH$[126] gave the glycosylated precursor **127** (85%). For the second glycosylation, choice of sugar protecting groups was key and had a significant impact on the glycosyl donor and acceptor reactivities. By switching the protecting group from a benzyl ether (5%) to an acetate, the protected disaccharide **129** was isolated in good yield and good stereoselectivity (84%, α/β = 8/1). Final deprotection, requiring TBS ether deprotection (80%), acetate hydrolysis (95%), N-terminus Cbz deprotection followed by hydrolysis of the methyl ester (85%, 2 steps), completed the first vancomycin total synthesis.

**4.2.2 Enzymatic Glycosylation—**In the biosynthesis of vancomycin, the carbohydrate introduction is achieved by two sequential glycosyltransferase (GtfD and GtfE) catalyzed reactions (Scheme 14).[36] The latter enzyme, GtfE, is D-glucosyltransferase responsible for introduction of the first sugar on both the vancomycin and teicoplanin aglycons where TDP-glucose **133** serves as the glycosyl donor. GtfB is an analogous glycosyltransferase found in a chloroeremomycin producing strain and is able to perform the same function of installing the glucose residue on the vancomycin aglycon.

GtfD catalyzes the second glycosylation with the cosubstrate TDP-vancosamine **136** to afford vancomycin (Scheme 14). Early *in vitro* studies with the enzymes were reported by Lilly in 1997.[113] The first glycosylation was achieved with a variety of NDP-sugar derivatives using Gtf'E (mutant GtfE; single amino acid mutation from serine to proline) and GtfB obtained from *Amycolatopsis orientalis,* which were expressed in *E. coli*. With use of the cell extracts containing the expressed enzymes, it was found that readily accessible and commercially available UDP-glucose (**134**) can be utilized as an alternative cosubstrate, displaying an indistinguishable glycosylation ability.

**4.2.2.1 Walsh Synthesis:** Walsh characterized the enzymatic activity of GtfB, D, and E that were obtained through subcloning from *Amycolatopsis orientalis*, heterologous expression and purification to homogeneity from *E. coli.*[108,109] The GtfE reaction with vancomycin aglycon (**50**) and UDP-glucose **134** was carried out through incubation with 75 mM tricine (pH 9), 2.5 mM tris-(2-carboxyethyl)-phosphine (TCEP), and 1 mg/mL BSA to afford the pseudoaglycon **135** on an analytical scale in which the product formation was established and quantified by HPLC analysis.[127] Consistent with previous results disclosed by Lilly with

cell extracts, GtfB displayed the same level of the enzymatic reactivity in this first glycosylation. It was also demonstrated that both UDP-glucose and TDP-glucose can be used as a cosubstrate.[127]

The second GtfD-catalyzed glycosylation of vancomycin pseudoaglycon **135** with synthetic TDP-vancosamine **136** was carried out in 75 mM tricine (pH 9), 2.5 mM tris-(2-carboxyethyl)-phosphine (TCEP), 2 mM $MgCl_2$, 1 mg/mL BSA to afford vancomycin (**1**). Unlike the first GtfE-catalyzed reaction, the second glycosylation is rapid and complete within 1.5 h.

After Walsh disclosed the enzymatic synthesis of vancomycin from the aglycon, Wong reported a one-pot glycosylation for introduction of the first sugar by using D-glucopyranosyl-1-phosphate **138** as a UDP-glucose precursor (Scheme 15).[111] This method allows in situ generation of the UDP-glucose **134** from the glucose monophosphate **138**. The one-pot sequence starts with coupling uridine 5′-triphosphate (UTP) and glucose phosphate **138** catalyzed by thymidyltransferase (Ep) to afford UDP-glucose **134**. This UDP-glucose can be then utilized as a cosubstrate for the glycosylation of vancomycin aglycon (**50**) to produce the pseudoaglycon **135** with release of uridine 5′-diphosphate (UDP). Finally, the catalytic cycle is completed by transforming UDP to UTP catalyzed by pyruvate kinase (PK) in the presence of phosphoenolpyruvate (PEP).

**4.2.2.2 Boger Synthesis:** Recently, Boger disclosed elegant total syntheses of two pocket modified vancomycin aglycons designed to address the threat of vancomycin resistance to glycopeptide antibiotics, which are detailed in Sections 7.2 and 7.3. In the course of these studies, the use of enzymatic glycosylations was pursued to install the carbohydrate on the redesigned vancomycin aglycons. Although GtfE and GtfD catalyzed glycosylations with a variety of modified sugar derivatives had been reported, there was no report at the time that utilized an aglycon containing deep-seated changes and none that used the approach on a preparative scale.

Conditions for both glycosylation reactions were established for use on a preparative scale and key elements of the aglycon scope for participation in the reactions were examined.[128] The first GtfE catalyzed glycosylation was achieved by a blend of conditions detailed by Walsh and Wong and provided the pseudoaglycon **135** in good yield (92%, 2.0 mg scale); 0.5 mM aglycon, commercial 2 mM UDP-glucose, 5 μM GtfE, 75 mM tricine (pH 9.0), 2.0 mM TCEP, 1 mM $MgCl_2$, 0.2 mg/mL BSA, glycerol (5% v/v), 37 °C, 42 h. The GtfD catalyzed glycosylation was performed with synthetic UDP-vancosamine, which was prepared by adapting a previously reported synthetic procedure disclosed by Kahne.[129] This GtfD reaction did not require significant changes to the Walsh reaction conditions[108,109] and afforded vancomycin (**1**) in good yield (87%, 1.5 mg scale); 0.5 mM pseudoaglycon, 2.0 mM UDP-vancosamine, 5.0 μM GtfD, 75 mM tricine (pH 9.0), 2.0 mM TCEP, BSA (0.2 mg/mL) 1.0 mM $MgCl_2$, glycerol (10% v/v), 37 °C, 2 h. Importantly, although the endogenous glycosyl donors for both enzymes are the TDP-sugars, the commercially available (**134**) or synthetic (**137**) UDP-sugars displayed the same level of reactivity. The availability of the recombinant enzymes and the synthetic UDP-sugars are such that this two-step introduction of the carbohydrate can be scaled by as much as 100-fold over that

reported for use in academic labs and even larger for production purposes. Its implementation by Boger completed a second total synthesis of vancomycin,[128] culminating with a two-step, sequential enzymatic catalyzed glycosylation of the fully functionalized and unprotected vancomycin aglycon (Scheme 16).

## 5. Total Synthesis of Teicoplanin Aglycon

Isolated from *Actinoplanes teicomyceticus* (ATCC 31121) in 1978,[130,131] teicoplanin[132,133] is one of the more complex glycopeptide antibiotics related to vancomycin.[3,4,29,30,134] Like vancomycin, it is a drug utilized in the clinic when resistant bacterial infections are encountered or for patients allergic to β-lactam antibiotics. Additional attributes compared to vancomycin include a 2–8 fold increased potency, a lower toxicological profile,[135–137] a longer half-life in patients (40 vs 6 h),[135–137] lower patient pharmacokinetic variability, and it may be administered as a single daily dose either IV or intramuscularly, making it suitable for outpatient therapy.[138,139] Although teicoplanin is an approved drug in Europe, Japan, and several other countries sold under the name Targocid,[140–142] it is not approved for use in the U.S..

The first total synthesis of the teicoplanin aglycon was reported in 2000 by Boger[143] and shortly thereafter, a second generation strategy[144] was disclosed (Figure 9). The teicoplanin ABCD ring system is identical in structure and stereochemistry to vancomycin. Additionally, the CDE atropisomer stereochemistry is identical. Key differences include the lack of a β-hydroxy group on the teicoplanin E ring phenylalanine and the presence of an additional FG ring system. As such, it represents a structurally and stereochemically more complex tetracyclic glycopeptide antibiotic aglycon than vancomycin. Both Boger and Evans disclosed total syntheses and enlisted approaches in which the teicoplanin EFG ring system was appended onto their preexisting (vancomycin) ABCD ring systems, permitting the late stage divergent total synthesis of both natural products from a common intermediate. The discussion that follows summarizes the first and second generation total synthesis reported by the Boger, followed by a summary of the later Evans total synthesis.

### 5.1 Boger Synthesis

The first and second generation total synthesis disclosed by Boger both enlisted synthesis of the same E, F and G ring subunits. The absolute stereochemistry found in the E ring (**139**) subunit was obtained through use of a cuprate-mediated Schöllkopf asymmetric alkylation[145] of the respective 4-fluoro-3-nitrobenzyl bromide. For rings F (**140**) and G (**141**), the absolute stereochemistry of the phenylglycines was introduced through Sharpless asymmetric aminohydroxylation of their respective styrene precursors.[146] The distinction in the two approaches was the order and timing of the closure of the DE and FG ring systems. Because of the facile residue 3 (F ring) phenylglycine epimerization observed within the confines of the teicoplanin FG ring system that provides the unnatural diastereomer (1% aq. $NaHCO_3$, 80 °C; >95:5 unnatural *R:S*),[147] the more conservative first generation total synthesis closed this ring system last. In addition, the FG diaryl ether was formed with acyclic phenylglycinol substrates incapable of epimerization. Thus, the F and G rings were coupled via a room temperature intermolecular $S_NAr$ reaction to provide **142** (70%), and

was followed by conversion of the activating nitro group to the requisite aryl methyl ether **145** (Scheme 17). After benzyl ether protection of the primary alcohol (91%), MEM ether cleavage, and hydrolysis of the trifluoroacetamide (96%), the linear EFG fragment **147** was obtained by peptide coupling of **141** and **146** (89%). Sequential Dess–Martin and Pinnick oxidation of the primary alcohol yielded **148** (86%), completing the synthesis of the precursor EFG fragment and allowing attachment of the free carboxylic acid to the ABCD ring system.

The coupling of the ABCD ring system **96** and EFG tripeptide precursor **148** was effected by DEPBT[148] (83%) without competitive epimerization (Scheme 18). In contrast to DEPBT, typical coupling reagents provided near 1:1 mixtures of epimers in this especially challenging coupling reaction. Room temperature macrocyclization upon treatment with CsF (DMSO) provided **149** in excellent yield (80%) and good atropodiastereoselecitivity (3:1), favoring the natural *P*-atropisomer. The second generation total synthesis improved this atropodiastereoselectivity (18:1).

Concurrent with cyclization, the N-terminus Teoc group was also cleaved. Subsequent TBS ether protection of the secondary alcohol (89%) followed by Troc protection of the primary amine (93%) proceeded smoothly to afford **151**. Single step, *O*-debenzylation and reduction of the aryl nitro group to the aniline was affected by treatment with $H_2$ and Pd/C. This was conducted under specially designed conditions (1% $Cl_3CCO_2H$–MeOH) that accelerated the sluggish benzyl ether hydrogenolysis and avoided competitive Troc dechlorination. Aniline diazotization and Sandmeyer substitution with $CuCl_2$–CuCl yielded the fully functionalized E ring and set the stage for FG ring closure. Stepwise oxidation of the primary alcohol **152** to the carboxylic acid **153** (74%), *N*-Troc deprotection (89%), and macrolactamization with PyBop provided **155** (66%) with closure of the 14-membered FG ring system. Lastly, the C-terminus was converted to the free carboxylic acid, and a global deprotection (48%) effected by treatment of **157** with $AlBr_3$–EtSH served to cleave the six methyl ethers, the TBS ether, and the *N*-Boc group and completed the first total synthesis of the teicoplanin aglycon (**158**).

Shortly following the initial disclosure, a second generation total synthesis of teicoplanin aglycon was published by Boger[144] that proved to be more convergent, eliminating 4 steps from the longest linear sequence, and proceeded with a much higher kinetic atropodiastereoselectivity (18:1 vs 3:1) for closure of the DE ring system. This was accomplished by altering the order of the ring closures such that the FG macrolactamization (95%) preceded coupling of EFG tripeptide to the ABCD ring system and subsequent DE ring closure. This latter $S_NAr$ macrocyclization with diaryl ether formation proceed with high diastereoselection (18:1, 76%) without competitive racemization, provided tempered reaction conditions were used.

From intermediate **145**, PyBop promoted coupling of the E ring subunit **139** with **159** after deprotection of the trifluoroacetamide provided **160** (Scheme 19). Stepwise oxidation of the primary alcohol to the carboxylic acid **161** (81%) followed by Teoc deprotection afforded **162** (87%). Macrolactamization of the 14-membered FG ring system with PyBop afforded **163** in excellent yield (95%). In preparation for the attachment to the ABCD ring system,

MEM ether cleavage, followed by stepwise oxidation of the released primary alcohol afforded the necessary carboxylic acid **165** of the EFG fragment.

With the two major subunits of the structural framework of teicoplanin in hand, amide bond coupling promoted by DEPBT[148] afforded the heptapeptide backbone of teicoplanin in 72% yield without competitive epimerization even for this challenging reaction (Scheme 20). This set the stage for the key $S_NAr$ reaction with formation of the last macrocycle. While the first generation total synthesis of teicoplanin aglycon was designed to avoid epimerization by not incorporating a rigid FG macrocycle prior to formation of the DE ring system, suppression of competitive epimerization proved possible. Although CsF-promoted macrocyclization under conventional reaction conditions (25 °C, DMSO) was not especially productive, affording **160** in low yields (23–37%) along with numerous epimeric or degradation products, the use of tempered reaction conditions (10 °C, DMF) provided **160** in high yield (76%) as essentially a single diastereomer (>10:1, ca. 18:1) with little or no competitive epimerization. The key macrocyclization proceeded with greater ease and with a much higher atropodiastereoselectivity with the intact FG ring system installed in the cyclization substrate. This contrasts with the more modest diastereoselectivity observed with **149**, bearing the intact ABCD ring system without the intact FG ring system (3:1) and the nonselective closure of the isolated teicoplanin DE ring system (1:1–3). Conversion of the nitro group to the corresponding chloride by reduction, aniline diazotization, and Sandmeyer substitution, followed by protection of the secondary alcohol as its TBS ether provided **168**, junctioning with a late stage intermediate in the first generation total synthesis. During these studies, the fully functionalized monocyclic FG and DEF ring systems and the bicyclic DEFG ring systems were prepared.[143,144,149] The isolated FG ring systems was found to adopt a single rigid solution conformation consistent with that found in teicoplanin. Atropisomerization of the teicoplanin DE ring system proved nearly identical to that of the vancomycin DE ring system, proceeding at comparable rates and with no thermodynamic atropisomer preference (*P* vs *M*). Most remarkable was the observation that the 16-membered vancomycin and teicoplanin DE ring systems isomerize at similar rates regardless of the presence of the FG ring system. Both equilibrate much more readily than the 16-membered CD ring system even in the absence of the confines of the AB ring system and both can be preferentially equilibrated in the presence of the ABCD ring system.[96,97,150]

### 5.2 Evans Synthesis

Shortly after the disclosure of both the first and second generation total synthesis of teicoplanin aglycon by Boger, Evans disclosed a route similar to the Boger second generation total synthesis with notable distinctions (Figure 10).[151] The EFG subunit outfitted with an E ring 4-fluoro-3-nitrophenylalanine for $S_NAr$ DE ring closure and complete with the macrocyclic FG ring system intact also served as the key advanced intermediate. In the Evans approach, the FG biaryl ether was installed by a Cu(II)-mediated phenol coupling with an aryl boronic acid[152,153] and the macrolactamization with closure of the FG ring system was conducted at a different amide site. An additional important difference was that the amino acid subunits were incorporated at the correct carboxylic acid oxidation state during the entirety of the synthesis of the EFG fragment, enlisting *N*-

methylamide protection from competitive epimerization that was subject to selective cleavage to the corresponding carboxylic acid when and as needed.

The construction of the E ring **169** was achieved through an asymmetric rhodium-catalyzed hydrogenation of methyl (*Z*)-2-acetamido-3-(4-fluoro-3-nitrophenyl) acrylate,[154] whereas the F ring **170** was prepared as an aryl boronic acid from the respective aryl bromide.

The appropriately protected E and G amino acid subunits were coupled with EDCI. After amine protecting group exchange (*N*-Boc to trifluoroacetamide),[155] the FG diaryl ether was formed through a $Cu(OAc)_2$-mediated coupling of phenol **175** with the arylboronic acid **170**, affording **176** in 80% yield (Scheme 21). The 14-membered macrocycle was formed upon macrolactamization with HATU after hydrolysis of the methyl ester and Boc removal. Lastly, the C-terminus *N*-methylamide was hydrolyzed to the corresponding carboxylic acid **180** upon selective nitrosation ($N_2O_4$, 0 °C) and mild nitrosamide hydrolysis (2:1 DMF–$H_2O$, 60 °C) in the absence of added base.

With the EFG ring system in hand, this fragment was coupled to the ABCD ring system with adoption of the DEPBT-mediated reaction conditions[143,144] used by Boger to provide the product in good yield without epimerization (Scheme 22). Closure of the DE ring system with 16-membered diaryl ether formation was effected by treatment with CsF to promote the intramolecular nucleophilic aromatic substitution reaction, using the tempered reaction conditions (DMF, 10 °C) disclosed by Boger and providing **182** in 75% yield with high (>15:1) atropodiastereoselectivity. Reduction of the E ring nitro group to the aniline, diazotization, and Sandmeyer reaction with CuCl and $CuCl_2$ installed the E ring chloro substituent (**183**). Lastly, hydrolysis of the C-terminus *N*-methylamide upon successive nitrosation ($N_2O_4$, 0 °C) and a pH neutral hydrolysis, followed by global demethylation and trifluoroacetamide cleavage provided teicoplanin aglycon (**158**).

## 6. Total Synthesis of Ristocetin A Aglycon

A ristocetin complex, Spontin containing both ristocetin A and B, was reported in 1956. It was isolated from *Amycolatopsis orientalis* subs. *Lurida*, collected in 1951 in Colorado Springs, CO, by Abbott Laboratories.[156] Shortly following this initial disclosure, the complex was introduced into the clinic in 1957. Reports of incidents of patient mortality forced this antibiotic to be pulled from the market after two years of clinical use.[157,158] A common link was identified where patients missing a platelet factor, those with von Willebrand's disease, suffered platelet aggregation, attributing to the deaths.[159–161] As a result, ristocetin A aggregation of patient platelet in drawn blood samples is used today to diagnosis this disease and to detect abnormalities in this protein.[162–164] Later, studies identified an aspect of the ristocetin structure that could be easily removed through selective enzymatic cleavage of rhamnose, which eliminated the induced platelet aggregation *in vivo*.[165]

Nearly 30 years after its isolation and based largely on the spectroscopic studies of Williams, the structure of ristocetin A (**4**) was elucidated by Harris in 1982 and confirmed by others.[166–168] Among the family of vancomycin related glycopeptides, ristocetin A uniquely

contains a tetrasaccharide bound to the central aryl subunit that is composed of arabinose, mannose, glucose, and rhamnose. Due to the presence of this tetrasaccharide, ristocetin A has the weakest dimerization constant compared to other glycopeptides when bound to a cell wall precursor substrate.[169] Like vancomycin, ristocetin A also was the only other glycopeptide within this family to receive FDA approval in the U.S. without further modification of the natural product. Since then, and with the clinical withdrawal of ristocetin A, focus shifted to semisynthetic means for its antimicrobial improvement. Notably, ristocetin A aglycon is slightly more active than ristocetin A itself, free of platelet aggregation activity, and emerged as an entry point for such semisynthetic antibiotic development.

### 6.1 Boger Synthesis

Given the importance of the glycopeptides, the total synthesis of ristocetin A aglycon was undertaken by Boger and reported in 2004.[100] The total synthesis of the ristocetin A aglycon, which constitutes a tetracyclic aglycon similar to teicoplanin, was heavily influenced by the second generation teicoplanin total synthesis previously discussed (Scheme 17–20).[144] In contrast to teicoplanin, (1) both the CD and DE rings of ristocetin no longer possess elements of planar chirality, lacking the aryl chlorides and simplifying the synthetic challenges. Ristocetin also incorporates (2) a β-hydroxy group on the E ring phenylalanine, (3) a methyl substituent on the F ring, and (4) a C-terminus capped as the methyl ester in place of a free carboxylic acid. Thus, the aglycon was prepared in a highly convergent approach from **185** and **186** representing the intact ABCD ring system and the EFG subunit complete with the preformed FG ring system (Figure 11). DE ring closure by a nucleophilic aromatic substitution reaction would not only introduce the diaryl ether linkage but also complete the assemblage of the tetracyclic ring system. The key DE ring closure was anticipated to benefit from preorganization of the substrate, resulting in closure under conditions much milder than those required of vancomycin and with a higher atropodiastereoselectivity. Offsetting this advantage is the propensity for epimerization under even mildly basic conditions which might have precluded implementation of this approach.

In turn, the ABCD ring system was prepared through sequential CD and AB ring closures analogous to the efforts on vancomycin. Control of the CD atropisomer stereochemistry is not an issue with ristocetin by virtue of its lack of a C ring aryl chloride rendering the diastereoselectivity of the diaryl ether macrocyclization unimportant. Thus, the stereochemical issue associated with this approach simplified to the control of the AB atropisomer stereochemistry. This could be effectively addressed with an anticipated thermodynamic preference for the natural stereochemistry (ca. 3:1) and easily adjusted on the biaryl precursor preceding AB macrolactamization.

Given the similarity between the total synthesis of ristocetin aglycon and the second generation total synthesis of teicoplanin aglycon, the reader can refer to both Section 5.1 and the disclosed report by Boger for full details.[100] The diaryl ether that links the FG ring of the EFG macrocycle was prepared from the appropriately substituted F ring **187** and G ring **141** through an intermolecular $S_NAr$ reaction, using NaH and affording **188** in 69% yield

(Scheme 23). Although this substitution reaction could be effected with $K_2CO_3$ in the total synthesis of teicoplanin, its use resulted in low yields for **188** (20–30%) due to the increased steric hindrance of the F ring methyl substituent. The nitro group on the G ring was transformed to the corresponding methoxy group, yielding **191**. After deprotection of the amine, the peptide bond between the FG fragment and the E ring was formed with HATU, which suppressed epimerization observed with other peptide coupling reagents. Notably, the synthesis of the E ring subunit was improved relative to that originally introduced with vancomycin through use of a diastereoselective anti-aldol reaction (94% de) of a glycine imine bearing an α-hydroxypinanone chiral auxiliary (94% ee).[170] Stepwise oxidation (Dess–Martin and Pinnick) of the primary alcohol and Teoc deprotection primed intermediate **196** for subsequent macrolactamization with PyBop, closing the 14-membered EFG ring system and providing **197** in superb yield (92%). Silyl ether protection of the β-hydroxy group (96%), followed by MEM ether cleavage and reintroduction of the *N*-Boc group (86%), and finally Jones oxidation of the primary alcohol (79%) completed synthesis of the EFG ring fragment **186**.

The cyclic tripeptide **86**, representing the CD ring system, was synthesized as previously discussed in Section 4.1.3. However, it is worth highlighting that the preparation of the C ring subunit was improved through use of a Schöllkopf[171] aldol-type addition of the transmetalated Zr anion,[95] leading to excellent control of not only the α-amino acid stereochemistry (>99:1), but also the β-hydroxy diastereoselectivity (5:1). Removal of the nitro group over two steps afforded **200** (77%), and Suzuki–Miyaura cross-coupling with the A ring provided **201** with nonselective formation of the biaryl axial chirality (Scheme 24). Thermal equilibration of the post-coupling mixture afforded a 3:1 (*P:M*) ratio in favor of the natural atropisomer (*P*)-**201**. The minor unnatural atropisomer was recycled by subjection to thermal equilibration in *o*-dichlorobenzene at 130 °C, regenerating the 3:1 (*P:M*) mixture and funneling all material into the synthesis. TBS deprotection of the natural atropisomer (*P*)-**201** with $Bu_4NF$ (95%), methyl ester hydrolysis with LiOH (96%), and Cbz hydrogenolysis with $H_2$–Pd/C yielded **204** (98%). Macrolactamization with EDCI closed the 12-membered AB macrocycle in 51% yield. Lastly, removal of the Boc group without affecting the MEM ether afforded the ristocetin A ABCD ring system **206**.

The EFG and ABCD ring systems were coupled with DEPBT[148] (Scheme 25), which after extensive exploration was determined to be the reagent of choice for minimizing epimerization, affording the product in excellent diastereoselectivity (>10:1). The DE ring closure was promoted by CsF in DMF, yielding the desired product **207** in exceptional yield (>95%) and excellent atropodiastereoselectivity (>15:1). Additionally, like teicoplanin, no epimerization was observed. The remaining steps and conditions are nearly identical to those developed in the second generation total synthesis of teicoplanin. Reduction of the nitro group, aniline diazotization, and in situ reduction provided **208** (79%). Protection of the secondary alcohols, MEM deprotection, and oxidation of the released C-terminus alcohol to the carboxylic acid followed by esterification afforded **211**. Next, global deprotection with $AlBr_3$–EtSH with removal of the six methyl ethers and cleavage of the methyl ester, two TBS ethers, and the terminal *N*-Boc group (10 protecting groups) provided **212** in remarkably high yield (78%). Finally, the Boc group was reintroduced on the N-terminus

(91%), and was followed by selective methylation of the carboxylic acid (93%), and acid-catalyzed Boc removal (98%) to afford ristocetin A aglycon (**215**).

## 7. Total Syntheses of Residue 4 Modified Vancomycins and Key Derivatives

### 7.1 [Φ[$CH_2NH$]$Tpg^4$]Vancomycin Aglycon

Boger extended his group's efforts to the total synthesis of novel redesigned vancomycin analogues with the ambitious goal of addressing vancomycin resistant bacterial infections. The elaborate mechanism of resistance orchestrates a simple one atom change in bacteria cell wall precursors that significantly reduces both the binding affinity of vancomycin for its target and its antimicrobial activity 1000-fold.[48] Boger began the studies by defining the origin of this loss in binding affinity by partitioning it into: (1) the loss of a H-bond, and (2) introduction of a destabilizing lone pair/lone pair repulsion between the vancomycin residue 4 amide carbonyl oxygen and the lactate ester oxygen (Figure 12).[172]

The binding studies were carried out with vancomycin and the model ligands **216**–**218**. This included the ketone ligand **217**, containing a linking methylene which lacks a lone pair and is incapable of H-bonding. These studies revealed that it is the destabilizing electrostatic repulsion (100-fold), more so than the H-bond (10-fold), that is responsible for the 1000-fold loss in binding affinity. This has significant ramifications on the redesign of vancomycin for treatment of vancomycin resistant bacteria, indicating that simply removing the destabilizing lone pair/lone pair interaction without reengineering a reverse H-bond could improve affinity and activity by as much as 100-fold. As a result and in initial studies, a binding pocket modification in the vancomycin core that replaced the residue 4/5 amide carbonyl with an aminomethylene linkage was targeted to remove the destabilizing lone pair interactions.[173] More subtly, such a modification provides the antibiotic with balanced dual ligand binding capabilities needed for vancomycin resistant organisms (D-Ala-D-Ala and D-Ala-D-Lac), while maintaining its ability to bind D-Ala-D-Ala required for vancomycin sensitive bacteria.

The plan for the synthesis the aminomethylene analogue **219** was based largely on the route implemented in the vancomycin aglycon total synthesis,[90] albeit with improvements as shown in Figure 13.[173] Key elements of the approach include synthesis of the modified vancomycin ABCD ring system featuring a reductive amination for installation of the amide modification, the first of two diaryl ether closures for formation of the modified CD ring system (76%, 2.5–3.1 kinetic atropodiastereoselectivity), a Suzuki coupling for installation of the hindered AB biaryl bond (90%) on which the atropisomer stereochemistry could be thermally adjusted, and a macrolactamization closure of the AB ring system (70%). Subsequent DE ring system introduction enlisted a room temperature aromatic nucleophilic substitution reaction for formation of the remaining diaryl ether (86%, 6–7:1 kinetic atropodiastereoselectivity), completing the carbon skeleton of **219**. The methyl carbamate was selected as the protecting group for the aminomethylene group, which was tolerant of all chemical transformations throughout the total synthesis, yet capable of removal in the final global deprotection step with $AlBr_3$–EtSH. Moreover, the relatively small carbamate protecting group minimized any undesired steric features that might have effected the CD and AB ring closures. Finally, and despite the apparent flexibility introduced into the CD

ring system by removal of the amide, the recognition that the rigid AB ring system complete with its *cis* amide controls the conformation of the surrounding CD ring system insured that the ABCD ring system as well as the final analogue **219** would adopt an overall conformation analogous to that of vancomycin.

The synthesis started with a reductive amination of aldehyde **222** with free amine **221** to produce **223** in good yield (75%) and in excellent diastereoselectivity (12:1) in spite of ease of epimerization of **222** or the intermediate imine (Scheme 26). Subsequent methyl carbamate protection of the secondary amine (85%), followed by benzyl ether deprotection upon treatment with Raney Ni (98%), and hydrolysis of the methyl ester afforded **224** (>99%). Peptide coupling of **76** with **224** effected by DEPBT[148] (70%, dr = 14:1) preceded a base-mediated ($K_2CO_3$–$CaCO_3$) $S_NAr$ cyclization to provide the CD ring system **226** in good yield (76%) and in good kinetic atropodiastereoselectivity (2.5–3:1, *P:M*). Reduction of the nitro group followed by aniline diazotization and Sandmeyer substitution afforded the aryl chloride **227** (70%). The same key aryl chloride **227** was also prepared in later efforts from thioamide **246**, which was synthesized in studies culminating in the total synthesis of the residue 4 thioamide of vancomycin aglycon (see Section 7.2). Reduction of the thioamide with $H_2$, Ra–Ni in the presence of formamidine acetate gave **228** while suppressing aryl dechlorination (60%). Methyl carbamate protection of the amine (91%) and selective cleavage of the phenol TBS ether also gave **227** in good yield (95%).

Suzuki coupling of **227** with the boronic acid **79** provided the biaryl atropisomers in a separable 1:1.3 ratio (90%) (Scheme 27). Thermal re-equilibration of the unnatural *M*-atropisomer upon simple heating provided a 1:1.1 separable atropisomer mixture, permitting the recycling of all material into the synthesis. TBS ether deprotection (80%), Cbz deprotection (95%), followed by methyl ester saponification (96%), and macrolactamization closure of the AB ring system with PyBop (70%) completed the synthesis of the modified ABCD ring system. Deprotection of the N-terminus Boc group by treatment with $HCO_2H$ provided the free amine **235** in good yield (84%).

The final peptide coupling of the ABCD ring system **235** and the E ring tripeptide **96** was carried out with DEPBT[148] to afford the heptapeptide in good yield (73%) with excellent diastereoselectivity (12:1), suffering little competitive racemization (Scheme 28). Subsequent ring closure of the DE ring system was achieved by $S_NAr$ cyclization that proceeded under milder reaction conditions (CsF–$CaCO_3$, 25 °C, DMF) than those disclosed for vancomycin and provided **236** in good yield (74%) and good atropodiastereoselectivity (6–7:1). To further improve the efficiency of the approach, focused efforts were made to optimize the E ring chloride introduction and the final global deprotection steps. Reduction of the aryl nitro group with zinc nanoparticles resulted in a rapid conversion (30 min) to the aniline compared to the previously reported conditions ($H_2$, Pd/C, 12 h). The subsequent diazonium salt formation and Sandmeyer substitution reaction for chloride introduction were carried out under improved conditions minimizing reduction (dechlorination) by changing the solvent ratio ($CH_3CN/H_2O$) and lowering the reaction temperature (–35 °C) to afford the aryl chloride **237**. Next, **237** was subjected to TBS ether protection of both secondary alcohols with $CF_3CONMeTBS$ to produce the TBS protected aryl chloride **238** in improved overall conversions (55–60% over 3 steps). MEM ether deprotection (80%) and a two-step

oxidation of the released primary alcohol provided the C-terminus carboxylic acid (80%), and was followed by hydration of the nitrile to afford the primary carboxamide **241** (87%). The final global deprotection, promoting the removal of four aryl methyl ethers, two TBS ethers, the *N*-Boc group, and the methyl carbamate, was carried out with $AlBr_3$–EtSH at a defined reaction concentration (0.1 M) to produce [Φ[$CH_2$NH]$Tpg^4$]vancomycin aglycon (**242**) in excellent yield (80%). When the global deprotection was conducted at more dilute reaction concentrations (0.01 M vs 0.1 M), only partial cleavage of the E ring TBS ether was observed.

### 7.2 [Φ[C(=S)NH]$Tpg^4$]Vancomycin and [Φ[C(=NH)NH]$Tpg^4$] Vancomycin Aglycons

Based on the initial success of a binding pocket modification of vancomycin aglycon, Boger explored additional vancomycin analogues with the potential of displaying greater activity by introduction of a residue 4 amidine (Figure 14).[174,175] Importantly, the amidine **243** was found to display dual binding affinity toward both the wild type dipeptide (D-Ala-D-Ala) and the modified resistant dipeptide (D-Ala-D-Lac), where the amidine serves as both a H-bond donor to reinstate the lost H-bond with the altered ligand, while maintaining the ability to serve as a H-bond acceptor toward the wild type cell wall peptidoglycan dipeptide.

At the time of the work, there was no precedent on which to base the expected results and, even today, reports of the use of an amidine as an amide isostere in cyclic peptides are limited.[176–178] Thus, the binding behavior of the amidine in **243** was not clear and it was not evident whether the ester oxygen of D-Ala-D-Lac could serve as a H-bond acceptor, or whether the amidine,[179] typically protonated under physiological conditions, could act as the H-bond acceptor for binding D-Ala-D-Ala. As a result, and even though it was perhaps the most important modification to examine, it was not the first binding pocket modified vancomycin analogue pursued by Boger.

The overall synthetic strategy envisioned for **243** relied on the synthetic route developed for the total synthesis of vancomycin aglycon (**50**)[90] and subsequently adopted for the aminomethylene vancomycin aglycon **242** (Figure 15).[173] Key to its synthesis, a residue 4 thioamide was chosen to serve as a masked precursor to be converted to the amidine in a final step and conducted on a fully functionalized and deprotected vancomycin aglycon. By design, this approach permits the divergent synthesis of additional pocket modified vancomycin analogs from a common late stage intermediate, including substituted amidines[180] and the aminomethylene derivative **242**. Its implementation required development of a new reaction for such a direct single step amidine formation on substrates only soluble in protic solvents. At the time of the work, it was established empirically that introduction of the residue 4 thioamide could only be introduced effectively on the early stage synthetic intermediate **88**, introducing a host of challenges for the ensuing total synthesis and requiring notable alterations in the approach.

The total synthesis started with preparation of cyclic tetrapeptide **88** as shown in Scheme 29. TBS protection of the phenol in **88** afforded **245** (100%), preventing competitive reaction with a thionation reagent. Subsequent thionation with Lawesson's reagent selectively generated the thioamide **246** in excellent yield (92%). Although the thioamide could be

subjected to Suzuki coupling with the Ring A boronic acid **79**, the reaction was not dependably reproducible. Even after careful removal of sulfur byproducts from the thionation reaction, which were thought to be poisoning the reaction, the coupling reaction remained capricious. It was suspected that the residue 4 thioamide itself might be affecting the coupling reaction. Thus, the residue 4 thioamide was masked as its less nucleophilic methyl thioimidate **247** by treatment of **246** with MeI/$K_2CO_3$ (92%). The thioimidate proved to be an effective and reproducible coupling partner for the Suzuki reaction with **79** and afforded the corresponding biaryl product as a separable mixture of atropisomers (1:1.2) in good yield (65–80%), displaying a reactivity similar to the corresponding amide substrate. Reintroduction of the thioamide upon treatment of the methyl thioimidate with $H_2S$ in the presence of collidine provided the thioamide (*P*)-**249** and its separable unnatural isomer (*M*)-**249** in good yield (95%). Recycling the unnatural atropisomer (*M*)-**249** was carried out by thermal equilibration, affording a 2.6–1.8:1 (*P:M*) separable mixture of atropisomers with 83–99% overall recovery. Completion of the synthesis of the modified ABCD ring system required alteration of the order of deprotections. Removal of Cbz group under ionic hydrogenolysis conditions with $Pd(OAc)_2$–$Et_3SiH$ (97%)[181,182] to avoid competitive thioamide reduction was carried out prior to TBS deprotection (95%). Hydrolysis of the methyl ester (95%), followed by macrolactamization of the AB ring system with DEPBT afforded thioamide **253** in good yield (71%, dr 7:1). Finally, Boc deprotection by treatment with $HCO_2H$ completed the synthesis of the modified ABCD ring system **254** in good yield (98%).

Introduction of the E ring tripeptide was effected by coupling **254** with **96** mediated by DEPBT or T3P to afford the product (56%) as shown in Scheme 30. The final DE diaryl ether macrocyclization was achieved upon treatment with $Cs_2CO_3$, promoting a room temperature $S_NAr$ cyclization to produce **255** in superb yield (74–78%) and good atropodiastereoselectivity (5–8:1), favoring the natural *P*-atropisomer. The minor unnatural isomer was recycled and funneled into the total synthesis by selective thermal atropisomer equilibration, generating additional amounts of the natural isomer as a separable mixture (1:1). Subsequent conversion of the E ring aryl nitro group to the chloride and the final global deprotection was further refined. In addition to adopting the Zn nanoparticle conditions for the nitro group reduction, a decrease in amounts of the diazotization reagent (1.0 vs 1.1 equiv of $HBF_4$/*t*-BuONO) in the chloride substitution process minimized competitive oxidative formation of the residue 4 amide. TBS protection of both secondary alcohols with $CF_3CONMeTBS$ afforded **257** (50–59%, over 3 steps). Subsequent MEM deprotection upon treatment with BCB followed by Boc reprotection of the N-terminus amine provided the primary alcohol **258** in good yield (75%). Complicated by the presence of the oxidation prone thioamide, the C-terminus oxidation with Dess–Martin periodinane, Swern oxidation, $SO_3$–Pyr, $Bu_4NRuO_4$ (TPAP), pyridinium dichromate (PDC),[183] pyridinium chlorochromate (PCC),[184,185] or 2-iodoxybenzoic acid (IBX) resulted in little formation of the desired carboxylic acid or resulted in a complex mixture. Remarkably, it was found that Jones oxidation ($CrO_3$, aq. $H_2SO_4$–acetone)[186,187] selectively oxidized the primary alcohol directly to the carboxylic acid (70%) in single step while generating the amide only as a minor byproduct (>10:1). It was additionally demonstrated that formation of the amide could be further minimized by conversion of an unusually stable contaminant

thioamide *S*-oxide (<10%) back to the thioamide in the subsequent global deprotection steps. After Jones oxidation, a purified mixture of the thioamide and the minor *S*-oxide (<10%) was treated with TFA to convert the nitrile to the primary carboxamide,[188] followed by global deprotection using $AlBr_3$–EtSH to afford the [Φ[C(=S)NH]Tpg$^4$]vancomycin aglycon (**244**, 44–52%, over 3 steps). Remarkably, the minor thioamide *S*-oxide tolerated the mild TFA-mediated hydration step without change, and was converted back to the thioamide in the global deprotection step. Finally, the residue 4 thioamide was transformed directly to the amidine **243** (50%) through use of a newly developed method (AgOAc–$NH_3$, MeOH) for the direct conversion. This reaction could be conducted on the fully deprotected and fully functionalized aglycon **244**, bearing both the C-terminus carboxylic acid and N-terminus free amine, in protic solvents where such substrates are soluble.

Full details of the development of this reaction and its use in the divergent synthesis of substituted amidine derivatives (=NMe and =NCN vs =NH) that clarified the protonation state of the amidine upon binding D-Ala-D-Ala and D-Ala-D-Lac were disclosed in a separate account.[180]

The three residue 4 modified vancomycin aglycons were examined for their ability to bind model D-Ala-D-Ala and D-Ala-D-Lac ligands and for their in vitro antimicrobial activity against vancomycin resistant enterococci (VanA VRE, Figure 16).

As designed, both **243** and **242** were found to exhibit dual ligand binding properties, each displaying equal affinities for D-Ala-D-Ala or D-Ala-D-Lac. The amidine exhibited the greater affinity for both ligands, establishing its productive behavior even though its success was not obvious at the onset of the studies. Moreover, the amidine **243** bound both ligands with an affinity nearly equivalent to that found for vancomycin and its binding to D-Ala-D-Ala, effectively mimicking this latter behavior. However, the amidine **243** also binds the D-Ala-D-Lac ligand 600-fold better than vancomycin. Beautifully, both **243** and **242** exhibited activity against VanA VRE, displaying potencies that perfectly mirror their relative binding affinities. Most notable, amidine **243** was found to be equipotent to vancomycin but also now displays this activity against vancomycin resistant organisms. Just as remarkable and initially surprising, the thioamide **244** failed to bind either D-Ala-D-Ala or D-Ala-D-Lac and displayed no antimicrobial activity against either vancomycin sensitive or resistant bacteria. This was attributed to the increased size of a sulfur atom and the longer thiocarbonyl bond length that serve to displace the ligand from the binding pocket. This behavior, which contrasts that of both **243** and **242**, highlight just how remarkable the successful behaviors of **243** and **242** are. It also provides an attractive target for preparation by coersed biosynthesis, providing a vancomycin analogue capable of semisynthetic conversion to the active pocket modified vancomycins that will not impede the growth of producing organisms.

### 7.3 [Φ[C(=S)NH]Tpg$^4$]Vancomycin, [Φ [C(=NH)NH]Tpg$^4$]Vancomycin, and [Φ [$CH_2$NH]Tpg$^4$]Vancomycin and Their (4-Chlorobiphenyl)methyl Derivatives

With the stunning results of the pocket modified vancomycin aglycon analogues in hand, Boger initiated efforts to install the disaccharide in preparation for their more comprehensive examination.[189] The results of these studies, enlisting two enzyme-catalyzed glycosylation

reactions on the fully deprotected aglycon and culminating in the completion of a total synthesis of vancomycin,[128] are summarized in part in Section 4.2.2. The use of this methodology for the total synthesis of three pocket modified analogues, each bearing a single atom change in the structure of vancomycin, is summarized below. With the residue 4 modified vancomycins in hand, Boger additionally pursued the development of analogues that would display even greater potency. The approach focused on the combined use of a binding pocket modification and an added peripheral modification. One of the most widely recognized peripheral modifications of glycopeptide antibiotics is the hydrophobic substitution of the vancosamine free amine first discovered at Eli Lilly and inspired by the lipophilic acyl groups found in teicoplanin.[190–192] To date, three semi-synthetic analogues; oritavancin (**259**, 2014, The Medicines Company),[193] telavancin (**260**, 2009, Theravance),[194,195] and dalbavancin (**261**, 2014, Vicuron Pharmaceuticals Inc.)[196–198] that bear such substitution have been approved for clinical use (Figure 17). Importantly, the hydrophobic substituent enhances the antibiotic potency against both vancomycin sensitive and resistant pathogens.[199–203] Boger examined the (4-chlorobiphenyl)methyl (CBP) group substitution of vancosamine on the residue 4 modified vancomycin derivatives (Figure 18).[189,204] The synthetic approach relied on a 3- or 4-step route from the fully functionalized and protecting group free pocket modified vancomycin aglycons. This sequence involved two sequential enzymatic glycosylations, primary amine *N*-alkylation via a reductive amination, and, in the case of the amidine, AgOAc–$NH_3$ promoted amidine formation from the residue 4 thioamide. By following the glycosylation procedure established for vancomycin (Section 4.2.2.2), the first GtfE catalyzed glycosylation of the residue 4 modified aglycons was examined by reverse phase HPLC, following product formation (Figure 18).

The thioamide (**244**) and aminomethylene vancomycin aglycons (**242**) displayed sufficient reactivity under the glycosylation conditions to preparatively provide the pseudoaglycons **263** (75%, HPLC conversion 86–92%), **264** (72%, HPLC conversion 85–95%), with only slightly reduced isolated yields compared to the parent vancomycin aglycon (**135**, 92%, HPLC conversion 100%). In contrast, the amidine substituted vancomycin aglycon (**243**) was not successfully glycosylated and only a trace amount of product **262** was detected.

The GtfD catalyzed second glycosylation of the pseudoaglycons with UDP-vancosamine was rapid and complete within 2 h to afford the disaccharides **265** (87%, HPLC conversion >95%) and **267** (76%, HPLC conversion >95%) in good yields (Scheme 31). Finally, the residue 4 thioamide was converted to **266** via AgOAc-promoted amidine formation (10 equiv of AgOAc, $NH_3$/MeOH, 25 °C, 6 h) without competitive deglycosylation.

Subsequent introduction of the (4-chlorobiphenyl)methyl group via reductive amination, using reported reaction conditions for the synthesis of CBP-vancomycin (**268**, 61–74%) disclosed by Kahne[205,206] (1.5 equiv of 4-(4-chlorophenyl)benzaldehyde, 5 equiv of *i*-$Pr_2NEt$, DMF, 50–70 °C; 100 equiv of $NaCNBH_3$, 70 °C, 5 h), provided the chlorobiphenyl derivatives **269** (57%) and **271** (41%). The reductive amination was conducted without competing alkylation of the N-terminus or residue 4 secondary amine. Finally, conversion of the residue 4 thioamide to the amidine was carried out with use of the AgOAc–$NH_3$

promoted amidine formation (10 equiv of AgOAc, $NH_3$/MeOH, 25 °C, 6 h) to afford **270** in 45% yield.

A summary of the *in vitro* antimicrobial activity of the pocket modified vancomycin analogues is presented in Figure 19. As expected, introduction of the disaccharide on the residue 4 modified vancomycin aglycons did not alter their antimicrobial potency. Like the aglycons, sequential improvements in activity against vancomycin resistant bacteria (VanA VRE) were observed with **267** and **266** that mirrored their dual ligand binding affinities and where the activity of amidine **266** matched the potency of vancomycin observed against sensitive bacteria. The CBP introduction on vancomycin enhanced the potency against both vancomycin sensitive and resistant strains (VSSA and MRSA) by 20-fold and 100-fold, respectively, but **268** still remains nearly 100-fold less active against vancomycin resistant bacteria. Both CBP-amidine **270** and CBP-aminomethylene **271** displayed 100-fold increases in antibiotic potency against VRE (VanA) and exhibited this same level of potency against vancomycin sensitive bacteria (e.g. VSSA and MRSA), reinstating potent antimicrobial activity against vancomycin resistant bacteria. Importantly, introduction of the CBP substituent on the thioamide vancomycin, lacking the ability to bind D-Ala-D-Ala/D-Ala-D-Lac, provided an analogue **269** that displayed less active, but equally potent activity against vancomycin sensitive and resistant strains. This reflects antibacterial activity derived from a second mechanism of action independent of D-Ala-D-Ala/D-Ala-D-Lac binding, one that is responsible for the improved activity of all CBP analogues in Figure 19. This second mechanism of action entails direct inhibition of transglycosylase also resulting in inhibition of bacterial cell wall biosynthesis.[199–203]

### 7.4 Development of Durable Antibiotics by Design

In a remarkable extension of these latter studies, Boger incorporated a second peripheral modification into the pocket modified vancomycin analogues that provided a different second mechanism of action independent of D-Ala-D-Ala/D-Ala-D-Lac binding and demonstrated that the antimicrobial activity similarly increased 200-fold against VanA VRE.[207] Further, this C-terminus modification could be combined with the peripheral CBP modification to provide even more potent antimicrobial agents whose activity can be attributed to three independent mechanisms of action, only one of which requires D-Ala-D-Ala/D-Ala-D-Lac binding. Importantly, such peripherally and binding pocket modified vancomycins display little propensity for acquired resistance and they display a durability as well as increased potency that follow now predictable trends: 3 > 2 > 1 mechanisms of action.

In these studies, an additional peripheral modification on the C-terminus was explored, introducing an amide bearing a permanent cationic charge.[207] A variety of commercially available quaternary ammonium salts are used as antimicrobial agents and many cationic naturally occurring antimicrobial peptides are known,[208–210] which serve to disrupt the cell membrane integrity and increase cell wall permeability.

Recently, Haldar disclosed that such functionalization of vancomycin provided compounds active against vancomycin resistant bacteria,[211,212] albeit without inhibiting the bacteria cell wall biosynthesis and displaying an independent mode of action. Thus, Boger envisioned

modifications first focused on combining the binding pocket modification and C-terminus quaternary ammonium salt functionalization. This study was conducted with [Φ[$CH_2$NH]Tpg$^4$]vancomycin (**267**), the most readily available pocket modified vancomycin analogue available through total synthesis (Figure 20).[173] It also represents the least potent of the two pocket modified analogues, permitting the most accurate assessment of the impact of sequential peripheral modifications. Several amines bearing a variety of quaternary ammonium salts were attached to the C-terminus carboxylic acid of vancomycin under modified reaction conditions with HBTU and NMM to afford the coupling products **272**–**276** in good yield (58–68%). Subsequent antimicrobial assessments indicated that the tetradecyl substituted ammonium salt was the most potent derivative, enhancing the antibacterial activity 125-fold against VanA VRE. Thus, the tetradecyl ammonium salt was introduced to the aminomethylene vancomycin **267** under the same coupling conditions to afford **276** in 64% yield. This peripherally modified pocket analogue **276** displayed more potent antimicrobial activity, further increasing the activity 200-fold, and it inhibited VanA VRE bacterial cell growth by two independent mechanisms of action, only one of which relied on dual D-Ala-D-Ala/D-Ala-D-Lac binding.

Next, the combination of the C-terminus quaternary ammonium salt modification with the vancomycin analogue that contained both a binding pocket modification and the peripheral CBP substituent was examined (Figure 21). Coupling CBP-vancomycin **268** with the same set of functionalized amines generated the products **277**–**281** in good yield (55–76%). Interestingly, the introduction a C14 ammonium salt did not alter the antibiotic activity against vancomycin resistant bacteria, but the simpler trimethyl ammonium salt proved enhance the potency against VRE 10-fold. When combined with CBP-[Φ[$CH_2$NH]Tpg$^4$]vancomycin, this C-terminus peripheral modification similarly improved the MIC values to the remarkable levels of 0.01–0.005 μg/mL. This molecule was shown to exert its impressive potency through three independent mechanisms of action, only one of which is dependent upon the dual D-Ala-D-Ala/D-Ala-D-Lac binding. The pocket modification reinstates inhibition of transpeptidase via D-Ala-D-Ala/D-Ala-D-Lac binding, the CBP modification results in direct inhibition of transglycosylase, and the C-terminus trimethyl ammonium salt induces cell wall permeability. Even more importantly, it was demonstrated that such peripherally and binding pocket modified vancomycins display little propensity for acquired resistance by VRE and that their durability against such challenges as well as their antimicrobial potency follow now predictable trends (3 > 2 > 1 mechanisms of action).

## 8. Total Synthesis of Chloropeptins and Complestatins

Complestatin (**282**, chloropeptin II) was first disclosed as an inhibitor of an alternate pathway of human complement in 1980 (Figure 22).[213–215] Its original isolation[216] from *Streptomyces lavendulae* and partial structure elucidation[217] were reported in 1989. Four years later, Omura reported the isolation[218–220] of chloropeptin I (**283**) and chloropeptin II (**282**, completstatin) from *Streptomyces sp.* along with details of their structure elucidation[221] and disclosed their biological activity against HIV infectivity and their cytopathic effect.[222] Because they inhibit HIV through two independent mechanisms of action, it is expected that resistance would develop only slowly. Singh and Patane later

demonstrated that complestatin (chloropeptin II) (**282**) can be converted to the less strained chloropeptin I (**283**) through a remarkable TFA-catalyzed rearrangement that proceeds with retention of the atropisomer stereochemistry.[223] Singh also isolated and characterized isocomplestatin, bearing the unnatural (*S*)-indole tryptophan-derived biaryl ether linkage.[222] Later in 2006, Hoveyda reported that the compound thought to be isocomplestatin was in fact complestatin (**282**).[224] The related complestatin A (**284**) and B (**285**), bearing a 2-oxindole or a 3-hydroxy-2-oxiindole, were isolated by Merck from *Streptomyces* sp. MA7234.[222] At the same time, these compounds were independently disclosed as neuroprotection A and B and were isolated from *Streptomyces* sp. Q27107.[225,226] Although they are not strictly members of the glycopeptide antibiotics, the natural products in this group contain structural features that place them in discussions of the class.

Although the complestatins and chloropeptins contain many of the same structural features and the overall complexity of glycopeptide antibiotics, the significant difference is the replacement of a central diaryl ether linkage with a tryptophan indole embedded in the macrocyclic core as part of a biaryl linkage that adopts a single (*R*)-atropisomer configuration incapable of thermal interconversion.

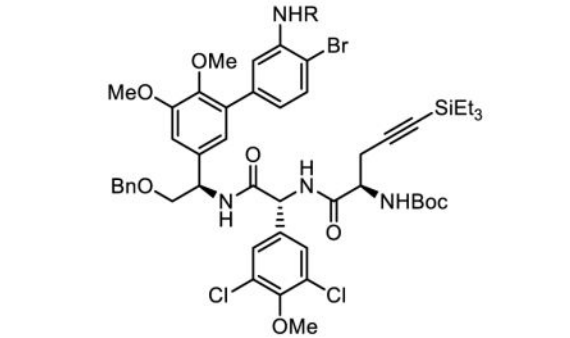
### 8.1. Snapper–Hoveyda Total Synthesis of Chloropeptin I

Snapper and Hoveyda reported the first total synthesis of chloropeptin I (**283**), the least strained of the two chloropeptins.[227] Their synthetic strategy enlisted a late stage intramolecular Stille coupling for biaryl formation on a substrate that contains the left-hand macrocycle and exclusively afforded the natural (*R*)-atropisomer (38–42%, 3 steps) (Figure 23). They also examined the extension of this strategy for the preparation of complestatin (**282**, chloropeptin II). It was found that the Suzuki coupling reaction exclusively provided isocomplestatin, bearing the unnatural biaryl (*S*)-atropisomer in 63% yield, whereas closure of the isolated ring system proceeded in a non-atropodiastereoselective manner (52%, 1:1 *R:S*).[224] The atropodiastereoselectivity of these macrocyclization reactions was also later confirmed by Zhu.[228] The first ring closure was carried out with use of a Cu(II)-mediated coupling reaction of a phenol with an aryl boronic acid for diaryl ether formation analogous to the reaction employed in the total synthesis of teicoplanin disclosed by Evans.[151]

### 8.2 Boger Total Synthesis of Chloropeptin I and II, and Complestatins A and B

By virtue of single step acid-catalyzed conversion of chloropeptin II (**282**) to chloropeptin I (**283**), Boger envisioned a total synthesis of both natural products by first preparing the more strained chloropeptin II and conducting its subsequent single step acid catalyzed rearrangement to chloropeptin I (**283**).[229–231] The key elements of their synthetic strategy were an intramolecular $S_NAr$ cyclization and Larock indole annulation for the ring closure of the BCD and DEF ring systems, respectively. The latter intramolecular Larock indole synthesis[232,233] utilized a 2-bromoaniline[234] and its reaction with an alkyne that incorporates a removable large terminal substituent ($-SiEt^3$) to sterically dictate the indole cyclization regioselectivity.[235,236] Importantly, the aniline acetamide not only served to deactivate the strained indole toward subsequent electrophilic reactions, but also favorably influenced the cyclization atropodiastereoselectivity.[237] They pursued two synthetic approaches, which are distinct in the order and timing of the key ring closures. In the first

generation total synthesis, the DEF ring system macrocyclization was first conducted via the Larock annulation to afford the functionalized right hand subunit in superb isolated yield (89%) and in good atropodiastereoselectivity (4:1). This represented the first reported example of an intramolecular Larock macrocyclization strategy (Figure 24). Later studies further improved on this atropodiastereoselectivity (20:1) by subtle alteration of the aniline acyl group (eq. 1).[229–231,237] The second macrocyclization via $S_NAr$ diaryl ether formation with closure of the BCD ring system afforded the cyclized compound in good yield (81%) and in superb atropodiastereoselectivity (>10:1). The first generation approach provided the first total synthesis of complestatin (chloropeptin II) and completion of an approach in which both chloropeptin I and II were prepared in a common route.




| substrate | product | |
|---|---|---|
| R = H | 67% (1:1 *R*:*S*) | R = H |
| R = $CO_2Me$ | 78% (2.2:1 *R*:*S*) | R = $CO_2Me$ |
| R = $COCH_3$ | 89% (4:1 *R*:*S*) | R = $COCH_3$ |
| R = $CO_2Bn$ | 74% (6.5:1 *R*:*S*) | R = $CO_2Bn$ |
| R = COPh | 70% (>20:1 *R*:*S*) | R = COPh |

(1)

The second generation synthesis was conducted by reversing the order of the macrocyclization reactions (Figure 25). Notably, the late stage Larock annulation provided the macrocycle exclusively as a single atropisomer (>20:1), possessing the natural (*R*)-configuration. Thus, the reverse macrocyclization order increased the Larock indole

annulation atropodiastereoselectivity, and further improved on their first generation approach. Most notable, it uniquely gives the (*R*)-atropisomer in high atropodiastereoselectivity, and represents a complete reversal of the atropodiastereoselectivity observed by Hoveyda[224] and Zhu[228] with the similar macrocyclization performed using a Suzuki–Miyaura coupling.

With the total synthesis of the chloropeptins completed, Boger also achieved the first divergent total syntheses of complestatin A (**284**) and B (**285**) (neuroprotectin A and B)[229–231] (Scheme 32). Mild reaction conditions were developed for two unique indole oxidations that take advantage of the strain in 16-membered macrocycle. The reactions selectively provide either a 2-oxindole or 3-hydroxy-2-oxindole by late stage treatment of **282** with concentrated aqueous HCl in DMSO[238,239] or stoichiometric NBS or NCS in aqueous THF,[240–246] respectively.

## 9. Conclusions

A series of total syntheses of members of the vancomycin related glycopeptide antibiotics, their aglycons, and key analogues have been completed as summarized herein. Key to their success was the development or advancement of new synthetic methodology that was enlisted for the preparation of the unnatural amino acid subunits. Powerful macrocyclization methodology was developed or adopted for closure of the imbedded biaryl or diaryl ether cross-linked 12-membered, 14-membered, and 16-membered ring systems, using kinetic, thermodynamic, or ordered adjustments for introduction of the non-conventional elements of axial or planar chirality (atropisomers) found in the individual ring systems. Finally, chemical or enzymatic methods were developed for the carbohydrate introductions. Beyond the total synthesis of the natural products themselves, this has provided a foundation on which previously inaccessible but important synthetic analogues that contain deep-seated modifications may be prepared. Already such efforts have not only provided key, rationally designed analogues of vancomycin that address the underlying molecular basis of vancomycin resistance, but they have even provided further modified derivatives that display remarkable antimicrobial potencies, multiple independent mechanisms of action, and antimicrobial durabilities that extend well beyond those of the natural products.

Finally, the studies detailed herein complement those conducted on other glycopeptide antibiotic classes including ramoplanin,[247–252] the total synthesis of other classes of naturally occurring antibiotics[253,254] and reviews that chronicle the role of organic synthesis in the exploration and development of antibiotics.[255]

## Acknowledgments

The authors gratefully acknowledge the financial support of the National Institutes of Health (CA041101, DLB) and the award of a National Institutes of Health postdoctoral fellowship (F32 GM114948, NAI).

## Abbreviations

| | |
|---|---|
| **BCB** | *B*-bromocatecholborane |
| **Boc** | *tert*-butyloxycarbonyl |

| | |
|---|---|
| **Bop** | (1-benzotriazolyloxy)tris(dimethylamino) phosphonium hexafluoride |
| **BSA** | bovine serum albumin |
| **dba** | dibenzylideneacetone |
| **DEAD** | diethyl azodicarboxylate |
| **DEPBT** | (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one) |
| **Ddm** | 4,4′-dimethoxydiphenylmethyl |
| **DPPA** | diphenyl phosphorazidate |
| **dppf** | 1,1′-bis(diphenylphosphino)ferrocene |
| **DTBMP** | 2,6-di-*tert*-butyl-4-methylpyridine |
| **EDCI** | 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide |
| **FDPP** | pentafluorophenyl diphenylphosphinate |
| **HATU** | 2-(1*H*-7-azabenzotriazol)-1-yl-1,1,3,3-tetramethyluronium hexafluorophosphate |
| **HBTU** | *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate |
| **HOAt** | 1-hydroxy-7-azabenzotriazole |
| **HOBt** | 1-hydroxybenzotriazole |
| **MEM** | 2-methoxyethoxymethyl ether |
| **NIS** | *N*-iodosuccinimide |
| **NMM** | *N*-methylmorpholine |
| **NMP** | *N*-methyl-2-pyrrolidone |
| **Piv** | pivalate |
| **PMP** | *p*-methoxybenzyl |
| **PyBop** | benztriazol-1-yl-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate |
| **PyBrop** | bromo-tris(pyrrolidino)phosphonium hexafluorophosphate |
| **MRSA** | methicillin-resistant *Staphylococcus aureus* |
| **Ms** | methanesulfonyl |
| **T3P** | propylphosphonic anhydride |
| **TBS** | *tert*-butyldimethylsilyl |
| **TCEP** | tris(2-carboxyethyl)phosphine |

| | |
|---|---|
| **Teoc** | 2-trimethylsilylethoxycarbonyl |
| **Tf** | trifluoromethylsulfonyl |
| **TFA** | trifluoroacetic acid |
| **TFAA** | trifluoroacetic anhydride |
| **TFFH** | fluoro-*N,N,N′,N′*-tetramethylformamidinium hexafluorophosphate |
| **TMS** | trimethylsilyl |
| **TMSE** | 2-(trimethylsilyl)ethyl |
| **Troc** | 2,2,2-trichloroethyl carbonyl |
| **VRE** | vancomycin resistant enterococcus |
| **VRSA** | vancomycin resistant *Staphylococcus aureus* |

## References


1. Malabarba A, Nicas TI, Thompson RC. Structural modifications of glycopeptide antibiotics. Med Res Rev. 1997; 17:69–137. [PubMed: 8979249]
2. Ashford PA, Bew SP. Recent advances in the synthesis of new glycopeptide antibiotics. Chem Soc Rev. 2012; 41:957–978. [PubMed: 21829829]
3. McCormick MH, Stark WM, Pittenger GE, Pittenger RC, McGuire JM. Vancomycin, a new antibiotic. I. Chemical and biologic properties. Antibiot Annu. 1955–1956:606–611.
4. Cooper, GL., Given, DB. Vancomycin, A Comprehensive Review of 30 Years of Clinical Experience;. Park Row Publications; Indianapolis, IN: 1986. The development of vancomycin; p. 1-5.
5. Walsh CT, Fischbach MA. New ways to squash superbugs. Sci Am. 2009; 301:44–51.
6. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, et al. Antibiotic resistance – the need for global solutions. Lancet Infect Dis. 2013; 13:1057–1098. [PubMed: 24252483]
7. [accessed Nov 30 2016] National Strategy for Combating Antibiotic Resistant Bacteria. Sep. 2014 http://www.cdc.gov/drugresistance/pdf/carb_national_strategy.pdf
8. Nagarajan, R., editor. Glycopeptide Antibiotics. Marcel Dekker Inc; New York: 1994.
9. James RC, Pierce JG, Okano A, Xie J, Boger DL. Redesign of glycopeptide antibiotics: back to the future. ACS Chem Biol. 2012; 7:797–804. [PubMed: 22330049]
10. Leclercq R, Derlot E, Duval J, Courvalin P. Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. N Engl J Med. 1988; 319:157–161. [PubMed: 2968517]
11. Weigel LM, Clewell DB, Gill SR, Clark NC, McDougal LK, Flannagan SE, Kolonay JF, Shetty J, Killgore GE, Tenover FC. Genetic analysis of a high-level vancomycin-resistant isolate of *Staphylococcus aureus*. Science. 2003; 302:1569–1571. [PubMed: 14645850]
12. Howden BP, Davies JK, Johnson PD, Stinear TP, Grayson ML. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. Clin Microbiol Rev. 2010; 23:99–139. [PubMed: 20065327]
13. Walsh TR, Howe RA. The prevalence and mechanisms of vancomycin resistance in *Staphylococcus aureus*. Ann Rev Microbiol. 2002; 56:657–675. [PubMed: 12142482]
14. Perichon B, Courvalin P. VanA-type vancomycin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 2009; 53:4580–4587. [PubMed: 19506057]

15. Woodford N, Johnson AP, Morrison D, Speller DCE. Current perspectives on glycopeptide resistance. Clin Microbiol Rev. 1995; 8:585–615. [PubMed: 8665471]
16. Murray BE. Vancomycin-resistant enterococci. Am J Med. 1997; 102:284–293. [PubMed: 9217598]
17. Levy SB. The challenge of antibiotic resistance. Sci Am. 1998; 3:46–53.
18. Brown ED, Wright GD. Antibacterial drug discovery in the resistance era. Nature. 2016; 529:336–343. [PubMed: 26791724]
19. Levine D. Vancomycin: a history. Clin Infect Dis. 2006; 42:5–12.
20. Marshall FJ. Structural studies on vancomycin. J Med Chem. 1965; 8:18–22. [PubMed: 14287259]
21. Smith KA, Williams DH, Smith GA. Structure studies on the antibiotic vancomycin; the nature of the aromatic rings. J Chem Soc Perkin Trans 1. 1974:2369–2376.
22. Smith GA, Smith KA, Williams DH. Structural studies on the antibiotic vancomycin: evidence for the presence of modified phenylgylcine and β-hydroxytyrosine units. J Chem Soc Perkin Trans 1. 1975:2108–2115.
23. Williams DH, Kalman JR. Structural and mode of action studies on the antibiotic vancomycin. Evidence from 270-MHz proton magnetic resonance. J Am Chem Soc. 1977; 99:2768–2774. [PubMed: 850033]
24. Sheldrick GM, Jones PG, Kennard O, Williams DH, Smith GA. Structure of vancomycin and its complex with acetyl-D-alanyl-D-alanine. Nature. 1978; 271:223–225. [PubMed: 622161]
25. Williamson MP, Williams DH. Structure revision of the antibiotic vancomycin. Use of nuclear Overhauser effect difference spectroscopy. J Am Chem Soc. 1981; 103:6580–6585.
26. Harris CM, Harris TM. Structure of the glycopeptide antibiotic vancomycin. Evidence for an asparagine residue in the peptide. J Am Chem Soc. 1982; 104:4293–4295.
27. Harris CM, Kopecka H, Harris TM. Vancomycin: structure and transformation to CDP-1. J Am Chem Soc. 1983; 105:6915–6922.
28. Perkins HR. Vancomycin and related antibiotics. Pharmacol Ther. 1982; 16:181–197. [PubMed: 6752974]
29. Williams DH. The glycopeptide story – how to kill the dealy ‘superbugs’. Nat Prod Rep. 1996; 13:469–477. [PubMed: 8972102]
30. Williams DH, Bardsley B. The vancomycin group of antibiotics and the fight against resistant bacteria. Angew Chem, Int Ed. 1999; 38:1172–1193.
31. Nicolaou KC, Boddy CNC, Bräse S, Winssinger N. Chemistry, biology, and medicine of the glycopeptide antibiotics. Angew Chem, Int Ed. 1999; 38:2096–2152.
32. Courvalin P. Resistance of enterococci to glycopeptides. Antimicrob Agents Chemother. 1990; 34:2291–2296. [PubMed: 2088183]
33. Courvalin P. Vancomycin resistance in Gram-positive cocci. Clin Infect Dis. 2006; 42:25–34.
34. Walsh CT. Vancomycin resistance: decoding the molecular logic. Science. 1993; 261:308–309. [PubMed: 8392747]
35. Hubbard BK, Walsh CT. Vancomycin assembly: nature’s way. Angew Chem, Int Ed. 2003; 42:730–735.
36. Kahne D, Leimkuhler C, Lu W, Walsh C. Glycopeptide and lipoglycopeptide antibiotics. Chem Rev. 2005; 105:425–448. [PubMed: 15700951]
37. Binda E, Marinelli F, Marcone GL. Old and new glycopeptide antibiotics: action and resistance. Antibiotics. 2014; 3:572–594. [PubMed: 27025757]
38. Butler MS, Hansford KA, Blaskovich MAT, Halai R, Cooper MA. Glycopeptide antibiotics: back to the future. J Antibiot. 2014; 67:631–644. [PubMed: 25118105]
39. Boneca IG, Chiosis G. Vancomycin resistance: occurrence, mechanisms and strategies to combat it. Expert Opin Ther Targets. 2003; 7:311–328. [PubMed: 12783569]
40. Anderson JS, Matsuhashi M, Haskin MA, Strominger JL. Lipid-phosphoacetylmuramyl-pentapeptide and lipid-phosphodisaccharide-pentapeptide: presumed membrane transport intermediates in cell wall synthesis. Proc Natl Acad Sci US A. 1965; 53:881–889.
41. Perkins HR. Specificity of combination between mucopeptide precursors and vancomycin or ristocetin. Biochem J. 1969; 111:195–205. [PubMed: 5763787]

42. Nieto M, Perkins HR. Modifications of the acyl-D-alanyl-D-alanine terminus affecting complex-formation with vancomycin. Biochem J. 1971; 123:789–803. [PubMed: 5124386]
43. Williams DH, Williamson MP, Butcher DW, Hammond SJ. Detailed binding sites of the antibiotics vancomycin and ristocetin A: determination of intermolecular distances in antibiotic/substrate complexes by use of the time-dependent NOE. J Am Chem Soc. 1983; 105:1332–1339.
44. Schäfer M, Schneider TR, Sheldrick GM. Crystal structure of vancomycin. Structure. 1996; 4:1509–1515. [PubMed: 8994975]
45. Bugg TD, Wright GD, Dutka-Malen S, Arthur M, Courvalin P, Walsh CT. Molecular basis for vancomycin resistance in *Enterococcus faecium* BM4147: biosynthesis of a depsipeptide peptidoglycan precursor by vancomycin resistance proteins VanH and VanA. Biochemistry. 1991; 30:10408–10415. [PubMed: 1931965]
46. Marshall CG, Lessard IAD, Park IS, Wright GD. Glycopeptide antibiotic resistance genes in glycopeptide-producing organisms. Antimicrob Agents Chemother. 1998; 42:2215–2220. [PubMed: 9736537]
47. Healy VL, Lessard IA, Roper DI, Knox JR, Walsh CT. Vancomycin resistance in enterococci: reprogramming of the D-Ala-D-Ala ligases in bacterial peptidoglycan biosynthesis. Chem Biol. 2000; 7:109–119.
48. Walsh CT, Fisher SL, Park IS, Prahalad M, Wu Z. Bacterial resistance to vancomycin: five genes and one missing hydrogen bond tell the story. Chem Biol. 1996; 3:21–28. [PubMed: 8807824]
49. Evans DA, Dinsmore CJ, Ratz AM, Evrar DA, Barrow JC. Synthesis and conformational properties of the M(4–6)(5–7) bicyclic tetrapeptide common to the vancomycin antibiotics. J Am Chem Soc. 1997; 119:3417–3418.
50. Evans DA, Barrow JC, Watson PS, Ratz AM, Dinsmore CJ, Evrard DA, DeVries KM, Ellman JA, Rychovsky SD, Lacour J. Approaches to the synthesis of the vancomycin antibiotics. Synthesis of orienticin C (bis-dechlorovancomycin) aglycon. J Am Chem Soc. 1997; 119:3419–3420.
51. Tsuji N, Kobayashi M, Kamigauchi T, Yoshimura Y, Terui Y. New glycopeptide antibiotics. I. The structures of orienticins. J Antibiot. 1988; 41:819–822. [PubMed: 3403380]
52. Evans DA, Ellman JA, DeVries KM. The oxidative macrocyclization of phenolic peptides. A biomimetic approach to the synthesis of the vancomycin family of antibiotics. J Am Chem Soc. 1989; 111:8912–8914.
53. Evans DA, Dinsmore CJ, Evrard DA, DeVries KM. Oxidative coupling of arylglycine-containing peptides. A biomimetic approach to the synthesis of the macrocyclic actinoidinic-containing vancomycin subunit. J Am Chem Soc. 1993; 115:6426–6427.
54. Evans DA, Dinsmore CJ. Kinetic and thermodynamic atropdiastereoselection in the synthesis of the M(5–7) tripeptide portion of vancomycin. Tetrahedron Lett. 1993; 34:6029–6032.
55. Nishiyama S, Nakamura K, Suzuki Y, Yamamura S. Synthesis of piperazinomycin, a novel antifungal antibiotic. Tetrahedron Lett. 1986; 27:4481–4484.
56. Suzuki Y, Nishiyama S, Yamamura S. Synthetic study vancomycin: synthesis of a macrocyclic tetrapeptide as a plausible active center in vancomycin. Tetrahedron Lett. 1989; 30:6043–6046.
57. Suzuki Y, Nishiyama S, Yamamura S. Synthesis of a bicyclic hexapeptide as a plausible active center in vancomycin. Tetrahedron Lett. 1990; 31:4053–4056.
58. Nakamura K, Nishiyama S, Yamamura S. Synthetic studies on vancomycin: synthesis of seco-aglucovancomycins. Tetrahedron Lett. 1995; 36:8621–8624.
59. Evans DA, Watson PS. Synthesis of the orienticin C M(2–4) macrocycle utilizing a nucleophilic aromatic substitution strategy. Tetrahedron Lett. 1996; 37:3251–3254.
60. Boger DL, Borzilleri RM, Nukui S. Synthesis of appropriately functionalized vancomycin CD and DE ring systems. Bioorg Med Chem Lett. 1995; 5:3091–3096.
61. Evans DA, Weber AE. Synthesis of the cyclic hexapeptide echinocandin D. New approaches to the asymmetric synthesis of β-hydroxy α-amino acids. J Am Chem Soc. 1987; 109:7151–7157.
62. Evans DA, Weber AE. Asymmetric glycine enolate aldol reactions: synthesis of cyclosporin's unusual amino acid, MeBmt. J Am Chem Soc. 1986; 108:6757–6761.
63. Evans DA, Britton TC, Ellman JA, Dorow RL. The asymmetric synthesis of α-amino acids. Electrophilic azidation of chiral imide enolates, a practical approach to the synthesis of (*R*)- and (*S*)-α-azido carboxylic acids. J Am Chem Soc. 1990; 112:4011–4031.

64. Evans DA, Evrard DA, Rychnovsky SD, Fruh T, Whittingham WG, DeVries KM. A general approach to the asymmetric synthesis of vancomycin-related arylglycines by enolate azidation. Tetrahedron Lett. 1992; 33:1189–1192.

65. Cacci S, Ciattini PG, Morera E, Ortar G. Palladium-catalyzed triethylammonium formate reduction of aryl triflates. A selective method for the deoxygenation of phenols. Tetrahedron Lett. 1986; 27:5541–5544.

66. Shine HJ, Rhee ES. Heavy-atom kinetic isotope effects and mechanism of the acid-catalyzed *o*-semidine and *p*-semidine rearrangements and disproportionation of 4,4′-dichlorohydrazobenzene. J Am Chem Soc. 1986; 108:1000–1006.

67. Bois-Choussy M, Beugelmans R, Bouillon JP, Zhu J. Synthesis of a modified carboxylate-binding pocket of vancomycin. Tetrahedron Lett. 1995; 36:4781–4784.

68. Evans DA, Carter PH, Dinsmore CJ, Barrow JC, Katz JL, Kung DW. Mild nitrosation and hydrolysis of polyfunctional amides. Tetrahedron Lett. 1997; 38:4535–4538.

69. Garcia J, Gonzales J, Segura R, Vilarrasa J. Nitrosation of peptide bonds. Cleavage of nitrosated peptides by pyrrolidine and α-amino esters. Tetrahedron. 1984; 40:3121–3127.

70. Evans DA, Wood MR, Trotter BW, Richardson TI, Barrow JC, Katz JL. Total syntheses of vancomycin and eremomycin aglycons. Angew Chem, Int Ed. 1998; 37:2700–2704.

71. Evans DA, Dinsmore CJ, Watson PS, Wood MR, Richardson TI, Trotter BW, Katz JL. Nonconventional stereochemical issues in the design of the synthesis of the vancomycin antibiotics: challenges imposed by axial and nonplanar chiral elements in the heptapeptide aglycons. Angew Chem, Int Ed. 1998; 37:2704–2708.

72. Boger DL, Borzilleri RM, Nukui S, Beresis RT. Synthesis of the vancomycin CD and DE ring systems. J Org Chem. 1997; 62:4721–4736.

73. Boger DL, Yohannes D. Total synthesis of deoxybouvardin and RA-VII: macrocyclization via an intramolecular Ullman reaction. J Am Chem Soc. 1991; 113:1427–1429.

74. Boger DL, Yohannes D. Total synthesis of L,L-isodityrosine and isodityrosine-derived agents: K-13, OF4949-III, and OF4949-IV. J Org Chem. 1999; 55:6000–6017.

75. Felix AM, Heimer EP, Lambros TJ, Tzougraki C, Meienhofer J. Rapid removal of protecting groups from peptides by catalytic transfer hydrogenation with 1,4-cyclohexadiene. J Org Chem. 1978; 43:4194–4196.

76. Nicolaou KC, Natarajan S, Li H, Jain NF, Hughes R, Solomon ME, Ramanjulu JM, Boddy CNC, Takayanagi M. Total synthesis of vancomycin aglycon—part 1: synthesis of amino acids 4–7 and construction of the AB–COD ring skeleton. Angew Chem, Int Ed. 1998; 37:2708–2714.

77. Nicolaou KC, Jain NF, Natarajan S, Hughes R, Solomon ME, Li H, Ramanjulu JM, Takayanagi M, Koumbis AE, Bando T. Total synthesis of vancomycin aglycon—part 2: synthesis of amino acids 1–3 and construction of the AB–COD–DOE ring skeleton. Angew Chem, Int Ed. 1998; 37:2714–2716.

78. Nicolaou KC, Takayanagi M, Jain NF, Natarajan S, Koumbis AE, Bando T, Ramanjulu JM. Total synthesis of vancomycin aglycon—part 3: final stages. Angew Chem, Int Ed. 1998; 37:2717–2719.

79. Nicolaou KC, Boddy CNC, Natarajan S, Yue TY, Li H, Bräse JM, Ramanjulu JM. New synthetic technology for the synthesis of aryl ethers: construction of C–O–D and D–O–E ring model systems of vancomycin. J Am Chem Soc. 1997; 119:3421–3422.

80. Kolb HC, Van Nieuwenhze MS, Sharpless KB. Catalytic asymmetric dihydroxylation. Chem Rev. 1994; 94:2483–2547.

81. Tao B, Schlingloff G, Sharpless KB. Reversal of regioselection in the asymmetric aminohydroxylation of cinnamates. Tetrahedron Lett. 1998; 39:2507.

82. Nicolaou KC, Li H, Boddy CNC, Ramanjulu JM, Yue TY, Natarajan S, Chu XJ, Bräse S, Rübsam F. Total synthesis of vancomycin—part 1: design and development of methodology. Chem Eur J. 1999; 5:2584–2601.

83. Nicolaou KC, Boddy CNC, Li H, Koumbis AE, Hughes R, Natarajan S, Jain NF, Ramanjulu JM, Bräse S, Solomon ME. Total synthesis of vancomycin—part 2: retrosynthetic analysis, synthesis of amino acid building blocks and strategy evaluations. Chem Eur J. 1999; 5:2602–2621.

84. Nicolaou KC, Koumbis AE, Takayanagi M, Natarajan S, Jain NF, Bando T, Li H, Hughes R. Total synthesis of vancomycin—part 3: synthesis of the aglycon. Chem Eur J. 1999; 5:2622–2647.

85. Nicolaou KC, Ramanjulu JM, Natarajan S, Bräse S, Li H, Boddy CNC, Rübsam F. A Suzuki coupling–macrolactamization approach to the AB–COD bicyclic system of vancomycin. Chem Commun. 1997:1899–1900.

86. Chen S, Xu J. Pentafluorophenyl diphenylphosphinate a new efficient coupling reagent in peptide chemistry. Tetrahedron Lett. 1991; 32:6711–6714.

87. Boger DL, Miyazaki S, Kim SH, Wu JH, Loiseleur O, Castle SL. Diastereoselective total synthesis of the vancomycin aglycon with ordered atropisomer equilibrations. J Am Chem Soc. 1999; 121:3226–3227.

88. Dess DB, Martin JC. A useful 12-I-5 triacetoxyperiodinane (the Dess–Martin periodinane) for the selective oxidation of primary or secondary alcohols and a variety of related 12-I-5 species. J Am Chem Soc. 1991; 113:7277–7287.

89. Abiko A, Roberts JC, Takemasa T, Masamune TS. $KMnO_4$ revisited: oxidation of aldehydes to carboxylic acids in the *tert*-butyl alcohol–aqueous $NaH_2PO_4$ system. Tetrahedron Lett. 1986; 27:4537–4540.

90. Boger DL, Miyazaki S, Kim SH, Wu JH, Castle SL, Loiseleur O, Jin Q. Total synthesis of the vancomycin aglycon. J Am Chem Soc. 1999; 121:10004–10011.

91. Boger DL, Nomoto Y, Teegarden BR. Vancomycin and ristocetin models: synthesis via the Ullmann macrocyclization reaction. J Org Chem. 1993; 58:1425–1433.

92. Boger DL, Borzilleri RM. An unusually facile $S_NAr$ 14-membered biaryl ether macrocyclization reaction suitable for preparation of the cycloisodityrosine subunit of bouvardin, deoxybouvardin and related agents. Bioorg Med Chem Lett. 1995; 5:1187–1190.

93. Boger DL, Zhou J, Borzilleri RM, Nukui S. Synthesis of (9*S*,12*S*)-cycloisodityrosine and its unnatural (9*R*,12*S*)-diastereomer. Bioorg Med Chem Lett. 1996; 6:1089–1092.

94. Boger DL, Zhou J, Borzilleri RM, Nukui S, Castle SL. Synthesis of (9*R*,12*S*)- and (9*S*,12*S*)-cycloisodityrosine and their *N*-methyl derivatives. J Org Chem. 1997; 62:2054–2069. [PubMed: 11671510]

95. Boger DL, Castle SL, Miyazaki S, Wu JH, Beresis RT, Loiseleur O. Vancomycin CD and DE macrocyclization and atropisomerism studies. J Org Chem. 1999; 64:70–80. [PubMed: 11674087]

96. Boger DL, Loiseleur O, Castle SL, Beresis RT, Wu JH. Thermal atropismerism of fully functionalized vancomycin CD, DE, and CDE ring systems. Bioorg Med Chem Lett. 1997; 7:3199–3202.

97. Boger DL, Beresis RT, Loiseleur O, Wu JH, Castle SL. Synthesis of the vancomycin CDE ring system. Bioorg Med Chem Lett. 1998; 8:721–724. [PubMed: 9871529]

98. Boger DL, Miyazaki S, Loiseleur O, Beresis RT, Castle SL, Wu JH, Jin Q. Thermal atropisomerism of aglucovancomycin derivatives: preparation of (*M*,*M*,*M*)- and (*P*,*M*,*M*)-aglucovancomycins. J Am Chem Soc. 1998; 120:8920–8926.

99. Boger DL, Borzilleri RM, Nukui S. Synthesis of (*R*)-(4-methoxy-3,5-dihydroxyphenyl)glycine derivatives: the central amino acid of vancomycin and related agents. J Org Chem. 1996; 61:3561–3565.

100. Crowley BM, Mori Y, McComas CC, Tang D, Boger DL. Total synthesis of the ristocetin aglycon. J Am Chem Soc. 2004; 126:4310–4317. [PubMed: 15053621]

101. Hartwig JF, Paul F. Oxidative addition of aryl bromide after dissociation of phosphine from a two-coordinate palladium(0) complex, bis(tri-*o*-tolylphosphine)palladium(0). J Am Chem Soc. 1995; 117:5373–5374.

102. Ge M, Thompson C, Kahne D. Reconstruction of vancomycin by chemical glycosylation of the pseudoaglycon. J Am Chem Soc. 1998; 120:11014–11015.

103. Thompson C, Ge M, Kahne D. Synthesis of vancomycin from the aglycon. J Am Chem Soc. 1999; 121:1237–1244.

104. Leimkuhler C, Chen Z, Kruger RG, Oberthur M, Lu W, Walsh CT, Kahne D. Glycosylation of glycopeptides: a comparison of chemoenzymatic and chemical methods. Tetrahedron: Asymmetry. 2005; 16:599–603.

105. Ritter TK, Mong KKT, Liu T, Nakatani T, Wong CH. A programmable one-pot oligosaccharide synthesis for diversifying the sugar domains of natural products: a case study of vancomycin. Angew Chem, Int Ed. 2003; 42:4657.

106. Nicolaou KC, Mitchell HJ, Jain NF, Winssinger N, Hughes R, Bando T. Total synthesis of vancomycin. Angew Chem, Int Ed. 1999; 38:240–244.

107. Nicolaou KC, Mitchell HJ, Jain NF, Bando T, Hughes R, Winssinger N, Natarajan S, Koumbis AE. Total synthesis of vancomycin–part 4: attachment of the sugar moieties and completion of the synthesis. Chem Eur J. 1999; 5:2648–2667.

108. Losey HC, Peczuh MW, Chen Z, Eggert US, Dong SD, Pelczer I, Kahne D, Walsh CT. Tandem action of glycosyltransferases in the maturation of vancomycin and teicoplanin aglycones: novel glycopeptides. Biochemistry. 2001; 40:4745–4755. [PubMed: 11294642]

109. Losey HC, Jiang J, Biggins JB, Oberthur M, Ye X, Dong SD, Kahne D, Thorson JS, Walsh CT. Incorporation of glucose analogs by GtfE and GtfD from the vancomycin biosynthetic pathway to generate variant glycopeptides. Chem Biol. 2002; 9:1305–1309. [PubMed: 12498883]

110. Oberthur M, Leimkuhler C, Kruger RG, Lu W, Walsh CT, Kahne D. A systematic investigation of the synthetic utility of glycopeptide glycosyltransferases. J Am Chem Soc. 2005; 127:10747–10752. [PubMed: 16045364]

111. Thayer DA, Wong CH. Vancomycin analogues containing monosaccharides exhibit improved antibiotic activity: a combined one-pot enzymatic glycosylation and chemical diversification strategy. Chem Asian J. 2006; 1:445–452. [PubMed: 17441081]

112. Thayer DA, Yu HN, Galan MC, Wong CH. A general strategy toward *S*-linked glycopeptides. Angew Chem Int Ed. 2005; 44:4596–4599.

113. Solenberg PJ, Matsushima P, Stack DR, Wilkie SC, Thompson RC, Baltz RH. Production of hybrid glycopeptide antibiotics *in vitro* and in *Streptomyces toyocaensis*. Chem Biol. 1997; 4:195–202. [PubMed: 9115410]

114. Fu X, Albermann C, Zhang CS, Thorson JS. Diversifying vancomycin via chemoenzymatic strategies. Org Lett. 2005; 7:1513–1515. [PubMed: 15816740]

115. Fu X, Albermann C, Jiang JQ, Liao JC, Zhang CS, Thorson JS. Antibiotic optimization via *in vitro* glycorandomization. Nat Biotechnol. 2003; 21:1467–1469. [PubMed: 14608364]

116. Toshima K, Tatsuta K. Recent progress in *O*-glycosylation methods and its application to natural products synthesis. Chem Rev. 1993; 93:1503–1531.

117. Kim SH, Augeri D, Yang D, Kahne D. Concise synthesis of the calicheamicin oligosaccharide using the sulfoxide glycosylation method. J Am Chem Soc. 1994; 116:1766–1775.

118. Raghavan S, Kahne D. A one-step synthesis of the ciclamycin trisaccharide. J Am Chem Soc. 1993; 115:1580–1581.

119. Gildersleeve J, Pascal RA, Kahne D. Sulfenate intermediates in the sulfoxide glycosylation reaction. J Am Chem Soc. 1998; 120:5961–5969.

120. Brown HC, Kanner B. 2,6-Di-butylpyridine–an unusual pyridine base. J Am Chem Soc. 1953; 75:3865.

121. Wang W, Kong F. New synthetic methodology for regio- and stereoselective synthesis of oligosaccharides via sugar ortho ester intermediates. J Org Chem. 1998; 63:5744–5745. [PubMed: 11672169]

122. Kusumoto S, Sakai K, Shiba T. 4-Azidobutyryl group for temporary protection of hydroxyl functions. Bull Chem Soc Jpn. 1986; 59:1296–1298.

123. Schmittling EA, Sawyer JS. Selective desilylation of *tert*-butyldimethylsilyl ethers of phenols using potassium fluoride–alumina and ultrasound. Tetrahedron Lett. 1991; 32:7207–7210.

124. Mukaiyama T, Murai Y, Shoda S. An efficient method for glucosylation of hydroxy compounds using glucopyranosyl fluoride. Chem Lett. 1981:431–432.

125. Nicolaou KC, Chucholowski A, Dolle RE, Randall JL. Reactions of glycosyl fluorides. Synthesis of *O*-, *S*-, and *N*-glycosides. J Chem Soc Chem Commun. 1984:1155–1156.

126. Guibe F, Saint M'leux Y. The allyloxycarbonyl group for alcohol protection: quantitative removal or transformation into allyl protecting group via π-allyl complexes of palladium. Tetrahedron Lett. 1981; 22:3591–3594.

127. Dong SD, Oberthur M, Losey HC, Anderson JW, Eggert US, Peczuh MW, Walsh CT, Kahne D. The structural basis for induction of VanB resistance. J Am Chem Soc. 2002; 124:9064–9065. [PubMed: 12149006]

128. Nakayama A, Okano A, Feng Y, Collins JC, Collins KC, Walsh CT, Boger DL. Enzymatic glycosylation of vancomycin aglycon: completion of a total synthesis of vancomycin and N- and C-terminus substituent effects of the aglycon substrate. Org Lett. 2014; 16:3572–3575. [PubMed: 24954524]
129. Oberthur M, Leimkuhler C, Kahne D. A practical method for the stereoselective generation of β-2-deoxyglycosyl phosphates. Org Lett. 2004; 6:2873–2876. [PubMed: 15330636]
130. Bardone MR, Paternoster M, Coronelli C. Teichomycins, new antibiotics from *Actinoplanes teichomyceticus* nov. sp. II. Extraction and chemical characterization. J Antibiot. 1978; 31:170–177. [PubMed: 649512]
131. Parenti F, Beretta G, Berti M, Arioli V. Teichomycins, new antibiotics from *Actinoplanes teichomyceticus* Nov. Sp. I. Description of the producer strain, fermentation studies and biological properties. J Antibiot. 1978; 31:276–283. [PubMed: 659325]
132. Hunt AH, Molloy RM, Occolowitz JL, Marconi GG, Debono M. Structure of the major glycopeptide of the teicoplanin complex. J Am Chem Soc. 1984; 106:4891–4895.
133. Barna JCJ, Williams DH, Stone DJM, Leung TWC, Doddrell DM. Structure elucidation of the teicoplanin antibiotics. J Am Chem Soc. 1984; 106:4895–4902.
134. Wiedemann, B., Grimm, H. Antibiotics in Laboratory Medicine. Lorian, V., editor. Williams and Wilkins; Baltimore: 1996. p. 900-1168.
135. De Lalla F, Tramarin A. A risk-benefit assessment of teicoplanin in the treatment of infections. Drug Saf. 1995; 13:317–328. [PubMed: 8785019]
136. Greenwood D. Microbiological properties of teicoplanin. J Antimicrob Chemother. 1988; 21(Suppl A):1–13.
137. Cavalcanti AB, Goncalves AR, Almeida CS, Bugano DD, Silva E. Teicoplanin versus vancomycin for proven or suspected infection. Cochrane Database Syst Rev. 2010:1–53.
138. Brogden RN, Peters DH. Teicoplanin. A reappraisal of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. Drugs. 1994; 47:823–854. [PubMed: 7520860]
139. Pea F, Brollo L, Viale P, Pavan F, Furlanut M. Teicoplanin therapeutic drug monitoring in critically ill patients: a retrospective study emphasizing the importance of a loading dose. J Antimicrob Chemother. 2003; 51:971–975. [PubMed: 12654757]
140. Jovetic S, Zhu Y, Marcone GL, Marinelli F, Tramper J. β-Lactam and glycopeptide antibiotics: first and last line of defense? Trends Biotechnol. 2010; 28:596–604. [PubMed: 20970210]
141. Rossolini, GM., Arena, F., Pollini, S. Novel infectious diseases and emerging Gram-positive multiresistant pathogens in hospital and community acquired infections. In: Marinelli, F., Genilloud, O., editors. Antimicrobials. Springer Verlag; Berlin Heidelberg, Germany: 2014.
142. Drugs.com website. [accessed Nov 15 2016] Targocid. http://www.drugs.com/international/targocid.html
143. Boger DL, Kim SH, Miyazaki S, Strittmatter H, Weng JH, Mori Y, Rogel O, Castle SL, McAtee JJ. Total Synthesis of the teicoplanin aglycon. J Am Chem Soc. 2000; 122:7416–7417.
144. Boger DL, Kim SH, Mori Y, Weng JH, Rogel O, Castle SL, McAtee JJ. First and second generation total synthesis of the teicoplanin aglycon. J Am Chem Soc. 2001; 123:1862–1871. [PubMed: 11456806]
145. Bois-Choussy M, Neuville L, Beugelmans R, Zhu J. Synthesis of modified carboxyl binding pockets of vancomycin and teicoplanin. J Org Chem. 1996; 61:9309–9322.
146. Reddy KL, Sharpless KB. From styrenes to enantiopure α-arylglycines in two steps. J Am Chem Soc. 1998; 120:1207–1217.
147. Barna JCJ, Williams DH, Strazzolini P, Malabarba A, Leung TWC. Structure and conformation of epimers derived from the antibiotic teicoplanin. J Antibiot. 1984; 37:1204–1208. [PubMed: 6238926]
148. Li H, Jiang X, Ye YH, Fan C, Romoff T, Goodman M. 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT): a new coupling reagent with remarkable resistance to racemization. Org Lett. 1999; 1:91–94. [PubMed: 10822541]
149. Mori Y, McAtee JJ, Rogel O, Boger DL. Alternative synthesis and thermal atropisomerism of a fully functionalized DEFG ring system of teicoplanin. Tetrahedron Lett. 2001; 42:6061–6064.

150. Boger DL, Weng JH, Miyazaki S, McAtee JJ, Castle SL, Kim SH, Mori Y, Rogel O, Strittmatter H, Jin Q. Thermal atropisomerism of teicoplanin aglycon derivatives: preparation of the *P,P,P* and *M,P,P* atropisomers of the teicoplanin aglycon via selective equilibration of the DE ring system. J Am Chem Soc. 2001; 122:10047–10055.

151. Evans DA, Katz JL, Peterson GS, Hintermann T. Total synthesis of teicoplanin aglycon. J Am Chem Soc. 2001; 123:12411–12413. [PubMed: 11734044]

152. Evans DA, Kart JL, West TR. Synthesis of diaryl ethers through the copper-promoted arylation of phenols with arylboronic acids. An expedient synthesis of thyroxine. Tetrahedron Lett. 1998; 39:2937–2340.

153. Chan AMT, Monaco KL, Wang RP, Winters MP. New N-and O-arylations with phenylboronic acids and copper acetate. Tetrahedron Lett. 1998; 39:2933–2936.

154. Evans DA, Campos KR, Tedrow JS, Michael FE, Gagné MR. Application of chiral mixed phosphorus/sulfur ligands to palladium-catalyzed allylic substitutions. J Am Chem Soc. 2000; 122:7905–7920.

155. Burk MJ, Allen JG. A mild amide to carbamate transformation. J Org Chem. 1997; 62:7054–7057.

156. Philip JE, Schenck JR, Hargie MP. Ristocetins A and B, two new antibiotics; isolation and properties. Antibiot Annu. 1956–1957:699–705.

157. Dries CP, Koch R. Ristocetin, a laboratory and clinical evaluation in children. J Pediatr. 1960; 56:498–504. [PubMed: 13818118]

158. Herting RL, Lees B, Zimmerman AJ, Berryman GH. Ristocetin; a statistical review of three hundred thirty-three cases. J Am Med Assoc. 1959; 170:176–178. [PubMed: 13640996]

159. Jawetz E. Polymyxins, colistin, bacitracin, ristocetin and vancomycin. Pediatr Clin North Am. 1968; 15:85–94. [PubMed: 4295552]

160. Howard MA, Firkin BG. Ristocetin–a new tool in the investigation of platelet aggregation. Thromb Diath Haemorrh. 1971; 26:362–369. [PubMed: 5316292]

161. Jenkins CSP, Meyer D, Dreyfus MD, Larreu MJ. Willebrand factor and ristocetin I. Mechanism of ristocetin-induced platelet aggregation. Brit J Haematol. 1974; 28:561–578. [PubMed: 4141901]

162. Macfarlane DE, Stibbe J, Kirby EP, Zucker MB, Grant RA, McPherson J. Letter: A method for assaying von Willebrand factor (ristocetin cofactor). Thromb Diath Haemorrh. 1975; 34:306–308. [PubMed: 1081281]

163. Weiss HJ, Rogers J, Brand H. Defective ristocetin-induced platelet aggregation in von Willebrand's disease and its correction by Factor VIII. J Clin Invest. 1973; 52:2697–2707. [PubMed: 4201262]

164. Othman M, Kaur H, Emsley J. Platelet-type von Willebrand disease: new insights into the molecular pathophysiology of a unique platelet defect. Semin Thromb Hemost. 2013; 39:663–673. [PubMed: 23934752]

165. Kuwahara S, Chambers WT. Destruction of the platelet aggregating activity of ristocetin A. Experientia. 1978; 34:532–534. [PubMed: 565300]

166. Harris CM, Harris TM. Structure of ristocetin A: configurational studies of the peptide. J Am Chem Soc. 1982; 104:363–365.

167. Nahoum V, Spector S, Loll PJ. Structure of ristocetin A in complex with a bacterial cell-wall mimetic. Acta Crystallogr Sect D: Biol Crystallogr. 2009; 65:832–838. [PubMed: 19622867]

168. Nahoum V, Spector S, Loll PJ. Structure of ristocetin A in complex with a bacterial cell-wall mimetic. Corrigendum. Acta Crystallogr D Biol Crystallogr. 2011; 67:832–838.

169. Mackay JP, Gerhard U, Beauregard DA, Westwell MS, Searle MS, Williams DH. Glycopeptide antibiotic activity and the possible role of dimerization: a model for biological signaling. J Am Chem Soc. 1994; 116:4581–4590.

170. Solladié-Cavallo A, Nsenda T. A four-step synthesis of erythro-*m*-chloro-3-hydroxy tyrosine ethyl ester enantiomerically pure. Tetrahedron Lett. 1998; 39:2191–2194.

171. Schöllkopf U, Nozulak J, Grauert M. Asymmetric synthesis via heterocyclic intermediates; XXIV1. Asymmetric synthesis of enantiomerically and diastereomerically pure D-threonine by the bis-lactim ether method. Synthesis. 1985:55–56.

172. McComas CC, Crowley BM, Boger DL. Partitioning the loss in vancomycin binding affinity for D-Ala-D-Lac into lost H-bond and repulsive lone pair contributions. J Am Chem Soc. 2003; 125:9314–9315. [PubMed: 12889959]
173. Crowley BM, Boger DL. Total synthesis and evaluation of [Φ[$CH_2$NH]$Tpg^4$]vancomycin aglycon: reengineering vancomycin for dual D-Ala-D-Ala and D-Ala-D-Lac binding. J Am Chem Soc. 2006; 128:2885–2892. [PubMed: 16506767]
174. Xie J, Pierce JG, James RC, Okano A, Boger DL. A redesigned vancomycin engineered for dual D-Ala-D-Ala and D-Ala-D-Ala binding exhibits potent antimicrobial activity against vancomycin-resistant bacteria. J Am Chem Soc. 2011; 133:13946–13949. [PubMed: 21823662]
175. Xie J, Okano A, Pierce JG, James RC, Stamm S, Crane CM, Boger DL. Total synthesis of [Φ[C(=S)NH]$Tpg^4$]vancomycin aglycon, [Φ[C(=NH)NH]$Tpg^4$]vancomycin aglycon, and related key compounds: reengineering vancomycin for dual D-Ala-D-Ala and D-Ala-D-Lac binding. J Am Chem Soc. 2012; 134:1284–1297. [PubMed: 22188323]
176. Kamenecka TM, Park YJ, Lin LS, Laszlo S, McCauley ED, Riper GV, Egger L, Kidambi U, Mumford RA, Sharon Tong S, et al. Amidines as amide bond replacements in VLA-4 antagonists. Bioorg Med Chem Lett. 2004; 14:2323–2330. [PubMed: 15081033]
177. Inokuchi E, Oishi S, Kubo T, Ohno H, Shimura K, Matsuoka M, Fujii N. Potent CXCR4 antagonists containing amidine type peptide bond isosteres. ACS Med Chem Lett. 2011; 2:477–480. [PubMed: 24900333]
178. Inokuchi E, Yamada A, Hozumi K, Tomita K, Oishi S, Ohno H, Nomizu M, Fujii N. Design and synthesis of amidine-type peptide bond isosteres: application of nitrile oxide derivatives as active ester equivalents in peptide and peptidomimetics synthesis. Org Biomol Chem. 2011; 9:3421–3427. [PubMed: 21423919]
179. Molcanov K, Kojic-Prodic B, Raos N. Analysis of the less common hydrogen bonds involving ester oxygen $sp^3$ atoms as acceptors in the crystal structures of small organic molecules. Acta Crystallogr. 2004; B60:424–432.
180. Okano A, James RC, Pierce J, Xie J, Boger DL. Silver(I)-promoted conversion of thioamides to amidines: divergent synthesis of a key series of vancomycin aglycon residue 4 amidines that clarify binding behavior to model ligands. J Am Chem Soc. 2012; 134:8790–8793. [PubMed: 22568755]
181. Coleman RS, Shah JA. Chemoselective cleavage of benzyl ethers, esters, and carbamates in the presence of other easily reducible groups. Synthesis. 1999:1399–1400.
182. Sakaitani M, Ohfune Y. Syntheses and reactions of silyl carbamates. 1. Chemoselective transformation of amino protecting groups via tert-butyldimethylsilyl carbamates. J Org Chem. 1990; 55:870–876.
183. Corey EJ, Schmidt G. Useful procedures for the oxidation of alcohols involving pyridinium dichromate in aprotic media. Tetrahedron Lett. 1979; 20:399–402.
184. Corey EJ, Suggs JW. Pyridinium chlorochromate. An efficient reagent for oxidation of primary and secondary alcohols to carbonyl compounds. Tetrahedron Lett. 1975; 16:2647–2650.
185. Corey EJ, Boger DL. Oxidative cationic cyclization reactions effected by pyridinium chlorochromate. Tetrahedron Lett. 1978; 19:2461–2464.
186. Bowden K, Heilbron IM, Jones ERH, Weedon BC. Researches on acetylenic compounds. Part I. The preparation of acetylenic ketones by oxidation of acetylenic carbinols and glycols. J Chem Soc. 1946:39–45.
187. Bowers A, Halsall TG, Jones ERH, Lemin AJ. The chemistry of the triterpenes and related compounds. Part XVIII. Elucidation of the structure of polyporenic acid C. J Chem Soc. 1953:2548–2560.
188. Moorthy JN, Singhal N. Facile and highly selective conversion of nitriles to amides via indirect acid-catalyzed hydration using TFA or AcOH–$H_2SO_4$. J Org Chem. 2005; 70:1926–1929. [PubMed: 15730325]
189. Okano A, Nakayama A, Schammel AW, Boger DL. Total synthesis of [Φ[C(=NH)NH]$Tpg^4$]vancomycin and its (4-chlorobiphenyl)methyl derivative: impact of peripheral modifications on vancomycin analogues redesigned for dual D-Ala-D-Ala and D-Ala-D-Lac binding. J Am Chem Soc. 2014; 136:13522–13525. [PubMed: 25211770]

190. Nicas TI, Mullen DL, Flokowitsch JE, Preston DA, Snyder NJ, Zweifel MJ, Wilkie SC, Rodriguez MJ, Thompson RC, Cooper RD. Semisynthetic glycopeptide antibiotics derived from LY264826 active against vancomycin-resistant enterococci. Antimicrob Agents Chemother. 1996; 40:2194–2199. [PubMed: 8878606]
191. Cooper RDG, Snyder NJ, Zweifel MJ, Staszak MA, Wilkie SC, Nicas TI, Mullen DL, Butler TF, Rodriguez MJ, Huff BE, Thompson RC. Reductive alkylation of glycopeptide antibiotics: synthesis and antibacterial activity. J Antibiot. 1996; 49:575–581. [PubMed: 8698642]
192. Nagarajan R, Schabel AA, Occolowitz JL, Counter FT, Ott JL, Felty–Duckworth AM. Synthesis and antibacterial evaluation of *N*-alkyl vancomycins. J Antibiot. 1989; 42:63–72. [PubMed: 2921228]
193. Markham A. Oritavancin: first global approval. Drugs. 2014; 74:1823–1828. [PubMed: 25239268]
194. Candiani G, Abbondi M, Borgonovi M, Romano G, Parenti F. *In vitro* and *in vivo* antibacterial activity of BI 397, a new semi-synthetic glycopeptide antibiotic. J Antimicrob Chemother. 1999; 44:179–192. [PubMed: 10473224]
195. Anderson VR, Keating GM. Dalbavancin. Drugs. 2008; 68:639–648. [PubMed: 18370443]
196. Judice JK, Pace JL. Semi-synthetic glycopeptide antibacterials. Bioorg Med Chem Lett. 2003; 13:4165–4168. [PubMed: 14622994]
197. Leadbetter MR, Adams SM, Bazzini B, Fatheree PR, Karr DE, Krause KM, Lam BMT, Linsell MS, Nodwell MB, Pace JL, et al. Hydrophobic vancomycin derivatives with improved ADME properties: discovery of telavancin (TD-6424). J Antibiot. 2004; 57:326–336. [PubMed: 15303493]
198. Corey GR, Stryjewski ME, Weyenberg W, Yasothan U, Kirkpatrick P. Telavancin. Nat Rev Drug Discovery. 2009; 8:929–930. [PubMed: 19949399]
199. Allen NE, Hobbs JN Jr, Nicas TI. Inhibition of peptidoglycan biosynthesis in vancomycin-susceptible and -resistant bacteria by a semisynthetic glycopeptide antibiotic. Antimicrob Agents Chemother. 1996; 40:2356–2362. [PubMed: 8891144]
200. Ge M, Chen Z, Onishi HR, Kohler J, Silver LL, Kerns R, Fukuzawa S, Thompson C, Kahne D. Vancomycin derivatives that inhibit peptidoglycan biosynthesis without binding D-Ala-D-Ala. Science. 1999; 284:507–511. [PubMed: 10205063]
201. Chen L, Walker D, Sun B, Hu Y, Walker S, Kahne D. Vancomycin analogues active against VanA-resistant strains inhibit bacterial transglycosylase without binding substrate. Proc Natl Acad Sci US A. 2003; 100:5658–5663.
202. Goldman RC, Baizman ER, Longley CB, Branstrom AA. Chlorobiphenyl-desleucyl-vancomycin inhibits the transglycosylation process required for peptidoglycan synthesis in bacteria in the absence of dipeptide binding. FEMS Microbiol Lett. 2000; 183:209–214. [PubMed: 10675585]
203. Allen NE, Nicas TI. Mechanism of action of oritavancin and related glycopeptide antibiotics. FEMS Microbiol Rev. 2003; 26:511–532. [PubMed: 12586393]
204. Okano A, Nakayama A, Wu K, Lindsey EA, Schammel AW, Feng Y, Collins KC, Boger DL. Total synthesis and initial examination of [Φ[C(=S)NH]Tpg$^4$]vancomycin, [Φ[C(=NH)NH]Tpg$^4$]vancomycin, [Φ[$CH_2$NH]Tpg$^4$]vancomycin and their (4-chlorobiphenyl)methyl derivatives: synergistic binding pocket and peripheral modifications for the glycopeptide antibiotics. J Am Chem Soc. 2015; 137:3693–3704. [PubMed: 25750995]
205. Chen Z, Eggert US, Dong SD, Shaw SJ, Sun B, LaTour JV, Kahne D. Structural requirements for VanA activity of vancomycin analogues. Tetrahedron. 2002; 58:6585–6594.
206. Kerns R, Dong SD, Fukuzawa S, Carbeck J, Kohler J, Silver L, Kahne D. The role of hydrophobic substituents in the biological activity of glycopeptide antibiotics. J Am Chem Soc. 2000; 122:12608–12609.
207. Okano A, Isley NA, Boger DL. Durable antibiotics by design: installation of peripheral modifications and additional mechanisms of action on pocket redesigned vancomycin analogs synergistically improves both antimicrobial potency and durability. J Am Chem Soc. 2016 submitted.

208. Jennings MC, Minbiole KPC, Wuest WM. Quaternary ammonium compounds: an antimicrobial mainstay and platform for innovation to address bacterial resistance. ACS Infect Dis. 2015; 1:288–303. [PubMed: 27622819]

209. Mitchell MM, Iannetta AA, Jennings MC, Fletcher MH, Wuest WM, Minbiole KPC. Scaffold-hopping of multicationic amphiphiles yields three new classes of antimicrobials. ChemBioChem. 2015; 16:2299–2303. [PubMed: 26316312]

210. Zasloff M. Antimicrobial peptide of multicellular organisms. Nature. 2002; 415:389–395. [PubMed: 11807545]

211. Yarlagadda V, Akkapeddi P, Manjunath GB, Haldar J. Membrane active vancomycin analogues: a strategy to combat bacterial resistance. J Med Chem. 2014; 57:4558–4568. [PubMed: 24846441]

212. Yarlagadda V, Samaddar S, Paramanandham K, Shome BR, Haldar J. Membrane disruption and enhanced inhibition of cell wall biosynthesis: a synergistic approach to tackle vancomycin-resistant bacteria. Angew Chem, Int Ed. 2015; 54:13644–13649.

213. Kaneko I, Fearon DT, Austen KF. Inhibition of the alternative pathway of human complement *in vitro* by a natural mirobial product, complestatin. J Immunol. 1980; 124:1194–1198. [PubMed: 6898640]

214. Tachikawa K, Hasumi K, Endo A. Enhancement of plasminogen binding to U937 cells and fibrin by complestatin. Thromb Haemost. 1997; 77:137–142. [PubMed: 9031464]

215. Tachikawa K, Hasumi K, Endo A. Enhancement of plasminogen binding and fibrinolysis by chloropeptin. Thrombosis Res. 1997; 87:571–576.

216. Kaneko I, Kamoshida K, Takahashi S. Complestatin, a potent anti-complement substance produced by *Streptomyces lavendulae*. J Antibiot. 1989; 42:236–241. [PubMed: 2925515]

217. Seto H, Fujioka T, Furihata K, Kaneko I, Takahashi S. Structure of complestatin, a very strong inhibitor of protease activity of complement in the human complement system. Tetrahedron Lett. 1989; 30:4987–4990.

218. Matsuzaki K, Ikeda H, Ogino T, Matsumoto A, Woodruff HB, Tanaka H, Omura S. Loropeptins I and II, novel inhibitors against gp120-CD4 binding from *Streptomyces* sp. J Antibiot. 1994; 47:1173–1174. [PubMed: 7961171]

219. Tanaka H, Matsuzaki K, Nakashima H, Ogino T, Matsumoto A, Ikeda H, Woodruff HB, Omura S. Chloropeptins, new anti-HIV antibiotics inhibiting gp120-CD4 binding from *Streptomyces* sp. I. Taxonomy, fermentation, isolation, and physico-chemical properties and biological activities. J Antibiot. 1997; 50:58–65. [PubMed: 9066767]

220. Matsuzaki K, Ogino T, Sunazuka T, Tanaka H, Omura S. Chloropeptins, a new anti-HIV antibiotics inhibiting gp120-CD4 binding from *Streptomyces* sp. II. Structure elucidation of chloropeptin I. J Antibiot. 1997; 50:66–69. [PubMed: 9066768]

221. Gouda H, Matsuzaki K, Tanaka H, Hirono S, Omura S, McCauley JA, Sprengeler PA, Furst GT, Smith AB. Stereostructure of (–)-chloropeptin I, a novel inhibitor of gp120-CD4 binding, via high temperature molecular dynamics, monte carlo conformational searching, and NMR spectroscopy. J Am Chem Soc. 1996; 118:13087–13088.

222. Singh SB, Jayasuriya H, Salituro GM, Zink DL, Shafiee A, Heimbuch B, Silverman KC, Lingham RB, Genilloud O, Teran A, Vilella D, Felock P, Hazuda D. The complestatins as HIV-1 integrase inhibitors. Efficient isolation, structure elucidation, and inhibitory activities of isocomplestatin, chloropeptin I, new complestatins, A and B, and acid-hydrolysis products of chloropeptin I. J Nat Prod. 2001; 64:874–882. [PubMed: 11473415]

223. Jayasuriya H, Salituro GM, Smith SK, Heck JV, Gould SJ, Singh SB, Homnick CF, Holloway MK, Pitzenberger SM, Patane MA. Complestatin to chloropeptin I via a quantitative acid catalyzed rearrangement. Absolute stereochemical determination of complestatin. Tetrahedron Lett. 1998; 39:2247–2248.

224. Shinohara T, Deng H, Snapper ML, Hoveyda AH. Isocomplestatin: total synthesis and stereochemical revision. J Am Chem Soc. 2005; 127:7334–7336. [PubMed: 15898781]

225. Kobayashi H, Shin-Ya K, Furhata K, Nagai K, Suzuki KI, Hayakawa Y, Seto H, Yun BS, Ryoo IJ, Kim JS, et al. Neuroprotectins A and B, dicyclohexapeptides protecting chick telencephalic neurons from excitotoxicity II. Structure determination. J Antibiot. 2001; 54:1019–1024. [PubMed: 11858655]

226. Kobayashi H, Shin-Ya K, Nagai K, Suzuki KI, Hayakawa Y, Seto H, Yun BS, Ryoo IJ, Kim JS, Kim CJ, et al. Neuroprotectins A and B, bicyclohexapeptides protecting chick telencephalic neuronal cells from excitotoxicity I. Fermentation, isolation, physico-chemical properties and biological activity. J Antibiot. 2001; 54:1013–1018. [PubMed: 11858654]

227. Deng H, Jung JK, Liu T, Kuntz KW, Snapper ML, Hoveyda AH. Total synthesis of anti-HIV agent chloropeptin I. J Am Chem Soc. 2003; 125:9032–9034. [PubMed: 15369357]

228. Jia Y, Bois-Choussy M, Zhu J. Synthesis of diastereomers of complestatin and chloropeptin I: substrate-dependent atropstereoselectivity of the intramolecular Suzuki–Miyaura reaction. Angew Chem, Int Ed. 2008; 47:4167–4172.

229. Garfunkle J, Kimball FS, Trzupek JD, Takazawa S, Shimamura H, Tomishima M, Boger DL. Total synthesis of chloropeptin II (complestatin) and chloropeptin I. J Am Chem Soc. 2009; 131:16036–16038. [PubMed: 19839632]

230. Shimamura H, Breazzano SP, Garfunkle J, Kimball FS, Trzupek JD, Boger DL. Total synthesis of complestatin: development of a Pd(0)-mediated indole annulation for macrocyclization. J Am Chem Soc. 2010; 132:7776–7783. [PubMed: 20469945]

231. Breazzano SP, Boger DL. Synthesis and stereochemical determination of complestatin A and B (neuroprotection A and B). J Am Chem Soc. 2011; 133:18495–18502. [PubMed: 21991993]

232. Larock RC, Yum EK. Synthesis of indoles via palladium-catalyzed heteroannulation of internal alkynes. J Am Chem Soc. 1991; 113:6689–6690.

233. Larock RC, Yum EK, Refvik MD. Synthesis of 2,3-disubstituted indoles via palladium-catalyzed annulation of internal alkynes. J Org Chem. 1998; 63:7652–7662.

234. Shen M, Li G, Lu BZ, Hossain A, Roschangar F, Farina V, Senanayaka CH. The first regioselective palladium-catalyzed indolization of 2-bromo- or 2-chloroanilines with internal alkynes: a new approach to 2,3-disubstituted indoles. Org Lett. 2004; 6:4129–4132. [PubMed: 15496116]

235. Ma C, Liu X, Li X, Flippen-Anderson J, Yu S, Cook JM. Efficient asymmetric synthesis of biologically important tryptophan analogues via a palladium-mediated heteroannulation reaction. J Org Chem. 2001; 66:4525–4542. [PubMed: 11421771]

236. Jeschke T, Wensbo D, Annby U, Gronowitz S, Cohen LA. A novel approach to Bz-substituted tryptophans via Pd-catalysed coupling/annulation. Tetrahedron Lett. 1993; 34:6471–6474.

237. Breazzano SP, Poudel YB, Boger DL. A Pd(0)-mediated indole (macro)cyclization reaction. J Am Chem Soc. 2013; 135:1600–1606. [PubMed: 23298368]

238. Savige WE, Fontana A. New procedure for oxidation of 3-substituted indoles to oxindoles: modification of tryptophan residues in peptides and proteins. J Chem Soc, Chem Commun. 1976:599–600.

239. Szabo-Pustay K, Szabo L. A simple general method for the oxidation of indoles to oxindoles. Synthesis. 1979:276–277.

240. Hinman RL, Bauman CP. Reactions of *N*-bromosuccinimide and indoles. A simple synthesis of 3-bromooxindoles. J Org Chem. 1964; 29:1206–1215.

241. Lawson WB, Witkop R. A simple method for the preparation of oxindoleacetic and propionic acids from the parent indoles. J Org Chem. 1961; 26:263–264.

242. Lawson WB, Patchornik A, Witkop R. Substitution, oxidation and group participation in the bromination of indoles. J Am Chem Soc. 1960; 82:5918–5923.

243. Fuchs JR, Funk RL. Total synthesis of (±)-perophoramidine. J Am Chem Soc. 2004; 126:5068–5069. [PubMed: 15099080]

244. Fuchs JR, Funk RL. Indol-2-one intermediates: mechanistic evidence and synthetic utility. Total syntheses of (±)-flustramines A and C. Org Lett. 2005; 7:677–680. [PubMed: 15704923]

245. Hino T, Tonozuka M, Nakagawa M. Bromination of 3-phenylindoles. Tetrahedron. 1974; 30:2123–2133.

246. Hino T, Nakamura T, Nakagawa M. Halogenation of 1-substituted skatoles. Preparation of 3-bromomethylindoles. Chem Pharm Bull Jpn. 1975; 23:2990–2997.

247. Walker S, Chen L, Hu Y, Rew Y, Shin D, Boger DL. Chemistry and biology of ramoplanin: a lipoglycodepsipeptide with potent antibiotic activity. Chem Rev. 2005; 105:449–476. [PubMed: 15700952]

248. Jiang W, Wanner J, Lee RJ, Bounaud PY, Boger DL. Total synthesis of the ramoplanin A2 and ramoplanose aglycon. J Am Chem Soc. 2003; 125:1877–1887. [PubMed: 12580615]

249. Rew Y, Shin D, Hwang I, Boger DL. Total synthesis and examination of three key analogues of ramoplanin: a lipoglycodepsipeptide with potent antibiotic activity. J Am Chem Soc. 2004; 126:1041–1043. [PubMed: 14746470]

250. Shin D, Rew Y, Boger DL. Total synthesis and structure of the ramoplanin A1 and A3 aglycons: two minor components of the ramoplanin complex. Proc Natl Acad Sci US A. 2004; 101:11977–11979.

251. Nam J, Shin D, Rew Y, Boger DL. Alanine scan of [L-dap$^2$]ramoplanin A2 aglycon: assessment of the importance of each residue. J Am Chem Soc. 2007; 124:8747–8755.

252. Boger DL. Vancomycin, teicoplanin, and ramoplanin: synthetic and mechanistic studies. Med Res Rev. 2001; 21:356–381. [PubMed: 11579438]

253. Seiple IB, Zhang ZY, Jakubec P, Langlois-Mercier A, Wright PM, Hog DT, Yabu K, Allu SR, Fukuzaki T, Carlsen PN, et al. A platform for the discovery of new macroclide antibiotics. Nature. 2016; 533:338–345. [PubMed: 27193679]

254. Charest MG, Lerner CD, Brubaker JD, Siegel DR, Myers AG. A convergent enantioselective route to structurally diverse 6-deoxytetracycline antibiotics. Science. 2005; 308:395–398. [PubMed: 15831754]

255. Wright PM, Seiple IB, Myers AG. The evolving role of chemical synthesis in antibacterial drug discovery. Angew Chem, Int Ed. 2014; 53:8840–8869.

## Biographies

Dale L. Boger is the Richard & Alice Cramer Chair in Chemistry at The Scripps Research Institute (1990–present) where he serves as Chairman (2012–present) of the Department of Chemistry. He received his B.S. in Chemistry from the University of Kansas (1975) and his Ph.D. in Chemistry from Harvard University (1980). He was on the faculty at the University of Kansas and Purdue University before joining TRSI in 1990.

Akinori Okano was born in 1981 in Hyogo, Japan, and received his B.S. degree in Pharmaceutical Sciences from Osaka University of Pharmaceutical Sciences in 2005. He moved to Osaka University and obtained his M.S. degree in Pharmaceutical Sciences from Osaka University under the supervision of Professor Hiroaki Ohno and Professor Tetsuaki Tanaka in 2007. He moved to Kyoto University to continue his Ph.D. research under the supervision of Professor Hiroaki Ohno and Professor Nobutaka Fujii (2009–2010; as a Japan Society for the Promotion of Science [JSPS] Research Fellow). After completion of his Ph.D. in 2010, he joined Professor Boger's group at The Scripps Research Institute as a post-doctoral research associate (2010–2011; as a JSPS Research Fellow). In 2013, he was appointed to research Assistant Professor in the Boger group.

Nicholas A. Isley received his B.S. from Western Washington University (2010). After being exposed to organometallic research as an undergraduate, he decided to obtain a Ph.D. at the University of California Santa Barbara (2015). Working with Bruce H. Lipshutz, he developed organic and organometallic reactions in water via micellar catalysis with benign "designer" surfactants. In 2015, he moved to San Diego for postdoctoral studies with Professor Boger at The Scripps Research Institute.

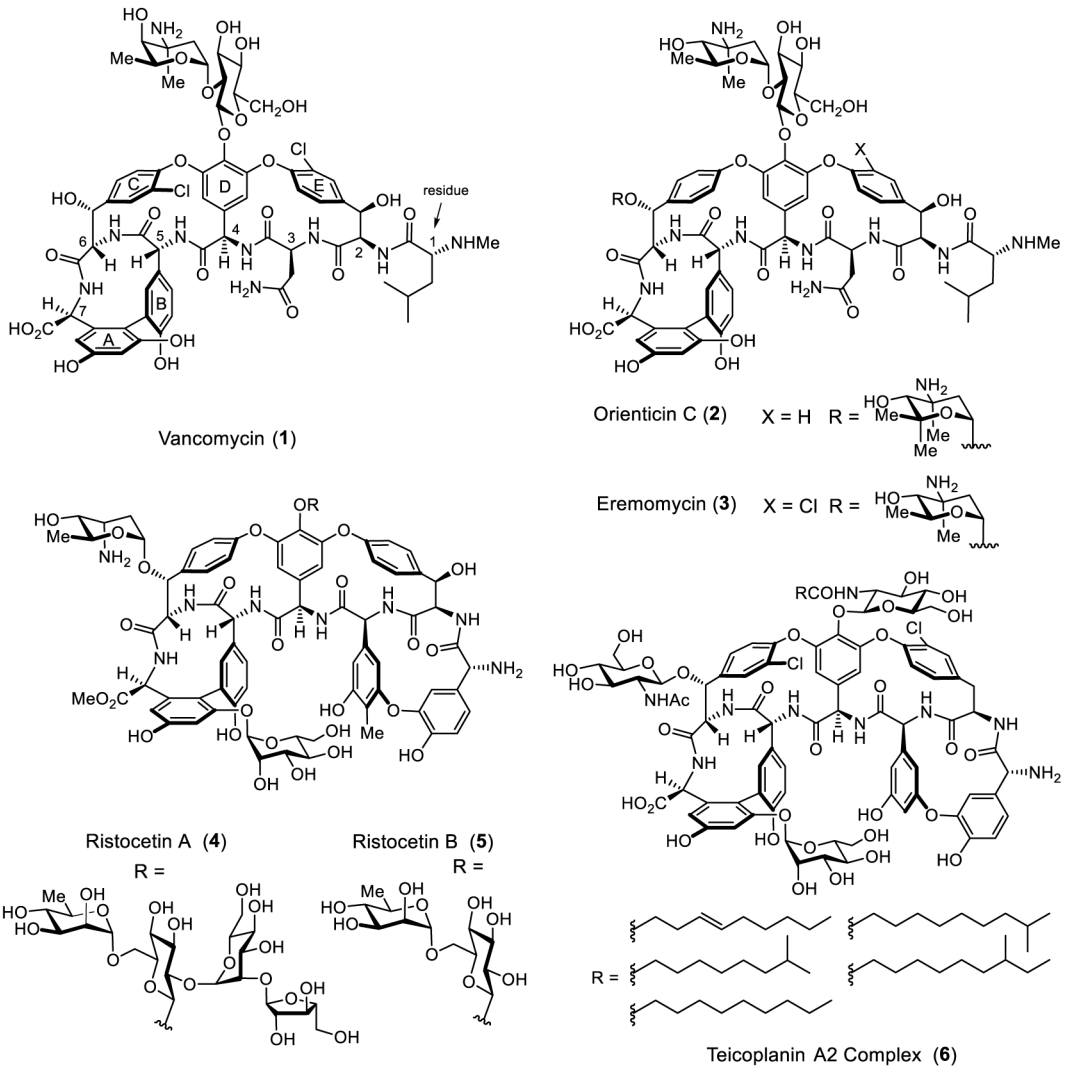



**Figure 1.**
Structures of Vancomycin and Representative Related Glycopeptide Antibiotics.

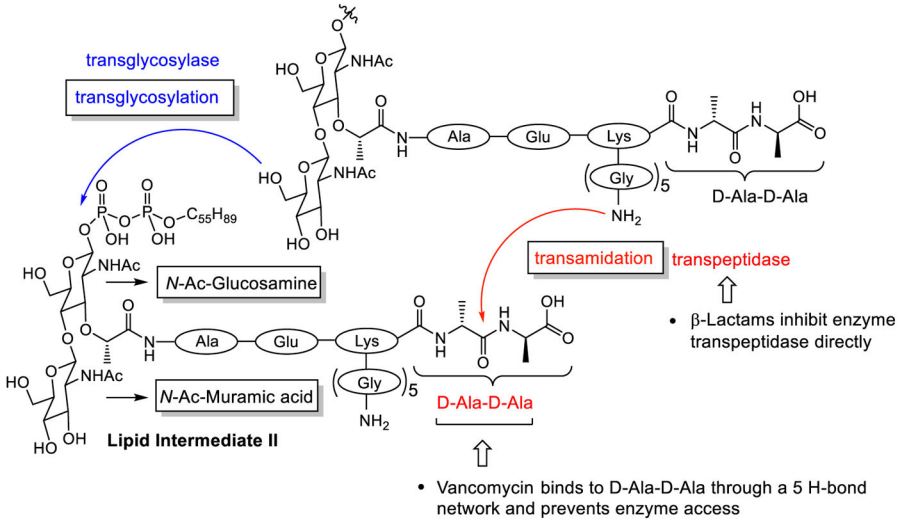
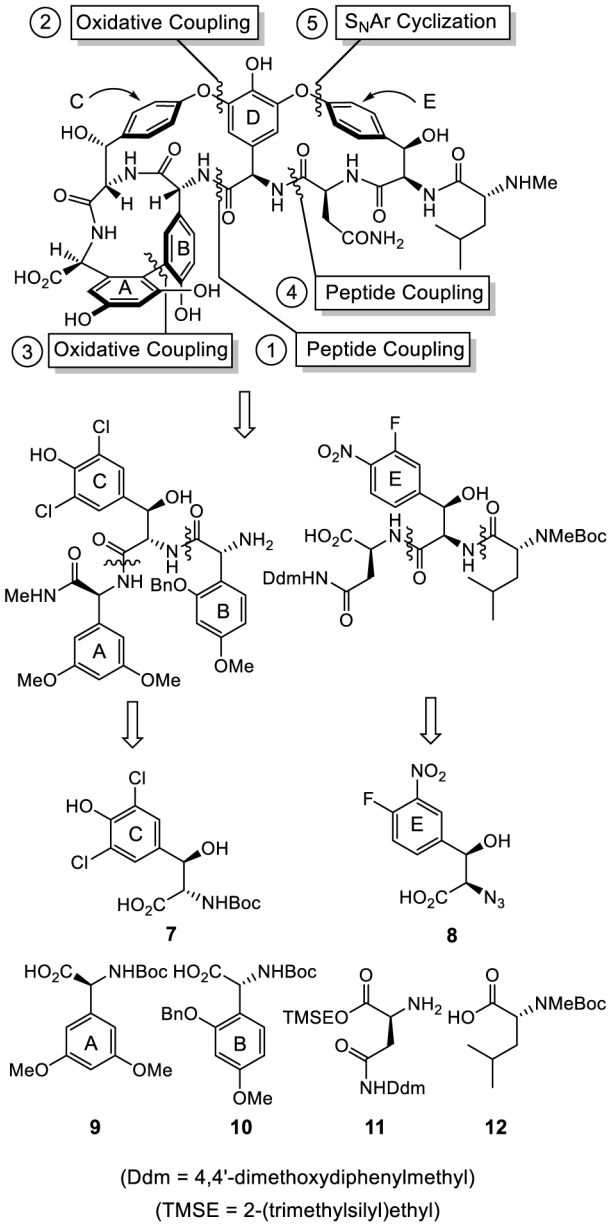



**Figure 2.**

Bacterial Cell Wall Precursors of Gram-positive Bacteria, and Vancomycin Binding to D-Ala-D-Ala.




7 8 9 10 11 12

**Figure 3.**
Evans Retrosynthetic Analysis of Orienticin C Aglycon.

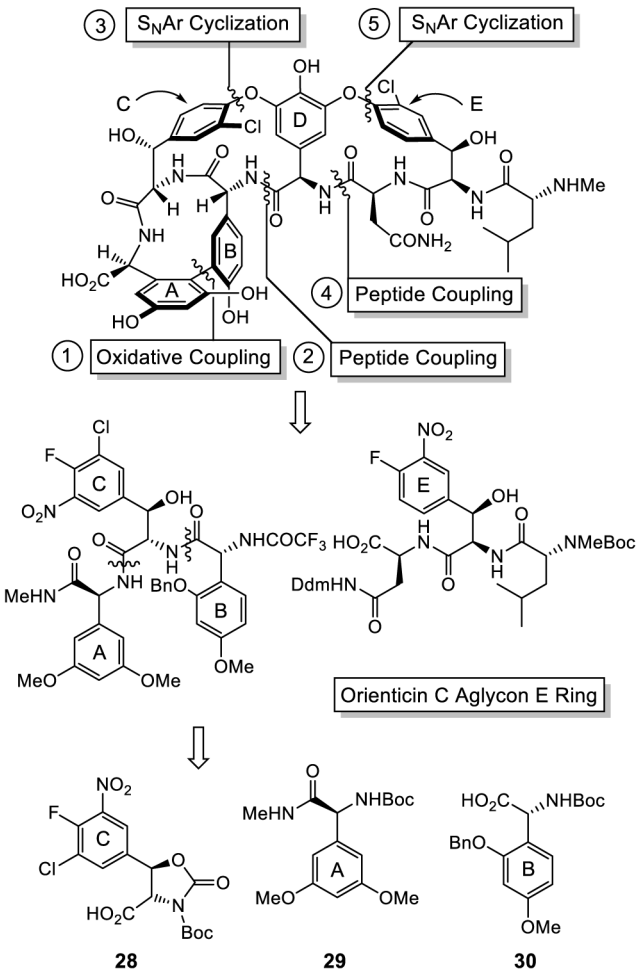



**Figure 4.**
Evans Retrosynthetic Analysis of Vancomycin Aglycon.

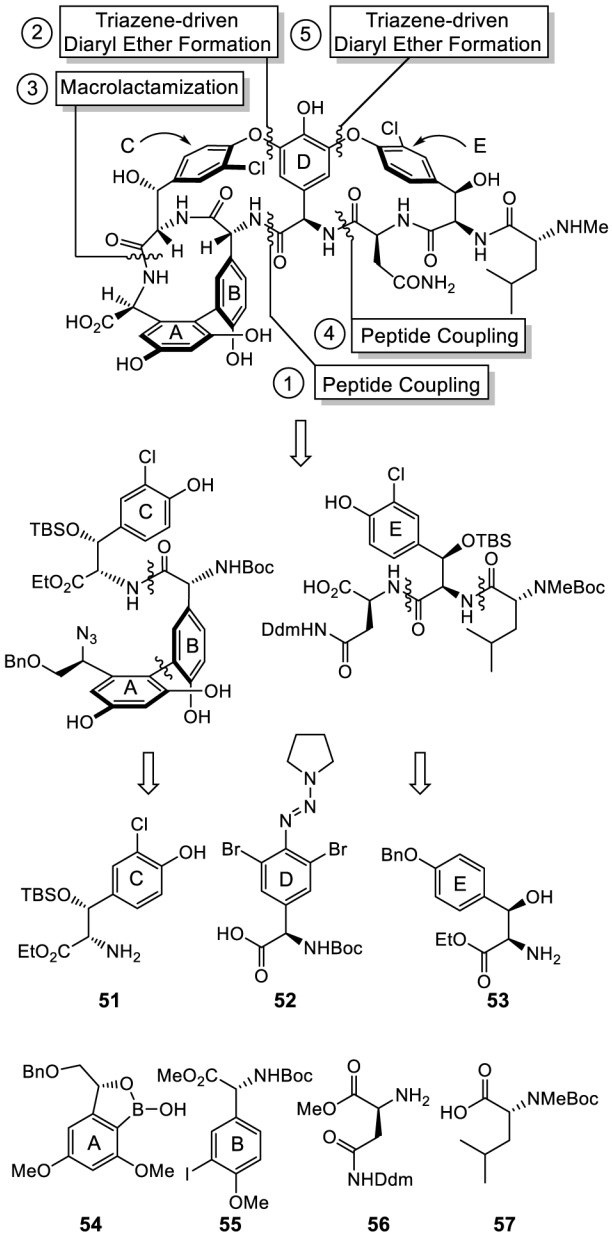



**Figure 5.**
Nicolaou Retrosynthetic Analysis of Vancomycin Aglycon.

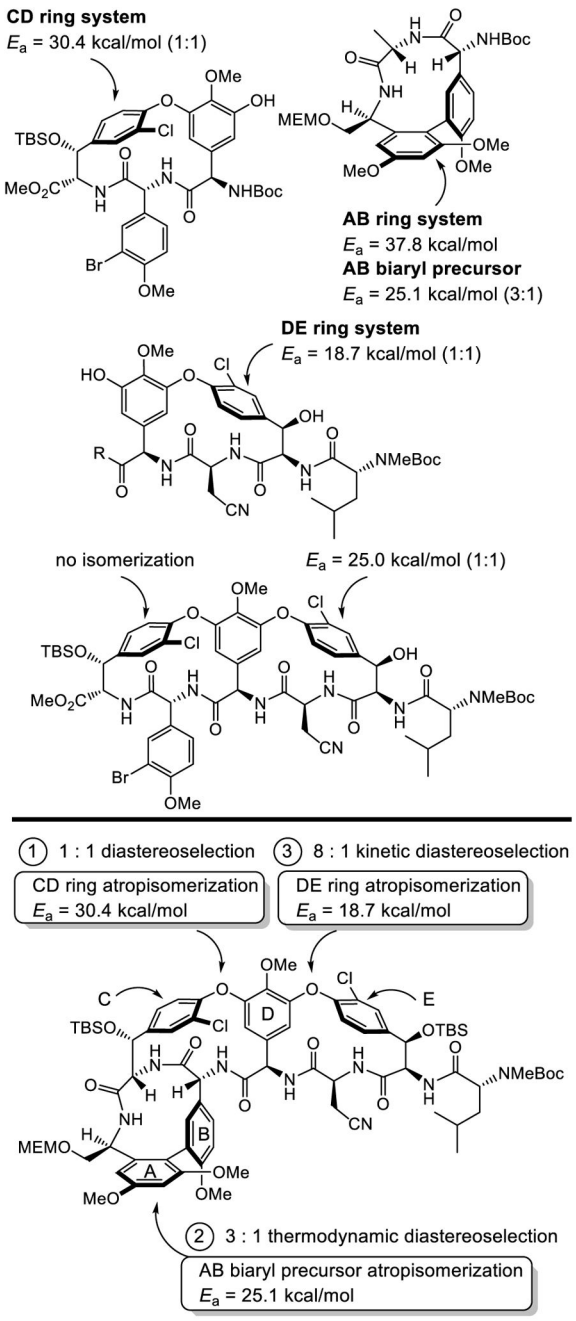



**Figure 6.**

Atropisomer Equilibration and Experimental $E_a$ of the Individual Vancomycin Ring Systems and Defined Order of Ring System Introductions.

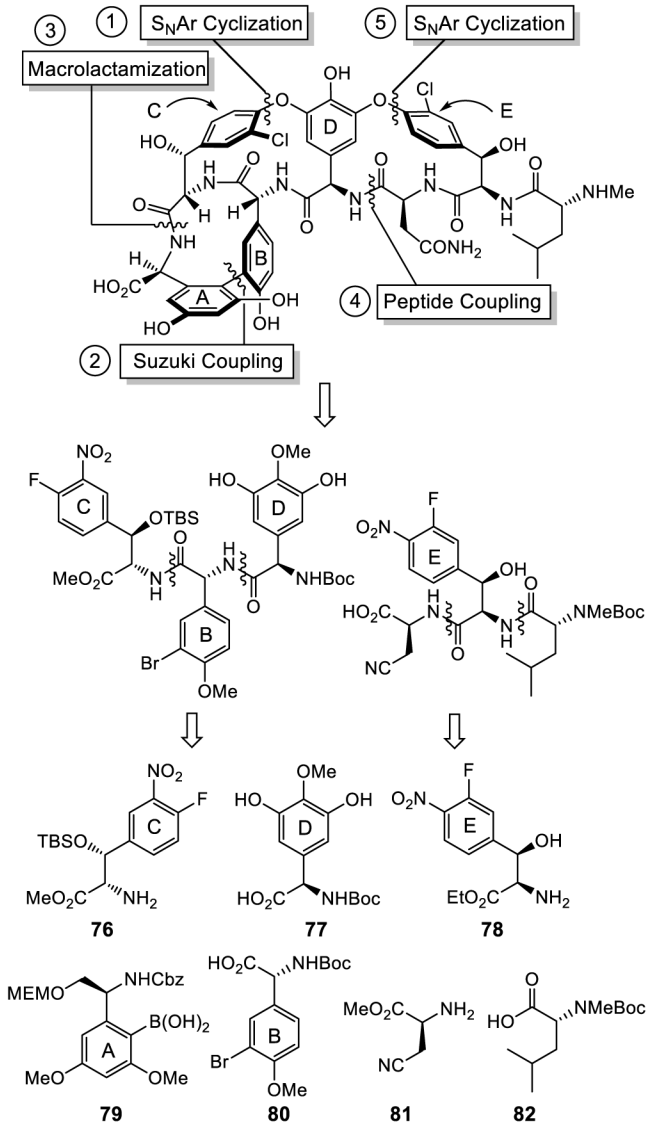



**Figure 7.**
Boger Retrosynthetic Analysis of Vancomycin Aglycon.

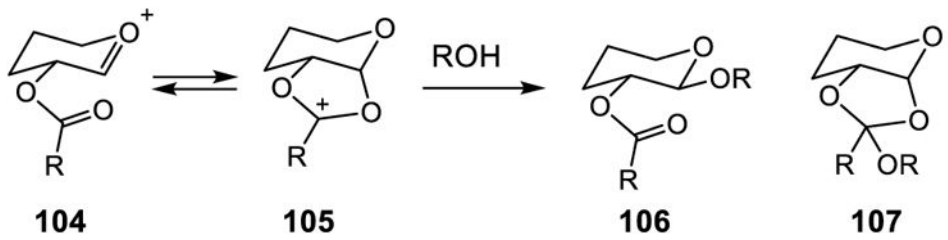



**Figure 8.**
Selective β-Glycoside Formation with Neighboring Group Participation.

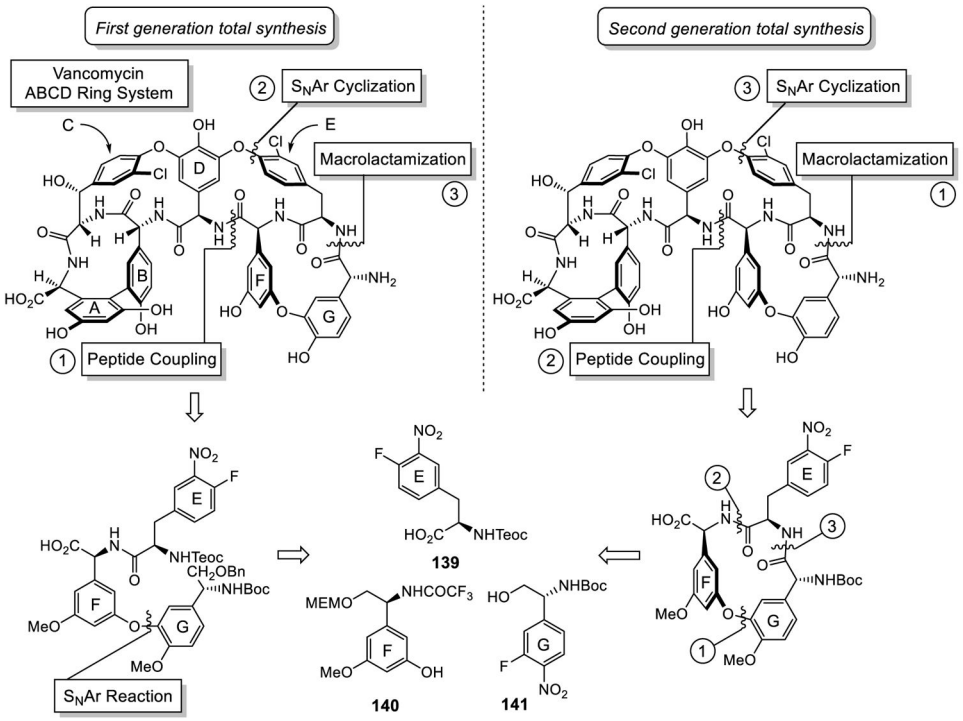



**Figure 9.**
Boger First and Second Generation Retrosynthetic Analysis of Teicoplanin Aglycon.

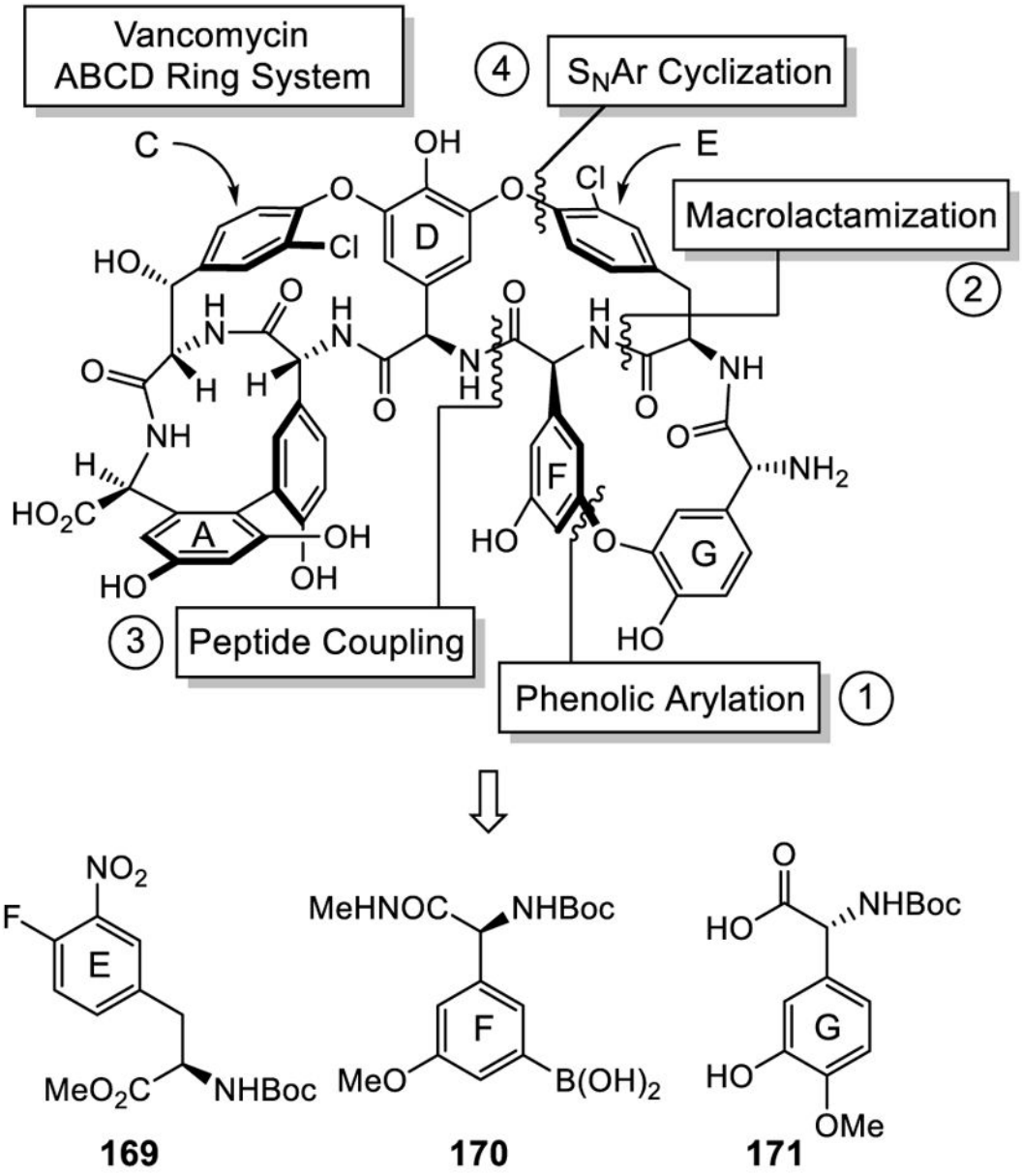



**Figure 10.**
Evans Retrosynthetic Analysis of Teicoplanin Aglycon.

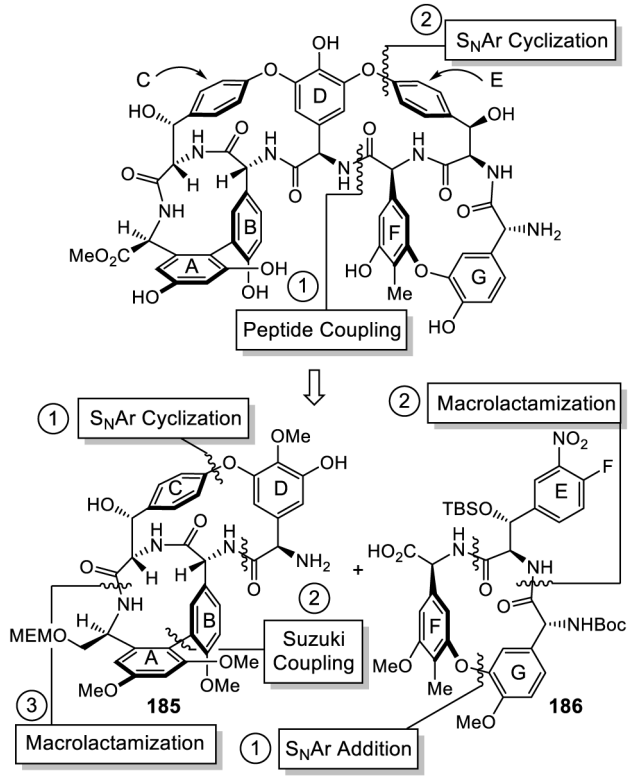



**Figure 11.**
Boger Retrosynthetic Analysis of Ristocetin A Aglycon.

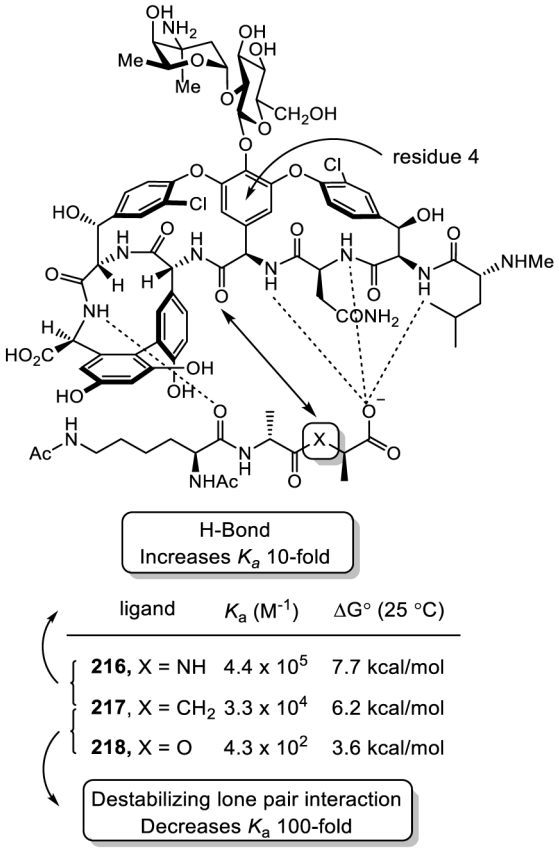



**Figure 12.**
Evaluation of Binding Affinity of Vancomycin with Model Ligands.

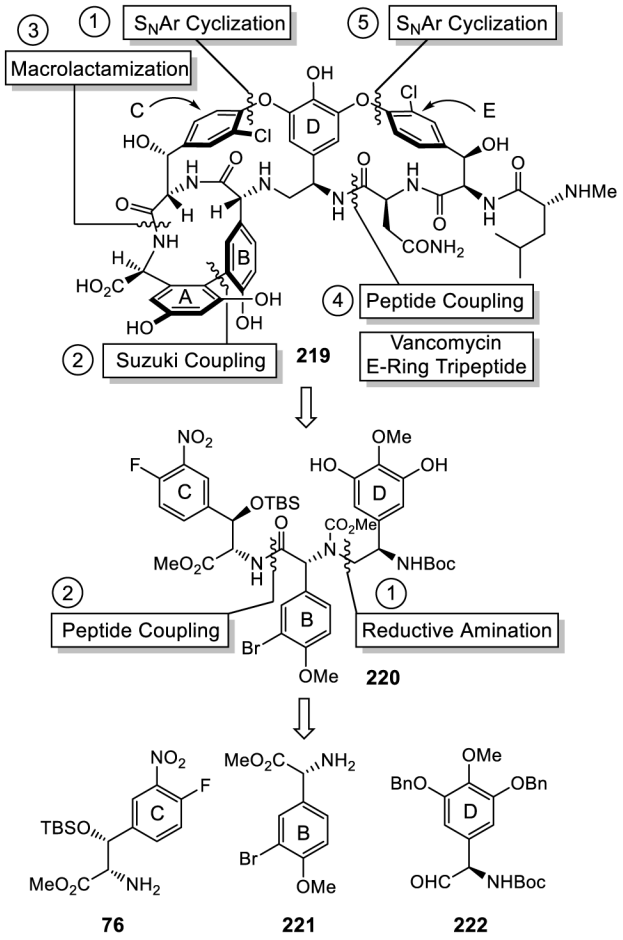



**Figure 13.**

Boger Retrosynthetic Analysis of [Φ[$CH_2NH$]$Tpg^4$]Vancomycin Aglycon.

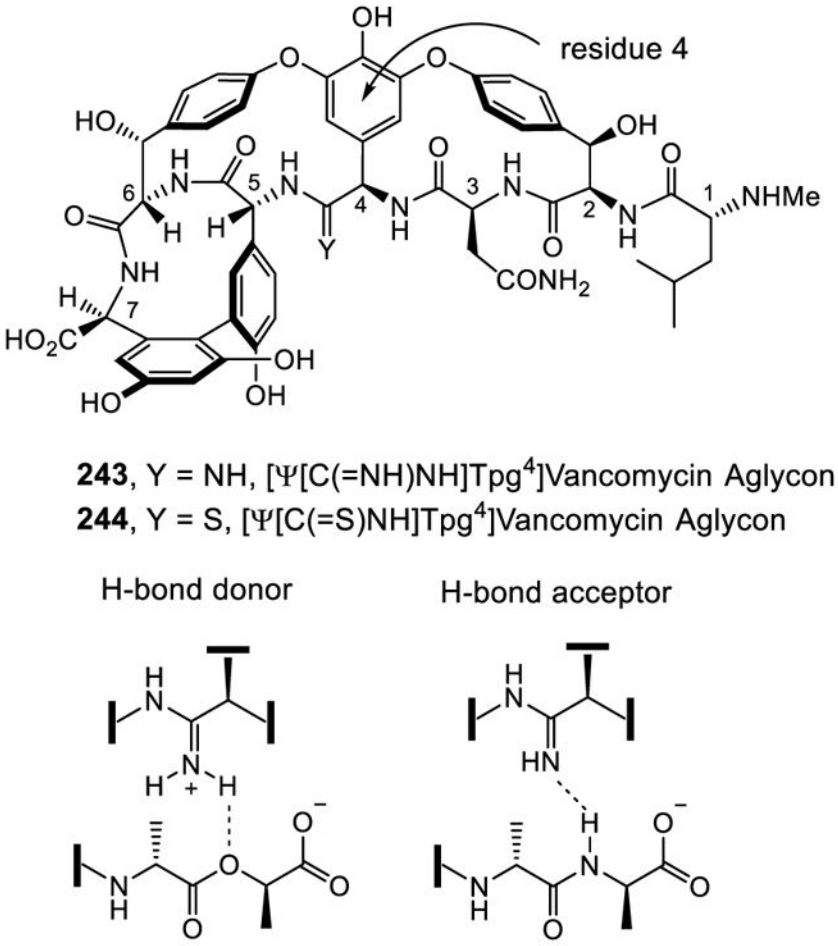



**Figure 14.**

Structures of [Φ[C(=NH)NH]Tpg$^4$]Vancomycin Aglycon (**243**), [Φ[C(=S)NH]Tpg$^4$] Vancomycin Aglycon (**244**), and the Dual Binding Behavior of the Amidine in **243**.

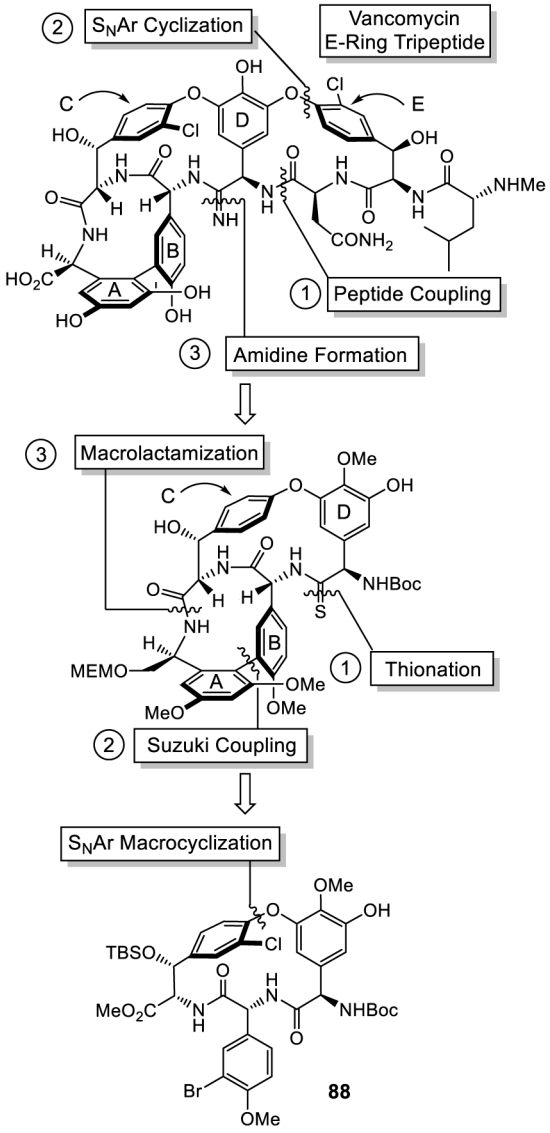
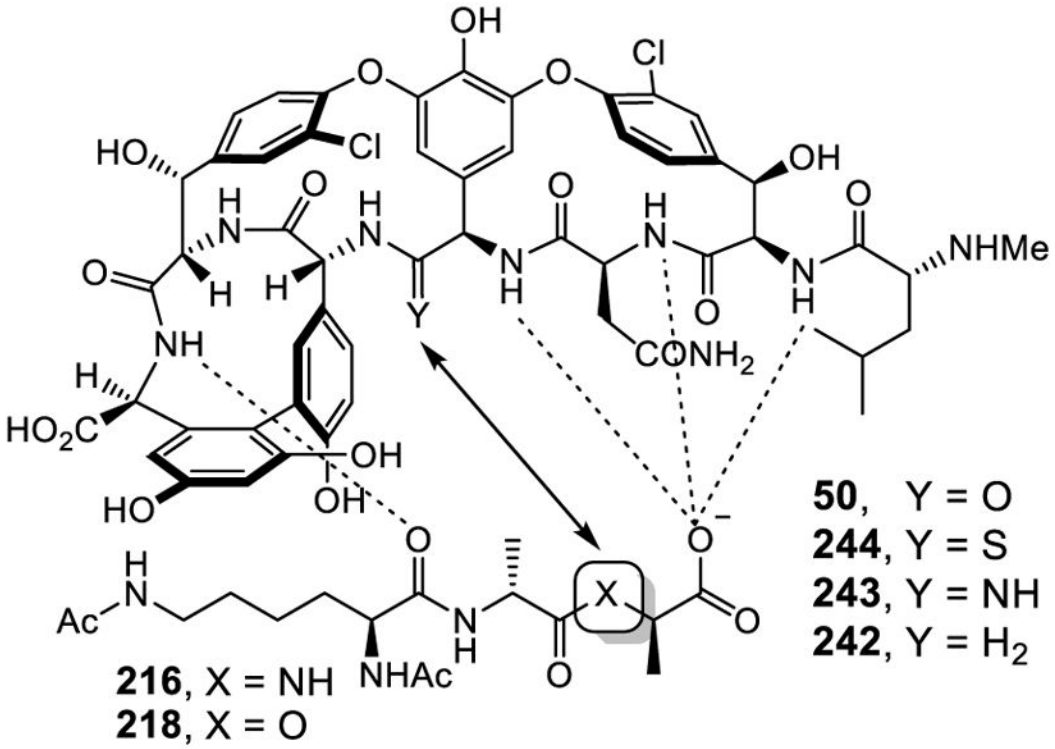



**Figure 15.**
Boger Retrosynthetic Analysis of [Φ[C(=NH)NH]Tpg[4]]Vancomycin Aglycon.




| compound | ligand, $K_a$ ($M^{-1}$) **216**, X = NH | **218**, X = O | $K_a$ (**216**/**218**) | VanA[a] MIC, μg/mL |
|---|---|---|---|---|
| **50**, Y = O | 1.7 x $10^5$ | 1.2 x $10^2$ | 1400 | 640 |
| **244**, Y = S | 1.7 x $10^2$ | 1.1 x $10^1$ | – | > 640 |
| **243**, Y = NH | 7.3 x $10^4$ | 6.9 x $10^4$ | 1.05 | 0.5 |
| **242**, Y = $H_2$ | 4.8 x $10^3$ | 5.2 x $10^3$ | 0.9 | 31 |

[a]Minimum inhibitory conc., *E. faecalis* (BM4166, VanA VRE).

**Figure 16.**
Biological Evaluation of Residue 4 Modified Vancomycin Aglycons.

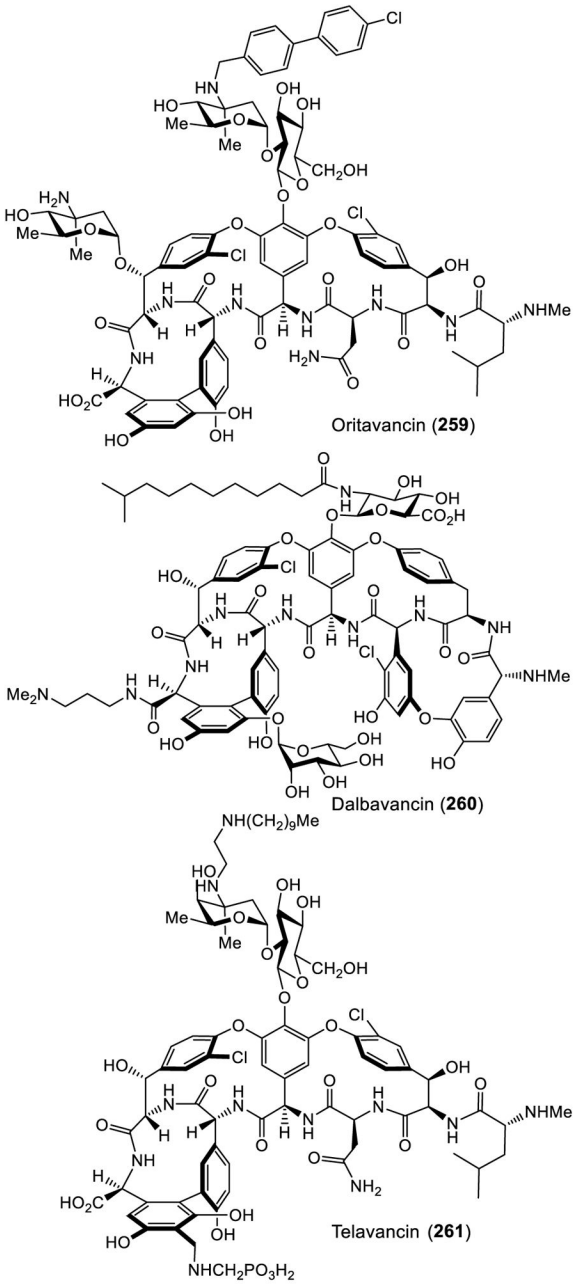



**Figure 17.**
Clinically Approved Semisynthetic Glycopeptide Antibiotics.

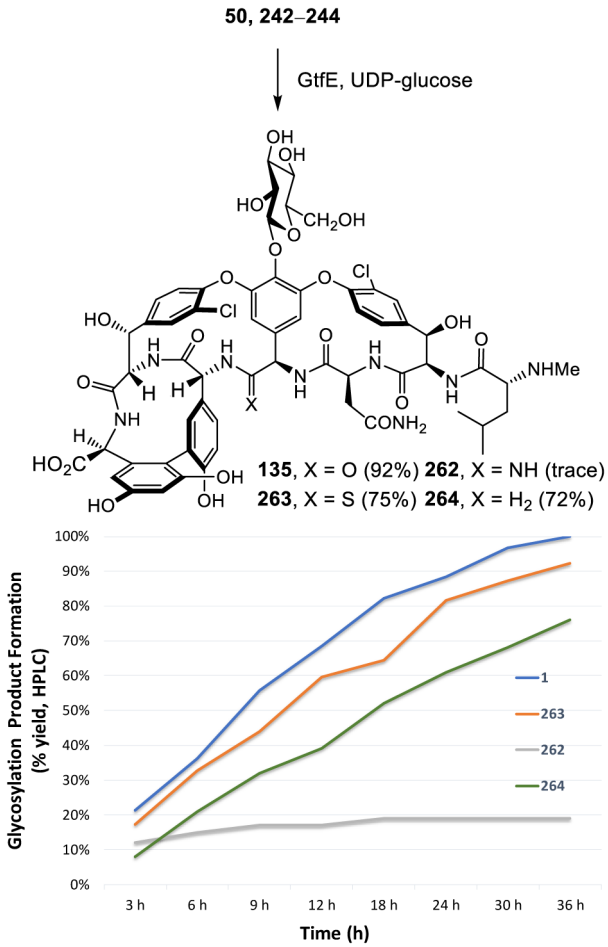
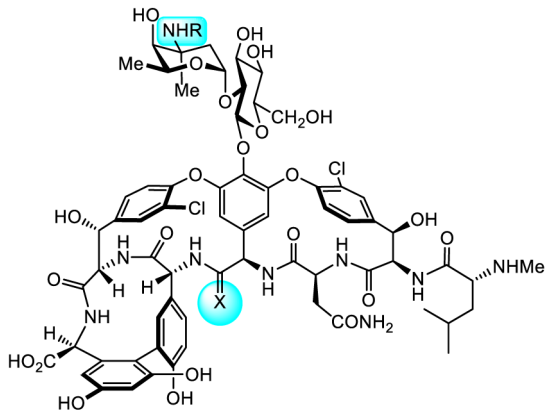



**Figure 18.**

Comparison of the Relative Rates and Efficiency of the GtfE-catalyzed Glycosylation Reaction of **50**, and **242**–**244**.

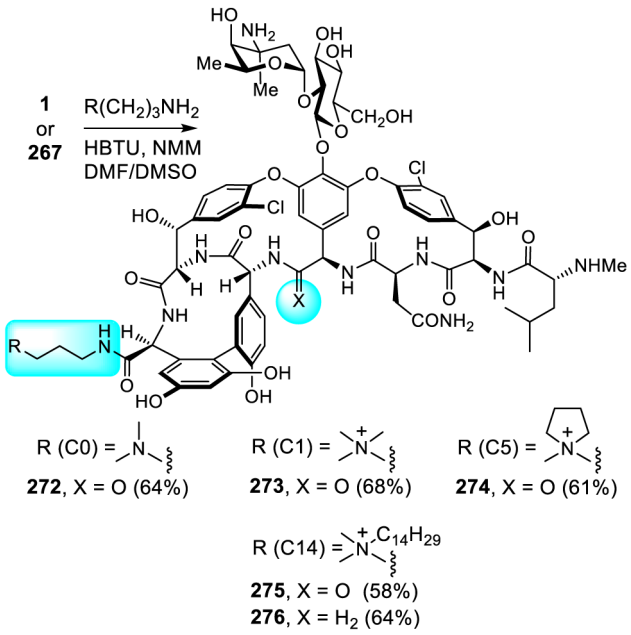



Antimicrobial Activity, MIC[a] (μg/mL)

| | sensitive | MRSA | VanA | | VanB |
|---|---|---|---|---|---|
| | *S. aureus*[b] | *S. aureus*[c] | *E. faecalis*[d] | *E. faecium*[e] | *E. faecalis*[f] |
| R = H | | | | | |
| **1**, X = O | 0.5 | 0.5 | 250 | 250 | 8 |
| **265**, X = S | >32 | >32 | >32 | >32 | >32 |
| **266**, X = NH | nd[g] | nd[g] | 0.5 | 0.5 | nd[g] |
| **267**, X = $H_2$ | nd[g] | nd[g] | 31 | 31 | nd[g] |
| R = CBP, (4-chlorobiphenyl)methyl | | | | | |
| **268**, X = O | 0.03 | 0.03 | 2.5 | 2.5 | 0.03 |
| **269**, X = S | 2 | 2 | 4 | 4 | 2 |
| **270**, X = NH | 0.03 | 0.06 | 0.005 | 0.005 | 0.06 |
| **271**, X = $H_2$ | 0.5 | 0.25 | 0.13 | 0.06 | 0.5 |

[a]MIC = Minimum inhibitory concentration. [b]ATCC 25923. [c]ATCC 43300. [d]BM 4166. [e]ATCC BAA-2317. [f]ATCC 51299. [g]not determined.

**Figure 19.**
*In vitro* Antimicrobial Activity.



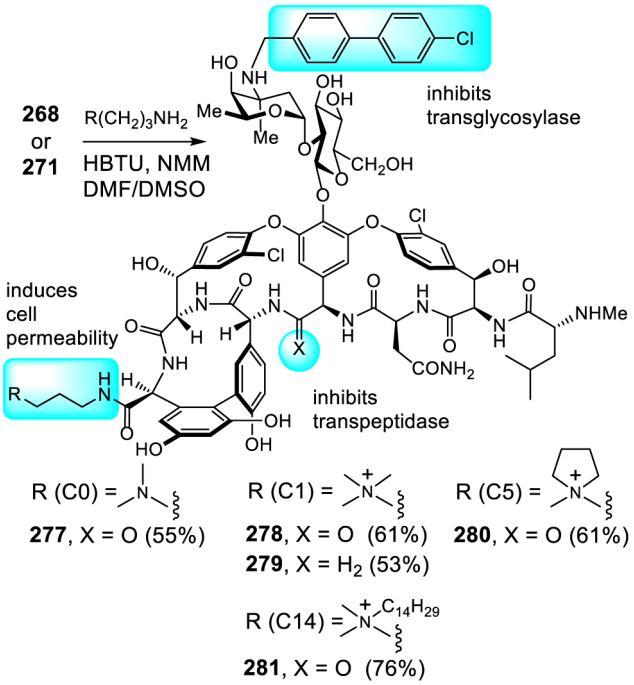

Antimicrobial Activity, MIC[a] (μg/mL)

| | VanA | |
|---|---|---|
| | *E. faecalis*[b] | *E. faecium*[c] |
| **1**, vancomycin | 250 | 250 |
| **272**, X = O (C0) | 500 | 500 |
| **273**, X = O (C1) | 63 | 126 |
| **274**, X = O (C5) | 4 | 2 |
| **275**, X = O (C14) | 2 | 2 |
| **267**, X = $H_2$ | 31 | 31 |
| **276**, X = $H_2$ (C14) | 0.16 | 0.16 |

[a]MIC = Minimum inhibitory concentration. [b]BM 4166. [c]ATCC BAA-2317.

**Figure 20.**

Peripheral C-terminus Modifications of Vancomycin and the Binding Pocket Modified Vancomycin Analogue **267**.




Antimicrobial Activity, MIC[a] (μg/mL)

| | VanA | |
|---|---|---|
| | *E. faecalis*[b] | *E. faecium*[c] |
| **1**, vancomycin | 250 | 250 |
| **268**, X = O (CBP) | 2.5 | 2.5 |
| **277**, X = O (CBP/C0) | 5 | 5 |
| **278**, X = O (CBP/C1) | 0.25 | 0.5 |
| **280**, X = O (CBP/C5) | 2 | 2 |
| **281**, X = O (CBP/C14) | 2 | 2 |
| **267**, X = $H_2$ | 31 | 31 |
| **271**, X = $H_2$ (CBP) | 0.13 | 0.06 |
| **279**, X = $H_2$ (CBP/C1) | 0.01 | 0.005 |

[a]MIC = Minimum inhibitory concentration. [b]BM 4166. [c]ATCC BAA-2317.

**Figure 21.**

Combined CBP and C-terminus Peripheral Modifications of Vancomycin and the Binding Pocket Modified Vancomycin Analogue **267**.

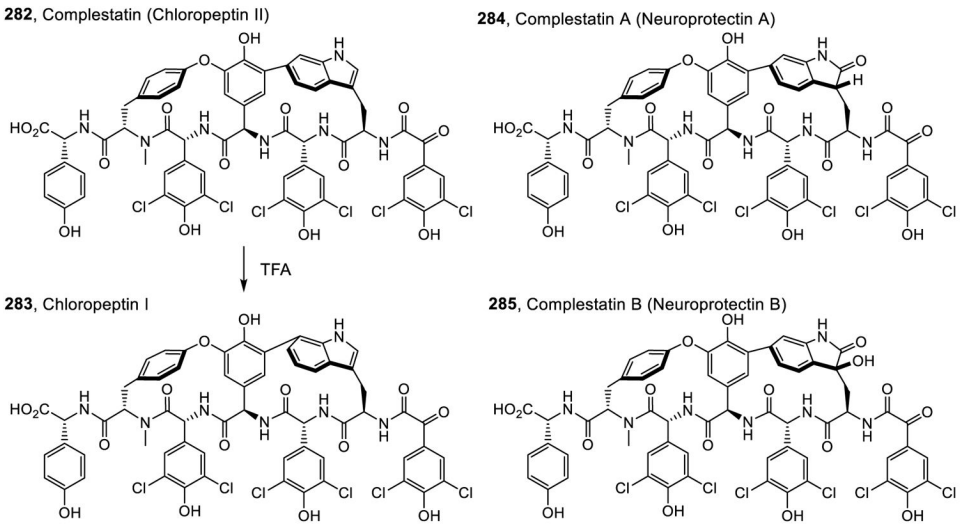



**Figure 22.**
Structure of Chloropeptins and Complestatins (Neuroprotectins).

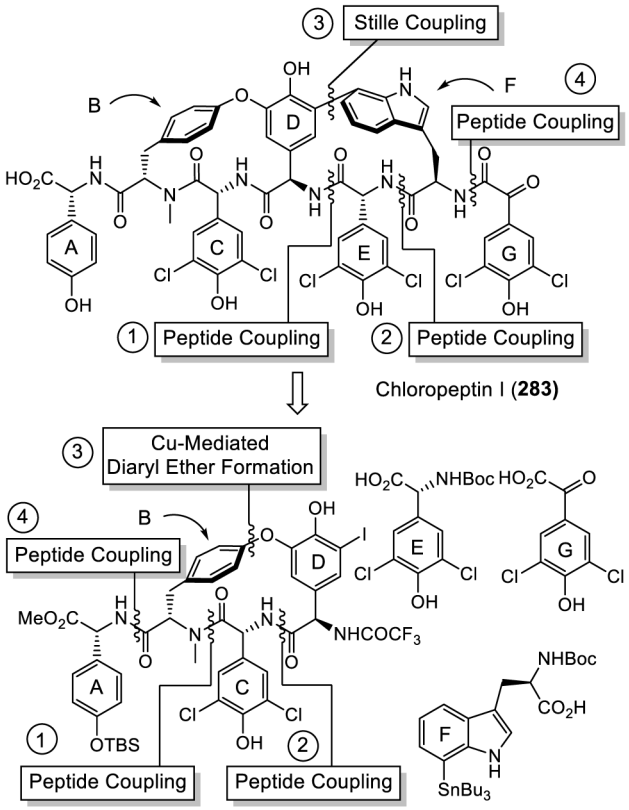



**Figure 23.**
Snapper and Hoveyda Retrosynthetic Analysis of Chloropeptin I.

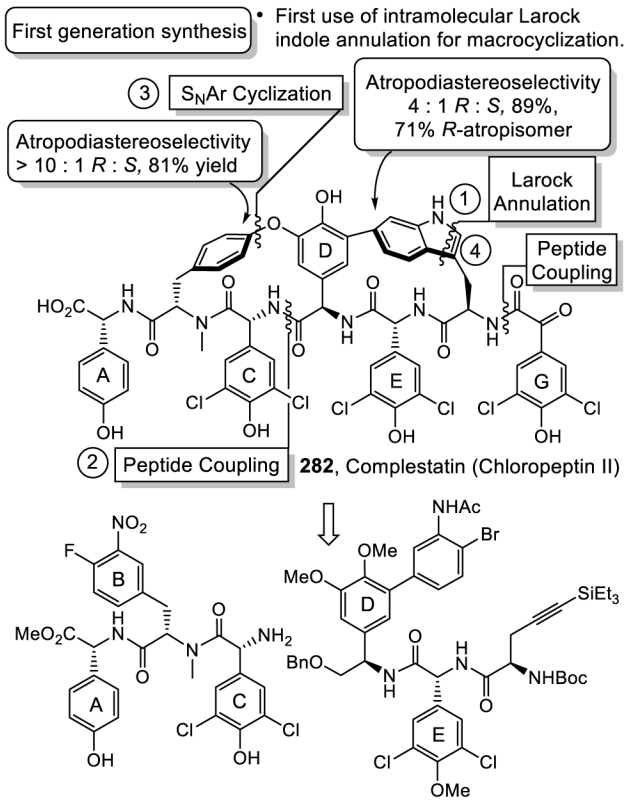



**Figure 24.**

Boger First Generation Total Synthesis of Complestatin (Chloropeptin II) and Chloropeptin I.

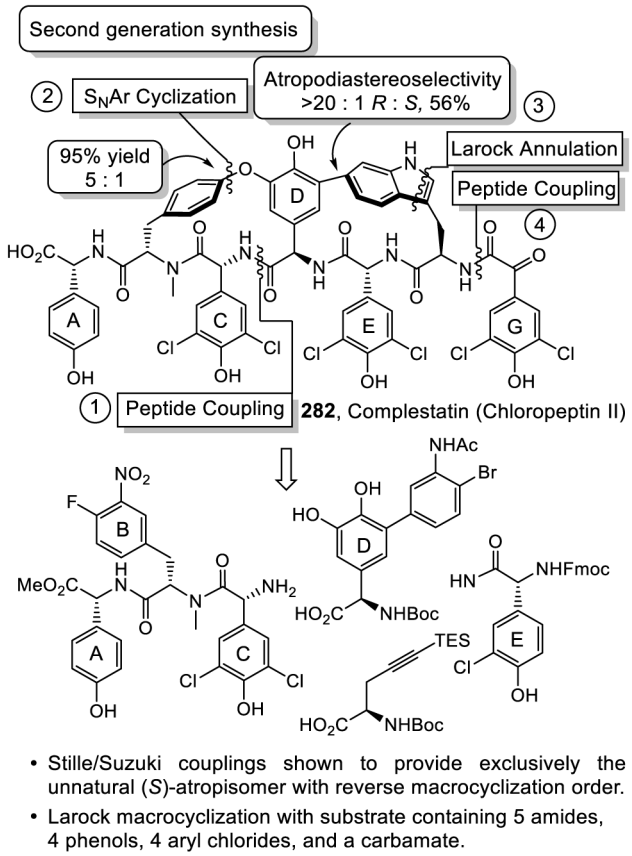
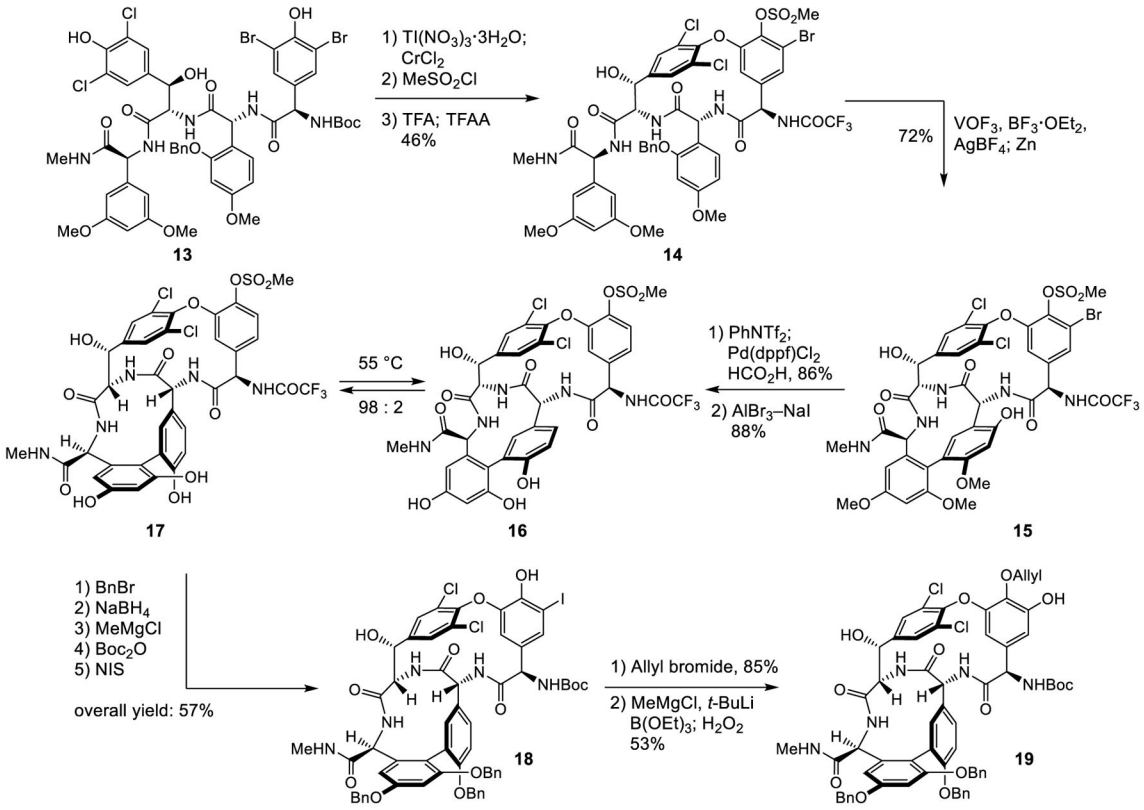


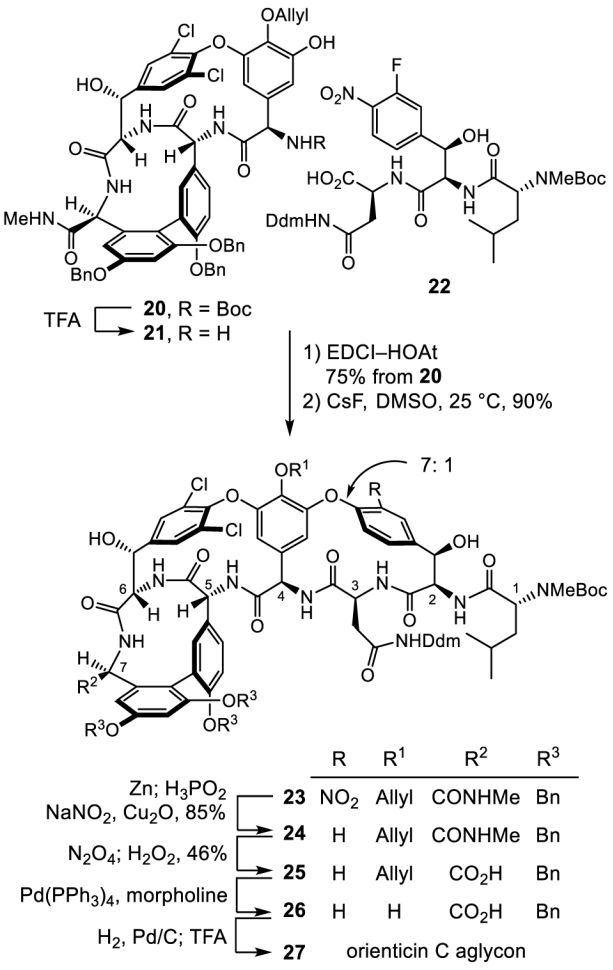

**Figure 25.**

Boger Second Generation Total Synthesis of Complestatin (Chloropeptin II) and Chloropeptin I.



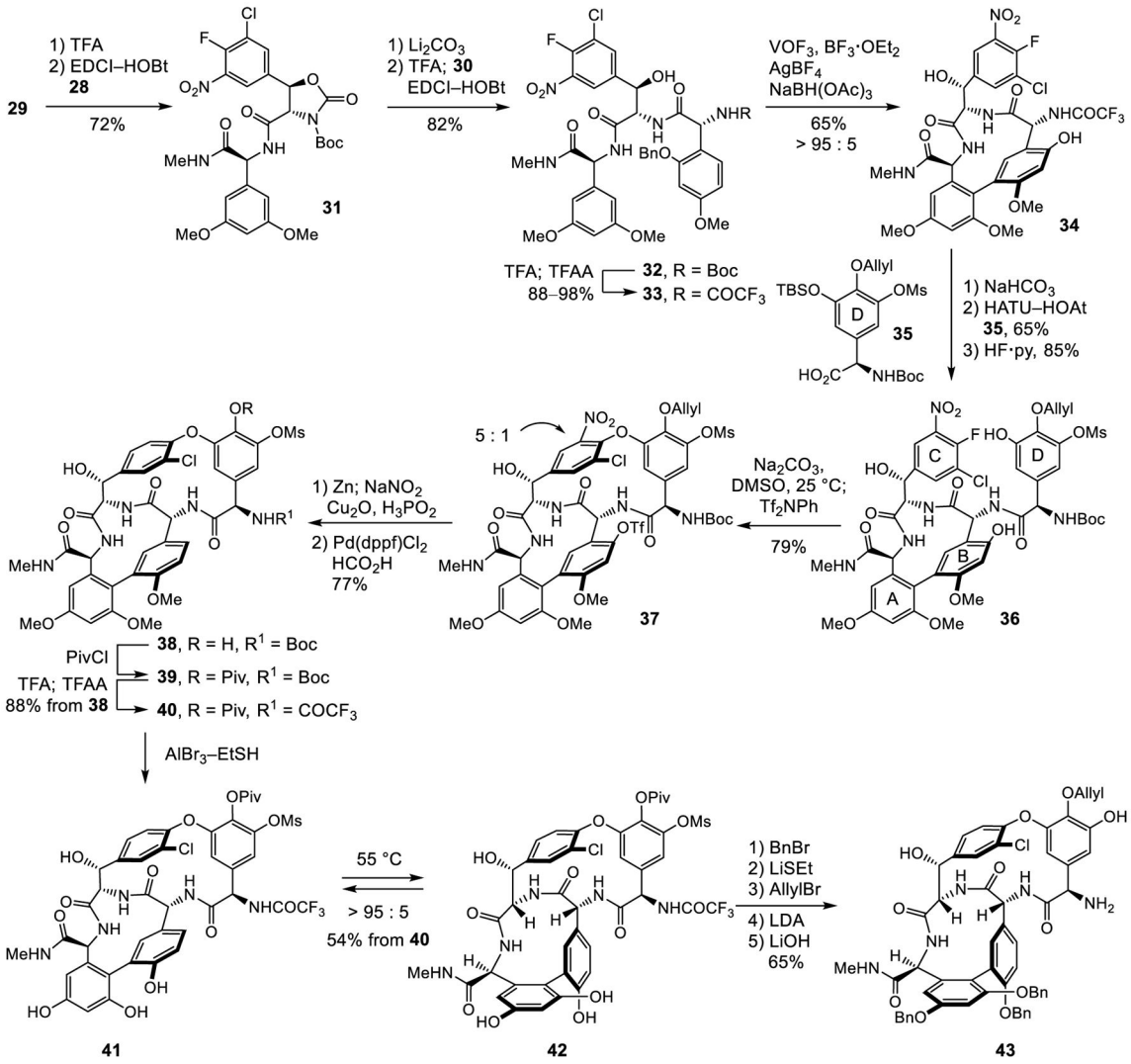

**Scheme 1.**

Evans Synthesis of the ABCD Ring System of Orienticin C Aglycon.



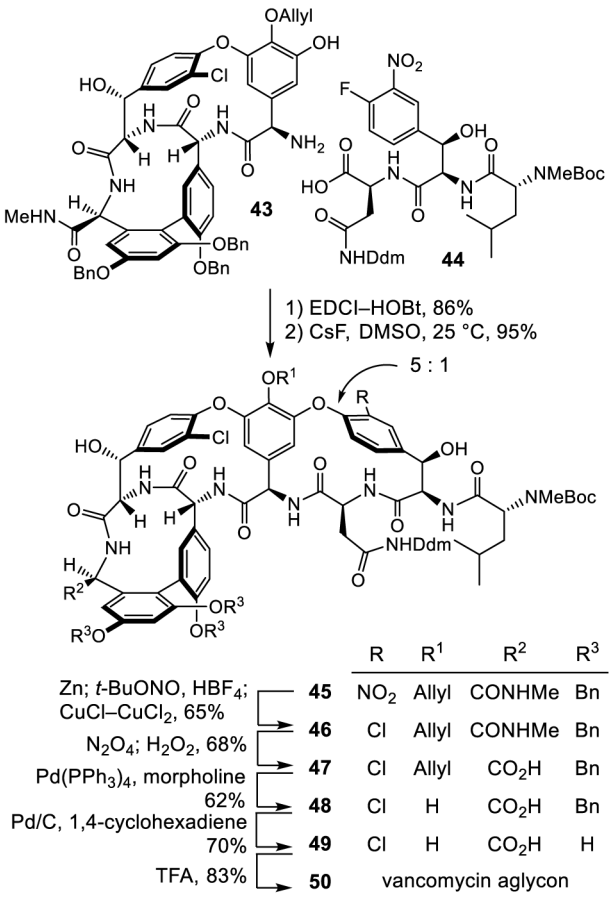

**Scheme 2.**

Final Stages of the Evans Total Synthesis of Orienticin C Aglycon.



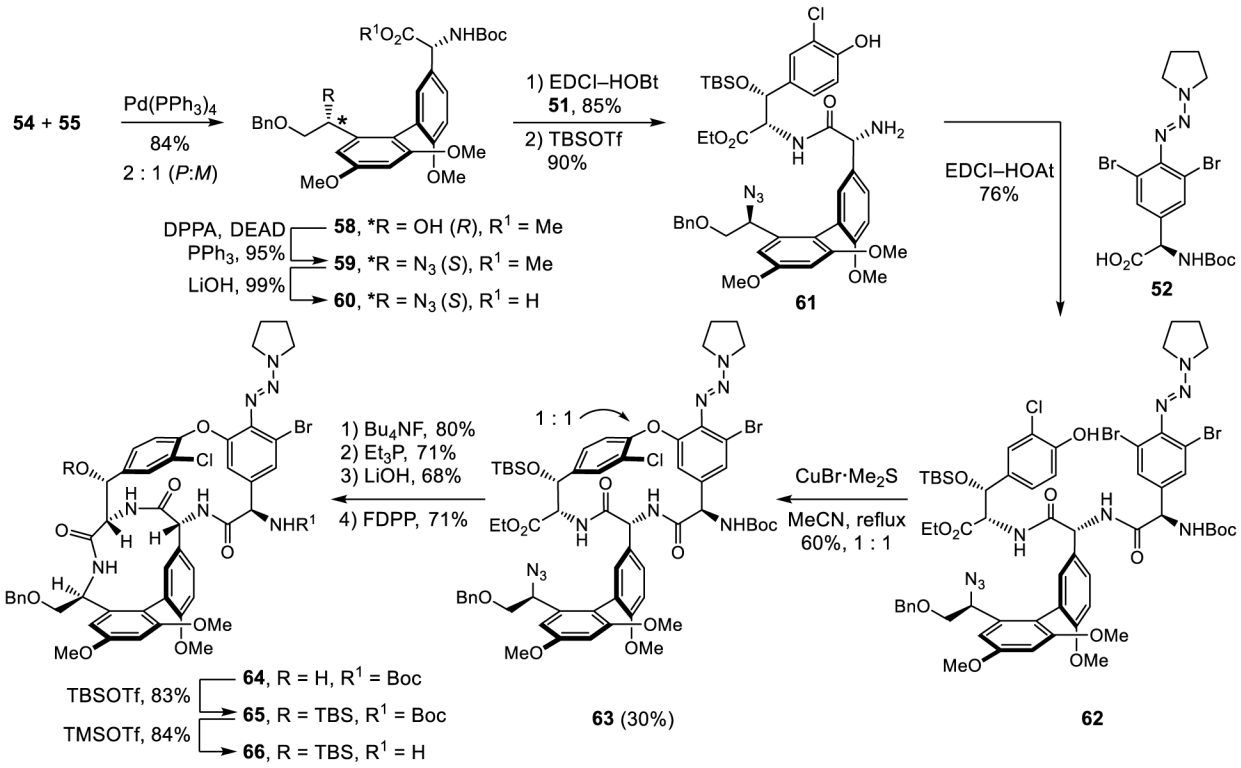

**Scheme 3.**

Evans Synthesis of the Vancomycin ABCD Ring System.

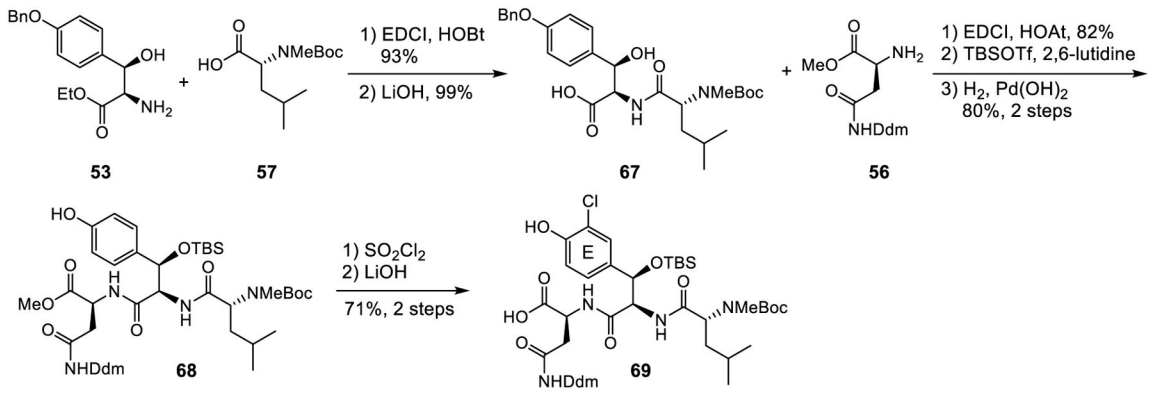



**Scheme 4.**

Final Stages of the Evans Total Synthesis of Vancomycin Aglycon.

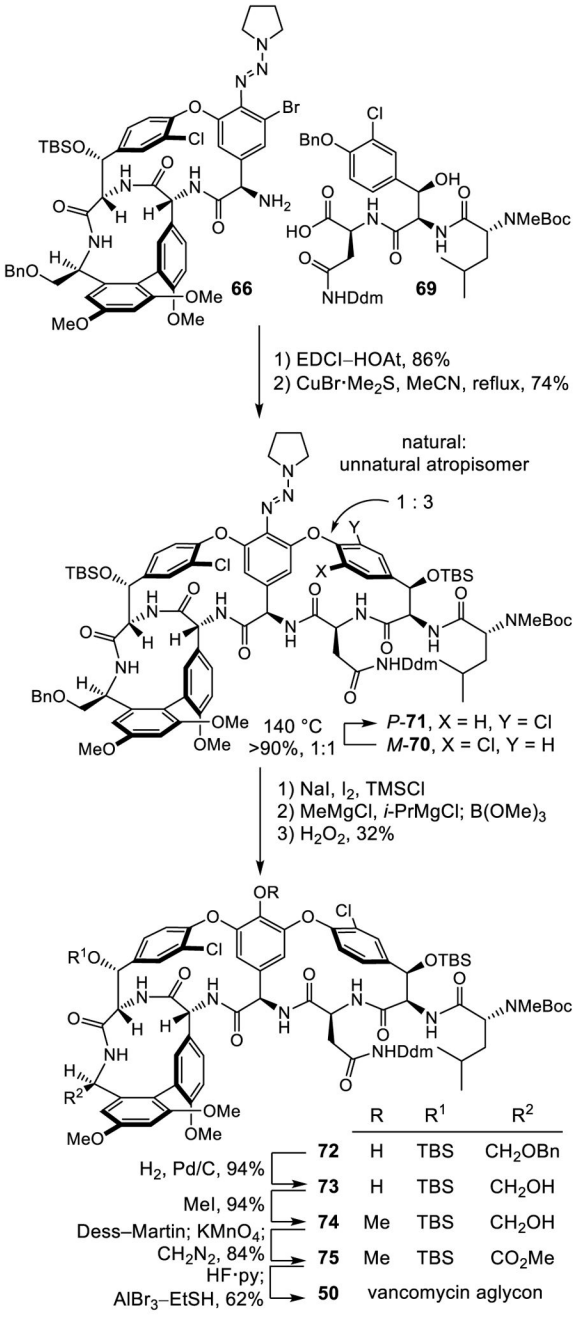



**Scheme 5.**
Nicolaou Synthesis of the Vancomycin ABCD Ring System.



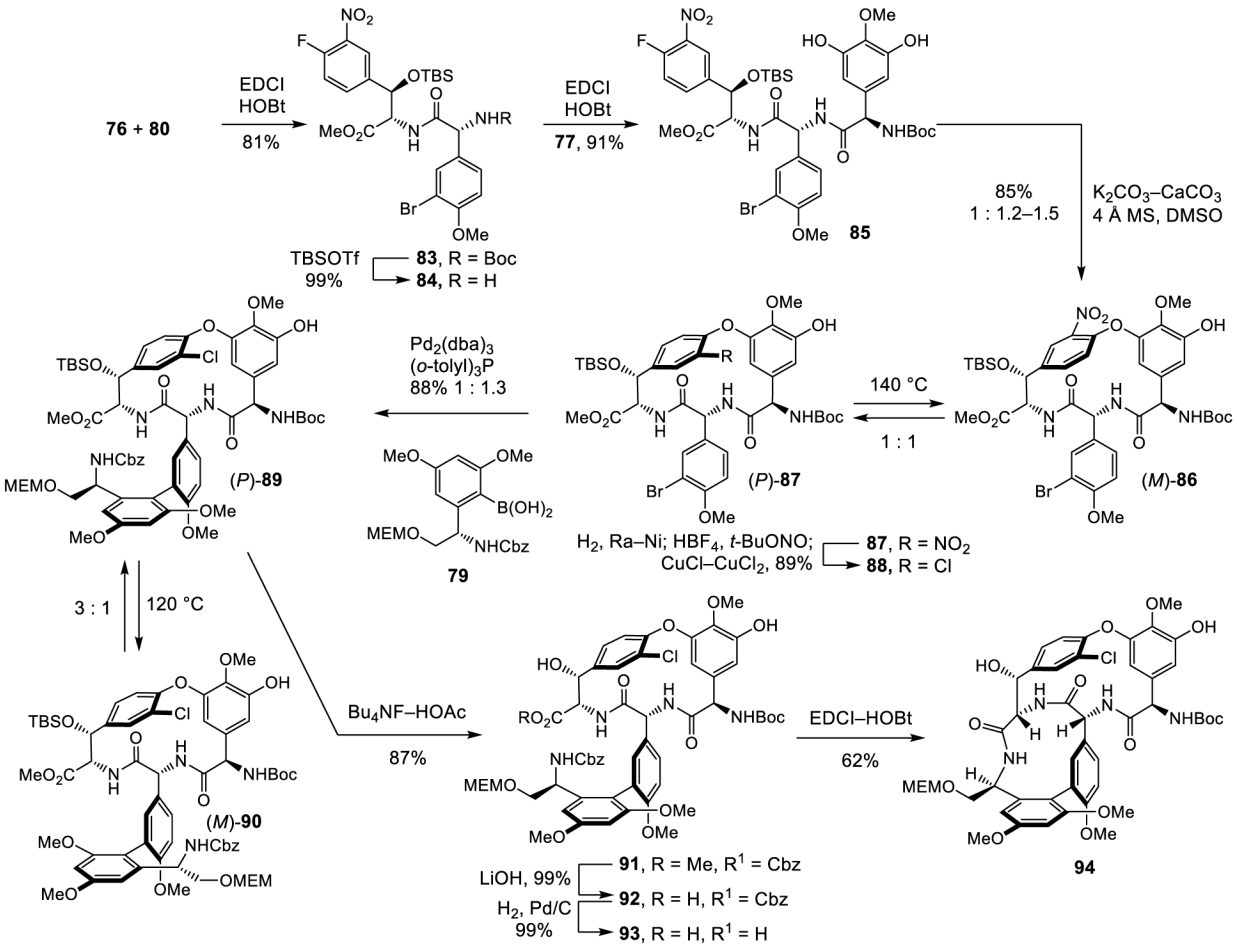

**Scheme 6.**

Nicolaou Synthesis of the E Ring Tripeptide.



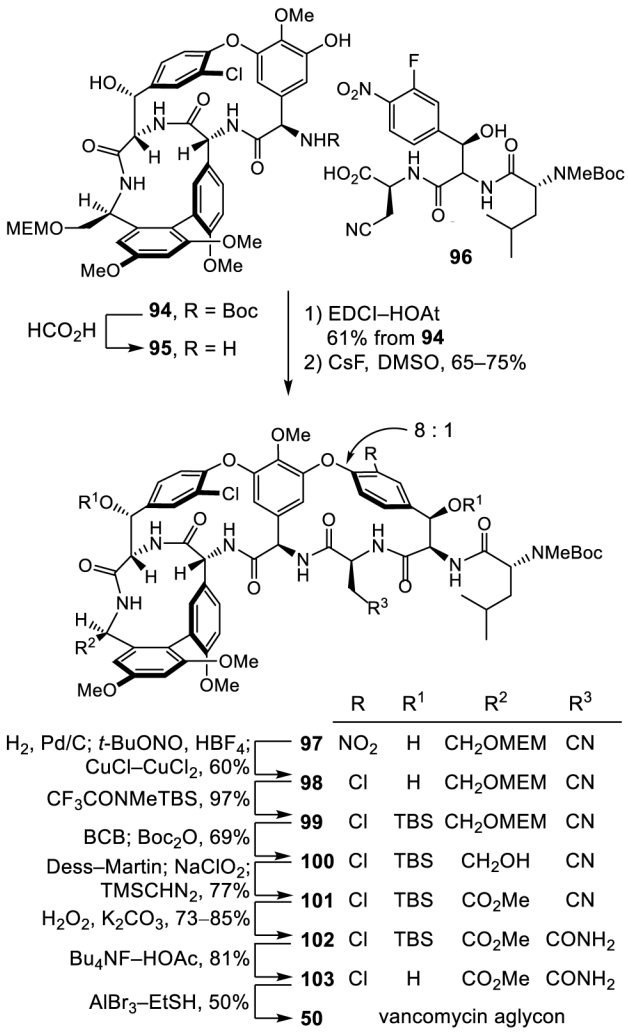

**Scheme 7.**

Final Stages of the Nicolaou Total Synthesis of Vancomycin Aglycon.



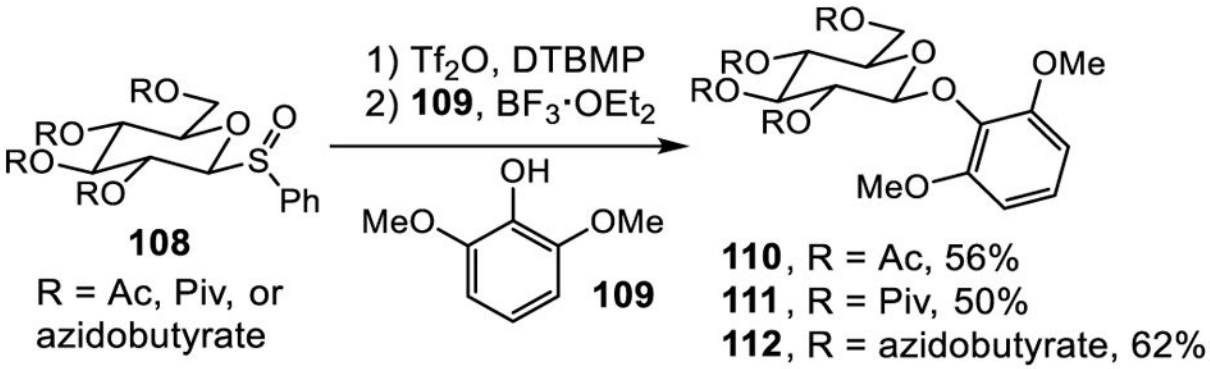

**Scheme 8.**

Boger Synthesis of the Vancomycin ABCD Ring System.

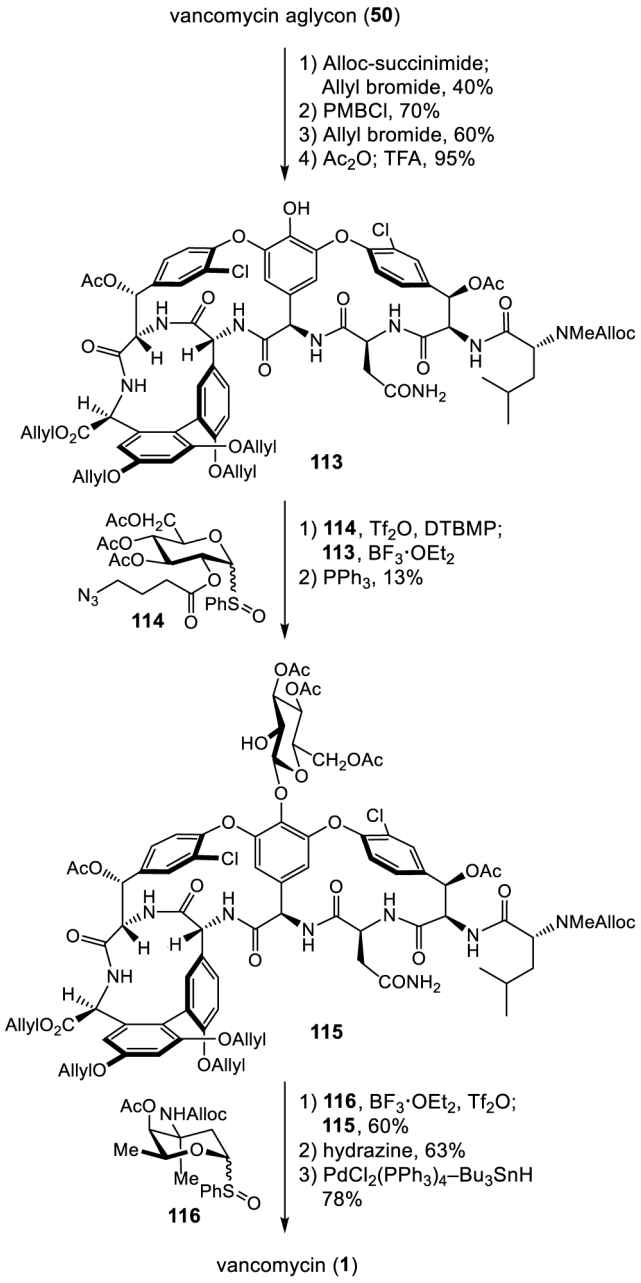



**Scheme 9.**

Final Stages of the Boger Total Synthesis of Vancomycin Aglycon.

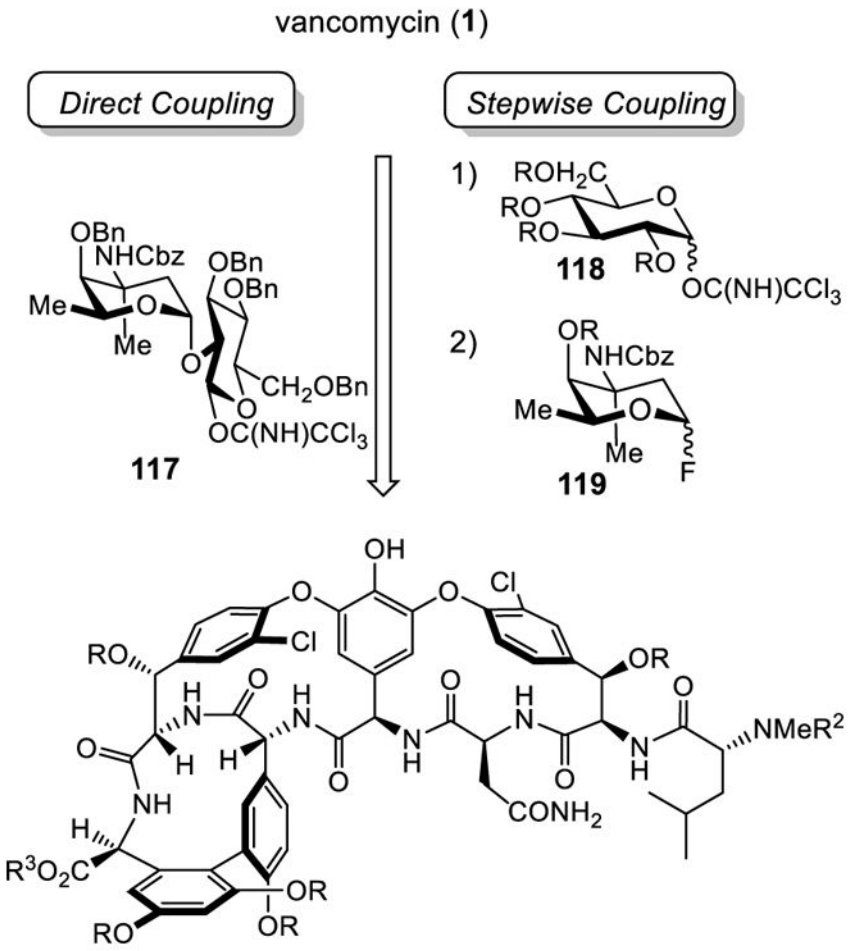



**Scheme 10.**
Examination of Impact of C2 Ester Functionality with Model Substrate **109**.

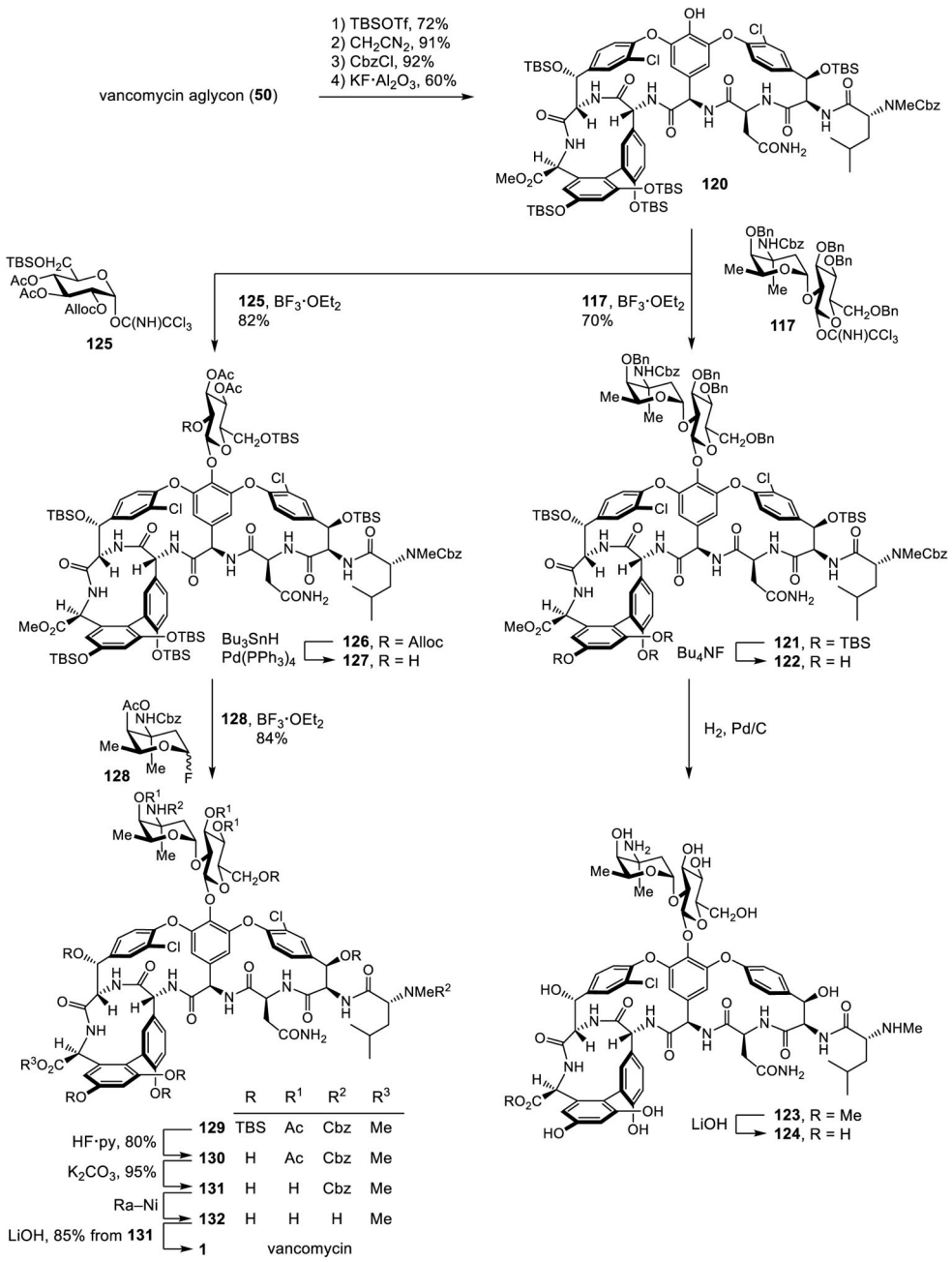



**Scheme 11.**

Kahne Synthesis of Vancomycin (**1**) from the Aglycon **50**.

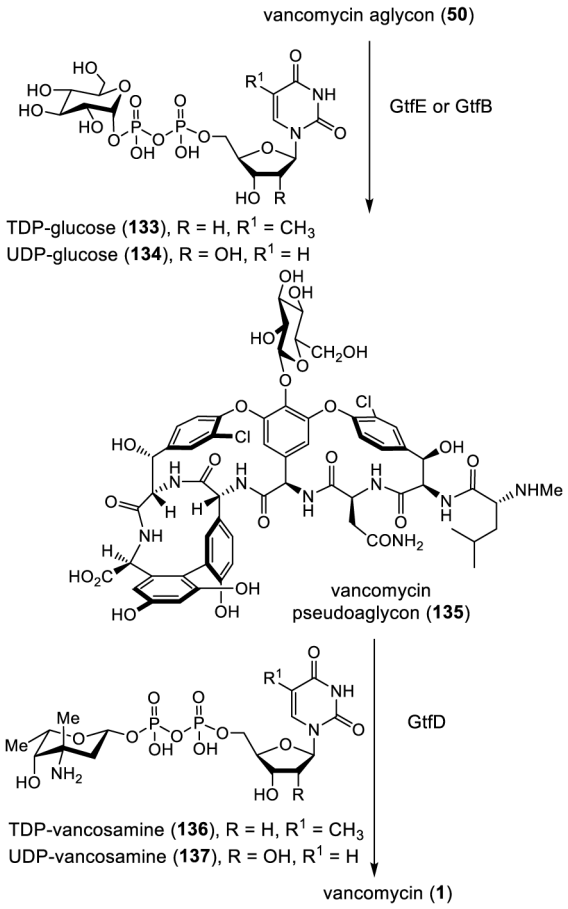



**Scheme 12.**
Complementary Synthetic Approaches for Chemical Glycosylation.



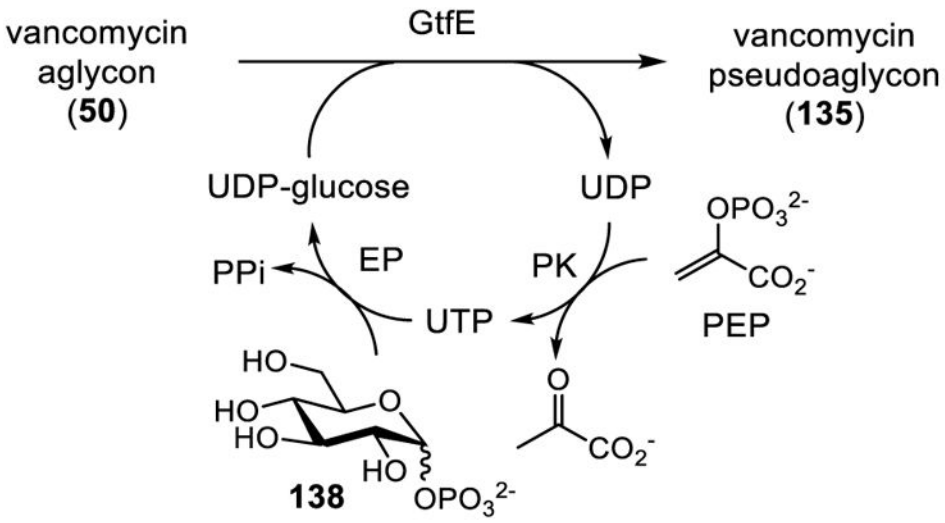

**Scheme 13.**

Direct and Sequential Glycosylations of a Protected Vancomycin Aglycon, Nicolaou Completion of the Total Synthesis of Vancomycin.

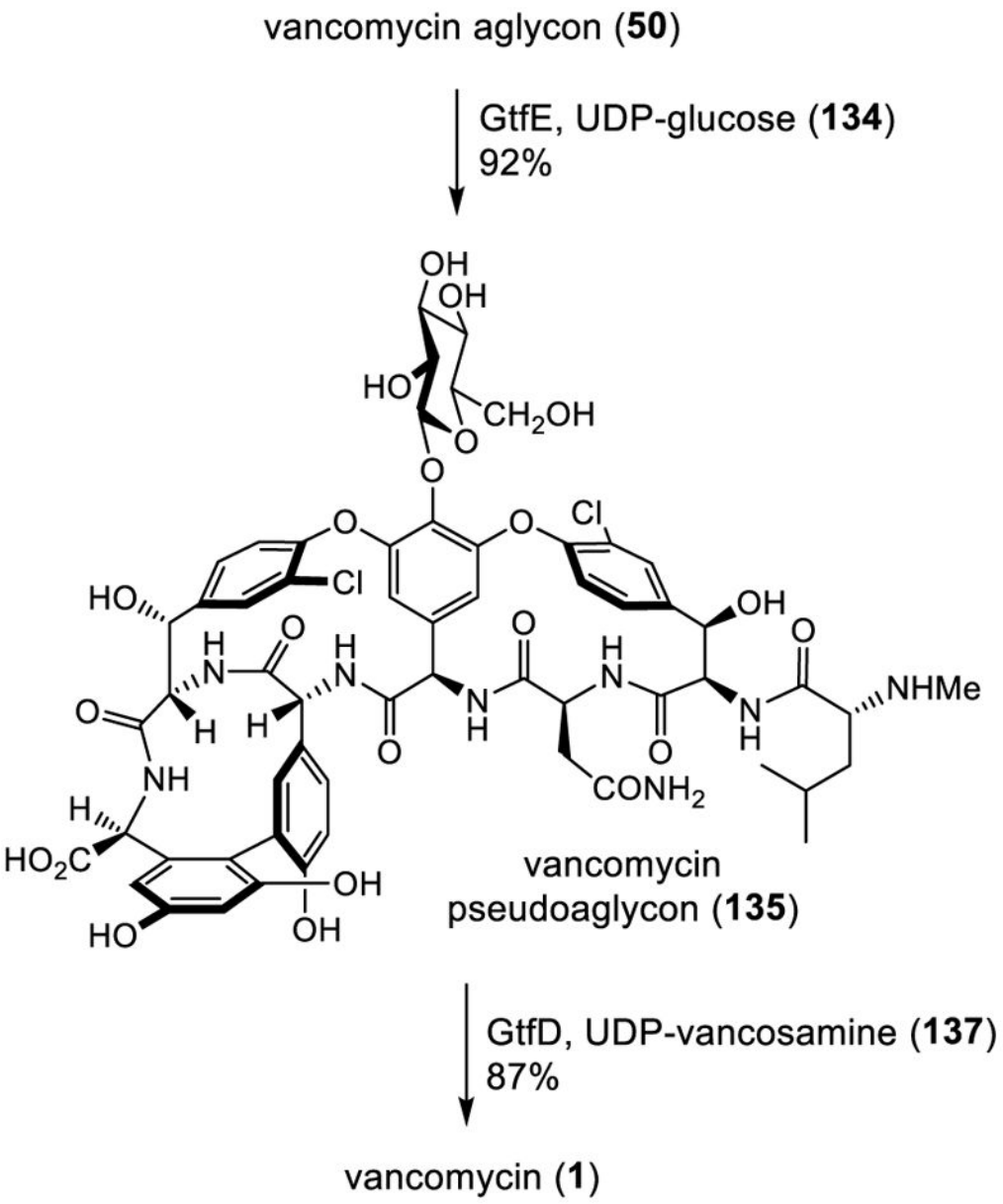



**Scheme 14.**

Enzymatic Carbohydrate Introduction on the Vancomycin Aglycon (**50**).

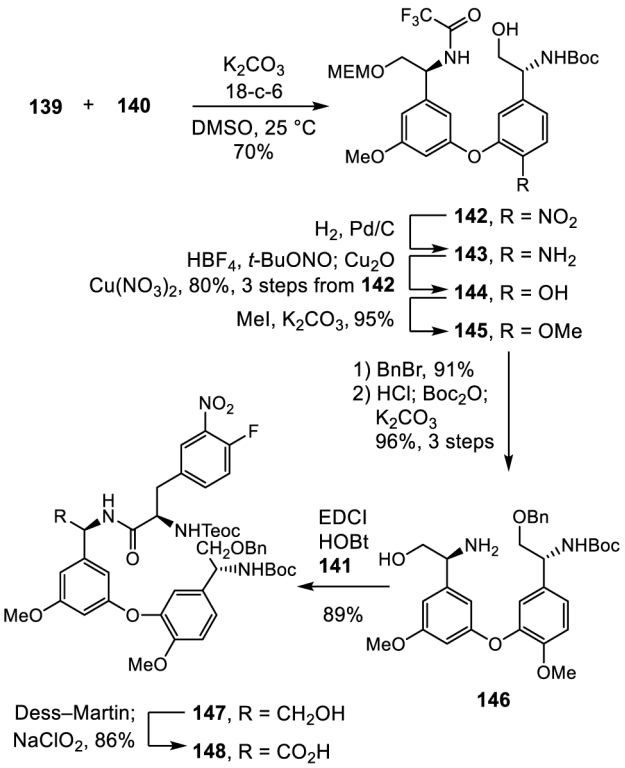



**Scheme 15.**
Wong One-pot Initial Glycosylation of Vancomycin Aglycon (**50**).



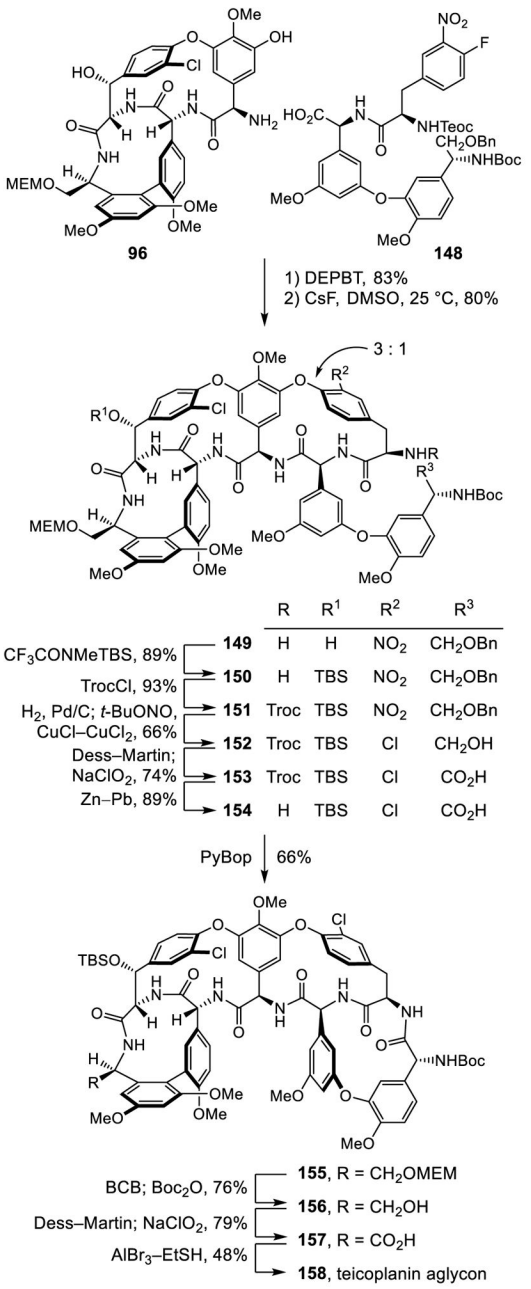

**Scheme 16.**

Boger Enzymatic Carbohydrate Introduction on the Vancomycin Aglycon (**50**), Completion of a Second Total Synthesis of Vancomycin.



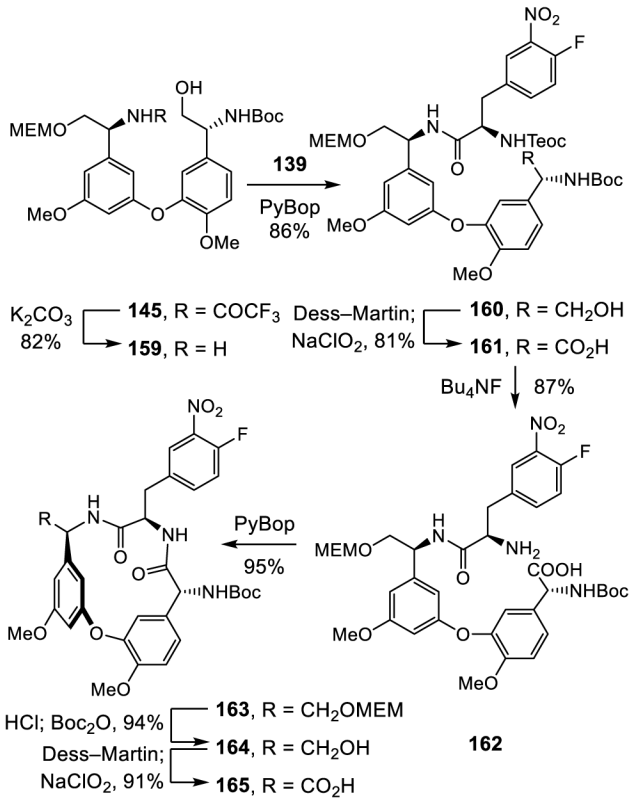

**Scheme 17.**

Boger First Generation Synthesis of the Acyclic EFG Tripeptide.



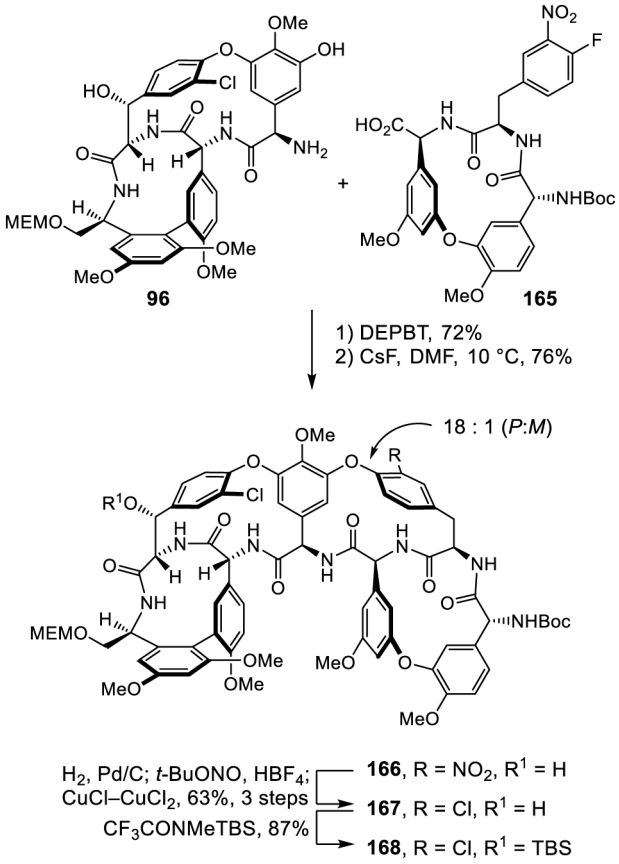

**Scheme 18.**

Final Stages of the Boger First Generation Total Synthesis of Teicoplanin Aglycon.



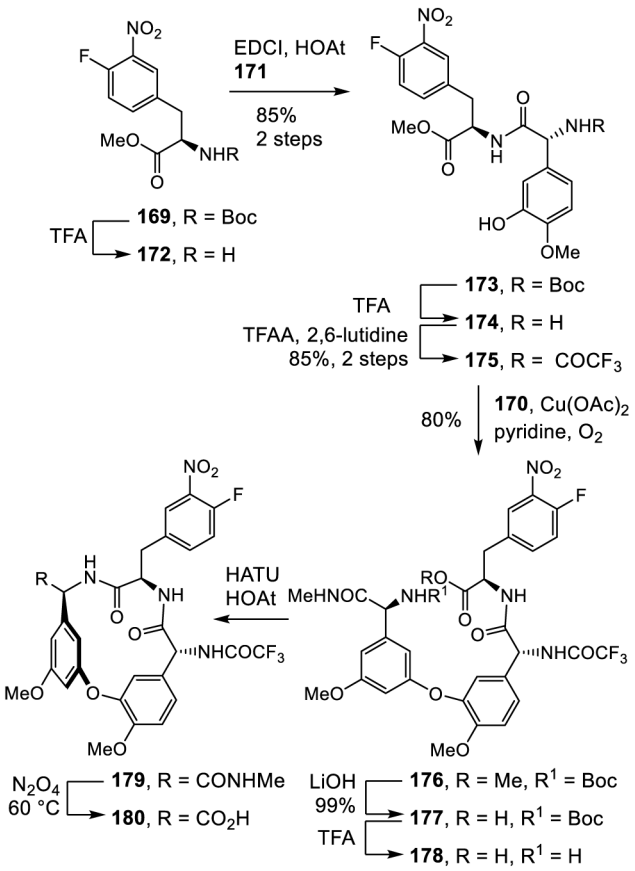

**Scheme 19.**

Boger Second Generation Synthesis of the Teicoplanin Aglycon FG Ring System.

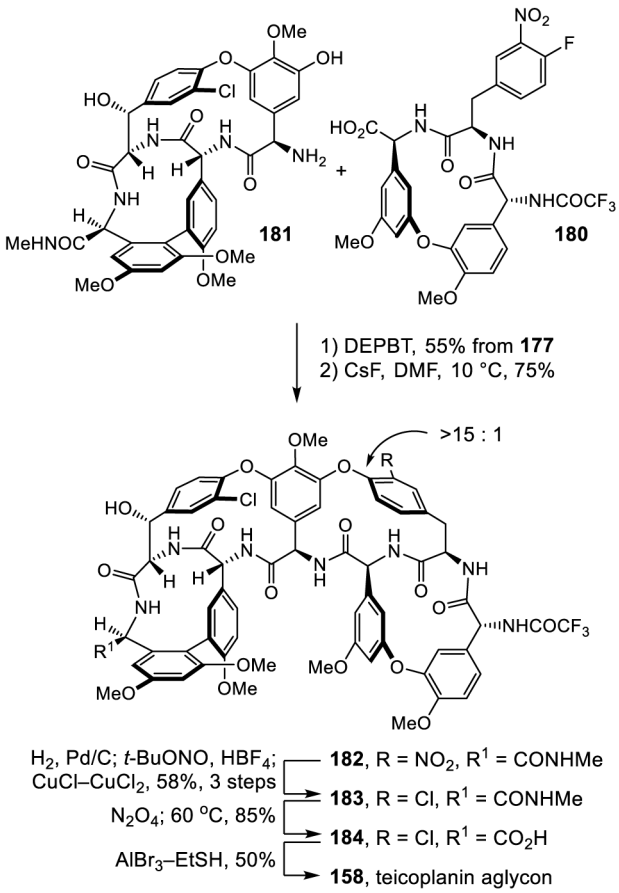



**Scheme 20.**

Final Stages of the Boger Second Generation Total Synthesis of Teicoplanin Aglycon.

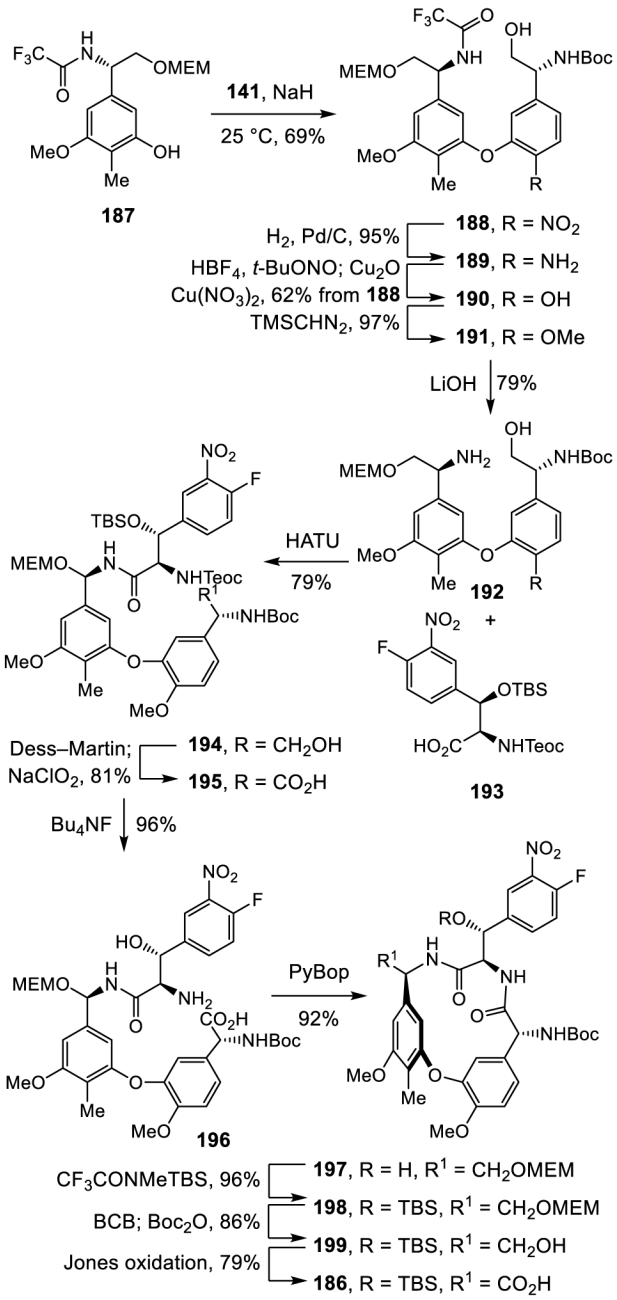



**Scheme 21.**
Evans Synthesis of the Teicoplanin EFG Fragment.



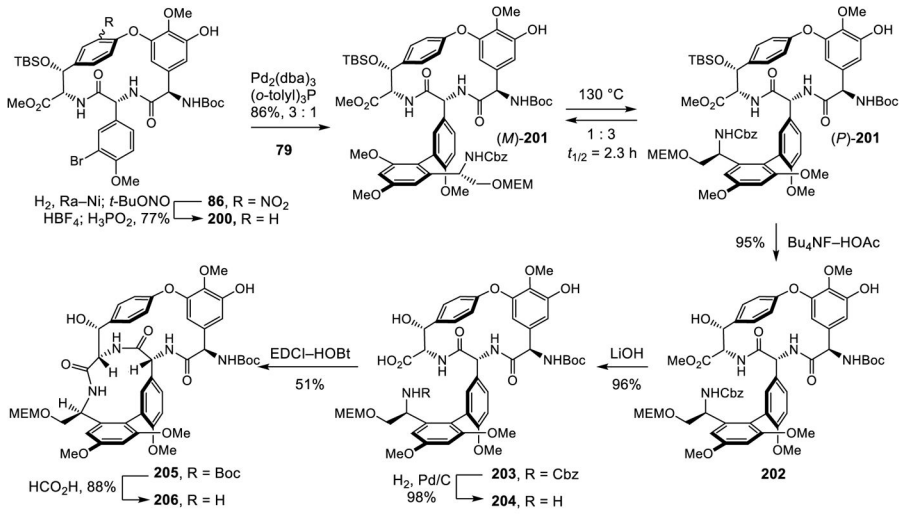

**Scheme 22.**

Final Stages of the Evans Total Synthesis of Teicoplanin Aglycon.



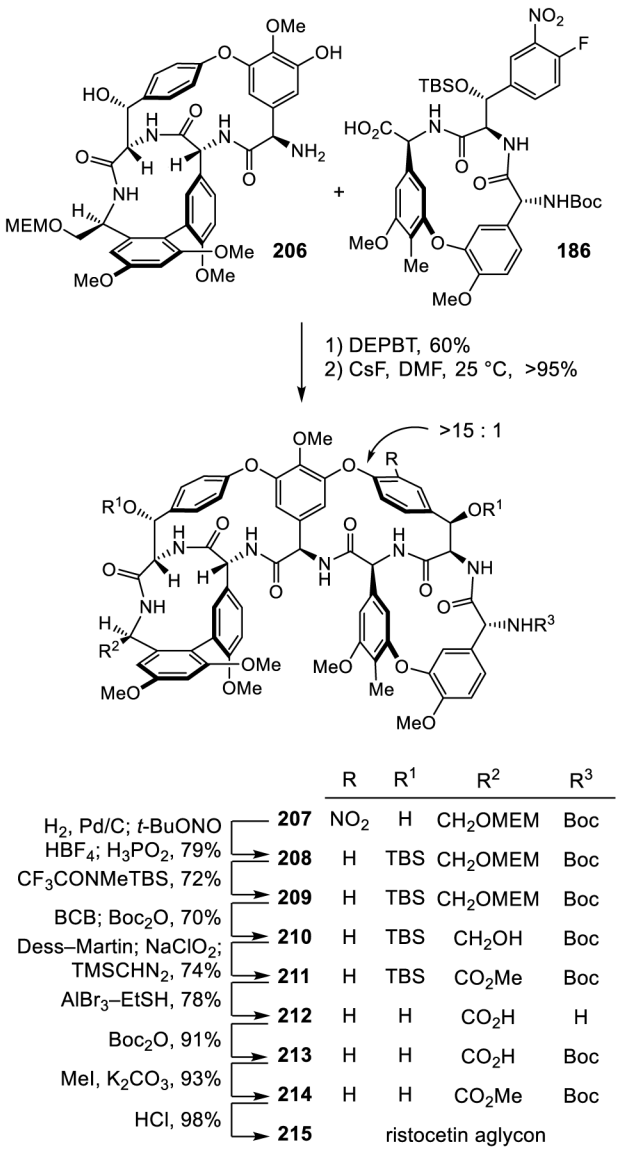

**Scheme 23.**

Boger Synthesis of the Ristocetin A EFG Fragment.



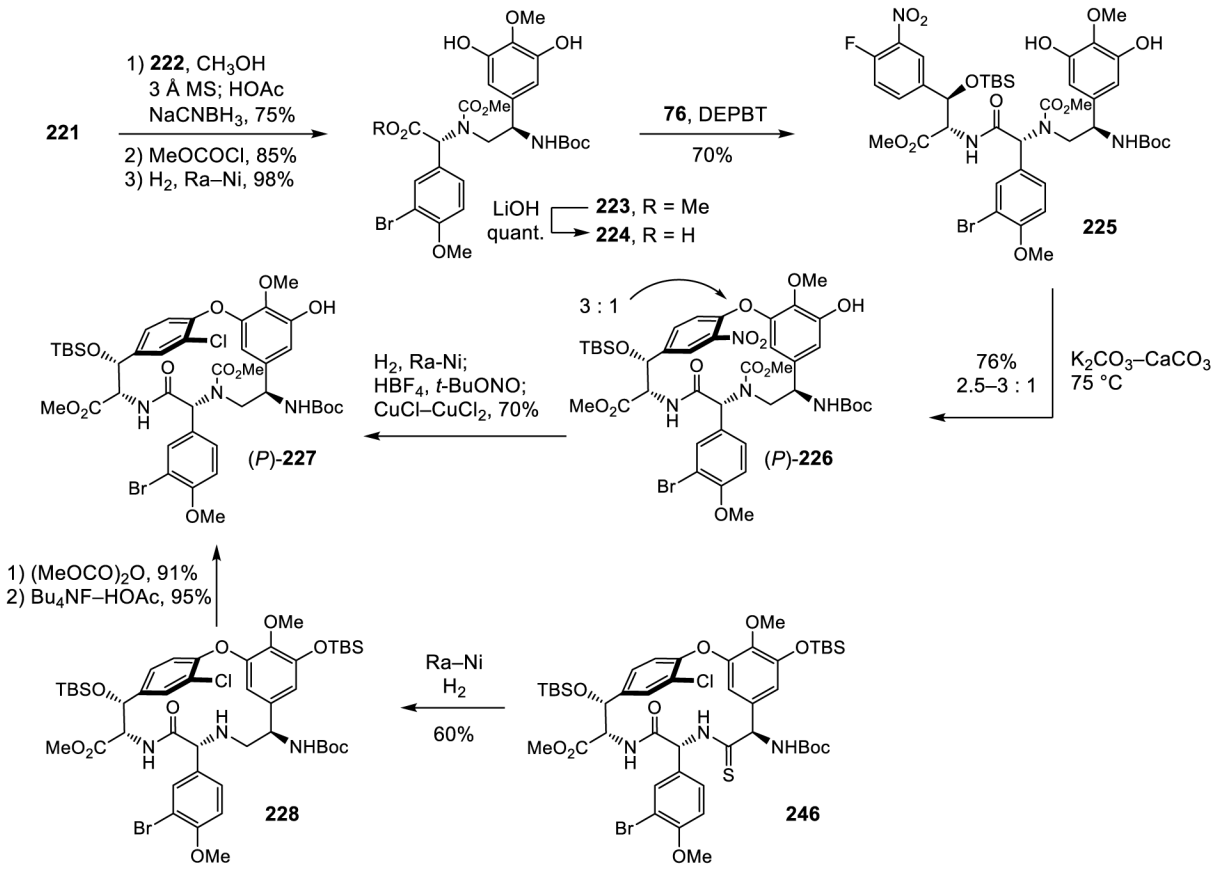

**Scheme 24.**

Boger Synthesis of the Ristocetin A ABCD Ring System.



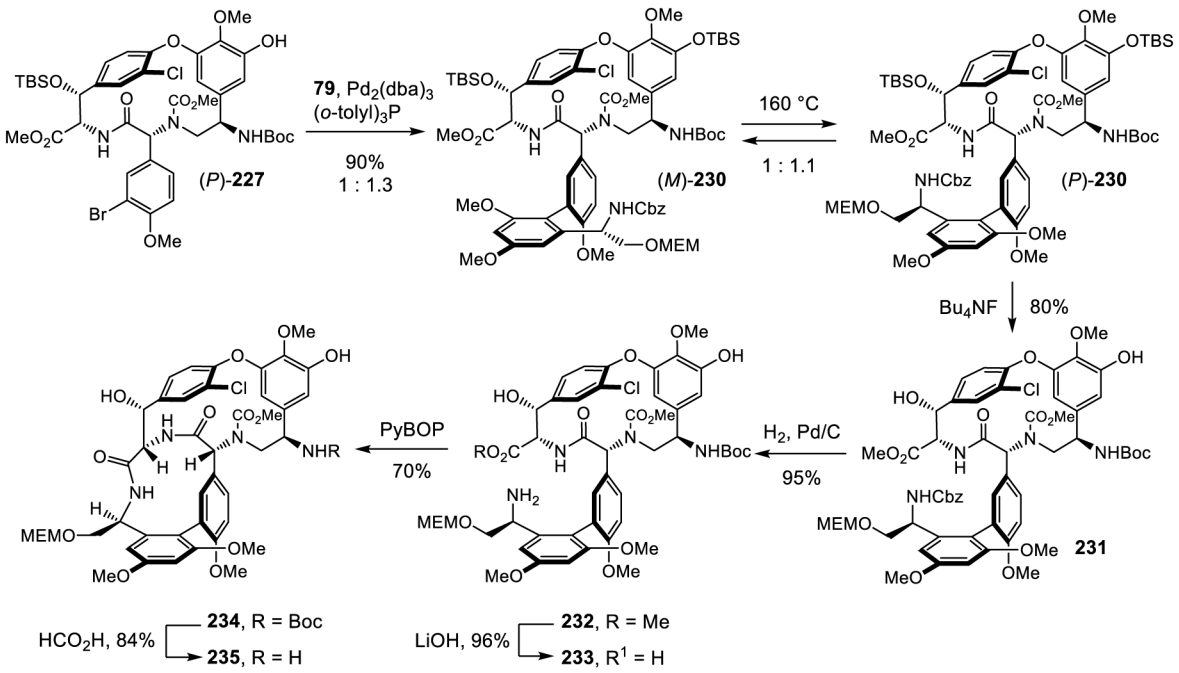

**Scheme 25.**

Final Stages of the Boger Total Synthesis of Ristocetin A Aglycon.

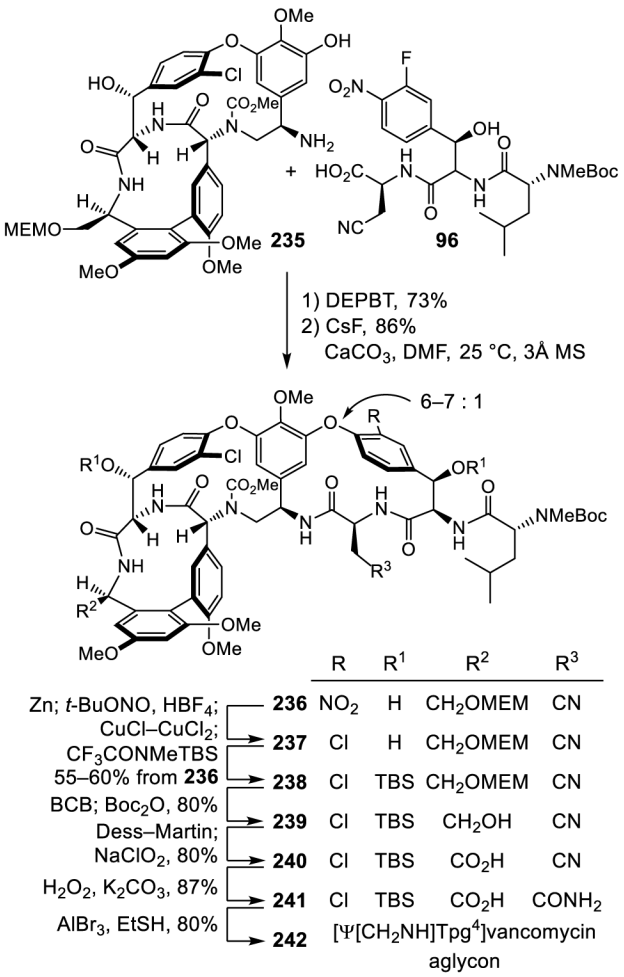



**Scheme 26.**

Synthesis of the Modified CD Ring System **227**.

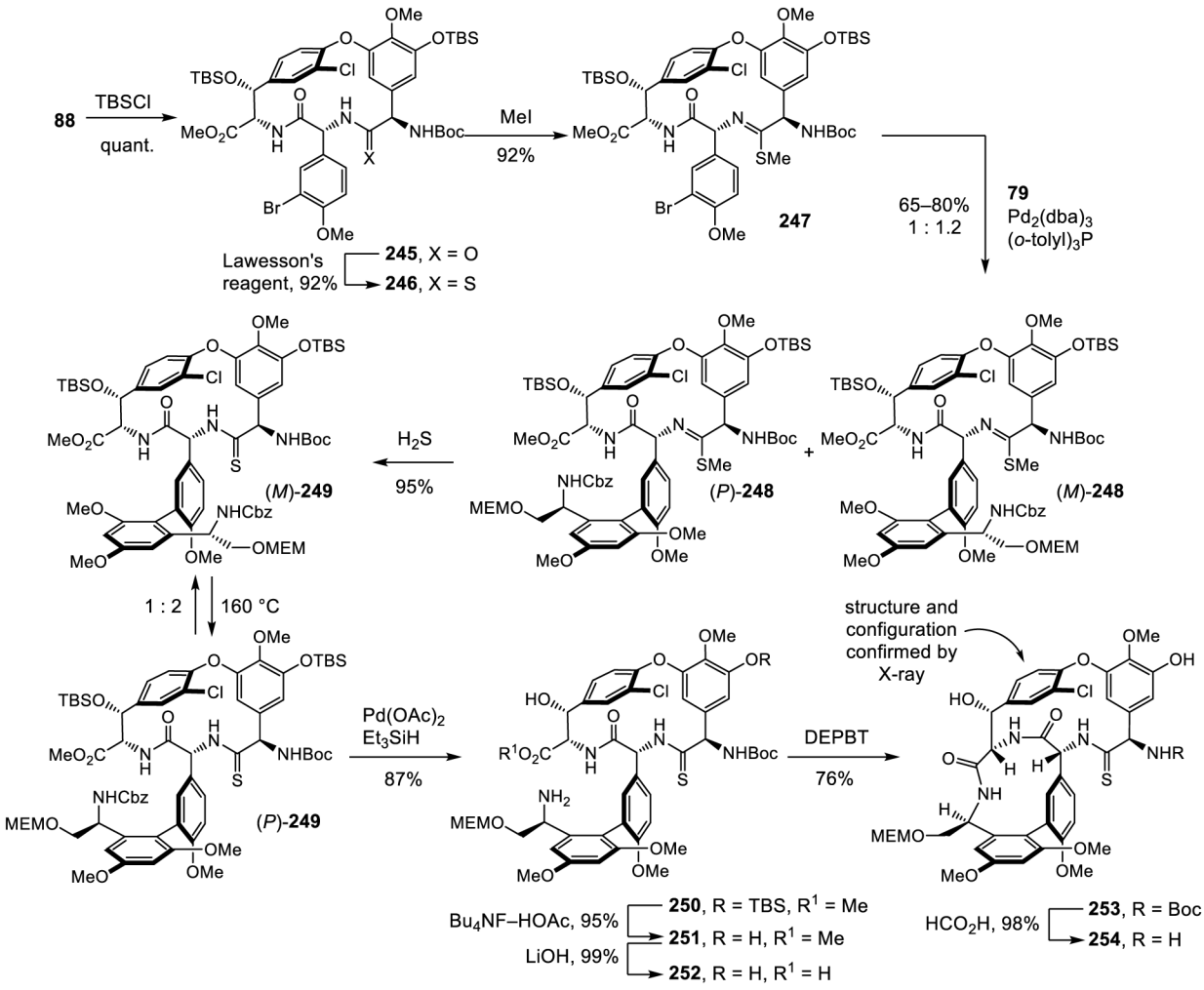



**Scheme 27.**
Synthesis of Modified ABCD Ring System **235**.



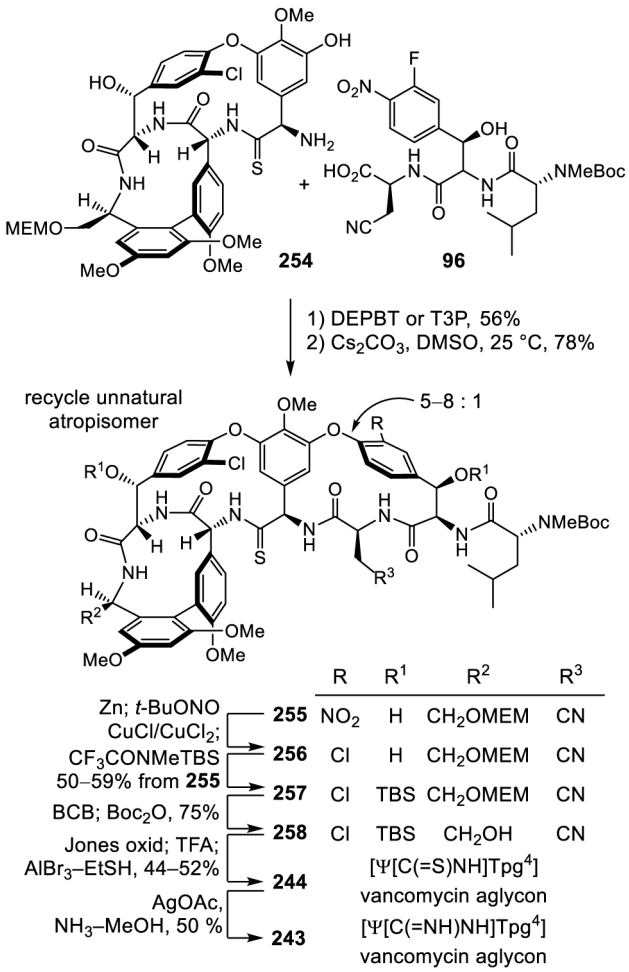

**Scheme 28.**

Completion of the Boger Total Synthesis of [Φ[$CH_2NH$]$Tpg^4$]Vancomycin Aglycon.



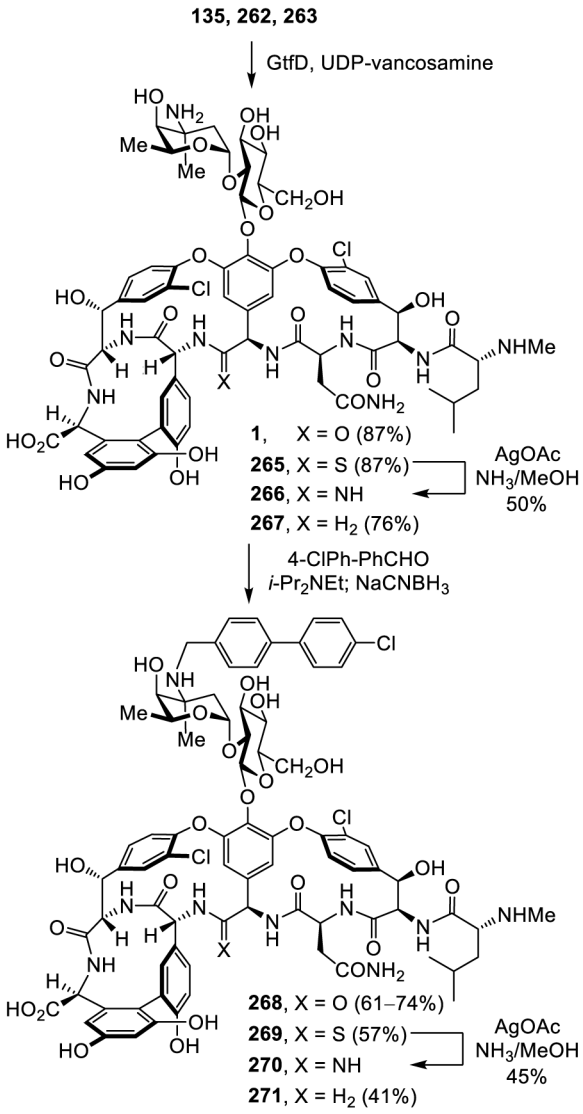

**Scheme 29.**

Synthesis of the ABCD Ring System Bearing a Residue 4 Thioamide.



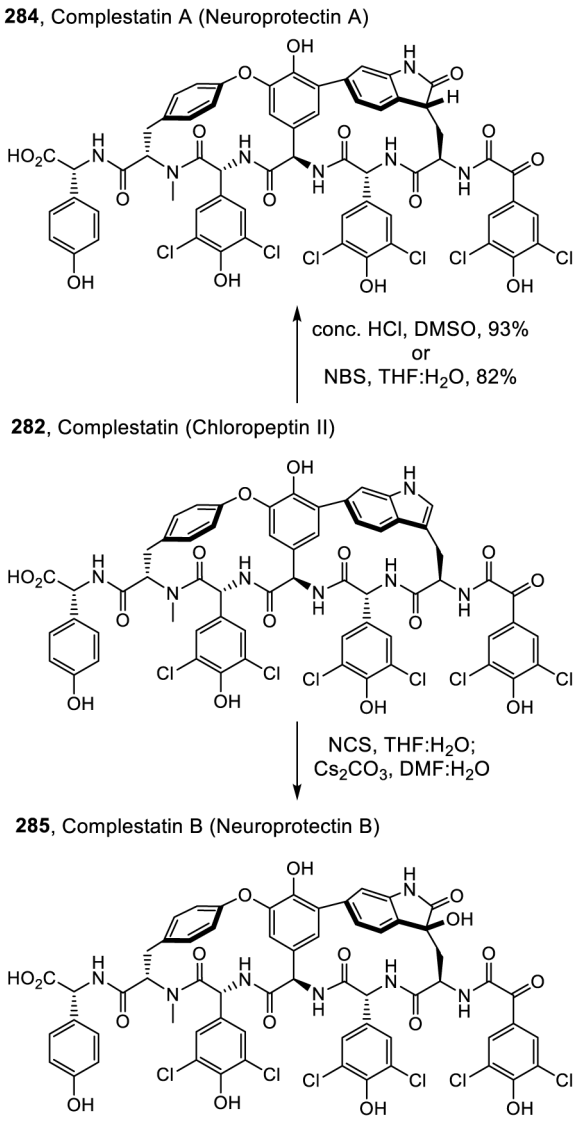

**Scheme 30.**

Completion of the Boger Total Synthesis of [Φ[C(=S)NH]Tpg$^4$]Vancomycin Aglycon and [Φ[C(=NH)NH]Tpg$^4$]Vancomycin Aglycon.




**Scheme 31.**

Synthesis of Residue 4 Modified Vancomycins and their CBP Derivatives.




**Scheme 32.**

Boger Synthesis of Complestatin A and B (Neuroprotectin A and B).