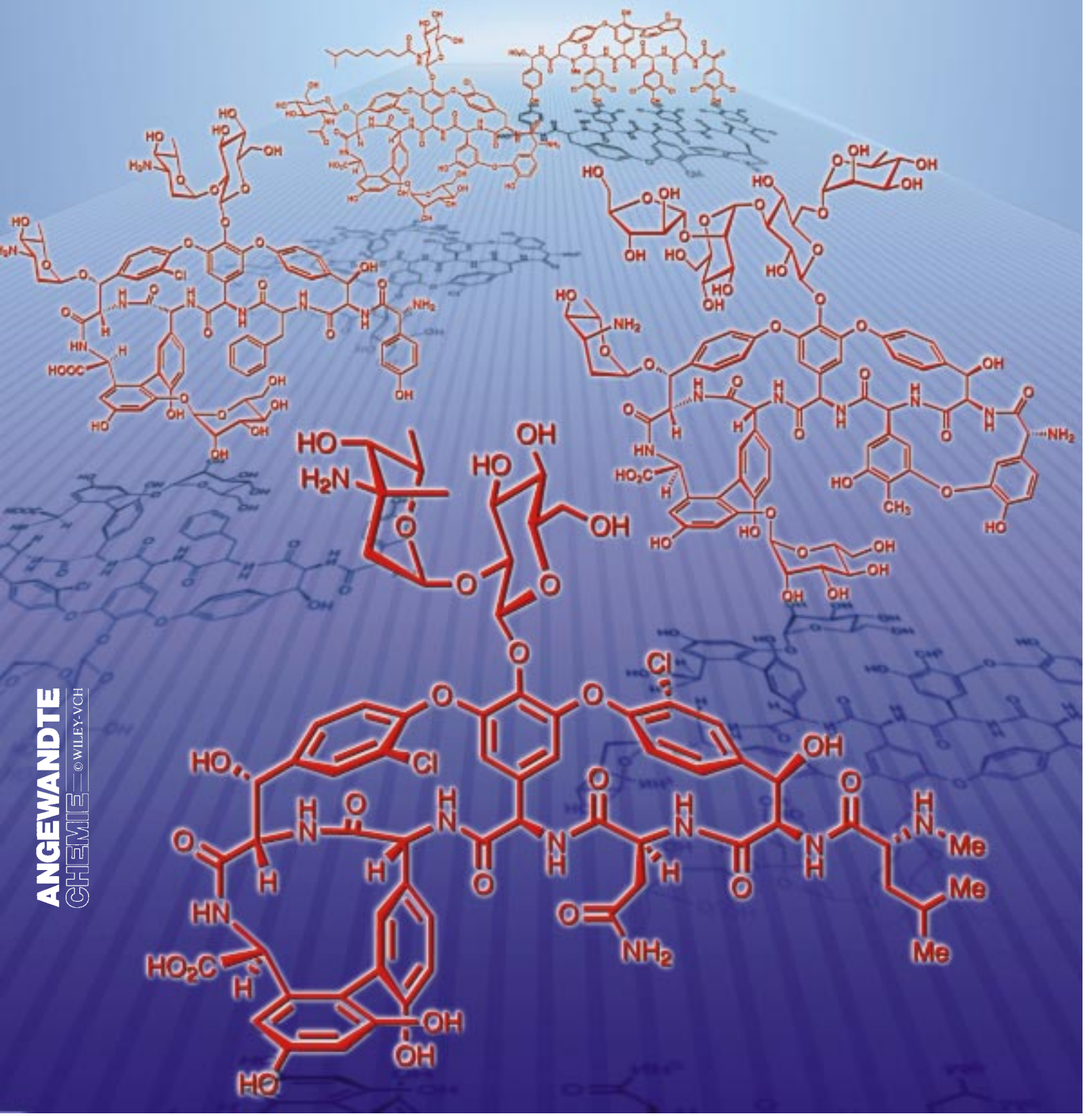
Chemistry, Biology, & Medicine of the Glycopeptide Antibiotics



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Chemistry, Biology, and Medicine of the Glycopeptide Antibiotics**

K. C. Nicolaou,* Christopher N. C. Boddy, Stefan Bräse, and Nicolas Winssinger

Throughout the ages humankind and bacteria have faced each other with different roles and intentions, ranging from harmonious symbiosis to waging wars against each other. This dynamic relationship is fast changing, with humans seeking to exploit the bacterial kingdom to their benefit while at the same time having to deal with serious infections caused by ever increasing drug-resistant bacterial strains. The constant challenge bacteria face from antibiotics results in the selection of resistant individuals, which renders, over time, the most widely used antibiotics ineffective. This fiercely fought challenge–resistance struggle has already disposed of certain early classes of antibiotics, threatens to render the β-lactams obsolete, and is now encroaching on the last bastion of clinically effective antimicrobial agents, vancomycin (**1**) and its relatives, the glycopeptide antibiotics. As a consequence, intense efforts have been initiated to explore the chemistry and biology of these highly complex and synthetically challenging molecules. These research efforts culminated in significant advances in the areas of new synthetic technology, model systems and semisynthetic analogues, and ultimately, the total synthesis of vancomycin. This review article presents the state of the art in the chemistry, biology, and medicine of the glycopeptide antibiotics and projects ahead into their future.

Keywords: biaryls · glycopeptides · mode of action · total synthesis · vancomycin

1. Introduction

The discovery of penicillin (**2**, Figure 1)[1] and its development as an antimicrobial agent during World War II marked a triumph for humankind over bacteria and heralded a new era of medicine against disease. But as we stand at the doorstep of the twenty-first century, there are clear and persistent signs that the victory was certainly not total and that the war against infectious bacteria is destined to go on. One of the most fierce bacterial enemies we face today is *Staphylococcus aureus* (*S. aureus*, Figure 2A), a species that managed to evade not only penicillin, but also a number of other classical antibiotics[2] such as erythromycin B (**3**, Figure 3)[3] and tetracycline (**4**, Figure 3).[4]

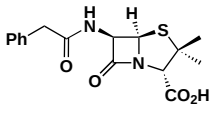

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Figure 1. Structure of penicillin (**2**).

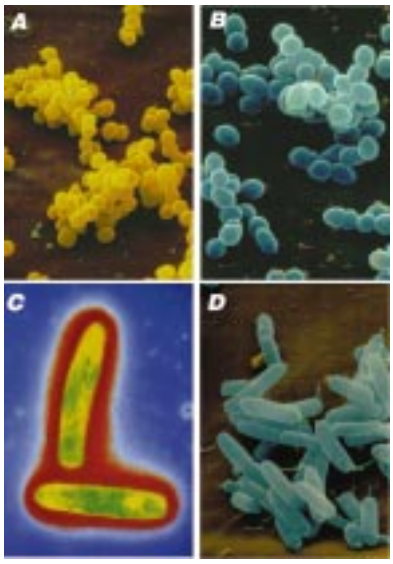

Figure 2. Cell cultures of *S. aureus* (A), *E. faecalis* (B), *M. tuberculosis* (C), and *P. aeruginosa* (D).

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[**] A list of abbreviations can be found at the end of the article.

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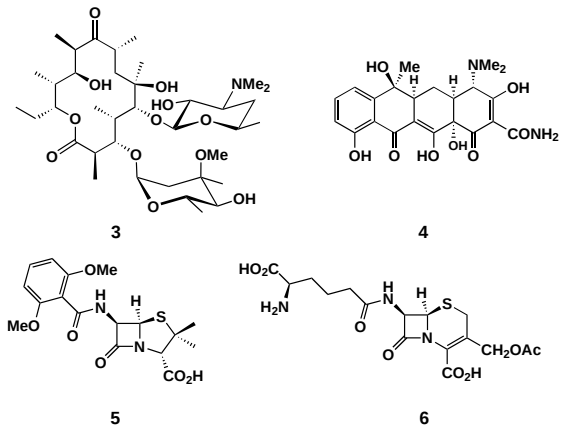

Figure 3. Classical antibiotics: erythromycin B (**3**), tetracycline (**4**), methicillin (**5**), and cephalosporin C (**6**).

2. The Discovery of Vancomycin

Thankfully, a last line of defense against the menace of *S. aureus* was erected by the discovery of the antibiotic vancomycin (**1**, Figure 4) by Eli Lilly in 1956.[5] But even this defense appears to be shaking from the ability of this, and other bacterial strains, to evolve rapidly into drug-resistant strains (Figure 5). In 1997, the first signs of resistance towards vancomycin by *S. aureus* were noted in patients hospitalized in three geographically different locations.[6] Given that vancomycin was the only weapon available against this bacteria, the alarm was taken seriously by health authorities around the world and foreshadows problems ahead. Furthermore, other bacteria such as *Enterococcus faecalis*, *Mycobacterium tuberculosis*, and *Pseudomonas aeruginosa* (Figure 2 B, C, and D, respectively) have already succeeded in deflecting

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K. C. Nicolaou, born in Cyprus and educated in England and the US, is currently Chairman of the Department of Chemistry at The Scripps Research Institute where he holds the Darlene Shiley Chair in Chemistry and the Aline W. and L. S. Skaggs Professorship in Chemical Biology as well is Professor of Chemistry at the University of California, San Diego. His impact on chemistry, biology, and medicine flows from his works in organic synthesis described in 450 publications and 60 patents and his dedication to chemical education as evidenced by his training of over 250 graduate students and postdoctoral fellows. His recent book titled "Classics in Total Synthesis", which he co-authored with Erik J. Sorensen, is used around the world as a teaching tool and source of inspiration for students and practitioners of organic synthesis.

Christopher N. C. Boddy was born in Edmonton, Alberta, Canada in 1973. He received his B.Sc. from the University of Alberta in 1995 while conducting research under the guidance of Professor Derrick L. J. Clive. He subsequently joined the Scripps Research Institute in sunny California as a graduate student. His work under Professor K. C. Nicolaou has focused on the total synthesis of vancomycin. His research interests include synthesis of biologically interesting molecules through both traditional chemical routes and through the coupling of synthetic chemistry with biosynthetic pathways.

Stefan Bräse was born in Kiel, Germany in 1967. He studied in Göttingen, Bangor (UK), and Marseille, and received his Ph.D. in 1995,while working with A. de Meijere in Göttingen. After postdoctoral appointments at Uppsala University (J. E. Bäckvall) and The Scripps Research Institute (K. C. Nicolaou), he began his independent research career at the RWTH Aachen in 1997 ("Habilitation", group of D. Enders). His research interests include asymmetric metal-catalyzed processes and combinatorial chemistry towards the synthesis of biologically active compounds.

Nicolas Winssinger was born in Belgium in 1970. He received his B.S. in chemistry from Tufts University conducting research in the laboratory of Professor M. D'Alarcao. Before joining The Scripps Research Institute as a graduate student in chemistry in 1995, he worked for two years under the direction of Dr. M. P. Pavia at Sphinx Pharmaceuticals in the area of molecular diversity focusing on combinatorial chemistry. At Scripps, he joined the laboratory of Professor K. C. Nicolaou where he has been working on methodologies for solid-phase chemistry and combinatorial synthesis. His research interests include natural products synthesis, molecular diversity, molecular evolution, and their application to chemical biology.

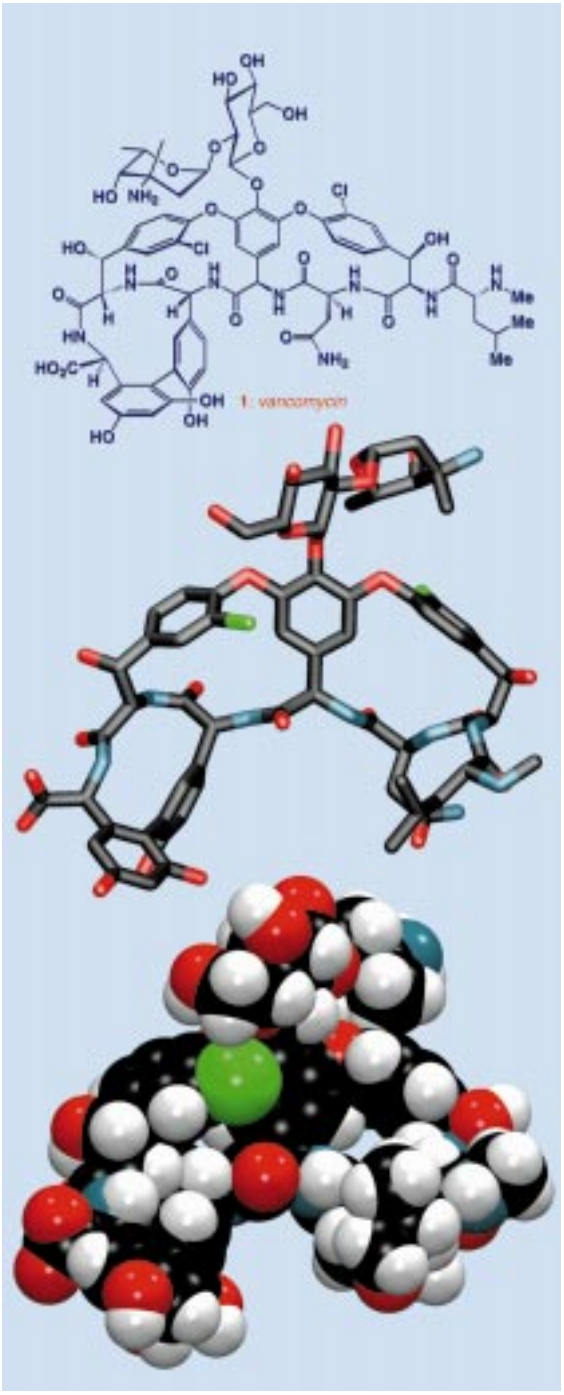


Figure 4. Structure of vancomycin (**1**).

essentially every arrow thrown against them by clinicians, and threaten humankind with unprecedented resistance. Characteristic of the menace is the increasing number of deaths from tuberculosis in the industrial world after years of decline and near eradication.[7]

Despite the recent incidences of bacterial resistance to vancomycin, this antibiotic became almost legendary because of its heroic performance against methicillin-resistant *S. aureus* (MRSA).[8] In the mid-1950s, scientists at Eli Lilly isolated vancomycin from a fermentation broth of the actinomycete *Streptomyces orientalis*, later renamed *Nocardia orientalis*, and finally reclassified as *Amycolatopsis orientalis*.[9] The

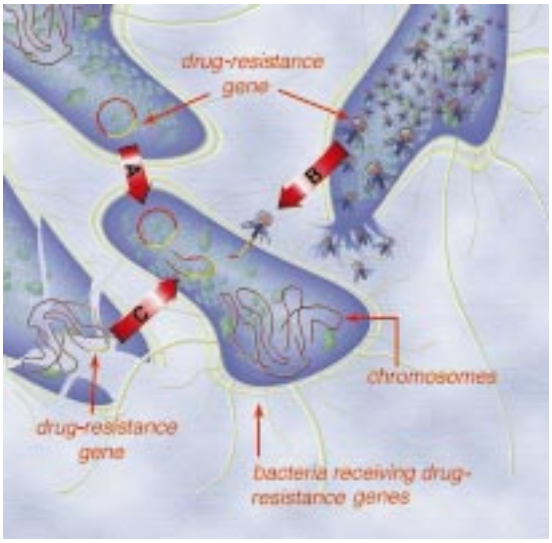


Figure 5. Three modes of resistance transfer between different bacteria: A) a plasmid containing the genes encoding for antibiotic resistance (yellow) is transferred from a donor bacterium to a new bacterium; B) bacterial DNA containing the genetic information for resistance is transferred through a virus to a new bacterium; C) incorporation of genes encoding for antibiotic resistance through DNA scavenged from dead cells.

bacteria were grown from a soil sample collected from the jungles of Borneo. The purified natural product exhibited lethal properties against all tested strains of *Staphylococcus* and other Gram-positive bacteria. Originally given the number O5865, the powerful substance was subsequently coined vancomycin, the name being derived from the verb "to vanquish". Vancomycin became available for clinical use upon its FDA approval in 1958. The introduction of vancomycin as an antistaphylococcal agent was followed shortly thereafter by methicillin (**5**, Figure 3),[10] the cephalosporins (**6**, Figure 3)[11] and the linomycins,[12] drugs which initially received wider clinical acceptance in contrast to vancomycin as a consequence of the apparent toxic side effects of the latter. Vancomycin became much more popular as its purity improved, which alleviated many of the side effects, and because of the increased drug resistance to other antibacterial agents (worldwide sales in 1997 were $417 million).[13] Today, vancomycin and its sister antibiotic teicoplanin (**10**, Figure 7) are indispensable weapons—indeed, in some cases, the last and only resort—of the clinician facing life-threatening situations with patients infected with drug-resistant bacterial strains.

A number of the top-selling antibiotics worldwide (Figure 6) are in danger of being rendered obsolete by the encroachment of antibiotic resistance. Such resistance proliferates readily within the bacterial kingdom through gene transfer as depicted in Figure 5. As a result of this desperate need for new, clinically effective antibiotics, a high priority has been placed on the discovery of antibacterial agents, both naturally occurring and synthetic. Thus, in addition to vancomycin and teicoplanin, hundreds of other related natural products have been discovered and thousands of semisynthetic analogues have been prepared. These constitute the large class of compounds collectively known as the glycopeptide antibiotics.[14] In this article, we review the

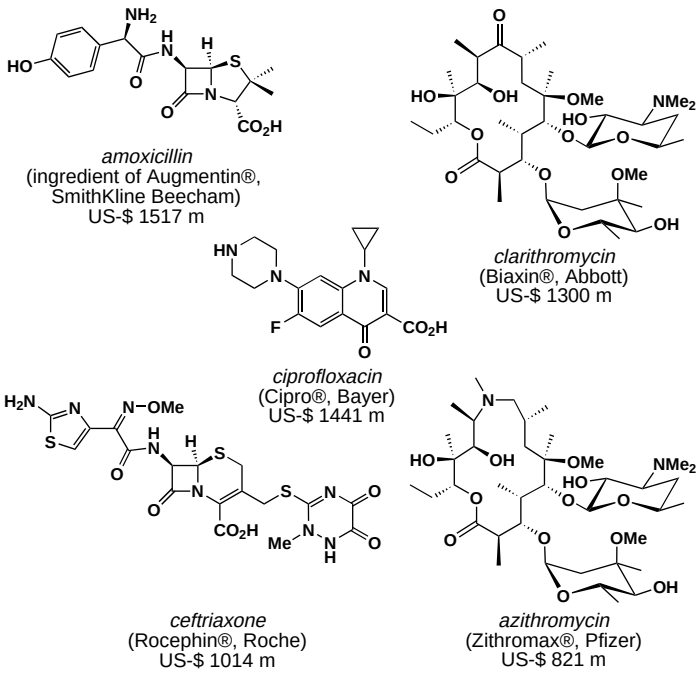


Figure 6. The top five best-selling antibiotics (1997 worldwide sales).[13]

chemistry, biology, and medicine of these substances with the aim of bringing the reader up to date with the latest developments in this field.

3. Structure, Classification, and Occurrence of the Glycopeptide Antibiotics

Prior to 1984, the glycopeptide class included few members beyond vancomycin (**1**), teicoplanin (**10**), ristocetin (**9**, Figure 7), and avoparcin (Table 1). With the acknowledgment of the threat posed by antibiotic resistance, the class swelled to include thousands of natural and semi-synthetic compounds. Structural studies on these compounds have clarified the biological mode of action and serve as a basis for reasonable predictions regarding structure – activity relationships.

Studies on the structure of vancomycin provided a foundation for the determination of all other glycopeptide antibiotics. Early attempts to elucidate the structure of vancomycin were hampered by impurities, lack of crystallinity, and structural complexity. As improvements in purification methods and newer spectroscopic techniques came along, the pioneering studies on the structure of vancomycin became possible. Most notable among these works was the first attempt at structural determination through degradative studies by F. J. Marshall (1965),[15] the NMR studies of D. H. Williams and J. R. Kalman (1977),[16] and the X-ray crystallographic analysis of the degradation product CDP-I by G. M. Sheldrick et al. (1978).[17] Building on these studies, Harris and Harris established the complete structure of vancomycin (**1**) in 1982.[18] Soon to follow were the full structural characterizations of ristocetin (**9**) and teicoplanin (**10**). In 1995, the first crystallographic analysis of an intact, naturally occurring glycopeptide antibiotic, balhimycin (**7**, Figure 7), was reported by Sheldrick et al.[19] Soon thereafter followed the crystal structures of vancomycin[20] and the parvodicin aglycon (1996).[21] The structure of vancomycin bound to a surrogate ligand (acetate) was solved by X-ray crystallographic techniques in 1997[22] and in 1998 the structure of vancomycin bound to *N*-acetate-D-alanine was solved,[23] which supported the proposed biological mechanism of action.

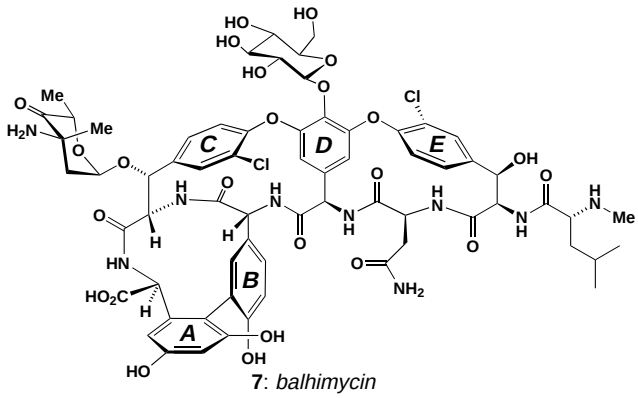
Based on these landmark achievements, the structures of hundreds of natural and semisynthetic glycopeptides have been, and are currently being, determined with relative ease. These structures are highly related and fall within five structural sub-types, I – V, as shown in Figure 7 and Table 1. These compounds are numbered and designated as illustrated in Figure 8 for vancomycin (**1**) and the teicoplanin aglycon (**14**). Thus, the seven amino acids of vancomycin are designated as AA-1 to AA-7,[24] and the five aromatic rings lettered *A* through *E*. The larger rings take the letters of their component aryl rings (*AB*, *CD*, *DE*). Often, however, the *CD* and *DE* ring systems are referred to as *C-O-D* and *D-O-E*, respectively, to indicate the presence of the bisaryl ether oxygen atom.[25] Of the varying structural sub-types, type I structures contain aliphatic chains in AA-1 and AA-3, whereas types II, III, and IV include aromatic side chains within these amino acids. Unlike types I and II, types III and IV contain an extra *F-O-G* ring system. Type IV compounds have, in addition, a long fatty-acid chain attached to the sugar moiety. Structures of type V, such as complestatin (**11**), chloropeptin I (**12**), and kistamicin A (**13a**) and B (**13b**) contain the characteristic tryptophan moiety linked to the central amino acid as shown in Figure 7.

A number of glycopeptide antibiotics are usually produced as a mixture by an individual bacterial organism. These compounds contain minor structural variations, usually with regards to their glycosidation state. Sophisticated analytical and purification techniques, such as HPLC, have allowed the isolation and characterization of a number of these compounds. Table 1 lists most of these naturally occurring glycopeptide antibiotics (also known as dalbaheptides),[26] in alphabetical order, together with the name of their producing organism[27] and other relevant information.

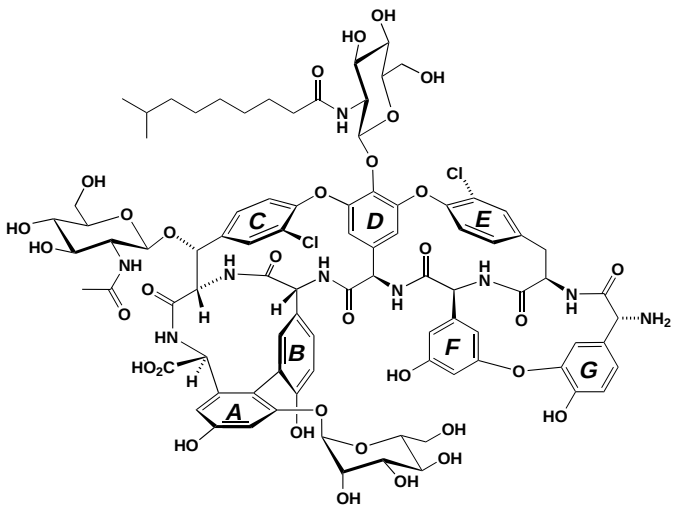
Within the last 20 years, a number of systematic approaches to the discovery of new antibiotics have been adopted.[81] Among the mechanism-based strategies are the utilization of antibiotic activity assays with and without a L-Lys-D-Ala-D-Ala binding peptide,[82] a solid-phase enzyme assay (SPERA),[83] and affinity chromatography using the D-Ala-D-Ala dipeptide as the ligand.[84]

4. Biosynthesis, Fermentation, and Isolation of Glycopeptide Antibiotics

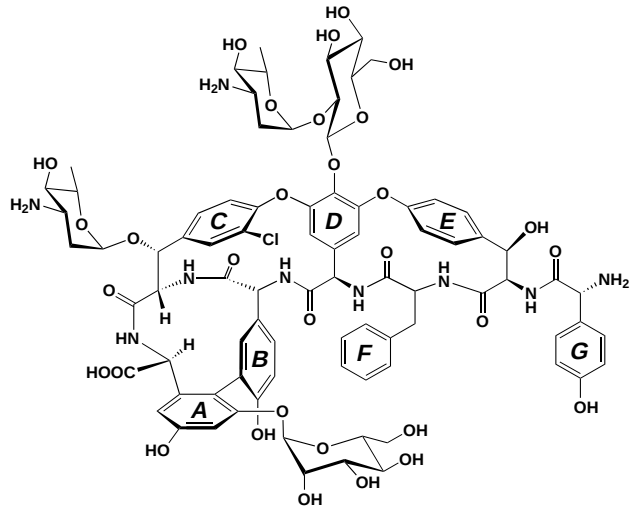
Considerable progress has been made towards understanding the biosynthetic sequence by which the glycopeptide antibiotics are produced within bacteria. Based upon other biosynthetic pathways, the formation of these structures was expected to proceed through construction of the amino acid building blocks, formation of the linear heptapeptide, oxida-



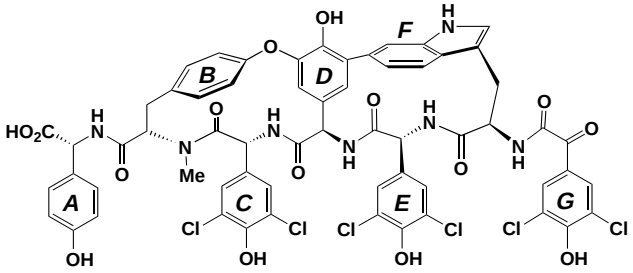
7: *balhimycin*
[***type I***: *contain aliphatic chains in AA-1 and AA-3*]



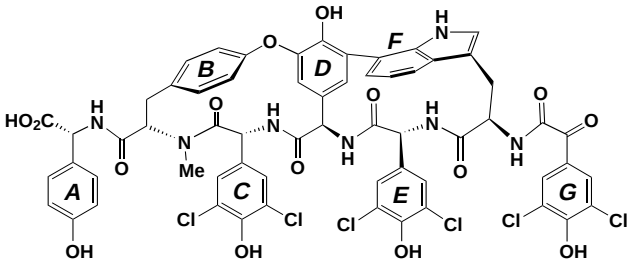
10: *teicoplanin A_2-2*
[***type IV***: *as in type II plus aliphatic side chains on sugar*]



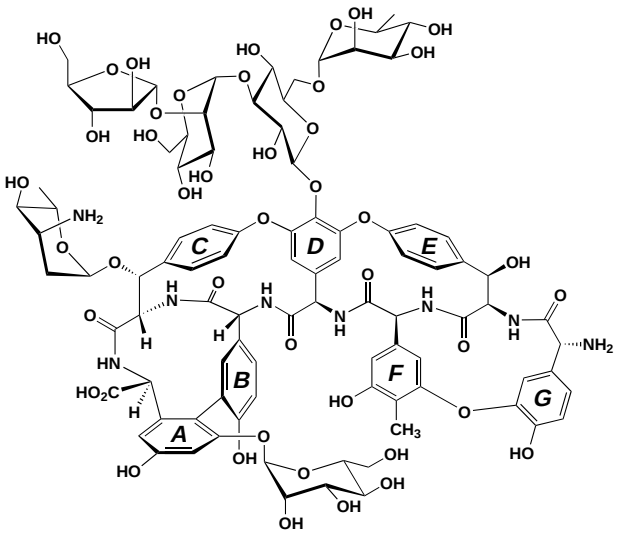
8: *actinoidin A*
[***type II***: *contain aromatic chains in AA-1 and AA-3*]



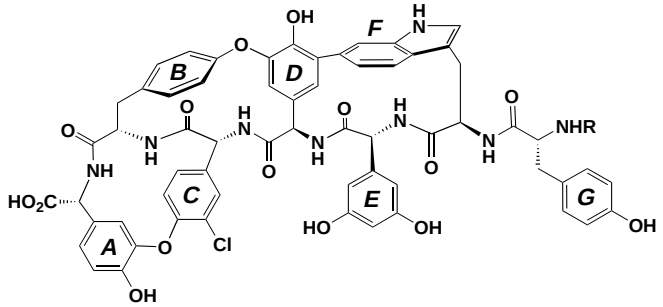
11: *complestatin*



12: *chloropeptin I*



9: *ristocetin A*
[***type III***: *as in type II plus extra F-O-G ring system*]

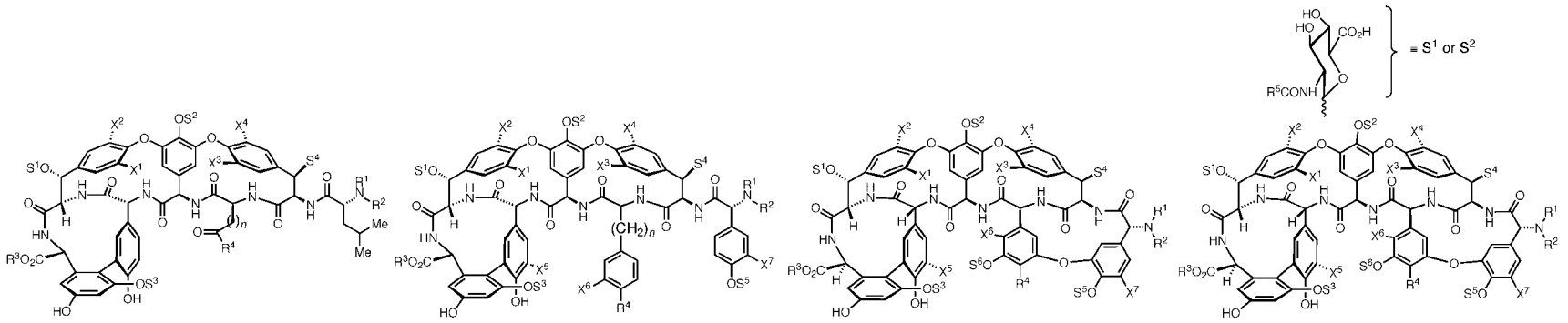


13a: *kistamicin A (R = H)*
13b: *kistamicin B (R = $CONHCH_2CH_2Ph$)*
[***type V***: *contain a tryptophan linked to central AA*]

Figure 7. Structural types of glycopeptide antibiotics: type I: balhimycin (**7**); type II: actinoidin A (**8**); type III: ristocetin A (**9**); type IV: teicoplanin A_2-2 (**10**); type V: complestatin (**11**), chloropeptin I (**12**), and kistamicin A (**13a**) and B (**13b**).

tive coupling processes, and glycosidations. Indeed, the biosynthetic experiments performed so far with vancomycin and ristocetin are in agreement with these considerations.[85] Thus, feeding experiments in vancomycin-producing bacteria with [1,2-$^{13}C_2$] acetate showed that the *m*-dihydroxyphenylglycine (AA-7) of vancomycin is formed through a polyketide

Table 1. Natural glycopeptide antibiotics.



Glycopeptide antibiotic		Type	Producing organism	Date[a]	Ref.	Use[b]	X^1	X^2	X^3	X^4	X^5	X^6	X^7	S^1[c]	S^2	S^3	S^4	S^5	S^6	R^1	R^2	R^3	R^4	R^5	n
A35512 A, C, E, F, G, H	B[d]		*Streptomyces candidus*	1980	[29]																				
A40926 (A, B, PB = parvodicin B_2,C_1, C_3)	PA	IV	*Actinomadura* sp. ATCC 39727	1984	[30]		Cl	H	H	H	H	Cl	H	H	β-glr	6-(*O*-Ac)-α-man	H	H	H	Me	H	H	H	$nC_{10}H_{21}$	–
A41030	A	III	*Streptomyces virginiae* NRRL 15156	1983	[31]		Cl	H	H	Cl	Cl	H	H	H	H	H	H	H	H	H	H	H	H	–	–
	B	III					Cl	H	H	Cl	H	H	H	H	H	H	H	H	H	H	H	H	H	–	–
	C	III					Cl	H	H	Cl	Cl	H	H	H	H	H	H	gal	H	H	H	H	H	–	–
	D[e]	III					Cl	H	H	H	Cl	H	H	H	H	H	H	H	H	H	H	H	H	–	–
	E	III					Cl	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	–	–
	F	III					Cl	H	H	Cl	Cl	H	H	H	H	H	H	gal-gal	H	H	H	H	H	–	–
	G[e]	III					Cl	H	H	Cl	Cl	H	H	H	H	H	H	gal-gal	H	H	H	H	H	–	
A42867		I	*Nocardia* sp. ATCC 53492	1989	[32]		H	H	H	Cl	–	–	–	β-van	((1→6)-α-rha)-β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
A477			*Actinoplanes* sp. NRRL 3884	1971	[33]																				
A47934		III	*Streptomyces toyocaensis*	1986	[34]		Cl	H	H	Cl	Cl	H	H	H	H	H	H	SO_3H	H	H	H	H	H	–	–
A51568 (A = *N*-demethyl-vancomycin)	B	I	*Nocardia orientalis*	1983	[35]		Cl	H	H	Cl	–	–	–	H	((1→2)-β-van)-β-glc	H	OH	–	–	H	H	H	NH_2	–	2
A80407	A, B		*Kibdelosporangium philippinensis*	1987	[36]																				
A83850		I	*Amycolatopsis albus*	1990	[37]	D	Cl	H	H	Cl	–	–	–	H	2-*O*-leu- β-glc	H	OH	–	–	Me	Me	H	NH_2	–	1
A84575	A IV B–H		*Streptosporangium carnosum*	1989	[38]		Cl	H	H	H	H	Cl	H	H	β-glc	α-man	H	H	H	H	H	H	H	iC_9H_{19}	–
AB65			*Saccharomonospora viride* T-80	1975	[39]																				
AM374			*Streptomyces eburosporeus*	1969	[40]	D																			
actaplanin (A4696, Kamoran®)	A	III	*Actinoplanes missouriensis*	1971	[41]	D	Cl	H	H	H	H	H	H	α-ria	((1→2)-α-man)-β-glc	α-man	H	H	α-man	H	H	Me	Me	–	–
	B_1	III					Cl	H	H	H	H	H	H	α-ria	((1→6)-α-rha)-β-glc	α-man	H	H	α-man	H	H	Me	Me	–	–
	B_2	III					Cl	H	H	H	H	H	H	α-ria	β-glc	α-man	H	H	α-man	H	H	Me	Me	–	–
	B_3	III					Cl	H	H	H	H	H	H	α-ria	((1→2)-α-man)-β-glc	α-man	H	H	H	H	H	Me	Me	–	–

	C_1	III					Cl	H	H	H	H	H	H	α-ria	((1→6)-α-rha)-β-glc	α-man	H	H	H	H	H	Me	Me	–	–
	C_2	III					Cl	H	H	H	H	H	H	α-ria	H	α-man	H	H	α-man	H	H	Me	Me	–	–
	C_3	III					Cl	H	H	H	H	H	H	α-ria	β-glc	H	H	H	α-man	H	H	Me	Me	–	–
	D_1	III					Cl	H	H	H	H	H	H	α-ria	H	α-man	H	H	H	H	H	Me	Me	–	–
	D_2	III					Cl	H	H	H	H	H	H	α-ria	H	H	H	H	α-man	H	H	Me	Me	–	–
	G	III					Cl	H	H	H	H	H	H	α-ria	β-glc	α-man	H	H	H	H	H	Me	Me	–	–
	K	III					Cl	H	H	H	H	H	H	α-ria	((1→2)-α-man)-β-glc	H	H	H	α-man	H	H	Me	Me	–	–
	L	III					Cl	H	H	H	H	H	H	α-ria	((1→6)-α-rha)-β-glc	H	H	H	α-man	H	H	Me	Me	–	–
	M	III					Cl	H	H	H	H	H	H	α-ria	((1→2)-α-man)-β-glc	H	H	H	H	H	H	Me	Me	–	–
	N	III					Cl	H	H	H	H	H	H	α-ria	((1→6)-α-rha)-β-glc	H	H	H	H	H	H	Me	Me	–	–
	O	III					Cl	H	H	H	H	H	H	α-ria	β-glc	H	H	H	H	H	H	Me	Me	–	–
actaplanin pseudoaglycon		III					Cl	H	H	H	H	H	H	α-ria	H	H	H	H	H	H	H	Me	Me	–	–
actinoidin (**8**)	A	II	*Proactinomyces actinoides*	1957	[42]		Cl	H	H	H	H	H	H	α-aca	((1→2)-α-aco)-β-glc	α-man	OH	H	–	H	H	H	H	–	1
	A_2	II					Cl	H	H	H	H	H	H	α-aca	((1→2)-α-rha)-β-glc	α-man	OH	H	–	H	H	H	H	–	1
	B	II					Cl	H	H	H	H	H	H	α-aca	((1→2)-α-aco)-β-glc	H	OH	H	–	H	H	H	H	–	1
ardacin (aricidin, AAD216)	A	IV	*Kibdelosporangium aridiu*	1983	[43]	D	Cl	Cl	H	Cl	H	Cl	H	H	β-glr	α-man	OH	H	H	Me	H	H	H	nC_9H_{19}	–
	B	IV					Cl	Cl	H	Cl	H	Cl	H	H	β-glr	α-man	OH	H	H	Me	H	H	H	$iC_{10}H_{21}$	–
	C	IV					Cl	Cl	H	Cl	H	Cl	H	H	β-glr	α-man	OH	H	H	Me	H	H	H	$iC_{11}H_{23}$	–
avoparcin (LL-AV290,	α	II	*Streptomyces candidus*	1968	[44]		Cl	H	H	H	H	H	H	α-ria	((1→2)-α-ria)-β-glc	H	O-α-man	α-rha	–	Me	H	H	OH	–	0
formulation: Avotan®)	β	II					Cl	H	H	H	H	Cl	H	α-ria	((1→2)-α-ria)-β-glc	H	O-α-man	α-rha	–	Me	H	H	OH	–	0
	ε	II					Cl	H	H	H	H	Cl	H	H	((1→2)-α-ria)-β-glc	H	O-α-man	α-rha	–	Me	H	H	OH	–	0
azureomycin	A, B		*Pseudonocardia azurea*	1979	[45]																				
balhimycin (**7**)		I	*Actinomyces* sp. Y-86,21022	1991	[46]		Cl	H	H	Cl	–	–	–	α-ovcn	β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
balhimycin V		I	*Actinomyces* sp. Y-86,21022	1996	[47]		Cl	H	H	Cl	–	–	–	α-ovcn	((1→2)-α-ovcn)-β-glc	H	OH	–	–	Me	H	H	NH_2	-	1
chloroorienticin (A =	A	I	*Amycolatopsis orientalis*	1986	[48]		Cl	H	H	Cl	–	–	–	α-ere	β((1→2)-α-ere)-β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
A82846 B, LY264826,	B	I					Cl	H	H	Cl	–	–	–	α-ere	β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
chloroeremomycin;	C	I					Cl	H	H	Cl	–	–	–	α-ere	H	H	OH	–	–	Me	H	H	NH_2	–	1
B,C, D,E = PA45052	D	I					Cl	H	H	Cl	–	–	–	α-ere	((1→2)-α-ere)-β-glc	H	OH	–	–	Me	Me	H	NH_2	–	1
B,C,D,E)	E	I					Cl	H	H	Cl	–	–	–	α-ere	β-glc	H	OH	–	–	Me	Me	H	NH_2	–	1
chloropeptin I (**12**)		V	*Streptomyces* sp. WK-3419	1994	[49]	B	see Figure 7 (**12**)																		
(II = complestatin (**11**))																									
chloropolysporin (D & E	A[f]	II	*Micropolyspora* sp. FERM BP-	1983	[50]	D	Cl	H	H	Cl	H	Cl	H	α-ria	β-glc	H	O-α-man	H	–	Me	H	H	OH	–	0
are artificial epimers	B		538, *Faenia interjecta*				Cl	H	H	Cl	H	Cl	H	α-ria	β-glc	H	O-α-man	α-rha	–	Me	H	H	OH	–	0
of B & C)	C						Cl	H	H	Cl	H	Cl	H	α-ria	β-glc	H	O-α-man	H	–	Me	H	H	OH	–	0
complestatin (**11**, chloro-		V	*Streptomyces lavendulae*	1989	[51]	B	see Figure 7 (**11**)																		
peptin II)																									
CUC/CSV			*Actinoplanes missouriensis*	1983	[52]																				
decaplanin (M86 – 1410)		I	*Kibdelosporangium deccaensis*	1988	[53]		H	H	H	Cl	–	–	–	α-ere	((1→2)-α-rha)-β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
dechlorobalhimycin V		I	*Actinomyces* sp. Y-86,21022	1996	[47]		Cl	H	H	Cl	–	–	–	α-ovcn	((1→2)-α-ovcn)-β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
deglucobalhimycin		I	*Actinomyces* sp. Y-86,21022	1996	[47]		Cl	H	H	Cl	–	–	–	α-ovcn	H	H	OH	–	–	Me	H	H	NH_2	–	1
N-demethylbalhimycin		I	*Actinomyces* sp. Y-86,21022	1996	[47]		Cl	H	H	Cl	–	–	–	α-ovcn	β-glc	H	OH	–	–	H	H	H	NH_2	–	1
N-demethylvancomycin		I	*Amycolatopsis orientalis*	1984	[35]		Cl	H	H	Cl	–	–	–	H	((1→2)-α-van)-β-glc	H	OH	–	–	H	H	H	NH_2	–	1
(A51568 A)																									
devancosamine-vancomycin		I			[54]		Cl	H	H	Cl	–	–	–	H	β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
(DVV)																									
eremomycin (=MM45289,		I	*Actinomycetes* sp. INA 238	1989	[55]		H	H	H	Cl	–	–	–	α-ere	((1→2)-α-ere)-β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
A82846 A)																									

Table 1. (Continued)

Glycopeptide antibiotic		Type	Producing organism	Date[a]	Ref.	Use[b]	X^1	X^2	X^3	X^4	X^5	X^6	X^7	$S^{1[c]}$	S^2	S^3	S^4	S^5	S^6	R^1	R^2	R^3	R^4	R^5	n
eremomycin Ψ		I					H	H	H	Cl	–	–	–	α-ere	H	H	OH	–	–	Me	H	H	NH_2	–	1
galacardin	A	II	*Actinomycetes* strain	1989	[56]		Cl	H	H	H	H	Cl	H	α-ria	((1→2)-α-ria)-β-glc	H	O-α-man	((1→4)-α-gal)-α-rha	–	Me	H	H	*O*-α-gal	–	0
	B	II					Cl	H	H	H	H	Cl	H	α-ria	((1→2)-α-ria)-β-glc	H	O-α-man	((1→4)-α-gal)-α-rha	–	Me	H	H	OH	–	0
helvecardin	A	II	*Pseudonocardia compacta*	1991	[57]		Cl	H	H	H	H	Cl	H	α-ria	((1→2)-α-ria)-β-glc	H	O-α-man	2-*O*Me-α-rha	–	Me	H	H	OH	–	0
	B	II					Cl	H	H	H	H	Cl	H	α-ria	((1→2)-α-ria)-β-glc	H	OH	2-*O*Me-α-rha	–	Me	H	H	OH	–	0
izupeptin	A, B		*Nocardia* AM-5289	1986	[58]																				
kibdelin (A, B, C_1 =	A	IV	*Kibdelosporangium aridum*	1986	[59]		Cl	Cl	H	Cl	H	Cl	H	H	β-gls	α-man	OH	H	H	Me	H	H	H	nC_9H_{19}	–
AAD609 A, B, C_1)	B	IV					Cl	Cl	H	Cl	H	Cl	H	H	β-gls	α-man	OH	H	H	Me	H	H	H	$iC_{10}H_{21}$	–
	C_1	IV					Cl	Cl	H	Cl	H	Cl	H	H	β-gls	α-man	OH	H	H	Me	H	H	H	$iC_{11}H_{23}$	–
	C_2	IV					Cl	Cl	H	Cl	H	Cl	H	H	β-gls	α-man	OH	H	H	Me	H	H	H	$nC_{11}H_{23}$	–
	D	IV					Cl	Cl	H	Cl	H	Cl	H	H	β-gls	α-man	OH	H	H	Me	H	H	H	$(\Delta^4)C_9H_{17}$	–
kistamicin A, B (**13**)		V	*Microtetraspora parvosata*	1993	[60]	B	see Figure 7 (**13**)																		
M43	A	I	*Amycolatopsis orientalis*	1984	[61]		Cl	H	H	Cl	–	–	–	H	((1→2)-α-van)-β-glc	H	OH	–	–	Me_2	Me^+	H	NH_2	–	1
	B	I					Cl	H	H	Cl	–	–	–	H	((1→2)-α-van)-β-glc	H	OH	–	–	Me_2	Me^+	H	OH	–	1
	C	I					Cl	H	H	Cl	–	–	–	H	β-glc	H	OH	–	–	Me_2	Me^+	H	NH_2	–	1
	D	I					Cl	H	H	Cl	–	–	–	H	((1→2)-α-van)-β-glc	H	OH	–	–	Me	Me	H	NH_2	–	1
	F	I					Cl	H	H	Cl	–	–	–	H	((1→2)-α-van)-β-glc	H	OH	–	–	Me	H	H	OH	–	1
mannopeptin			*Streptomyces platenis*	1975	[62]																				
methylbalhimycin		I	*Actinomyces* sp. Y-86,21022	1996	[47]		Cl	H	H	Cl	–	–	–	α-ovcn	β-glc	H	OH	–	–	Me	Me	H	NH_2	–	1
MM47761		I	*Amycolatopsis orientalis*	1990	[63]		H	H	H	Cl	–	–	–	α-ere	((1→2)-α-ere)-β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
MM47766[g]		II	*Amycolatopsis orientalis*	1988	[64]		Cl	H	H	H	H	H	Cl	α-aca	((1→2)-α-aco)-β-glc	H	OH	H	–	Me	H	H	H	–	1
MM47767[g]		II	*Amycolatopsis orientalis*	1988	[64]		Cl	H	H	H	H	H	Cl	α-aca	((1→2)-α-aco)-β-glc	H	OH	H	–	Me	H	H	H	–	1
MM49721		I	*Amycolatopsis orientalis*	1988	[63]		H	H	H	H	–	–	–	α-ere	((1→2)-α-ere)-β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
MM 49727		I	*Amycolatopsis orientalis*	1988	[63]		H	H	H	Cl	–	–	–	α-ere	H	H	OH	–	–	Me	H	H	NH_2	–	1
MM55256[g]		II	*Amycolatopsis orientalis*	1988	[64]		Cl	H	H	H	H	H	Cl	α-aca	((1→2)-α-aco)-β-glc	H	OH	H	–	Me	H	H	H	–	1
MM55260[g]		II	*Amycolatopsis orientalis*	1988	[64]		Cl	H	H	H	H	H	Cl	α-aca	((1→2)-α-aco)-β-glc	H	OH	H	–	Me	H	H	H	–	1
MM55266		IV	*Amycolatopsis* sp. NCIB 40089	1988	[65]		Cl	Cl	H	Cl	Cl	Cl	H	α-glr	β-man	β-glc	OH	H	H	Me	H	H	H	iC_8H_{17}	–
MM55268		IV	*Amycolatopsis* sp. NCIB 40089	1988	[65]		Cl	Cl	H	Cl	Cl	Cl	H	α-glr	β-man	β-glc	OH	H	H	Me	H	H	H	nC_9H_{19}	–
MM55270, MM55271, MM55272			*Amycolatopsis* sp. NCIB 40086	1988	[66]																				
MM56597		IV	*Amycolatopsis* sp. NCIB 40089	1990	[67]		Cl	Cl	H	Cl	Cl	Cl	H	α-glr	β-man	β-glc	OH	H	H	Me	H	H	H	iC_9H_{19}	–
MM56598			*Amycolatopsis* sp. NCIB 40089	1990	[67]		Cl	Cl	H	Cl	Cl	Cl	H	α-glr	β-man	β-glc	OH	H	H	Me	H	H	H	nC_9H_{19}	–
nogabecin F			*Nocardia* Y-86,20095	1990	[68]																				
OA7653[h]	A	I	*Streptomyces hygroscopicus* s	1980	[69]		Cl	H	H	Cl	–	–	–	α-glc	H	H	H	–	–	Me	Me	H	NH_2	–	2
orienticin (A = UK72051,	A	I	*Amycolatopsis orientalis*	1988	[70]		Cl	H	H	H	–	–	–	α-ere	((1→2)-α-ere)-β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
C = A82846 C, MM47756,	B	I					Cl	H	H	H	–	–	–	α-ere	((1→2)-α-oli)-β-glc	H	OH	–	–	Me	H	H	NH_2	–	1
dechloroeremomycin)	C	I					H	H	H	H	–	–	–	α-ere	((1→2)-α-ere)-β-glc	H	OH	–	–	Me	H	H	NH_2	–	1

	D	I					Cl	H	H	H	–	–	–	α-ere	((1→2)-α-ere)-β-glc	H	OH	–	–	Me	Me	H	NH_2	–		1
PA42867 (A = orienticin A)	B	I	*Amycolatopsis orientalis*	1986	[71]		Cl	H	H	H	–	–	–	α-ere	β-glc	H	OH	–	–	Me	H	H	NH_2	–		1
PA45052 (A,B,C,D,E = chloroorienticin A,B,C,D,E)	F	I	*Amycolatopsis orientalis*	1988	[72]	D	Cl	H	H	Cl	–	–	–	α-ere	H	H	OH	–	–	Me	Me	H	NH_2	–		1
parvodicin (AAJ271)	A	IV	*Actinomadura parvosata* ATCC	1986	[73]	D	Cl	H	H	H	H	Cl	H	H	β-glr	α-man	H	H	H	Me	H	H	H	nC_9H_{19}	–	
(B_2,C_1 = A40926 A, B)	B_1	IV					Cl	H	H	H	H	Cl	H	H	β-glr	α-man	H	H	H	Me	H	H	H	$iC_{10}H_{21}$	–	
	B_2	IV					Cl	H	H	H	H	Cl	H	H	β-glr	α-man	H	H	H	Me	H	H	H	$nC_{10}H_{21}$	–	
	C_1	IV					Cl	H	H	H	H	Cl	H	H	β-glr	α-man	H	H	H	Me	H	H	H	$iC_{11}H_{23}$	–	
	C_2	IV					Cl	H	H	H	H	Cl	H	H	β-glr	α-man	H	H	H	Me	H	H	H	$nC_{11}H_{23}$	–	
	C_3	IV					Cl	H	H	H	H	Cl	H	H	β-glr	6-*O*Ac-α-man	H	H	H	Me	H	H	H	$iC_{11}H_{23}$	–	
	C_4	IV					Cl	H	H	H	H	Cl	H	H	β-glr	6-*O*Ac-α-man	H	H	H	Me	H	H	H	$nC_{11}H_{23}$	–	
rhamnosyl–balhimycin		I	*Actinomyces* sp. Y-86,21022	1996	[47]		Cl	H	H	Cl	–	–	–	α-ovcn	rha-1,2-glc	H	OH	–	–	Me	H	H	NH_2	–		1
ristocetin (**9**) (ristomycin, spontin®)	A	III	*Amycolatopsis orientalis*	1956	[74]	C	H	H	H	H	H	H	H	α-ria	((1→2)-α-ara-(1→2)-α-man)-((1→6)-α-rha)-β-glc	α-man	OH	H	H	H	H	Me	Me	–		–
	B	III					H	H	H	H	H	H	H	α-ria	((1→6)-α-rha)-β-glc	α-man	OH	H	H	H	H	Me	Me	–		–
ristocetin Ψ		III			[75]		H	H	H	H	H	H	H	α-ria	H	H	OH	H	H	H	H	Me	Me	–		–
symnonicin (CWI785) A,B,C[i]	A	II	*Actinomycete* ATCC 53296	1986	[76]	D	Cl	H	H	H	H	–	H	α-ria	H	H	OH	H	–	Me	H	H	–	–		–
teicoplanin (**10**)	A_2-1	IV	*Actinoplanes teichomyceticus*	1978	[77]	A	Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	β-gls	α-man	H	H	H	H	H	H	H	$(\Delta^4)C_9H_{17}$	–	
(teichomycin, MDL507, Targocid®)	A_2-2	IV					Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	β-gls	α-man	H	H	H	H	H	H	H	iC_9H_{19}	–	
	A_2-3	IV					Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	β-gls	α-man	H	H	H	H	H	H	H	nC_9H_{19}	–	
	A_2-4	IV					Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	β-gls	α-man	H	H	H	H	H	H	H	$sC_{10}H_{21}$	–	
	A_2-5	IV					Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	β-gls	α-man	H	H	H	H	H	H	H	$iC_{10}H_{21}$	–	
	A_3-1	III					Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	H	α-man	H	H	H	H	H	H	H	–		–
teicoplanin 2[i]	1	IV	*Actinoplanes teichomyceticus*	1996	[78]		Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	β-gls	α-man	H	H	H	–	–	H	H	$(\Delta^4)C_9H_{17}$	–	
	2	IV					Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	β-gls	α-man	H	H	H	–	–	H	H	iC_9H_{19}	–	
	3	IV					Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	β-gls	α-man	H	H	H	–	–	H	H	nC_9H_{19}	–	
	4	IV					Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	β-gls	α-man	H	H	H	–	–	H	H	$sC_{10}H_{21}$	–	
	5	IV					Cl	H	H	Cl	H	H	H	β-*N*Ac-gls	β-gls	α-man	H	H	H	–	–	H	H	$iC_{10}H_{21}$	–	
UK68597[i]		III	*Actinoplanes* ATCC 53533	1988	[79]		Cl	H	H	Cl	Cl	H	Cl	H	((1→2)-α-van)-β-glc	SO_3H	H	H	H	–	–	H	H	–		–
UK69542		III	*Saccharothix aerocolonigenes*	1990	[80]	D	Cl	Cl	H	Cl	H	Cl	H	β-rho	H	H	OH	H	H	Me	H	H	H	–		–
ureido–balhimycin		I	*Actinomyces* sp. Y-86,21022	1996	[47]		Cl	H	H	Cl	–	–	–	α-urvcn	α-glc	H	OH	–	–	Me	H	H	NH_2	–		1
vancomycin (**1**, K288, vancin®, vancled®)		I	*Amycolatopsis orientalis*	1956	[5]	A	Cl	H	H	Cl	–	–	–	H	((1→2)-α-van)-β-glc	H	OH	–	–	Me	H	H	NH_2	–		1
vancomycin aglycon (**19**, AGV)		I					Cl	H	H	Cl	–	–	–	H	H	H	OH	–	–	Me	H	H	NH_2	–		1

[a] Date of first isolation. [b] A: clinically used antibiotic. B: antiviral compound. C: cause platelet aggregation. D: animal feed supplement and growth promoter. [c] Abbreviations for the carbohydrate groups are defined in Table 2. [d] A35512B contains the sugar residues glucose, mannose, rhamnose, and 3-epi-vancosamine. [e] Factors D and G contain two equivalent butyl groups attached to the peptide nucleus at an undetermined site. [f] Chloropolysporin A contains one galactose unit at an undetermined site. [g] MM47766, MM47767, MM55256, and MM 55260 differ with respect to the stereochemistry of AA-1 as well as the position of the mannose residue. [h] AA-1 is a *N*,*N*-dimethylalanine residue. [i] AA-3 is L-methionine sulfoxide in CWI785A and L-methionone in CWI785B and CWI785C. CWI785A and B contain glucose, rhamnose, and mannose at undetermined sites; CWI785C contains rhamnose and glucose at undetermined sites. [j] In teicoplanin 2 and UK68597 the $HCNR^1R^2$ group is replaced by a CO group.

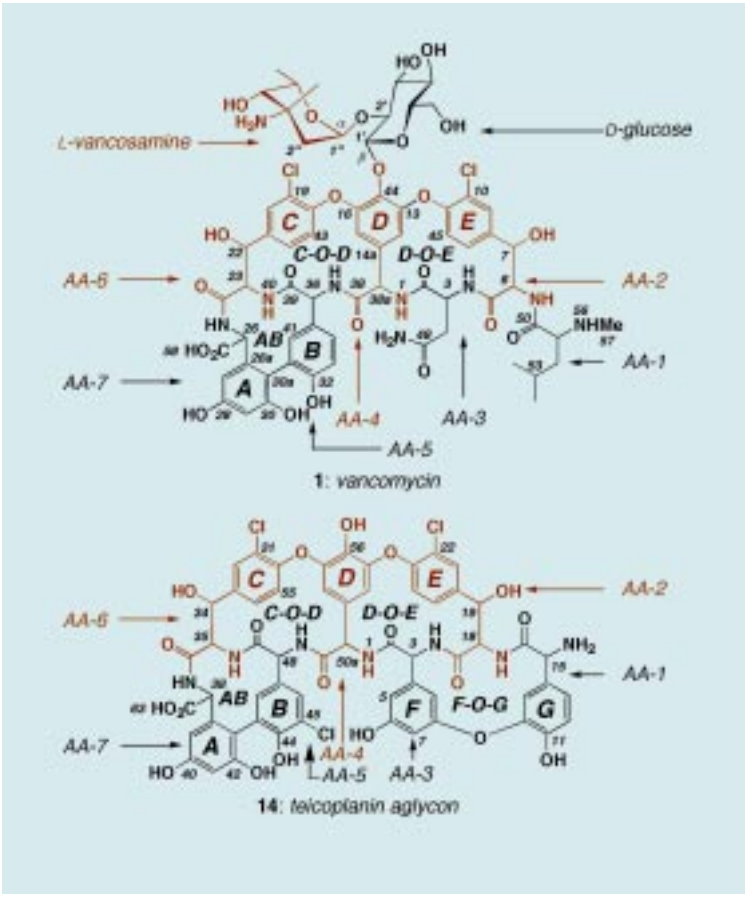


Figure 8. Numbering and designation of rings and amino acids (AA) for vancomycin (**1**) and teicoplanin aglycon (**14**).[28]

pathway from four units of acetate.[85a] Similar experiments with ristocetin-producing organisms revealed that both AA-7 and AA-3 were formed in a similar manner.[85b] DNA sequencing data obtained from the organism that produces ardacin also supports this hypothesis.[86] Furthermore, (*S*)-tyrosine was shown to be the precursor for both AA-2 and AA-6, as well as AA-4 and AA-5 of vancomycin. These experiments demonstrate that the producing bacteria generate *p*-hydroxyphenylglycine from tyrosine and that epimerization is involved in setting the α-carbon stereochemistry, whereas hydroxylation with retention of configuration sets the stereochemistry of the β-carbon atom in AA-2 and AA-6.[85a] Additional experiments with CH_3-[^{13}C]-methionine showed incorporation into the *N*-methyl group of AA-1 in avoparcin, implicating methionine-mediated methylation in the biosynthesis of AA-1.[44c]

Assembly of the component amino acids of the glycopeptide antibiotics into the heptapeptide backbone occurs through a non-ribosomal peptide synthesis mechanism, called the multienzyme thiotemplate mechanism (Figure 9). According to this mechanism, and as shown in Figure 9A, each amino acid is recognized and activated by the appropriate enzyme module. This is followed by covalently linking the amino acid to the enzyme complex through a thioester–pantetheine cofactor unit. Formation of a peptide bond then occurs between two enzyme-bound amino acids (Figure 9B). Subsequent epimerization, if necessary, and further couplings complete the construction of the peptide.[87]

In the specific case of the heptapeptide backbone of type I glycopeptides, three peptide synthetases, CepA, CepB, and CepC were deemed to be required. This was determined based on the analysis of the genes involved in the biosynthesis of the glycopeptide antibiotic chloroeremomycin.[88] Thus, CepA recognizes *N*-Me-(*R*)-leucine and condenses it with (*S*)-tyrosine (**15**$\rightarrow$**16**, Figure 9B), which is then subjected to epimerization. The dipeptide is then condensed with bound (*S*)-asparagine and the formed tripeptide (**17**) is transferred to peptide synthetase CepB where it is coupled with (*S*)-4-hydroxyphenylglycine. Epimerization of the latter fragment is then followed by a second condensation with (*S*)-4-hydroxyphenylglycine and a second epimerization. CepB completes its function by condensing a molecule of (*S*)-tyrosine to form a hexapeptide. Transfer to CepC and coupling of the final amino acid, (*S*)-3,5-dihydroxyphenylglycine, followed by cleavage from the enzyme complex, affords the completed heptapeptide (**18**).

The final steps leading to the aglycon from the linear heptapeptide require seven oxidative processes. These include hydroxylation of AA-2 and AA-6, ring closures to form the bisaryl ethers and the biaryl system,[89] and chlorination of the aromatic rings of AA-2 and AA-6 to obtain the vancomycin aglycon (**19**). The precise sequence of events and mechanistic details for these steps have not yet been fully determined.

Glycosidation, which is thought to be the final biosynthetic operation, is catalyzed by TDP-glucose transferase (an enzyme that can use TDP-Glc, UDP-Glc, and UDP-Gal as substrates) for the attachment of the sugar onto the free AA-4 hydroxyl group of the vancomycin aglycon (**19**).[90] More recently, other glucotransferases with varying substrate specificities have been isolated and used to glycosidate vancomycin aglycon as well as the heptapeptide cores of A47934 and A41030A.[91] Other as yet undetermined glycotransferases are required for further glycosidation, such as formation of oligosaccharides and attachment of sugars at other locations on the aglycon. Finally, it has also been shown, through the ^{14}C-labeled ardacin aglycon, that the last step in the biosynthesis of the kibdelins (same aglycon as ardacin) is the oxidation of carbon-6 of glucosamine to a carboxyl group affording the unusual 2-amino-2-deoxy-glucuronic acid sugar.[92]

All glycopeptide antibiotics isolated to date have their origins in the order of *Actinomycetales*. It is noteworthy that only a few of these compounds, those of type III, are produced by *Streptomycetes*, the most prolific genus for antibiotic production. Practically all type I glycopeptides are produced by *Actinomycetes* (originally classified as *Nocardia*). The producing organism of ristocetin (**9**, Figure 7, type III glycopeptide) and most probably that of actinoidin (**8**, Figure 7, type II) belong to the genus *Proactinomyces*. Actaplanin

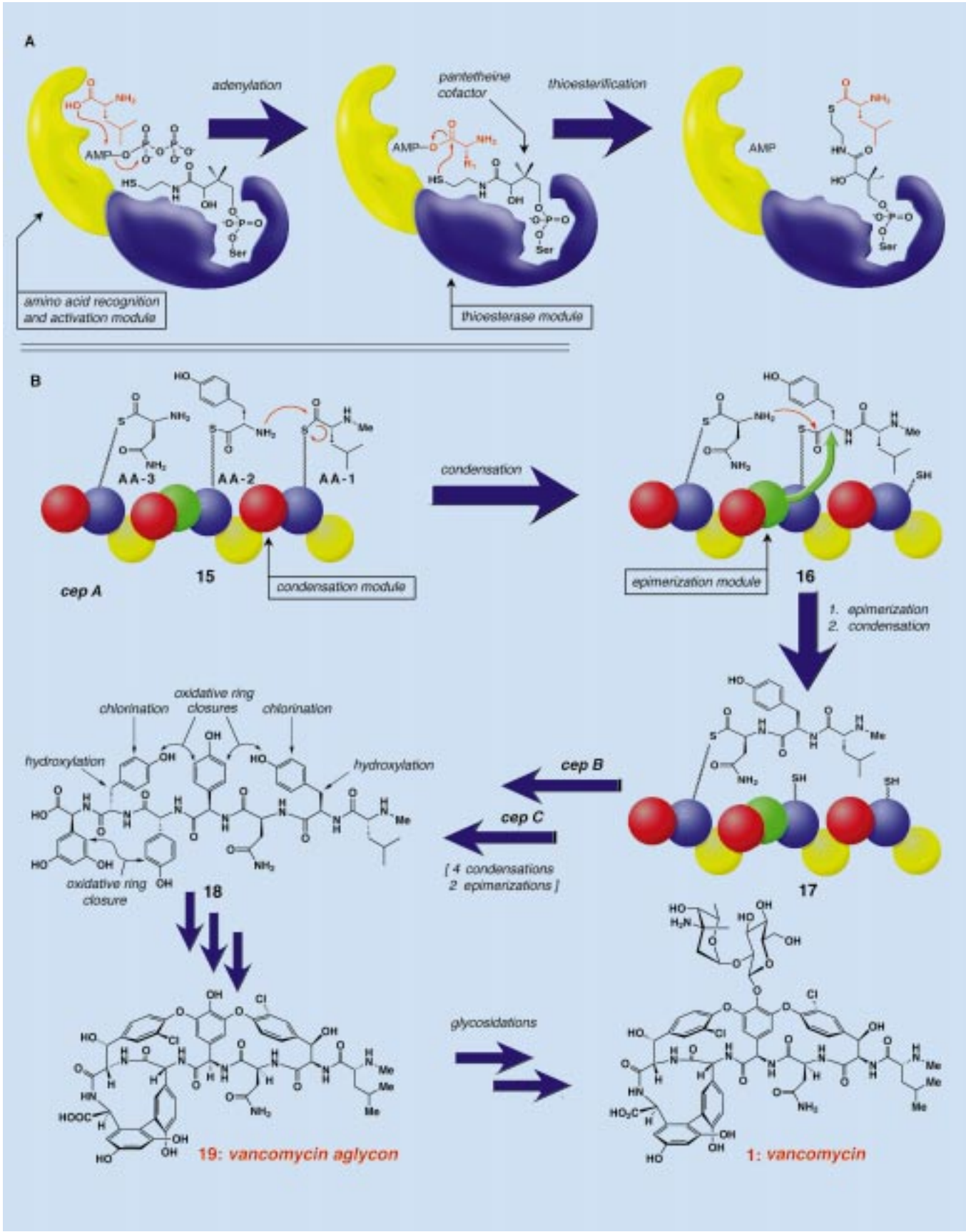


Figure 9. Multienzyme thiotemplate mechanism for the biosynthesis of the peptide backbone of the glycopeptide antibiotics.

(Table 1, type III) and teicoplanin (**10**, Figure 7, type IV) were isolated from species of *Actinoplanes*. The remaining type IV glycopeptides are produced by either *Actinomadura* species or by strains of *Kibdelosporangium*, a newly discovered genus.

Standard fermentation techniques are utilized to produce glycopeptide antibiotics. A nitrogen source, glucose, glycerol, starch or dextrin, and occasionally oleates are necessary. Lower-yielding preparations have been attributed to carbon catabolite regulation. This can be circumvented by the use of slowly metabolized carbohydrates such as galactose or glycerol, rather than glucose.[93] The yields of ardacins and of the related kibdelins, produced in fermentations of *Kibdelosporangium* species, are significantly higher in the presence of methyl oleate, a fact attributed to the oleate's facile conversion to acetyl-CoA, a precursor of both *m*-dihydroxyphenylglycine and of the fatty acid groups of ardacins and kibdelins.[94] Soy meal, peptone, or yeast extract are frequently employed as nitrogen sources in the fermentation. Finally, several reports point to feedback inhibitions in the biosynthetic pathway.[95]

Glycopeptides are usually produced in low yields and as mixtures of varying glycosidation states. They are found not only in the fermentation broth, but in the mycelia mass as well. Rigorous purification protocols are then necessary for isolation of the desired compounds. They are, in general, water-soluble with widely varying isoelectric points (pH 3.2 for A47934 to pH 8.1 for ristocetin). Thus, the strategy for their isolation is greatly dependent upon their structure. In general, the aqueous solution of the culture filtrate is processed by ion-pairing and extraction with butanol or a related solvent. Adsorption onto Dowex, Amberlite IR, acidic alumina, cross-linked polymeric adsorbents (such as Diaion HP), Amberlite XAD, cation-exchange dextran gel (Sephadex), or polyamides furnishes semipurified or enriched material. These mixtures can then be further resolved into their components by special extractions and HPLC purifications.[96] Ion-exchange and affinity resins can also be used in the final stages of purification. The recent example of balhimycin (**7**, Figure 7) shown in Figure 10 is illustrative of such isolation procedures.[47]

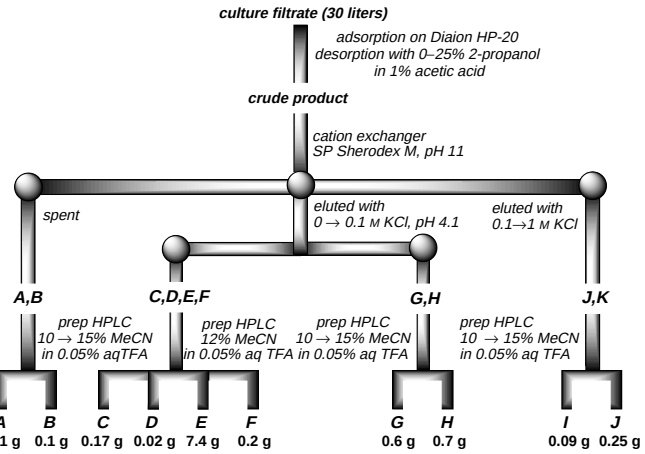
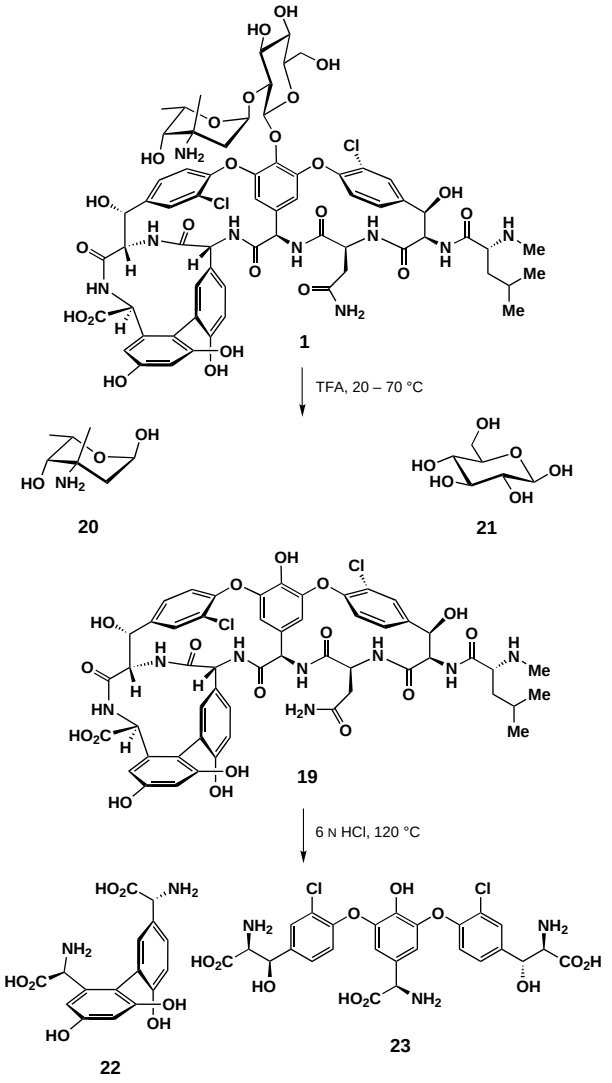


Figure 10. Typical isolation and purification of glycopeptides: balhimycin (**7**, Figure 7) from *Amycolaoptis* sp. Y-86,21022. ***A*** = devancosamine – vancomycin, ***B*** = ureido-balhimycin, ***C*** = M43 C, ***D*** = deglucobalhimycin, ***E*** = balhimycin, ***F*** = rhamnosyl – balhimycin, ***G*** = methylbalhimycin, ***H*** = demethylbalhimycin, ***I*** = dechlorobalhimycin, ***J*** = balhimycin V (diagram adapted from ref. [47]).

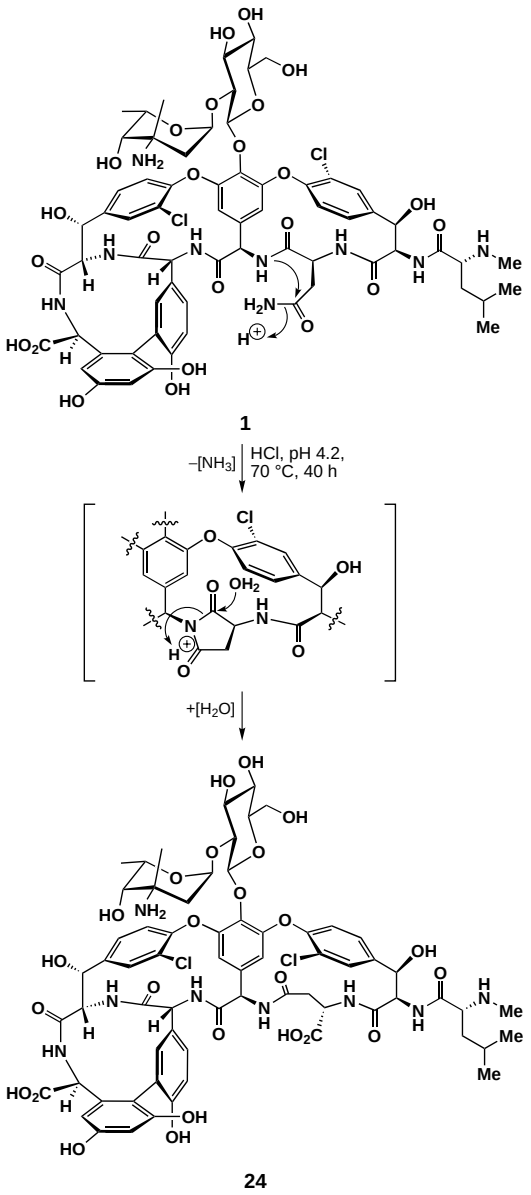
5. Early Degradation and Structural Studies of the Glycopeptide Antibiotics

Early attempts to elucidate the structure of vancomycin (**1**) relied heavily on degradative studies. Although these studies were severely hampered by the complexity and high molecular weight of the molecule, a number of interesting fragments were isolated. Under acidic conditions, for example, vancomycin (**1**) yielded vancomycin aglycon (**19**) and its two carbohydrate components, vancosamine (**20**) and glucose (**21**) (Scheme 1).[97] Subjecting the aglycon to more drastic conditions yielded actinoidinic acid (**22**) and vancomycin acid (**23**).[98]

Degradation studies of vancomycin also produced a non-biologically active crystalline product CDP-I (**24**, Scheme 2). X-ray crystallographic analysis of CDP-I revealed that it contained an expanded *D-O-E* ring, which was originally



Scheme 1. Degradation of vancomycin (**1**).



Scheme 2. Aspartic–isoaspartic acid rearrangement: formation of CDP-I (**24**) from vancomycin (**1**).

thought to be representative of the class.[17] It was quickly established, however, that CDP-I actually arose from an unusual aspartic–isoaspartic rearrangement (see Scheme 2).[18, 99] Furthermore, the expanded 17-membered *D-O-E* ring in CDP-I allowed for equilibration between the two atropisomers of this ring system.[99] Interestingly, the more stable atropisomer has the chlorine atom in the opposite stereochemistry to that of vancomycin (**1**).

Williams and co-workers pioneered extensive NMR studies on vancomycin and its relatives.[100] Their work led to the elucidation of many of the structural features in these substances and demonstrated their dimerization in solution as will be discussed in Section 9.1.[101–105]

In 1995, the structure of the ureido–balhimycin dimer was solved using X-ray crystallographic analysis.[19] A number of other X-ray structures have since followed, including those of vancomycin[20, 22, 23] and of the parvodicin aglycon.[21]

6. Synthetic Studies

Synthetic studies in the area of glycopeptide antibiotics were initially slow, but have intensified rapidly in recent years. Despite the large body of structural information available, it was not until the late 1980s that serious consideration was given to their possible total synthesis. The recognition of their increasing importance as unique antibiotics, their full structural elucidation, and their fascinating mechanism of action are undoubtedly responsible for their emergence as attractive synthetic targets. Their daunting structures, complicated by the unusual challenge of atropisomerism sites, made progress slow at first. Ultimately, these efforts culminated in a wealth of new chemistry, including the total synthesis of the vancomycin aglycon (**19**) and vancomycin (**1**) itself (see Sections 7 and 8). In the section below, we focus on selected highlights from these synthetic advances.[106]

6.1. Amino Acids

The amino acid components of the glycopeptide antibiotics are of special interest to synthetic organic chemists as a result of their unusually sensitive nature, uncommon functional groups, and challenging stereochemistry. The aryl glycines, for example, which often account for three of the seven amino acids present in the glycopeptide antibiotics, suffer from facile racemization under basic conditions. The β-hydroxy tyrosines possess two stereocenters, both of which need to be controlled in any efficient synthesis. Enantioselective synthesis of these substances, therefore, became a topic of high interest.

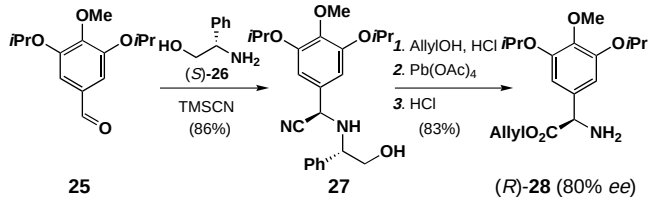
6.1.1. Synthesis of Aryl Glycines

The synthesis of aryl glycines, representing AA-4, AA-5, and AA-7 of vancomycin and AA-1, AA-3, AA-4, AA-5, and AA-7 of the types II, III, and IV of the glycopeptides, has been reviewed recently,[107] and, therefore, we will only highlight here the main strategies and more recent approaches to them. The ninefold rate increase in the racemization of phenylglycine, relative to alanine, is indicative of the potential stereochemical problems associated with these amino acids and the peptides derived from them. Epimerization often occurs during deprotections and macrocyclizations, which greatly limits protecting groups and requires carefully controlled reaction conditions. The reported synthetic sequences to the glycopeptide aryl glycines can be classified into three approaches: a) those involving manipulation of naturally occurring aryl glycines; b) additions at the carbon atom alpha to the aromatic moiety; and c) introduction of glycine equivalents to suitably substituted arenes.

Derivatization of naturally occurring aryl glycines is certainly the simplest approach. For example, the readily available dibrominated *p*-hydroxyphenyl glycine **264** (see Scheme 75) was used by Evans et al. in his thallium(III) nitrate-based synthesis of the model *C-O-D-O-E* ring system of vancomycin and in his orienticin C aglycon synthesis (**280**, see Scheme 76).[108, 109] Furthermore, through elaboration of

the same phenylglycine derivative to the 3,4,5-trioxygenated phenylglycine (see Scheme 77), Evans and co-workers were able to complete the synthesis of the vancomycin aglycon.

Additions to aromatic aldehydes, olefins, and enolates are also convenient and effective methods for the generation of aryl glycines. An asymmetric version of the Strecker reaction was applied to the synthesis of amino acid derivative (*R*)-**28** of vancomycin from anisaldehyde derivative **25** and phenylglycinol (*S*)-**26** in 80 % enantiomeric excess via the cyanamine **27**, as shown in Scheme 3.[110, 111]

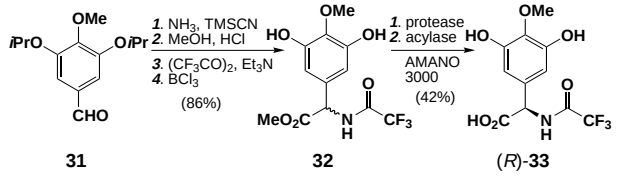


Scheme 3. Synthesis of AA-4 derivative (*R*)-**28** of vancomycin utilizing the asymmetric Strecker reaction according to Zhu et al.[111]

Strecker-type reactions have also been employed as exemplified by the addition of ethyl aluminum cyanoalkoxides to optically active sulfinimines, such as **29**, affording a variety of aryl glycines, such as **30**, in good yields and high enantiomeric excess (Scheme 4).[112]

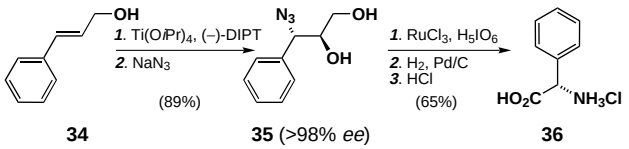
Scheme 4. Synthesis of AA-4 derivative **30** of vancomycin utilizing the addition to sulfinimines according to Davis et al.[112]

Enzymatic resolution of racemic aryl glycines generated from Strecker syntheses has also been utilized as a means to obtain enantiopure materials.[113, 114] Though less appealing than asymmetric synthesis, this method circumvents the loss of optical purity of the sensitive aryl glycines during the hydrolysis of the cyano functionality (Scheme 5).

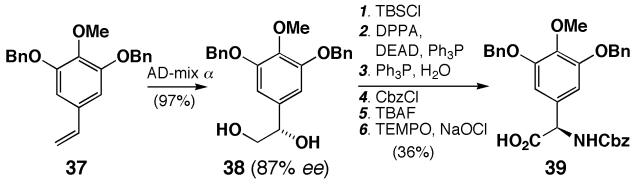


Scheme 5. Synthesis of AA-4 derivative (*R*)-**33** of vancomycin through enzymatic resolution according to Zhu et al.[114]

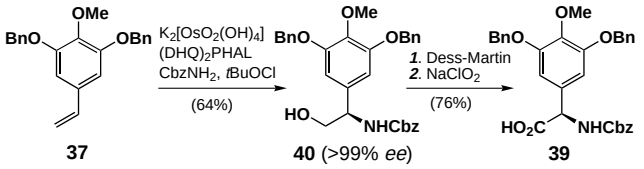
The catalytic asymmetric epoxidation (AE) of allylic alcohols,[115] the asymmetric dihydroxylation (AD) of olefins[116] and the asymmetric aminohydroxylation (AA) of olefins,[117] all developed by the Sharpless group, have been applied productively to the synthesis of aryl glycines as shown in Schemes 6,[118] 7,[119] and 8,[120] respectively.



Scheme 6. The Sharpless asymmetric epoxidation approach to the AA-4 derivative **36** of vancomycin according to Sharpless et al.[118]

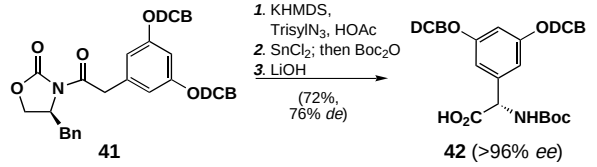


Scheme 7. The Sharpless asymmetric dihydroxylation approach to the AA-4 derivative **39** of vancomycin according to Boger et al.[119]



Scheme 8. The Sharpless asymmetric aminohydroxylation approach to the AA-4 derivative **39** of vancomycin according to Boger et al.[119, 120]

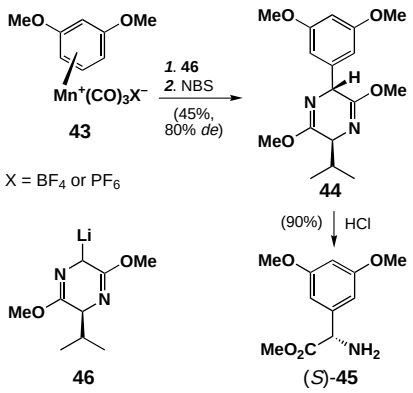
The electrophilic amination of oxazolidinone derived enolates was developed by the Evans group in the late 1980s. Since the starting oxazolidinones are easily accessible from amino acids, this method offers access to a variety of substituted phenyl glycines and tyrosines with excellent stereoselectivities.[121–125] For example, 3,5-hydroxyphenylglycine **42** was synthesized from oxazolidinone **41** as shown in Scheme 9.[124]



Scheme 9. Synthesis of 3,5 dihydroxyphenyl glycine **42** from oxazolidinone **41** according to Evans et al.[124]

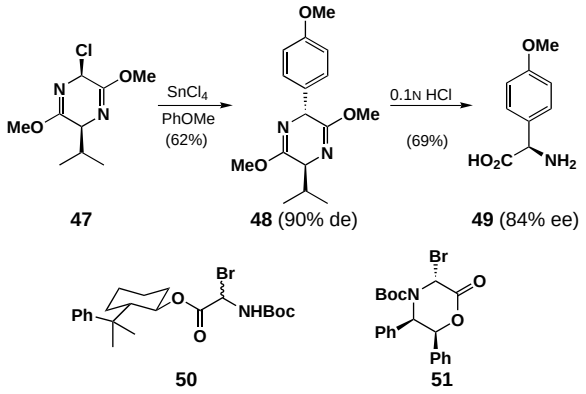
Introduction of glycine equivalents into aromatic systems can also afford aryl glycines. Thus, the arene metal complex **43**[126] (Scheme 10), reacted with the Schöllkopf[127] auxiliary **46** to afford compound **44**, which, upon treatment with acid, released the aryl glycine derivative (*S*)-**45**. In this sequence, the nucleophilic addition of the glycinate equivalent **46** is facilitated by the electron-withdrawing effect of the cationic metal carbonyl moiety in **43**.

The synthesis of *p*-alkoxyaryl glycines, AA-4 and AA-5 of vancomycin, has also been accomplished by the combination of various electrophilic glycine equivalents and aryl Grignard reagents. The bromoglycinates **50**, derived from 8-phenylmenthol, and **51**, derived from L-erythro-α,β-diphenyl-β-hydroxyethylamine,[128] can be treated with aryl Grignard[129] or cuprate[130] compounds to give the aryl glycines. Alterna-



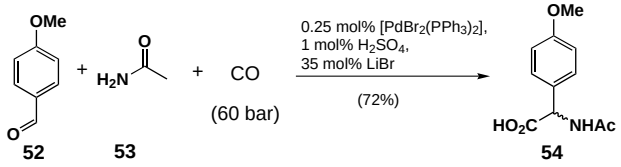
Scheme 10. Asymmetric synthesis of aryl glycines (for example, (*S*)-**45**) by the Schöllkopf bislactim ether method according to Pearson et al.[126]

tively, the chlorinated bislactim ether **47** can undergo Friedel–Crafts alkylation in the presence of Lewis acids to give the required amino acid derivatives in good yield and diastereomeric excess (Scheme 11).[131]



Scheme 11. Electrophilic glycinates used in the synthesis of aryl glycines, for example, **49**.

Carbonylation of imines, generated in situ from aryl aldehydes such as anisaldehyde (**52**), potentially provides a one-pot synthesis of aryl glycines **54**. Recently, this process was dramatically improved through the use of a Pd-catalyzed variant as shown in Scheme 12.[132] Mechanistic studies on this reaction revealed that the intermediate hemiaminal undergoes an oxidative addition and subsequent CO insertion. Unfortunately, an asymmetric version of this reaction remains elusive.

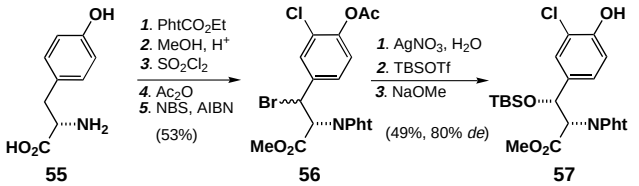


Scheme 12. Palladium-catalyzed carbonylation of imines as a one-step route to aryl glycines by Beller et al.[132]

Finally, a recent disclosure suggests the asymmetric catalytic hydrogenation of enamides as a potentially facile route to aryl glycines.[133]

6.1.2. Synthesis of β-Hydroxytyrosines

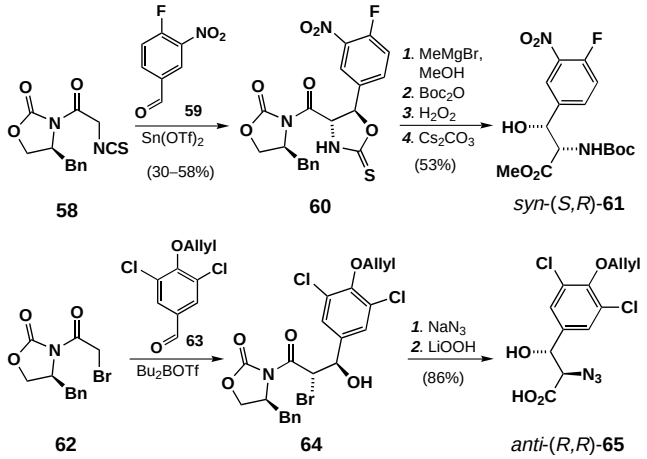
Within vancomycin reside two β-hydroxytyrosines: AA-2, which has *anti*-(*R*,*R*) stereochemistry, and AA-6, which is of the *syn*-(*S*,*R*) configuration. The ready availability of (*S*)-tyrosine (**55**) makes this compound an appealing starting material for the synthesis of these two β-hydroxytyrosines. Indeed, a route for the construction of the *syn*-(*S*,*R*)-β-hydroxytyrosine derivative **57** from (*S*)-tyrosine (**55**) has been developed as shown in Scheme 13. Formation of the phthalimide derivative was followed by esterification, chlorination,



Scheme 13. Conversion of tyrosine (**55**) to its protected β-hydroxyl derivative **57** according to Rama Rao et al.[134]

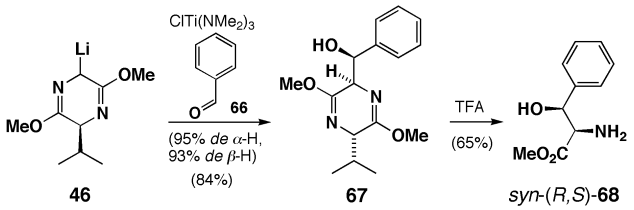
acetylation, and benzylic bromination, leading to an equimolar diastereomeric mixture of bromides **56**.[134] The promotion of the conversion of this mixture into the corresponding β-hydroxy derivatives by silver nitrate afforded a 9:1 mixture of *syn* and *anti* diastereomers.[135] Completion of the synthesis of **57** required TBS protection and liberation of the phenolic hydroxyl group.

Routes to equivalents of both β-hydroxytyrosines of vancomycin were developed by the Evans group.[136] The aldol-based methodology employed delivers both the *syn*-(*S*,*R*) and the *anti*-(*R*,*R*) derivatives **61**[111] and **65**[108] as summarized in Scheme 14.



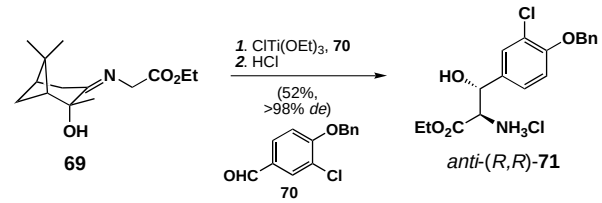
Scheme 14. Synthesis of β-hydroxytyrosine derivatives *syn*-(*S*,*R*)-**61** (AA-2) by Zhu et al.[111] and *anti*-(*R*,*R*)-**65** (AA-6) by Evans et al.[108]

The aldol reaction has also been used in conjunction with the Schöllkopf auxiliary **46**[127, 137] to convert benzaldehyde (**66**) into β-hydroxyphenylalanine methyl ester (*R*,*S*)-**68** stereoselectively from compound **67** according to Scheme 15.[138]



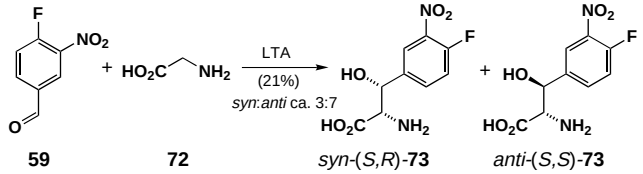
Scheme 15. Synthesis of β-hydroxyphenylalanine methyl ester **68** utilizing the Schöllkopf chiral auxilary.[138]

In a similarly concise manner, the aldol reaction was employed to couple the optically active hydroxypinanone iminoglycinate **69** with aryl aldehyde **70** (Scheme 16).[139] Use of a titanium(IV) enolate in this case resulted in the formation of the *anti*-(*R*,*R*) diastereomer **71** in excellent diastereomeric excess.



Scheme 16. Synthesis of β-hydroxytyrosine **71** through iminoglycinate aldol methodology.[139]

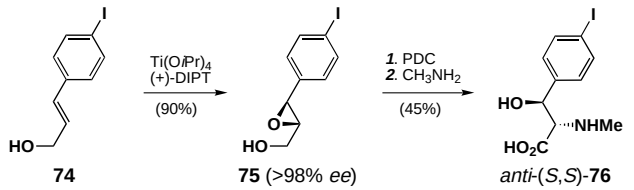
An enzymatic version of the aldol approach to these systems is also available from the Wong laboratory.[140] It employs L-threonine aldolase (LTA) and fluoronitrobenzaldehyde **59** as shown in Scheme 17 and produces both the (*S*,*R*) and (*S*,*S*) products **73**. Similarly, the use of D-threonine



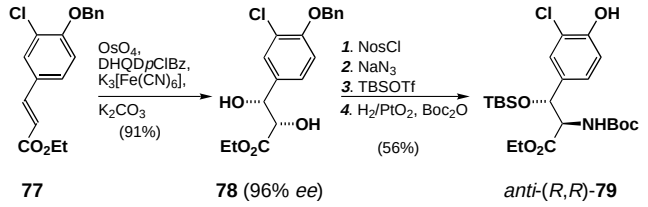
Scheme 17. Enzymatic synthesis of β-hydroxytyrosines **73** according to Wong et al.[140]

aldolase (DTA) affords the (*R*,*S*) and (*R*,*R*) diastereomers.[140]

The Sharpless asymmetric epoxidation, dihydroxylation, and amino-hydroxylation reactions have all been used for the synthesis of various stereoisomers of β-hydroxytyrosine. The asymmetric epoxidation and dihydroxylation are depicted in Schemes 18[141] and 19,[134] respectively. The asymmetric



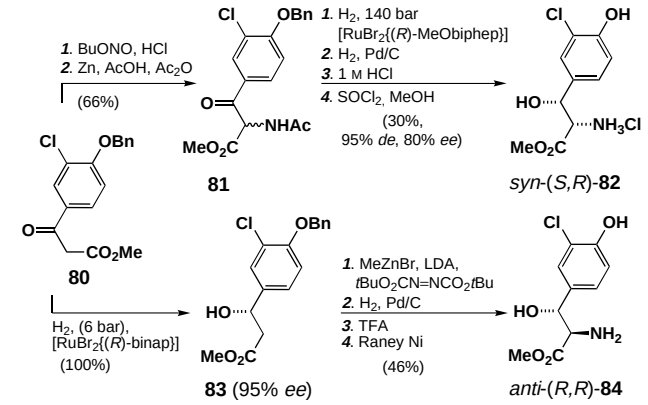
Scheme 18. Synthesis of (*S*,*S*)-hydroxytyrosines **76** by the Sharpless asymmetric epoxidation reaction according to Boger et al.[141]



Scheme 19. Synthesis of (*R*,*R*)-hydroxytyrosine **79** by the Sharpless asymmetric dihydroxylation according to Rama Rao et al.[134]

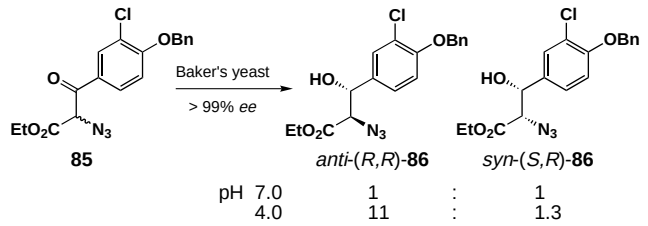
aminohydroxylation-based synthesis of β-hydroxytyrosine can be seen in the context of the total synthesis of vancomycin by Nicolaou et al., as will be discussed in section 8.[142, 143]

Asymmetric catalytic hydrogenation has also been applied to the synthesis of the vancomycin-type β-hydroxytyrosines. Scheme 20 summarizes the sequence adopted by Genêt et al. for the construction of *anti*-(*R*,*R*)-**84** and *syn*-(*S*,*R*)-**82** starting



Scheme 20. Synthesis of β-hydroxytyrosines *syn*-(*S*,*R*)-**82** and *anti*-(*R*,*R*)-**84** by asymmetric catalytic hydrogenation according to Genêt et al.[144]

with the aryl-β-ketoester **80** and using optically active ruthenium catalysts.[144] This reductive transformation can also be effected enzymatically. Thus, as shown in Scheme 21, immmobilized Baker's yeast is used to convert α-azido-β-ketoester **85** into *anti*-(*R*,*R*)-**86** and *syn*-(*S*,*R*)-**86** in excellent



Scheme 21. Synthesis of β-hydroxytyrosines *anti*-(*R*,*R*)-**86** and *syn*-(*S*,*R*)-**86** through enzymatic reduction according to Fadnavis et al.[145]

diastereomeric and enantiomeric excesses at low pH values. The diastereoselectivity is lost under neutral conditions. This is attributed to the relative rates of epimerization at C-2 versus reduction of compound **85**. At low pH values there is kinetic resolution of enantiomers. That is to say, epimerization at C-2 is rapid and reduction of the favored enantiomer takes place preferentially affording a single diastereomer. At higher

pH values epimerization becomes much slower and reduction of the racemic mixture predominates, giving a 1:1 mixture of diastereomers.[145]

6.2. Carbohydrates

As their name suggests the glycopeptide antibiotics are usually decorated with sugar moieties. These carbohydrate units are attached to the aglycon through glycosidic bonds to phenolic or secondary hydroxy groups. The sugar groups of the glycopeptides play important roles in delivering the antibiotic to its target by enhancing its solubility. It has also been shown that the sugar domains of these molecules, particularly the polar amino fragments, promote the dimerization process, resulting in stronger binding and improved in vivo activity (see Section 9.1).

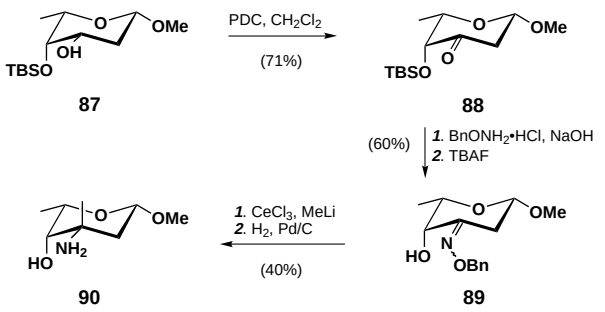
6.2.1. Structures and Synthesis of Carbohydrate Moieties

A wide variety of carbohydrates have been found to occupy positions on the peptide backbone of the glycopeptide antibiotics (see Table 2). Most of these units fall within two categories: the hexo- and 6-deoxyhexopyranosides, such as D-glucose and L-fucose, and the aminotrideoxyhexopyranosides,[146] such as L-ristosamine and L-vancosamine. A number of rare sugars such as 4-oxovancosamine and ureidovancosamine found in the recently reported balhimycin family of glycopeptides, D-glucosamine found in teicoplanin, and a glucuronic acid derivative found in ardacin expand the range of glycopeptide associated carbohydrates even further.

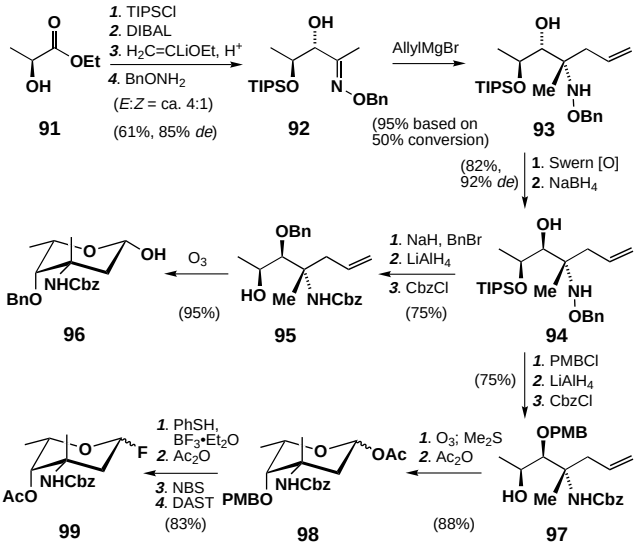
One of the most prominent and frequently occurring carbohydrate units in the glycopeptide antibiotics is L-vancosamine (**20**, Table 2 and Scheme 1). Vancosamine is a C-3 methyl analogue of daunosamine,[146] an essential component of the anthracycline anticancer antibiotics. The same sugar, as its *N*,*N*-dimethyl derivative, is found as a *C*-glycosidic residue in the anthra[1,2b]pyran antibiotics, kidamycin,[147] pluramycin A,[148] and hedamycin,[149] as well as sporaviridin[150] and aculeximycin.[151] In view of a recent review covering most of the synthetic work on the glycopeptide carbohydrates,[152] we will include here only the most recent work in the field, beginning with two new syntheses of L-vancosamine derivatives.

Scharf et al. recently reported a route to L-vancosamine methyl glycoside (**90**) starting from the pyranoside **87**. This sequence features formation of an oxime ether followed by an addition of a cerium reagent to install the C-3 methyl group stereoselectively (Scheme 22).[182]

A de novo synthesis of L-vancosamine derivatives suitable for attaching to glycopeptide aglycons was recently developed in these laboratories (Scheme 23).[183, 187] Thus, protection and reduction of L-lactate **91** led to an aldehyde to which was added, stereoselectively, the lithio derivative of ethyl vinyl ether. Subsequent hydrolysis to the ketone and oxime ether formation led to compound **92** as a mixture of *E*/*Z* isomers. Addition of allylmagnesium bromide, followed by inversion of the resulting secondary alcohol **93** through an oxidation–reduction sequence gave compound **94**. Benzyl protection of



Scheme 22. Synthesis of L-vancosamine α-methyl glycoside **90** by Scharf et al.[182]



Scheme 23. Synthesis of vancosamine derivatives **96** and **99** by Nicolaou et al.[183, 187]

the secondary hydroxyl group followed by concomitant cleavage of the silyl ether and hydroxylamine and Cbz protection of the liberated amino group gave compound **95**. Ozonolysis of the latter compound led to the vancosamine derivative **96**.[183] The glycosyl fluoride **99** used in the total synthesis of vancomycin by Nicolaou et al. was also generated from intermediate **94** as shown is Scheme 23.[187] Thus, *p*-methoxybenzylation of the free hydroxyl group was followed by cleavage of the hyroxylamine and silyl ether and protection of the resulting amine as a Cbz derivative leading to compound **97**. Ozonolysis, followed by acylation gave derivative **98**. Formation of the phenylthioglycoside with simultaneous deprotection of the PMB group followed by reprotection of the C-4 hydroxyl group allowed for facile conversion into the glycosyl fluoride **99**.

6.2.2. Glycosidation Degree and Glycosidation Studies

The glycopeptide antibiotics exhibit various degrees of glycosidation ranging from displaying no sugar residues to carrying several sugar units with up to four glycosidic bonds linking them to the heptapeptide core. Table 3 includes a number of examples of bioactive compounds, their glycosidation degree ranging from the vancomycin aglycon (none) to

Table 2. Sugar components of the glycopeptide antibiotics.

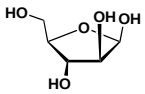
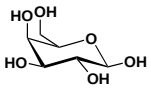
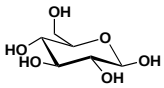
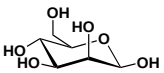
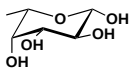
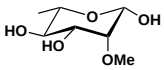
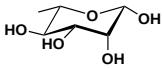
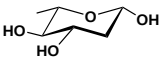
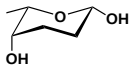
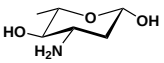
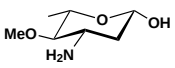
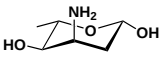
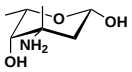
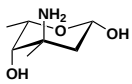
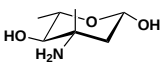
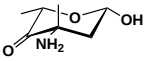
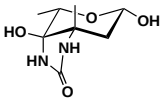
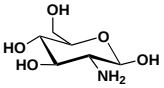
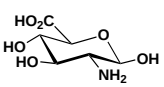
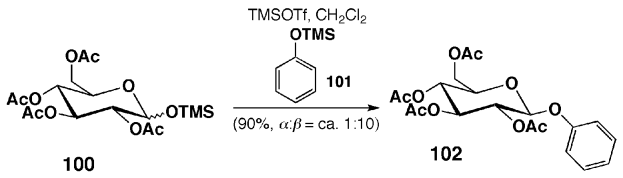
Sugar	Structure	Antibiotic	Reference
D-arabinose (ara)		ristocetin A	[a]
D-galactose (gal)		A41030 C, F, G, chloropolysporin A	[a]
D-glucose (glc, **21**)		actaplanin A, B_{1-3}, C1, C3, G, K, L, M, N, O, actinoidin, avoparcin, A35512 B, A51568 B, A42867, chloroorienticin A, B, chloropolysporin A – C, dechlorobalhimycin V, demethylbalhimycin, demethylvancomycin, devancosamine-vancomycin, eremomycin, galacardin, helvecardin A, B, methylbalhimycin, M43, MM47761, MM47767, MM49721, MM55256, MM55266, MM55268, orienticin, OA7653, PA42867 B, ristocetin A, B, vancomycin CDP-I, vancomycin	[a]
D-mannose (man)		actaplanin A, $B_{1,3}$, C_1, C_2, D_1, D_2, G, K, L, M, actinoidin, ardacin, avoparcin, A35512 B, A40926, chloropolysporins A – C, helvecardin A, kibdelin, MM55266, MM55268, ristocetin A, B, teicoplanin $A_2$1 – 5, A_3, teicoplanin 2 1 – 5	[a]
L-fucose (fuc, 6-deoxy-L -galactose)		A35512 B	[a]
2-*O*-methyl-L-rhamnose (*O*-Me-rha, 6-deoxy-2*O*-methyl-L-mannopyranose)		helvecardin	
L-rhamnose (rha, 6-deoxy-D-mannopyranose)		actaplanin B_1, C_1, avoparcin, A35512 B, A42867, chloropolysporin B, MM47761, MM49721, ristocetin A, B, rhamnosyl-balhimycin, actinoidin A_2	[a]
L-olivose (oli, 2,6-dideoxy-L-*arabino*-hexopyranose)		orienticin B	[153 – 157]
L-rhodinose (rho, 2,3,6-trideoxy-L-*threo*-hexopyranose)		UK69542	[158 – 162]
L-acosamine (aco, 3-amino-2,3,6-trideoxy-L-*arabino*-hexopyranose)		actinoidin A, MM47767, MM55256	[163 – 169]
L-actinosamine (aca, 3-amino-2,3,6-trideoxy-4*O*-methyl -L-*arabino*-hexopyranose)		actinoidin, MM47767, MM55256	[164]
L-ristosamine (ria, 3-amino-2,3,6-trideoxy-L-*ribo*-hexopyranose)		actaplanin, avoparcin, chloropolysporin A – C, galacardin, symnonicin A, B, C, helvecardin, ristocetin A, B	[170 – 175]
L-vancosamine (van, 3-amino-2,3,6-trideoxy- 3*C*-methyl-L-*lyxo*-hexopyranose, **20**)		A42867, A51568 B, dechlorovancomycin, demethylvancomycin, M43, vancomycin CDP-I, vancomycin	[176 – 183]
3-*epi*-L-vancosamin (3-amino-2,3,6-trideoxy- 3*C*-methyl-L-*xylo*-hexopyranose)		A35512 B	[178 – 180, 182]
L-eremosamine (ere, 3-amino-2,3,6-trideoxy- 3*C*-methyl-L-*arabino*-hexose, 4-*epi*-L -vancosamine)		chloroorienticin, dechloroeremomycin, eremomycin, MM47761, MM49721, orienticin,	[177,180, 184 – 186]
4-oxovancosamine (ovcn, 3-amino-2,3,6-trideoxy-3*C*-methyl-L-*threo*-hexopyranos-4-ulose)		A83850 B, balhimycin, balhimycin V, dechlorobalhimycin V, deglucobalhimycin, demethylbalhimycin, methylbalhimycin	[177]
ureido-4-oxovancosamine (urvcn, ((3a*R*,4*S*,6*R*,7a*S*)-octahydro-3a-hydroxy-4,7a-dimethyl-2-oxopyrano[3,4-d]imidazol-6-yl))		ureido-balhimycin	
D-glucosamine (gls, 2-amino-2-deoxyglucose)		teicoplanin $A_2$1 – 5, A_3, teicoplanin 2 1 – 5	[a]
2-amino-2-deoxy-D-glucuronic acid (glr)		ardacin, kibdelin A, B, $C_{1,2}$, D, A40926, parvodicin A, $B_{1,2}$, C1 – 4, X, MM55266, MM55268	

Table 3. Classification of the glycopeptide antibiotics by the number of glycosidic bonds to the heptapeptide core.

None	Mono	Bi	Tri	Tetra
A41030 A, B, D, E, vancomycin aglycon (**19**, Scheme 1)	A41030 C, F, G, A51568 B, A83850, actaplanin pseudoaglycon, chloroorienticin C, deglucobalhimycin V, demethylvancomycin, devancosamine-vancomycin, M43, MM49727, OA7653, PA45052 F, UK68597 UK69542 ristocetin pseudoaglycon, vancomycin (**1**, Figure 4),	A40926 PA, A42867, A84575, actaplanin D_1, D_2, M, N, O, actinoidin B, ardacin, arvoparcin ε, balhimycin (**7**, Figure 7), balhimycin V, chloroorienticin A, B, D, E decaplanin, dechlorobalhimycin V, demethylbalhimycin, eremomycin, kibdelin, methylbalhimycin, MM47761, MM4972, orienticin, PA42867 B, parvodicin, ramnosyl-balhimycin, teicoplanin A_3, ureido-balhimycin	actaplanin B_3, C_1, C_2, C_3, G, K, L, actinoidin A (**8**, Figure 7), A_2, avoparcin α, β, chloropolysporin A – C, galacardin B, helvecardin B MM55266, MM55268, MM56597, MM56598, ristocetin A (**9**, Figure 7), B teicoplanin $A_2$1 – 5 (**10**, Figure 7), teicoplanin 2 1 – 5,	actaplanin A, B_{1-2} galacardin A, helvecardin A

the highly adorned galacardin A (two disaccharides and two monosaccharides directly linked to the heptapeptide core).

The formation of aryl-β-glycosides is often a challenging task. Such a bond was formed stereoselectively by Tietze et al. by employing aryl trimethylsilyl ether **101** and peracetylated 1-trimethylsilyl glycoside **100** in the presence of trimethylsilyl triflate to construct **102** as shown in Scheme 24.[188]

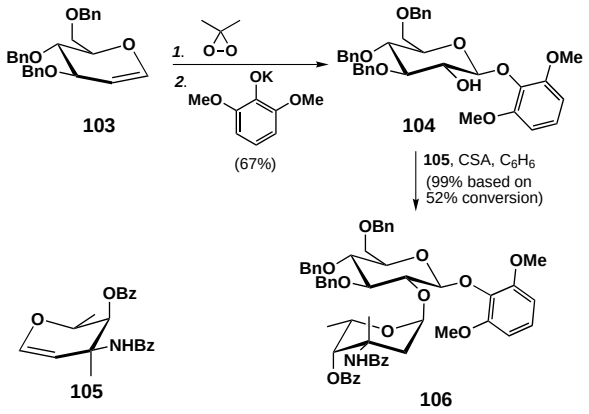


Scheme 24. Stereoselective aryl β-glycosidation according to Tietze et al.[188]

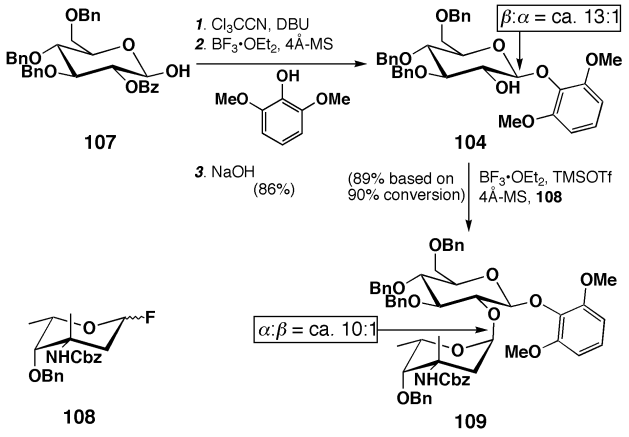
The daunting task of generating the vancomycin glycosidic bonds was addressed by a number of groups. The Danishefsky strategy, demonstrated with a model acceptor, is shown in Scheme 25.[189] This approach features glycals **103** and **105** as intermediates to construct the protected model system **106** in a stereoselective manner by utilizing an dimethyldioxirane-induced epoxidation and an acid-driven glycosidation.

Model studies in our laboratories employed trichloroacetimidate chemistry[190] to form the β-linked aryl glycoside and glycosyl fluoride methodology to introduce the vancosamine residue in high yields and varying degrees of stereoselectivity as shown in Schemes 26 – 28.[183, 191] These model studies established the sequence shown in Scheme 28 as a favorite strategy for an eventual total synthesis of vancomycin by virtue of its efficiency, high stereoselectivity, and protecting group compatibility.

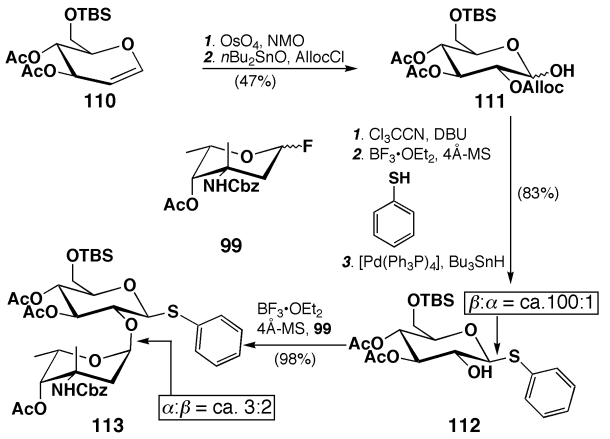
Kahne's group utilized sulfoxide-based methodology, as shown in Scheme 29, for the construction of a similar model



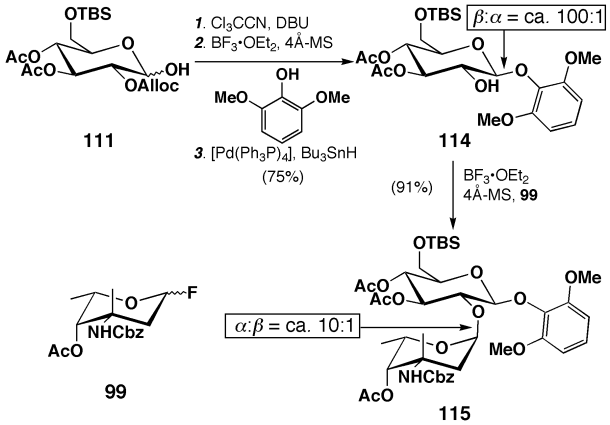
Scheme 25. Synthesis of a model vancomycin disaccharide (**106**) by Danishefsky et al.[189]



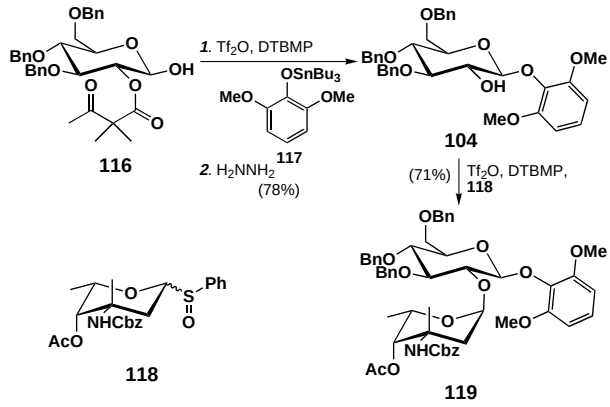
Scheme 26. Synthesis of a model vancomycin disaccharide (**109**) by Nicolaou et al.[183]



Scheme 27. Synthesis of a sulfur-containing model vancomycin disaccharide (**113**) by Nicolaou et al.[191]

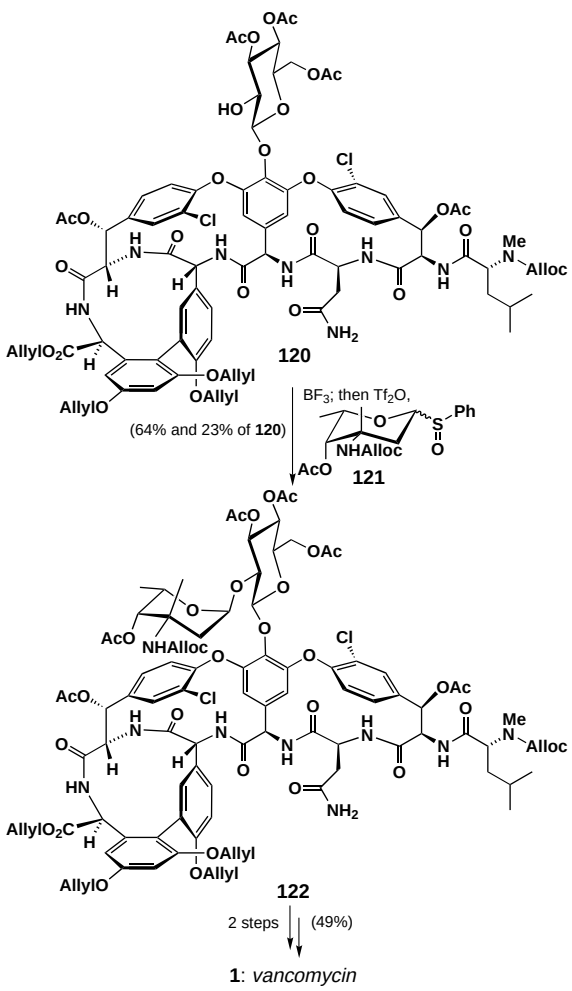


Scheme 28. Synthesis of a model vancomycin disaccharide (**115**) by Nicolaou et al.[191]



Scheme 29. Synthesis of a model vancomycin disaccharide (**119**) by Kahne et al.[192]

disaccharide **119** as that obtained by the Danishefsky group and our own. This methodology was also applied with success to the attachment of the vancosamine residue **121** to the vancomycin pseudoaglycon **120** as demonstrated in Scheme 30. Deprotection of the resulting product **122** furnished semi-synthetic vancomycin (**1**).[192]



Scheme 30. Glycosidation of the pseudoaglycon (**120**) of vancomycin by Kahne et al.[192]

6.3. Macrocyclic Systems

The unusual and challenging structures of the glycopeptide antibiotics stimulated a plethora of model studies directed at the development of suitable methodologies for their construction. These studies will be discussed below under two separate sections depending on whether they relate to the bisaryl ether or the biaryl systems of the cyclopeptide backbone. First, however, we shall discuss the phenomenon of atropisomerism, which complicates the construction of such systems.

6.3.1. The Atropisomerism Problem in Vancomycin and Related Structures

By virtue of their structures, the glycopeptide antibiotics are associated with the rather uncommon phenomenon of atropisomerism. Free rotation of ordinary single bonds is prevalent as a consequence of the low energy barrier (for example, 2.9 kcal mol^{-1} for ethane). In cases where structural features such as strained rings and bulky substituents are present the energy barrier for interconversion between two distinct conformational states can be raised to such a level as

to give rise to observable atropisomers. Vancomycin and its relatives possess two different types of restricted rotation, one in the region of the biaryl system (*AB*) and the other in regions of the two bisaryl ether sites (*C-O-D* and *D-O-E*; Figure 11). For the synthesis of vancomycin, therefore, there are not only the eighteen chiral carbon centers that must be addressed, but three elements of atropisomerism as well.

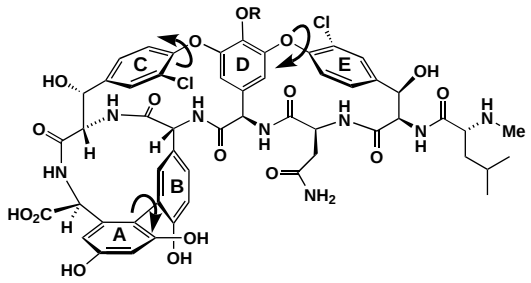


Figure 11. Atropisomerism in the vancomycin structure.

The atropisomerism of substituted biaryl systems has been extensively studied. In these systems, at least three *ortho* substituents are required for restricted rotation that leads to resolvable enantiomers (see Figure 12). A number of such isomers can be interconverted thermally through slightly puckered transition states (Figure 12).

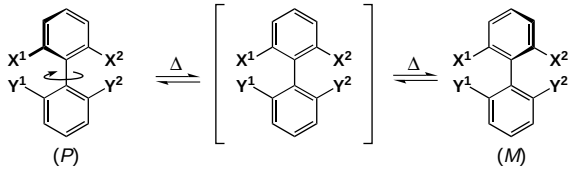
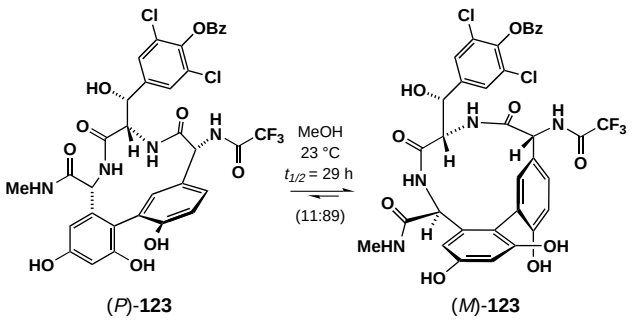


Figure 12. Atropisomerism in the biaryl moiety.

The substituents present on the biaryl moiety of the glycopeptide antibiotics and the constrained nature of the 12-membered ring within which this system resides are responsible for this atropisomerism phenomenon. It is interesting to note that the biaryl system rests in the *M* configuration for all known naturally occurring glycopeptides.

As expected, the barrier of rotation around the central biaryl bond in vancomycin-related systems is dependent on the substituents attached to its phenolic groups. Thus, a study by the Evans group has demonstrated that model system (*P*)-**123** undergoes equilibration with its *M* atropisomer (*M*)-**123** at 23 °C in methanol with a half-life of 29 h and an energy of interconversion of 21 kcal mol^{-1} (Scheme 31).[193] During this isomerization process the amide bond between AA-5 and AA-6 is concomitantly inverted from a transoid to a cisoid configuration to better accommodate the new ring geometry. The trimethoxy derivative of (*P*)-**123**, however, in which all three phenolic groups are methylated, does not undergo isomerization under the same conditions or at higher temperatures (160 °C in DMSO).

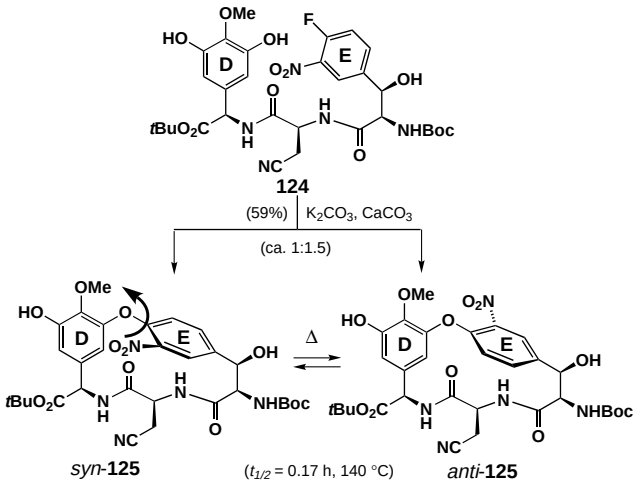
Atropisomers are also present in the bisaryl ether systems. The hindered rotation about the axes spanning the *C* and *E*



Scheme 31. Atropisomerism study of the vancomycin AB model ring system **123** by Evans et al.[193]

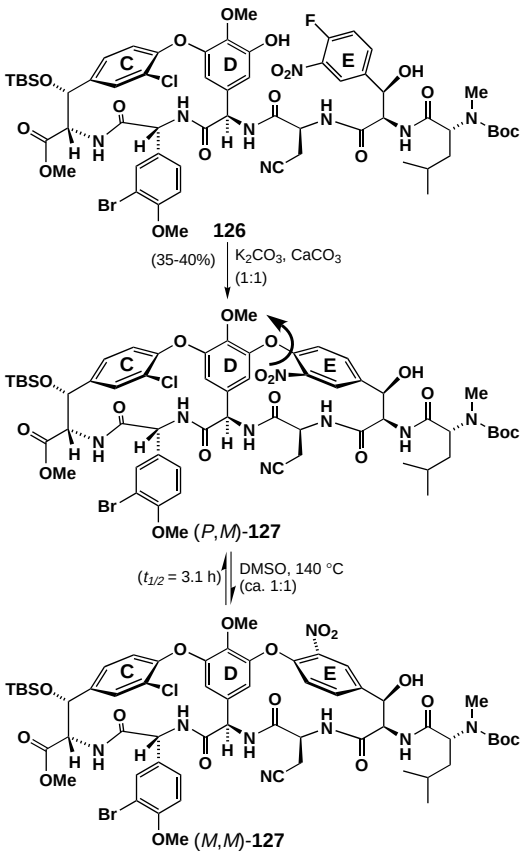
rings of vancomycin along with the presence of the chlorine substituents is responsible for these further elements of atropisomerism. This hindered rotation is a result, specifically, of the rigidity of the ring systems. Thus, within the 16-membered rings of the vancomycin molecule, the two chlorine atoms reside at specific and restricted spacial locations (see Figure 11) leading to a single stable atropisomer, even though the opportunity exists for four. Interestingly, the chlorine substituents occupy positions *trans* to the benzylic hydroxyl groups of the tyrosine residues creating a pseudo-C_2 symmetry. It is suspected that this particular orientation plays a functional role, since chlorination regulates, to some extent, the degree of dimerization of these antibiotics and hence their antibacterial activity.

Studies by the Boger group with model *D-O-E* (**125**, Scheme 32)[120] and *C-O-D-O-E* (**127**, Scheme 33)[194, 195] ring



Scheme 32. Studies of atropisomerism of *D-O-E* model ring system **125** by Boger et al.[120]

systems, as well as a degradatively derived vancomycin aglycon (**128**, Scheme 34),[196] demonstrated a higher flexibility for the *D-O-E* framework relative to the *C-O-D* system. Thus, in bi- or tri-macrocyclic systems, such as **127** and **128**, no thermal isomerization could be observed in the *C-O-D* ring system.

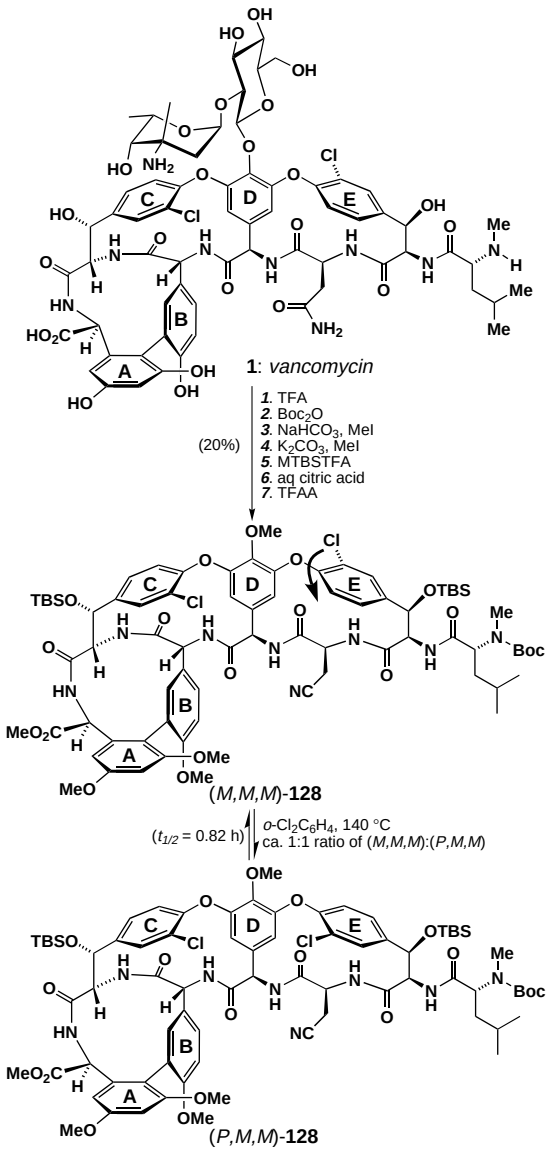


Scheme 33. Studies of atropisomerism of *C-O-D-O-E* model ring system **127** by Boger et al.[194, 195]

6.3.2. *Synthesis of Cyclic Bisaryl Ethers*

The incentive for the development of new synthetic methodology for the construction of cyclic bisaryl ethers was amplified by the challenge, not only of the glycopeptide skeleton, but also by the presence of this structural architecture in a variety of other naturally occurring substances. Among them are the antitumor antibiotics containing L,L-isodityrosine (**135**),[197–203] bouvardin (**136**),[141, 204] deoxybouvardin (**137**)[204b–208] and RA VII,[204b–207] the aminopeptidase B inhibitors OF4949 I – IV (**130** – **133**),[209–213] the angiotensin I converting enzyme inhibitor K-13 (**129**),[212–217] and the antimicrobial and antifungal agents piperazinomycin (**134**),[218–220] combretastatin D-2[221, 222] and bastadin-6 (Figure 13).[223]

But the main force driving new discoveries and inventions in the cyclic bisaryl ether field has been the structures of the vancomycin-type antibiotics and the recognition of the role this moiety plays in the biological action of these molecules. The easily epimerized structural components of the glycopeptide antibiotics (for example, phenylglycine residues) have, as well, necessitated the development of mild protocols for the formation of cyclic bisaryl ethers. The approaches to these systems are categorized as lactamization strategies, oxidative phenolic couplings, *o*-nitro-activated nucleophilic aromatic substitution, metal-activated nucleophilic aromatic substitution, classical Ullmann-type reactions, triazene-driven etherifications, boronic acid-mediated couplings, and miscellaneous processes.



Scheme 34. Studies of atropisomerism of degradatively derived vancomycin aglycon system **128** by Boger et al.[196]

6.3.2.1. *Early Lactamization Strategies*

The first model for the *D-O-E* ring system (**143**) of vancomycin was provided by Hamilton et al. (Scheme 35). The initial step relied on a nucleophilic substitution reaction assisted by two nitro groups to assemble the requisite bisaryl ether moiety. The subsequent macrolactamization step, however, to **143** proceeded in only 10 % yield.[224]

Later studies by the groups of Williams[225] and Brown[226] afforded similar results. Thus, aryl ether **144** was formed by displacement of an aryliodonium salt, but cyclization gave a low yield of macrolactam **145** (Scheme 36). Interestingly, the *D-O-E* macrocycle **145** exhibited antibacterial activity in vitro, while its enantiomer was ineffective.[226]

Gallagher et al. were able to cyclize the vancomycin depsipeptide model system **146** using HOBt and EDC as coupling reagents to afford two diastereoisomers, (*M*)-**147** (natural atropisomer) and (*P*)-**147** (unnatural atropisomer) in 41 % total yield (Scheme 37).[227]

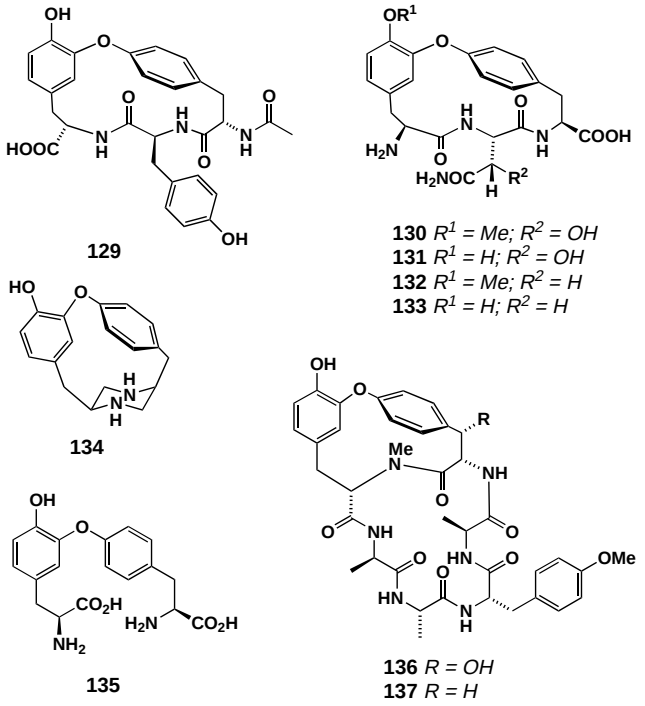
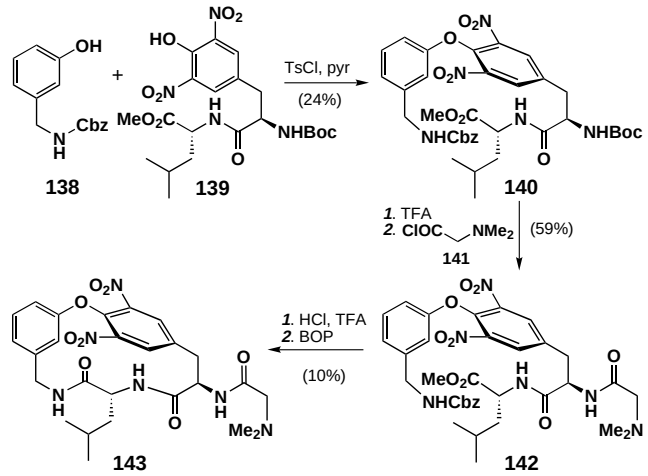
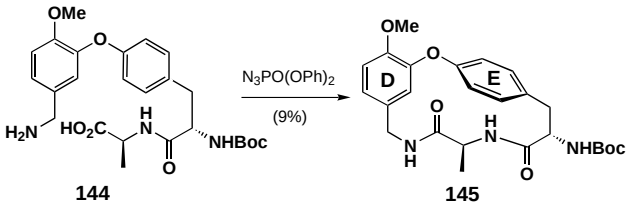


Figure 13. Selected naturally occurring compounds containing bisaryl ethers.

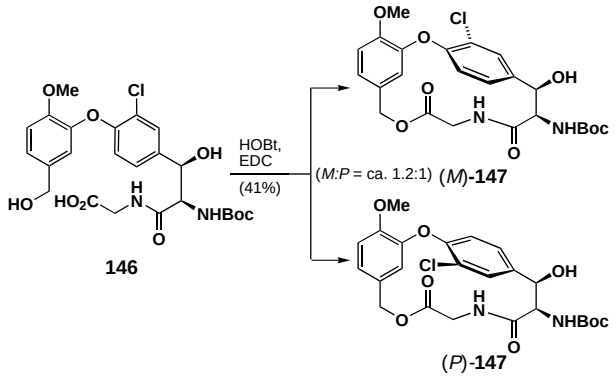


Scheme 35. Synthesis of the first model for the *D-O-E* ring system (**143**) of vancomycin by Hamilton et al.[224]

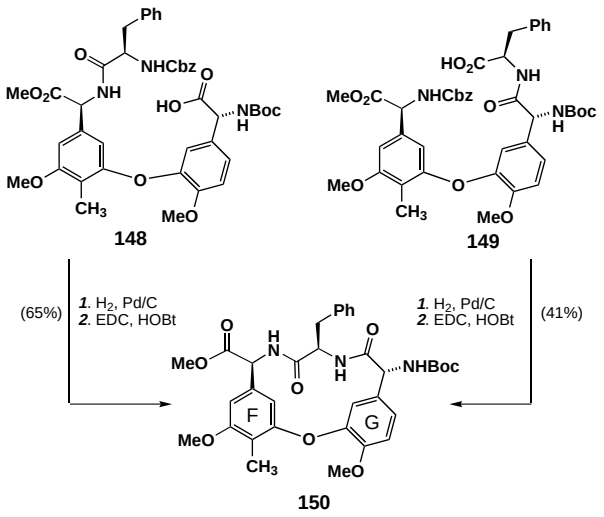


Scheme 36. Synthesis of a *D-O-E* vancomycin model system **145** by Brown et al.[226]

In a further advance, the Pearson group succeeded in forming the 14-membered model ring system **150** of ristocetin's *F-O-G* framework as a mixture of atropisomers from two different precursors, **148** and **149** (Scheme 38).[228]



Scheme 37. Synthesis of a depsipeptide *D-O-E* model system **147** by Gallagher et al.[227]



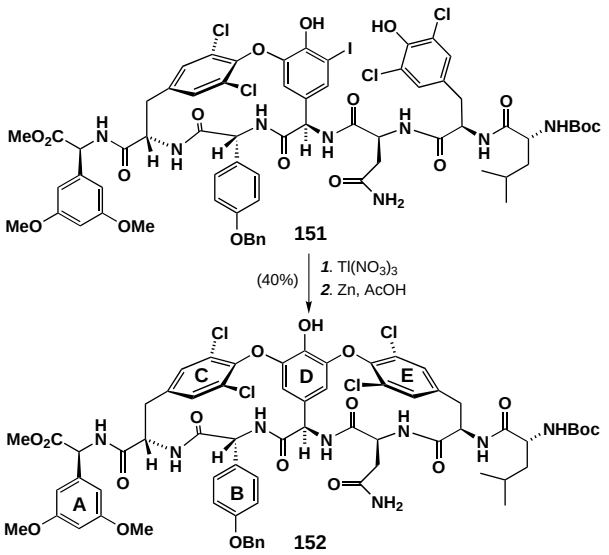
Scheme 38. Synthesis of ristocetin's *F-O-G* model ring system **150** by Pearson et al.[228]

6.3.2.2. *Oxidative Phenolic Coupling Reactions*

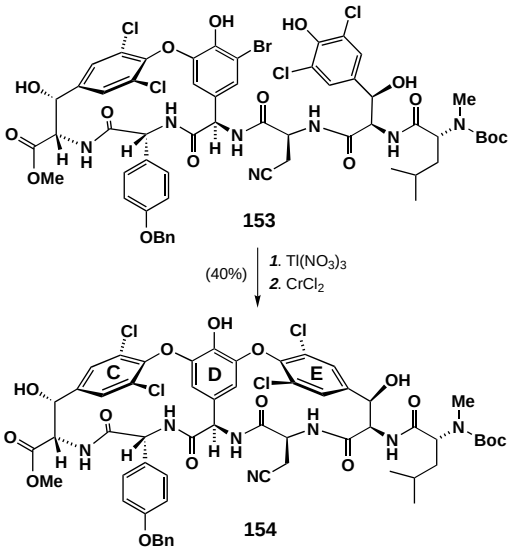
Inspired by biosynthetic considerations, synthetic chemists adopted oxidative coupling procedures for the synthesis of bisaryl ethers. This approach, pioneered by the Yamamura group, typically involves intramolecular coupling of a dihalophenol (donor) with a 2-halophenol (acceptor) in the presence of an oxidant such as thallium(III)nitrate or an anode (electrochemical).[229] The early examples of the oxidative strategy to cyclic bisaryl ethers include the total synthesis of K-13 (**129**),[217] piperazinomycin (**134**),[219] isodityrosine (**135**),[197, 199] dityrosine,[199] bastadine-6,[223] (see Figure 13), and a number of vancomycin models, including the one shown in Scheme 39.[230]

The Evans group also has adopted the oxidative strategy and applied it to the synthesis of the advanced vancomycin model system **154** as shown in Scheme 40.[108]

In general, this method allows the construction of the appropriate bisaryl ether fragment of the glycopeptide antibiotics under extremely mild conditions. Its major drawback is the required use of 2,6-dihalophenols, which necessitates the further transformation of the cyclized product to obtain the proper halogenation patterns found in the targeted molecules. Selective removal of a single halogen turned out to be



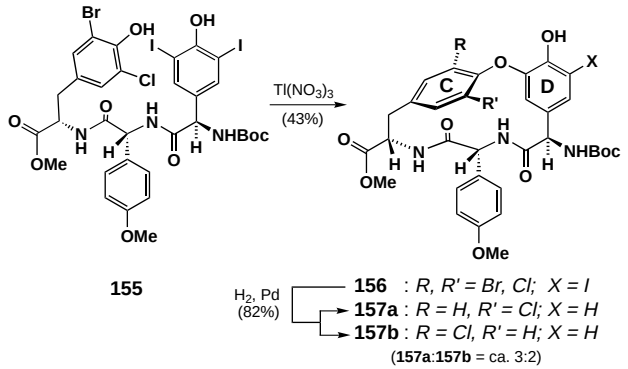
Scheme 39. Synthesis of the *C-O-D-O-E* model system **152** utilizing oxidative coupling by Yamamura et al.[230]



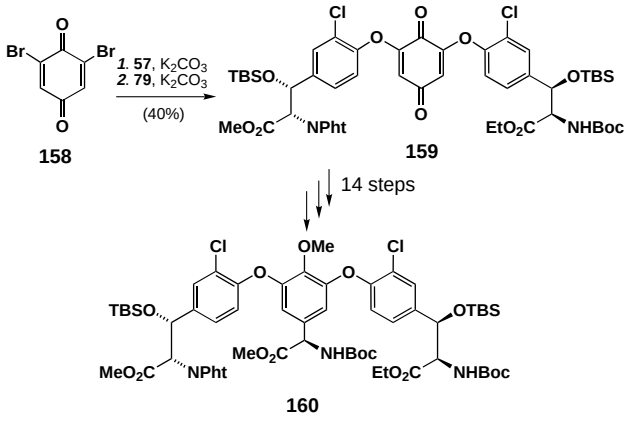
Scheme 40. Synthesis of the advanced *C-O-D-O-E* model system **154** utilizing oxidative phenolic coupling by Evans et al.[108]

exceedingly difficult. Fortunately, Yamamura et al. were able to show, through mixed halogenated (Br, Cl) substrates such as **156**, that formation of the desired atropisomer was possible. This is illustrated in Scheme 41 where a mixture of separable atropisomers **157a** and **157b** was obtained (ca. 3:2 ratio).[231]

In a related reaction system, Rama Rao et al. extensively examined the treatment of *ortho*-dibrominated quinones such as **158** (Scheme 42) with phenols. This affords the bis-aryloxy quinones, which, in turn, can be converted into suitable precursors for the bisaryl ether region of the glycopeptide antibiotics.[232] Although not applicable to ring closures, this work led to the first synthesis of a protected vancomycin acid **160**[233] as shown in Scheme 42, as well as to a formal synthesis of K-13 (**129**, see Figure 13).[214b]



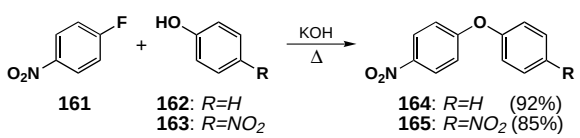
Scheme 41. Oxidative ring closure and manipulation of mixed halogenated phenols by Yamamura et al.[231]



Scheme 42. The dibromoquinone substitution route for a protected vancomycinic acid (**160**) according to Rama Rao et al.[233]

6.3.2.3. Nitro-Group-Activated Nucleophilic Aromatic Substitution

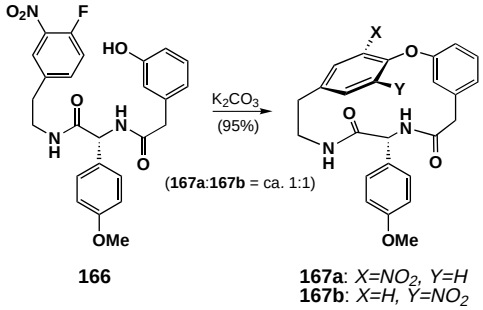
Both nucleophilic aromatic substitution (SNAr) and the formation of bisaryl ethers have long been of great importance in synthetic organic chemistry. Thus, it is not surprising that some of the first instances of bisaryl ether formation through nucleophilic displacement occurred years before the discovery and elucidation of the structure of vancomycin.[234] Intermolecular treatment of nitro-activated arylfluorides with phenoxide anions proved, very early on, to be an excellent route to bisaryl ethers. Thus, Rarick et al. showed in 1933 that *p*-nitrofluorobenzene (**161**) reacted with a variety of aryloxides (**162**, **163**) to afford the bisaryl ethers **164** and **165** in excellent yields (Scheme 43).[235]



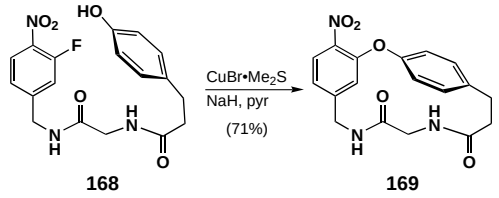
Scheme 43. Synthesis of bisaryl ethers using SNAr methodology by Rarick et al.[235]

It was not until recently, however, that this reaction was applied to the synthesis of complex systems. Thus, Beugelmans et al.,[236] Rama Rao et al.,[237] Boger et al.[194, 195, 238] and, subsequently, Roussi et al.[239] and Evans et al.[109] utilized the

SnAr methodology for the synthesis of K-13 (**129**)[214a, 215] and deoxybouvardin (**137**),[208] as well as for the construction of bisaryl ether model systems and intermediates of vancomycin and teicoplanin. The intramolecular version of this reaction was disclosed originally by Beugelmans and co-workers,[236c] and shortly thereafter, by Rama Rao et al.[237a] (Schemes 44 and 45).



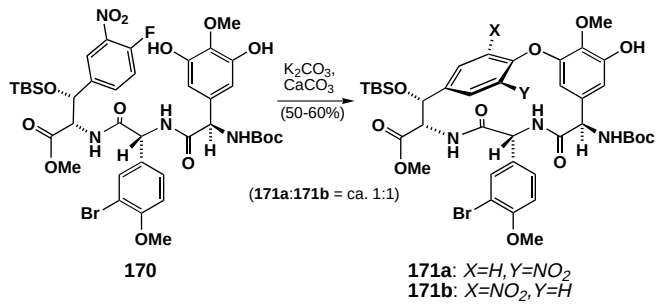
Scheme 44. Construction of vancomycin model system **167** through *o*-nitrofluoro SnAr macrocyclization by Beugelmans and Zhu et al.[236c]



Scheme 45. Synthesis of vancomycin model system **169** through *o*-nitrofluoro SnAr macrocyclization by Rama Rao et al.[237a]

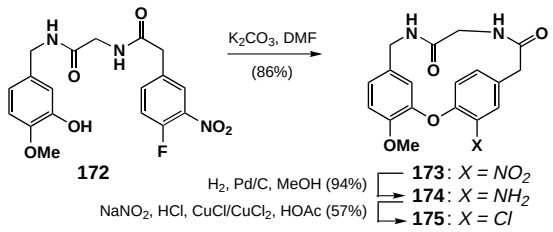
The *o*-nitrofluoro SnAr reaction also proceeds smoothly under neutral conditions and at low temperatures when the reacting phenolic group is protected as a silyl ether and catalytic amounts of fluoride ion are utilized.[240]

The SnAr strategy has been utilized by the Boger group in their construction of vancomycin model systems. Thus, the fully functionalized *C-O-D* and *D-O-E* ring systems as well as the complete *C-O-D-O-E* scaffold of vancomycin were constructed using the *o*-nitrofluoride–phenol methodology.[120, 194, 238] Shown below in Scheme 46 is the construction of the *C-O-D* model ring system **171** of vancomycin by Boger et al. The Boger group's most recent results can be seen above (Section 6.3.1).



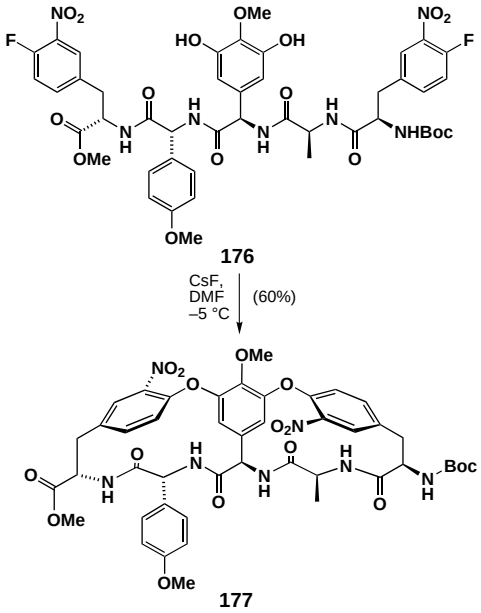
Scheme 46. Synthesis of *C-O-D* vancomycin intermediate **171** through SnAr methodology by Boger et al.[120]

Roussi et al. accomplished the synthesis of a 15-membered macrocyclic model system **175** of kistamicin (Scheme 47)[239] as well as a synthesis of a chloropeptin model.



Scheme 47. The SnAr strategy in the synthesis of the kistamicin model system **175** by Roussi et al.[239]

Applying the SnAr strategy, Zhu et al. were able to successfully establish the *C-O-D-O-E* ring system **177** of the vancomycin-type antibiotics by both a stepwise[241] and, more spectacularly, a concerted manner (Scheme 48).[242] The same



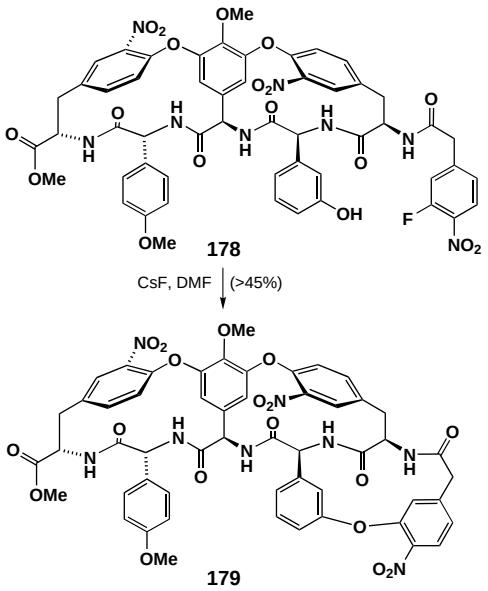
Scheme 48. Synthesis of the *C-O-D-O-E* model ring system **177** of vancomycin through double SnAr ring closure by Zhu et al.[242]

group recently disclosed the construction of the advanced teicoplanin model system **179** (Scheme 49).[243] A recent review by Zhu[244] summarizes several other examples from that group.

Evans et al. also applied this strategy in their total synthesis of both the orienticin C and the vancomycin aglycons as will be discussed in a subsequent section below.

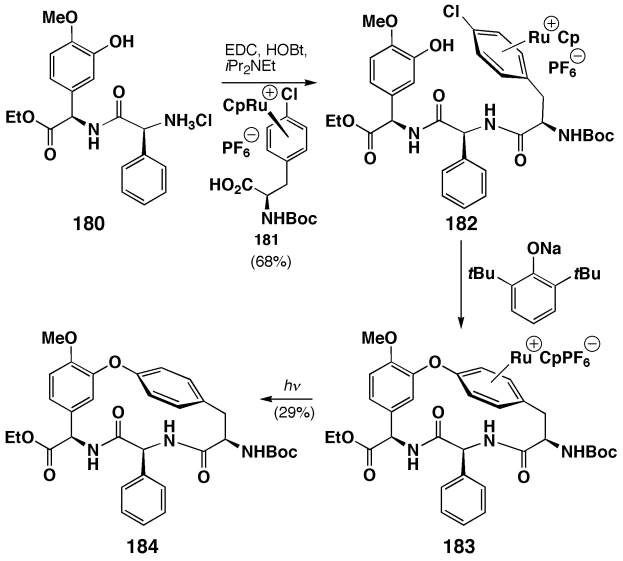
6.3.2.4. Metal-Activated Nucleophilic Aromatic Substitution

The well-known strategy of activating the aryl nucleus towards nucleophilic aromatic substitution by complexation to transition metals has been advantageously exploited by Pearson et al. in their synthesis of cyclic bisaryl ethers. Thus, by employing a variety of either tricarbonyl manganese,[245]



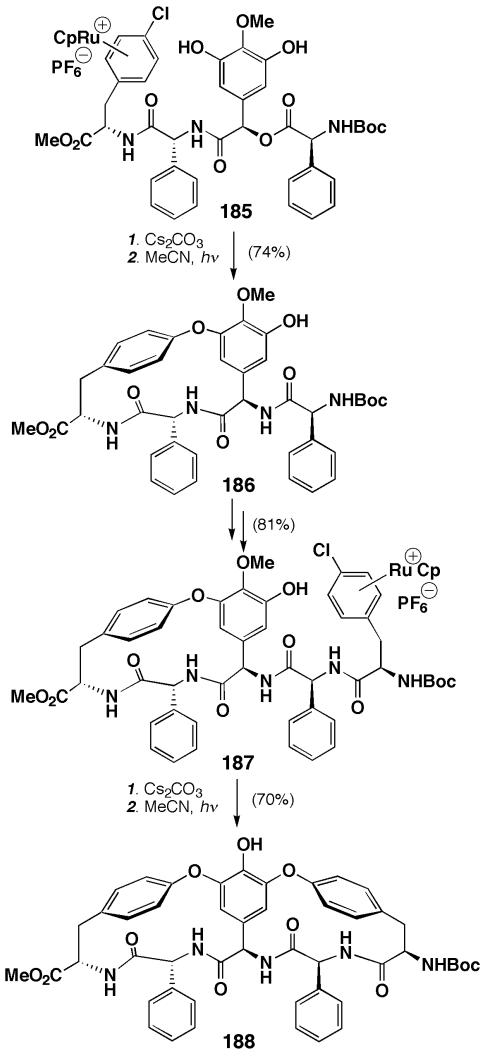
Scheme 49. Synthesis of the teicoplanin *C-O-D-O-E-F-O-G* ring system **179** through SNAr cyclization by Zhu et al.[243]

cyclopentadienyl ruthenium,[246] or cyclopentadienyl iron[247] complexes this group succeeded in constructing certain subunits of vancomycin, K-13 (**129**),[216] and teicoplanin as demonstrated for the latter case in Scheme 50.[248] The synthesis of a more advanced framework of teicoplanin was recently accomplished by the same group applying this methodology (Scheme 51).[249]

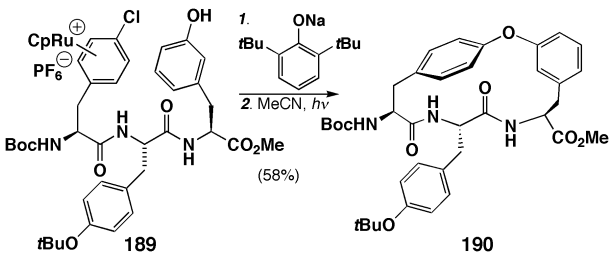


Scheme 50. Metal-activated nucleophilic aromatic substitution in the synthesis of teicoplanin model system **184** by Pearson et al.[248]

A related example was published by Rich et al. in which a model system for the angiotensin I converting enzyme inhibitor K-13 (**129**, Figure 13) was constucted by using an intramolecular SNAr reaction facilitated by metal complexation as shown in Scheme 52.[250] The potential recovery of the ruthenium from the final product at the decomplexation stage provides partial consolation for the use of stoichiometric amounts of the metal.



Scheme 51. Metal-activated nucleophilic aromatic substitution in the synthesis of the advanced ristocetin A model system **188** by Pearson et al.[249]

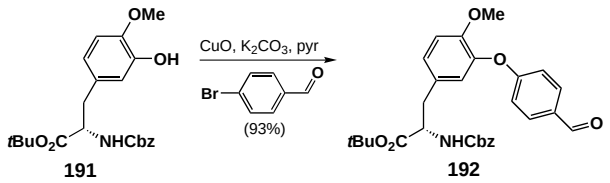


Scheme 52. Metal-activated cycloetherification in the synthesis of system **190** by Rich et al.[250]

6.3.2.5. The Classical Ullmann Reaction in Bisaryl Ether Synthesis

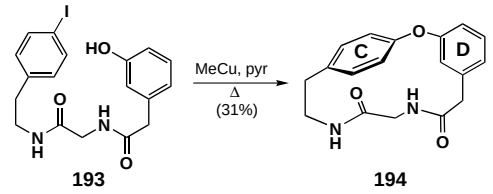
The classical Ullmann aryl ether synthesis[251] can provide an efficient route for the construction of the bisaryl ether systems of the glycopeptide antibiotics. This procedure usually involves the coupling of an aryl halide with a phenoxide moiety at high temperatures and is mediated by a copper catalyst. Schmidt et al. disclosed such a strategy for

the synthesis of OF4949-III (**132**, Figure 13) in 1988 as shown in Scheme 53.[211]

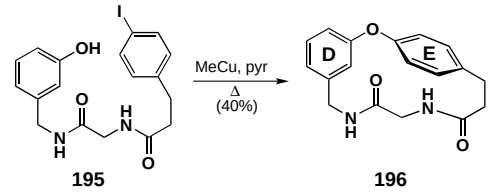


Scheme 53. Classical Ullmann bisaryl ether formation by Schmidt et al.[211]

The Boger group was able to develop a macrocyclization procedure based on the intramolecular Ullmann-type reaction by modifying the classic reaction conditions and judiciously choosing the reaction partners. This protocol helped realize the total synthesis of bouvardin (**136**),[141] combretastatin D 2,[221] deoxybouvardin (**137**),[206a, d] piperazinomycin (**134**, Figure 13),[220] and RA VII.[206a, d] It was also used in the construction of model *C-O-D* (**194**) and *D-O-E* (**196**) vancomycin ring systems as shown in Schemes 54 and 55.[252]

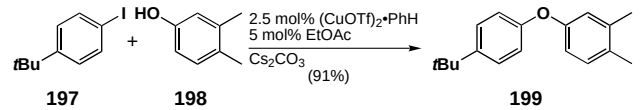


Scheme 54. Synthesis of the model *C-O-D* ring system **194** of vancomycin by Boger et al.[252]



Scheme 55. Synthesis of the model *D-O-E* ring system **196** of vancomycin by Boger et al.[252]

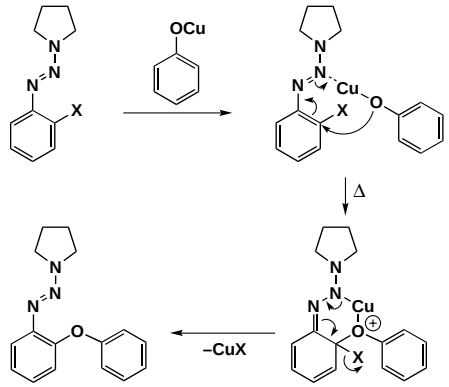
Buchwald and co-workers have also investigated copper-mediated generation of bisaryl ethers.[253] Thus, by utilizing a stoichiometric amount of cesium carbonate they were able to couple unactivated aryl halides with phenols in the presence of a $(CuOTf)_2 \cdot PhH$ catalyst (Scheme 56).



Scheme 56. Copper-mediated synthesis of bisaryl ether **199** by Buchwald et al.[253]

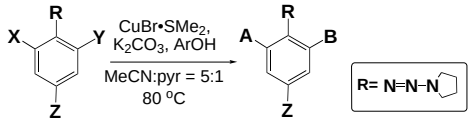
6.3.2.6. The Triazene-Driven Bisaryl Ether Synthesis

The Nicolaou group developed a mild method for the synthesis of bisaryl ethers based on triazene chemistry. The underpinning mechanistic rationale leading to this discovery is shown in Scheme 57. This reaction proceeds under mildly basic conditions in refluxing acetonitrile. The generality and scope of this procedure is demonstrated in Table 4. Furthermore, a number of cyclic systems related to the glycopeptide antibiotics were successfully constructed by this method, including the *C-O-D* (**201**, Scheme 58) and the *D-O-E* (**203**, Scheme 59) ring systems of vancomycin.[254, 255]

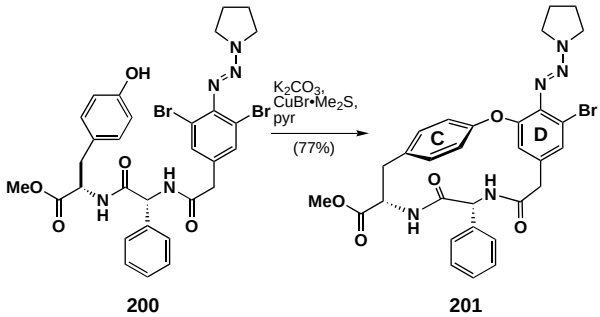


Scheme 57. Mechanistic rationale for the triazene-driven bisaryl ether synthesis by Nicolaou et al.[254, 255]

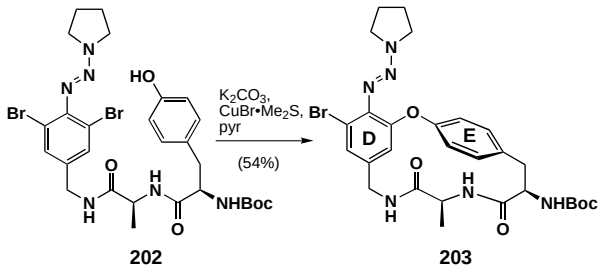
Table 4. Scope and generality of the triazene-driven bisaryl ether synthesis.[254, 255]



Entry	X	Y	Z	ArOH	A	B	Yield [%]
1	I	H	H	PhOH	PhO	H	78
2	Br	H	H	PhOH	PhO	H	65
3	Br	H	H	*o*-Cl-C_6H_4OH	*o*-Cl-C_6H_4O	H	70
4	Br	H	H	*p*-Me-C_6H_4OH	*p*-Me-C_6H_4O	H	64
5	Br	H	H	*o*-Cl-*p*-Me-C_6H_3OH	*o*-Cl-*p*-Me-C_6H_3O	H	67
6	I	I	Me	PhOH	PhO	A	83
7	Br	Br	Me	PhOH	PhO	A	89
8	Br	Br	Br	PhOH	PhO	A	91
9	Br	Me	Me	PhOH	PhO	Me	56
10	Br	Br	Me	*o*-Cl-C_6H_4OH	*o*-Cl-C_6H_4O	A	78
11	Br	Br	Me	*p*-Me-C_6H_4OH	*p*-Me-C_6H_4O	A	70
12	Br	Br	Me	*o*-Cl-*p*-Me-C_6H_3OH	*o*-Cl-*p*-Me-C_6H_3O	A	74
13	Br	Br	Me	PhSH	PhS	A	84



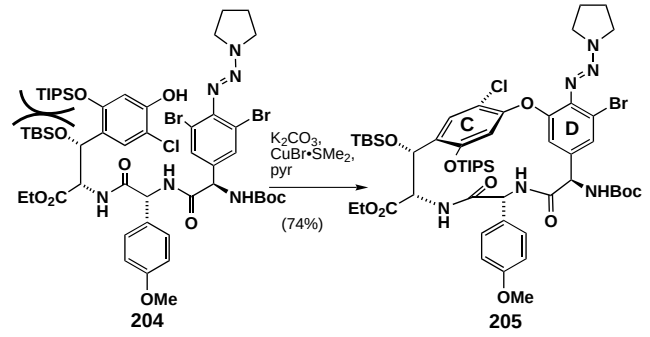
Scheme 58. The triazene-driven approach to the vancomycin model *C-O-D* ring system **201** by Nicolaou et al.[254, 255]



Scheme 59. The triazene-driven approach to the vancomycin model *D-O-E* ring system **203** by Nicolaou et al.[254, 255]

The triazene-driven bisaryl ether synthesis has several advantages such as the absence of epimerization at sensitive sites and the fertility of the triazene group for further transformations. Thus, replacement of this group with a hydrogen atom, an amine group, a diazonium salt, a phenol, or a halide is possible.

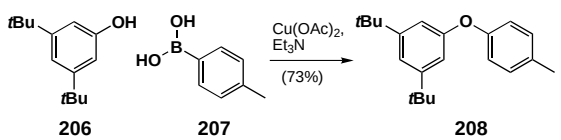
Most importantly, atropselectivity could be controlled by judiciously introducing bulky substituents onto the aromatic ring involved in the cyclization, thereby conferring chirality from the β-hydroxyl group to the cyclized system. Thus, in a proof of concept experiment it was possible to achieve complete atropselectivity (**204**→**205**) as shown in Scheme 60.[256] Chlorination in the 3- rather than 5-position should afford the other atropisomer. This predicable control of atropselectivity holds promise for a stereoselective synthesis of vancomycin and related systems.



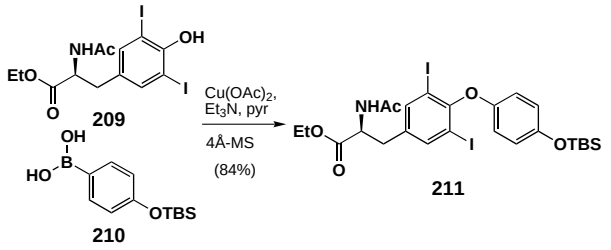
Scheme 60. Atropselective synthesis of the vancomycin *C-O-D* ring system **205** by Nicolaou et al.[256]

6.3.2.7. The Boronic Acid-Driven Bisaryl Ether Synthesis

The arylboronic acid method for the construction of bisaryl ethers was published simultaneously by two groups. Chan et al. utilized partners **206** and **207** in their synthesis of bisaryl ether fragment **208** (Scheme 61),[257] whereas the Evans group combined components **209** and **210** to construct the bisaryl ether system **211** (Scheme 62).[258]



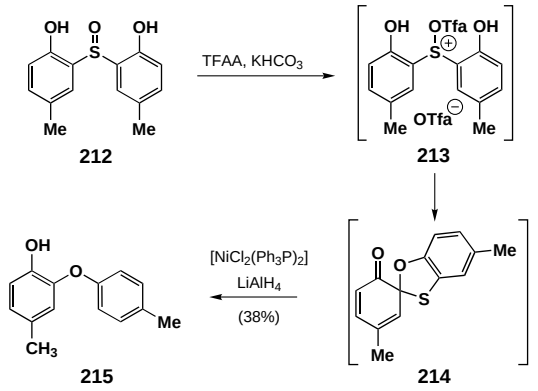
Scheme 61. Arylboronic acid-based synthesis of bisaryl ethers acording to Chan et al.[257]



Scheme 62. Arylboronic acid-based synthesis of bisaryl ethers acording to Evans et al.[258]

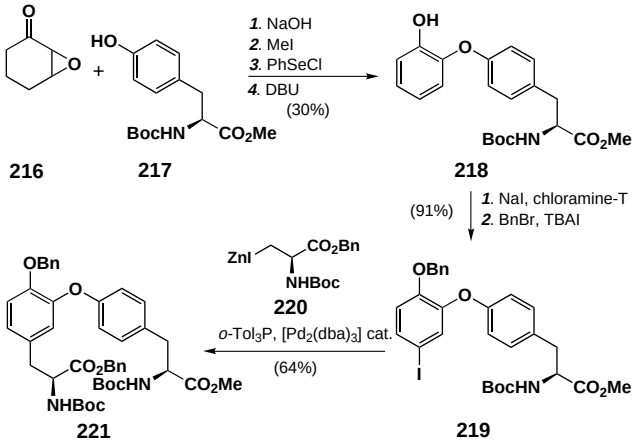
6.3.2.8. Miscellaneous Strategies

Formation of bisaryl ethers has been demonstrated by a variety of other methods. Jung et al., for example, have recently shown that it is possible to form bisaryl ethers such as **215** from bisaryl sulfoxides such as **212** through a Pummerer-type rearrangement and subsequent reduction, as shown in Scheme 63.[259]



Scheme 63. The Pummerer-rearrangement strategy towards bisaryl ethers according to Jung et al.[259]

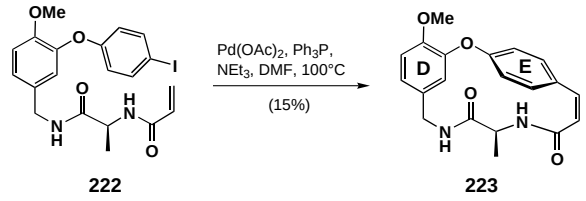
The Jung group also demonstrated a construction of bisaryl ethers based on an epoxide opening as shown in Scheme 64. Thus, opening of epoxyketone **216** with the phenoxide derived from **217**, followed by aromatization and further elaboration, led to aryliodide **219** via compound **218**. Palladium-catalyzed



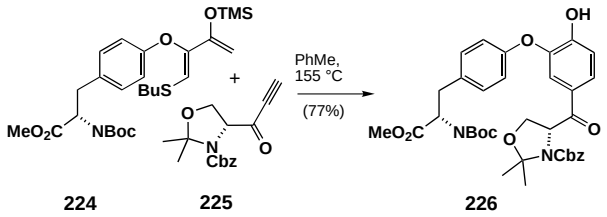
Scheme 64. The epoxide opening-based synthesis of bisaryl ethers according to Jung et al.[201]

coupling of **219** with the alanyl zincate **220** gave the isodityrosine precursor **221**.[201]

The above mentioned methods are based on cyclizations involving C–O or C–N bond formation. Presently, there are only a few examples of C–C bond forming reactions leading to vancomycin-type bisaryl ethers. One method developed in these laboratories is the ring closure based on the Heck reaction,[260] leading to macrocycle **223**, albeit in low yield, as shown in Scheme 65.[261] Another example, developed by Olsen et al., involves a Diels–Alder reaction to construct the second aromatic ring of a bisaryl ether system (Scheme 66).[262]



Scheme 65. The construction of the *D-O-E* ring model system **223** by an approach based on the Heck reaction to according to Nicolaou et al.[261]



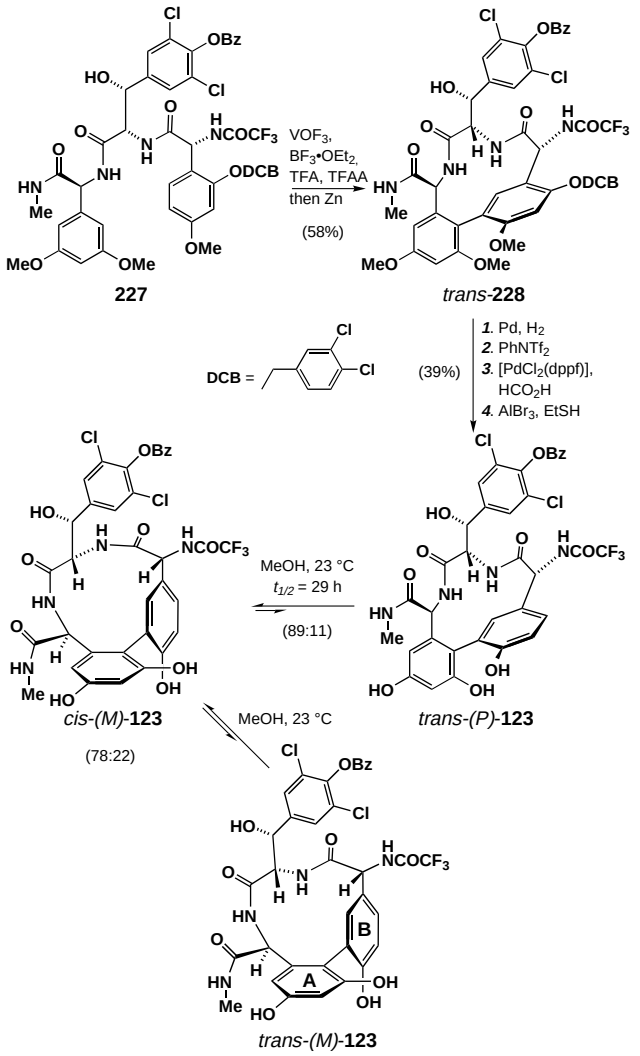
Scheme 66. A Diels–Alder-based strategy towards a bisaryl ether system (**226**) according to Olsen et al.[262]

6.3.3. Synthesis of Cyclic Biaryl Systems

The construction of biaryl-containing macrocycles[263] of vancomycin and related systems presents a serious synthetic challenge. Its daunting nature stems from the strained condition of the 12-membered ring containing a cisoid amide bond (AA-5/AA-6) and the substituted biaryl moiety. Furthermore, the phenomenon of atropisomerism, already discussed above (Section 4.3), complicates the matter by introducing stereoselectivity issues. Both the Evans and the Nicolaou groups have accomplished the construction of model systems of this region of the glycopeptide antibiotics, while a number of other groups have provided novel methods for the generation of the important biaryl bond in open-chain systems. Metals have played a crucial role in these successes.

6.3.3.1. Vanadium-Induced Ring Closures

The Evans group, inspired by the proposed biosynthetic oxidative coupling of electron-rich arenes to form biaryl bonds, developed a vanadium-based approach to the biaryl ring system of vancomycin (Scheme 67).[193] Thus, the VOF_3-induced ring closure of **227**, containing an extra oxygen-containing substituent for further activation, led to the unnatural isomer *trans*-**228**. After the removal of the activating hydroxy group from ring *B* and demethylation of the



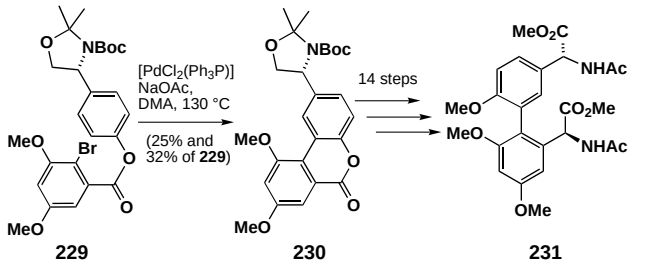
Scheme 67. VOF_3-induced construction of the *A*–*B* biaryl ring system **123** by Evans et al.[193]

remaining phenolic groups, *trans*-(*P*)-**123** was obtained. Equilibration of this system in methanol at ambient temperature led to isomers *cis*-(*M*)-**123** and *trans*-(*M*)-**123** in the ratios indicated in Scheme 67.

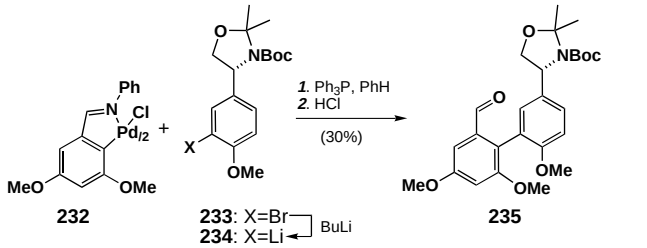
6.3.3.2. Palladium-Based Methods

A number of groups have applied palladium-induced reactions to the construction of the central biaryl bond[264] of the glycopeptide antibiotics. Thus, the Rama Rao group used a clever strategy in forming the vancomycin-related biaryl ring system **231** by first tethering the two aryl moieties together through an ester bond, and then employing an intramolecular palladium-catalyzed coupling to form the central bond, followed by rupture of the ester group (Scheme 68).[265] The same group accomplished the synthesis of biaryl compound **235** by coupling the palladated imine **232** with the lithio reagent **234** (Scheme 69).[266]

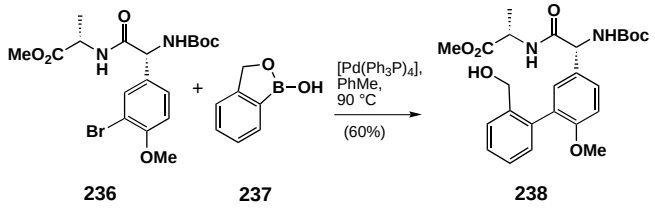
The powerful Suzuki coupling reaction[267] was utilized by Edwards and co-workers in bringing together the bromoarene **236** with boronic acid derivative **237** in the construction of the model system **238** (Scheme 70).[268] Similarly, Gurjar's group



Scheme 68. Palladium-catalyzed approach to biaryl systems **231** by Rama Rao et al.[265]

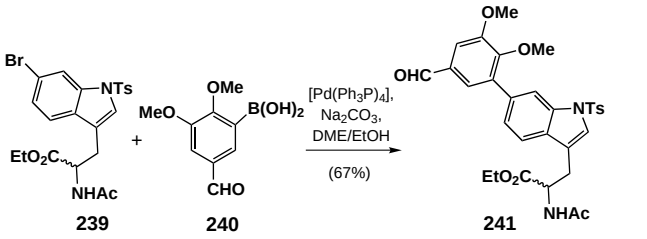


Scheme 69. Palladium-mediated approach to biaryl systems **235** by Rama Rao et al.[266]



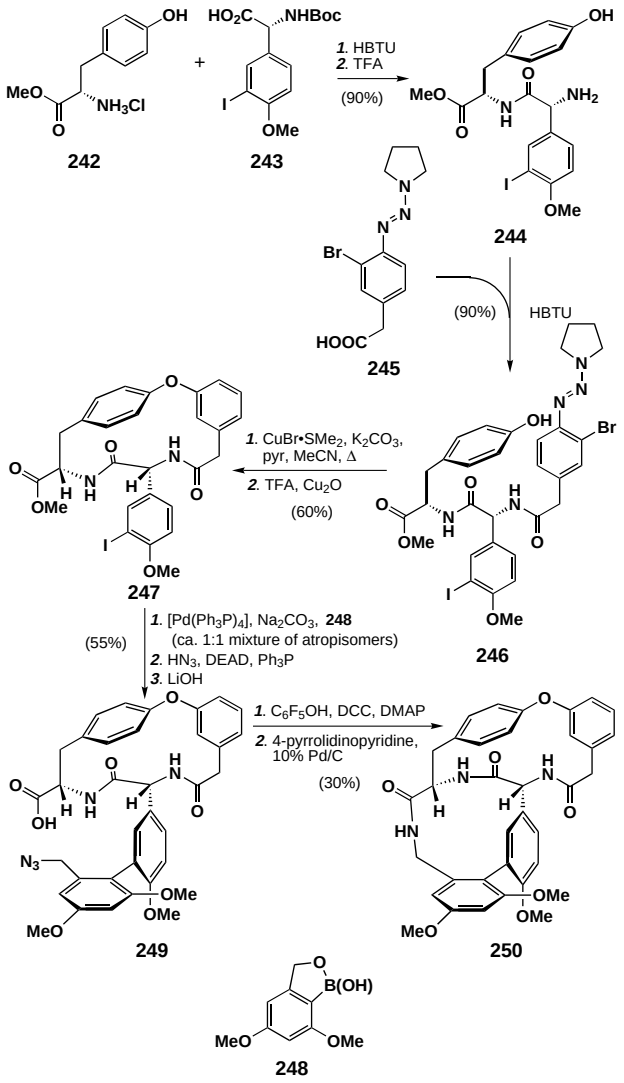
Scheme 70. Suzuki-type coupling approach to biaryl systems **238** by Edwards et al.[268]

constructed the complestatin fragment **241** by utilizing bromo compound **239** and the aryl boronic acid **240** (Scheme 71).[269]



Scheme 71. Suzuki-type coupling appoach for the complestatin model **241** by Gurjar et al.[269]

Constructing the central carbon – carbon bond of the biaryl system does not necessarily translate into a successful synthesis of the strained 12-membered system of the vancomycin-type structures. Indeed, several attempts to form this ring system have been met with unacceptable yields.[268] In an exploratory attempt to determine the effect of preorganization prior to ring closure, we designed the model study shown in Scheme 72. The plan called for preorganization by formation of the *C-O-D* ring system **247** by first using a triazene-driven cyclization, followed by a Suzuki-type coupling to form the biaryl linkage and lactamization to complete the *A-B-C-O-D* model framework **250** of vancomycin as shown.[255, 270] The strategy of pre-rigidification, which was also employed independently by the Evans group in their synthesis of the orienticin C aglycon (see Scheme 76), proved quite successful and provided the foundation for our eventual drive towards vancomycin (see Section 8).



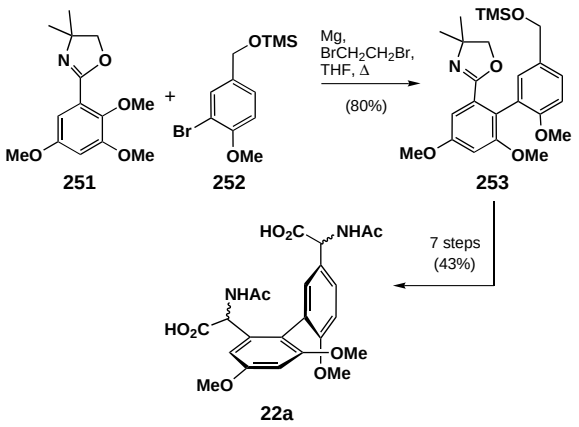
Scheme 72. The Suzuki-lactamization strategy towards the *A-B-C-O-D* model framework **250** of vancomycin by Nicolaou et al.[255, 270]

6.3.3.3. The Magnesium-Mediated Approach to Biaryl Systems

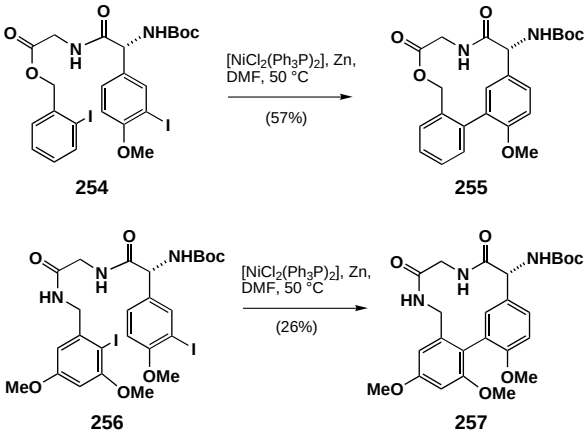
The Meyers and co-workers approach to biaryl systems utilizing activated oxazolines and arylmagnesium reagents[271] has been applied by Zhu et al. in their synthesis of an optically inactive diastereomeric mixture of the protected actinoidinic acid **22a** from the biaryl system **253** as shown in Scheme 73.[272]

6.3.3.4. The Nickel-Mediated Approach to Biaryl Systems

The nickel-mediated coupling of aryl iodides to form biaryl systems[273] was employed, in an intramolecular fashion, to construct model systems of the *AB* ring system of the glycopeptide antibiotics by our group as shown in Scheme 74.



Scheme 73. Meyers oxazoline-type approach to biaryl systems according to Zhu et al.[272]

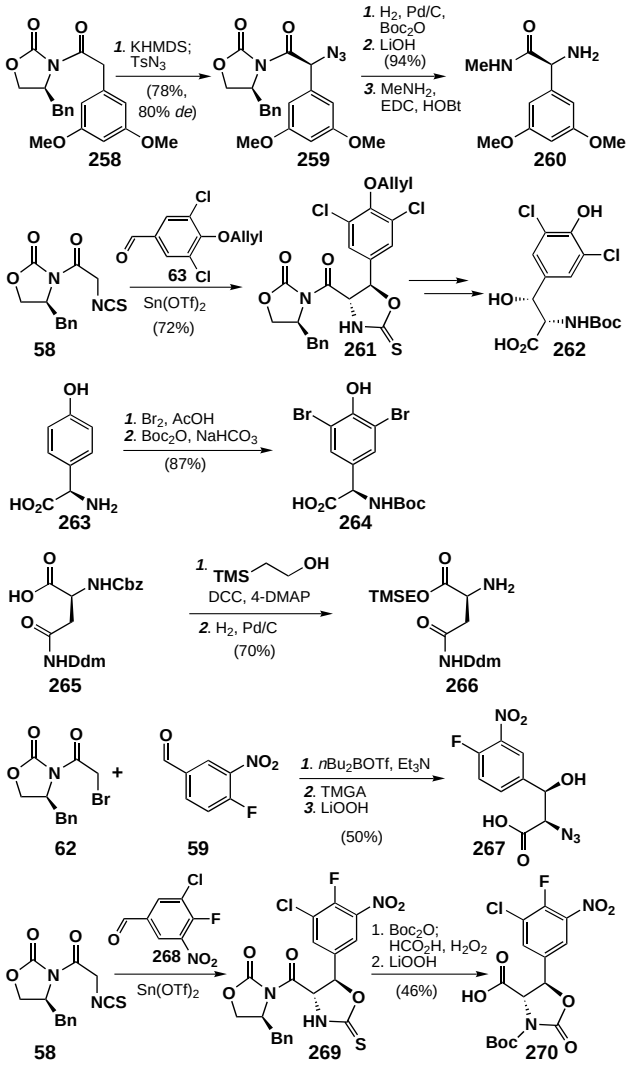


Scheme 74. Nickel-mediated approach to cyclic biaryl systems by Nicolaou et al.[255, 274]

While the less substituted depsipeptide system **255** was obtained as a single compound, the trimethoxy compound **257** was formed as two isolable isomers in about 3:1 ratio (in favor of the natural atropisomer). By-products in this reaction included dimeric materials and open-chain reduced compounds (iodine replaced by hydrogen).[255, 274] The modest yields obtained were attributed to the short Ni–C bond length, as well as the highly substituted nature of the biaryl system, both of which introduce steric congestion in the transition state.

7. The Total Syntheses of Orienticin C and Vancomycin Aglycons by Evans and Co-workers

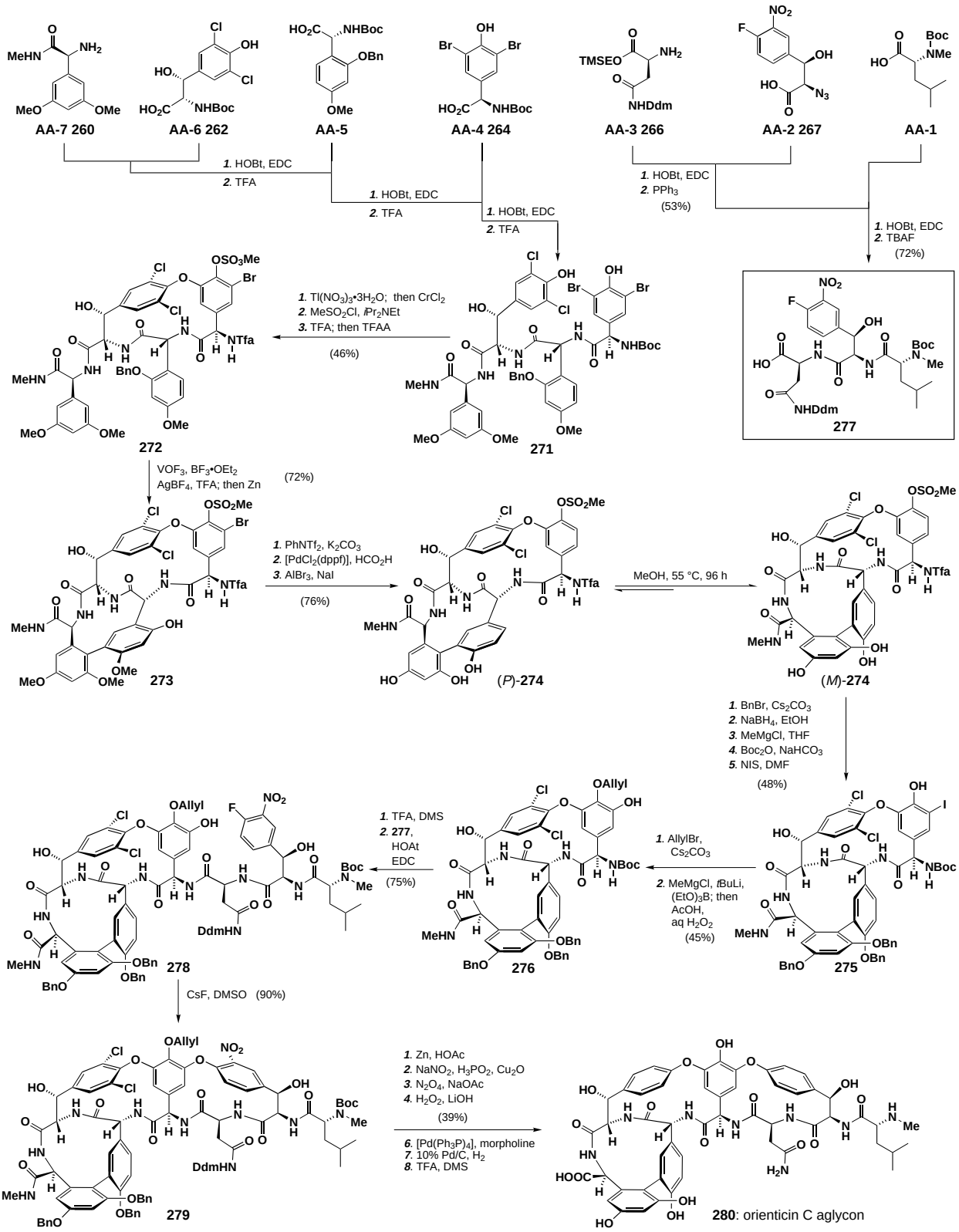
The Evans group was the first to accomplish the total synthesis of a complete framework of a glycopeptide antibiotic. Reported in 1997, their synthesis of orienticin C aglycon, summarized in Scheme 76, utilized the amino acid building blocks AA-1 through AA-7 synthesized as highlighted in Scheme 75.[275, 276] Thus, the *C-O-D* ring system **272** was efficiently assembled by coupling amino acid equivalents AA-4 to AA-7, followed by cyclization induced by thallium(III) nitrate. Vanadium-induced biaryl formation established the *A-B-C-O-D* ring skeleton (**273**) of unnatural stereo-



Scheme 75. Synthesis of key amino acid building blocks for the total synthesis of orienticin C and vancomycin aglycons by Evans et al.

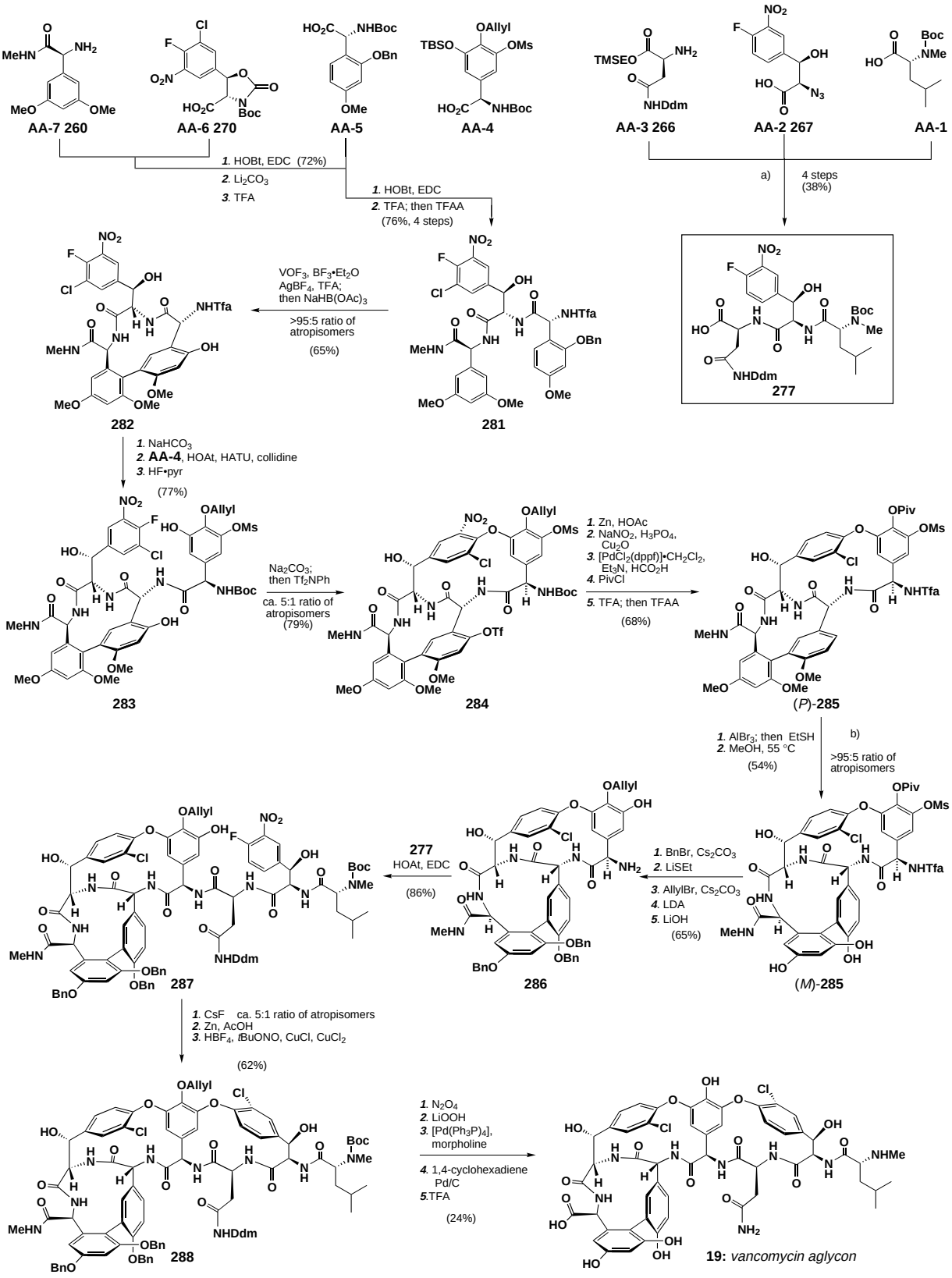
chemistry (both amide and atrop geometry), which was suitably elaborated and equilibrated to the natural form by heating in methanol at 55 °C. Further elaboration resulted in intermediate **276**, which was coupled with the *o*-nitrofluoroaryl-containing tripeptide **277** to obtain the cyclization precursor **278**. Successful ring closure of **278** under the influence of CsF furnished the desired polycyclic skeleton of orienticin C, **279**, which was elaborated to the targeted orienticin C aglycon, **280**, by dechlorination, denitration, and deprotection as shown in Scheme 76. Initial attempts to append the *D-O-E* ring system onto **274** by the oxidative coupling induced by thallium(III) nitrate, as was originally intended by the Evans group, met with only modest success. This failure was attributed to the sensitivity of the reaction to transannular effects across the *C-O-D* ring system (that is, the chlorination pattern of the *C*-ring), as well as to conformational effects imparted from the *A*–*B* biaryl ring system.[277] Thus, the SNAr technology became a viable alternative in this instance.

A significantly different approach was utilized by the Evans group in their total synthesis of the vancomycin aglycon (**19**) which they completed in 1998.[278] As summarized in



Scheme 76. Total synthesis of the orienticin C aglycon (**280**) by Evans et al.[276]

Scheme 77, this synthesis required amino acid building blocks AA-1 through AA-7, synthesized as outlined in Scheme 75, and proceeded through initial construction of the *A*–*B* ring system. Thus, exposure of tripeptide **281** to VOF_3 resulted in the formation of the doubly unnatural stereoisomer (wrong atropisomer, transoid amide bond). Elaboration of **282** furnished precursor **283**, whose ring closure by the *o*-nitrofluoride technology led to the *A*-*B*-*C*-*O*-*D* ring system **284** with the appropriate chlorination pattern (favored ca. 5:1 in the ring closure).[279] Further steps removed the auxiliary, nitro

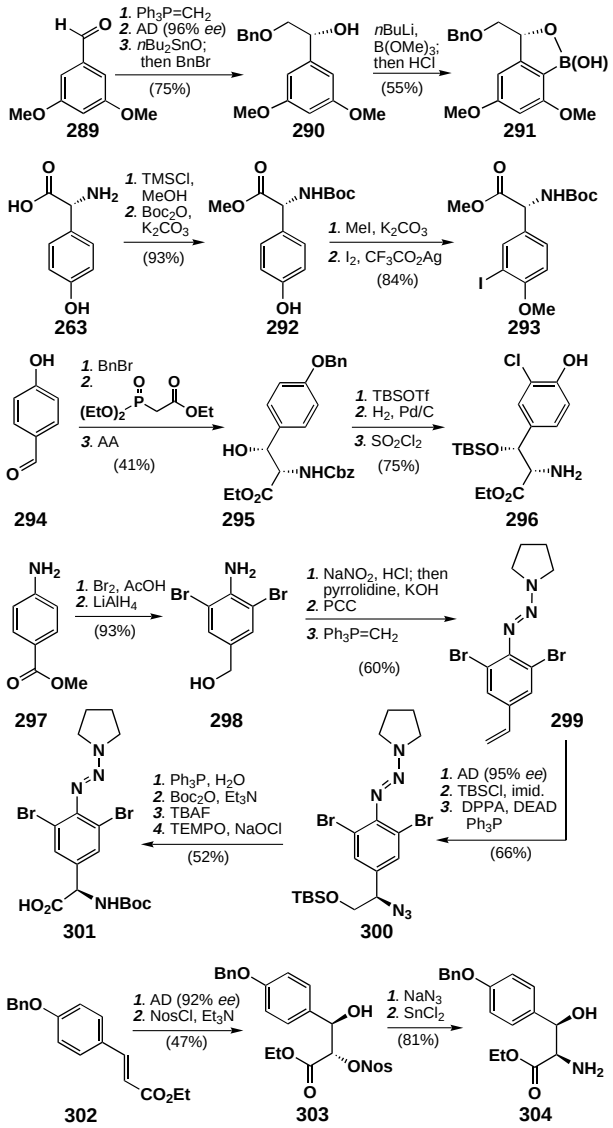


Scheme 77. Total synthesis of the vancomycin aglycon (**19**) by Evans et al.[278] a) The same procedure was used as for orienticin C aglycon synthesis (see Scheme 76). b) Atropisomerization and transoid to cisoid isomerization.

and phenolic groups from rings *C* and *A*, respectively, and, after isomerization of both the biaryl system and the amide bond, led to intermediate **285**. Coupling of **286** with tripeptide **277**, followed by *o*-nitrofluoroarene ring closure, led to the required tri-macrocycle, which was elaborated to vancomycin aglycon (**19**) as indicated in Scheme 77.

8. The Total Synthesis of Vancomycin Aglycon and Vancomycin by Nicolaou and Co-workers

Based on the triazene-driven bisaryl ether forming reaction[254, 255] and the Suzuki coupling/macrolactamization strategy,[255, 270] our laboratory completed the total synthesis of vancomycin and its aglycon.[143, 191, 280] The key amino acid building blocks utilized are shown in Scheme 78. These amino



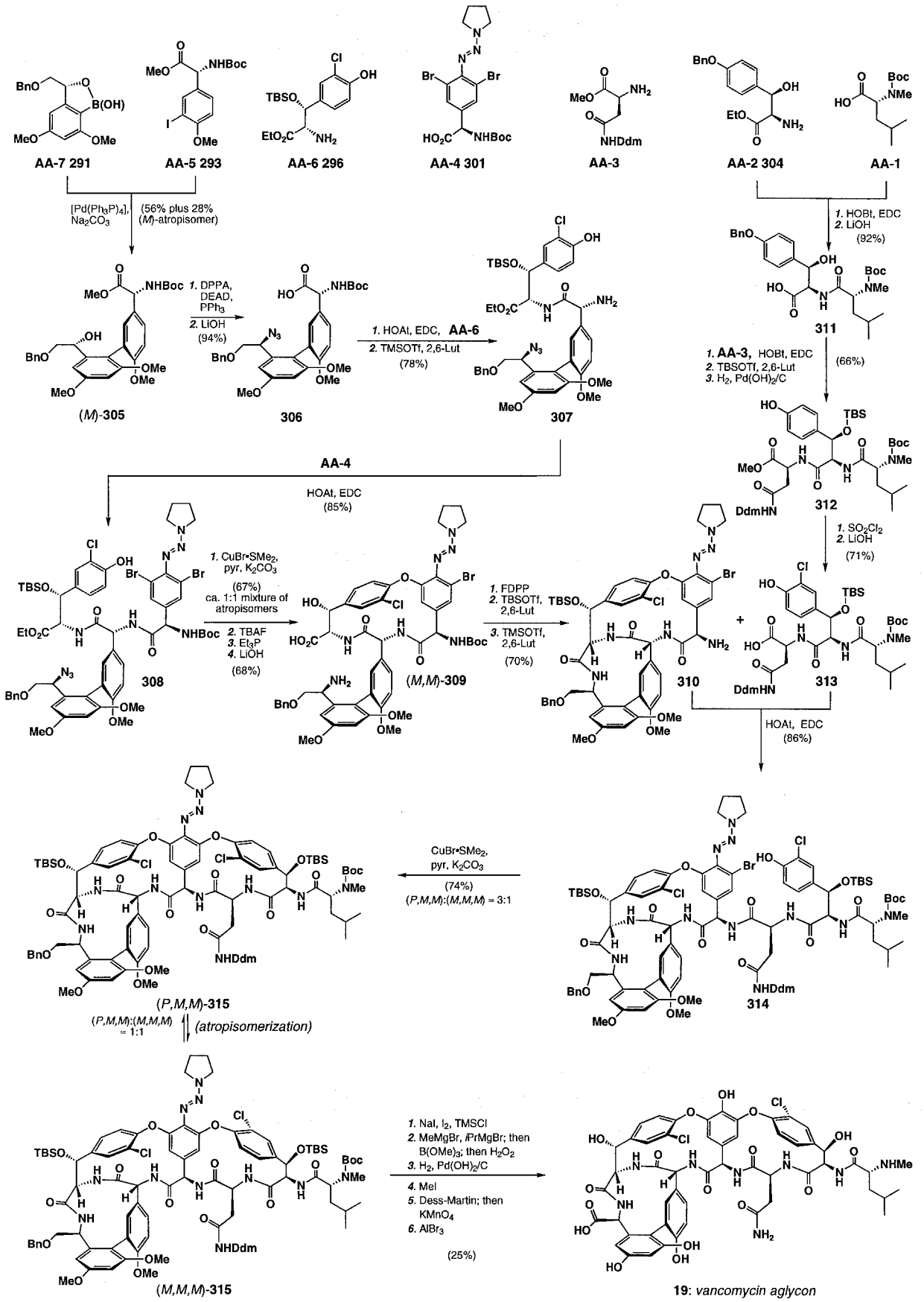
Scheme 78. Synthesis of key amino acid building blocks for the total synthesis of vancomycin by Nicolaou et al.

acid building blocks were constructed as single enantiomers by asymmetric synthesis or by utilizing natural amino acids.[143] Their coupling and elaboration to vancomycin aglycon (**19**) is shown in Scheme 79. Thus, Suzuki-type coupling of AA-5 and AA-7 led, stereoselectively, to the biaryl system (*M*)-**305**, which was elaborated and coupled with AA-6 to furnish **307**. The latter was joined to the central amino acid equivalent AA-4, leading to **308**, which was cyclized under the influence of $CuBr \cdot SMe_2$ to give the *C-O-D* ring system (mixture of atropisomers, ca. 1:1). After appropriate elaboration, macrolactamization of **309** led to the desired *A-B-C-O-D* ring framework with the correct configuration in both the *A* – *B* and *C-O-D* regions.[142, 280] The tripeptide **313**, prepared conventionally as shown, was then attached onto the main framework **310**, thus establishing the cyclization precursor **314**. The final macrocyclization led to a mixture of unnatural ((*P*,*M*,*M*)-**315**) and natural ((*M*,*M*,*M*)-**315**) atropisomers at the *D-O-E* junction (ca. 3:1 ratio). After equilibration of the wrong atropisomer (*P*,*M*,*M*), the desired isomer (*M*,*M*,*M*)-**315**[280, 281] was carried through the indicated sequence to the vancomycin aglycon (**19**) as summarized in Scheme 79.[280, 282]

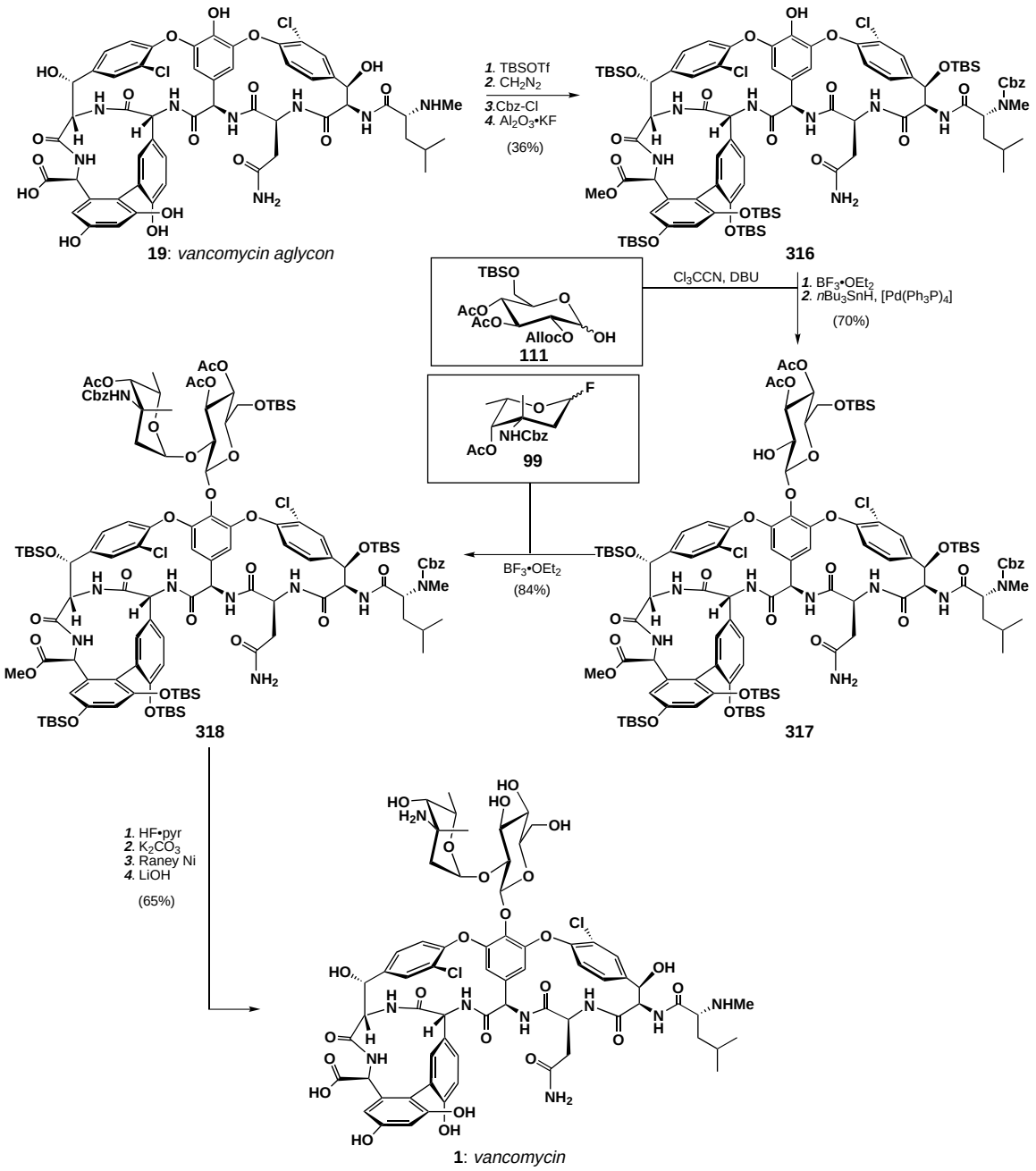
The total synthesis of vancomycin (**1**) proceeded through its aglycon (**19**) as depicted in Scheme 80. Thus, sequential protection of the hydroxyl groups, the carboxylate moiety, and the amine function, followed by selective monodesilylation led to the aglycon derivative **316**, which served well as a carbohydrate acceptor. The requisite glucose and vancosamine donors, components **111** and **99**, were synthesized as summarized in Schemes 27 and 23, respectively. Coupling of **316** with the trichloroacetimidate of **111** proceeded smoothly to afford, after selective deprotection of the 2′-hydroxyl group, the monoglycosylated system **317**. The second glycosidation involving **317** and glycosyl fluoride **99** also proceeded in excellent yield and stereoselectivity, affording the protected vancomycin derivative **318**, from which the natural substance, vancomycin (**1**), was liberated by a series of deprotections as shown in Scheme 80.[187, 191]

As a part of our program towards the total synthesis of vancomycin, a number of degradation studies were undertaken in order to facilitate the final stages of the synthesis. Among them was the particularly useful degradative pathway leading to key intermediate **316** as shown in Scheme 81.[187, 191] The final removal of the sugar residues (**320** → **316**) utilized a modification of the standard protocol (TFA, 50 °C) for cleavage of glycopeptide sugar residues. The addition of dimethyl sulfide to the trifluoroacetic acid decreases the acidic nature of the TFA while promoting a SN2-type reaction mechanism.[283] These conditions preserve the silyl groups while smoothly removing the sugar residues.

A comparison of the approaches of the Evans and Nicolaou groups to vancomycin's aglycon (**19**) reveals both striking similarities and differences. Both are highly convergent and lead to the target molecule from its constituent amino acids. The latter building blocks were constructed by different methods, but in each case employing modern asymmetric reactions to achieve high enantiomeric excesses. The longest linear sequence in both syntheses were between 25 and 30 steps depending on the starting point of counting. The most distinct difference between the two approaches lies within the methods and strategies of construction of the macrocyclic framework of the molecule. The Evans group generated the *A* – *B* ring system first, as the unnatural atropisomer with a transoid amide bond, through a vanadium-mediated oxidative coupling. This system then facilitated the formation of the *C-O-D* ring system, which was formed predominantly as the natural atropisomer. Isomerization of the biaryl system and transoid amide bond led to the natural *A-B-C-O-D* skeleton. In contrast, the Nicolaou group opted for forming the *C-O-D* ring system first which, in turn, facilitated the construction of



Scheme 79. Total synthesis of the vancomycin aglycon (**19**) by Nicolaou et al.[142, 281, 282]

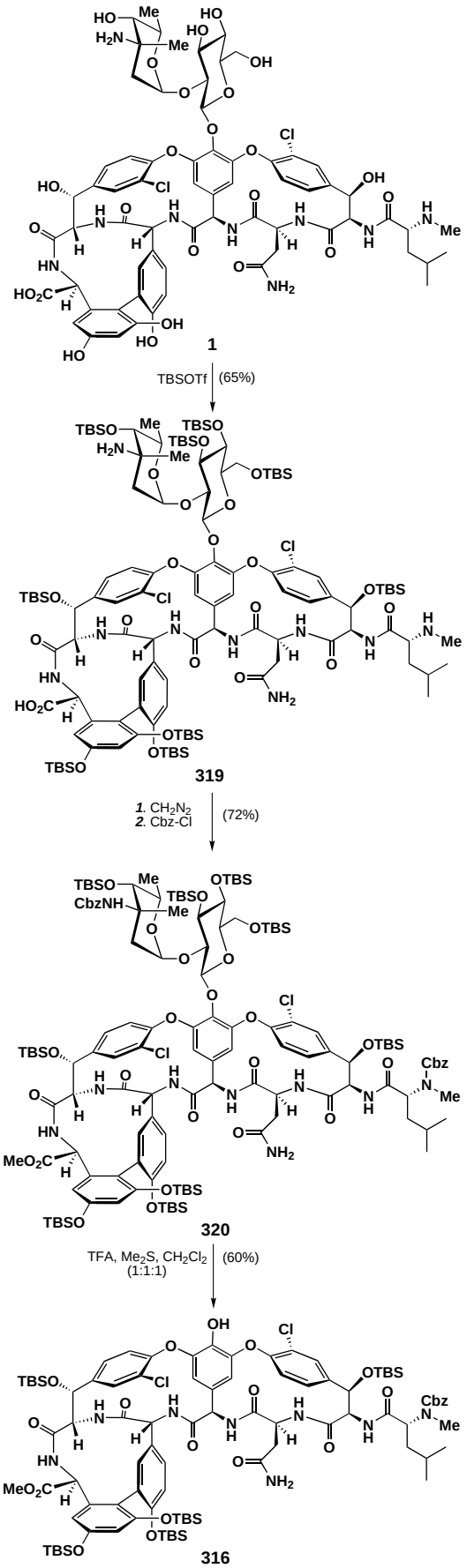


Scheme 80. Total synthesis of vancomycin (**1**) by Nicolaou et al.[187, 191]

the *A* – *B* ring system by a strategy involving a stereoselective Suzuki coupling followed by a macrolactamization. Unfortunately, the *C*-*O*-*D* ring system was formed as a 1:1 mixture of atropisomers.

Both approaches chose to form the *D*-*O*-*E* macrocycle last. The Evans group applied the nucleophilic substitution of an aryl fluoride with an activated *o*-nitro group (see Section 6.3.2.3) while the Nicolaou group utilized their triazene-driven ring closure (see Section 6.3.2.6). Here the Evans group received a 5:1 ratio of atropisomers in favor of the desired atropisomer. The Nicolaou group, on the other hand, obtained a 3:1 ratio in favor of the unnatural atropisomer, a misfortune that was somewhat compensated for by the selective atropisomerization of the *D*-*O*-*E* ring system into a separable 1:1 mixture of atropisomers. Both groups faced the inevitable task of converting the activating groups necessary for the ring closures into desired functionalities (Evans: NO_2 to Cl; Nicolaou: triazene to OH) and final deprotections.

At present, both routes to the vancomycin aglycon are more symbolic than practical. While they speak volumes of the power of organic synthesis to reach formidable targets, at the same time they stand second to the rapid and succinct manner in which nature produces these compounds. In contrast to the aglycon synthesis, the final stages of the total synthesis of vancomycin (**1**) through attachment of the sugar units as demonstrated by the Nicolaou group (see Scheme 80) are quite efficient. Furthermore, the availability of the requisite aglycon intermediate from vancomycin (see Scheme 81)



Scheme 81. Degradative path leading from vancomycin (**1**) to key intermediate **316** by Nicolaou et al.[187, 191]

makes the production of combinatorial libraries of semisynthetic glycopeptides for biological screening a practical proposition.

9. Biology

Bacteria are fascinating, unicellular organisms that are commonly classified into two groups according to the structure of their protective cell wall. Those that stain in the Gram stain test are called Gram-positive and those that do not are Gram-negative. These designations reflect the thickness of the peptidoglycan layer, as well as the absence or presence of an outer membrane, respectively, as shown in Figure 14. In the case of Gram-positive bacteria, the stain test

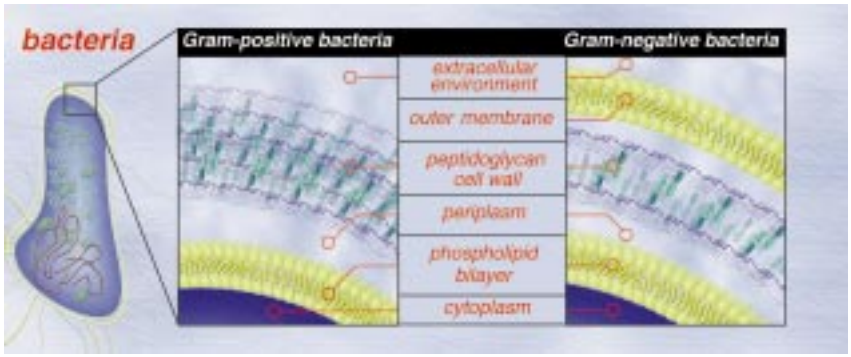


Figure 14. The cell wall of Gram-positive and Gram-negative bacteria. Gram-positive bacteria have a thicker peptidoglycan layer than Gram-negative bacteria but lack the outer membrane at the cell surface.

reveals the interaction of the dye with the thick peptidoglycan layer of the bacterial cell wall. Upon treatment, dye becomes trapped within the thick layer of peptidoglycan and can not be washed out, even when the cells are treated with a non-aqueous solvent. In the case of Gram-negative bacteria, the dye is easily washed out of the thin peptidoglycan structure leaving no staining. The peptidoglycan layer of Gram-negative bacteria is generally thinner (2 to 7 nm in width) than that of Gram-positive bacteria (20 – 40 nm); however, in both cases, it serves as a structural support for the cell wall, which prevents it from lysing under the cells' own positive osmotic pressure.[284]

The glycopeptide antibiotics specifically attack the peptidoglycan layer of the bacterial cell wall as we will shortly discuss. This structure is also the specific target of the β-lactam antibiotics (such as the penicillins, cephalosporins, carbapenem, monobactams, nocardins, and clavulanic acid), fosfomycin, mersacidin, moenomycin, and tunicamycin. Figure 15 shows the site of action of these antibiotics in relation to the rest of the cell topology. Other antibiotics exert their action against bacteria by inhibiting either the biosynthesis of nucleic acids (sulfanil amides, diaminobenzylpyrimidines, gyrase blockers, or ansamacrolides) or the biosynthesis of proteins (aminoglycosides, chloramphenicol, lincomycins, and tetracyclines).

The peptidoglycan layer of the bacterial cell wall is composed of a cross-linked polymeric network made from

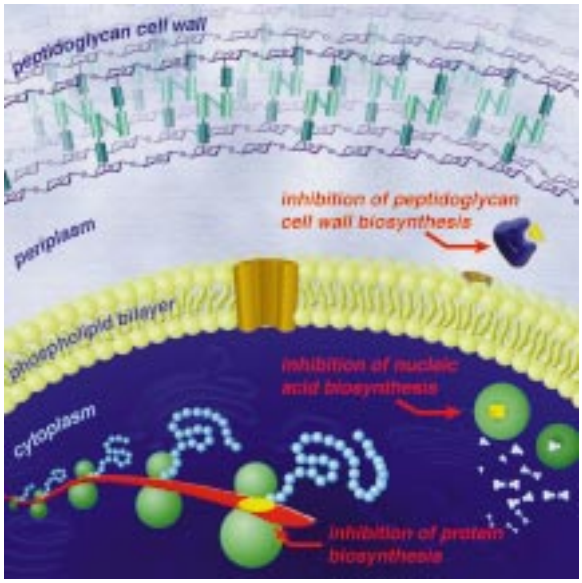


Figure 15. Antibiotics kill bacteria by interfering with essential bacterial processes: inhibition of cell wall biosynthesis, nucleic acid biosynthesis, or protein biosynthesis.

disaccharide units and peptide chains. The disaccharide module consists of one unit of *N*-acetylglucosamine (*N*-AcGlc) and one unit of *N*-acetylmuramic acid (*N*-AcMur) connected with a (1 →4)-β-glycosidic linkage. This disaccharide moiety is repeated up to one hundred times and cross-linked to other oligosaccharide strands to instill rigidity through a peptide framework. The peptide unit consists of an L-Ala-D-Glu-L-Lys-D-Ala-D-Ala fragment[285] that is attached to the carboxylate group of the muramic acid through the *N*-terminus of L-Ala. The free amino group of the L-lysine residue allows for the dense cross-linking of the peptidoglycan by a pentapeptide bridge to the D-Ala of a second peptide chain (Scheme 82).

The biosynthetic pathway to the peptidoglycan has been well established. As shown in Scheme 82 the biosynthesis of this complex structure begins in the intracellular region of the bacterial cell (cytoplasm) with UDP-*N*-acetylglucosamine formed from UTP and *N*-acetylglucosamine-1-phosphate and ends at the outer region of the cell with peptidoglycan. Briefly, the construction proceeds by transfer of pyruvate to afford UDP-Glc-*N*-Ac-enolpyruvate, followed by reduction to yield UDP-*N*-acetylmuramic acid. The latter is coupled sequentially with the three amino acids L-Ala, D-Glu, and L-Lys, followed by attachment of the dipeptide D-Ala-D-Ala. The D-Ala-D-Ala moiety is formed through the action of alanine racemase, which epimerizes L-Ala to D-Ala, and D-Ala-D-Ala ligase, which couples two units of D-Ala. A translocase enzyme then transports the biosynthesized *N*-acetylmuramic acid pentapeptide through the membrane as the undecaprenylpyrophosphate (P-P-C_{55}) is attached.[286] This lipophilic pyrophosphate is embedded in the phospholipid bilayer, which keeps the growing peptidoglycan layer in the periplasm. Here, the *N*-AcGlc unit is incorporated and the peptide segment is further elongated by the introduction of a pentaglycine fragment to give the completed peptidoglycan monomeric unit. Polymerization by the action of the transglycosidase enzyme then leads to growing peptidoglycan frameworks, which are finally released from the membrane and cross-linked by the action of a transpeptidase enzyme, forming peptidoglycan.[287] The glycopeptide antibiotics inhibit the transglycosidation step as shown in Scheme 82 and Figure 15, which also indicates points of interference by a number of other well-known antibacterial agents. Below, we discuss the details of the mode of action of the glycopeptide antibiotcs.

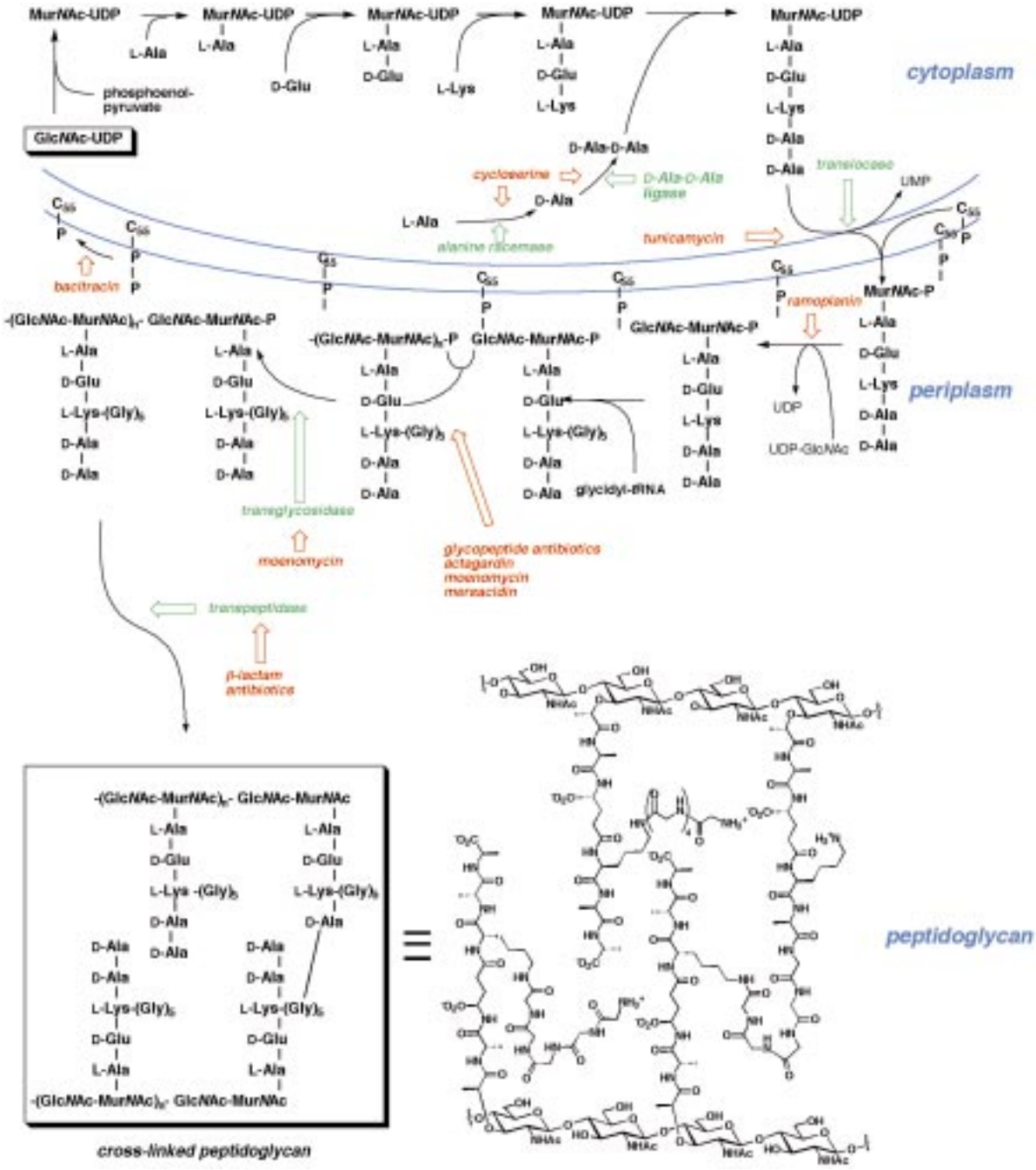
9.1. Mode of Action

Binding of vancomycin to the bacterial cell wall was known long before its structural elucidation. Today, a precise structural picture for this interaction has been uncovered by NMR and X-ray crystallographic techniques. It is known that vancomycin binds reversibly to the L-Lys-D-Ala-D-Ala fragment of the peptidoglycan monomer. This reversible, noncovalent interaction inhibits transglycosidation and transpeptidation from occurring (Figure 16). Inhibition of these processes leads to the collapse of the peptidoglycan by decisively shifting its dynamic equilibrium towards de-assembly, which precipitates cell lysis and bacterial death.

The strong binding of vancomycin to L-Lys-D-Ala-D-Ala is a consequence of five well-defined hydrogen bonds as shown in Figure 17.[100] In Gram-positive bacteria the glycopeptide antibiotics easily diffuse through the peptidoglycan layer and reach the periplastic space where the peptidoglycan polymerization takes place. By grabbing onto the L-Lys-D-Ala-D-Ala tails of the monomers the antibiotic positions itself to inhibit the transglycosidase from joining the carbohydrate ends as shown in Figure 16.

While the antibacterial action of the glycopeptide antibiotics is attributed to their ability to bind L-Lys-D-Ala-D-Ala and inhibit the peptidoglycan growth, a number of secondary effects contribute to the enhancement of their potency. Prominent among these secondary effects are the abilities of a number of glycopeptides to dimerize in solution and of others to anchor themselves into the phospholipid bilayer by using lipophilic tails. Primarily as a result of the elegant NMR studies by D. H. Williams et al. at Cambridge,[288, 289] but also from recent X-ray crystallographic data,[19–23] we now know that ristocetin A, vancomycin, and a number of other glycopeptides dimerize in solution to form head-to-tail complexes. The dimeric structures, held together by four hydrogen bonds, contain two binding sites for L-Lys-D-Ala-D-Ala units as depicted in Figure 18.

The propensity of glycopeptide antibiotics to dimerize has been correlated with their potency. This has been explained through two hypotheses. The first of these predicts a higher activity for a dimer since once half of the dimer binds to the substrate as usual, the other half then finds its target through what now becomes essentially intramolecular binding. This cooperative effect decreases the entropy factor for binding. The second hypothesis predicts increased activity through



Scheme 82. The biosynthesis of peptidoglycan in *Staphylococci*. C_{55} = bactoprenol (undecaprenol), P = inorganic phosphate, Mur = muramic acid. Color code: antibiotics: red, enzymes: green.

allosteric effects. Thus, the hydrogen bonding within the dimer enhances the ability of the binding pocket to bind the ligand by polarizing the amide bonds. This effect works in reverse as well. That is to say, the binding of the ligand also enhances the ability of the glycopeptide antibiotic to dimerize.[290]

The back-to-back mode of dimerization may not be the only dimeric form contributing to the enhanced antibacterial activity. A recent X-ray crystallographic analysis of a complex between vancomycin and *N*-acetyl-D-alanine revealed, in addition to the back-to-back form, a face-to-face dimeric form of the antibiotic.[23]

In contrast to vancomycin and ristocetin A, teicoplanin exhibits high antibiotic activity despite its inability to dimerize in solution. An explanation for the enhanced potency of teicoplanin is provided by another secondary effect exhibited by a number of glycopeptide antibiotics, that of anchoring into the cell's phospholipid bilayer through a long hydrocarbon chain. Thus, the lipophilic chain of teicoplanin attached to one of its carbohydrate units localizes the antibiotic to its site of action.[291] The two modes of antibacterial activity enhancement, dimerization and anchoring are graphically shown in Figure 19.

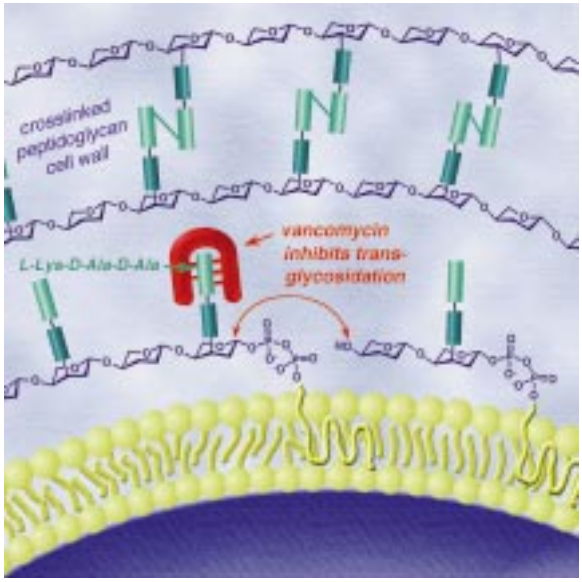


Figure 16. Mechanism of action of the glycopeptide antibiotics: vancomycin binds to the peptide portion of the peptidoglycan monomer and prevents the transglycosidase enzyme from polymerizing the peptidoglycan monomers and results in cell death.

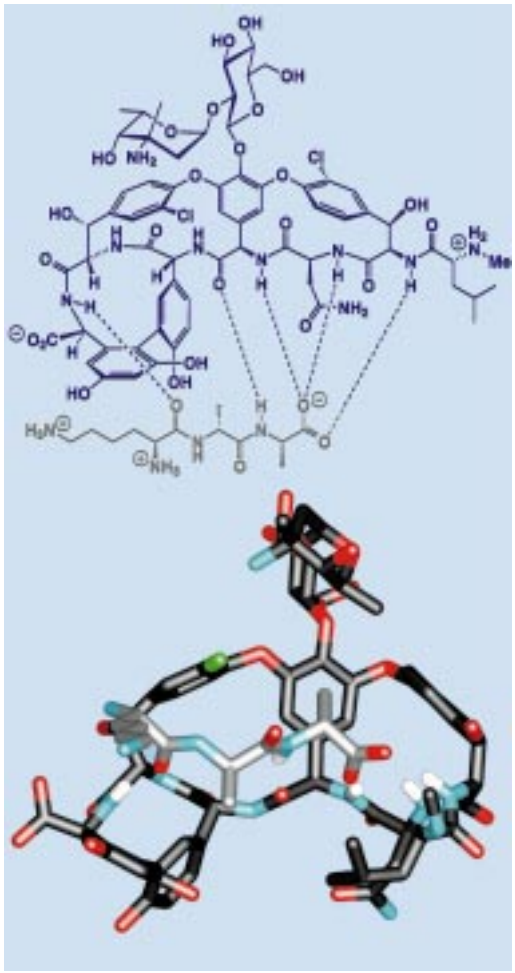


Figure 17. The hydrogen bonding arrangement between vancomycin (**1**) and L-Lys-D-Ala-D-Ala tripeptide. In the tube structure vancomycin is depicted in black and the L-Lys-D-Ala-D-Ala tripeptide in gray.

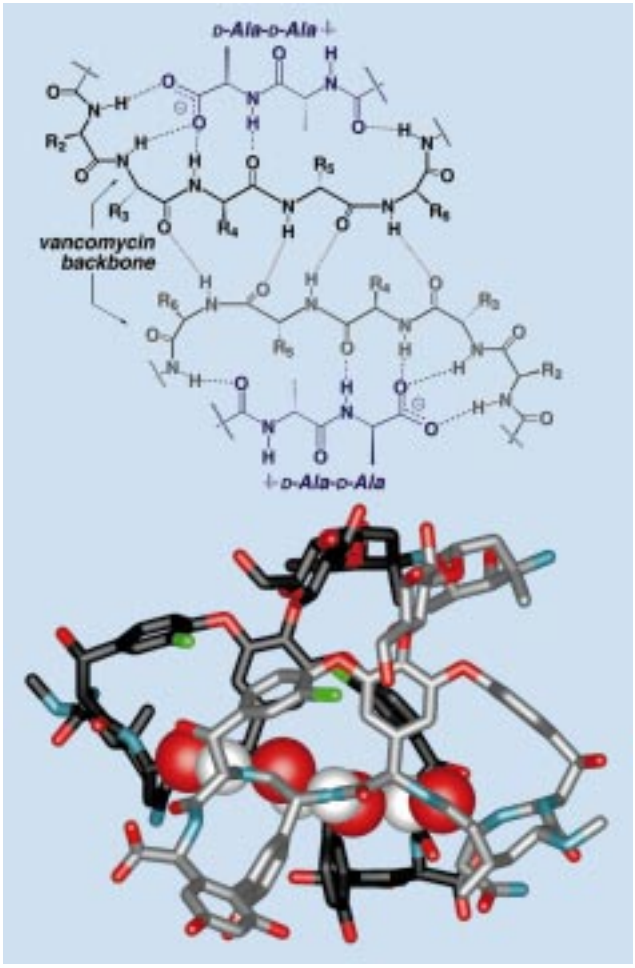


Figure 18. The hydrogen-bonding network in the vancomycin dimer: the peptide backbones of two molecules of vancomycin dimerize forming four hydrogen bonds. In the structure above, two units of the D-Ala-D-Ala ligand dock in the two binding pockets of the dimer through five hydrogen bonds each. Shown below is an X-ray crystal structure of the vancomycin dimer with the hydrogen and oxygen atoms involved in the hydrogen bonding network depicted in CPK style.

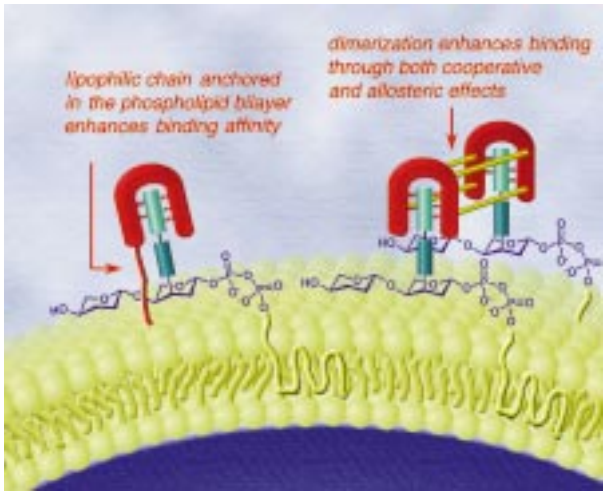


Figure 19. Modes of antibiotic-activity enhancement in glycopeptide antibiotics: dimerization which increases cooperativity in binding (right); and anchoring which helps localize the antibiotic (left).

9.2. Resistance

In 1988, the emergence of vancomycin-resistant *Enterococci* (VRE) was recognized for the first time.[292, 293] Despite the nonpathogenic nature of *Enterococci* towards healthy individuals, the alarm was taken seriously because these bacteria can infect immunodeficient patients, such as AIDS patients and organ transplant recipients. Furthermore, the genetic machinery of such resistant bacteria could be transferred to more dangerous species such as MRSA. In fact, this type of transfer has already been shown to occur in the laboratory.[294]

The vancomycin-resistant *Enterococci* bacteria are clinically divided into three categories: types A, B, and C.[295] Types A and B VRE are characterized by the replacement of D-Ala-D-Ala with D-Ala-D-Lac within their peptidoglycan. This modification removes one hydrogen bond between vancomycin and its target (Figure 20),[287, 296] resulting in an up to 1000-fold loss of activity. Fortunately, a number of semisynthetic derivatives possessing both dimerization and anchoring properties were found to be effective in combating this mutation (see below).[297]

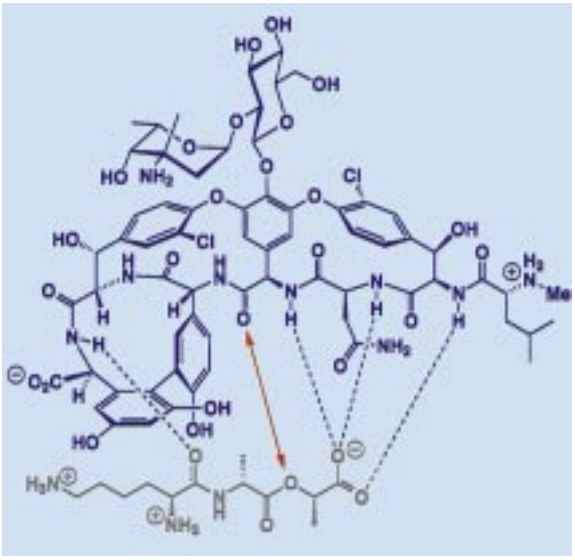
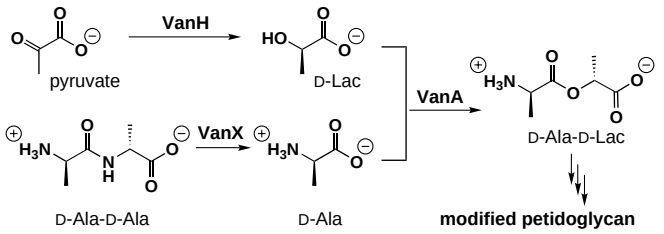


Figure 20. The molecular basis of vancomycin resistance by *Enterococci*: The hydrogen-bonding network between vancomycin (**1**) and L-Lys-D-Ala-D-Lac lacks one of the hydrogen bonds present in the binding of vancomycin to L-Lys-D-Ala-D-Ala thereby decreasing the binding affinity up to a 1000-fold and rendering the antibiotic ineffective.

Type C resistance is significantly different from types A and B. It presents only modest resistance to vancomycin and appears to be chromosomal rather than plasmid-born. In other words, it appears to be part of the natural makeup of the cell rather than a response to selective pressures applied by the use of antibiotics. The peptidoglycan in these resistant organisms terminates, not in D-Ala-D-Ala or D-Ala-D-Lac, but rather in D-Ala-D-Ser.[298] The exact nature of the disruptive effect in these bacteria is still speculative, but it is suspected to involve unfavorable interactions of the bulky serine residue with the convex face of vancomycin.[299]

The genetic background of vancomycin resistance in *Enterococci* has recently been elucidated to a considerable degree, primarily from the works of Courvalin et al.[300–303] and Walsh et al.[287, 301, 302, 304] It is now well understood that VRE types A and B express their resistance through five plasmid-born genes (*van*S, *van*R, *van*H, *van*A, and *van*X).[300] These genes are switched on by inhibitors of the late-stage biosynthetic steps of peptidoglycan biosynthesis.[305] Enzymes VanH, VanA, and VanX act together to modify the peptidoglycan structure as shown in Scheme 83. The α-keto reductase,



Scheme 83. The molecular basis of the development of vancomycin resistance in bacterial cells: biosynthesis of D-Ala-D-Lac.

VanH, reduces pyruvate to D-lactate,[301] while the depsipeptide ligase, VanA, then couples the lactate (Lac) to D-Ala affording D-Ala-D-Lac.[302] In a synergistic manner, VanX, a D-Ala-D-Ala dipeptidase,[303] suppresses the biosynthesis of the D-Ala-D-Ala-containing peptidoglycan by hydrolyzing the D-Ala-D-Ala dipeptide preferentially, while its D-Ala-D-Lac counterpart builds up (Scheme 83).[304] The *van*S and *van*R genes result in a two-component signal transduction pathway which activates transcription of *van*H, *van*A, and *van*X. Whether vancomycin itself is the inducing agent or whether it acts indirectly by altering the balance of peptidoglycan biosynthesis is still unclear.[287]

An additional gene, *van*Z, has been isolated and shown to cause low-level teicoplanin resistance, which does not involve incorporation of D-Lac into the peptidoglycan.[306]

The mechanism of resistance observed in the recently isolated vancomycin-resistant, methicillin-resistant *Staphylococcus aureus* is not yet fully understood. It is clear, however, that it does not involve incorporation of genes similar to those found in vancomycin-resistant *Enterococci*.[307] Instead, resistance is thought to arise from the alteration of the structural organization of the cell wall. Increased incorporation of *N*-acetylglucosamine in the cell wall, increased supply of cell-wall monomer, and increased production of penicillin binding protein 2 (PBP2) all serve to decrease the effectiveness of the antibiotic. Furthermore, this resistance is associated with a significant thickening of the peptidoglycan layer, as well as a remarkable decrease in peptidoglycan cross-linking.[308, 309] This may serve to sequester the antibiotic, preventing it from reaching its site of action. A more detailed mechanistic understanding of vancomycin-resistant *S. aureus* is yet to emerge.

10. Semisynthetic Glycopeptide Antibiotics

A large number of semi-synthetic glycopeptides have been constructed from naturally occurring antibiotics. The design of these constructs is based either on the mechanism of action

of the glycopeptide antibiotics or on chemical methods for their structural modification. The semisynthetic approaches to designed glycopeptides fall broadly into three strategies: those aimed at modifying the outer sphere of the parent antibiotics (strategy I), those involving degradation and reassembly of the cyclopeptide core with incorporation of new amino acid components (strategy II), and those utilizing dimerization or trimerization of vancomycin through covalent tethering (strategy III).

Even though the full potential of these strategies has not yet been realized, a number of interesting analogues have been synthesized. A selected number are listed in Table 5, together with their origin, strategy of modification, and properties. Schemes 84–88 show a selection of semisynthetic glycopeptide structures and the reaction sequences employed for their production.

Chemists drew from both chemical and enzymatic methods in their attempts to modify the outer core of the glycopeptides (strategy I). Removal of the carbohydrate units can be effected, as well as the attachment of new sugars. Acylation or reductive amination at the aminosugar site allowed the synthesis of several new analogues.[310, 311] Most notable among them is LY333328 (**322**, Scheme 84), synthesized by a group at Eli Lilly from chloroorienticin A **321**.[297] Equipped with a *p*-chlorobiphenyl moiety, this compound was constructed from chloroorienticin A as shown in Scheme 84. Currently in clinical trials, LY333328 was found, somewhat surprisingly, to be highly effective against *Staphylococci*, MRSA, and Gram-positive bacteria, in addition to types A and B vancomycin-resistant *Enterococci*.[312] Apparently, the combination of the enhanced anchoring and dimerization properties of this molecule compensates for any reduced affinity towards D-Ala-D-Lac present in VRE.[313]

In an attempt to expand the scope of the glycopeptide antibiotics to include fighting Gram-negative bacteria, scientists prepared vancomycin–siderophore conjugates. Siderophores are natural iron chelators that are utilized by many microorganisms for the binding and the uptake of iron.[314] It was hoped that such conjugates could reach the periplasm by penetrating the outer cell wall and thus inhibit peptidoglycan biosynthesis. However, this strategy has resulted, so far, in only a moderate increase in the activity of the antibiotics against Gram-negative bacteria.[315] With the same goal in mind, chemists at Lepetit Laboratories, in Italy, prepared mideplanin (**323**, Scheme 84) by 3-(*N*,*N*-dimethylamino)propylamidation of teicoplanin A_2-2 **10**.[316] This derivative, and the one similarly derived from the teicoplanin aglycon, are active against both *Staphylococci* and Gram-negative bacteria.[317] Furthermore, the teicoplanin aglycon-derived poly(aminopropyl)amides **324** and **325** (Scheme 84) also exhibited significant antibiotic activity against Gram-negative bacteria.[318] In their mode of action, these modified glycopeptides do not differ from their parent compounds except for their ability to traverse the outer membrane of the Gram-negative bacteria by a self-promoted uptake mechanism.[319]

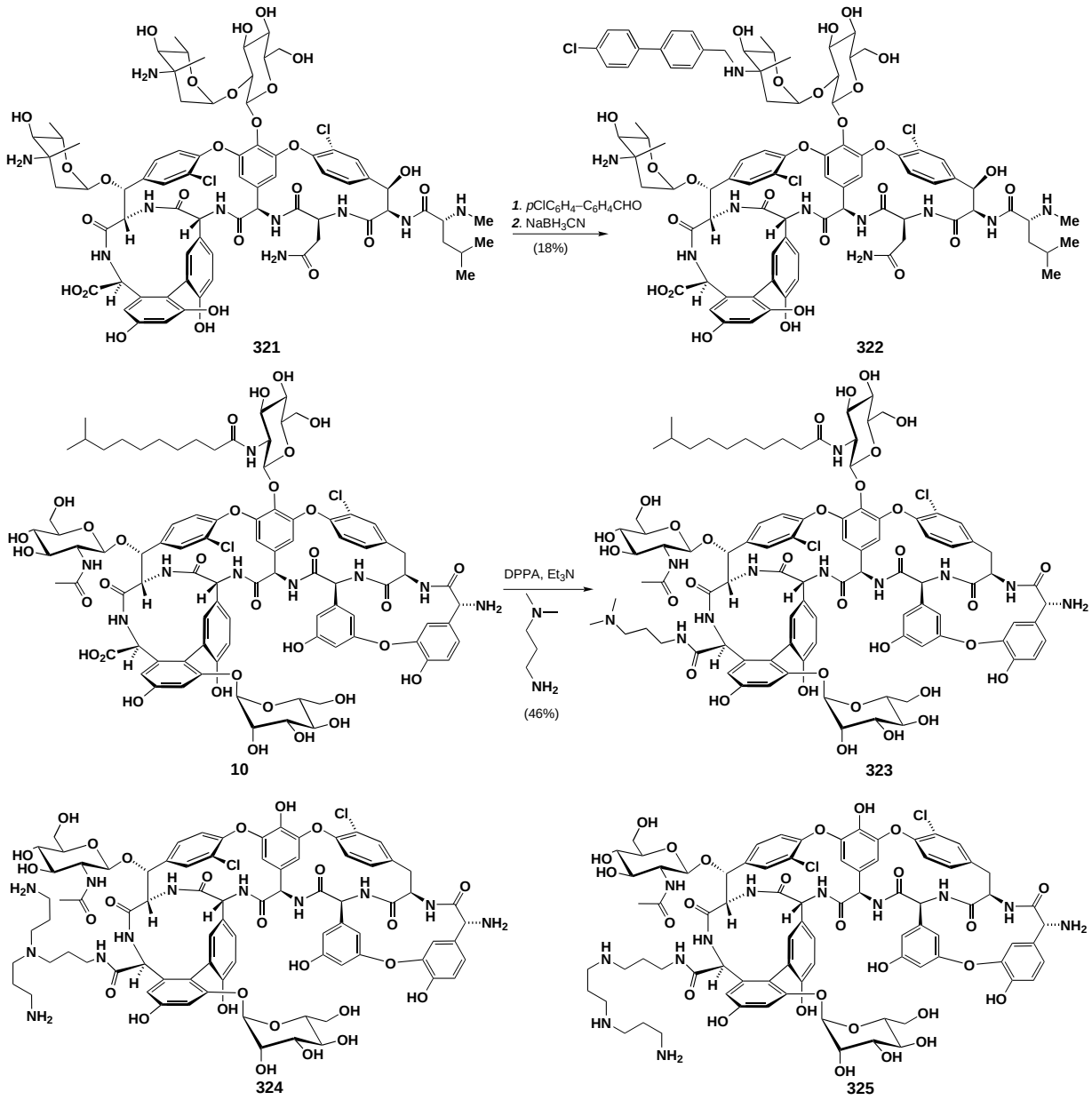
Considerable efforts have been expended in modifying the cyclopeptide core of the glycopeptide antibiotics. Early attempts aimed at tinkering with the degree of chlorination of vancomycin.[320] Removal of the chlorine atom from AA-2 by hydrogenation led to the conclusion that this substituent is responsible for a tenfold boost in activity; the chlorine on AA-6 was found to be less influential. NMR studies with eremomycin revealed a stabilizing effect of the chlorine atom on the dimer of this molecule, exerted through its filling of lipophilic pockets along the interface of the two monomeric units.[321] Epimerization of the α-carbon atom of AA-3 of teicoplanin resulted in a major change in the binding pocket of the molecule by forcing rotation around the AA-2/AA-3 amide bond. The consequence of this change was the removal of the hydrogen bonding opportunity for this amide hydrogen and the total loss of antibiotic activity.[322]

Recent studies demonstrated the feasibility of rupturing certain amide bonds selectively and of excising certain amino acids from the glycopeptide backbone and replacing them with new, even unnatural ones. Hydrolysis of the AA-6/AA-7 amide bond of vancomycin and teicoplanin can be carried out under acidic conditions.[76, 323] On the other hand, exposure of various glycopeptides to sodium borohydride caused reductive cleavage of the AA-1/AA-2 or AA-2/AA-3 amide bond,[324, 325] depending on the conformation of the glycopeptide antibiotic. In Boc-protected teicoplanin aglycon **326**, cleavage of the AA-1/AA-2 amide bond opened a pathway to analogue **328** with an enlarged *F-O-G* ring system, as shown in Scheme 85. Unfortunately, this modification led to loss of activity as a result of the disturbance of the binding site of the antibiotic.[325] This chemistry also allowed the synthesis of MDL63166 (**331**, Scheme 86). Thus, reductive opening of the AA-2/AA-3 amide bond of teicoplanin aglycon allowed double Edman degradation to remove AA-1 and AA-3 from **330**. This was followed by further elaboration and insertion of an L-phenylalanine residue. Ring closure and attachment of a new AA-1 fragment afforded compound **331** (MDL63166).[326] This analogue, which has proved to be superior to both vancomycin and teicoplanin against type A resistant *Enterococcus faecalis*, entices chemists for further explorations in this area. An expanded discussion on modification of the glycopeptide antibiotics through strategies I and II can be found in a recent review by Malabarba, Nicas, and Thompson.[327]

The appreciation of vancomycin's ability to dimerize and thus enhance its potency stimulated the design and synthesis of covalently linked dimeric and trimeric glycopeptides (strategy III). Thus, Griffin et al.[328] made the initial foray towards such compounds by linking two vancomycin molecules in a head-to-head fashion by bridging their carboxylate groups with a variety of diamines, as exemplified in Scheme 87 for the formation of compound **332**. A 60-fold increase in antibiotic activity against VRE relative to vancomycin was observed for **332**, demonstrating the beneficial effects of covalently bound dimeric glycopeptides.[328] In complementary work, Williams et al.[329] synthesized head-to-tail dimers of vancomycin. The *N*-terminus of one molecule of vancomycin was linked to the *C*-terminus of another with either 3-aminopropionic acid or 5-aminopentanoic acid, leading, in the case of the former, to compound **333**, as shown in Scheme 87.[329] Such head-to-tail dimers are expected to be able to couple and form higher aggregates, unlike the head-to-head dimers of Griffin et al.[329]

Table 5. Some semisynthetic glycopeptides.

Entry	Parent glycopeptide	Strategy	Product	Modification	Properties	Ref.
1	A42867	I	A42867 pseudoaglycon	Deglycosidation	MIC 1 $\mu g\,mL^{-1}$ against *Streptococcus aureus* L165	[332]
2	chloroorienticin A	I	chloroorienticin C	deglycosylated	ED_{50} 0.40 $mg\,kg^{-1}$/2 (2 doses administered) s.c. in mice against *Streptococcus pyogenes*	[333]
3	chloropolysporin B	I	demannosyl chloropolysporin B	enzymatic deglycosidation	–	[334]
4	chloropolysporin B	I	chloropolysporin C	enzymatic deglycosidation	–	[335]
5	MM47767	I	MT55261, MT55262	deglycosidation	active against *bacillus*, *corynebacterium*, *sarcin*, and *Staphylococci*	[64]
6	vancomycin	I	deglucovancomycin	deglycosidation	exhibited antibiotic activity	[97]
7	vancomycin, demethylvancomycin, M4310, A51568 B residues	I	–	glycosidation	ED_{50} 0.8 $mg\,kg^{-1}$ i.v. to mice against *Streptococcus aureus*	[336]
8	A40926	I	MDL63246, MDL63042	*N*63-carboxamides	lower MIC against VanB,C *Enterococci*	[337]
9	A40926	I	–	*N*63-carboxamides	high in vitro activity against glycopeptide-resistant *Enterococci* and *Staphylococci*	[338]
10	ardacin	I	–	*N*63-carboxamides	MIC 50 – 200 $\mu g\,mL^{-1}$ against *Staphylococcus aureus*	[339]
11	deoxyteicoplanin	I	–	*N*63-carboxamides	MIC $< 2\ \mu g\,mL^{-1}$ against *Streptococcus faecalis*	[340]
12	teicoplanin	I	MDL62208, MDL62211, MDL62873 (Mideplanin)	aminopropyl *N*63-carboxamides	more active than teicoplanin	[341, 342]
13	LY264826	I	LY191145	reductive alkylation of amino sugar	500 times more active than vancomycin against VRE	[343]
14	LY264826	I	LY333328	reductive alkylation of amino sugar	active against VRE	[344, 345]
15	A51568 B, demethylvancomycin, M43 D, vancomycin	I	–	reductive alkylation of amino sugar	MIC 0.125 – 16 $\mu g\,mL^{-1}$ against *Staphylococcus aureus*	[346]
16	chloroorienticin A	I	–	reductive alkylation of amino sugar	MIC $\leq 0.06\ \mu g\,mL^{-1}$ against *Staphylococcus aureus*	[347]
17	chloroorienticin A, orienticin C, eremomycin, PA46867 A	I	–	*N*-acyl and *N*-alkyl derivatives	ED_{50} 0.43 $mg\,kg^{-1}$/2 s.c. to mice against *Streptococcus pyogenes*	[348]
18	vancomycin (**1**)	I	–	acylation of amino sugars and *N*15	no improvement compared to vancomycin	[349]
19	vancomycin (**1**)	I	–	acylation of amino sugars and *N*15	ED_{50} 1.4 – 12.9 $mg\,kg^{-1}$ against *Streptococcus aureus*, *S. pyogenes, S. Pneumoniae*	[350]
20	vancomycin (**1**)	I	–	acylation of amino sugars or *N*15	MIC 0.5 – 32 $\mu g\,mL^{-1}$ against Gram positive bacteria	[351]
21	A35512 A, B, C, E, H, A35512 pseudoaglycon, A41030 A – G, A47934, actaplanin A – O, actaplanin pseudoaglycon, ristocetin A, ristocetin pseudoaglycon,	I	–	*N*15-acylation	MIC 2 – 4 $\mu g\,mL^{-1}$ against *Streptococcus* group 9960	[352]
22	teicoplanin aglycon	I	–	*O*56-ethers and *N*-63-carboxamides/esters	no improvement compared to teicoplanin aglycon	[353]
23	deglucobalhimycin	I	–	hydroxylimine derivative of deglucovancomycin	potent against MRSA	[354]
24	actaplanin A	I	CUC/CSV	biotransformation	active against Gram-positive bacteria, increase feed efficiency, enhance milk production in ruminants	[355]
25	teicoplanin	I	–	enzymatic deacylation followed by reductive alkylation	potent activity against both *Staphylococci* and VRE	[356]
26	CWI785	I	HPB3, HPB4, HPB-2M	acid hydrolysis	–	[76]
27	teicoplanin	II	dechloroteicoplanin	dechlorination	–	[357]
28	vancomycin (**1**)	II	mono- and didechlorovancomycin	dechlorination	less active than vancomycin	[320]
29	A35512, actaplanin, A41030, A47934, ristocetin A	II	–	oxidation of *O*-34	exhibited antibiotic activity	[358]
30	teicoplanin aglycon	II	MDL63166, MDL64945, MDL64468	replacement of AA-1 and AA-3 with Phe, Lys, MeLeu	more active against VanA *Enterococci*	[326]
31	teicoplanin A_2 – 2	II	pentapeptides	reductive cleavage of 59,60 amide bond	MIC 1 $\mu g\,mL^{-1}$ against *Streptococcus pyogenes* C203	[359]
32	vancomycin	III	bis(vancomycin) carboxamides	head-to-head dimerization	60-fold more active against VRE than vancomycin	[328]



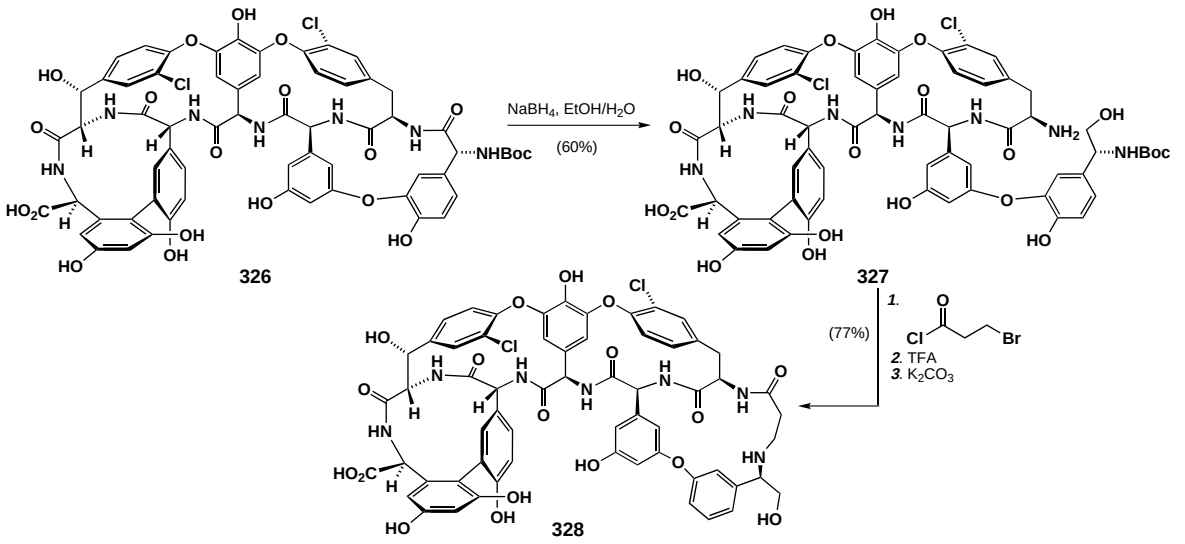
Scheme 84. Modification to the outer sphere of glycopeptide antibiotics: structures of L333328 (**322**) and mideplanin (**323**), **324** and **325**.

Whitesides et al.[330] have recently constructed covalently linked dimers and trimers of vancomycin such as those shown in Scheme 88, and performed studies of their binding to covalently-linked di- and trimeric D-Ala-D-Ala species. Remarkably, the tris(vancomycin carboxamide) **337** binds the trivalent ligand tris(D-Ala-D-Ala-carboxamide) **338** with an exceedingly high affinity, $K_d = 4 \times 10^{-17}$ M, which makes this system (**339**) the most stable small molecule receptor/ligand complex known.[330]

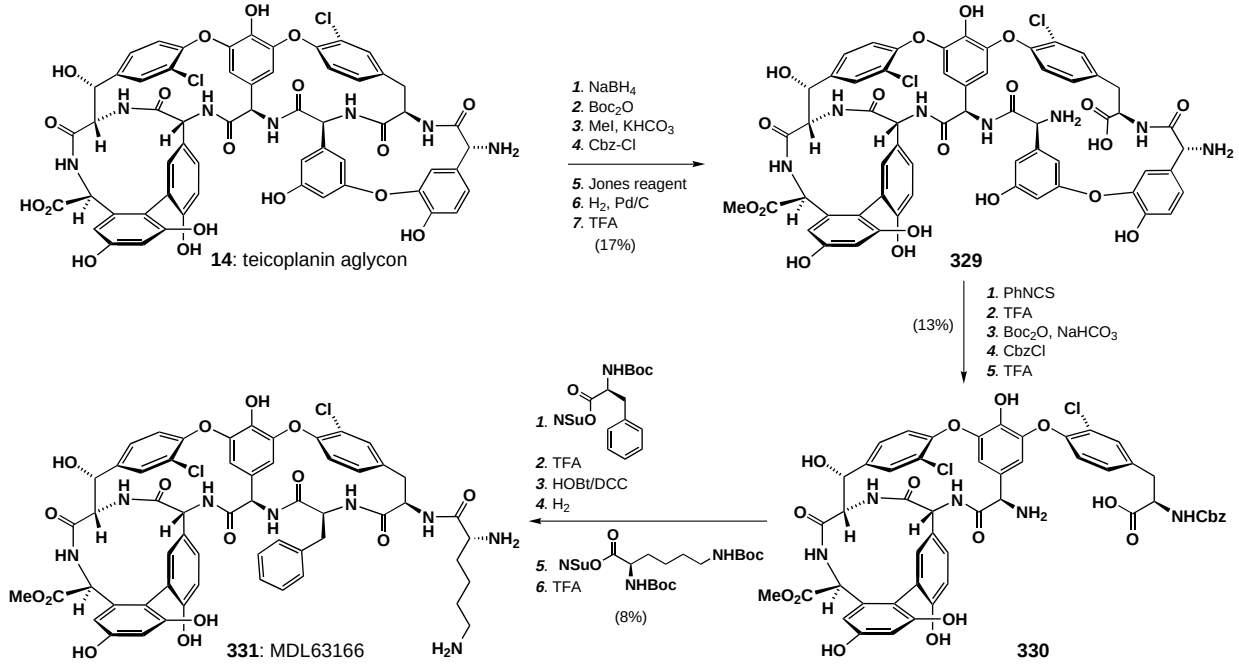
One of the most serious clinical shortcomings of the glycopeptide antibiotics is their poor oral availability. A nonpeptidic small molecule that will mimic the action of these antibiotics will, therefore, be highly welcome. In order to succeed as a drug, however, such a compound must fulfill not only the high affinity binding to D-Ala-D-Ala, but must also be equipped with the proper functionality for solubility, delivery to the site of action, and metabolic stability. While synthetic chemists are currently far away from such an accomplishment, recent results from the Diederich laboratories are encouraging. Thus, design and chemical synthesis of compound **341** (Figure 21) allowed binding studies that revealed the ability of the compound to bind small ligands such as D-Ala-D-Ala (K_a of 51 L mol^{-1}).[331]

11. Pharmacology and Medical Applications of the Glycopeptide Antibiotics

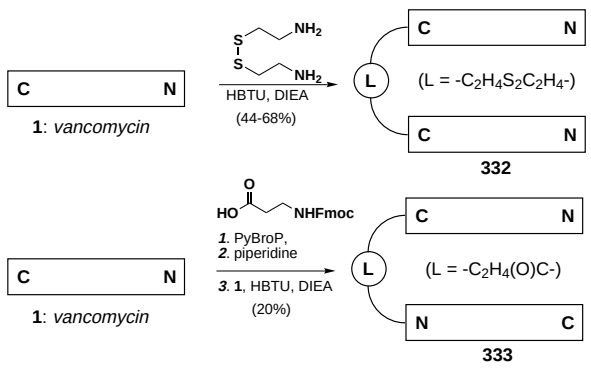
Vancomycin and teicoplanin are indispensable, widely used antibiotics today. Both are typically administered parenterally with an infusion rate of one hour (intraperitonially, i.p.) to treat severe *staphylococcal* infections, including MRSA.



Scheme 85. Synthesis of a peptide backbone-modified glycopeptide, the expanded *F-O-G* ring analogue of teicoplanin (**328**).



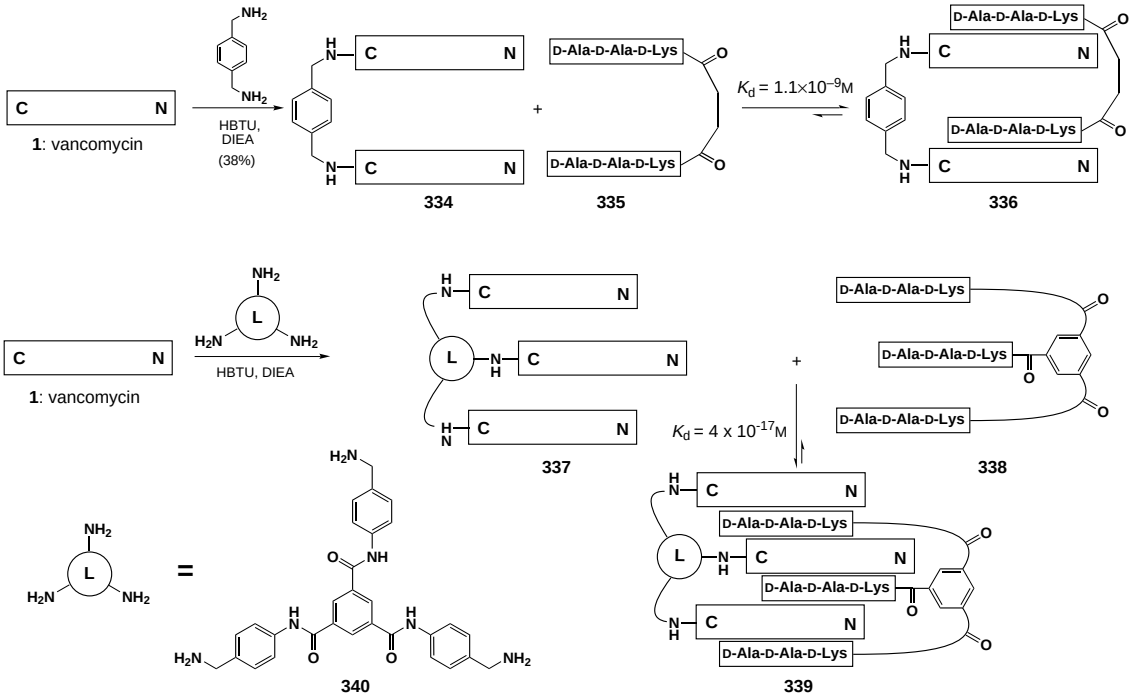
Scheme 86. Synthesis of the peptide backbone-modified glycopeptide MDL63166 (**331**).



Scheme 87. Synthesis of head-to-head and head-to-tail dimers of vancomycin by Griffen et al.[328] (top) and Williams et al.[329] (bottom).

Vancomycin, in conjunction with aminoglycoside antibiotics, is also used to treat *enterococcal* infections. Side-effects of vancomycin include ototoxicity (transient or permanent loss of hearing, mostly observed in patients receiving excessive doses) and pain and irritation in the area of administration. Another side-effect of vancomycin associated with precipitous administration is known as the "red man" syndrome and is characterized by a sudden and profound fall in blood pressure, often accompanied by a red rash over the upper body.

A sub-group of glycopeptide antibiotics (structural type V, see Section 3) exhibit antiviral rather than antibiotic activity. Thus, chloropeptin (**12**), complestatin (**11**), and kistamicins A (**13a**) and B (**13b**) (Figure 7) have been shown to inhibit in



Scheme 88. Synthesis and studies of bis and tris(vancomycin carboxamide) species **335** and **337** by Whitesides et al.[330]

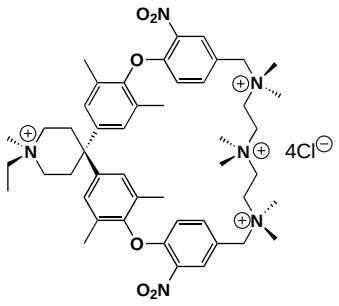


Figure 21. Nonpeptidic mimic for the vancomycin binding site synthesized by Diederich et al.[331]

vitro binding of the HIV-1 gp 120 receptor to CD-4 receptor and HIV replication in peripheral human lymphocytes. Kistamicins A and B also exhibit activity against type A influenza viruses.

Other applications of glycopeptide antibiotics include vancomycin's prophylactic use in prosthetic implants. Here, it is used to prevent infections that are highly likely at the interface of the prosthetic device and tissue. Ristocetin A (**9**) has been shown to cause platelet aggregation. This property was used advantageously in developing an assay to diagnose Willebrand's disease.[360] Avoparcin is, as well, commonly used as a feed additive since it increases both growth rate and food conversion efficiency.[361] Finally, glycopeptide antibiotics, especially vancomycin,[362] ristocetin A,[363] and avoparcin,[364] have recently been found to provide an effective chiral stationary phase for HPLC separation of enantiomers.

12. Conclusion

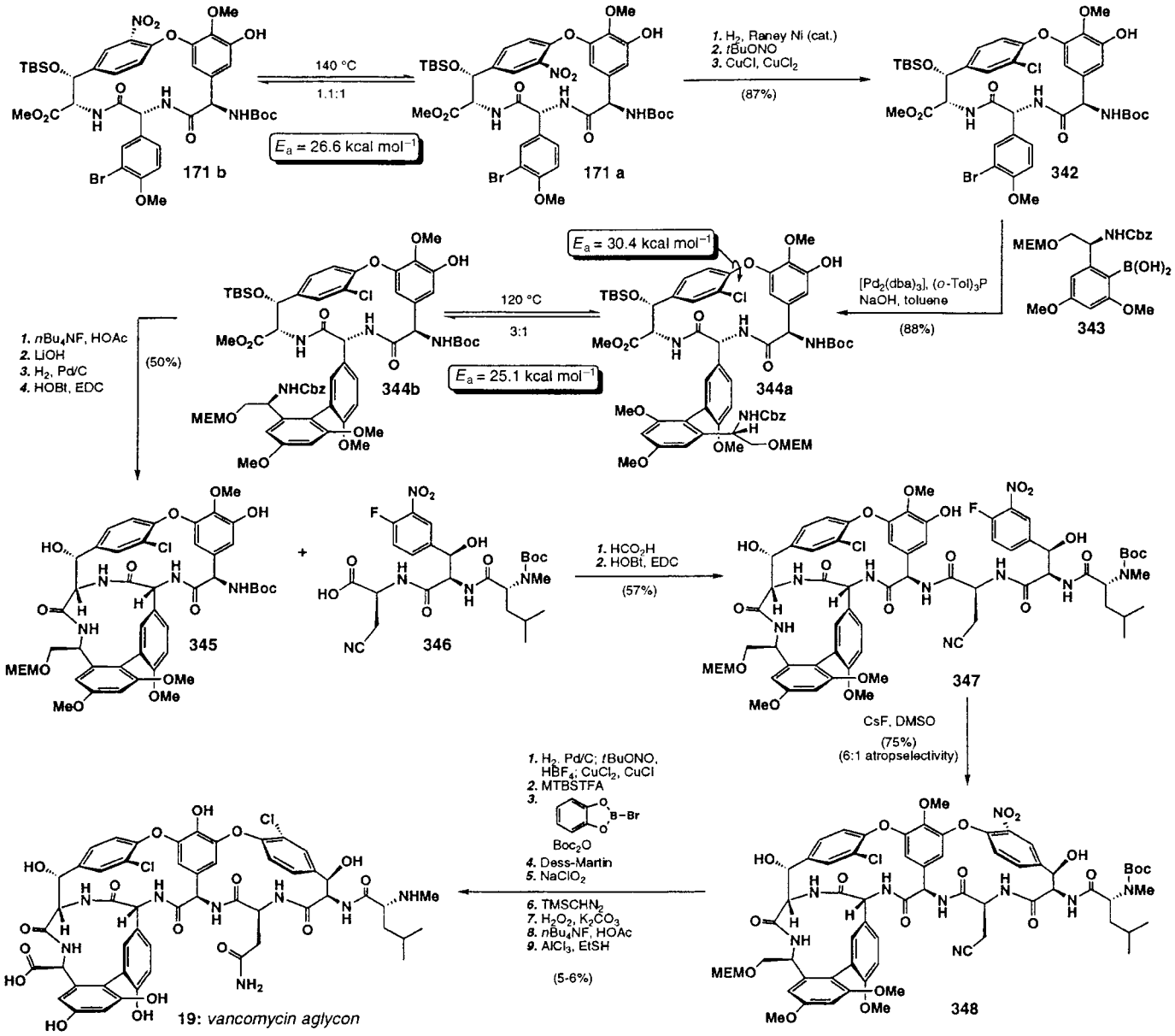
Vancomycin and teicoplanin have provided a strong line of defense against certain drug-resistant bacteria for some time now. Our ability to successfully confront bacteria using these and other antibiotics has saved millions of human lives, but at the same time has given rise to the birth of more dangerous bacteria that are currently threatening to wreak havoc on society around the world. This ominous situation was brought about by the ability of bacteria to evade the strongest of our weapons through selective evolution and was exacerbated by unnecessary and unfortunate overuse of antibiotics. Thankfully, new glycopeptides and other types of antibiotics constantly appear on the horizon, promising to arrest the spread of the latest drug-resistant bacterial strains and provide a safe haven for patients infected by them.

Progress made in the chemistry, biology, and medicine of the glycopeptide antibiotics, as described in this article, has positioned scientists for even further advances in this area. Thus, the understanding of their mechanism of action should guide, in a rational manner, the molecular design of new analogues, while the knowledge gained from the synthetic endeavors and total syntheses of vancomycin and its aglycon, in conjunction with combinatorial chemistry, should facilitate the construction of libraries of such analogues. Partial synthesis from readily available, naturally occurring glycopeptides and solid-phase chemistry are some of the most promising strategies to arrive at this goal through chemistry, whereas biological approaches, such as combinatorial microbiology and biosynthesis, may provide a complementary avenue to such libraries.

As we enter the 21st century, we realize that our battles with deadly, drug-resistant bacteria will have to be fought with a new generation of desperately needed antibiotics. Chemical synthesis and chemical biology are destined to play a crucial role in discovering them.

Addendum

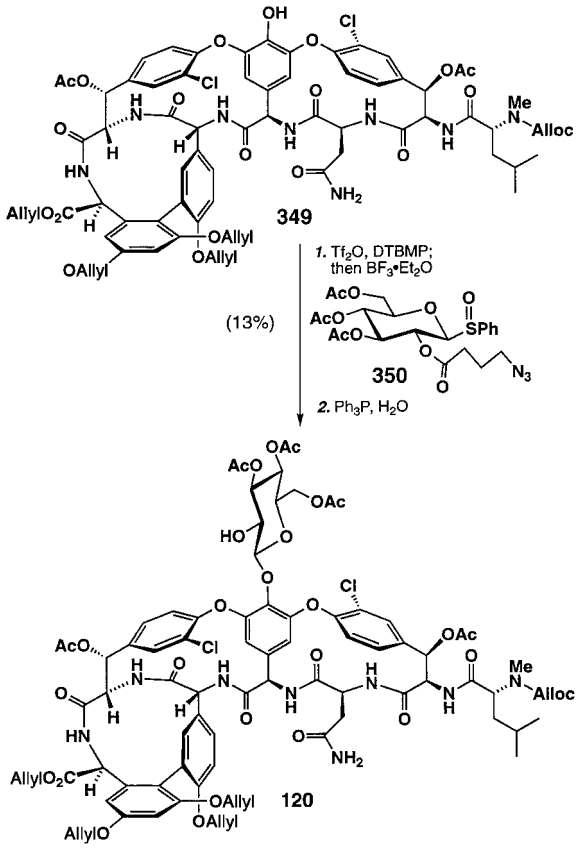
Since the completion of the writing of this review article there have been a host of interesting and important contributions to the field of glycopeptide antibiotics. This addendum brings the review current up to May, 1999. In the area of synthetic chemistry, there have been many advances, from synthesis of the constituent amino acids to that of the aglycon and even of vancomycin itself. Gurjar and co-workers have developed a novel route to generate the β-hydroxytyrosines (AA-2 and AA-6) of vancomycin, through condensation of a functionalized aryl Grignard reagent onto the appropriate enantiomer of the aldehyde.[365] The daunting task of constructing the aglycon has been accomplished recently by the Boger group (Scheme 89).[366] Their strategy followed a similar route to that of the Nicolaou effort. First, the *C-O-D* ring system was generated through *o*-nitro group-activated nucleophilic substitution of an aryl fluoride (**171a** and **171b**, Scheme 46). Replacement of the nitro group with a chlorine atom and subsequent stereoselective Suzuki coupling with boronic acid **343** afforded a 3:1 mixture of the natural biaryl system **344b** to the unnatural **344a**. Protecting group manipulations followed by macrolactamization afforded the *A-B-C-O-D* ring system **345**. Coupling with the tripeptide **346** gave the heptapeptide **347**. Note that AA-3 had the primary amide masked as a nitrile, unlike both the approaches of the Evans and Nicolaou groups where it was a protected amide. Cyclization through the *o*-nitro group-activated SNAr methodology provided the tricyclic system **348**, as a 6:1 mixture of atropisomers with the natural atropisomer prevailing. Conversion of the nitro group into a chlorine atom through the Sandmeyer substitution reaction gave the appropriately chlorinated tricyclic system. Further manipulation, including oxidation of the primary alcohol of AA-7 to an acid



Scheme 89. Total synthesis of the vancomycin aglycon (**19**) by Boger et al.[366]

functionality and unmasking of the primary amide in AA-3, yielded the aglycon (**19**).[366]

Kahne et al.[367] have succeeded in transforming the vancomycin aglycon into vancomycin itself. The glycosyl acceptor **349** was obtained from the aglycon **19** through a series of protections. Treatment with the sulfoxide **350**, in the presence of both $BF_3 \cdot Et_2O$ and 2,6-di-*t*-butyl-4-methylpyridine (DTBMP), followed by removal of the azidobutyryl group gave the vancomycin pseudoaglycon **120** in 13% yield (Scheme 90).[367] Further conversion of the pseudoaglycon



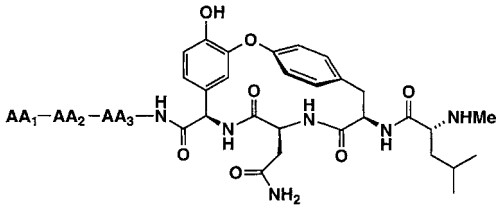
Scheme 90. Synthesis of the vancomycin pseudoaglycon (**120**) by Kahne et al.[367]

into vancomycin can be seen in Scheme 30. Kahne and co-workers have also obtained some intriguing preliminary results that suggest that the sugar portion of the molecule may impart some biological activity without binding to D-Ala-D-Ala.[368] These results need to be investigated further before any conclusions can be drawn regarding the mechanism of action of the new molecules.

Recently, as well, crystallographic analysis of the complex between vancomycin and *N*-Acetyl-D-Ala-D-Ala has been performed. McPhail, Cooper, and Freer were able to crystallize this important complex and obtain 2.8 Å resolution data.[369] This work will hopefully yield a high resolution structure of the complex, thus confirming the mechanism of action and the hydrogen bonding network. Dimerization is widely recognized as an important aspect of vancomycin's antibiotic activity (see Section 9.1). Whitesides and co-workers at Harvard have examined the degree to which this dimerization enhances binding to the D-Ala-D-Ala ligand.[370] This work utilized the novel approach of surface plasmon resonance (SPR) as an analytical technique. SPR was used to measure the binding of vancomycin and a covalent vancomycin dimer to *N*-acetyl-L-Lys-D-Ala-D-Ala which was presented on a self-assembled monolayer. This study confirmed that dimerization contributes to the observed antibiotic activity of vancomycin.

Significant advances have also been made in understanding the mechanism of resistance found in vancomycin resistant *Enterococci*. Lessard and Walsh, through mutational analysis of active site residues, have confirmed the molecular mechanism of the D-Ala-D-Ala dipeptidase VanX (see Section 9.2).[371] In addition, the pathway that signals the transcription of the required genes from vancomycin resistance in *Enterococci* has also been investigated. Ulijasz and Weisblum have shown that signal transduction pathway, which initiates the resistance response, functions by transfer of a phosphate group from VanS to VanR. This, in turn, activates transcription of *van*H, *van*A, and *van*X conferring resistance to the bacteria (see section 9.2).[372] The molecular mechanism of activation of VanS still remains to be determined.

Ellman and co-workers have constructed simple peptide-based analogues of the glycopeptide antibiotics that show promising binding to both D-Ala-D-Ala and D-Ala-D-Lac.[373] This work utilized a simplified *D-O-E* ring system that was appended to a library of tripeptides (Figure 22). This library



352 : AA_1-AA_2-AA_3 = L-Tpi-L-His-L-Dapa
353 : AA_1-AA_2-AA_3 = L-*N*-Me-Phe-D-L-Disc-L-Tyr

	binding constant [M^{-1}]	
	N-Ac_2-L-Lys-D-Ala-D-Ala	*N*-Ac_2-L-Lys-D-Ala-D-Lac
vancomycin	K_a = 550 000 ± 12 000	K_a = 6 300 ± 1 400
352	K_a = 75 400 ± 9 000	K_a = 17 300 ± 3 400
353	K_a = 102 400 ± 41 000	K_a = 31 900 ± 15 000

Figure 22. A peptide-based library of vancomycin analogues that maintain the *D-O-E* ring system constructed by Ellman et al.[373]

of analogues was then screened for binding to both the D-Ala-D-Ala and the D-Ala-D-Lac ligands. These results provide a promising platform from which to explore simplified, synthetically accessible analogues of the glycopeptide antibiotics.

Finally, since the writing of this document, the reported instances of vancomycin resistant *Staphylococcus aureus* infections have been on the rise. This resistance appears, for the most part, to be an intermediate resistance and typically occurs in patients who have been treated with an extended course of vancomycin to combat MRSA. The development of vancomycin resistant MRSA underscores further the importance of prudent use of antibiotics as well as the need for rigorous infection control precautions to prevent the spread of resistance.[374–376] This also emphasizes the importance of basic

research into the structure–functionality relationships of antibiotics, their modes of action, and the mechanisms of bacterial resistance.

Abbreviations

AA	amino acid
Ac	acetyl
AD	asymmetric dihydroxylation
ADP	adenosine diphosphate
AE	asymmetric epoxidation
AIBN	2,2′-azobisisobutyronitrile
Alloc	allyloxycarbonyl
ATCC	American Type Culture Collection
ATP	adenosine-5′-triphosphate
binap	[1,1′-binaphalene]-2,2′-diylbis(diphenylphosphane)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOP	(1-benzotriazolyloxy) tris(dimethylamino)-phosphonium hexafluoride
Bz	benzoyl
Cbz	benzyloxycarbonyl
CoA	coenzyme-A
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DAST	(diethylamino)sulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	3,4-dichlorobenzyl
DCC	dicyclohexylcarbodiimide
Ddm	4,4′-dimethoxydiphenylmethyl
DEAD	diethyl azodicarboxylate
DHQD*p*Cl	dihydroquinidine *p*-chlorobenzoate
$(DHQ)_2PHAL$	hydroquinone 1,4-phthalozinediyl diether
DIBAL	diisobutylaluminum hydride
DIEA	*N*,*N*-diisopropylethylamine
DIPT	diisopropyl tartrate
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
DSM	Deutsche Sammlung von Mikroorganismen
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
ED_{50}	Effective Dose (50%)
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
FDPP	pentafluorophenyl diphenylphosphinate
Fmoc	9H-fluoren-9-ylmethoxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′*N*′-tetramethyluronium hexafluorophosphate
HBTU	*O*-benzotriazol-1-yl-*N*,*N*,*N*′*N*′-tetramethyluronium hexafluorophosphate
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxy-1*H*-benzotriazole
HPLC	high performance liquid chromatography
Im	imidazole
LDA	lithium diisopropylamide
Lut	2,6-lutidine
MEM	methoxyethoxymethyl
MeObiphep	2,2′-bis(diphenylphosphanyl)-6,6′-dimethoxy-1,1′-biphenyl
MIC	minimal inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
MTBSTFA	*N*-(*tert*-butyltrimethylsilyl)-*N*-methyltrifluoroacetamide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine-*N*-oxide
Nos	4-nitrophenylsulphonyl
NRRL	Northern Utilization Research and Development Division
NSu	succinimidyl
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pht	phthalimidyl
Piv	pivaloyl = trimethylacetyl
PMB	*p*-methoxybenzyl
PyBroP	bromo-tris-pyrrolidinophosphonium hexafluorophosphate
pyr	pyridine
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TDP	thymidine diphosphate
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TFA	trifluoroacetic acid
tfa	trifluoroacetyl
TFAA	trifluoroacetic anhydride
TIPS	triisopropylsilyl
TMGA	tetramethylguanidinium azide
TMS	trimethylsilyl
TMSE	trimethylsilylethyl
Tol	tolyl
Trisyl	2,4,6-triisopropylphenylsulphonyl
Ts	tosyl = 4-methylphenylsulphonyl
UDP	uridine-5′-diphosphate
UMP	uridine-5′-monophosphate
VRE	vancomycin-resistant *Enterococci*

It is with great pleasure that we acknowledge the important contributions of our collaborators on this project. Their names appear in the original publications. This work was financially supported by the Skaggs Institute for Chemical Biology, Novartis, the National Institutes of Health, USA, and the Hewitt Foundation. We also wish to thank our friends from industry for their support of our programs: Abbott Laborato-

ries, Amgen, Boehringer Ingelheim, Bristol–Myers Squibb, Dupont, Glaxo Wellcome, Hoffmann LaRoche, Merck & Co., Parke Davis, Pfizer, and Schering–Plough.

Received: January 19, 1999 [A 320 IE]
German version: *Angew. Chem.* **1999**, *111*, 2230–2287

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[25] Another nomenclature assigned the *C-O-D* ring as M(4-6), the *D-O-E* ring as M(2-4), the *AB* ring as M(5-7) and the *F-O-G* ring as M(1-3) system, respectively, see D. A. Evans, K. M. DeVries in *Glycopeptide Antibiotics* (Ed.: R. Natarajan), Marcel Dekker, New York, **1994**, pp. 63–104.

[26] D-*Al*anyl-D-alanine *b*inding *a*ntibiotics with *hept*apep*tide* structure.

[27] The names of the organisms listed in Table 1 are the most recent taxonomic designation. In many cases, these do not agree with the initial classification.

[28] Vancomycin is: [3*S*-[3*R**,6*S**(*S**),7*S**,22*S**,23*R**, 26*R**,36*S**,38a*S**]]-3-(2-amino-2-oxoethyl)-44-[[2-O-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy]-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[[4-methyl-2-(methylamino)-1-oxopentyl]amino]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-m][10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid; ristocetin aglycon is: methyl 15-amino-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,19,34,40,42,44,56-octahydroxy-7-methyl-2,16,36,50,51,59-hexaoxo-1*H*,15*H*,34*H*-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-m][10,2,16]-benzoxadiazacyclotetracosine-38-carboxylate.

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