Syntheses around the Transglycosylation Step in Peptidoglycan Biosynthesis

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Peter Welzel received his Ph.D. degree from the University of Bonn (supervisor R. Tschesche). After a postdoctoral stay at Imperial College (with D. H. R. Barton) and his habilitation at the University of Bonn, he became Professor of Natural Products Chemistry at the Ruhr University of Bochum (1973–1993). In 1993 he moved to the University of Leipzig (Chair of Organic and Natural Products Chemistry). His research interests include the organic and bioorganic chemistry of natural products such as the moenomycin antibiotics, forskolin, strigol, cardiac steroids, and ecdysteroids. In 1999 he received the Otto Wallach medal of the German Chemical Society (GDCh).

1. Introduction

Bacteria are surrounded by the netlike polymer peptidoglycan, which is responsible for a defined cell shape and preserves cell integrity by withstanding internal osmotic pressure. Disruption of peptidoglycan biosynthesis leads to cell lysis. Peptidoglycan consists of repeating β-1,4-linked *N*-acetylglucosaminyl-*N*-acetylmuramyl units cross-linked via short peptide chains (for a schematic representation, see Figure 1[1]). About 100 chemically different peptidoglycan types have been identified, varying mainly within the peptide moiety. Figure 2 shows a typical structure. In the course of peptidoglycan biosynthesis the last monomeric intermediate is lipid II (Figure 2), which consists of *N*-acetylglucosamine 1→4-linked to *N*-acetylmuramic acid pentapeptide. C-1 of the *N*-acetylmuramic acid moiety is connected to a C_{55} isoprenoid lipid (bacterioprenol) via a diphosphate bridge. The lipid II biosynthesis takes place in the cytoplasm and at the inner surface of the cytoplasmic membrane (after attachment of the lipid part).[2] Peptidoglycan is subsequently formed from lipid II by two (polymerization) reactions that occur at the outside surface of the cytoplasmic membrane. First, the sugar chains are assembled by a so-called transglycosylation reaction which is in fact a nucleophilic substitution reaction (see the schematic representation in Figure 3) involving the displacement of the diphosphoundecaprenyl group by a GlcNAc 4-OH group.[3] The reaction proceeds with inversion of configuration. The last step is then the transpeptidation, (formally) a nucleophilic reaction between the free amino group of one peptide chain (see *meso*-diaminopimelic acid and L-lysine in Figure 2) and the terminal peptide bond of another chain, resulting in loss of the terminal D-Ala and formation of a cross-linking peptide bond between the two strands (see the schematic representation in Figure 3; other species-dependent amino acids may be part of the cross-linking peptide bridge).[2,4] The transglycosylation reaction is catalyzed by a number of multimodular bifunctional polymerases (which also cata-

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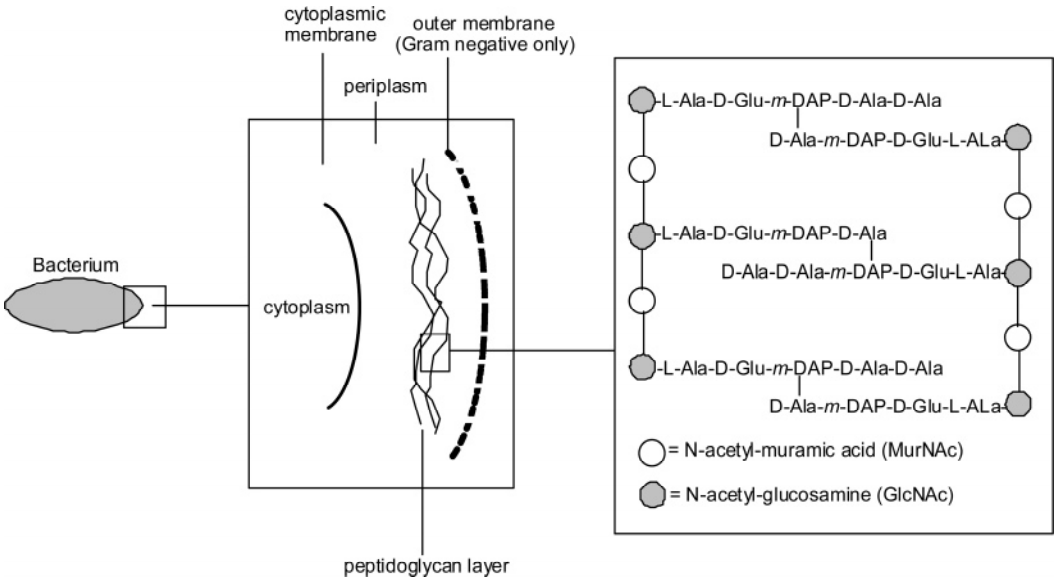


Figure 1. Schematic representation of the peptidoglycan layer of bacterial cell walls. Reprinted with permission from ref 1. Copyright 1993 The Royal Society of Chemistry.

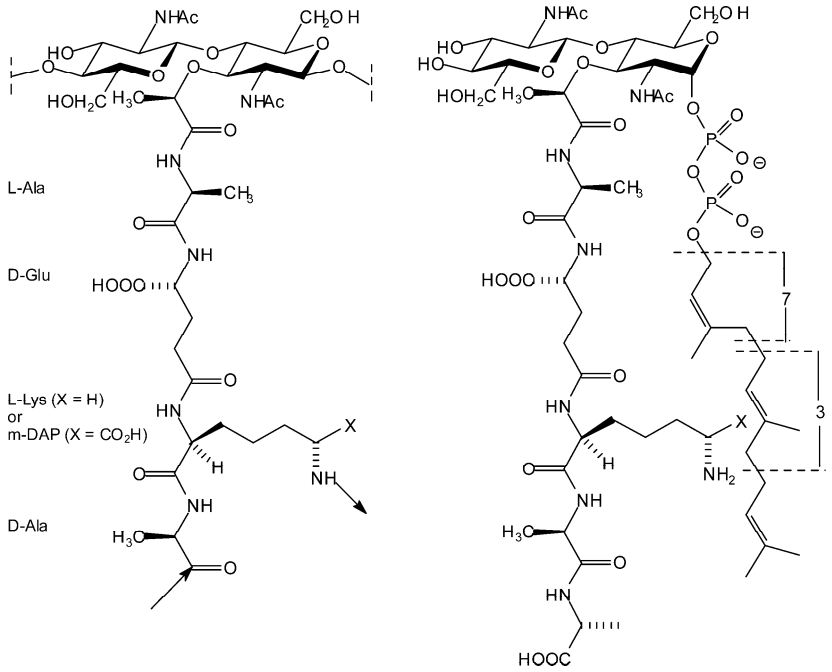


Figure 2. Primary peptidoglycan structure (for *E. coli*, X = CO_2H) and structure of lipid II.

lyze the transpeptidation reaction) designated as class A *high molecular mass penicillin-binding proteins* (PBPs).[5−7] Of these, PBP1b from *Escherichia coli* has been studied in the greatest detail.[8] It comprises 844 amino acid residues and contains a short cytosolic N-terminus, a membrane span, the D198−G435 glycosyl transferase module, and the Q447−N844 acyl transferase module.[9] Within the glycosyl transferase module, Glu233 has been shown to be central to the transglycosylation, and in the active site of the acyl transferase is the essential serine 510, the acylation of which forms the basis of the antibiotic properties of the β-lactams. Schwartz and co-workers deduced from a kinetic characterization of the *E. coli* PBP1b transglycosylase activity that a doubly charged metal ion bound to the diphosphate group assists departure of the leaving group whereas the essential glutamate 233 acts as a base, removing the proton from the 4-OH group of the glycosyl acceptor (see Figure 4).[10] The soluble extracellular region of PBP1b from *Streptococcus pneumoniae*[11] and *E. coli*[12] has been expressed and characterized biochemically.[13] Walker and co-workers concluded from their experiments that the transglycosylase module is shorter than previously assumed, the C-terminal boundary lying between amino acids 385 und 409.[12] Recently, the heterologous overexpression and purification of *Staphylococcus aureus* PBP2, the first purified Gram-positive class A PBP, have been described.[14] The enzyme was found to have good transglycosylase activity (several orders of magnitude higher than that of the extracellular region of recombinant *S. pneumoniae* PBP2a[15]). Kinetically, *Staph. aureus* PBP2 differs from *E. coli*

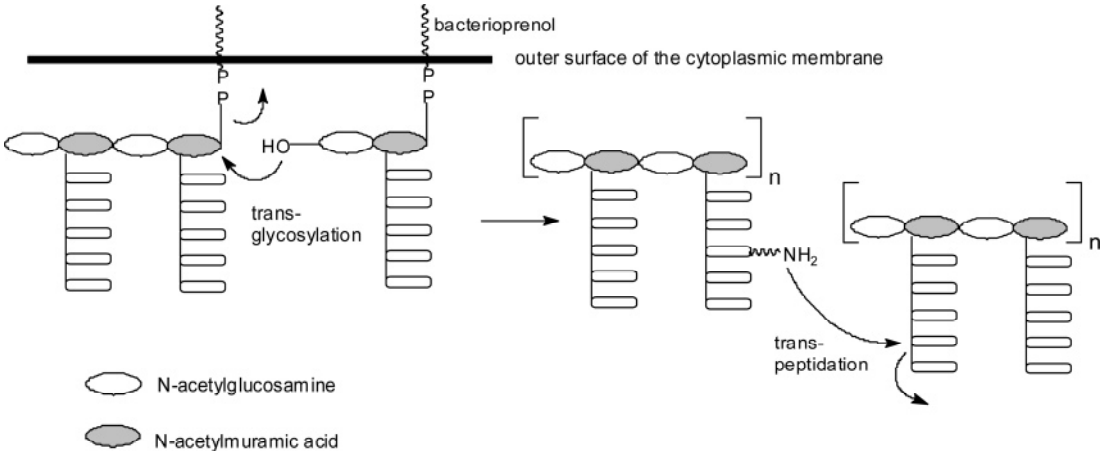


Figure 3. A schematic representation of the polymerization reactions in peptidoglycan biosynthesis.

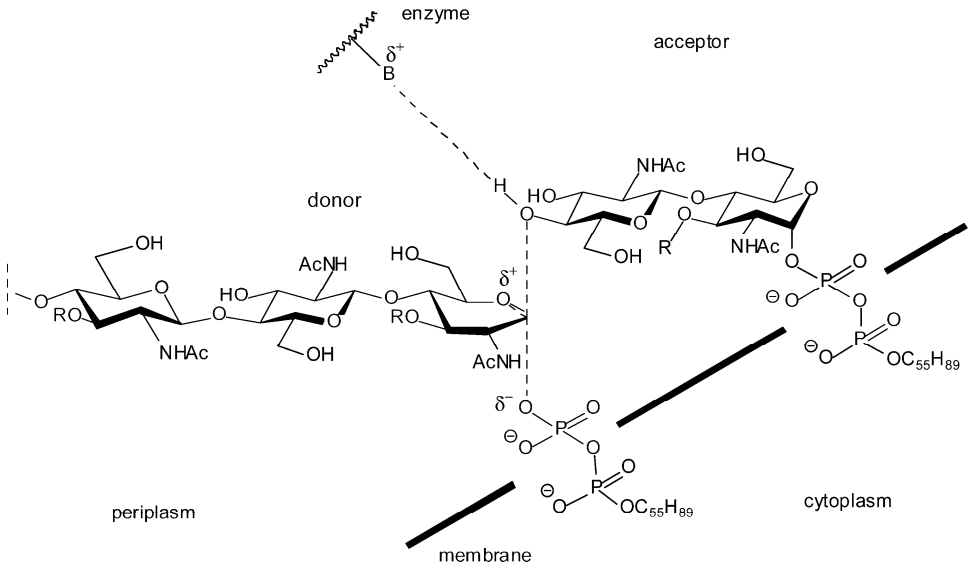


Figure 4. Transglycosylation with lipid II as glycosyl acceptor.

PBP1b in that it has a different pH optimum (4.5−5.5 for *Staph. aureus* PBP2 and 7.5−8.0 for *E. coli* PBP1b) and is less sensitive to doubly charged metal ions which assist the PBP1b-catalyzed transglycosylation (vide supra). Besides bifunctional polymerases, a number of membrane-bound monofunctional glycosyltransferases capable of catalyzing the formation of un-cross-linked peptidoglycan are known.[3]

The transglycosylases involved in peptidoglycan biosynthesis are very promising targets for new anti-infectives as highlighted by Wong and Ritter: "Among the enzymes involved in the biosynthesis of peptidoglycan, the transglycosylase...is perhaps the most interesting target.... The enzyme is located on the cell surface, thus making it easily accessible to small molecular drugs. In addition, the polysaccharide backbone always remains intact in wild-type and resistant strains. New antibiotics that target the transglycosylation step may therefore be less prone to resistance development." [16,17] We shall describe here total syntheses of lipid II and analogues which are acceptor substrates of the transglycosylases and of compounds that interfere with the transglycosylation reaction. But before doing so, one more important aspect of the transglycosylation has to be discussed.

There are two possible directions of sugar chain extension. Either the growing sugar chain serves as the glycosyl donor and the disaccharide monomer lipid II as the glycosyl acceptor (Figure 4) or lipid II is the glycosyl donor and the growing sugar chain the glycosyl acceptor (Figure 5). For reasons that will be apparent below, we shall discuss here the evidence that suggests that the peptidoglycan sugar chains are presumably formed by the first mode of chain extension.

Rietschel and co-workers have derived the (not undisputed[18]) concept that the glycan strands in the microbial wall run perpendicular to the plasma membrane, each strand being cross-linked with four other strands by peptide bridges (Figure 6). For the biosynthesis it is assumed that both the synthesis and the translocation of the glycan chain across the membrane occur concomitantly as the polymer grows out of the enzyme complex.[19] For topological reasons chain elongation must proceed as indicated in Figure 4, i.e., with lipid II as the glycosyl acceptor.[20−22] The same conclusion was reached on the basis of experimental evidence obtained years ago in H. R. Perkin's laboratory. It was argued that if newly synthesized disaccharide peptide units were added to the nonreducing end of the growing glycan chains, the

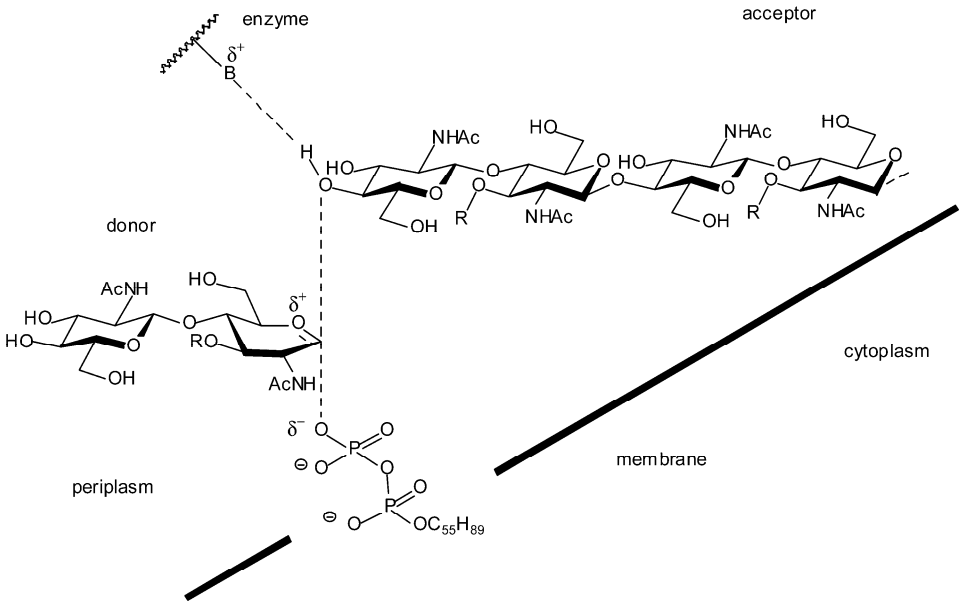


Figure 5. Transglycosylation with lipid II as glycosyl donor.

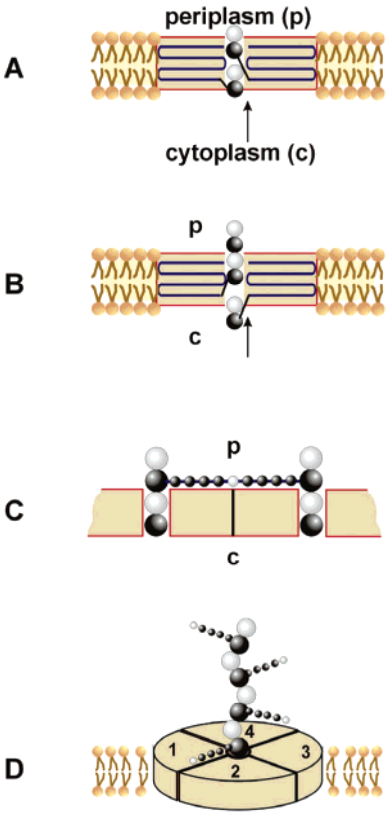


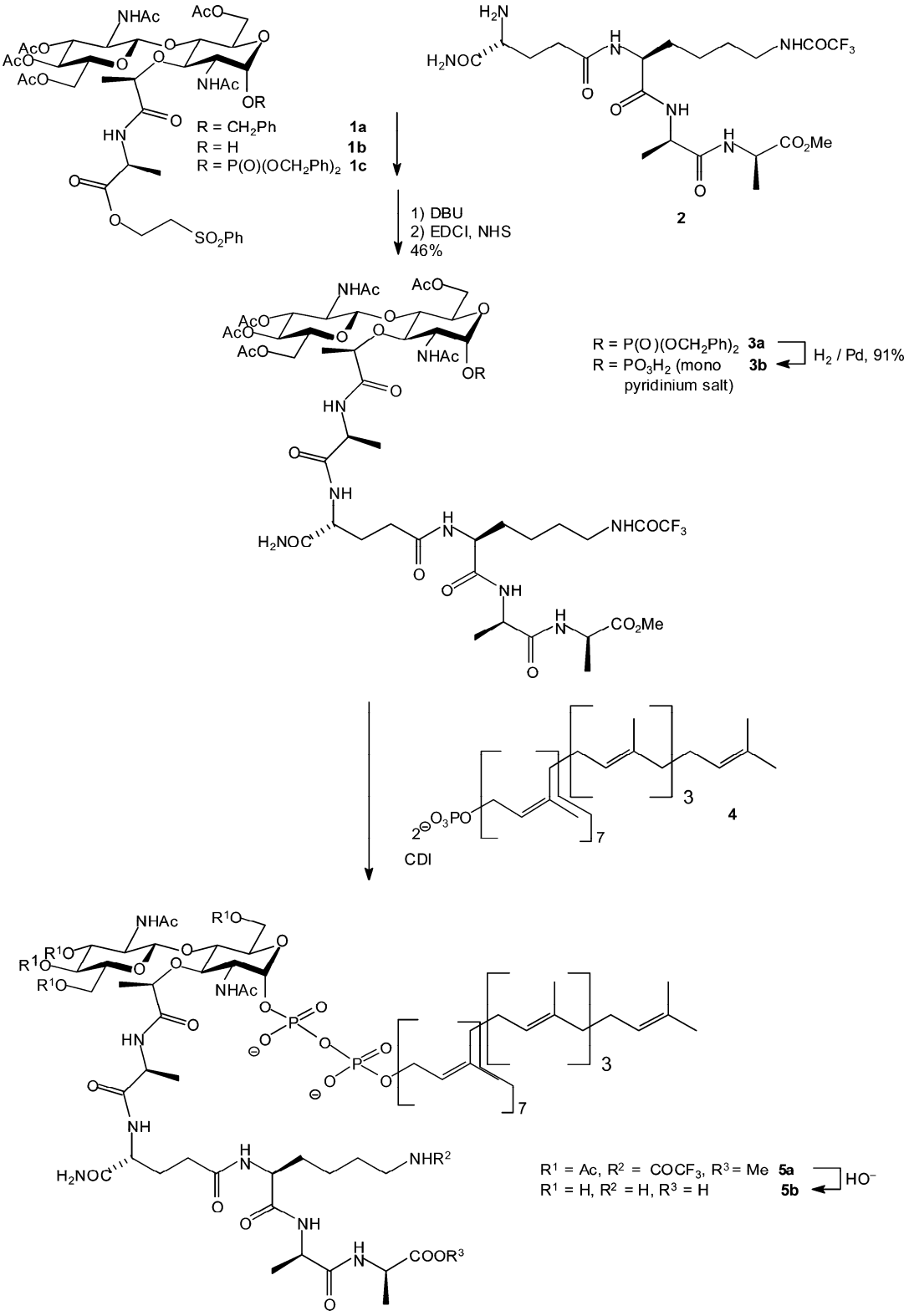
Figure 6. Schematic presentation of peptidoglycan biosynthesis according to Rietschel and co-workers: (A, B) transglycosylation, (C, D) transpeptidation. p = periplasm, and c = cytoplasm. Reprinted with permission from ref 20. Copyright 1999 Springer-Verlag.

N-acetylglucosaminyl residue of the disaccharide should be susceptible to periodate oxidation. On the other hand, periodate oxidation would not occur if the units were added to the reducing, i.e., *N*-acetylmuramyl, terminus. In addition, units added this way would undergo a β-elimination reaction to yield a lactyl peptide, provided a free reducing group were present. This proved to be the case in un-cross-linked peptidoglycan synthesized by membranes of *Bacillus licheniformis*[23,24] where the newly incorporated *N*-acetylglucosamine residues were periodate-resistant and lactyl peptides were obtained after mild acid hydrolysis to yield free reducing groups in the newly synthesized peptidoglycan. Similar results have been reported for *Bacillus megaterium*[25] and *Micrococcus luteus*.[26] In each case, the reducing termini were blocked by linkages labile to mild acid hydrolysis. Thus, in the process of glycan chain elongation the *N*-acetylmuramyl terminus of the growing chain is transferred from its link with the membrane to the nonreducing *N*-acetylglucosamine terminus of lipid II. Until termination of chain elongation the growing chain remains linked to the lipid carrier and is finally released by formation of a 1,6-anhydro bond.[20,27]

2. Syntheses of Lipid II, the Monomeric Precursor of Peptidoglycan[28]

Lipid II (**5b**) contains a number of features which pose major difficulties for a total synthesis. It is an amphiphilic compound with all the problems caused by aggregate formation. There is an acid-sensitive α-glycosyl diphosphate as well as an acid-sensitive allyl diphosphate moiety. Thus, as can be seen from Scheme 1 (Eli Lilly synthesis), the undecaprenyl-linked diphosphate moiety was installed at a late stage and all protecting groups within the immediate precursor **5a** are base-labile. In compound **1a** triple orthogonality of the protective groups is built in to ensure selective unmasking of the functional groups at the appropriate point of the synthesis. Starting from compound **1a**, the anomeric hydroxyl group was released by hydrogenolysis, and lactol **1b** was converted into phosphoric acid triester **1c**, making use of the phosphoramidite method. An elimination reaction (treatment of the phenylsulfonylethyl ester with DBU) liberated the L-alanyl carboxylic group. The acid after activation as its *N*-hydroxysuccinamide derivate was treated with tetrapeptide **2** to give **3a**. The phosphate protecting groups were then removed by hydrogenolysis to provide **3b**, and the phosphate

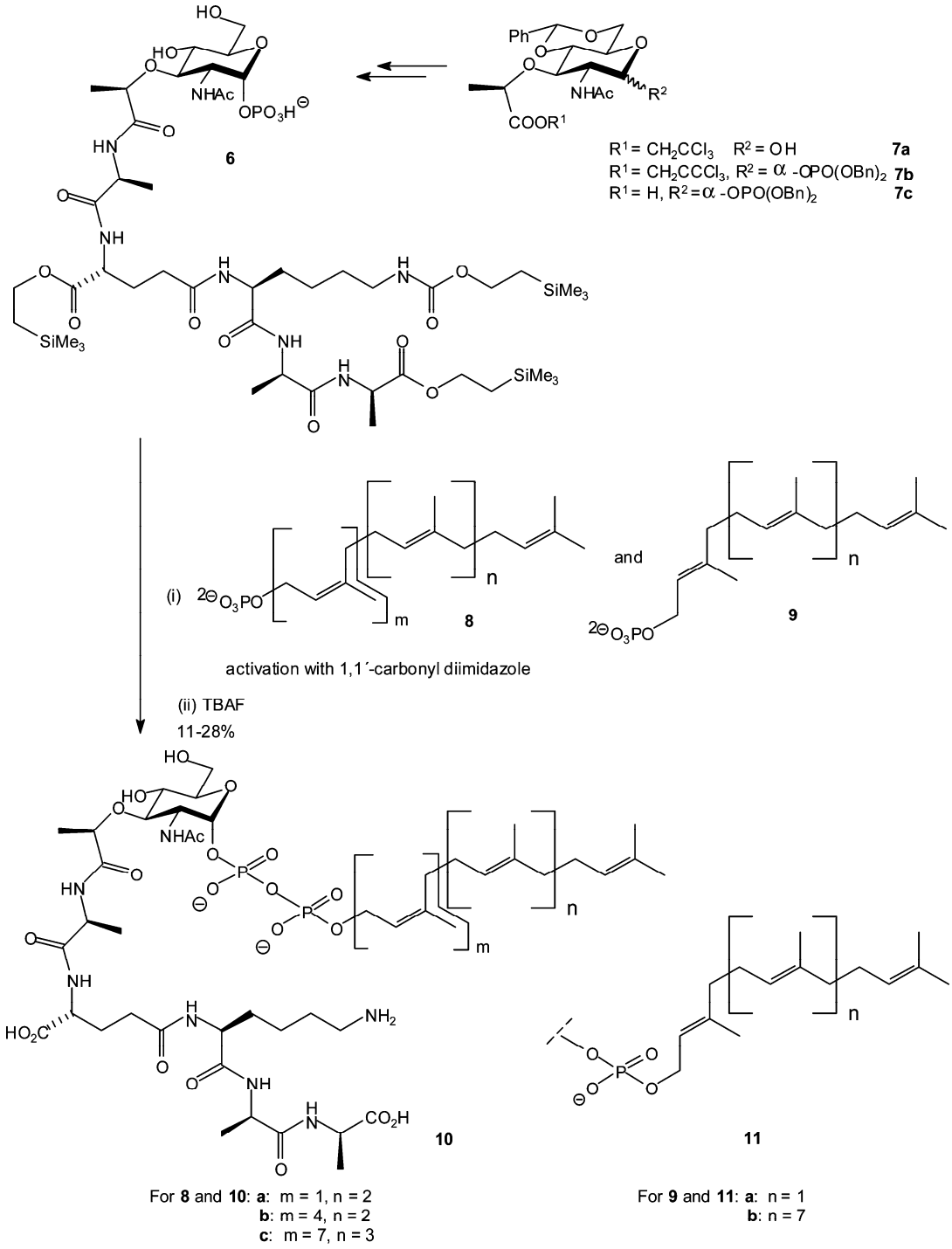
Scheme 1. Eli Lilly Synthesis of Lipid II



group was activated by treatment with 1,1′-carbonyldiimidazole. Reaction of the resulting phosphoroimidazolidate with the diammonium salt of commercially available compound **4** in the presence of tetrazol provided the fully protected lipid II (**5a**) from which lipid II (**5b**)[29] was obtained by global deprotection with aqueous NaOH in an overall yield of 24% (based on **3a**).[30] The total synthesis published by Schwartz and co-workers[31] followed essentially the same pattern. The protecting group chemistry was slightly different.

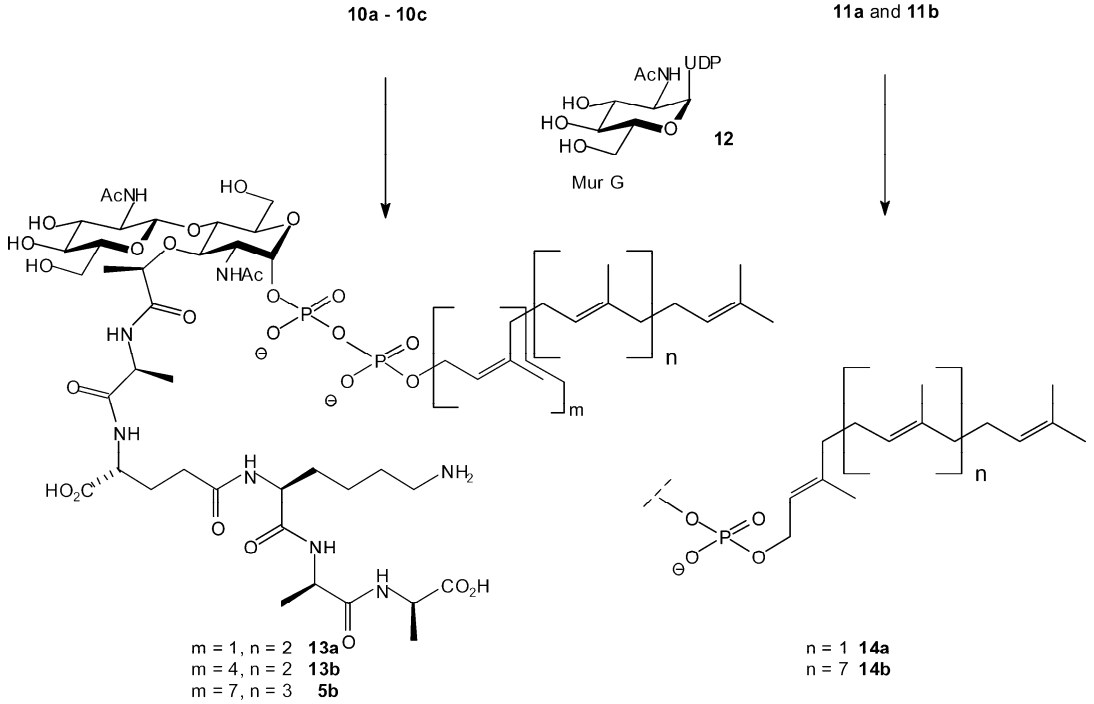
A chemoenzymatic approach to lipid II developed by Walker and co-workers[32] relies on a different order of assembling the building blocks (Schemes 2 and 3). α-Phosphate **7b** was prepared from **7a** via the corresponding phosphite. The carboxylic acid was liberated reductively with Zn (**7b** → **7c**) and after activation (HOBt, PyBop, DIEA) coupled with the protected

Scheme 2. Walker's Chemoenzymatic Synthesis of Lipid II and Analogues, Part 1



pentapeptide part to furnish **6**. Muramic acid-derived sugar phosphate **6** was treated with the CDI-activated lipid phosphates **8** and **9** to provide after protecting group removal diphosphates **10** and **11**. The latter on treatment with (^{14}C-labeled) UDP-activated *N*-acetylglucosamine (**12**) and the purified (membrane-bound) *N*-acetylglucosaminyltransferase MurG furnished lipid II (**5b**, ^{14}C-labeled) as well as analogues **13a**, **13b**, **14a**, and **14b**. Incubation studies with *E. coli* membranes[33] revealed a distinctly different acceptance of lipid II and its analogues by the transglycosylase depending on both the chain length and the double bond geometry. Compound **13a** (which has much shorter lipid chains than the natural C_{55} substrate **5b)** or analogues **14a** and **14b** (which contain an allylic double bond with *E*- rather than *Z*-configuration) are not accepted by the transglycosylase. Under the experimental conditions compound **13b** turned out to be the best substrate which was accepted by the transglycosylase, even better than the natural substrate lipid II (**5b**). **13b** has more suitable physicochemical properties than lipid II and has already shown its merits in studies which will be described below. The strength of the Walker synthesis is that it avoids extensive protecting group chemistry and that analogues with modified lipid parts are readily available provided that the intermediates of types **10** and **11** are accepted by MurG.

Scheme 3. Walker's Chemoenzymatic Synthesis of Lipid II and Analogues, Part 2



A purely enzymatic synthesis of lipid II and analogues containing polyprenyl chains composed of 2−25 isoprene units has been reported by Breukink et al.[34] UDP-GlcNAc, UDP-MurNac pentapeptide, and the appropriate prenyl phosphate were incubated with membrane preparations (right-side-out membrane vesicles of *Micrococcus flavus*) with sufficient activities of the two necessary enzymes (MraY and MurG). It was reported that the method allows production of 50−100 mg quantities of lipid II and the analogues.

A dansylated lipid II derivative has been prepared either by direct acylation of the lipid II Lys ϵ-amino group with dansyl chloride[30] or by synthesis making use of a dansylated (at the ϵ-amino group of lysine) oligopeptide building block.[10] The compound was

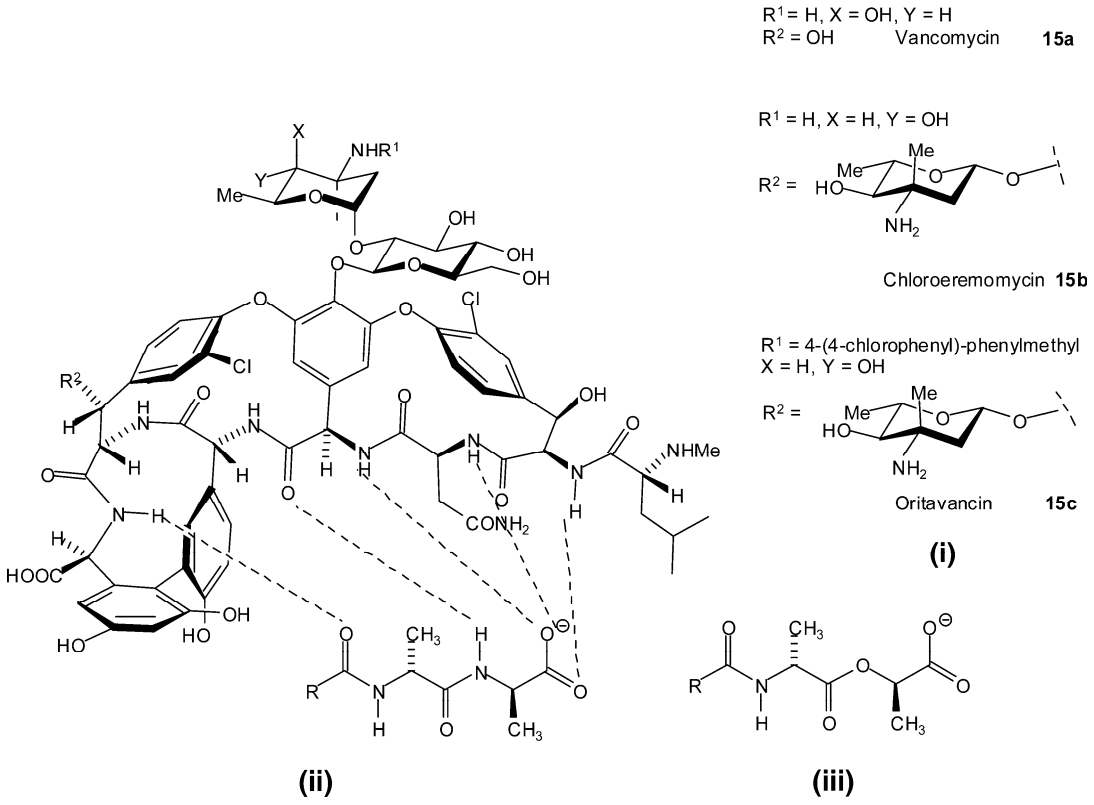
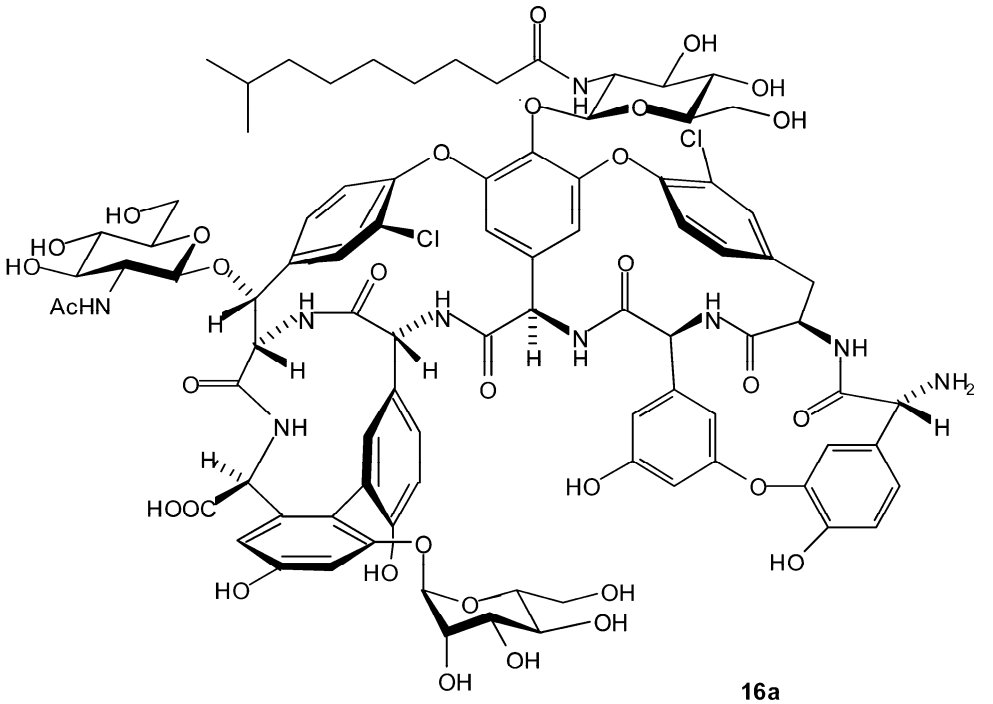


Figure 7. (i) Structures of vancomycin (**15a**), chloroeremomycin (**15b**), and oritavancin (**15c**). (ii) Schematic representation of the hydrogen bonds between vancomycin and the D-Ala-D-Ala terminus of the pentapeptide side chain of peptidoglycan precursors. (iii) D-Ala-D-Lac terminus of the peptide side chain of vancomycin-resistant strains.



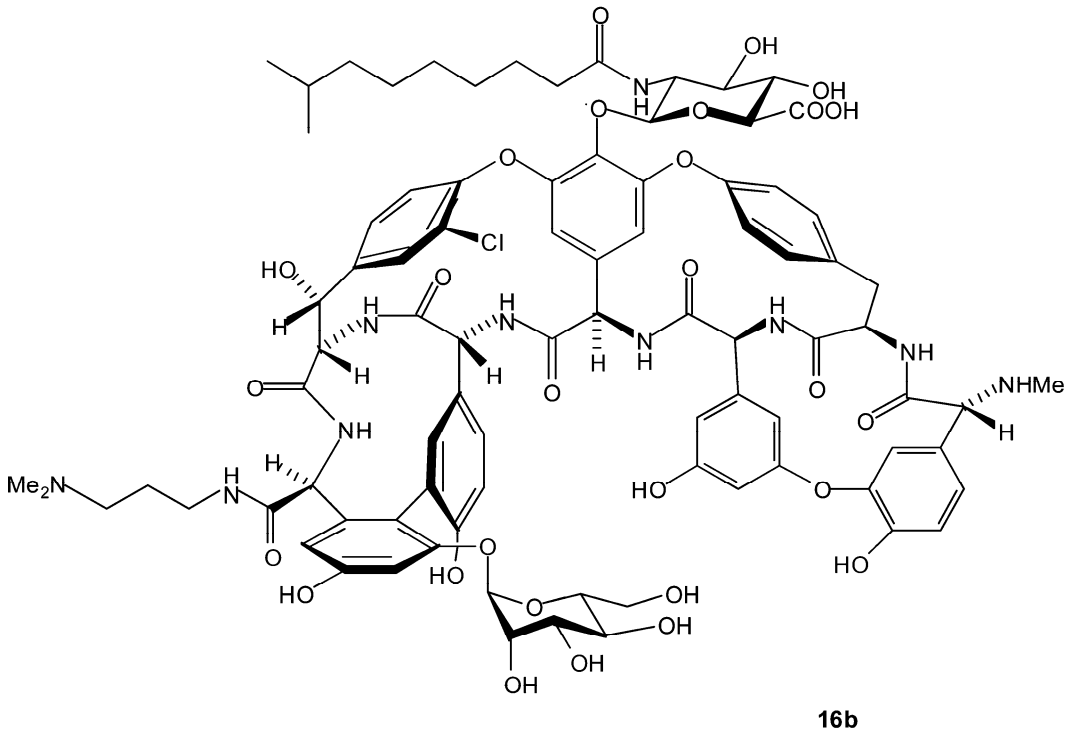


Figure 8. Teicoplanin A_2-2 (**16a**) and dalbavancin (**16b**).

already used as a valuable analytical tool.[10,11,35] Breuking et al. have shown that UDP-MurNac pentapeptide pyrene-labeled at the Lys amino group is accepted by their membrane preparation. A pyrene-labeled lipid II was prepared this way.[34]

3. Teicoplanin

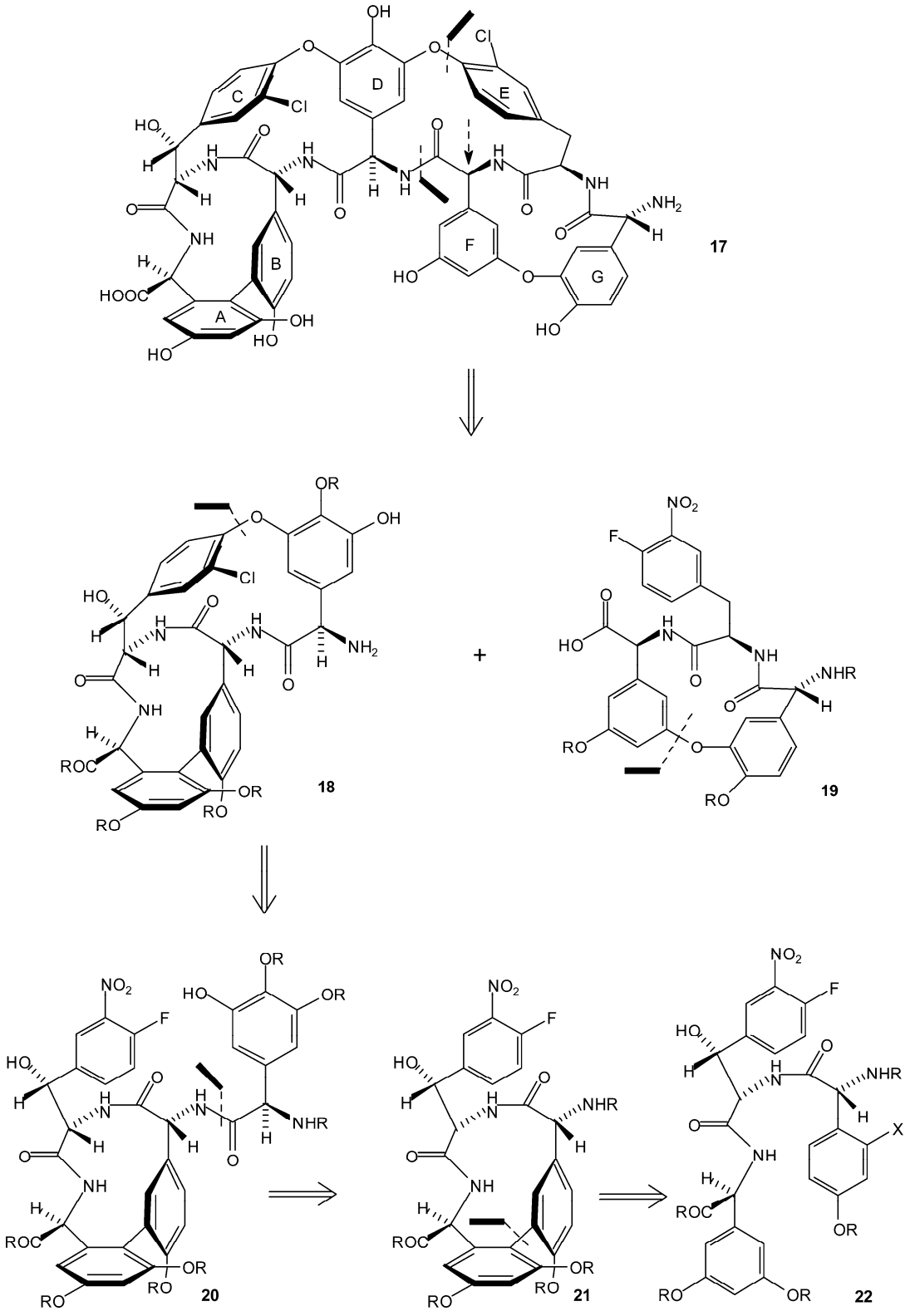
3.1. Mode of Action

The glycopeptide antibiotics are a large number of naturally occurring and semisynthetic compounds that are characterized by a heptapeptide backbone. Two members of the family are in clinical use: vancomycin (**15a**) and teicoplanin (**16a**).[36−38]

Vancomycin (which is often called an antibiotic of last resort in the treatment of infections with methicillin-resistant Gram-positive bacterial strains) inhibits peptidoglycan biosynthesis binding to the terminal D-Ala-D-Ala dipeptide of bacterial cell wall precursors mainly by means of five hydrogen bonds (see Figure 7).[39]

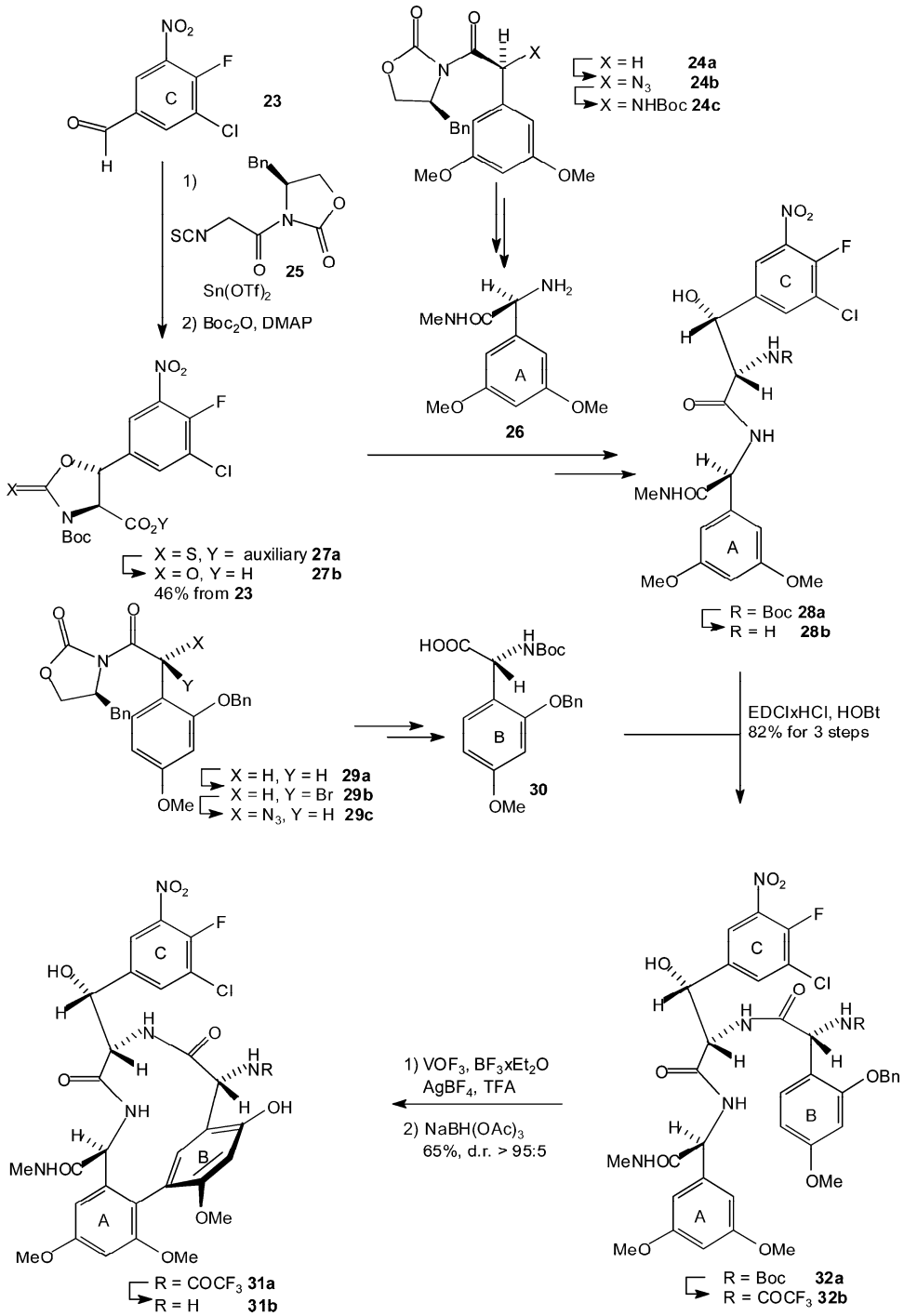
Most probably the primary site of inhibition is the transpeptidation step (vide supra).[40] In vancomycin-resistant enterococci (VRE) D-Ala-D-Ala termini are

Scheme 4. Teicoplanin Retrosynthetic Analysis (Evans)



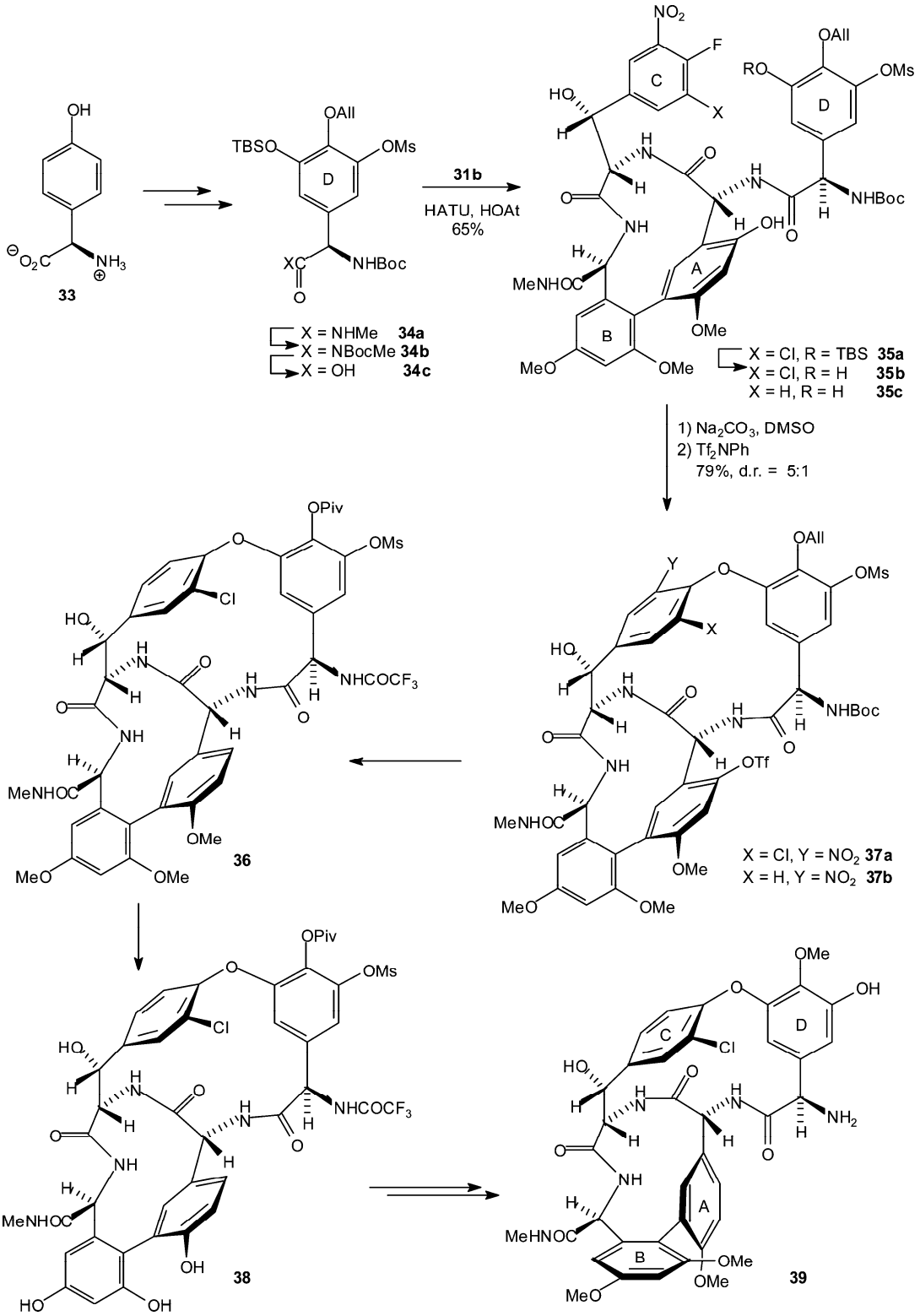
replaced by D-Ala-D-Lac,[41−44] which reduces the affinity to the antibiotic by a factor of over 1000. The decrease of binding results from the replacement of one CO···HN hydrogen bond by a repulsive CO↔O interaction.[45,46] Lipidated glycopeptide antibiotics such as teicoplanin (active against the VanB phenotype) and semisynthetic compounds such as LY333328 (oritavancin, **15c**) and dalbavancin (**16a**; Figure 8), which are prepared from their precursors (chloroeremomycin in the case of **15c**[47] and a member of the teicoplanin family in the case of **16a**[48]) by reductive amination[49,50] and N-acylation, respectively, have potent activity against resistant enterococci.[51−53] The antibacterial activity of such compounds against bacteria that lack the D-Ala-D-Ala binding site was explained on the basis of two different hypotheses. One, suggested by D. H. Williams, assumes a combination of membrane anchoring and dimerization to

Scheme 5. Evans' Synthesis of 32b (Vancomycin and Teicoplanin ABC Part)



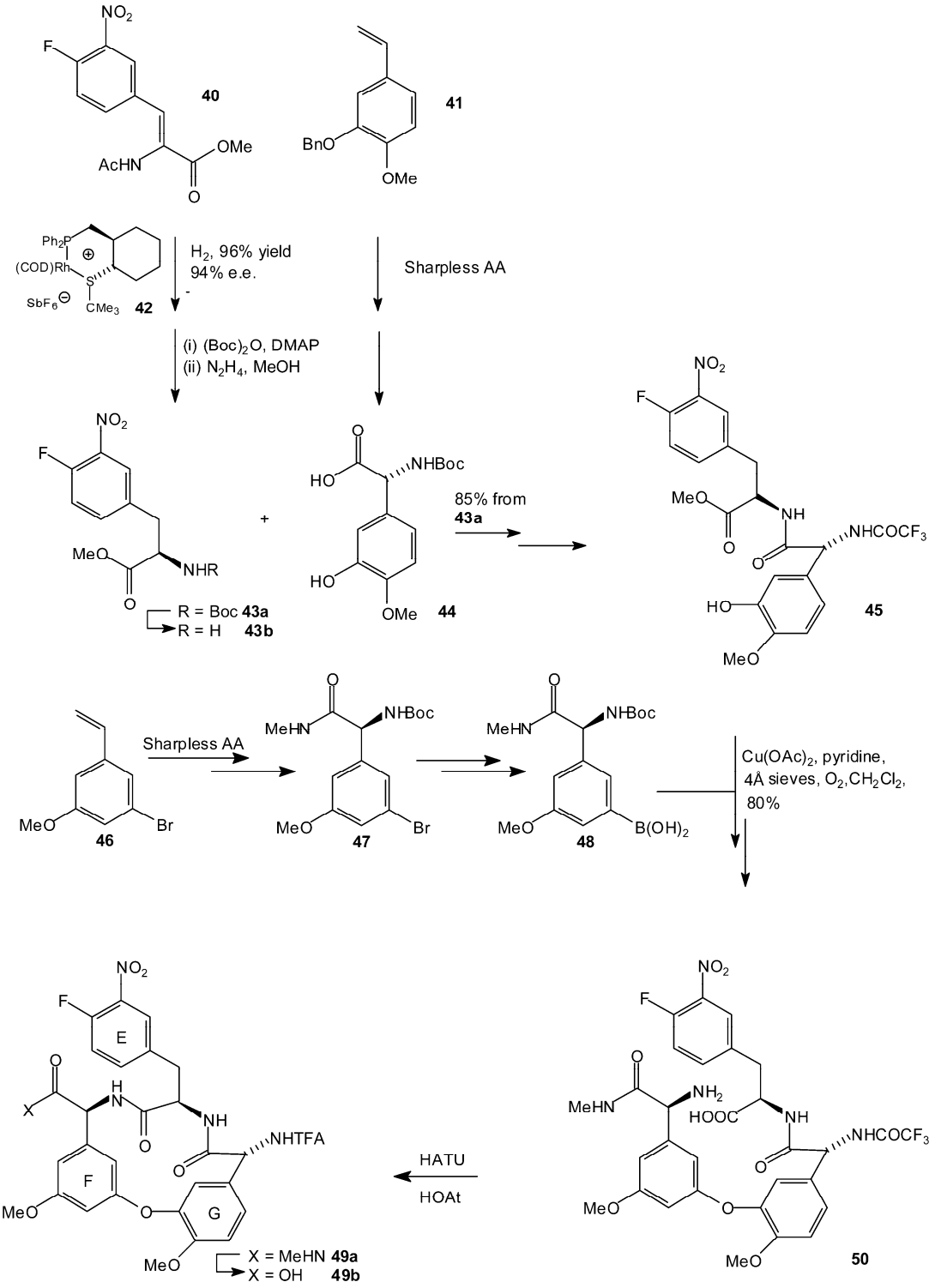
increase the interaction with D-Ala-D-Lac.[47,54,55] In view of this, covalent vancomycin dimers have been synthesized in several laboratories, many of which showed high potency against both vancomycin-susceptible and vancomycin-resistant strains.[56] However, Ellman and co-workers found that dimers of vancomycin and damaged vancomycin inhibit the PBP1b biosynthesis in the absence of substrate binding.[57−59] Similar results have been published by Printevskaya and co-workers.[60] The other theory (put forward by D. Kahne) proposes a second mode of action, namely, interaction with the transglycosylation reaction. In an assay that reveals the step at which peptidoglycan synthesis is inhibited,[40] teicoplanin, vancomycin derivatives with an N-alkylated vancosamine unit, and hydrophobic derivatives of eremomycin and des(*N*-methyl-D-leucyl)eremomycin[61] were found to block the transglycosylation.[52,62,63] Support for this hypothesis was provided by Sinha Roy et al., who have demonstrated that PBP1b is retained on an affinity column derivatized with a vancomycin analogue N-alkylated at the vancosamine substituent.[64] Furthermore, REDOR NMR probing of the peptidoglycan binding site of an analogue of LY3333328 (containing a F rather than a Cl in the biphenyl part) gave no indication of dimer formation and insertion of the fluorobiphenyl group into the cytoplasmic membrane.[65] Recent studies in Boger's

Scheme 6. Evans' Synthesis of 39 (Teicoplanin Aglycon ABCOD Part)



group have revealed that a simple hydrophobic derivative of the teicoplanin aglycon is able to overcome VanB resistance. The aglycon is active only against sensitive *Staph. aureus*, in contrast to teicoplanin itself, which is equally effective against VanB *Enterococcus faecalis* and sensitive *Staph. aureus*. However, on methylation of the phenolic OH groups and the carboxylic acid function of the aglycon, an analogue was obtained which was equipotent against both sensitive *Staph. aureus* and VanB *Ent. faecalis*. Methylation may, thus, confer properties related to the lipid side chain of teicoplanin or the hydrophobic substituents of vancoasamine-derivatized vancomycin analogues.[66] Clearly, the field is not yet fully explored, but it is under very active investigation in many laboratories.[67] The present knowledge on the modes of action of glycopeptide and lipoglycopeptide antibiotics, the mechanisms of resistance, and the means to overcome resistance were recently comprehensively reviewed by Kahne et al.[52,68]

Scheme 7. Evans' Synthesis of 49b (EFOG Part of the Teicoplanin Aglycon)



In the present review, assuming that lipidated glycopeptide antibiotics and a simple derivative of the teicoplanin aglycon are able to overcome VanB resistance, probably by interfering with the transglycosylation reaction, we shall describe the Evans and the Boger total syntheses of the teicoplanin aglycon, as well as Nicolaou's approach to the ABOCOD ring system of the vancomycin aglycon, which is identical with that of the teicoplanin aglycon. Inferring from the available evidence that vancomycin inhibits the cross-linking transpeptidation reaction, we shall not include the total syntheses of vancomycin and its aglycon, which have been summarized excellently elsewhere.[69]

3.2. Teicoplanin Aglycon

The structure of the teicoplanin aglycon **17** is more complex than that of the vancomycin aglycon (cf. Figure 7). The latter is a tricyclic heptapeptide containing nine stereogenic centers. In addition, each of the three ring systems contains a helical axis.[70] The ABCOD ring system is identical in the vancomycin and the teicoplanin aglycon, but the latter possesses a further (F−O−G) ring system which is

not present in vancomycin. This F−O−G part is derived from two racemization-prone arylglycine residues. An especially sensitive position is C-2 of unit F (see the arrow in formula **17**). In the D−O−E part teicoplanin lacks the benzylic hydroxy group which is found in vancomycin.

The synthesis of such a glycopeptide aglycon requires solutions for several synthetic problems: (i) enantioselective synthesis of the amino acid building blocks, (ii) efficient protocols for the peptide couplings, (iii) suitable methods for the diaryl ether formation, (iv) control of the configuration around the three helical axes. In all published glycopeptide syntheses the stereogenic centers were efficiently either derived from the chiral pool or created by auxiliary- and reagent-controlled reactions. On the other hand, control of the configuration around the helical axes constituted a major issue in all syntheses, and different approaches have been used to meet this challenge.

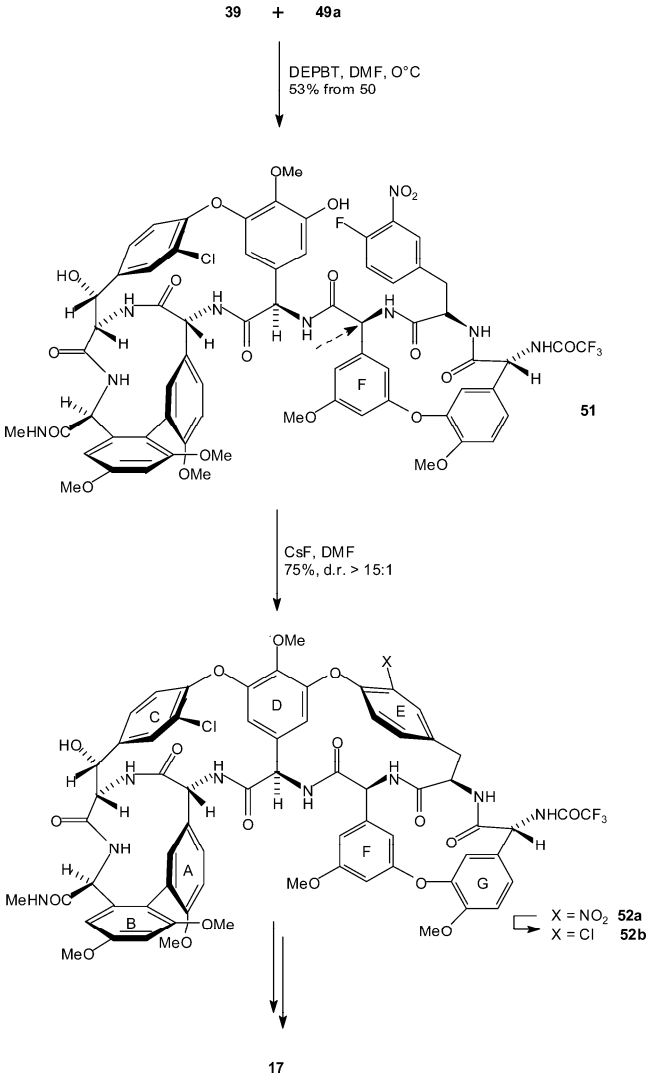
3.3. Evans Total Synthesis of the Teicoplanin Aglycon

In Evans' total synthesis,[71−73] the C−O−D and the D−O−E biaryl ether linkages were formed by nucleophilic aromatic substitution reactions (see Scheme 4, **17** and **18**) whereas the F−O−G ether was constructed by a $Cu(OAc)_2$-mediated coupling of a phenol and an arylboronic acid (as developed in Chan's and in Evans' laboratories;[74,75] see **19**) since the latter conditions were assumed to be milder than those of the nucleophilic aromatic substitution reactions and would not lead to epimerization at the sensitive arylglycine moieties of the F−O−G part. The AB biaryl formation was achieved by an oxidative coupling (see **21**). The configuration at the helical axes was established by both kinetic and thermodynamic control.

The Evans synthesis of the ABCOD part amino acids relied mainly on the oxazolidinone method. Thus, the synthesis of **28b** started with a $Sn(OTf)_2$-mediated aldol reaction of **23** with oxazolidinone **25**, which contained the amino group of unit C in the form of an isothiocyanate (Scheme 5). The *syn*-product **27a** obtained with good stereoselectivity (dr = 95:5) was converted by functional group manipulations into **27b**. A key step of the synthesis of amino acid derivative **24c** was trapping of the (*Z*)-enolate derived from **24a** with 2,4,6-triisopropylbenezenesulfonyl azide to give (after sulfinic acid removal with KOAc) the azide **24b** (dr = 90:10),[76] which was converted into **26** by standard operations via **24c**. Carbodiimide/1-hydroxybenztriazole-mediated coupling of **26** with **27b** provided a dipeptide from which on carefully controlled cleavage of the oxazolidinone (Li_2CO_3, MeOH) and subsequent removal of the Boc protecting group (with TFA and dimethyl sulfide) AC precursor **28b** was obtained.

The B building block **30** was derived from oxazolidinone **29a** via boron enolate formation and trapping with NBS to give **29b** and subsequent nucleophilic substitution with tetramethylguanidinium azide (**29b** → **29c**). Coupling of **30** with **28b** (to give **32a**) and subsequent protecting group exchange provided **32b** (ABC part) in high yield.

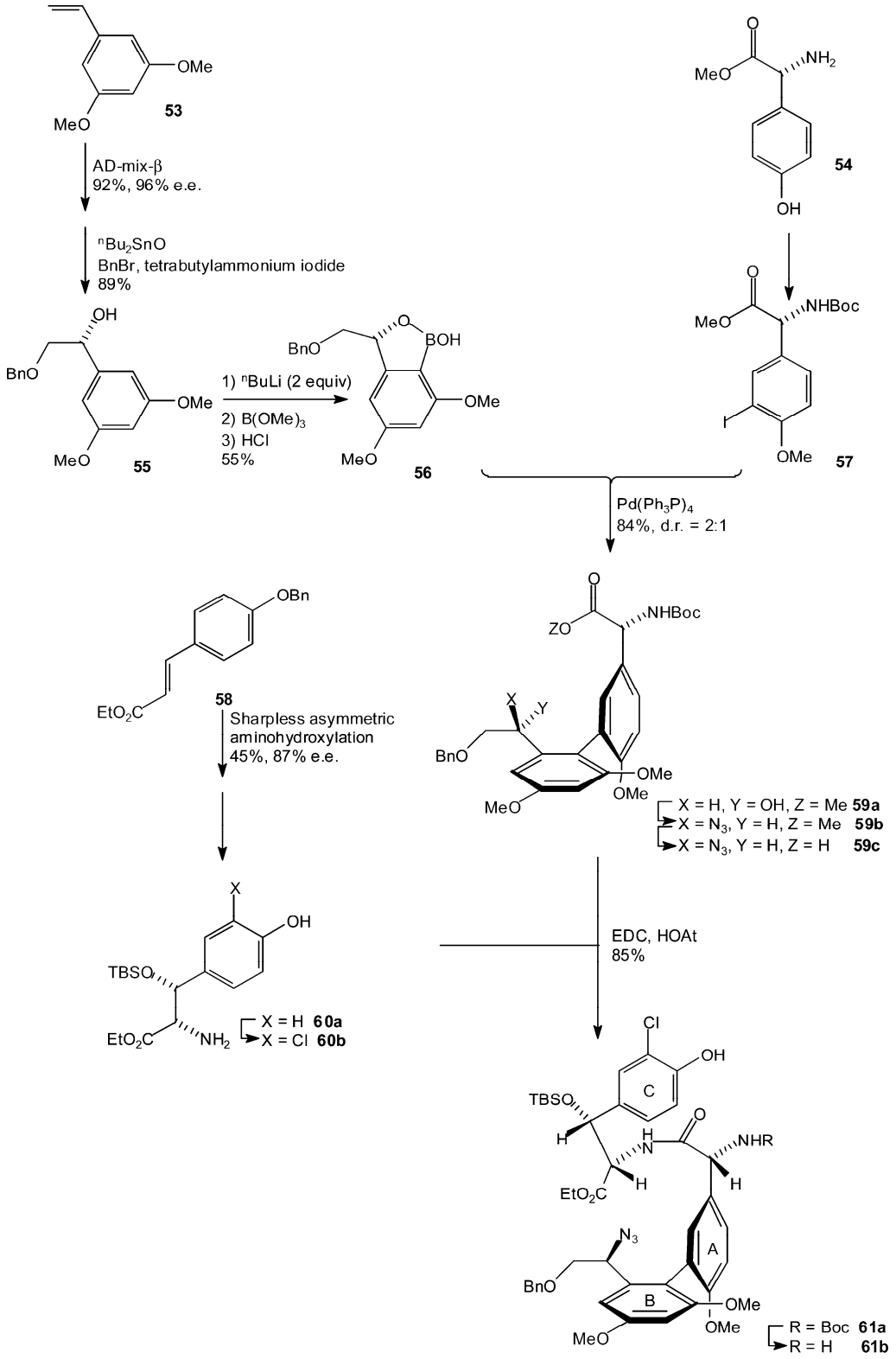
Scheme 8. Final Steps of Evans' Teicoplanin Aglycon Synthesis



Oxidative cyclization with VOF_3 in the presence of $BF_3{\cdot}Et_2O$ (added to prevent oxygen nucleophile attack on the putative ring A radical cation) and subsequent quenching with $NaBH(OAc)_3$ furnished **31a** by reduction of the radical ion derived from the initial coupling product and loss of the benzyl protecting group (as desired). Mild base treatment removed the trifluoroacetyl group to furnish **31b**. One should notice that only in the presence of the extra oxygen function in the ring B 4-position of **32b** was the oxidative cyclization successful. This extra hydroxyl group had to be removed at a later stage. Stereochemically, the oxidative cyclization gave the wrong (*M*)-isomer, which means that the configuration at the biaryl axis had to be corrected at a later stage.

The synthesis of D building block **34c** commenced from 4-hydroxyphenylglycine (**33**; Scheme 6). Bromination in the 3- and 5-positions, protection of the amino, phenolic hydroxyl, and carboxylic acid groups followed by *stepwise* Br → OR conversion through halogen−metal exchange (first excess MeMgCl to deprotonate the amide functions and for Br → MgX

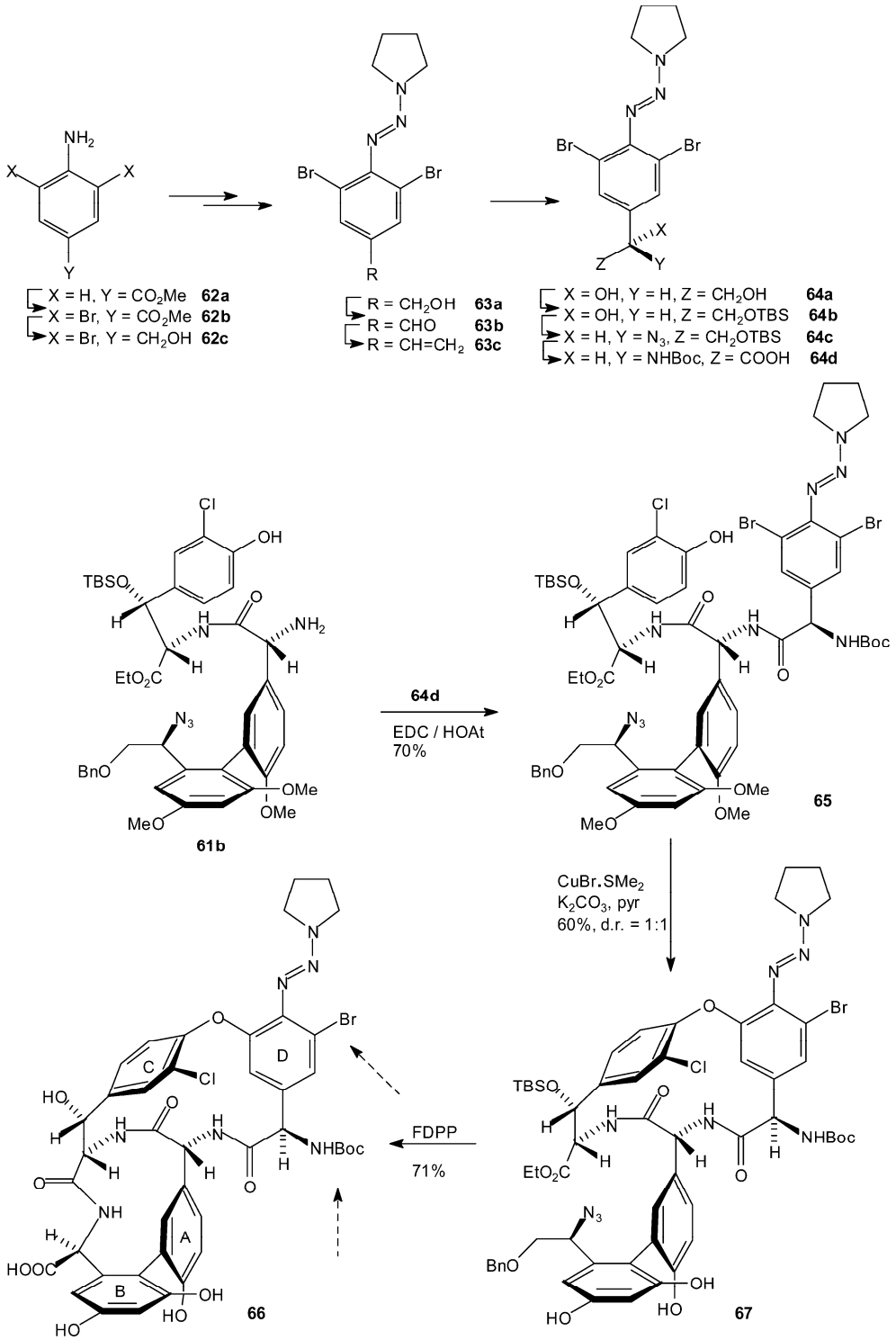
Scheme 9. Nicolaou's Synthesis of 61b (ABC Part of the Vancomycin and Teicoplanin Aglycon)



exchange and then MgX → Li exchange with ^{t}BuLi), subsequent $B(OMe)_3$ quenching, oxidative workup, and protection of the newly generated phenolic OH group furnished (after two rounds) **34a**, from which the *N*-methylamide group could not be removed as desired via the nitroso amide. Instead, a carefully tuned sequence of reactions had to be performed with **34b** as the intermediate, which allowed amide cleavage (LiOOH/THF/H_2O) to give **34c** without major side reactions.

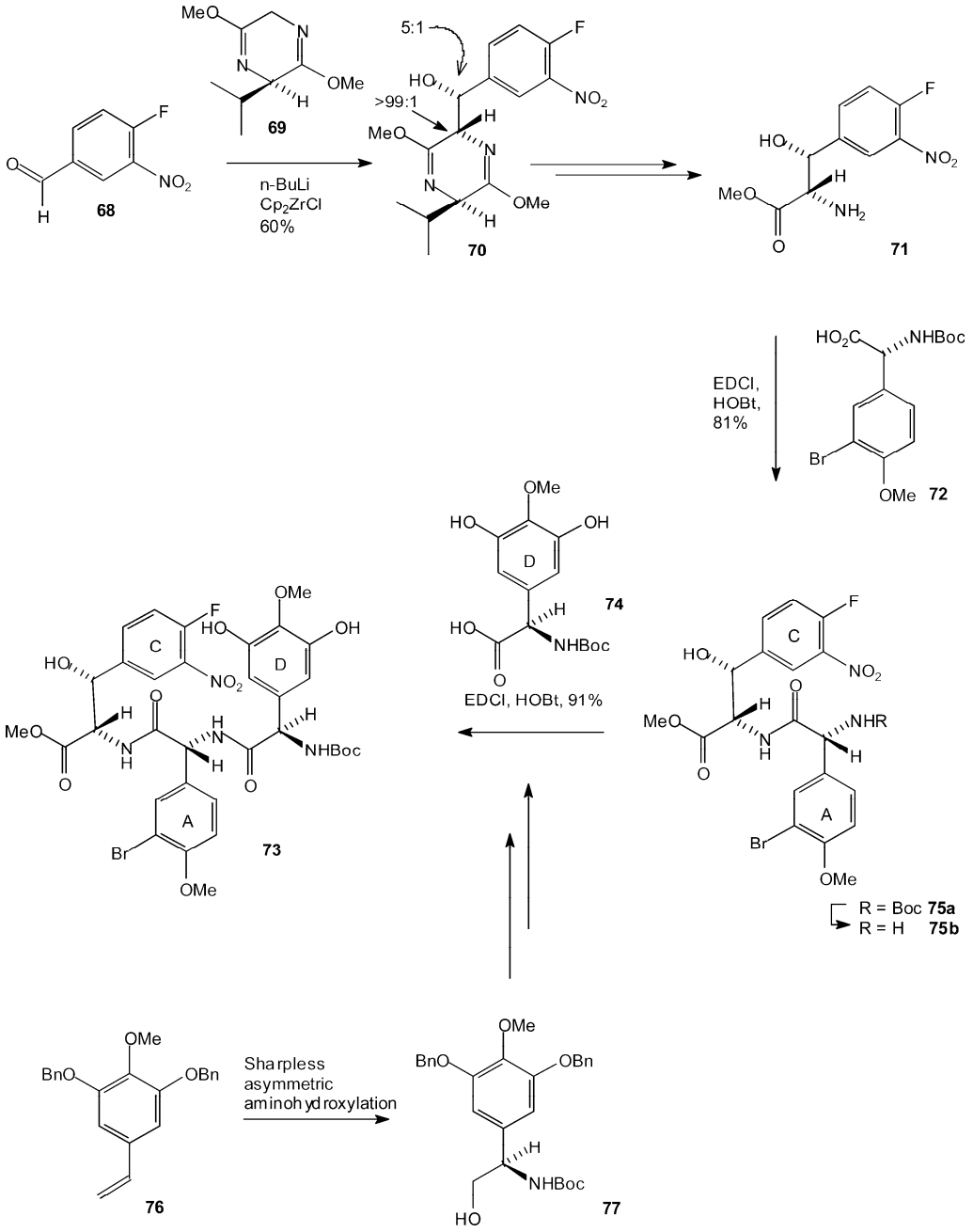
Coupling of **34c** with **31b** gave **35a**, from which the silyl protecting group had to be removed under acidic conditions (HF·pyr) because of the great sensitivity of the electron-poor aromatic ring C (**35a** → **35b**). Treatment of **35b** with Na_2CO_3 in DMSO followed by OH → OTf conversion with Tf_2NPh led to biaryl

Scheme 10. Nicolaou's Synthesis of 67 (ABCOD Part of the Vancomycin and Teicoplanin Aglycon)



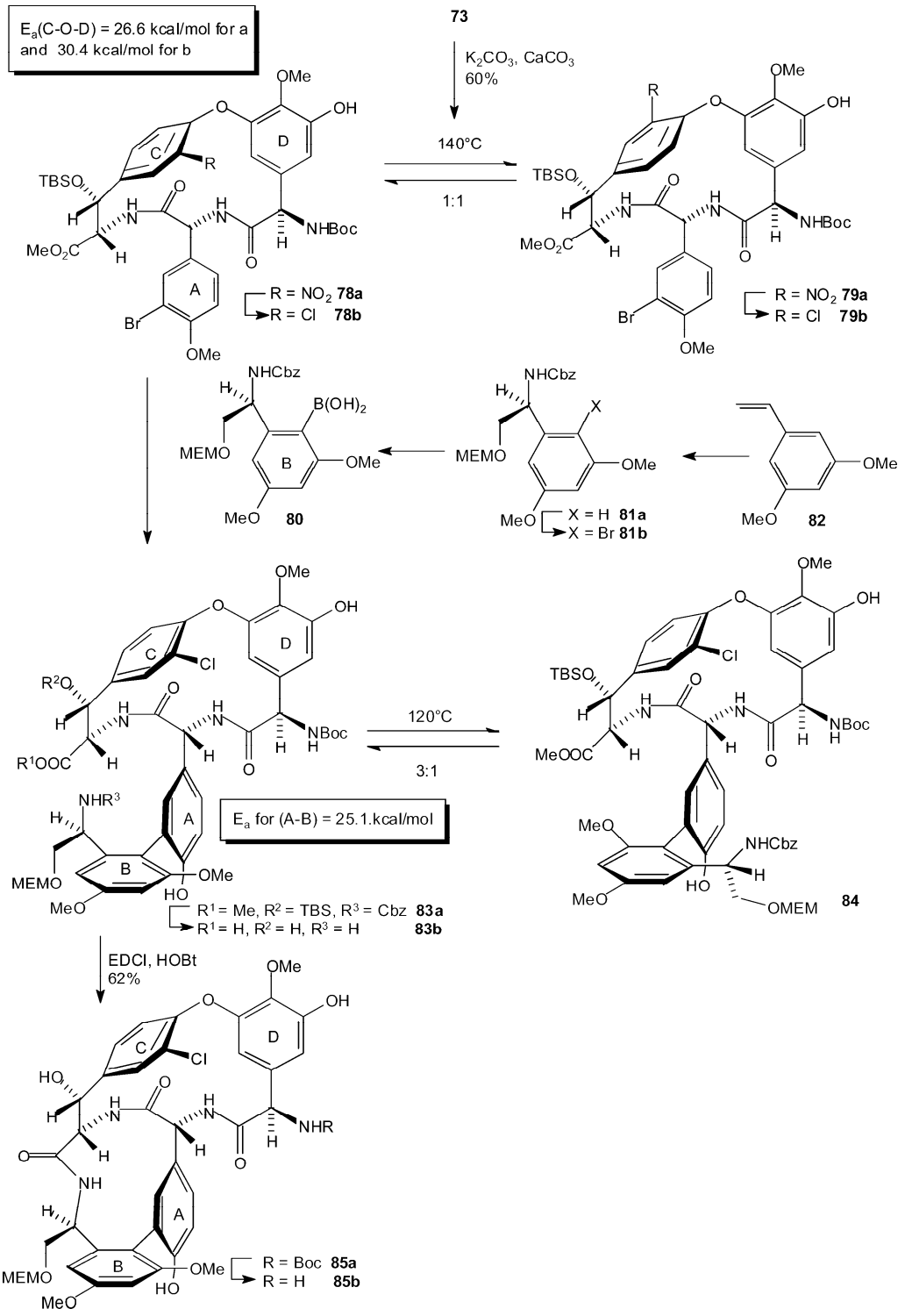
ether **37a** (79% yield and 5:1 dr). At this stage, the masterful design of the Evans synthesis should be highlighted. Both the nitro and the chloro substituents at ring C were carried through the synthesis to decide which would eventually become the ring C chloro substituent of vancomycin and teicoplanin, depending on the stereochemical outcome of the diaryl ether formation. As it turned out, cyclization of model compound **35c** (followed by OH → OTf conversion) gave **37b** with the wrong configuration at the axis. This means that from **37a** the NO_2 rather than the Cl substituent had to be removed to arrive at the desired steroisomeric series. This was achieved by $NO_2 \rightarrow NH_2$ conversion (Zn) followed by diazotation and Pd-mediated reduction with formic acid. Under the latter conditions not only did the $N_2^+ \rightarrow H$ conversion occur, but the allyl protecting group and the superfluous triflate group were also removed. Protecting group adjustment provided **36**. After methyl ether cleavage (AlB_3, EtSH, **36** → **38**) heating to 55 °C in methanolic solution caused epimerization at the biaryl axis (dr > 95:5) to furnish (after protecting group adjustment) **39** with the correct *P*-configuration at the biaryl axis of the ABCOD part.

Scheme 11. Boger's Synthesis of 73 (ACD Part of the Vancomycin and Teicoplanin Aglycon)



Starting materials for the E−F−O−G part were **40**, **41**, and **46** (Scheme 7). Asymmetric hydrogenation of dehydroamino acid **40** catalyzed by chiral Rh complex **42**[77] followed by protecting group exchange under the conditions of Burk and Allen[78] provided **43a**. **44** was prepared from **41** via a Sharpless asymmetric aminohydroxylation.[79] Coupling of **43b** (obtained from **43a** by Boc removal with TFA/dimethyl sulfide) and **44** (activation with EDCI/1-hydroxy-7-azabenzotriazole) afforded dipeptide **45** (after protecting group adjustment). A key step of the conversion of **46** into **47** was again a Sharpless asymmetric aminohydroxylation. The boronic acid group was introduced by the sequence described above (excess MeMgCl and THF for amide deprotonation and Br → MgX exchange, then ^{t}BuLi, and then $B(OH)_3$). For reasons that were discussed above for the formation of **50**, the $Cu(Oac)_2$-mediated diaryl ether synthesis was chosen. Indeed, no epimerization was found at either arylglycine moiety. The subsequent ester hydrolysis also occurred without side reactions. Finally, Boc deprotection (TFA/dimethyl sulfide) furnished **50**. The macrolactamization (HATU, HOAt) had to be performed under carefully chosen conditions because of the low solubility of **49a** in standard organic solvents. Next the *N*-methylamide protecting group had to be removed, which proved challenging. On treatment with N_2O_4 in DMF in the absence of a base, mononitrosation took place. The nitrosoamide was then hydrolyzed to give the free carboxylic acid **49b**. For the coupling of **49a** and **39** 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) in the absence of a base was the coupling reagent of choice as found by Boger and coworkers (vide infra) and provided tricycle **51** as a 15:1 mixture of C-2^F epimers (see the arrow in formula

Scheme 12. Boger's Synthesis of 85b (ABCOD Part of the Vancomycin and Teicoplanin Aglycon)

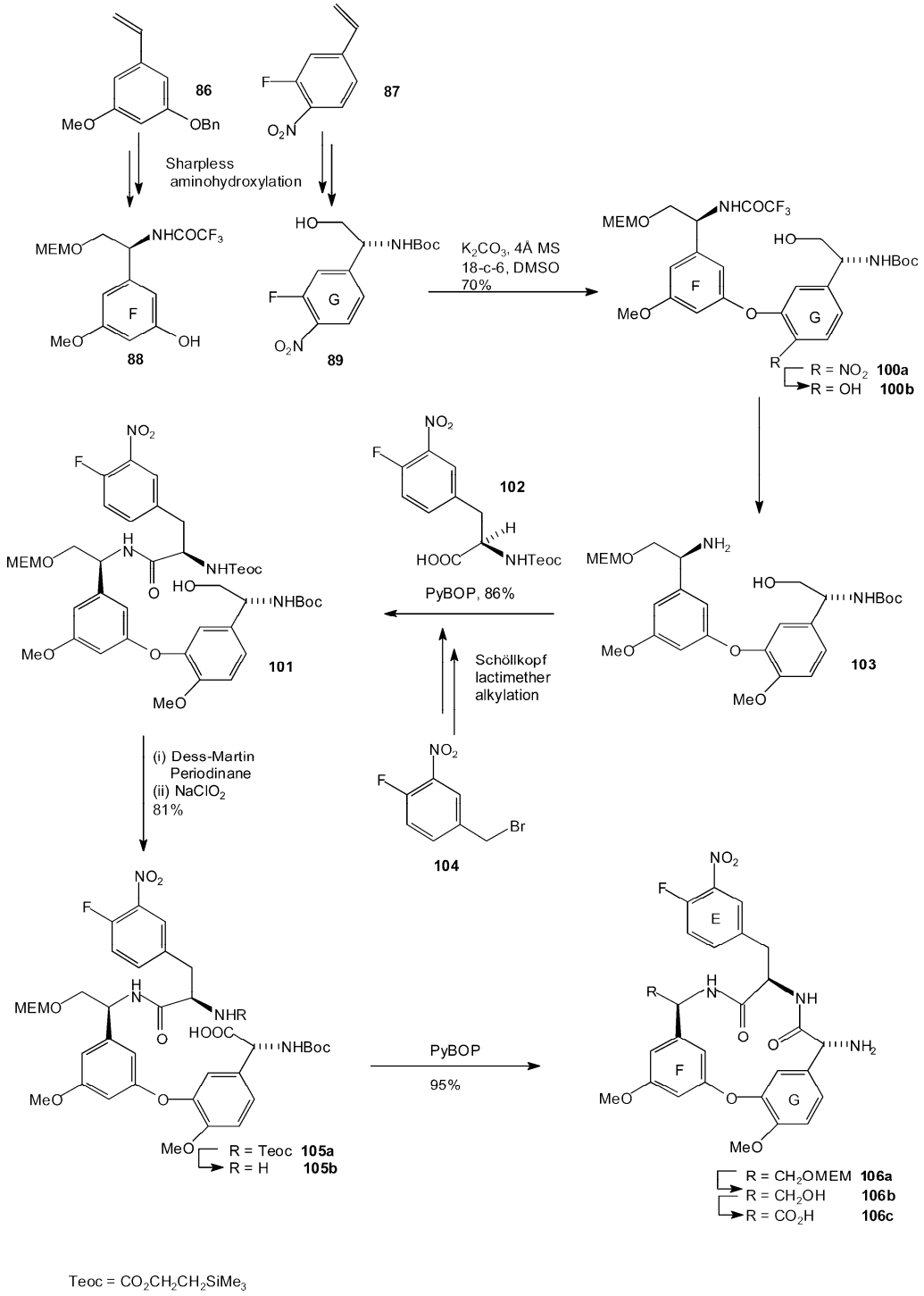


51) that could not be separated (Scheme 8). Nucleophilic aromatic substitution (with CsF in DMF) installed the D−O−E junction and proceeded with high atropdiastereoselectivity (>15:1). After purification **52a** was obtained as a single stereoisomer. Reduction of the nitro group and Sandmeyer reaction served to establish the desired chlorine substituent and afforded **52b** (58%). The *N*-methylamide of **52b** was then cleaved on treatement with N_2O_4 and subsequent hydrolysis of the nitrosoamide under neutral conditions (85% yield). Finally, global demethylation and trifluoroacetamide hydrolysis were effected by treatment with $AlBr_3$ and EtSH to afford the teicoplanin aglycon **17** in 50% yield.

3.4. Nicolaou Synthesis of the ABCOD Part[80−82]

Nicolaou's synthesis of the ABCOD part is summarized in Schemes 9 and 10. The preparation of the individual amino acid building blocks relied very much on Sharpless chemistry. A key step of the synthesis of **55** was a Sharpless asymmetric dihydroxylation of **53**. The diol was converted into **55** via an intermediate tin acetal.[83] The boronic acid function was created by deprotonation of **50** with ^{n}BuLi

Scheme 13. Boger's Synthesis of 106c (EFOG Part of the Teicoplanin Aglycon)

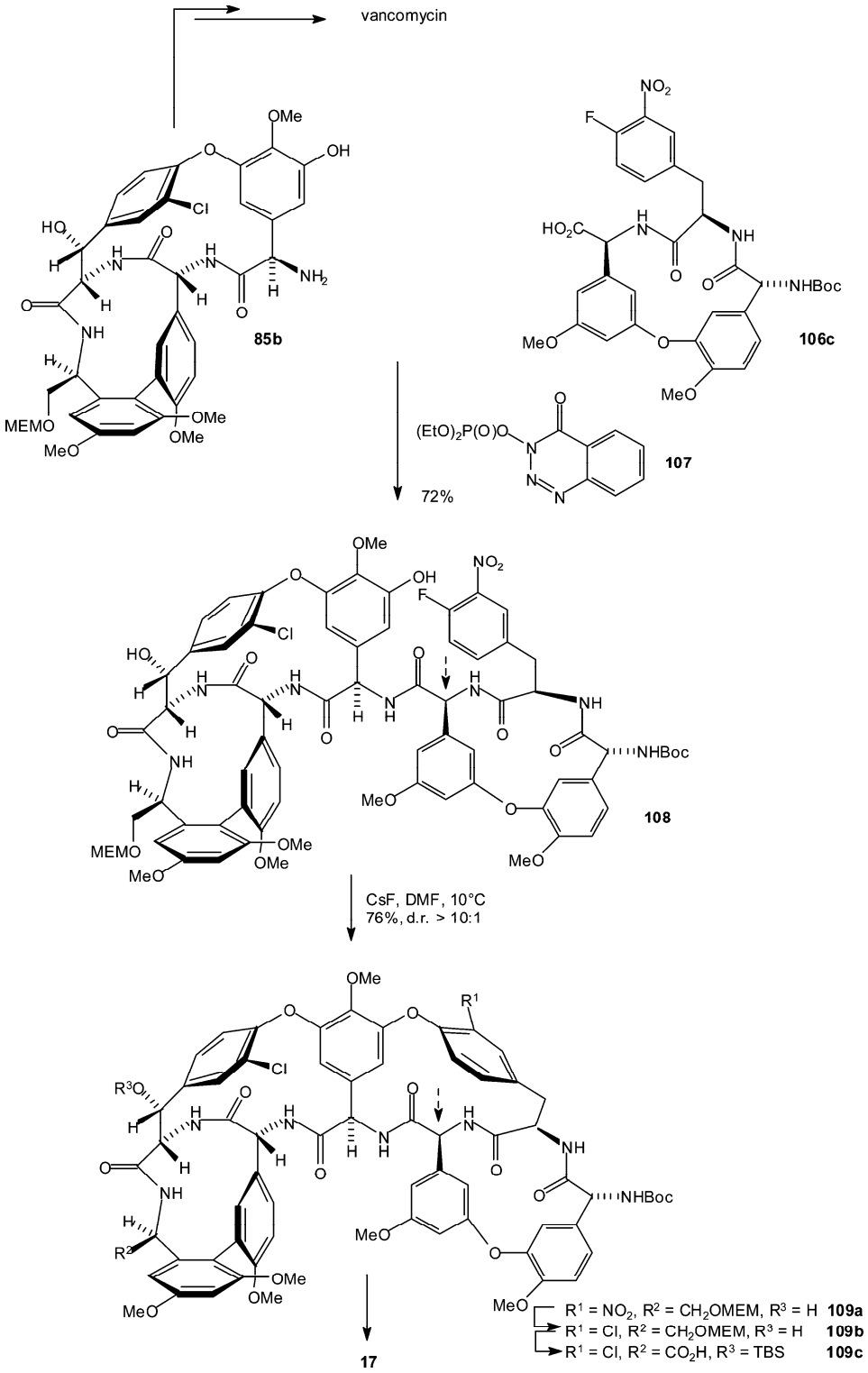


(2.2 equiv), followed by quenching with $B(OMe)_3$ and boronic ester hydrolysis. **57** was straightforwardly obtained from **54**. Suzuki coupling of **56** and **57** proceeded in good yield (84%) but with only moderate stereoselectivity (dr = 2:1 in favor of **59a**). The free hydroxyl group was then replaced by an azide function under Mitsunobu conditions (**59a** → **59b**). Ester hydrolysis furnished **59c**. The synthesis of **60b** from **58** included an asymmetric aminohydroxylation and an aromatic chlorination with SO_2Cl_2 (**60a** → **60b**). Coupling of **60b** with **59c** followed by Boc removal provided ABC intermediate **61b**.

The preparation of building block **64d** commencing from **62a** included (i) an aromatic bromination reaction followed by ester reduction (**62a** → **62b** → **62c**), (ii) triazene formation via the diazonium salt (**62c** → **63a**), (iii) conversion of **63a** into **63c**, (iv) an asymmetric dihydroxylation (AD-mix α, 95%, 95% ee, **63c** → **64a**), (iv) a Mitsunobu OH → N_3 exchange with inversion of configuration (**64a** → **64c**), and (v) functional group adjustments (N_3 → NHBoc and CH_2OTBS → COOH, **64c** → **64d**).

Coupling of **61b** with **64d** (EDC/HOAT activation) provided tripeptide **65** (70%). A notable feature of the

Scheme 14. Final Steps of Boger's Second-Generation Teicoplanin Synthesis



Nicolaou synthesis is the activation of ring D for a nucleophilic substitution reaction by a triazene moiety.[84] Thus, treatment of **65** with CuBr, SMe_2, K_2CO_3, and pyridine in boiling acetonitrile resulted in diaryl ether formation. The yield was 60%, but again, the diastereoselectivity was low (dr = 1:1; only diastereosiomer **67** is shown). Finally, OTBS → OH conversion (TBAF), Staudinger reduction of the azido group (PPh_3 in the presence of water), ester hydrolysis, and lactamization with the reagent of Chen and Xu (pentafluorophenyl diphenylphosphinate (FDPP);[85] the yield of this step was 71%) provided the ABCOD part **66** of both vancomycin and teicoplanin. The arrowed positions could be utilized as the handles to attach the missing constituents of teicoplanin.

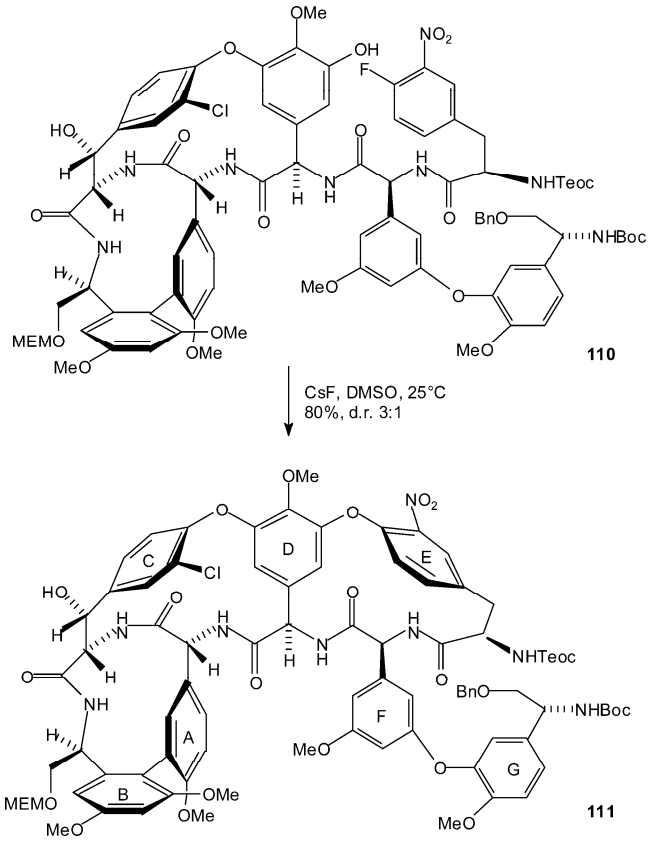
3.5. Boger's Synthesis of the Teicoplanin Aglycon[86−90]

The strategy Boger had in mind to acquire the right stereoisomer in each helical axis generating step is

fundamentally different from that the Evans synthesis is based on. In model studies it was found that the energy barriers for the isomerization at the three stereogenic axes in the ABCODOE ring system (see formula **17** in Scheme 4) are substantially different (E_a(COD) > E_a(AB) > E_a(DOE). This information was employed in that the C−O−D axis was formed first, followed by the A−B biaryl axis and finally the D−O−E helical unit. Thus, the ring-forming reactions were ordered in such a way that at each newly formed helical unit equilibration could be performed without impacting any previously equilibrated system. This procedure allowed for optimization of the amount of the desired atropisomer before moving forward. The biaryl ethers were formed by nucleophilic aromatic substitution reactions at nitro-activated aromatic rings. Generation of the stereogenic centers relied mainly on the Sharpless asymmetric aminohydroxylation and on Schöllkopf's bis(lactim ether) method.[91] Thus, addition of the organometallic reagent obtained from bis(lactim ether) **69** by deprotonation with ^{n}BuLi and transmetalation with zirconocene dichloride to aldehyde **68** provided **70** with >99:1 dr at C-2 and a dr of 5:1 at C-3 (β-hydroxyphenylalanine numbering). Removal of the auxiliary (with CF_3COOH) and alcohol protection gave **71**, which was coupled to **72** (with EDCI and HOBt, 81% yield) to generate dipeptide **75a**. Amine deprotection (**75a** → **75b**) and coupling the latter to EDCI/HOBT-activated **74** (obtained from **76** via a Sharpless asymmetric aminohydroxylation, **76** → **77** →→ **74**) furnished tripeptide **73** in high yield (Scheme 11). On treatment with K_2CO_3/$CaCO_3$ in DMF at 45 °C, diaryl ether formation took place, leading to the two diastereoisomers **78a** and **79a** in a 1:1 ratio. In this reaction the calcium ion served as a fluoride scavenger, securing survival of the silyl ether. The two stereoisomers were isolated, and the isomer with the wrong configuration at the helical axis was thermally equilibrated at 140 °C (E_a = 26.6 kcal/mol for X = NO_2) to the 1:1 mixture of the two stereoisomers, finally allowing all material to be funneled into the desired (*P*)-stereoisomer **78a**.

The nitro group was then converted into the chloro substituent (**78a** → **78b**) by (i) reduction, (ii) diazonium salt formation, and (iii) Sandmeyer reaction ($CuCl_2$/CuCl). The B moiety was attached to the ACOD part, making use of a Suzuki coupling. The required boronic acid was prepared from styrene **82** with a Sharpless asymmetric aminohydroxylation as a key step. The boronic acid function was introduced by the usual procedure ((i) bromination, **81a** → **81b**, (ii) Br → Li exchange, (iii) trapping of the organolithium intermediate with $B(OMe)_3$, and (iv) boronic ester hydrolysis). Success of the Suzuki coupling was strongly dependent on the reaction conditions. When a catalyst system was used that was developed by Paul and Hartwig[92] (a two-coordinate Pd(0) complex prepared from bis(dibenzylideneacetone)palladium and tris(*o*-tolyl)phosphane), **83a** and **84** were obtained as a 1:1.3 mixture in excellent yield (88%). Thermal isomerization at 120 °C led to a 3:1 equilibrium mixture in which the desired stereoisomer with *P*-configuration around the diaryl axis predominated. After separation, the minor isomer was again submitted to the thermal equilibration. The energy barrier for the equilibration of **83a** and **84** is 25.1 kcal/mol; thus, the equilibration could be achieved under conditions where the C−O−D configuration was stable. Deprotection of **83a** to give **83b** and macrolactamization (activation with EDCI/HOBt) furnished **85a**, from which the Boc protecting group was removed with formic acid (**85a** → **85b**, Scheme 12).

Scheme 15. D−O−E Diaryl Ether Formation in Boger's First-Generation Teicoplanin Synthesis



The building blocks **88**, **89**, and **102** of the E−F−O−G part were again prepared making use of the Sharpless asymmetric aminohydroxylation and Schöllkopf's bis(lactim ether) method (see Scheme 13). From **88** and **89** biaryl ether **100a** was obtained by a nucleophilic aromatic substitution (70% under optimized conditions). Reduction of the nitro group, followed by diazotation and treatment of the intermediate diazonium salt with Cu_2O/$Cu(NO_3)_2$, provided phenol **100b** in 80% (over three steps). Liberation of the amino group (**100** → **103**) followed by coupling of **103** with **102** (activation with PyBop[93]) provided **101** (86%). Two-step oxidation (first Dess−Martin and then $NaClO_2$ (Pinnick oxidation[94])) furnished carboxylic acid **105a** (81%). Following removal of the Teoc protecting group with TBAF[95] (**105a** → **105b**), macrolactamization was achieved in the presence of sodium hydrogen carbonate after activation of the carboxyl group with ByBop (**105b** → **106a**, 95% yield). After protecting group adjustment (**106a** → **106b**) the primary alcohol was oxidized ((i) Dess−Martin, (ii) $NaClO_2$) to yield carboxylic acid **106c**, thus completing the synthesis of the E−F−O−G part.

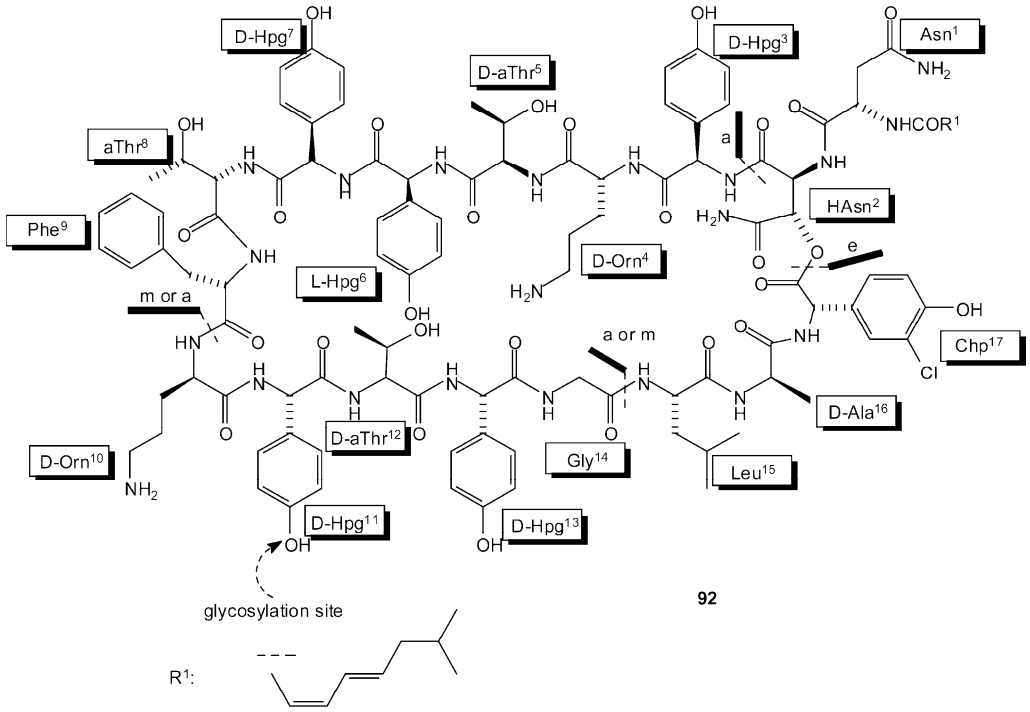


Figure 9. Aglycon of ramoplanin A2 and of ramoplanose and sites of assembly of subunits (a), ester formation (e), and macrolactamization (m).

For the coupling of **85b** with **106c** DEPBT (see formula **107** in Scheme 14), a reagent first introduced by Ye and co-workers,[96,97] was employed as activator. The reaction gave **108** in 72% yield, and no epimerization at the sensitive C-2^3 center (see the arrow in formula **108**) was observed. The critical diaryl ether formation (**108** → **109a**) occurred with unexpected ease (CsF, DMF, 10 °C, 76%) and with high stereoselectivity (>10:1), allowing abstention from the originally intended thermal equilibration (cf. also the Evans synthesis). Again, there was no (or little) epimerization at C-2^3 (see the arrow in **109**). NO_2 → Cl conversion by the usual three-step procedure (reduction, diazonium salt formation, substitution (**109a** → **109b**)) and conversion of the CH_2O(MEM) into a COOH function provided **109c**. Deprotection completed a remarkably well-organized synthesis of the teicoplanin aglycon **17** (Scheme 14). The total synthesis described here is the so-called second-generation total synthesis of the teicoplanin aglycon. In the first-generation synthesis the D−O−E diaryl ether was formed at the stage of **110**. Here the diastereoselectivity was lower (3:1 in favor of the desired (*P*)-diastereoisomer **111**, Scheme 15).

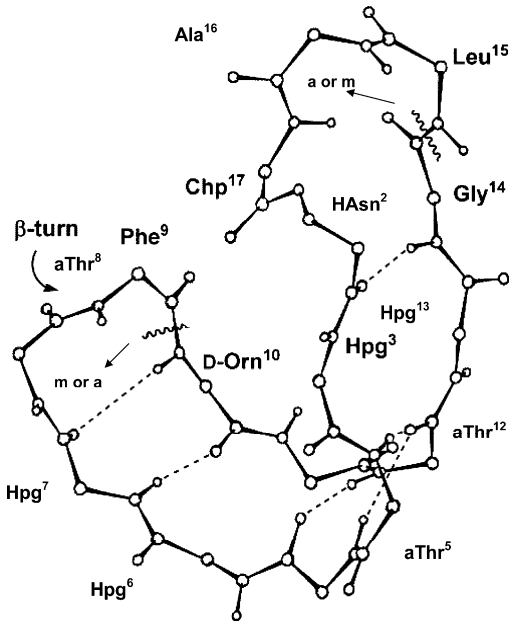
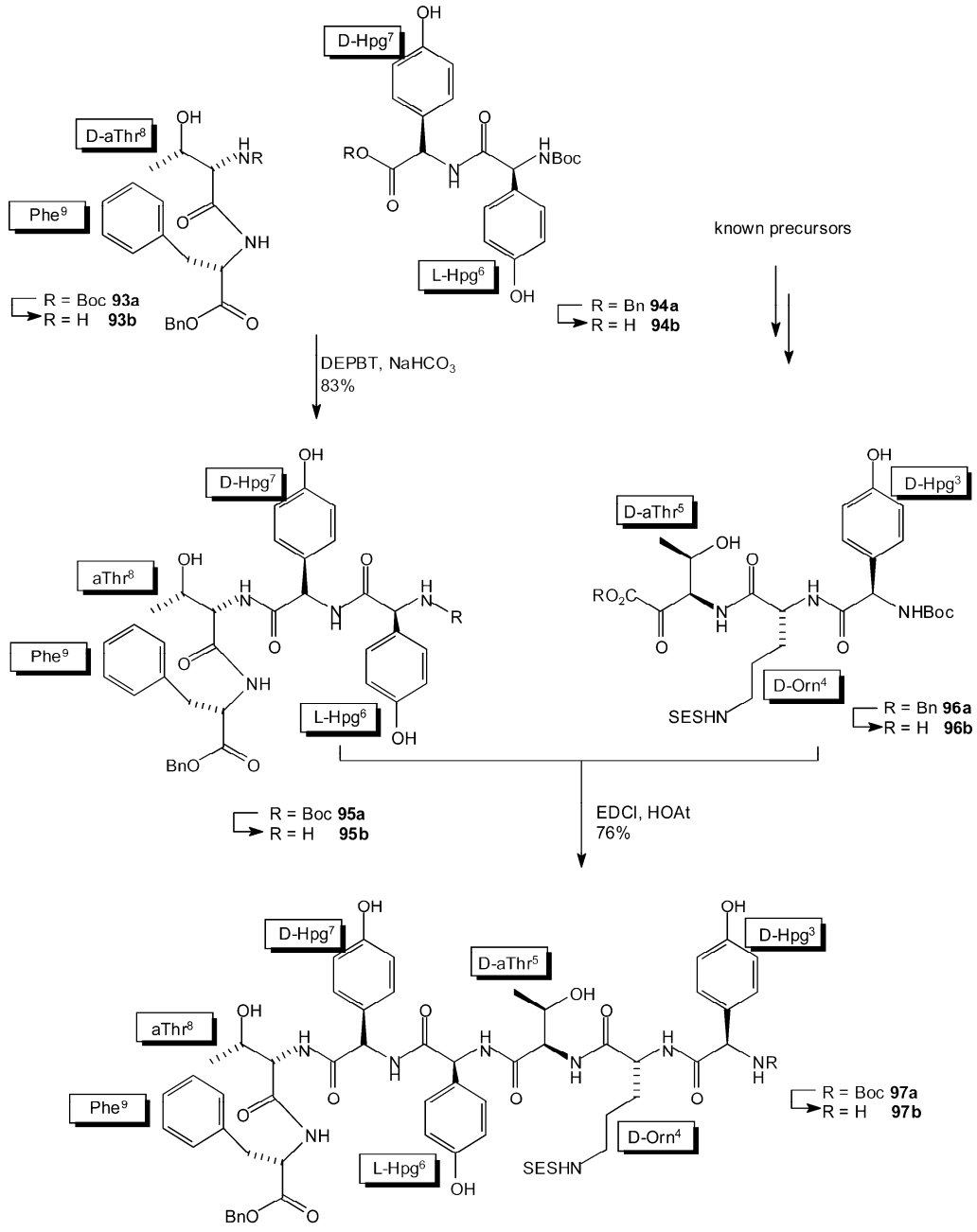


Figure 10. NMR structure of the ramoplanin A2 aglycon and possible sites of assembly of subunits (a) and of macrolactamization (m; compare Figure 9). Dotted lines represent hydrogen bonds. Adapted from ref 116.

3.6. Glycosylation of the Peptide Framework of the Glycopeptide Antibiotics

The chemical glycosylation of the vancomycin aglycon and analogues has been achieved making use of Kahne's sulfoxide glycosylation procedure[98−100] and of Schmidt's trichloroacetimidate method in conjunction with a glycosyl fluoride donor for disaccharide formation.[50,101] Glycopeptide glycosyltransferases have been shown to catalyze the glycosylation of aglycon substrates.[100,102,103] A systematic study of the substrate specificity of a subgroup that transfers 2-deoxy-L-sugars from their nucleotide diphosphate donor derivatives to natural aglycons was recently performed by Kahne and co-workers.[104] Knowledge of the biosynthetic gene clusters of both the vancomycin- and teicoplanin-type antibiotics has been exploited to carry out combinatorial glycosylations.[105−108] As early as in 1991 the microbial demannosylation and mannosylation of teicoplanin derivatives by cultures of *Nocardia orientalis* NRRL 2450 or *Streptomyces candidus* NRRL 3218 were reported.[109]

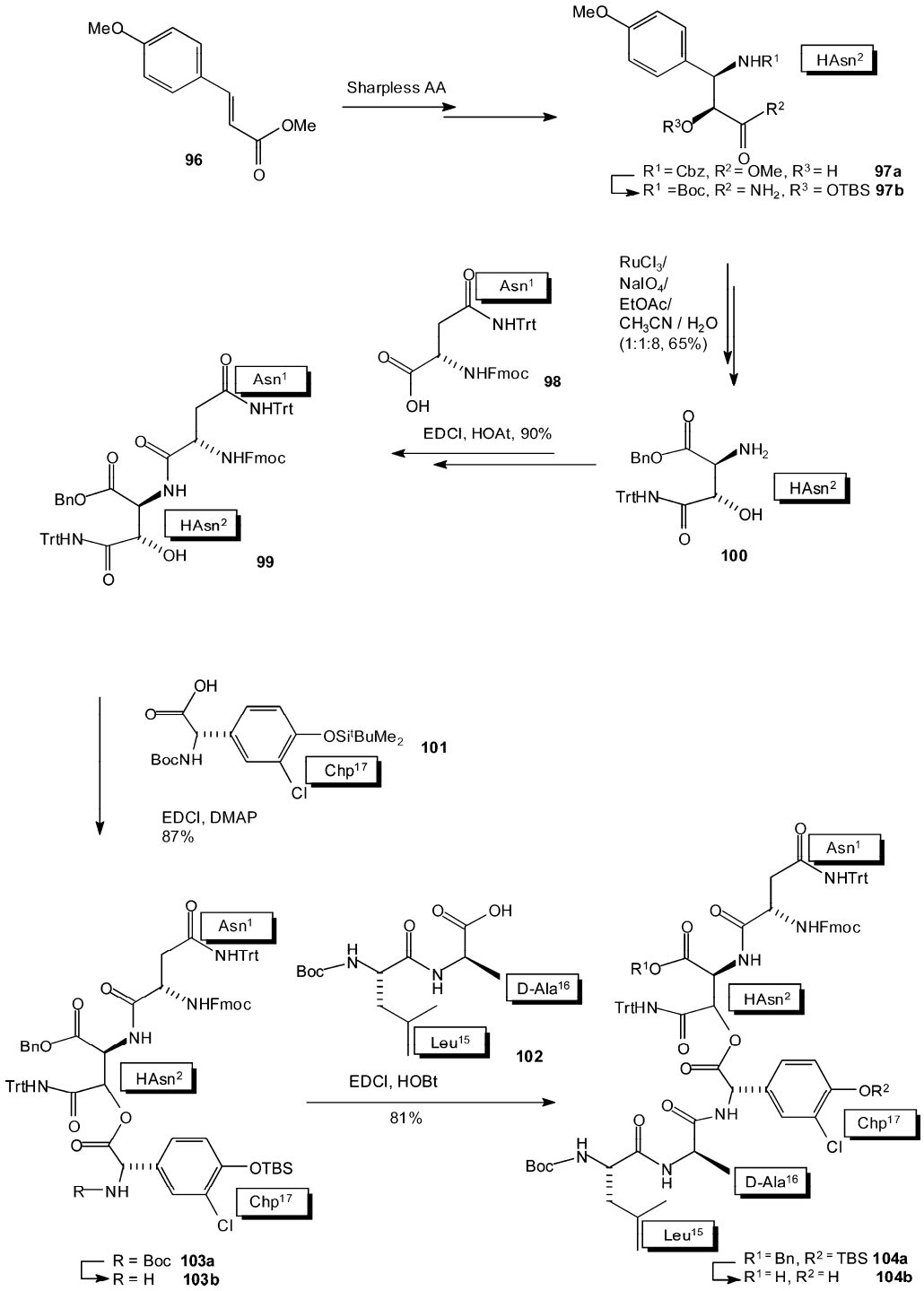
Scheme 16. Synthesis of the Ramoplanin A2 (and Ramoplanose) Aglycon: Synthesis of 97b (Heptapeptide 3−9)



4. Ramoplanin

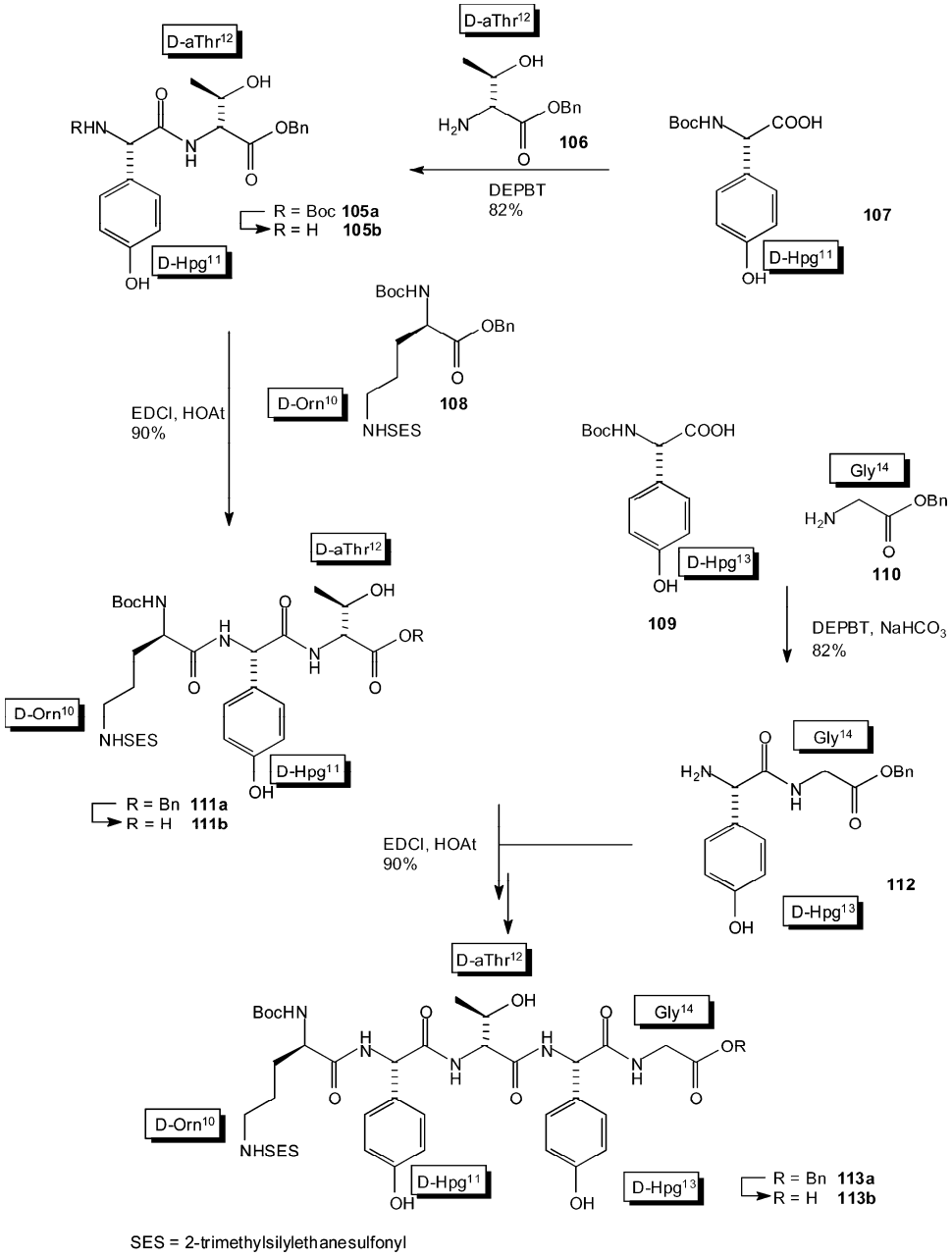
The cyclic lipoglycodepsipeptide antibiotic ramoplanin A2 (the structure of the aglycon is shown in Figure 9) is emerging as a promising clinical candidate for treatment of Gram-positive bacterial infections, particularly those of vancomycin-resistant *Enterococcus faecium* (phase III clinical trials) and methicillin-resistant *Staph. aureus* (phase II clinical trials). It is a member of a family of compounds isolated from the culture broths of *Actinoplanes* strains (actinomycetes).[110] Sahl and co-workers provided the first evidence that the antibiotic activity of ramoplanin is based on its interaction with lipid intermediates of peptidoglycan biosynthesis,[111] thus occluding these substrates from proper utilization by the enzyme that catalyzes the formation of lipid II from lipid I at the inner face of the cyctoplasmic membrane (MurG)[112] and/or by the transglycosylases. Although the mode of action of ramoplanin A2 is not yet completely understood, recent results provided by Walker and co-workers indicate that complexation of ramoplanin with lipid II at the extracellular face of the cytoplamic membrane is responsible for the in vivo antimicrobial effect.[113−115] All members of the ramoplanin family contain a common 49-membered ring depsipeptide skeleton composed of 17 amino acids in which the C-terminal (*S*)-3-chloro-4-hydroxyphenylglycine forms a lactone bond with the hydroxyl group of (2*S*,3*S*)-3-hydroxyasparagine[2]. [Italic superscripts indicate the ramoplanin building blocks.] The

Scheme 17. Synthesis of the Ramoplanin A2 (and Ramoplanose) Aglycon: Synthesis of 104b (Pentadepsipeptide 1, 2, and 15−17)



phenolic OH group at (*S*)-4-hydroxyphenylglycine[11] carries usually a dimannosyl group (there are members of the group with three mannosyl units (ramoplanose) and one mannosyl residue). To the (*S*)-Asn[1] amino group are attached acyl residues derived from C_8, C_9, and C_{10} fatty acids.[110] In the case of ramoplanin A2 (and ramoplanose) it is a doubly unsaturated branched C_9 acid. Of special interest is the presence of β-hydroxylated amino acids and of 4-hydroxyphenylglycine constituents both of the (2*R*)- and the (2*S*)-series.[110] The three-dimensional structure of ramoplanin A2 (in 4:1 H_2O/DMSO-d_6) was determined NMR-spectroscopically by Kurz and Guba.[116,117] The structure (Figure 10) is characterized by two antiparallel β-strands which are formed by residues 2−7 and 10−14. The β-strands are connected by six intramolecular hydrogen bonds and a reverse β-turn which is formed by Thr[8] and Phe[9]. Residues 2 and 14 are connected by a loop consisting of L-Leu[15], D-Ala[16], L-Chp[17], and the side chain of HAsn[2]. The conformation is stabilized by a hydrophobic cluster of aromatic side chains of residues 3, 9, and 17. The overall topology of the β-sheet is U-shaped with the β-turn at one end and the loop at the other end. From NMR titrations (also in DMSO/water mixtures) of ramoplanin A2 with lipid I model

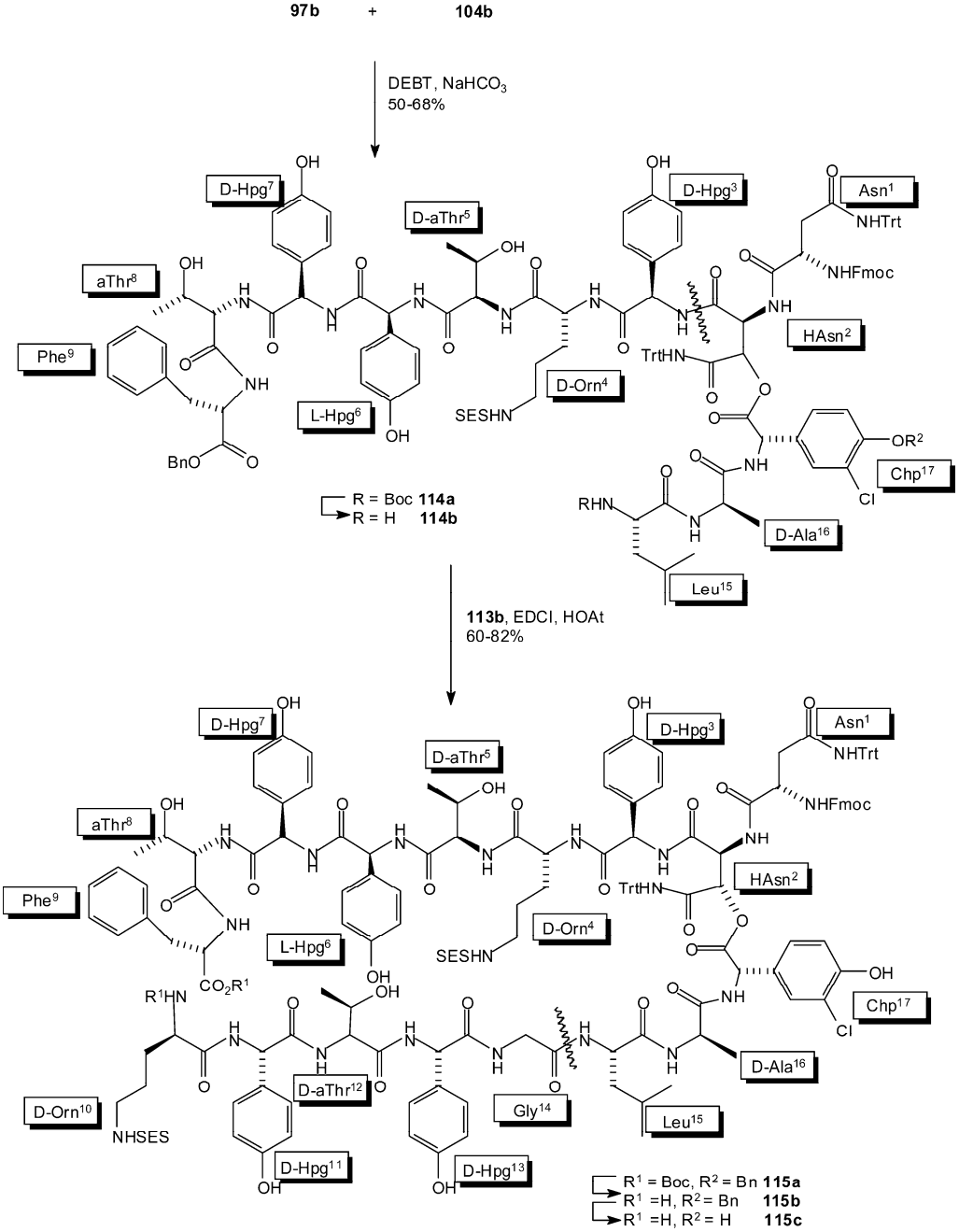
Scheme 18. Synthesis of the Ramoplanin A2 (and Ramoplanose) Aglycon: Synthesis of 113b (Subunit 10−14)



compounds, Cudic et al. concluded that the ramoplanin octapeptide D-Hpg[3]-D-Orn[4]-D-alloThre[5]-L-Hpg[6]-D-Hpg[7]-L-alloThr[8]-L-Phe[9]-D-Orn[10] recognizes the MurNAc-Ala-γ-D-Glu pyrophosphate part of peptidoglycan precursors, i.e., a binding motif that is different from that targeted by vancomycin.[115,118] The Walker group showed that ramoplanin forms a 2:1 complex with lipid II which is assumed to shield lipid II from approaching the transglycosylase.[114] It was shown that the (*R*)-Orn[4] amino group can be modified without eliminating substrate binding or biological activity whereas acylation of (*R*)-Orn[10] greatly reduces substrate binding and biological activity.[119] From their results Walker and co-workers concluded that on dimerization a cleft is formed flanked by (*R*)-Orn[10] which serves as the binding site for the lipid II binding epitope.[113] Recent results demonstrate, however, that antibiotic activity of ramoplanin A2 does not solely originate from lipid II binding (vide infra).

In their solution-phase total synthesis of the ramoplanin A2, Boger and co-workers[120] assembled the ramoplanin A2 and the identical ramoplanose aglycon from three key subunits containing (i) heptapeptide 3−9, (ii) pentadepsipeptide 1, 2, and 15−17, and (iii) pentapeptide 10−14 (Figure 9). For the unparalleled formation of the 49-membered ring, two options were considered: (i) macrolactamization at (*S*)-Phe[9]-(*R*)-Orn[10], i.e., at the corner of the β-turn profiting both from closure at an (*R*)-amino acid terminus which was shown previously to support cyclic peptide formation[121,122] and from β-sheet preorganization, and (ii) macrolactamization at Gly[14]-(*S*)-Leu[15] because in this case razemization-free carboxylic acid activation is possible (see Figures 9 and 10).

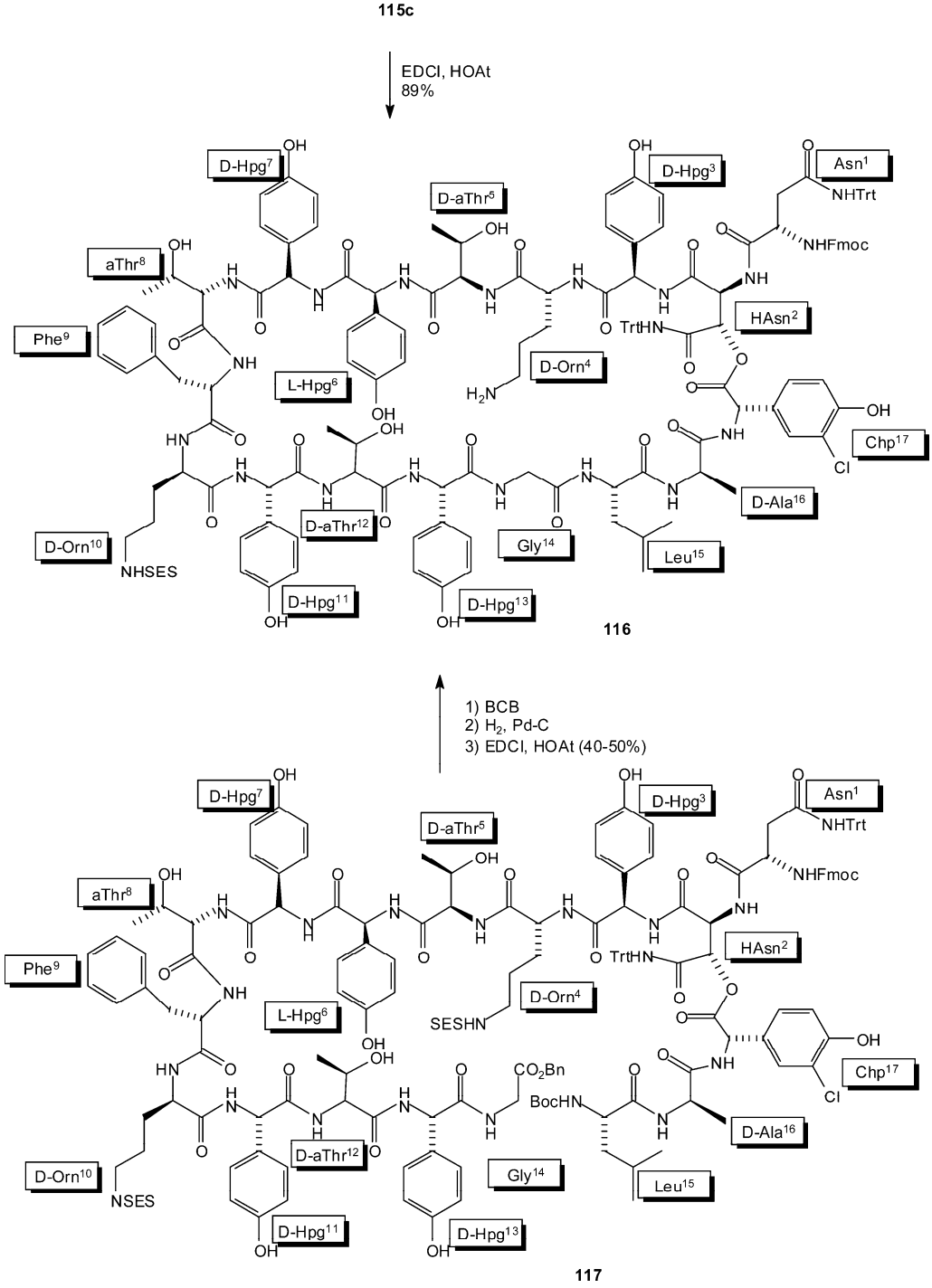
Scheme 19. Synthesis of the Ramoplanin A2 (and Ramoplanose) Aglycon: Assembly of the Three Subunits 97b, 104b, and 113b



Noteworthy is the use of the 2-trimethylsilylethanesulfonyl (SES) protecting group[123,124] for the ornithine residues. Heptapeptide **97** was assembled from precursors **93b**, **94b**, and **96b** (Scheme 16). **93a** and **94a** were prepared from known precursors. Deprotection of **93a** (HCl/EtOAc) gave **93b**, and the free carboxylic acid group in **94b** was released from benzyl ester **94a** by hydrogenolysis. The coupling of **93b** with **94b** was achieved after activation of the latter with DEPBT (see formula **107** in Scheme 14). Both the conversion **94a** → **94b** (hydrogenolysis) and the racemization-free peptide formation between the sensitive (*R*)-4-hydroxyphenylglycine[7] moiety **94b** and the (2*S*,3*S*)-3-hydroxyasparagine[8] residue **93b** (activation of **94b** with DEPBT) could be achieved only under the carefully selected conditions described above that avoided racemization at the sensitive residue 7 as well as β-elimination in residue 8.

Scheme 17 summarizes the synthesis of pentadepsipeptide 1, 2, and 15−17 (**104b**). Key steps of the formation of (2*S*,3*S*)-3-hydroxyasparagine[2] building block **99**[125] were an asymmetric aminohydroxylation of **96** and an oxidative degradation of the anisole ring at the stage of **97b** with in situ generated RuO_4 to give a carboxylic acid function.[126] Protecting group adjustment followed by amide formation with **98** (EDCI, HOAt, 90%) furnished **99**. The next step, ester formation between the hindered alcohol in **99** with **101**, failed under many established conditions and could be achieved only by EDCI activation in the presence of Steglich's base[127] to give **103a** in 87% yield. Epimerization at the sensitive C-2 center of the

Scheme 20. Synthesis of the Ramoplanin A2 (and Ramoplanose) Aglycon: Macrolactamization



arylglycine unit occurred only to a minor extent (dr = 87:8). Removal of the Boc protecting group with *B*-bromocatecholborane[128] (**103a** → **103b**) and coupling with **102** provided **104a**. TBS removal and benzyl ester hydrogenolysis (note the orthogonal set of protecting groups in these steps) yielded the desired depsipeptide **104b**.

The synthesis of pentapeptide **113** (Orn^{10}−Gly^{14}) highlights again how meticulously protecting groups and coupling reagents were selected to avoid β-elimination at β-hydroxylated amino acid 12 and stereoisomerization at C-2 of the arylglycine units (Scheme 18). **106** and **107** were coupled (activation with DEPBT) to give **105a**. NHBoc deprotection and coupling with the D-Orn^{10} building block **108** provided tripeptide **111a**. Dipeptide **112a** was obtained from **109** and **110**, again with DEPBT as coupling reagent. Finally, hydrogenolytic debenzylation of **111a**, Boc removal from **112a** (HCl/EtOAc), and coupling of **111b** with **112b** furnished tetrapeptide **113a**.

The assembly of the three subunits is summarized in Scheme 19. Amide formation to furnish **114a** by carboxylic acid activation at unit 2 of **104b** and reaction with **97b** was plagued by β-elimination (acyloxy leaving group). Of the reagents tested only DEPBT allowed achievement of the desired reaction, giving **114a** in 50−68% yield. Boc removal with *B*-bromocatecholborane (**114a** → **114b**) and coupling

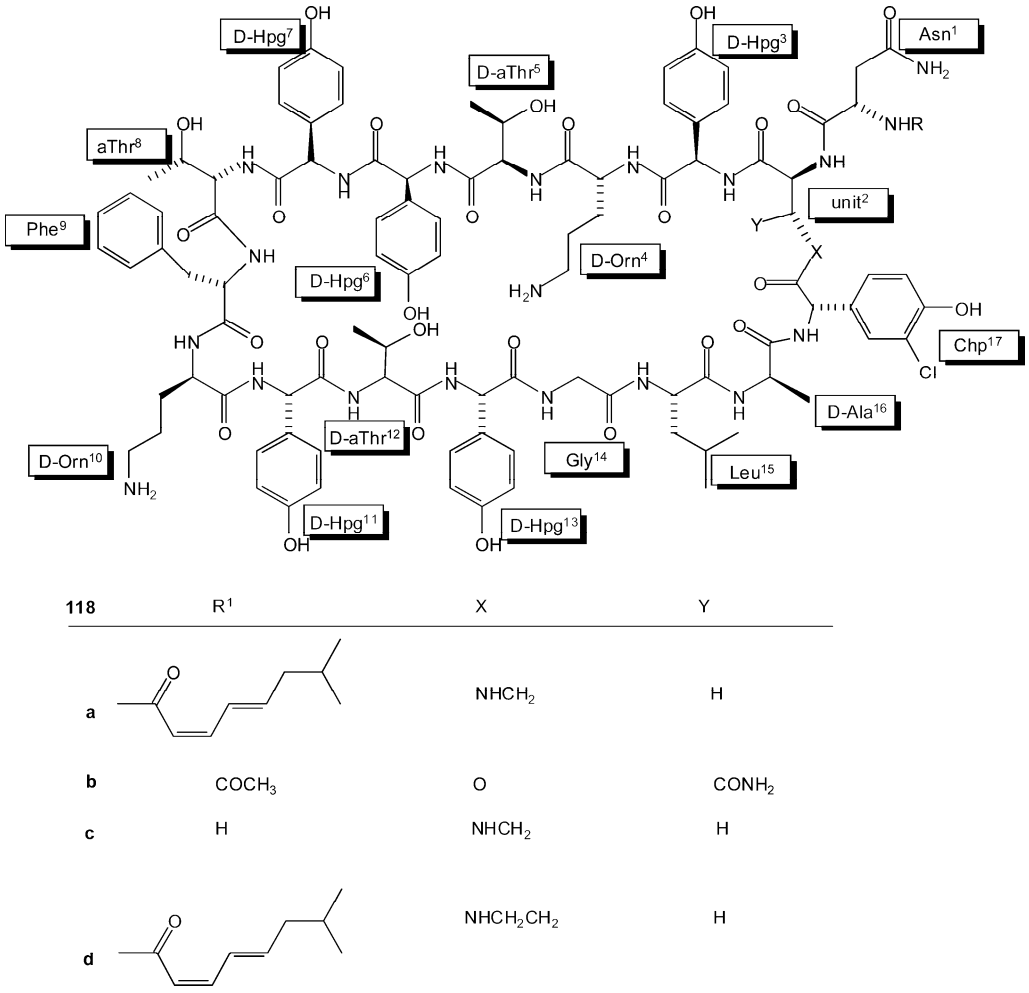


Figure 11. Ramoplanin analogues.

with **113b** (EDCI, HOAt) provided the *seco*-ramoplanin precursor **115a**. Liberation of the amino group at unit 10 (with *B*-bromocatecholborane, **115a** → **115b**) and the carboxylic acid function at unit 9 (by hydrogenolysis, **115b** → **115c**) followed by macrolactamization (EDCI, HOAt) closed the 49-membered ring (**115c** → **116**, Scheme 20). The marvelous yield of 89% is attributed to the factors that are discussed above.

The same compound was obtained, when the macrocycle was closed at Gly[14]-Leu[15] (Scheme 20). Boc deprotection at unit 15 of **117** with *B*-bromocatecholborane and release of the free carboxylic acid function of unit 14 by hydrogenolysis, followed by macrolactamization (EDCI, HOAt), also worked quite well (although possibly not as facile as in the **115c** → **116** cyclization) and provided **116**.

For completion of the total synthesis the side chain fatty acid had to be introduced and the protecting groups had to be removed. Although the protecting groups were chosen as being orthogonal, deprotection was far from trivial. Conventional Fmoc removal was impossible because of the sensitive depsipeptide ester. Finally, it was found that **116** on treatment with Bu_4NF and $^{i}PrOH$ in DMF lost the Fmoc protecting group in good yield (90%). Reaction of the free amine with the anhydride of the doubly unsaturated fatty acid served to form the desired amide. The removal of the remaining SES and trityl protecting occurred without incident to furnish the ramoplanin A2 and ramoplanose aglycon **92** in more than 80% yield.

Ramoplanin A2 and its aglycon show comparable antimicrobial activity against *Staph. aureus*, whereas other compounds obtained en route to **92** show greatly reduced activity.

The Boger approach has been used to prepare analogues **118a**−**118d** (Figure 11).[129,130] Interestingly, all compounds bind to lipid II with about the same affinity as ramoplanin A2 and with the same 2:1 inhibitor:lipid II stoichiometry, but only compound **118a** is antibiotically as active as ramoplanin A2 against a number of Gram-positive bacteria. This shows that lipid II binding and antibiotic activity are not straightforwardly connected. The reduced activity of **118d** may (in part) be due to its high tendency to aggregate in solution.[131]

5. Nisin

The lantibiotics (lantionin-containing antibiotics) are a group of ribosomally synthesized antimicrobial peptides containing didehydroamino acids and the rare thioether amino acids lantionine (Ala−S−Ala) and/or 3-methyllanthionine, which are generated via post-translational modification, i.e., dehydration of Ser and Thr residues, yielding the α,β-unsaturated amino acids 2,3-didehydroalanine and 2,3-didehy-

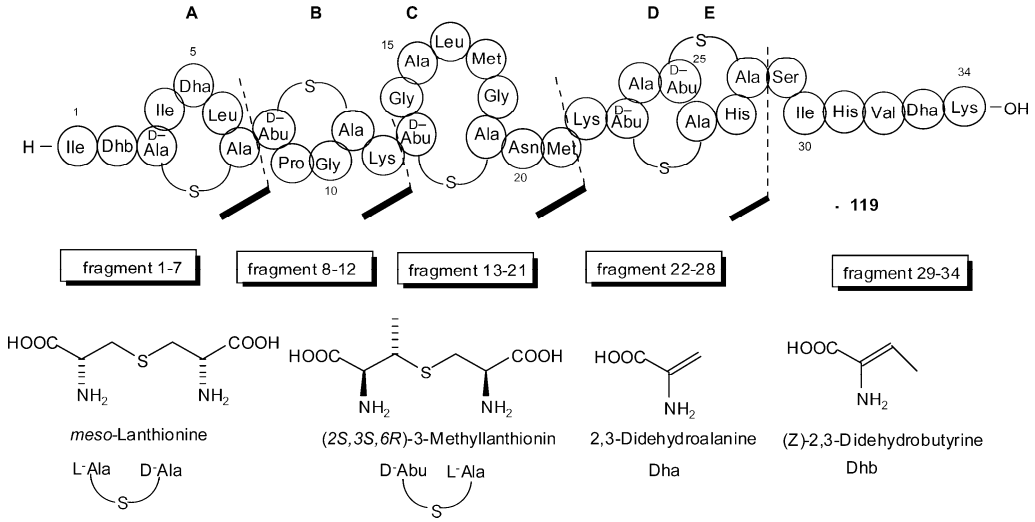


Figure 12. Structures of nisin (**119**) and some of its constitutents. A–D denote the different ring systems. From the five fragments shown nisin was assembled in the Shiba–Wakamiya total synthesis.

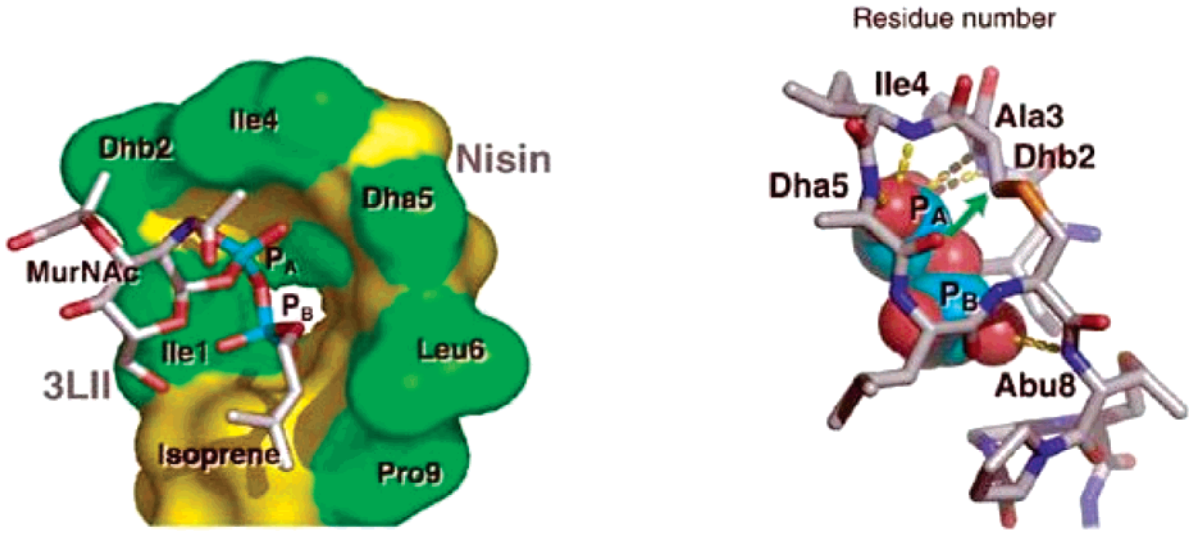


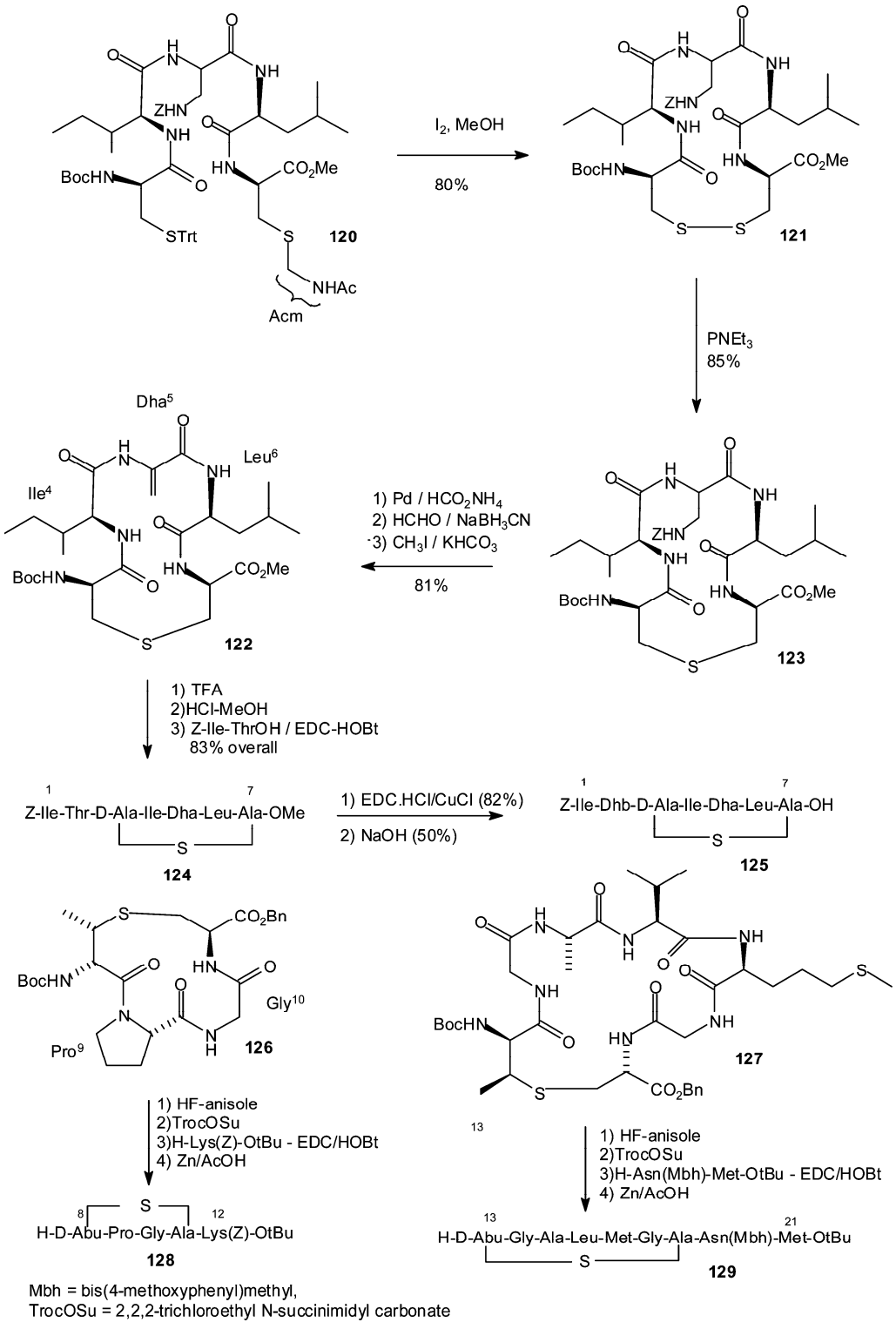
Figure 13. Left: N-terminal part of nisin encaging the pyrophosphate moiety of the lipid II analogue. Right: Hydrogen-bonding network of the lipid II analogue and nisin. Reprinted with permission from *Nat. Struct. Mol. Biol.* (http://www.nature.com), ref 138. Copyright 2004 Nature Publishing Group.

drobutyrine, respectively, and intramolecular Michael additions with neighboring Cys residues to furnish the sulfide bridges (see Figure 12).[132,133] On the basis of structural differences and different modes of action, lantibiotics have been grouped by Jung into two major classes.[134] Type A lantibiotics are flexible elongated amphipathic peptides with a net positive charge. They act by a process that gives rise to the formation of pores. The permeabilization of the cytoplasmic membrane causes immediate cell death. In contrast, type B lantibiotics have a rigid globular shape and either no net charge or a net negative charge. For mersacidin and actagardine it was shown that they form a tight complex with lipid II and interfere with cell wall biosynthesis at the level of transglycosylation.[135]

The most prominent member of the group A lantibiotics is nisin (produced by *Lactococcus lactis*), which has been widely used as a food preservative without inducing substantial bacterial resistance. Nisin is a pentacyclic peptide composed of 34 amino acids including a single lanthionine residue and four 3-methyllanthionine, three didehydroalanine, and two didehydrobutyrine residues (see Figure 12). There are two naturally occurring forms of nisin, nisin A and nisin Z, differing only in one residue (His or Asn at position 27).[136]

The process of pore formation has been studied in great detail and was demonstrated to commence with the formation of a 1:1 complex between nisin and lipid II.[133,137] After anchoring of nisin to lipid II conformational changes take place, leading to the assembly of a higher order oligomeric complex. The solution structure of the 1:1 complex of nisin with a lipid II analogue with a shortened isoprene chain (three isoprene units, prepared by the Breukink approach described above) has recently been determined using high-resolution NMR spectroscopy and has revealed a novel lipid II binding motif in which the diphosphate of the lipid II analogue is primarily coordinated by the N-terminal backbone amides of nisin (rings A–C) via five intermolecular hydrogen bonds (see Figure 13).[138]

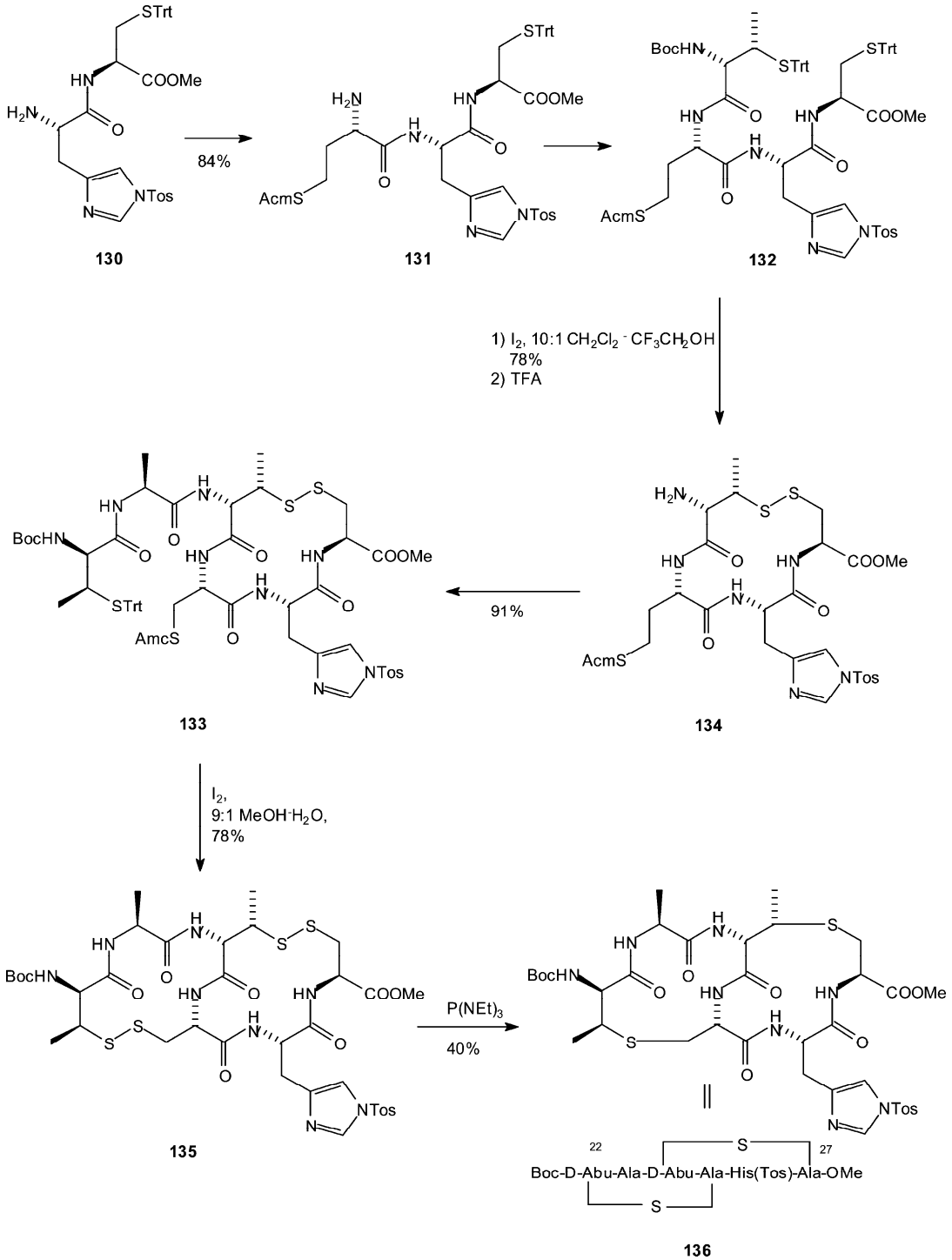
Scheme 21. Total Synthesis of Nisin: Synthesis of 125 (Fragment 1−7 with Ring A), of 128 (Fragment 8−12 with Ring B), and of 129 (Fragment 13-21 with Ring C)



Nisin is the only lantibiotic a total synthesis has been described for. The antibiotic was assembled by Shiba and Wakamiya and their co-workers from the five fragments indicated in Figure 12.[139] The most interesting feature of the formidable synthesis is the formation of the different ring systems (A−E).

The synthesis of fragment 1−7 (containing ring A) is summarized in Scheme 21.[140] The protected tetrapeptide **120** was prepared starting from the C-terminus (activation with DCC/NHS). Disulfide formation directly from the trityl- and acetamidomethyl-protected cysteine residues (**120** → **121**) was achieved by oxidation with iodine in methanolic solution, making use of a method developed by Kamber et al.[141] Sulfur extrusion from disulfide **121** to furnish sulfide **123** was accomplished with $P(NEt_2)_3$ in DMF solution.[142,143] Catalytic transfer hydrogenation removed the Z protecting group, and the free amine was monomethylated by reductive methylation with formaldehyde/$NaBH_3CN$. Subsequent treatment with ex-

Scheme 22. Total Synthesis of Nisin: Synthesis of 136 (Fragment 22−27 Containing Rings D and E)

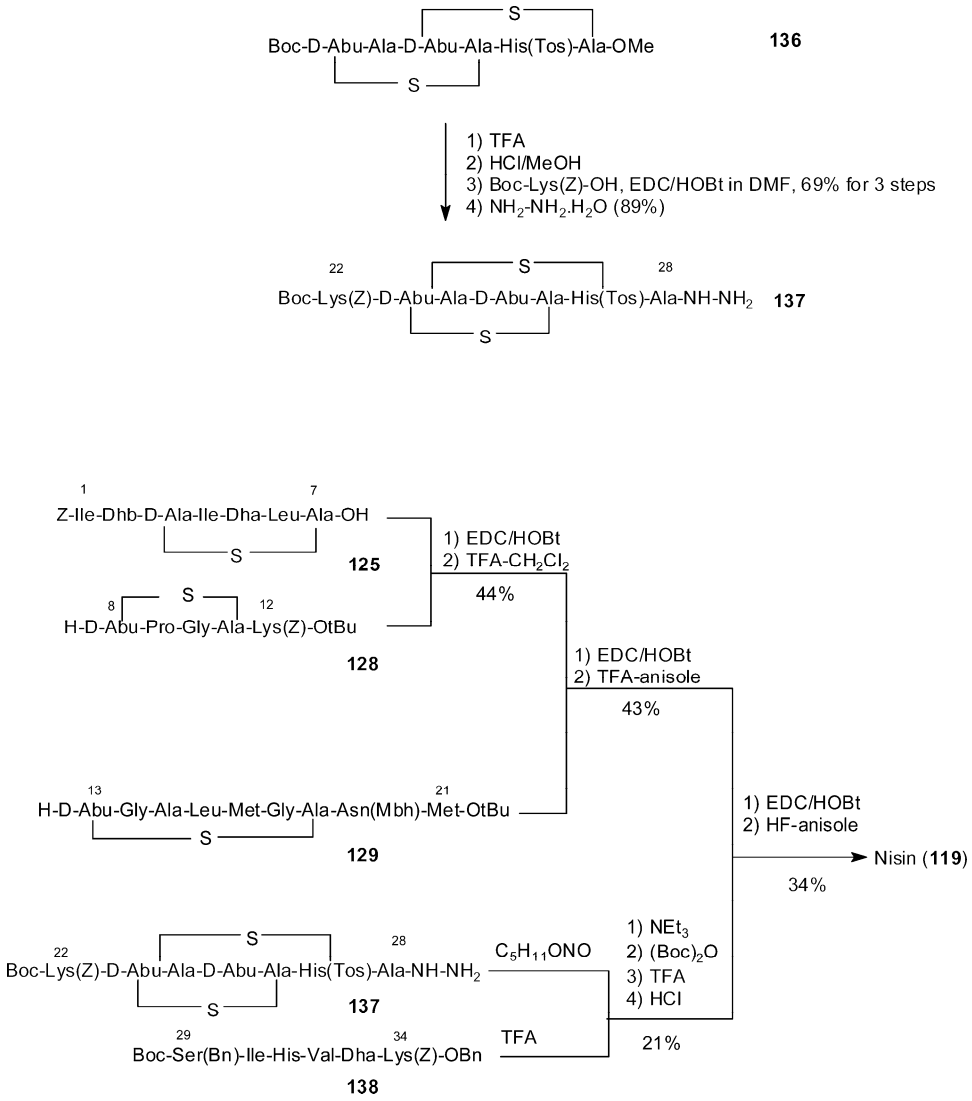


cess CH_3I in the presence of $KHCO_3$ gave the desired Hofmann elimination product **122**. Boc removal and coupling with Z-Ile-ThrOH furnished **124**. The subsequent dehydration (in the Thr unit) to give the desired (*Z*)-diastereoisomer of the didehydrobutyrine component in good yield was best accomplished with EDC·HCl/CuCl.[144] Finally, the methyl ester was cleaved to arrive at fragment **125**. The synthesis of fragment 8−12 (containing ring B) is also found in Scheme 21.[145] The synthesis proceeded along the lines just described. Most importantly, in the desulfurization reaction leading to **126**, the configuration at C-3 of the 3-methylcysteine unit was retained, meaning that in the disulfide precursor the phosphane attack occurred at the sulfur remote from the methyl branch. Protecting group adjustment followed by coupling with Z- and *tert*-butyl-protected lysine and subsequent reductive Troc removal furnished building block 8−12 (**128**). Similarily, **129** (fragment 13−21, containing ring C) was assembled (Scheme 21).[146] Note that for the asparagine residue the bis(4-methoxyphenyl)methyl protecting group was used to prevent dehydration and imide formation.[147]

The synthesis of **136** (fragment 22−27 with rings D and E) is summarized in Scheme 22.[148]

For protection of the thiol groups trityl and acetamidomethyl groups were chosen for reasons discussed below. The amino and carboxyl groups were

Scheme 23. Total Synthesis of Nisin: Synthesis of 137 (Fragment 22−28) and Fragment Condensation



protected with Boc and as a methyl ester, respectively. The histidine imidazole ring was protected with a tosyl group. The linear precursor peptide **132** was prepared successively from the C-terminal by *N*-hydroxysuccinimide (peptides **130** and **131**), DCC (peptide **132**), or symmetrical anhydride activation (coupling of the Ala residue to **134**). In the further peptide coupling steps activation with benzotriazol-1-yl diethyl phosphate (BDP)[149] was employed to overcome very low reaction rates resulting from the steric influence of a cyclic sulfide or disulfide. From the work of Kamber[141] it is known that *S*-trityl oxidation with I_2 occurs faster than *S*-acetamidomethyl oxidation. Thus, treatment of **132** with I_2 under carefully optimized conditions (in 10:1 CH_2Cl_2/CF_3CH_2OH) furnished the cyclic disulfide **134** in 78% yield without touching the acetamidomethyl-protected cysteine residue. **134** was then elongated to hexapeptide **133**. Oxidation with I_2, again under optimized conditions (9:1 MeOH/H_2O), gave the desired bisdisulfide **135**. On treatment with $P(NEt_2)_3$ in benzene solution both disulfide groups were desulfurized to give **136** in 40% yield. The linear hexapeptide fragment 29−34 (**138**) was prepared starting from the C-terminus using standard solution peptide chemistry (Scheme 23). The didehydroalanine moiety was again formed by Hofmann elimination as described for ring A at the dipeptide stage. In this case elimination was performed in a one-pot reaction, treating the free primary 3-amino group with excess CH_3I in the presence of $KHCO_3$.

The end game of the synthesis consisted of coupling of the building blocks as summarized in Scheme 23. With one exception activation was performed with EDC/HOBt in DMF. Coupling of **137** (fragment 22−28, prepared from **136** as summarized in Scheme 23, top) with **138** (fragment 29−34) made use of the azide method. It is worth mentioning that the didehydroamino acids were stable under the acidic deprotection conditions (TFA in different solvents, HF/anisole). The synthetic nisin was in all respects identical with the natural product, confirming the proposed structure.[150]

Recently, the synthesis of a crossed alkene-bridged mimic of the nisin Z DE ring system by ring-closing alkene metathesis[151] and a ring-closing alkyne metathesis approach toward the synthesis of alkyne micics of the A, B, C, and DE ring systems of nisin Z have been reported from Liskamp's laboratory.[152]

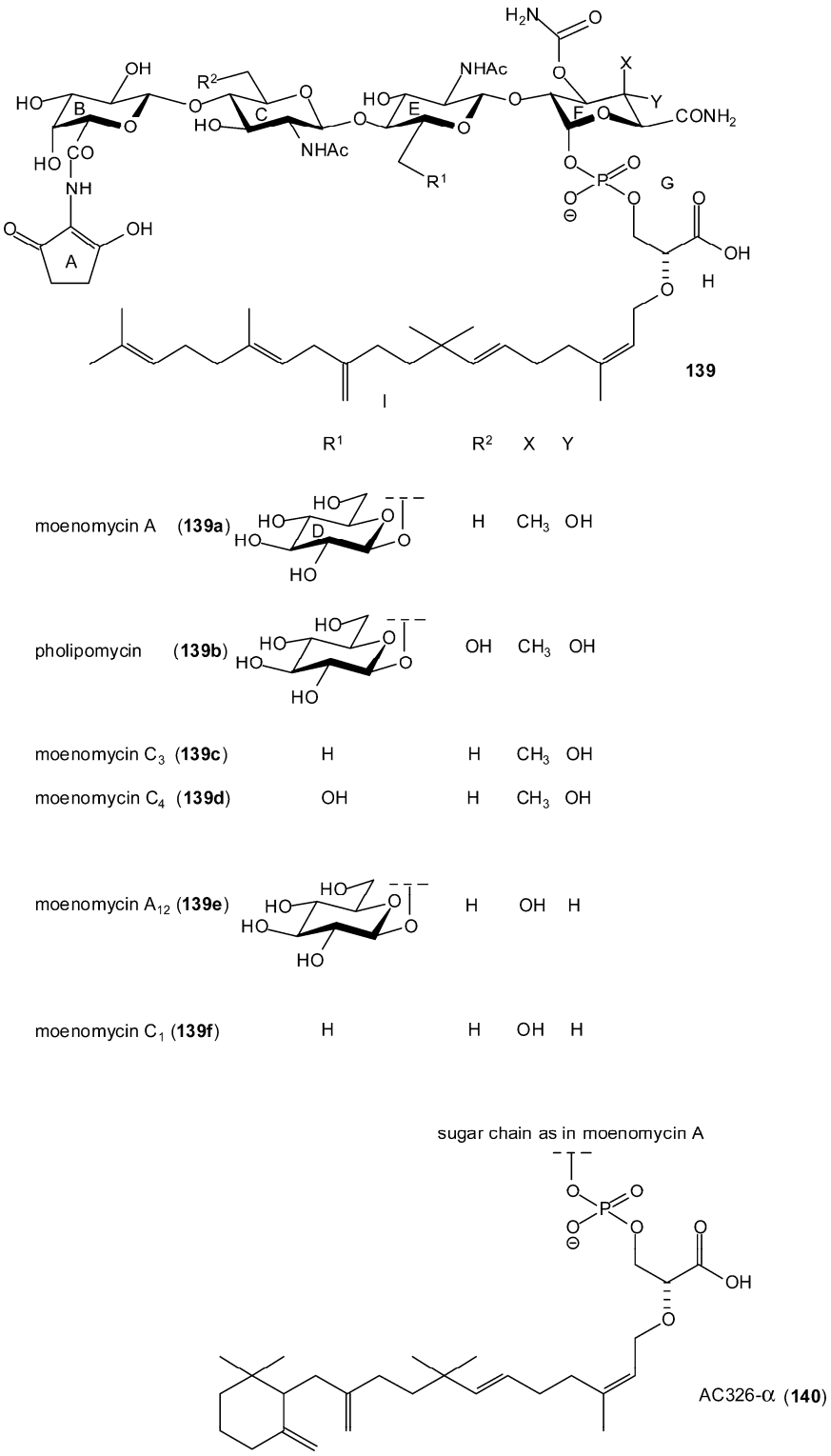


Figure 14. Structures of the moenomycin antibiotics.

6. Moenomycins

6.1. Structures and Mode of Action

The family of the moenomycin-type antibiotics includes the components of the flavomycin complex (from *Streptomyces ghanaensis*), the prasinomycins, the diumycins (macarbomycins), 11837 RP, 8036 RP (quebemecin), 19402 RP, ensanchomycin, prenomycin, teichomycin, pholipomycin, and AC326-α.[153] All of them seem to contain an oligosaccharide part, a phosphoric acid diester group, and a C_{25} lipid unit which may be either moenocinol (unit I in **139**) or diumycinol, an isomer of moenocinol with one six-membered ring (see unit I in **140**). In some of these antibiotics a so-called chromophore moiety (unit A in **139**) is present which is lacking in others which may contain glycine instead.[154] Until now the full structures of moenomycin A,[155−158] pholipomycin,[159] moenomycins C_3,[158,159] C_4,[158,159] A_{12},[158,160] and C_1,[158,161]

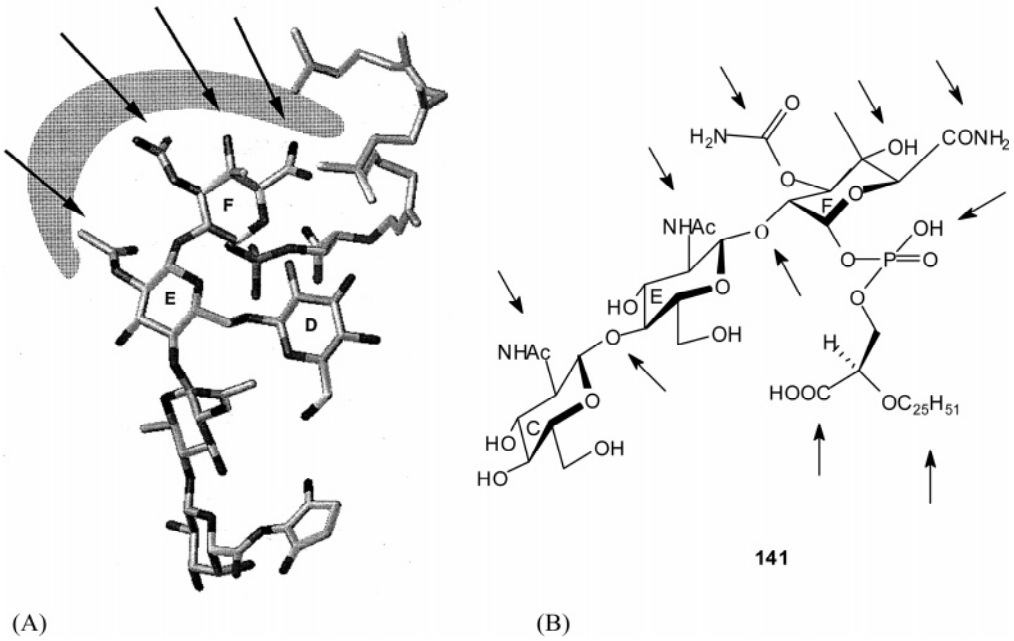
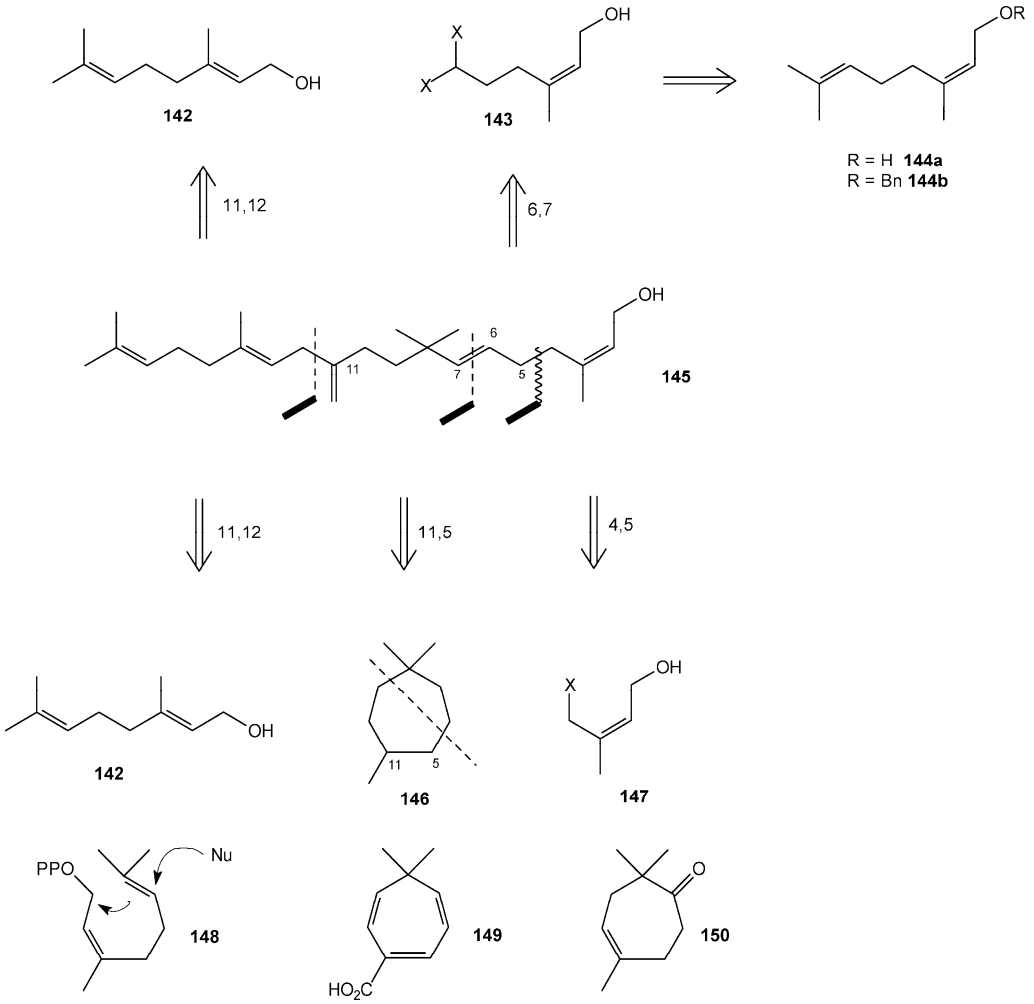


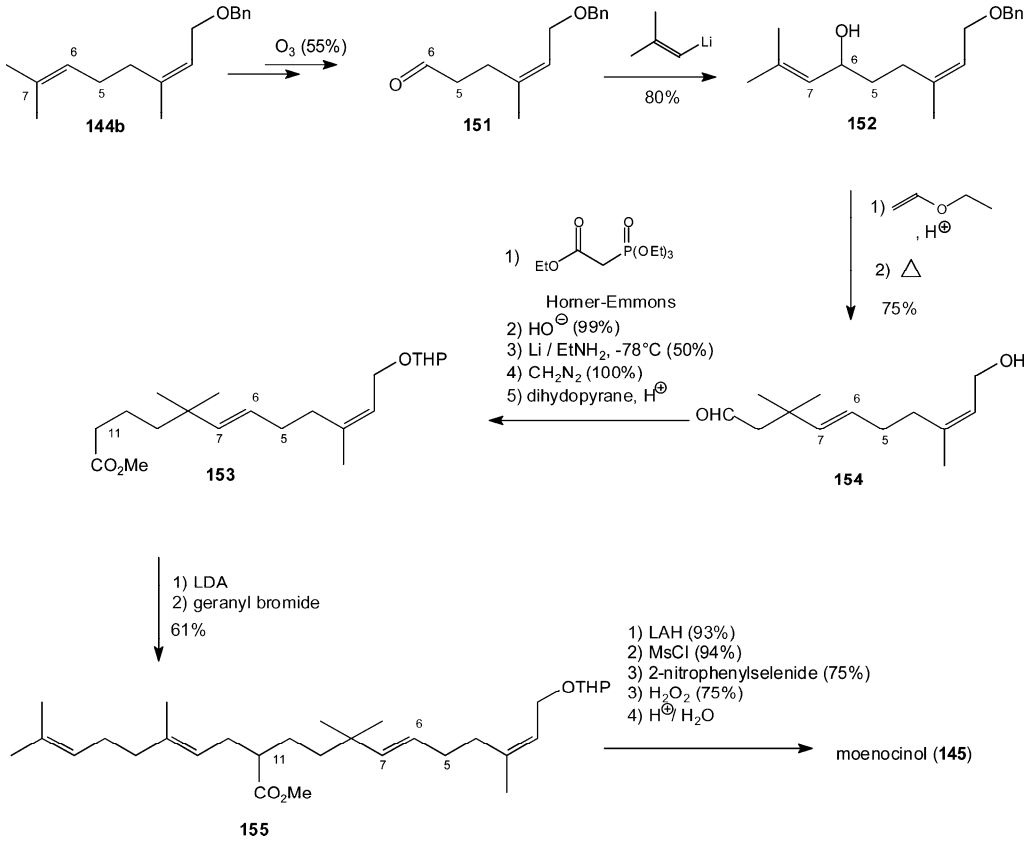
Figure 15. (A) NMR structure of moenomycin A. Reprinted with permission from ref 157. Copyright 1998 Blackwell. (B) Structure−activity relationships (arrows in **141** show essential functional groups for antibiotic activity; many of these groups point to one side of the molecule in the NMR structure (see arrows in (A))).

Scheme 24. Moenocinol Retrosynthetic Analysis

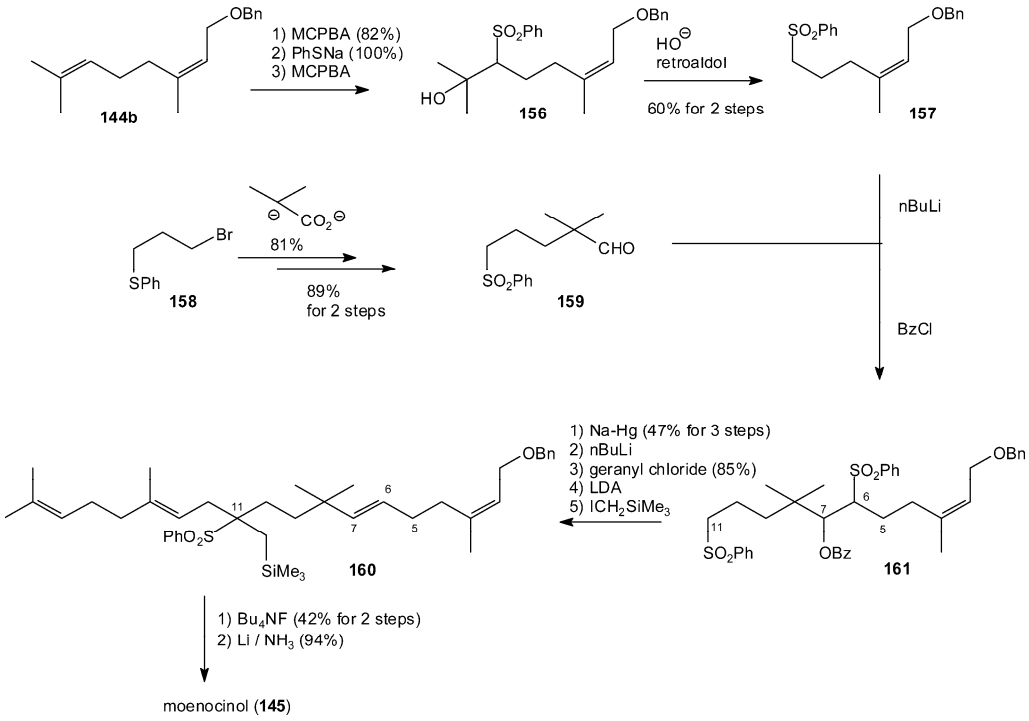


and AC326-α[162] have been determined (Figure 14). They may be divided into two groups depending on whether the uromamide unit F has D-*galacto* or D-*gluco* configuration. In the latter case there is an axial methyl group in the 4^F-position which originates from methionine.[163]

Scheme 25. Grieco Moenocinol Synthesis

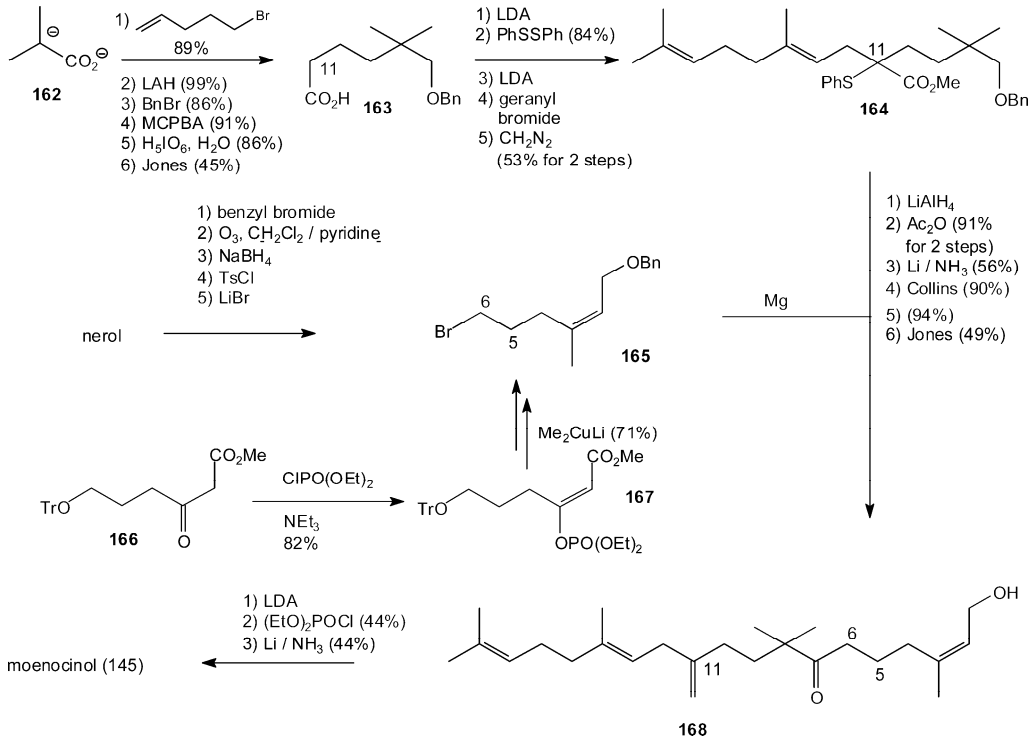


Scheme 26. Kocienski Moenocinol Synthesis



The moenomycins are known to interfere with the transglycosylation reaction. They are the only compounds known to date that exert their activity not by binding to a substrate of the transglycosylase such as nisin or ramoplanin. The moenomycins rather inhibit the transglycosylase by interacting with the enzyme (*E. coli* PBP1b) reversibly.[3,17] The structural similarities between the moenomycins and both the glycosyl donor and the glycosyl acceptor of the transglycosylation reaction are obvious (see Figure 4). From structure−activity relationships[164] it has been concluded that the moenomycins first bind to the cyctoplasmic membrane via their lipid moiety[165] and that membrane anchoring is an essential step

Scheme 27. Coates and the Stumpp–Schmidt Moenocinol Syntheses

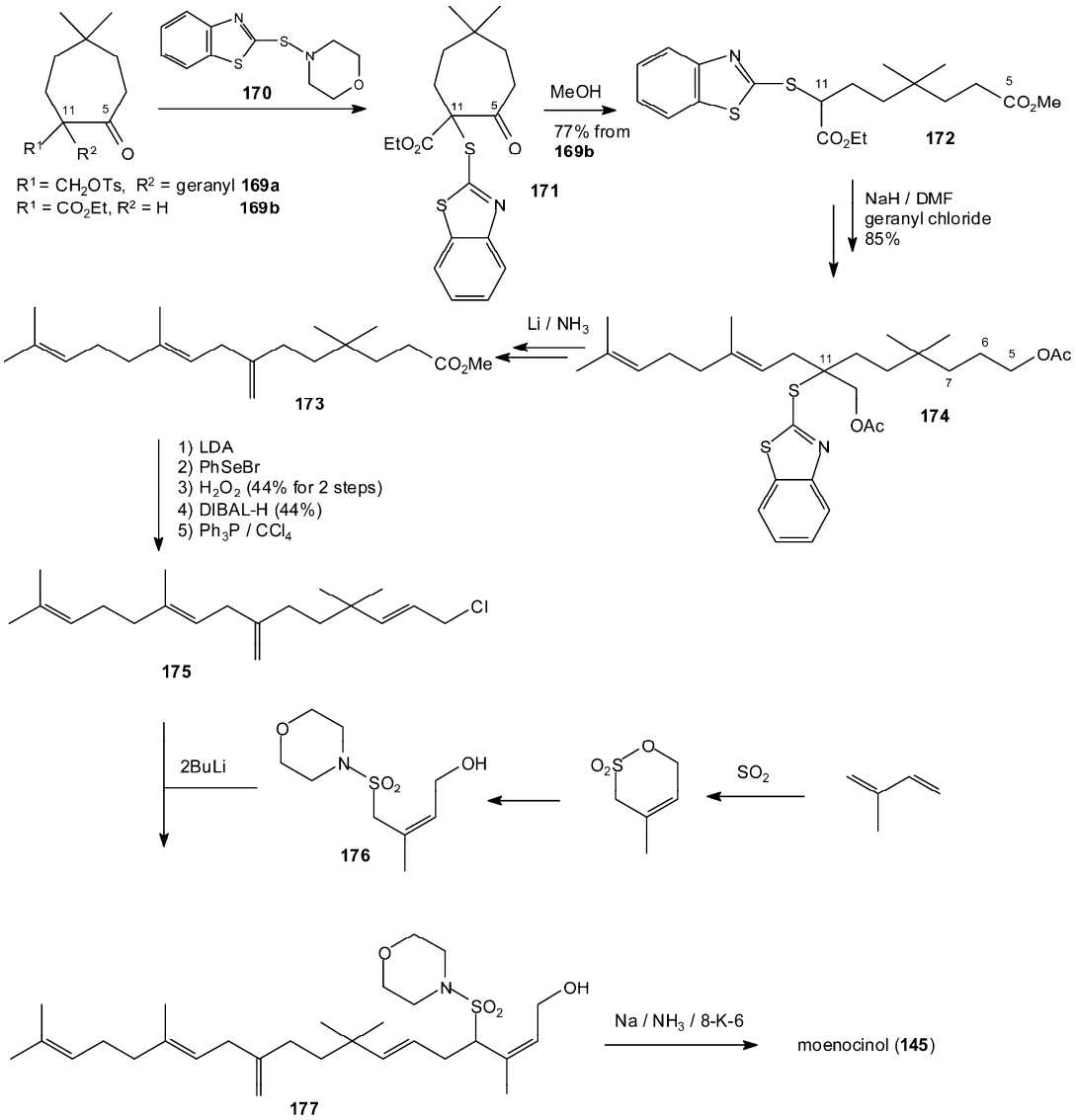


preceding the highly selective binding of the sugar part to the *donor* binding site of the enzyme. The structural features that are known to be responsible for the antibiotic activity are indicated by arrows in formula **141** (Figure 15). Units C and E of **141** are identical (with the exception of the peptide appendix) with the second and the third sugars of the sugar chain elongation *donor* component (see Figure 4). The different junctions of the first two sugars (1→4 in the growing peptidoglycan strand versus 1→2 in **139** and **141**) have been suggested on the basis of computer modeling to be responsible for the inhibition of the enzyme. More specifically, the nucleophilic *N*-acetylglucosamine 4-OH group of the acceptor (lipid II; see Figure 4) cannot reach the 1-position of the phosphate-carrying carbon of **139** and **141** in the proper orientation for a nucleophilic attack.[166,167] It should be stressed that all structure–activity relationships (MIC values) correlate well with the strength of binding of moenomycin and structural analogues to a PBP1b preparation as deduced from surface plasmon resonance (competition) experiments.[168] The results of these studies are well in agreement with NMR results. A three-dimensional structure of moenomycin in aqueous solution was proposed by Kurz et al.[156,157] as illustrated in Figure 15A. The fact that the groups that have been shown to be essential for the antibiotic activity (see arrows) are exposed in close proximity at the surface of the molecule has been taken as evidence that they are part of the polar binding epitope. A direct confirmation of this assumption has been obtained from STD NMR experiments which have demonstrated that the *N*-acetyl groups of units C and E of a moenomycin analogue are in contact with the enzyme in the moenomycin analogue–PBP1b complex.[169] Finally, from affinity labeling experiments the conclusion could be drawn that moenomycin indeed interacts with the transglycosylase domain of PBP1b.[170]

Thus, all experimental results collected so far point to the fact that the three sugar units C, E, and F of moenomycin are necessary for antibiotic activity and are most probably in contact with the enzyme. This means that the moenomycin antibiotics compete with the growing sugar strand rather than with lipid II for the appropriate binding site at the enzyme. The mechanistic picture for the antibiotic activity of the moenomycins described above is based on the assumption that the growing oligosaccharide strand forms the donor component in the transglycosylation reaction, an assumption that is well in agreement with all experimental evidence so far available as discussed in the beginning. We stress this point since in a recent publication of Kahne and co-workers[171] describing competition experiments between moenomycin A and lipid II all this evidence was ignored. In addition, Kahne and co-workers did not take into account that an IC_{50} of ca. 2×10^{-9} mol L^{-1} has been determined for moenomycin (using a cell-wall membrane preparation of *E. coli*).[172] Thus, moenomycin is most probably a tight-binding inhibitor which cannot be removed by lipid II from the donor binding site (which is not the lipid II binding site anyway, possibly with the exception of the initiating step of the sugar chain formation, vide supra). Even to the acceptor binding site, the affinity of lipid II is only moderate (ca. 2–3 μM).

A total synthesis of a moenomycin antibiotic has not yet been achieved, but there have been considerable activities in the syntheses of the unusual lipid part of the moenomycins, of optically active 2-*O*-alkylglyceric acid derivatives, and of antibiotically active trisaccharide analogues.

Scheme 28. Böttger–Welzel Moenocinol Synthesis



6.2. Syntheses of Moenocinol and Diumycinol

In the structure of the C_{25} alcohol moenocinol (**145**), three isoprene units can easily be identified whereas the central C_{10} part (C-5 through C-22) does not obey the isoprene rule in an obvious way. A number of total syntheses of moenocinol have been reported[173] based on disconnections between C-11 and C-12 and between C-6 and C-7, leading to geraniol (**142**; C_{10}) and via **143** (C_7) to nerol (**144a**) as starting materials (Scheme 24). The central C_8 part was constructed in different ways. On the contrary, Böttger and Welzel[174] assumed moenocinol to be a fully terpenoid compound and prepared it from two C_{10} precursors and one C_5 precursor. The central C_{10} part was reconnected (in the retrosynthetic sense) between C-5 and C-11 to give a ring system of type **146** which was assumed to originate from neryl or linalyl diphosphate by an anti-Markovnikov cyclization. For example, thujic acid (**149**) and kharahanaenone (**150**) have this carbon skeleton. The first moenocinol synthesis (based on disconnections between C-11 and C-12 and between C-6 and C-7) was reported by Grieco (Scheme 25).[175] Notable steps are (i) the addition of 1-lithio-2-methyl-1-propene to aldehyde **151**, (ii) a Claisen rearrangement (**152** ⟶ **154**), and (ii) an *o*-nitrophenylselenoxide elimination to introduce the 11,22-double bond (**155** ⟶ **145**). Whereas Grieco converted the benzyl ether of nerol (**144b**) ozonolytically into the *electrophilic* C_7 aldehyde **151**, Kocienski[176,177] converted the same starting material into the *nucleophilic* C_7 sulfone **157** using entirely different chemistry (Scheme 26). In a Julia olefination sequence, the anion derived from sulfone **157** was treated with aldehyde **159** and the 6,7-double bond was introduced by a reductive β-elimination. The methylene group was constructed by alkylation of an 11-sulfonyl anion with ICH_2SiMe_3 followed by a Bu_4NF-mediated β-elimination (see **160** → **145**). The synthesis of Coates[178] (Scheme 27) shares several similarities with that of Kocienski. In both of them the dimethylated C-8 (moenocinol numbering) originates from 2-methylpropionic acid (cf. **162**). Whereas anion stabilization at C-11 in the alkylation step with geranyl bromide was achieved by a sulfone group in the Kocienski synthesis, Coates used an α-phenylthio ester with the advantage that the extra (carboxylic) carbon in the C_8 intermediate (compare with Kocienski's **157** (C_7)) became later C-22 of moenio-

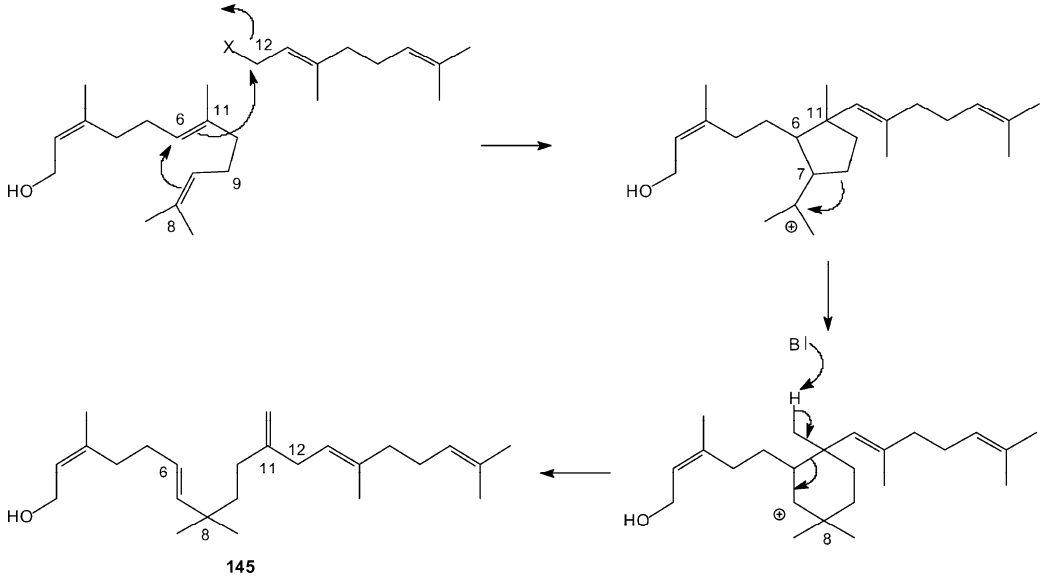
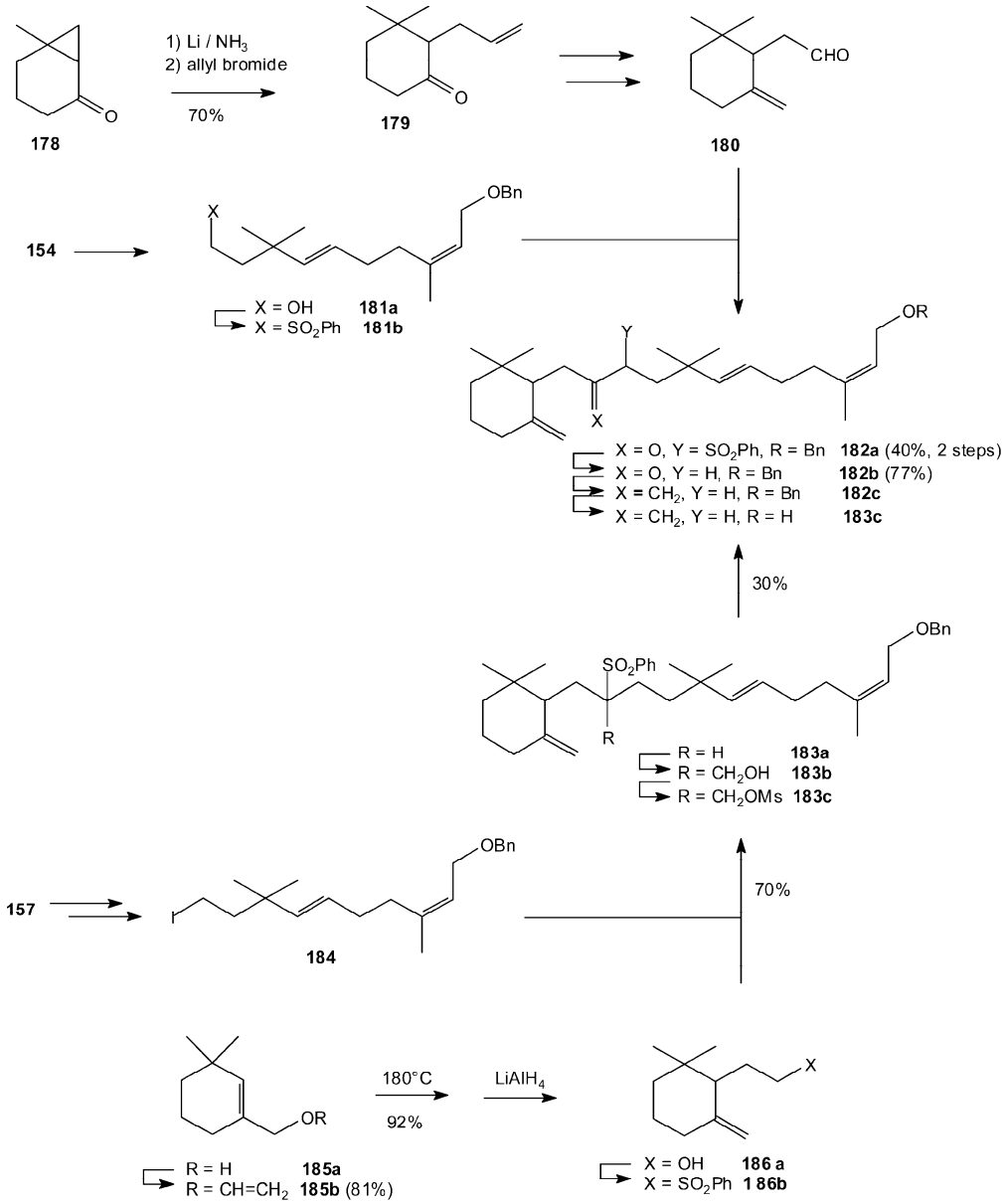
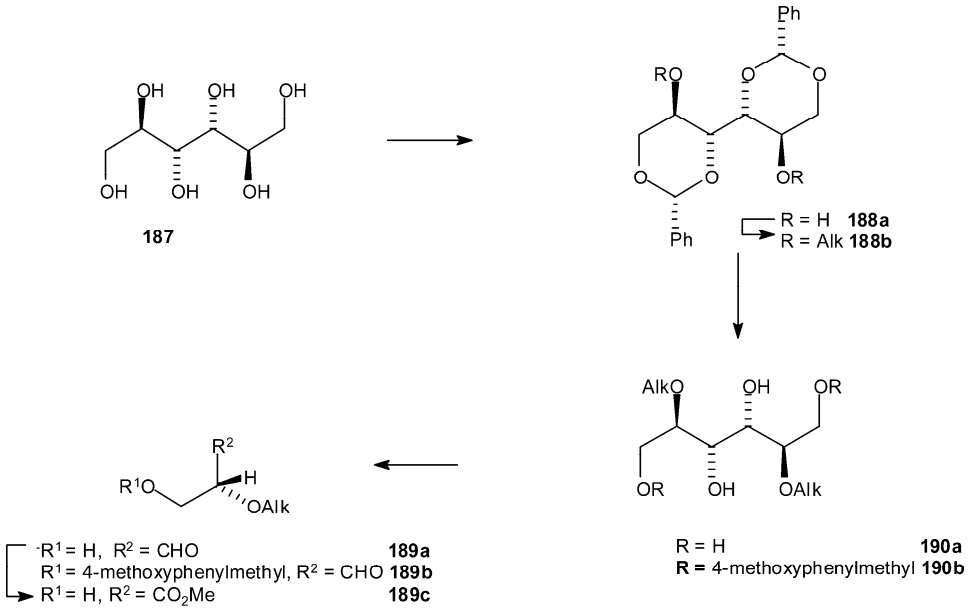


Figure 16. Biosynthesis of moenocinol from a C_{10} and a C_{15} precursor.

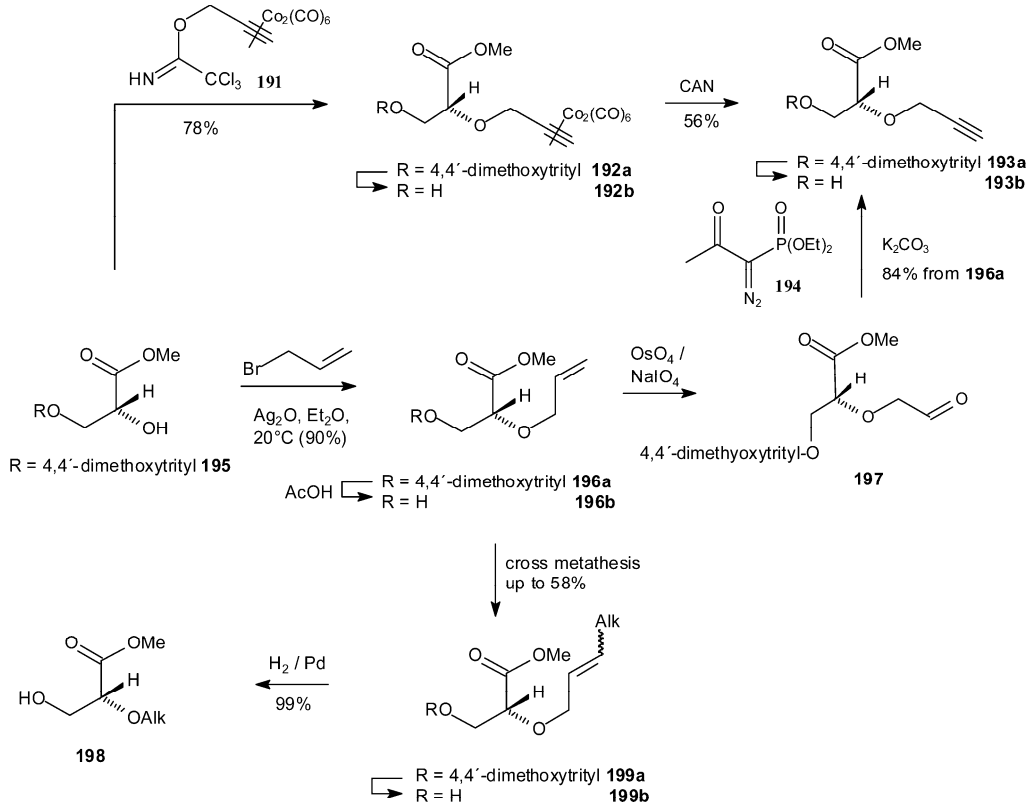
Scheme 29. Grieco's and Kocienski's Diumycinol Syntheses



Scheme 30. GHI Building Blocks for Moenomycin Analogues via a Mannitol Route

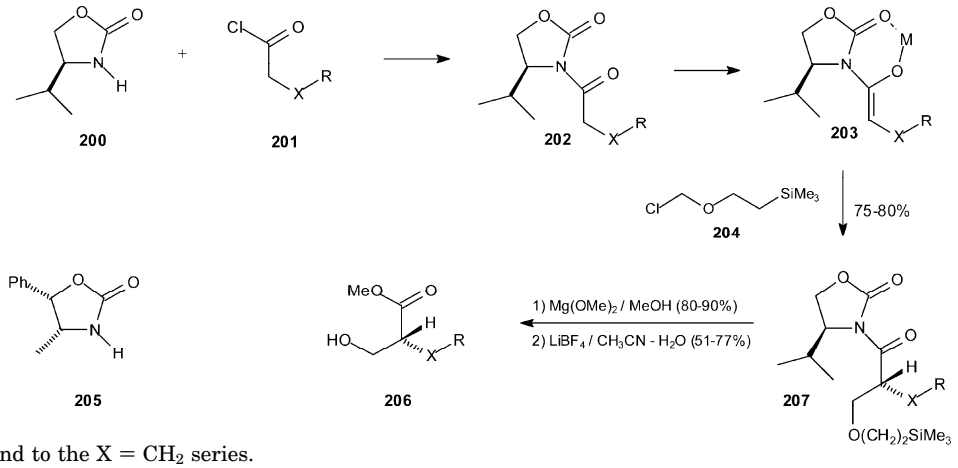


Scheme 31. GHI Building Blocks for Moenomycin Analogues Based on Glycerate 2-O-Allylation



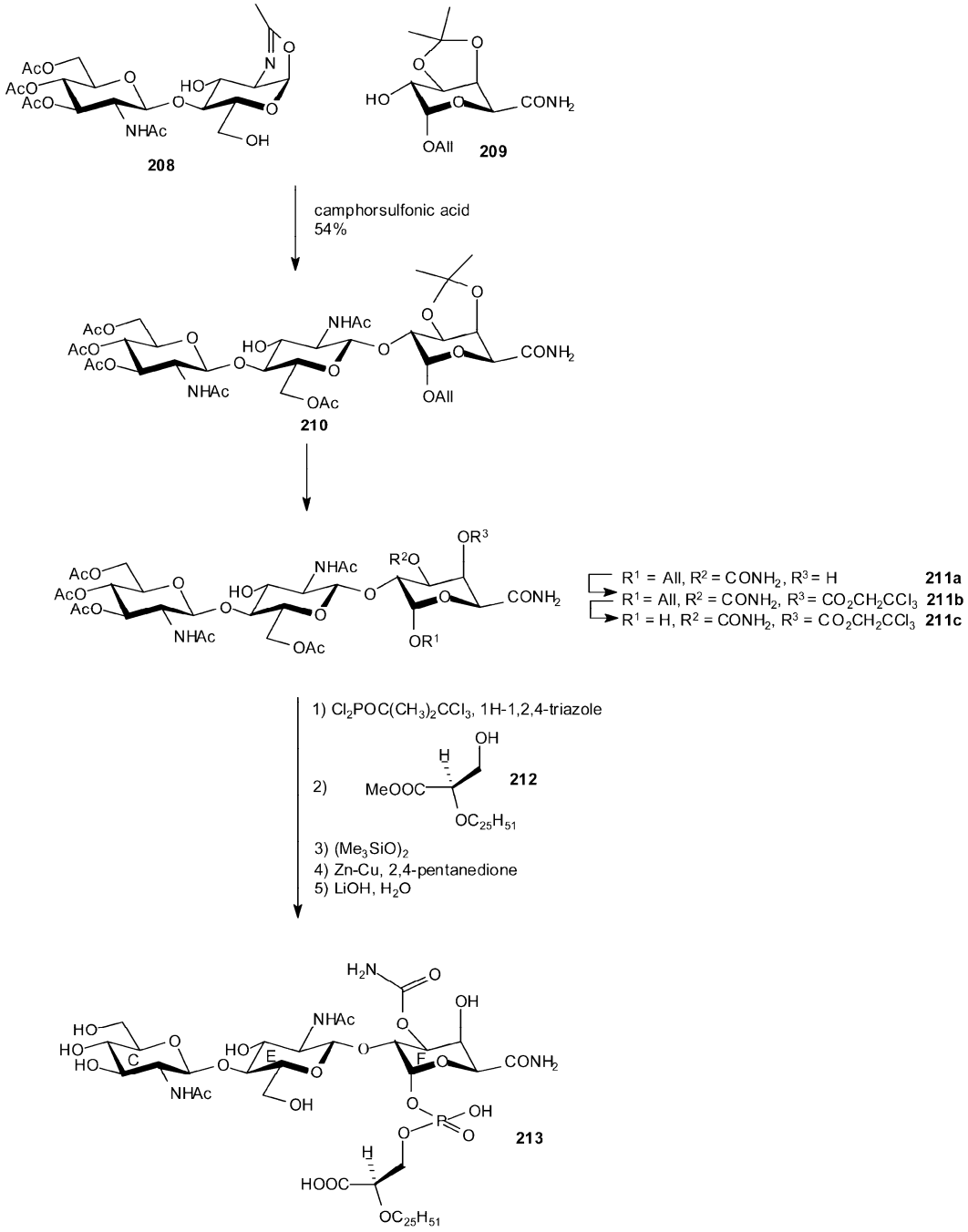
cinol. The 11,22-olefinic moiety was created in the Coates synthesis by submitting the acetoxymethyl sulfide (obtained from **164** by $LiAlH_4$ reduction and acetylation of the resulting primary alcohol) to a Li/NH_3 reductive β-elimination. Nerol-derived bromide **165** was added in a Grignard reaction to the aldehyde prepared from **164**, and the resulting alcohol was oxidized to furnish **168**. The ketone−alkene conversion was achieved by reduction of the intermediate enol phosphate. The Stumpp−Schmidt approach[179] merged into the Coates synthesis. The C-1 through C-6 fragment **165** was in this case not derived from nerol. It was constructed by Weiler's stereocontrolled enol phosphorylation of **166** (itself obtained via an acetoacetate dianion alkylation) and a subsequent phosphate/methyl exchange with dimethyl cuprate (*Z*:*E* ratio 5:1).[180] In the Stumpp−Schmidt synthesis the 11,22-double bond was introduced via a β-hydroxy selenide.[181] Böttger and Welzel[174] prepared moenocinol from purely isoprenoid starting materials. Originally it was planned to open the seven-membered ring of **169a** with an alkoxide by a Grob fragmentation. It turned out, however, that the Grob fragmentation of 2-tosyloxycycloalkanones is restricted to five-membered rings whereas in larger ring systems C- and O-alkylation processes prevail.[182] On the other

Scheme 32. GHI Building Blocks of Moenomycin Analogues via an Evans Route[a]

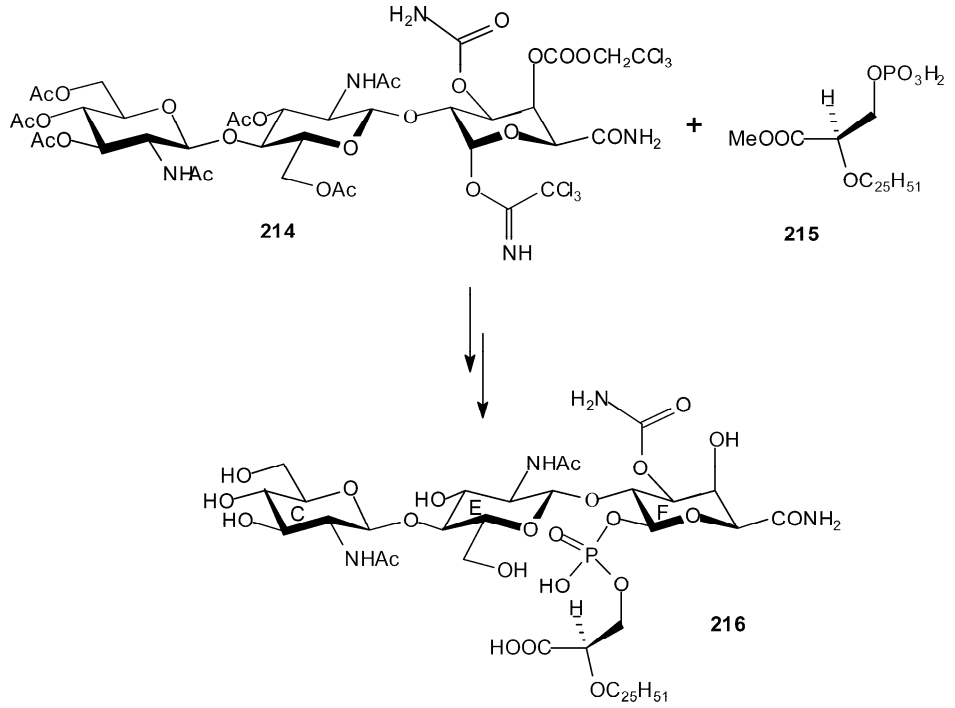


[a] Yields correspond to the X = CH_2 series.

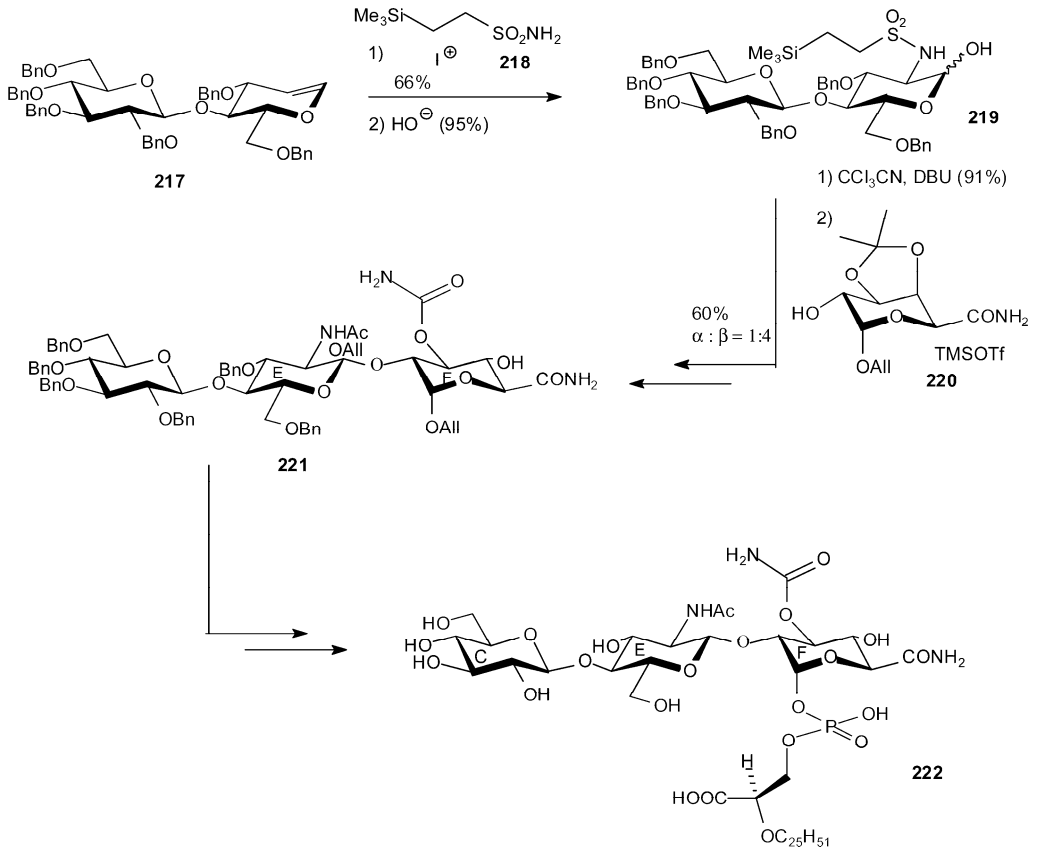
Scheme 33. Synthesis of Moenomycin Trisaccharide Analogue 213



Scheme 34. Synthesis of Moenomycin Trisaccharide Analogue 216

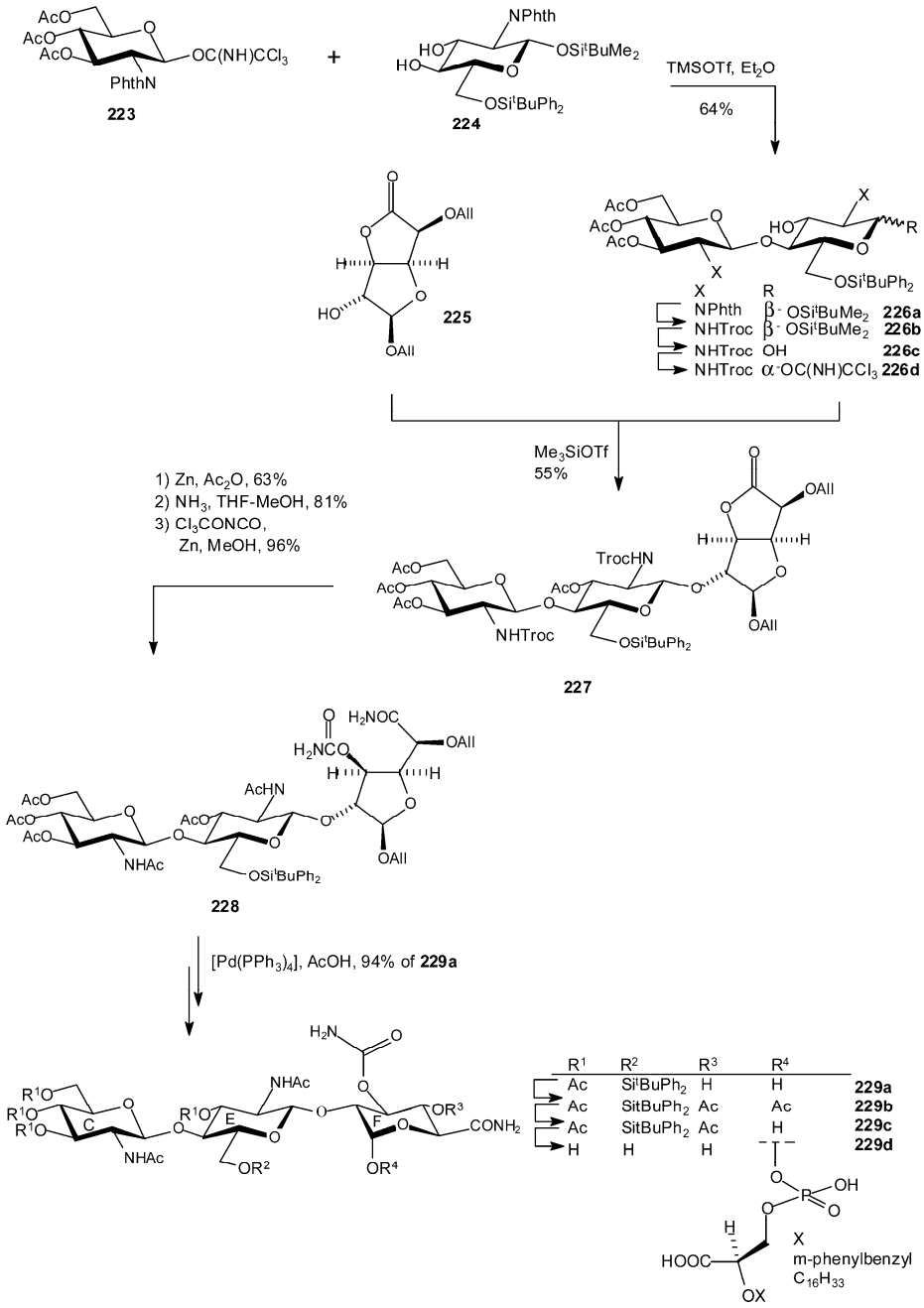


Scheme 35. Synthesis of Moenomycin Trisaccharide Analogue 222



hand, a sulfenylating β-ketoester cleavage[183] of **169b** furnished **172** via **171** (77%) (Scheme 28). Formation of the more stabilized ester enolate and alkylation with geranyl chloride, followed by ester reduction and acetylation, led to **174**, which on reductive β-elimination provided **173**. The next steps served to introduce the missing 6,7-double bond (moenocinol numbering) and to convert the unsaturated ester into allylic chloride **175**. Alkylation of the dianion of Moiseenkov's reagent **176**[184] with **175** furnished **177**, which on reduction gave moenocinol (**145**). Although the assumptions underlying the "biogenetically oriented" Böttger−Welzel synthesis were later shown to be oversimplified, it is clear now that moenocinol is indeed fully terpenoid (formed via the non-mevalonate pathway) and that the C_{25} structure

Scheme 36. Synthesis of Moenomycin Trisaccharide Analogue 229d



is assembled from a C_{10} and a C_{15} precursor as indicated in Figure 16.[163,185]

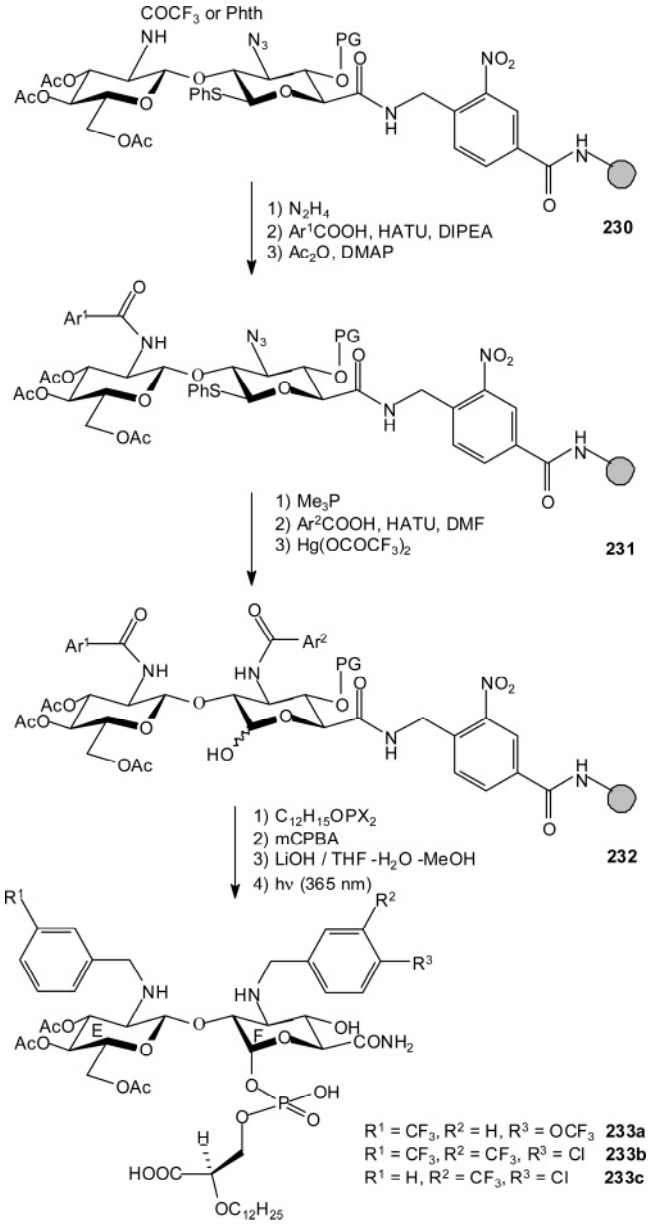
The structures of moenocinol (**145**) and diumycinol (**182d**) are closely related, but still the adaption of the moenocinol route to the diumycinol synthesis was far from straightforward especially for the Kocienski approach (Scheme 29). In Grieco's synthesis[186] reductive allylation of cyclopropyl ketone **178** furnished **179**, which was converted into **180** by some standard operations. Metalation of sulfone **181b** (obtained in a few steps from the known aldehyde **154** via **181a**) followed by addition of aldehyde **180** yielded a hydroxy sulfone which was directly oxidized to provide **182a** (40% overall). Reductive desulfonization (**182a** → **182b**), Wittig methylenation, and reductive debenzylation then gave diumycinol (**182c**). In their optimized approach Kocienski and co-workers converted **185a** via **185b** into **186a** by a Claisen rearrangement followed by reduction. Functional group interconversions gave sulfone **186b**, which was alkylated with the iodide **184**[177] to furnish **183a** (70%). Lithium anion formation from **183a** and subsequent treatment with formaldehyde provided hydroxymethyl derivative **183b**, which on mesylation (**183b** → **183c**) and subsequent reductive β-elimination with sodium amalgam yielded diumycinol benzyl ether (30% from **183a**).[187]

6.3. 2-*O*-Alkylglycerates

The configuration at C-2 of the glycerate part of moenomycin A has been determined to be *R*.[188] Although it is not clear whether the configuration at this position is of any significance for the antibiotic activity, routes were developed which allow the

synthesis of optically active 2-*O*-alkylglycerates. The direct alkylation of a 3-*O*-silyl-protected glycerate could not be realized.[189,190] However, (i) alkylation of the 1,3:4,6-di-*O*-benzylidene derivative of D-mannitol (**188a** → **188b**), (ii) acetal hydrolysis (**188b** → **190a**) and reductive acetal cleavage (**188b** → **190b**),[191,192] (iii) diol cleavage with sodium periodate (**190a/190b** → **189a/189b**), and (iv) oxidation/esterification make the desired 2-*O*-alkylglycerate **189c** easily available.[164,189,193−196] For the oxidation of aldehyde **189b** Ag(II),[189] Ag(I),[193,194,196] and (probably most conveniently) Br_2[164,189,195] have been employed (Scheme 30). A more direct route to these compounds makes use of the observation that methyl glycerate, 3-O-protected with a 4,4′-dimethoxytrityl group (**195**), can be allylated with allyl bromide in a silver oxide-promoted reaction (**195** → **196a**). The allylation proceeds with high yield (90%) and without any detectable racemization as shown by a Mosher ester analysis after removal of the 4,4′-dimethoxytrityl group. Chain elongation was achieved by cross-metathesis using the first-generation Grubbs catalyst. In the presence of the 3-*O*-protecting group only (*E*)-olefins were formed, whereas from **196b** *E*/*Z* mixtures were obtained. Catalytic hydrogenation converted the metathesis products into the 2-*O*-alkylglycerates **198**.[197] The direct ether formation between **195** and propargyl bromide failed. However, it was possible to prepare **193a** making use of a modified Nicholas reaction (Scheme 31).[198] Thus, the hexacarbonyldicobalt complex of propargyl alcohol was converted into its trichloroacetimidate **191**. BF_3-promoted reaction of **191** with **195** furnished **192a** (78% yield), from which **193a** was obtained by oxidative decomplexation. Mosher ester analysis at the stages of both **192b** and **193b** revealed that the Nicholas reaction was accompanied by massive racemization.[199] **193a** was also obtained by oxidative double bond cleavage of **196a** with $OsO_4/NaIO_4$ and submitting the resulting aldehyde **197** to the Ohira−Bestmann modification[200,201] of a reaction discovered by Colvin and Hamill (using reagent **194**).[202,203] The yield was high (84%), and no racemization was detected by Mosher ester analysis (after removal of the 4,4′-dimethoxytrityl group).[199] Chain elongation has been achieved by Sonogashira and Suzuki couplings.[204] 2-Substituted 3-hydroxypropionates can also be prepared stereoselectively, making use of the Evans auxiliaries (**200** and **205**, Scheme 32). The sequence is especially successful for *C*-analogues **206** (X = CH_2). Thus, acylation of auxiliary **200** with a carboxylic acid (**200** + **201** → **202**), hydroxymethylation of the boron or lithium enolate, and removal of auxiliary and protecting groups provided **206** (X = CH_2). Of the hydroxymethylating agents tried trimethylsilyloxymethyl chloride (**204**)[205] was found to be the most convenient one. According to Mosher ester analyses, the compounds were obtained in high enantiomeric excess. A certain disadvantage for the synthesis of 2-*O*-alkylglycerates **206** (X = O) by this method is the fact that the hydroxymethylation in the alkoxyacetic acid series proceeds with lower yields probably as the result of a lower enolate nucleophilicity.[206]

Scheme 37. Principle of the Library Synthesis of Moenomycin Disaccharide Analogues



6.4. Moenomycin Trisaccharide Analogues.

It is absolutely necessary for the moenomycin-type antibiotics to differentiate between in vitro transglycosylase inhibition and antibiotic activity. A number of disaccharide analogues of moenomycin A have been shown to inhibit the transglycosylase in in vitro experiments but lack antibiotic activity.[164,207] From all available experimental evidence it can be concluded that antibiotically active moenomycin analogues must contain at least three carbohydrate units (C, E, and F; see formula **141**, Scheme 15). Therefore, only the synthesis of trisaccharide analogues will be described here, and the synthetic work on disaccharide[194,196,208−211] and monosaccharide[193,194,196,206,209,212] as well that on *C*-glycoside[213] analogues will be omitted although especially the disaccharide analogues may be interesting compounds for exploring the acceptor binding site of the transglycosylase. A

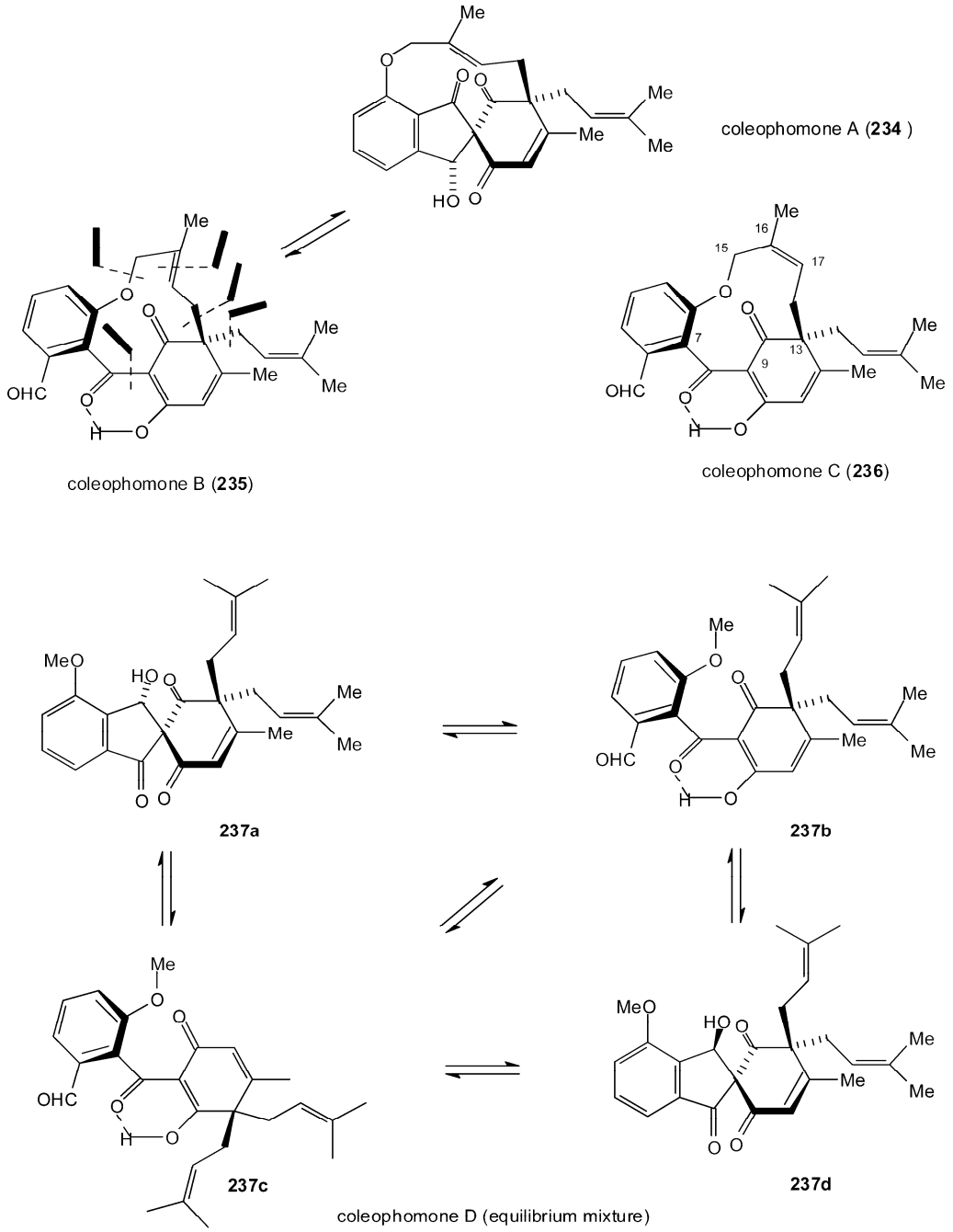
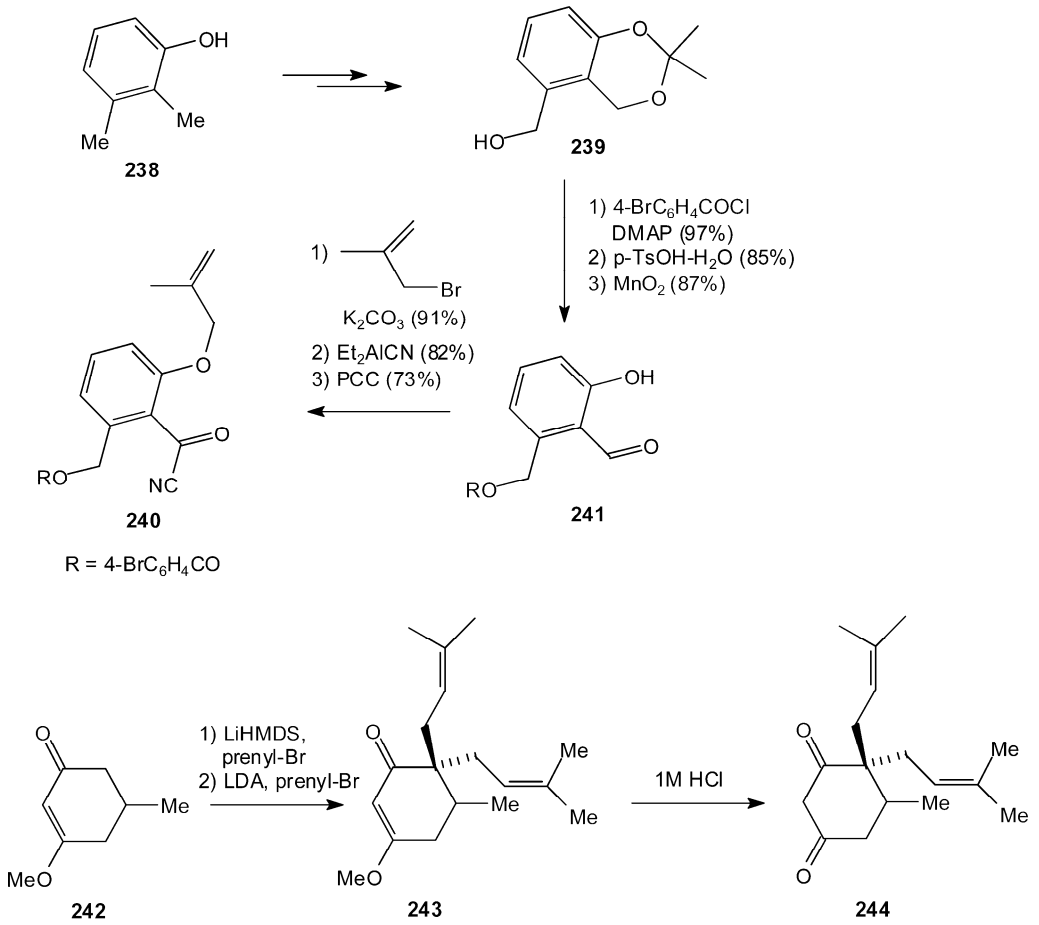


Figure 17. Structures of the coleophomones.

combinatorial approach to disaccharide analogues will, however, be included because of its methodic value.

In the first synthesis of a trisaccharide analogue a camphorsulfonic acid-promoted coupling of oxazoline **208**[214] and D-galacturonamide derivative **209**[211] furnished **210** in 54% yield (Scheme 33). After acetonide cleavage the urethane group was introduced by reaction with trichloroacetyl isocyanate followed by reductive removal of the trichloroacetyl group with Zn dust in methanol (**210** → **211a**).[215] The 4^F-OH group of **211a** was protected by formation of the trichloroethoxycarbonyl derivative, and the allyl glycoside was removed by double bond rearrangement with the cationic Ir complex $[Ir(PCH_3(C_6H_5)_2)_2COD]PF_6$[216] in THF and subsequent cleavage of the propenyl ether by hydroxymercuration (**211b** → **211c**). The phosphoric acid diester was installed making use of the phosphite methodology.[215] Thus, 2,2,2-trichloro-1,1-dimethylethyl dichlorophosphinite[217] was converted into the bistriazolide. Ugi and co-workers have shown that this reagent allows the selective stepwise formation of mixed phosphorous acid triesters since the first triazolyl exchange proceeds faster than the second one.[218] Furthermore, the bulky 2,2,2-trichloro-1,1-dimethylethyl protecting group renders the intermediate phosphite and phosphate triesters quite stable.[217] Treatment of the bistriazolide first with trisaccharide **211c** and then with the moenomycin degradation product **212**[219] gave the phosphorous acid triester. The oxidation to the corresponding phosphate was performed with bis(trimethylsilyl)-peroxide[220−222] in 4:1 CH_2Cl_2/pyridine, i.e., under nonsolvolytic conditions to avoid degradation of the

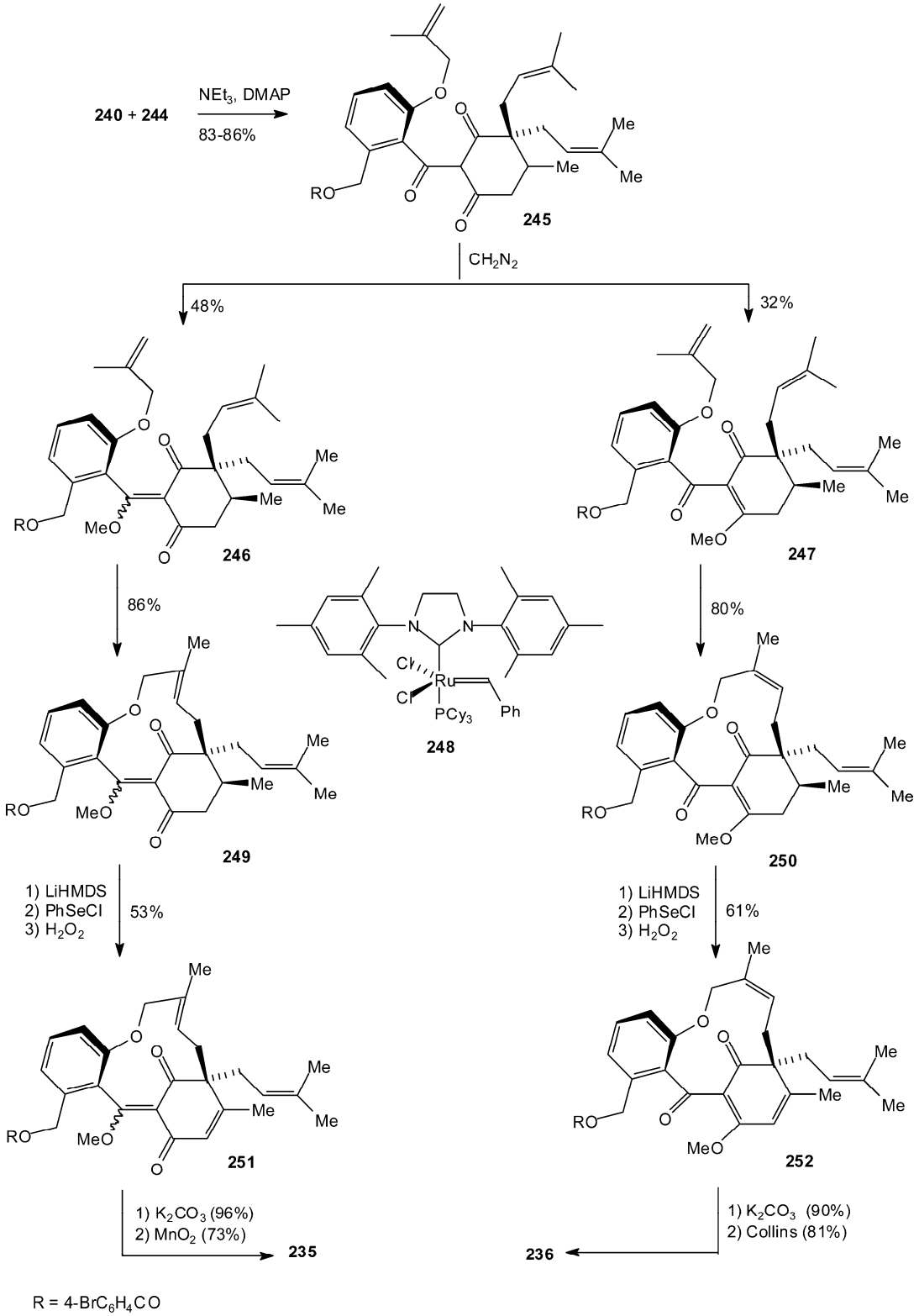
Scheme 38. Synthesis of the Coleophomone Building Blocks 240 and 244



sensitive phosphoric acid triester. Reductive removal of the trichloroethyl-type protective groups[223,224] was performed with a freshly prepared Zn−Cu couple under the conditions reported by Imai and Torrence,[225] i.e., in the presence of 2,4-pentanedione added to chelate zinc ions and to guarantee a clean metal surface. Finally, careful hydrolysis of the ester groups provided **213**.[226] Analogue **216**, which differs from **213** only by the configuration at C-1 of unit F, was prepared as summarized in Scheme 34, making use of a method developed by Schmidt and Stumpp.[227] Reaction of trichloroacetimidate **214** (prepared by treatment of **211c** with trichloroacetonitrile and K_2CO_3 in dioxane[228]) and phosphoric acid monoester **215** (obtained from a moenomycin enzymatic degradation product[188] by hydrogenation and methyl ester formation) followed by photolytic removal of the Troc protecting group in the presence of triethylamine[229] and subsequent ester hydrolysis furnished **216**.[230]

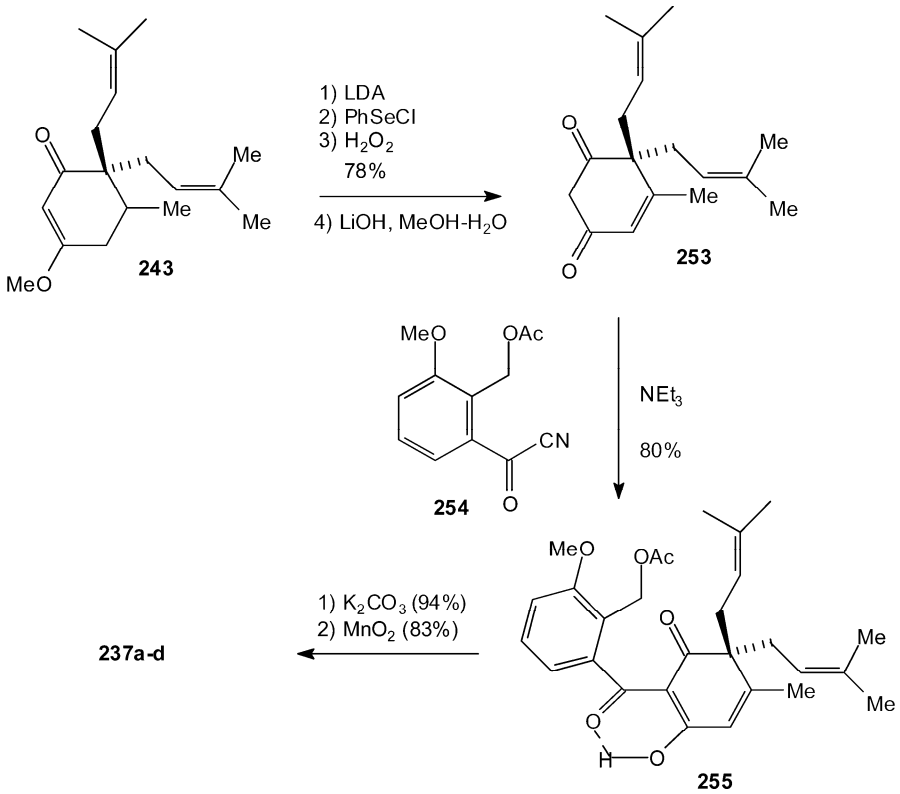
Trisaccharide **222** was prepared starting from perbenzylated cellobial, making use of Danishefsky's sulfonamidoglycosylation procedure (Scheme 35).[231,232] Thus, treatment of **217** with 2-(trimethylsilyl)ethanesulfonamide[233] in the presence of iodonium di-*sym*-collidine perchlorate (IDCP)[234] provided a 2-iodo-α-D-mannopyranosyltrimethylsilylethanesulfonamide in 66% yield which was converted via a sulfonylaziridine intermediate into **219** by treatment with aqueous lithium hydroxide in THF (95% yield). The formation of trisaccharide **221** made use of Schmidt's trichloroacetimidate procedure.[228] The conversion into the final product **222** was achieved in a way similar to that described above.[166,235,236] The most advanced approach to this class of compounds commences from three monosaccharide building blocks and is flexible in that it allows the introduction of different substituents at C-6 of unit E, the substitution of which is unimportant as far as antibiotic properties are concerned (Scheme 36).[164] Probably reporter groups can be attached to this position, which is much closer to the contact site with the enzyme than unit A of moenomycin A (**139a**), which has been used until now to attach reporter groups.[169,170,237] Me_3SiOTf-promoted coupling of monosaccharide building blocks **223** and **224** (prepared by known and well-established procedures, respectively) in ether led to the 1,4-linked disaccharide **226a** in 64% yield; a 21% yield of the corresponding 1→3-isomer was also isolated. Remarkably, when the reaction was performed in dichloromethane, the 1→3-linked disaccharide was the main product (65%). It turned out to be necessary to change the *N*-protecting groups at this stage, which was achieved by treatment of **226a** with ethane-1,2-diamine in BuOH, followed by *N*-(trichloroethoxy)carbonylation and subsequent O-acetylation (**226a** → **226b**). Selective removal of the $^tBuMe_2Si$ group from the anomeric position with $[PdCl_2(MeCN)_2]$[238] yielded compound **226c** in 55% yield. Coupling with the advanced ring F acceptor building block **225** (D-*gluco* configuration) using the trichloroacetimidate procedure gave trisaccharide **227** in 55% yield. Conversion of the NHTroc groups

Scheme 39. Nicolaou's Synthesis of Coleophomones B and C



in **227** to NHAc functions was achieved on reaction with activated zinc dust[239] or Zn−Cu complex[240] in acetic anhydride (63%). Subsequent treatment with saturated NH_3 in THF−MeOH (9:1) opened the lactone ring to give a uronamide (81%) into which the carbamoyl group was introduced on reaction of the free 3-OH group with trichloroacetyl isocyanate (TAI) and subsequent reductive removal of the trichloroacetyl group from the trichloroacetyl-urethane (**227** ⟶ **228**).[211] Deallylation applying the Nakayama method[241] led to **229a** with a pyranoid ring F (94%). Acetylation of **229a** yielded **229b**, from which the anomeric acetyl group was selectively removed with hydrazinium acetate in DMF[242,243] to give **229c**. The conversion into analogue **229c** was achieved combining **229** and methyl 2-decyloxy-3-hydroxypropionate and methyl 2-[1,1′-biphenyl]-3-ylmethoxy-3-hydroxypropionate via the phosphoric

Scheme 40. Nicolaou's Coleophomone D Synthesis



acid diester bridge using the phosphite approach as described above.[210,244,245]

Trisaccharide **213** was shown to inhibit the transglycosylase and to be antibiotically active (*Staph. aureus*);[226] the corresponding 1^E-β-isomer **216** turned out to be inactive in both test systems.[230] The same result was obtained for **222**, underscoring the importance of the 2-acylamino function in position 2 of unit C.[166a] **229c** (X = $C_{16}H_{33}$), too, was inactive in both the in vitro and the in vivo test systems most probably because the lipid chain is too short to provide sufficient binding energy on interaction with the cytoplasmic membrane.[246]

6.5. Moenomycin Disaccharide Analogues from a Combinatorial Library

The synthesis of a library of 1300 disaccharide analogues using solid-phase combinatorial chemistry has been reported by Sofia and co-workers.[247] The compounds differed by the substitution at C-2 of unit E and at C-3 of unit F and by the lipid moiety. For compounds **233a**−**c** the principle of the synthesis is shown. A photolabile *o*-nitrobenzyl linker[248,249] was used for attachment to the resin. Starting from **230**, different amide groups were established at C-2 of unit E. After Staudinger reduction of the azide function (see **231**), amide and urethane groups were set up at C-3 of unit F. The phosphodiester was created using the phosphite method, and release from the resin was achieved by irradiation at 365 nm (Scheme 37).

The antibacterial activity of the compounds has been tested. They are orders of magnitude less active than moenomycin, and their mode of action may be different.[207,247,250]

7. Coleophomones

Coleophomones A−D (Figure 16) are fungal metabolites that were first isolated at Shionogi from the broth of *Stachybothrys* strains.[251,252] Coleophomones A (**234**) and B (**235**) were also isolated at Merck from a *Coleophomas* sp. (MF 6338) fermentation.[253] The only difference between coleophomones B and C is the configuration around the 16,17-double bond. Coleophomone A rearranges at pH > 7 completely into coleophomone B, whereas both compounds were reported to exist in equilibrium with each other under "physiological conditions" (CH_3CN/water mixtures) via an aldol−retro-aldol equilibration.[253] In coleophomone D the macrocyclic ring is missing. The compound has been reported to be an equilibrium mixture formed by aldol−retro-aldol reactions and tautomerization with rotation around the 8,9-bond. In an essay with permeabilized (ether-treated) *E. coli* W7[40] cells, coleophomones A nd B were found to inhibit the transgylcosylation step of peptidoglycan biosynthesis with an IC_{50} = 62 μM.[253] They have other pharmacological activities as well.

The total synthesis of coleophomones B and C by Nicolaou and co-workers[254,255] demonstrates again the magnificent power of the ring-forming metathesis for the construction of large ring systems.[256] In formula **235** the disconnections of the retrosynthetic analysis are indicated.

Nicolaou and co-workers assembled coleophomones B and C from building blocks **240** and **244** (Scheme 38). **238** was converted into **239** using a known route. Esterification, acetal cleavage, and MnO_2 oxidation furnished **241**, which was alkylated with 3-bromo-2-methylpropene. Subsequent cyanohydrin formation and oxidation provided acyl cyanide **240**, which was

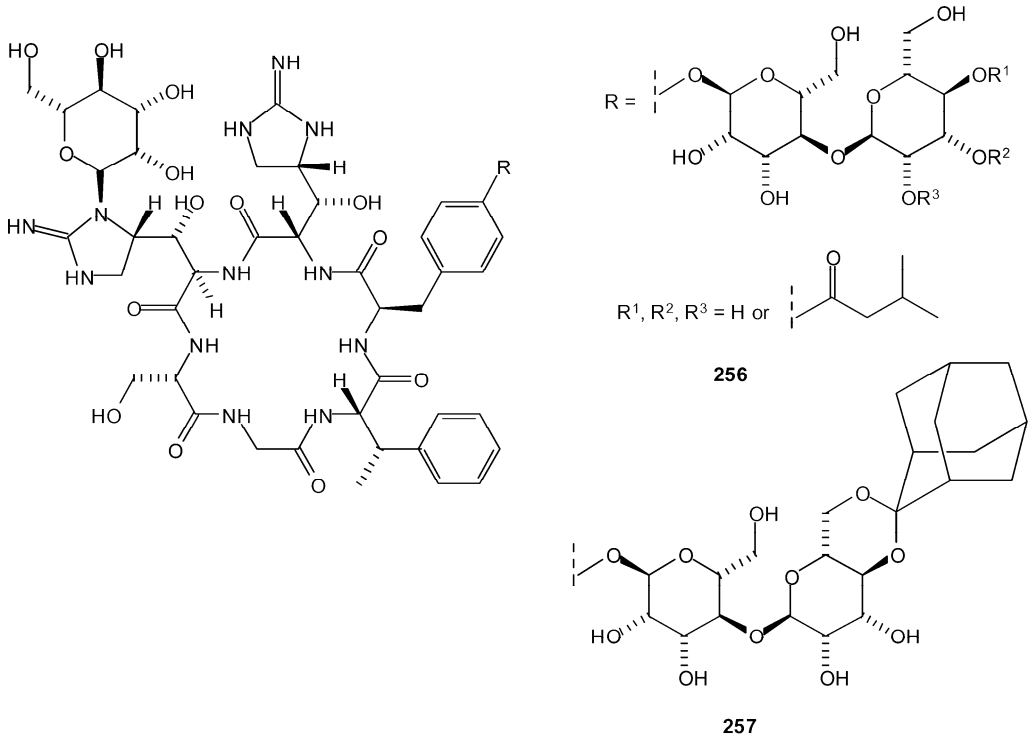


Figure 18. Structures of mannopeptimycins α−ϵ (**256**) and of the cyclic acetal **257** (AC 98-6446).

selected as an acylating reagent because of the known propensity of acyl cyanides to react with enolates by C-acylation.[257] **244** was obtained from **242** by a two-step bisprenylation (**242** → **243**) followed by enol ether hydrolysis (**243** → **244**). The reaction of **244** with **240** in the presence of NEt_3 and DMAP furnished the C-acylation product **245** in high yield (83−86%) as desired. It was found difficult to handle tricarbonyl compounds of type **245**. Thus, **245** was treated with diazomethane to furnish three constitutionally different enol ethers. **246** was a mixture of four stereoisomers (*E*/*Z* and *P*/*M*), whereas **247** was a single compound (Scheme 39). A third structural isomer was isolated in 16% yield in which the more congested carbonyl group within the six-membered ring had been converted into the enol ether. Both **246** and **247** underwent with remarkable stereoselectivity and in high yield the desired metathesis reaction when they were exposed to Grubbs catalyst **248**.[258] From **246** exclusively the Δ^{16}-(*E*)-isomer **249** (1:1 mixture of configurational isomers around the vinylogous ester double bond), was obtained whereas the Δ^{16}-(*Z*)-isomer **250** was formed from **247**. Neither the alternative ring-forming reaction between the methallyl and the prenyl group *trans* to the methyl substitutent nor the metathesis reaction between the two prenyl groups which would have led to a five-membered ring occurred. The missing double bond was then introduced into **249** and **250** by enolate formation, trapping with PhSeCl, oxidation to the selenoxide, and *syn*-elimination. Finally, removal of the protecting groups from **251** and **252** and subsequent primary alcohol oxidation (MnO_2 and Collins reagent, respectively) provided coleophomone B (**235**) and coleophomone C (**236**), respectively. With the synthetic sample of **235** in hand, Nicolaou and coworkers were unable to reproduce the equilibration of coleophomone B (**235**) with coleophomone A (**234**) which had been reported by the Merck chemists (vide supra).

For the synthesis of the coleophomone D mixture (Scheme 40) the carbon−carbon double bond was introduced into the bisprenylated ring at the stage of **243** by enolate trapping with PhSeCl (formation of two diastereomeric selenides), oxidation with H_2O_2, and elimination. The subsequent cleavage of the vinylogous ester had to be performed under carefully controlled conditions (LiOH in methanol/water) to avoid aromatization (loss of one prenyl group). Acylation of **253** with acyl cyanide **254** under mild conditions provided **255** in 80% yield. Finally, ester hydrolysis and oxidation of the benylic alcohol with MnO_2 furnished **237a**−**d**.[259]

8. Mannopeptimycins

The mannopeptimycins are novel glycopeptide antibiotics (from *Streptomyces hygroscopicus*, LL-AC98) that are active against a wide variety of Gram-positive bacteria including vancomycin-restistant enterococci, penicillin-resistant *S. pneumoniae*, and methycillin-resistant *Staph. aureus*.[260] The structures of the mannopeptimycins α−ϵ are summarized in Figure 17. The peptide core is identical for all of them; R may be H or the dimannosyl residue which is displayed in Figure 18. R^1, R^2, and R^3 may all be H, or one of them may be isovaleric acid.[261] It was found that the antibiotic activity originates from an interaction with lipid II and that the antibiotic activity of several mannopeptimycin derivatives correlates with their affinity to lipid II. This interaction is different from that of lipid II with vancomycin and of the lantibiotic mersacidin.[260] A total synthesis of a mannopeptimycin has not yet been reported. It was,

however, found that semisynthetic modifications such as cyclic acetal **257** (AC 98-6446) have improved antibiotic properties.[260,262]

9. Outlook

The problem of antibiotic resistance[263] demands development of anti-infectives with novel modes of action.[264] It is hoped that the present review demonstrates the transglycosylation reaction to be a promising target for new anti-infectives for a number of reasons: (i) the reaction occurs at the extracellular surface of the cytoplasmic membrane, (ii) the methods for isolating the enzyme(s) that are involved have improved considerably, (iii) the monomeric substrate, lipid II, can now be made in sufficient amounts, (iv) interesting lead structures for compounds are available that efficiently inhibit the transglycosylation reaction, and their chemistry is in many cases well developed, (v) new and efficient in vitro test systems have been developed which conveniently allow monitoring of the binding of inhibitors to the enzyme and to lipid II as well as the inhibition of the incorporation of lipid II into un-cross-linked peptidoglycan.

10. Abbreviations

BDP	benzotriazol-1-yl diethyl phosphate
CDI	*N*,*N*′-carbonyldiimidazole
DCC	dicyclohexylcarbodiimide
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
EDCI (EDC)	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
FDPP	pentafluorophenyl diphenylphosphinate
HATU	1-[(dimethylamino)(dimethyliminium)methyl]-1*H*-1,2,3-triazolo[4,5-*b*]pyridine 3-oxide hexafluorophosphate
HOAt	1-hydoxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
NHS	*N*-hydroxysuccinimide
PyBOP	benzotriazolyloxytris[pyrrolidino]phosphonium hexafluorophosphate
SES	2-trimethylsilylethanesulfonyl

11. Acknowledgment

It is with great pleasure and gratitude that I thank my collaborators, whose names appear in the references. Their skillful and dedicated efforts allowed development of the organic and bioorganic chemistry of the moenomycins. My special thanks go to Jean van Heijenoort (Universitë Paris-Sud, Orsay) for many years of fruitful collaboration. Our work has generously been funded by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, Hoechst AG, Hoechst Marion Roussel, Sandoz Industrial Products GmbH (formerly BC Biochemie GmbH), and the Universities of Bochum and Leipzig.

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