Chemistry and Biology of the Streptogramin A Antibiotics

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Abstract: The streptogramin A antibiotics have proven to be highly active against Gram positive bacteria, particularly methicillin-resistant *Staphylococcus aureus*. Members of this group of compounds are characterized by a 23-membered macrocycles containing polyene, oxazole, amide and ester functionality. The chemistry and biology of these valuable antimicrobial agents is covered.

Keywords: Antibiotics, biosynthetic origin, mode of action, total synthesis, synthetic studies.

1. INTRODUCTION

The increased use of antibiotics has led to the occurrence of multidrug resistant strains. In particular, the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) is recognized as a serious problem. Recently, up to 18% of all infections in European Intensive Care Units were attributed to oxacillin or methicillin resistant *S. aureus* [1]. These infections include skin and skin structure infections, nosocomial pneumonia infections, and catheter related infections. Nearly 60% of the ICU acquired *S. aureus* infections were reported to be MRSA [2]. Patients with MRSA infections are linked to increased risk of mortality (greater than twice as many deaths "on ward") and prolonged hospitalization (ca. twice as long) compared to patients with methicillin susceptible *S. aureus* [3]. Certain risk factors are associated with the development of MRSA infections, including previous antibiotic use, prolonged hospitalization, severe underlying disease, old age and multiple invasive procedures [4]. Not only is there a human toll, but also an increased financial burden associated with these infections [5]. Thus, there is clearly the need for antibiotics effective against such resistant pathogens. One such class of agents is the streptogramin antibiotics. The streptogramin antibiotics, isolated from several species of *Streptomyces*, may be classified into one of two subgroups. One subgroup is peptidic in nature and is known as group B, while the group A compounds are characterized by a 23-membered macrocyclic ring, an oxazole ring, and a conjugated dienyl amine. This review will primarily deal with the chemistry and biology of the group A streptogramin antibiotics.

2. BIOLOGY OF STREPTOGRAMIN A ANTIBIOTICS

2.1 Isolation and Structural Assignment

The early literature of the type A streptogramin antibiotics can be somewhat confusing due to the different names which were given for these compounds by different research groups. For example, the isolation of two group A streptogramin antibiotics from *Streptomyces osteogrycin* (originally termed osteogrycins A and G) was reported in 1958 [6]. These were assigned the structures **1** and **2** (Fig. **1**) by Todd and co-workers in 1966 on the basis of chemical degradation, and NMR spectroscopy and mass spectrometry [7]. A crystal structure of **1** eventually corroborated the spectroscopy-based assignment [8]. Compound **1** was also isolated from *Streptomyces olivaceus* ATCC 12019 [9a] (termed PA114A), from *Streptomyces mitakaensis* [9b] (termed mikamycin A], from *Streptomyces liodensis* ATCC 11415 [9c] (termed vernamycin A), from *Streptomyces pristinaespiralis* [9d] (termed pristinamycin II_A), and from *Micromonospora* sp. SC 12,650 [9e] (referred to as vernamycin A). Compounds **1** and **2** are now most frequently identified as virginiamycin M_1 and M_2 respectively.

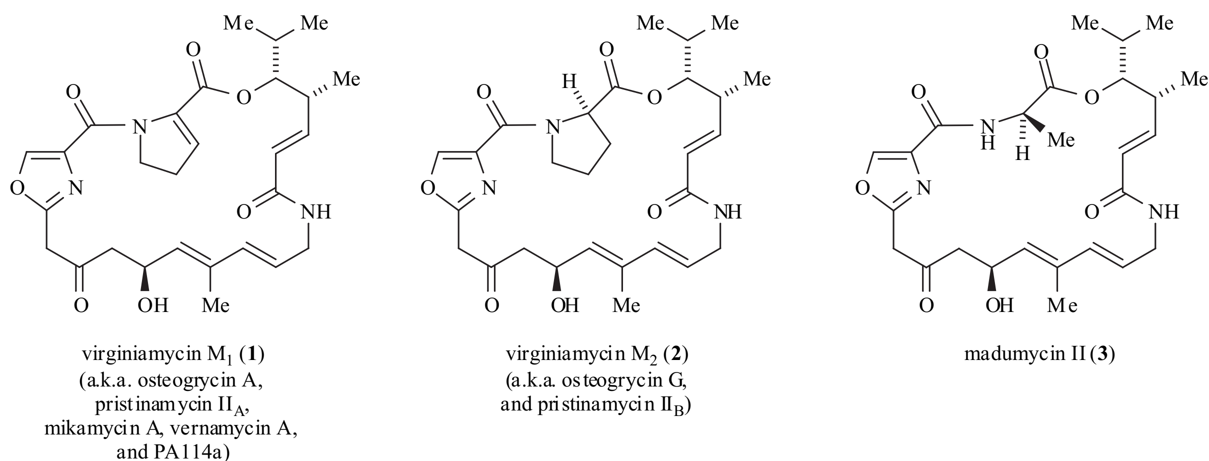

Fig. (1).

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A structurally related streptogramin antibiotic was isolated from *Actinomadura flava* and several species of *Actinoplanes*, and its structural assignment was reported as **3** (Fig. **1**) by several groups during the period 1975-79 [10]. This compound is most commonly known as madumycin II, however different groups have variously referred to **3** as A2314A, A15104V, A17002F, and CP-35,763. The structure of **3** differs from the virginiamycins in that the proline/dihydroproline group is replaced by a D-alanine unit.

Griseoviridin is a broad spectrum antibiotic isolated from *Streptomyces griseus* [11]. Extensive degradation studies as well as IR and UV spectroscopic analysis led to two proposed structures **4** and **5** for griseoviridin (Fig. **2**), with the former being originally favored [12]. Eventually, the structure of griseoviridin was reassigned as **5** on the basis of X-ray diffraction analysis [13], although one of these references incorrectly assigned the relative stereochemistry for the C18-C20 diol as *trans*. The correct stereochemistry of this group is *cis*- as is indicated in structure **5** [13]. Since the configuration at C5 was known from degradation studies, this allowed for the complete stereochemical assignment. More recently, the macrolide conformation of griseoviridin in d_6-DMSO solution was determined on the basis of 2-D NMR spectroscopy and restrained molecular dynamics calculations [14]. The solution structure is similar to that in the crystal state with minor variations in the diendiol segment.

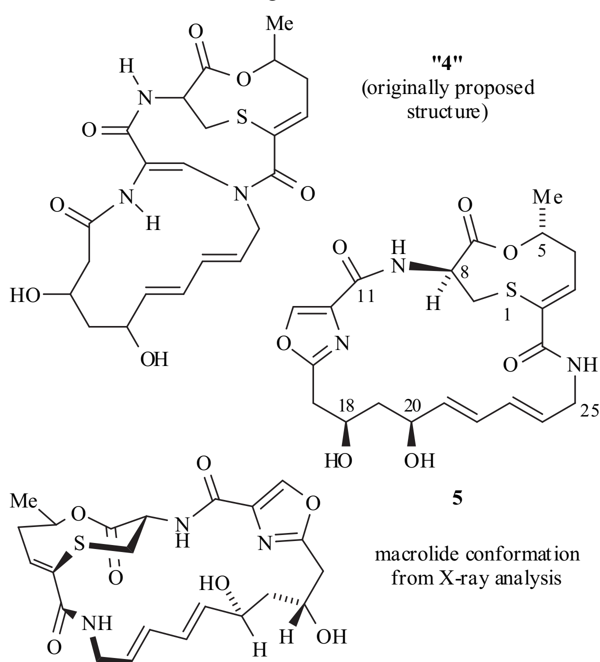


Fig. (2).

2.2 Biosynthetic Pathways

2.2.1 Biosynthesis of Virginiamycin M_1

Kingston's group has investigated the biosynthetic origin of virginiamycin M_1 (**1**) based on incorporation of ^{13}C and ^{14}C labeled precursors into the antibiotic produced by *Streptomyces virginiae* strain PDT 30 (Fig. **3**) [15]. The antibiotic produced in the presence of [1-^{13}C] acetate exhibited enrichment at C5, C7, C12, C14, C16, and C18, while **1** produced in the presence of [2-^{13}C] acetate exhibited enrichment at C4, C6, C11, C13, C15, C17, as well as at C33. Notably, growth of the microorganism fed with [1,2-$^{13}C_2$] acetate afforded virginiamycin M_1 which exhibited ^{13}C-^{13}C couplings between C4 and C5, C6 and C7, C11 and C12, C13 and C14, C15 and C16, and C17 and C18. *Notably, there was no coupling between C12 and C33.*

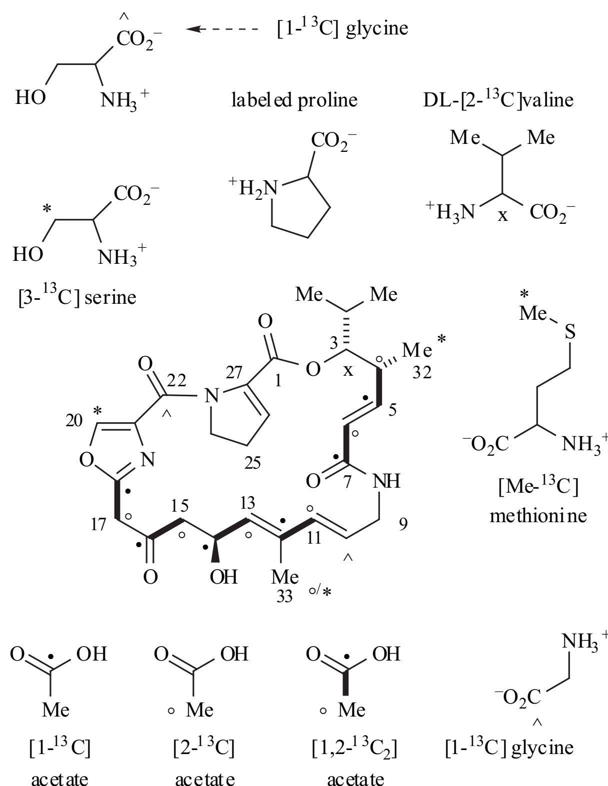
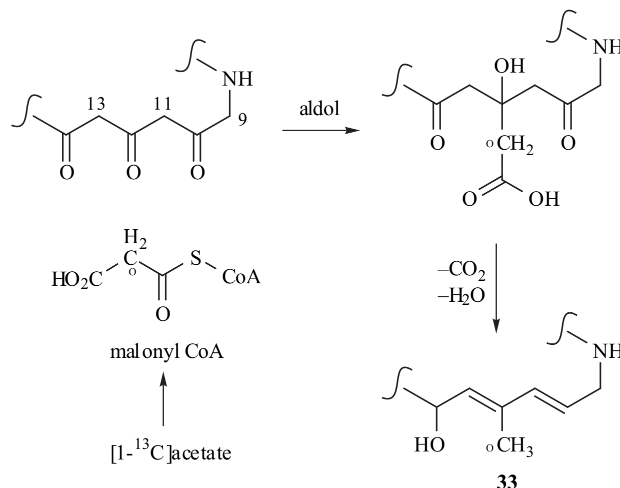


Fig. (3).

The most likely route for introduction of the C33 methyl group involves aldol condensation of an individual acetate unit (presumably in the form of malonyl CoA), followed by decarboxylation and dehydration (Scheme **1**).



Scheme 1.

Growth of *S. virginiae* in the presence of racemic [3-^{13}C] serine, produced **1** which was significantly enriched (ca. 7%) at the C20 oxazole carbon, indicative of the origin of this ring. Enrichment was also observed at the methyl groups C32 and C33. It was proposed that enrichment at C33 results from conversion of serine into acetyl CoA *via* pyruvate, while enrichment at C32 results from methyl transfer to methionine.

To this end, microbial production of the antibiotic in the presence of racemic [Me-^{13}C] methionine resulted in enrichment at C32.

Feeding [1-^{13}C] glycine to *S. virginiae* resulted in **1** which was enriched at C10 and C22. This is consistent with the N8-C9-C10 segment arising from glycine. Isotopic labeling at C22 is due to conversion of glycine to serine by N^5,N^{10}-methylene-tetrahydrofolate and serine hydroxymethylenetransferase. Microbial production of **1** in the presence of racemic [2-^{13}C] valine exhibited significant ^{13}C enrichment only at C3.

Finally, growth of *S. virginiae* in the presence of radiolabeled proline (L-[3,4-$^3H_2$] proline or L-[U-^{14}C] proline) indicated that this amino acid was responsible for the N23-C1 dehydroproline segment.

2.2.2 Biosynthesis of Madumycin II

LeFevre and Kingston have elucidated the biosynthetic origin of madumycin II (produced by *Actinoplanes philippinensis*) using ^{13}C and ^{2}H labeled precursors [16]. By analogy to the biosynthesis of virginiamycin M_2 (*vide supra*), the C4-C7 and C10-C18 chains are likely derived from acetate. Evidence in support of this was obtained in the ^{13}C NMR spectra of madumycin II generated in the presence of [1,2-$^{13}C_2$] acetate (Fig. **4**). Unfortunately, signal overlap for C11, C12, and C13 did not allow for either detection of ^{13}C enrichment or ^{13}C-^{13}C couplings. As with virginiamycin, microbial production of madumycin II in the presence of racemic [2-^{13}C] valine exhibited significant ^{13}C enrichment only at C3.

Madumycin II produced in the presence of racemic [1,2,3-$^{13}C_3$] serine exhibited ^{13}C enrichment at the oxazole carbons C20, C21, C22, the dienyl amine carbons C9 and C10, and at the exocyclic methyl C30. Labeling at C9 and C10 arises due to interconversion of serine and glycine (*vide supra*), while labeling at C30 presumably arises *via* conversion of the labeled serine into methionine, followed by incorporation. Notably, the madumycin produced under these conditions did not exhibit any significant ^{13}C enrichment at the C1, C24, or C25 carbons

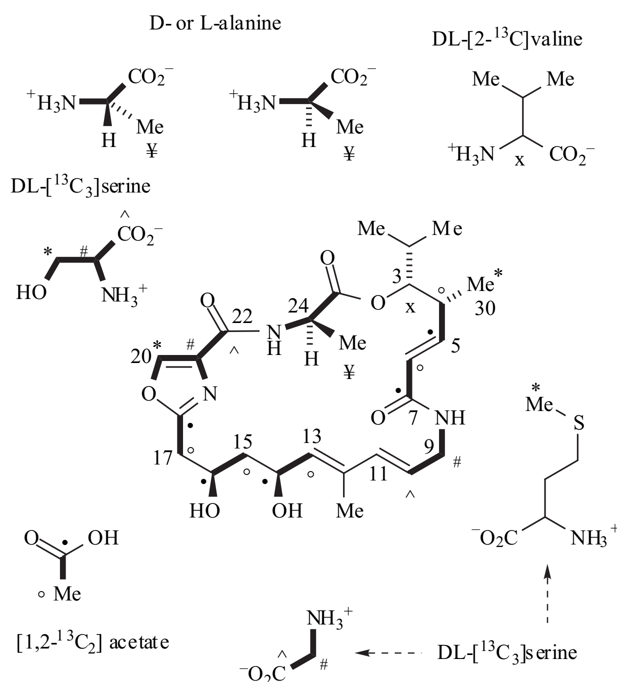


Fig. (4).

of the alanine segment, thus indicating that the biological origin of this segment is not from serine.

The biosynthetic origin of the D-alanine segment (N23,C24,C1) was examined by feeding *A. philippinensis* with doubly labeled L-alanine (L-[3-^{13}C,3,3,3-$^2H_3$] alanine). The madumycin thus produced exhibited both ^{13}C and three ^{2}H labels present. Since no ^{2}H isotopic label was lost, the intermediacy of dehydroalanine or 24,25-dehydromadumycin could be ruled out. Furthermore, competitive incorporation of labeled L- and D-alanine indicated that there was no preference for incorporation of either enantiomer of this amino acid. This suggests the occurrence of a facile alanine racemase system, which is operative prior to incorporation of D-alanine into the madumycin skeleton.

2.3 Mode of Action

Both streptogramin type A and type B antibiotics inhibit protein synthesis in Gram-positive bacteria [17]. Bacterial ribosomes are comprised of a 50S and 30S subunit, which join into a 70S particle as the initiation step for protein synthesis. The sequence of steps in protein synthesis involve positioning of an amino acyl-tRNA (at the A site of the ribosome) and a peptidyl-tRNA (at the P site). Peptide bond formation between the NH_2 of the amino acyl-tRNA and the CO_2H of the peptidyl-tRNA is catalyzed by the peptidyl transferase center (PTC) of the 50S ribosome, resulting in formation of an elongated chain at the A site. The final step is for translocation of the elongated chain from the A site to the P site in order for the process to occur again.

Type A streptogramins block the positioning of both amino acyl-tRNA at the A site and peptidyl-tRNA at the P site of the ribosome [18]. However, while type A streptogramins can bind either the 50S subunit, or the assembled 70S ribosome, it can not bind to ribosomes already engaged in protein synthesis [19]. It is believed that these polyene macrolides bind only to the free arms of peptidyl transferase. Binding of streptogramin A antibiotics is believed to cause a conformational change in the 50S subunit [20]. To this end, *in vitro* incubation of the 50S subunit with virginiamycin M produced inactive particles, even at substoichiometric quantities of the antibiotic. Removal of virginiamycin M from these inactivated 50S particles by column chromatography did not restore the activity.

Recently the crystal structure of virginiamycin M_1 bound to the 50S ribosome of *Haloarcula marismortui* was reported (Fig. **5**) [21]. The structure was solved to the 3.0 Å level; the location, orientation, and conformation of **1** in the bound form was unambiguous in the difference electron density map. The C14 hydroxyl is hydrogen-bonded to the phosphate of A2538, the oxazole ring is positioned in a hydrophobic pocket of the A site, with the remainder of **1** extending over the ribosome P site. The most notable structural change upon binding of **1** is that the conjugated amide functionality (C5-C7) occupies an area which is originally populated by the nitrogen base of adenosine 2103 in the native structure. This nitrogen base is rotated ca. 90° with respect to its original position, and the plane of the aromatic base is positioned such that it is parallel to the C5-C6 olefin. The amide carbonyl is also hydrogen-bonded to the 2' hydroxyl of A2103.

The crystal structure of **1** bound to the protein Vat(D), a streptogramin A acetyltransferase from a human urinary isolate

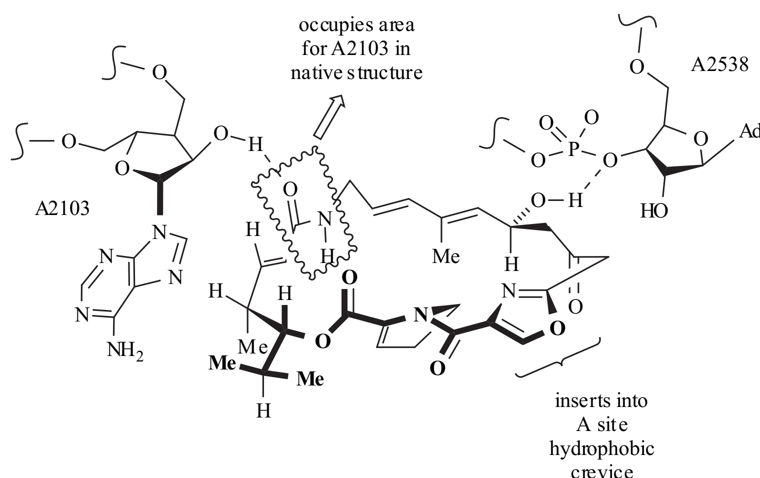


Fig. (5).

of *E. faecium*, exhibits essentially the same conformation of the macrolide ring [22]. This type of enzyme mediates acetylation of the C14 hydroxyl of streptogramin A antibiotics, and is linked to acquired drug resistance in *S. aureus* due to drug efflux. In comparison, unbound **1** adopts a different macrolide conformation in its crystal state (as evidenced by X-ray structure) [8], or in $CDCl_3$, CD_3OD, or d_6-DMSO solution, as determined by 2D NMR spectroscopy [23]. The solution structures are more compact compared to those observed for bound **1**.

Type B streptogramins inhibit protein synthesis by blocking peptide bond synthesis [24]. These compounds interact with ribosomes actively engaged in protein synthesis indicating that the type B streptogramins bind to a portion of the PTC area distinct from the A or P sites or the catalytic site. Thus the type A and B streptogramin antibiotics inhibit different stages of the protein synthesis sequence. Furthermore, the action of the two streptogramin types is synergic. Notably, streptogramin B depsipeptides can be displaced from the ribosomal complex by the erythromycin antibiotics. However, in the presence of a type A streptogramin, this displacement of the depsipeptide is not observed (i.e. tighter binding than erythromycin). This increase in affinity for the type B streptogramin, in the presence of a type A, is attributed to the conformational change in the 50S subunit due to type A binding [25].

Utilization of the interaction between type A and type B streptogramin antibiotics culminated in formulation of an injectible mixture of two semi-synthetic streptogramin antibiotics, quinupristin and dafloprisitin (3:7), approved by the FDA in 1999 and marketed under the name “Synercid” by Aventis Pharmaceuticals (Fig. **6**)[26]. Synercid is active against gram positive bacteria including vancomycin resistant *Enterococcus faecium* (VREF) and methicillin-susceptible *Staphylococcus aureus* (MSSA), however it is not active against *E. faecalis*. This synergic interaction between type A and type B streptogram antibiotics may have additional benefits, since bacteria must develop resistance to the action of both type A and B inhibition.

In spite this synergic action, there are cases of quinopristin-daflopristin resistant *E. faecium*, isolated from farm animal sources, reported in both the USA and Europe [27]. This may be due to the FDA approved use of Virginiamycin [a mixture of virginiamycin M and virginiamycin S (a streptogramin type B similar to quinopristin)] in chickens, turkeys, swine and cattle for weight gain. However a causative relationship between the

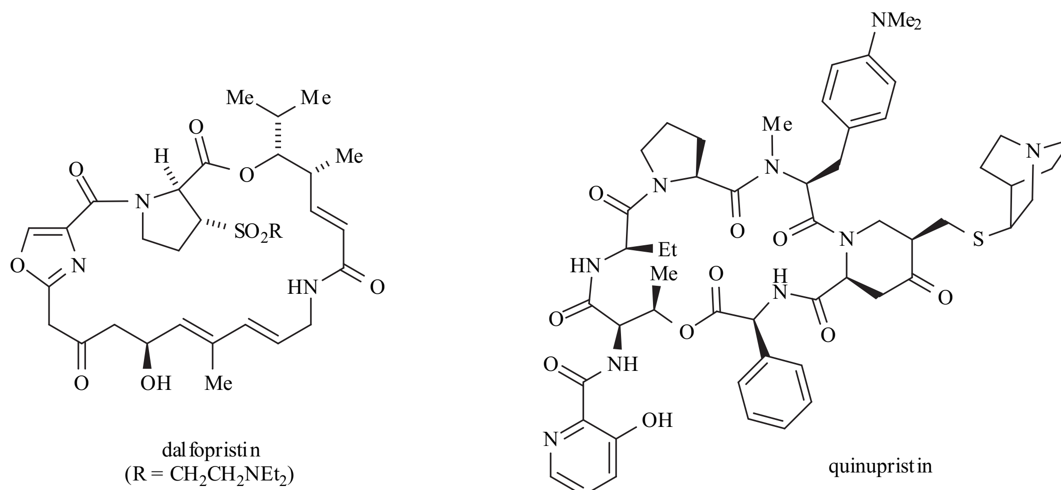


Fig. (6).

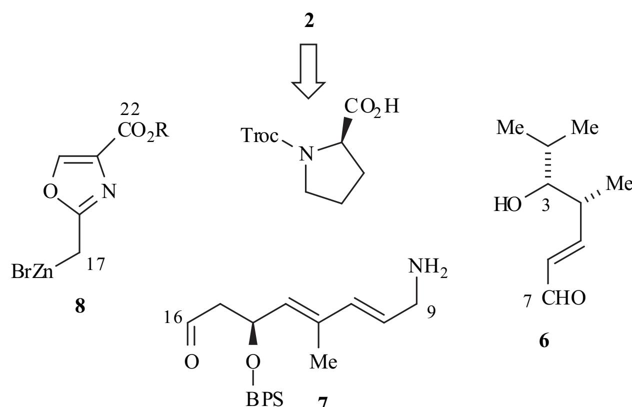
use of Virginiamycin in animals and resistant strains in humans could not be definitively established due to the lack of an animal control group for comparison (i.e. animal populations not given Virginiamycin). Limiting the use of streptogramin antibiotics has been recommended [28] and Denmark has banned the use of Virginiamycin as a growth-promoting agent.

3. SYNTHESES OF STREPTOGRAMINS A

3.1 Syntheses/Synthetic Studies of Virginiamycin M_2

3.1.1 Schlessinger/Li Synthesis of Virginiamycin M_2

Schlessinger and Li were the first to report a synthesis of virginiamycin M_2 (**2**) [29]. Their retrosynthetic strategy (Scheme **2**) dissected the target molecule into a C3-C7 enal (**6**), a C9-C16 dienylamine (**7**), and a metallated 2,4-oxazole (**8**). This strategy relied on condensations of the anion derived from vinylogous urethanes to set the C3 and C14 carbinol stereocenters.

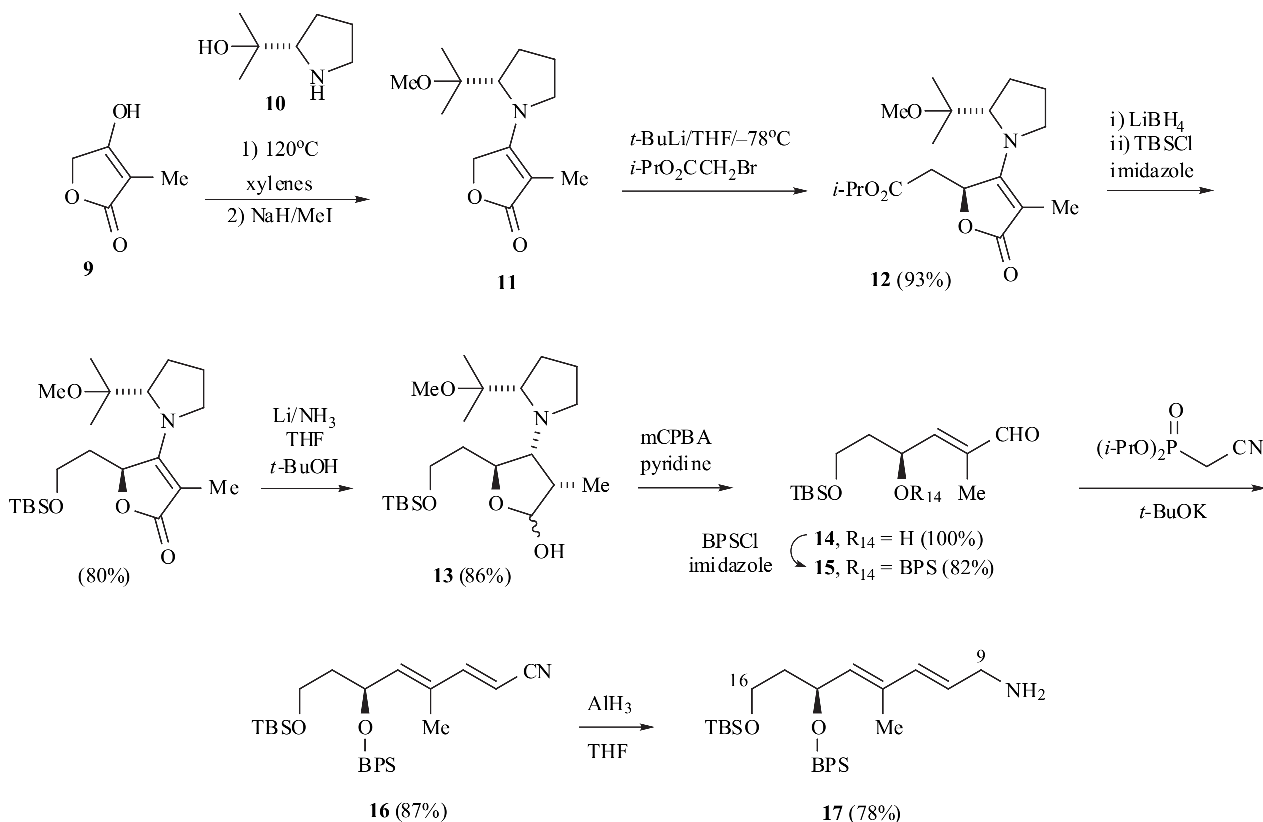


Scheme 2.

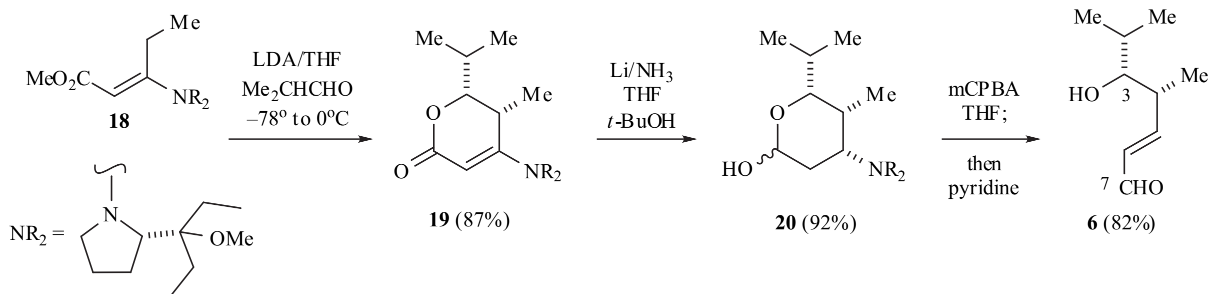
Condensation of **9** with the pyrrolidine **10** (from L-proline) followed by methylation gave the vinylogous urethane lactone **11** (Scheme **3**). Deprotonation of **11** followed by reaction with isopropyl 2-bromoacetate gave a single substituted lactone **12** by alkylation on the less hindered face. Reduction of the isopropyl ester, subsequent protection of the 1° alcohol and Li metal reduction of the unsaturated lactone gave the lactol **13**. Oxidative elimination of the pyrrolidine from **13** afforded the enal **14**, which was protected at the *t*-$BuPh_2Si$ ether (**15**). Horner-Emmons olefination gave the *E,E*-dienyl nitrile **16** which upon reduction with alane gave the dienyl amine **17**.

Preparation of the C3-C7 enal began with the vinylogous urethane **18** (Scheme **4**). Aldol condensation of **18** with isobutyraldehyde proceeded with erythro selectivity and the resultant alcohol condensed on the ester to afford the unsaturated lactone **19** with 96% de. Dissolving metal reduction of **19** gave the lactol **20** which upon oxidative elimination of the pyrrolidine generated the moderately stable enal **6**.

Coupling of the C3-C7 hydroxy enal **6** with *N*-Troc protected D-proline afforded the ester **21** (Scheme **5**). Oxidation of the aldehyde functionality with $NaClO_2$ gave the corresponding carboxylic acid. Condensation of acid **22** with the dienyl amine **17** under Mukiayama conditions [30] generated the amide **23**. Selective cleavage of the 1° TBS ether in the presence of the 2° BPS ether, followed by oxidation gave the aldehyde **24**. Addition of the organozinc reagent [31] from 2-bromomethyl-1,3-oxazole **25** with aldehyde **24** gave 2°



Scheme 3.



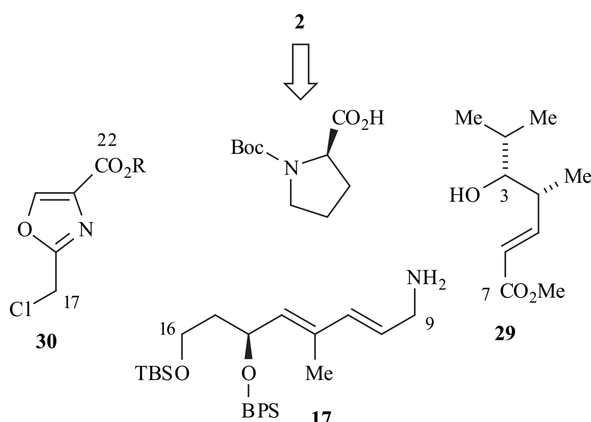
Scheme 4.

alcohol **26** as a mixture of diastereomers which were protected as their triethylsilyl ethers **27**. Reductive removal of the Troc protecting group and hydrolysis of the oxazole methyl ester set the stage for a Mukiayama macrolactamization to generate cyclic amide **28**. Deprotection of the TES ether under mild acid conditions, Dess-Martin periodinane oxidation, and finally removal of the BPS with HF-pyridine completed the synthesis of virginiamycin M_2. The synthesis proceeded in 22 steps, 2.8% overall yield from lactone **9**.

Scheme 5.

3.1.2 Breuilles/Uguen Synthesis of Virginiamycin M_2.

In 1998 Breuilles and Uguen, at the Universite Louis Pasteur, reported a synthesis of virginiamycin M_2 (a.k.a. pristinamycin II_B) [32]. Their retrosynthetic strategy (Scheme **6**) was similar to that of Schlessinger's group; the target was dissected into a protected proline, a C3-C7 hydroxyenoate **29**, a C9-C16 dienylamine (**17**), and a 2,4-disubstituted oxazole **30**.



Scheme 6.

The C14 stereocenter inherent in the dienylamine segment **17** was derived from dimethyl (*S*)-malate. Reduction to the butanetriol, followed by reaction with *p*-methoxybenzaldehyde gave the dioxalane **31** (Scheme **7**) [32a]. Moffat oxidation of **31** afforded a sensitive aldehyde **32** which was immediately reacted with excess ylide derived from bromomethyltriphenylphosphonium bromide to give a mixture of *E*- and *Z*-alkenylbromides **33**. Elimination gave the alkyne **34** which was deprotected. Selective protection of the 1° alcohol of diol **35** required considerable experimentation; eventually it was found that slow addition of the diol to PMB trichloroacetimidate and PPTS led to the monoprotected **36** (48%) along with unreacted **36** (23%) and diprotected diol (11%) all of which were separable by chromatography. After protection of the remaining hydroxyl group, homologation was accomplished by deprotonation with *n*-butyl lithium and addition to paraformaldehyde. The 2° TMS ether was subsequently cleaved with HF·pyridine to afford the diol **37**. Carbometallation of **37** with methylmagnesium

Scheme 7.

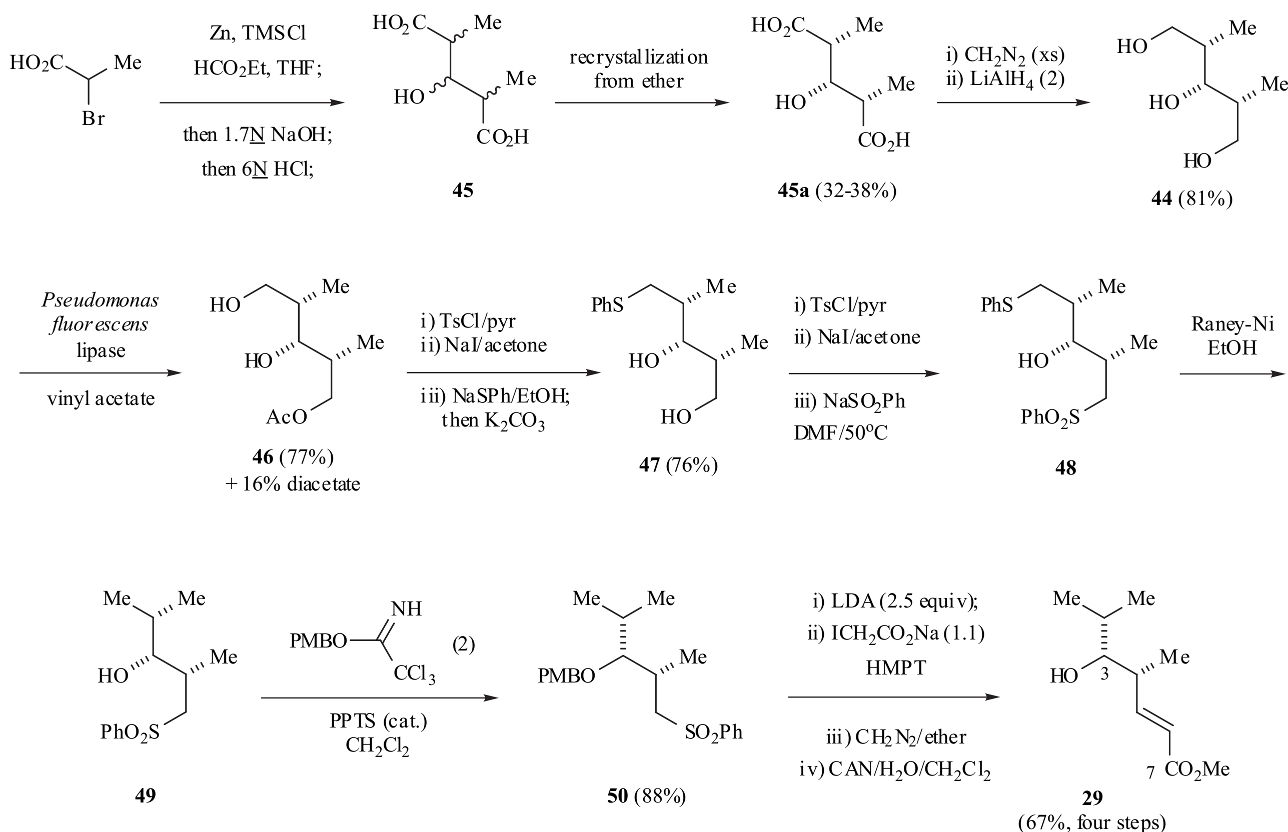
chloride in the presence of 0.5 equivalents of CuI proceeded with modest regioselectivity to give an inseparable mixture of regioisomers **38a** and **39a** (1:3). Reaction of this mixture with 1.8 equivalents of diphenyl-*t*-butoxysilyl chloride gave a separable mixture of disilylated **39b** and monosilylated **38b**. After separation, cleavage of the silyl protecting groups from **39b** gave diol **40**. A sequence of protection-deprotection steps gave 1° allylic alcohol **41** which was oxidized to the enal **42**. From this point, completion of the C9-C16 segment closely followed Schlessinger's route (c.f. Scheme **3**). Olefination gave **43** which upon C16 protecting group exchange and reduction of the nitrile gave dienylamine **17**. The synthesis of **17** by Breuilles and Uguen is considerably longer (21 steps) than that by Schlessinger's group.

The Breuilles/Uguen preparation of the C3-C7 segment relies on the desymmetrization of the meso triol **44** (Scheme **8**) [32b-d]. This triol was prepared on multi-gram scale by Reformatsky reaction of two equivalents of 2-bromopropanoic acid with ethyl formate to give diacid **45** as a mixture of diastereomers. Recrystallization of the mixture from ether gave the meso-*syn,syn* diastereomer **45a**, which was converted into triol **44** by diazomethane esterification followed by reduction. Desymmetrization of the triol was accomplished by *P. fluorescens* lipase catalyzed acylation [32c]. Conversion of the remaining primary hydroxyl group of **46** into a thio ether followed by acetate hydrolysis gave the diol **47**. The diol was then transformed into phenylsulfonate **48**, which was subjected to Raney-Ni desulfurization to give the sulfone **49** which was protected as the PMB ether. Reaction of the anion derived from **50** with sodium iodoacetate, followed by diazomethane esterification and cleavage of the PMB protecting group afforded enoate **29** [32d].

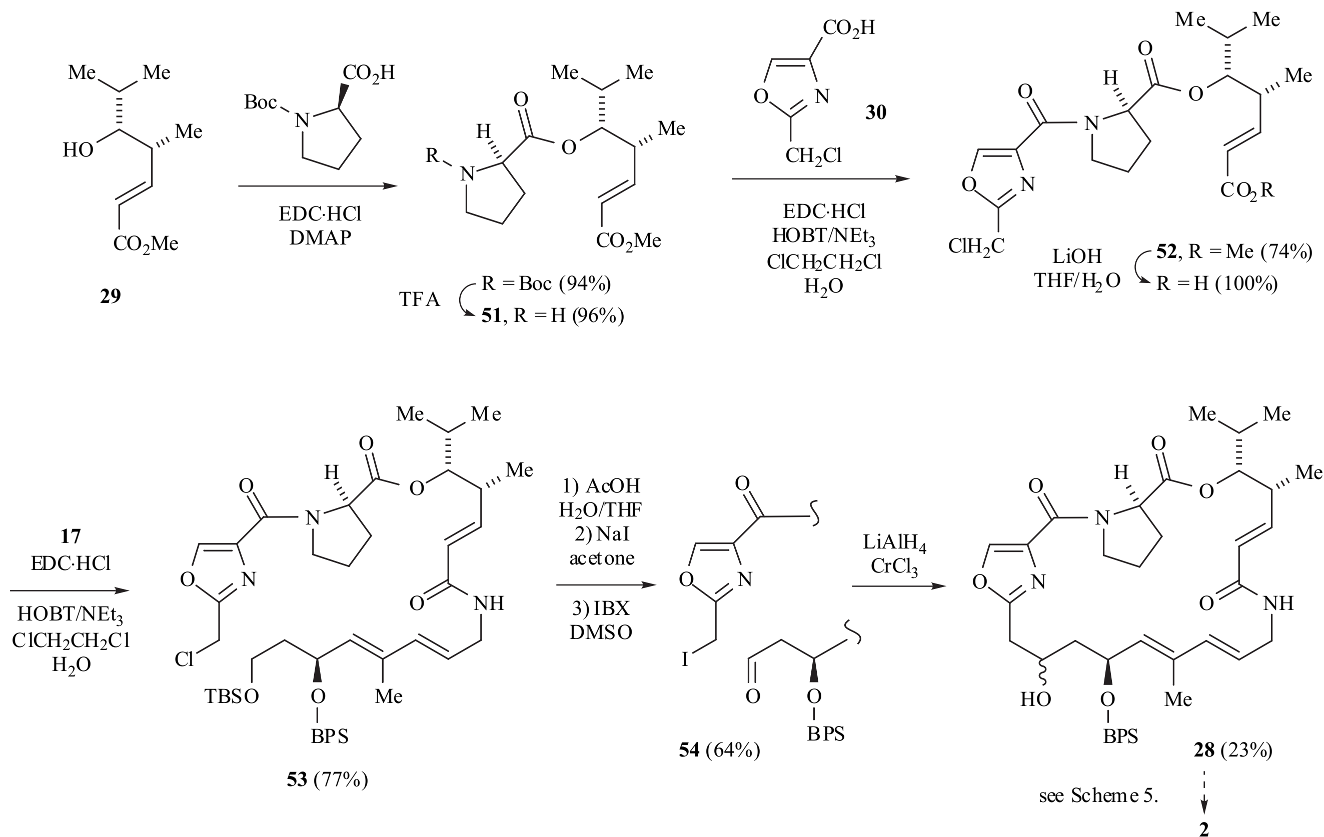
Esterification of hydroxyenoate **29** with *N*-Boc-D-proline followed by removal of the *N*-Boc protecting group gave **51** (Scheme **9**). Coupling of this segment with 2-chloromethyl-oxazole-4-carboxylic acid gave the amide **52**. Saponification of the enoate methyl ester, followed by condensation with the C9-C16 dienylamine **17** afforded the diamide **53**. Selective deprotection of the TBS ether, followed by iodide substitution and oxidation of the 1° alcohol gave **54** setting the stage for macrocyclization. To this end, reaction of **54** with a large excess of the chromous reagent prepared *in situ* from the reaction of $CrCl_3$ with $LiAlH_4$ resulted in formation of the C16-C17 bond to give **28**, as a mixture of diastereomers, along with an unidentified de-iodinated product. Preparation of **28** constitutes a formal total synthesis of virginiamycin M_2, since this compound was previously transformed into **2** by Schlessinger and Li (see Scheme **5**). This synthesis of **2** proceeded in 28 steps (longest linear sequence); < 0.2% overall yield from (*S*)-butanetriol.

3.1.3 Helquist Synthesis of the C9-C23 Segment

Prior to the Schlessinger/Li or Breullies/Uguen total syntheses, Helquist's group reported a synthesis of the C9-C23 diene segment [33] utilizing nucleophilic addition of an oxazolylmethane nucleophile to a dienal [31]. Their synthesis begins with free-radical bromination of ethyl 3-methyl-2-butenoate, followed by a Arbuzov reaction of the allylic halide with triethylphosphite to give the phosphonate ester **55** (Scheme **10**). Horner-Wadsworth-Emmons olefination of *N*-Boc-glycinal **56** with **55** gave predominantly the *E,E*-dienamine **57**. The stereochemistry of the newly formed C10-C11 double bond is *E*- (>50:1) while the major stereochemistry of the C12-C13 double bond is also *E*- (10:1). Reduction of the ester group,

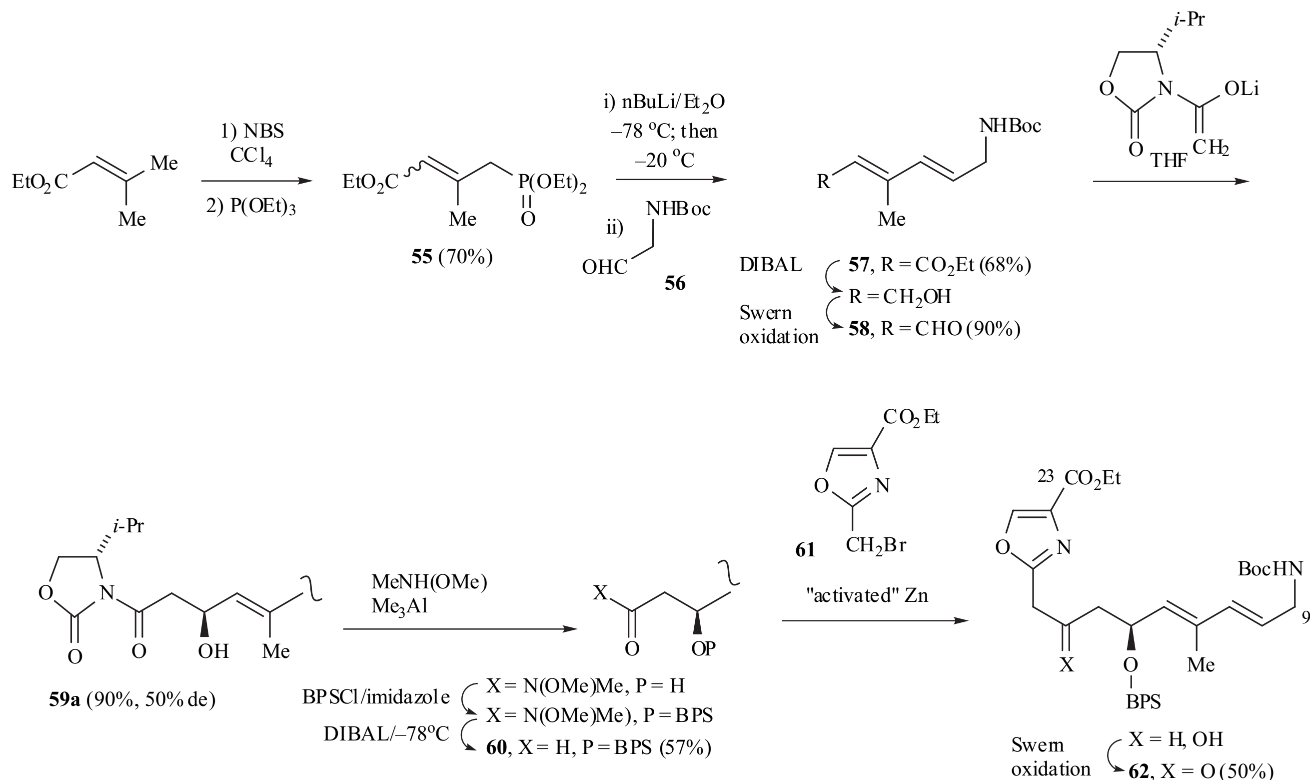


Scheme 8.

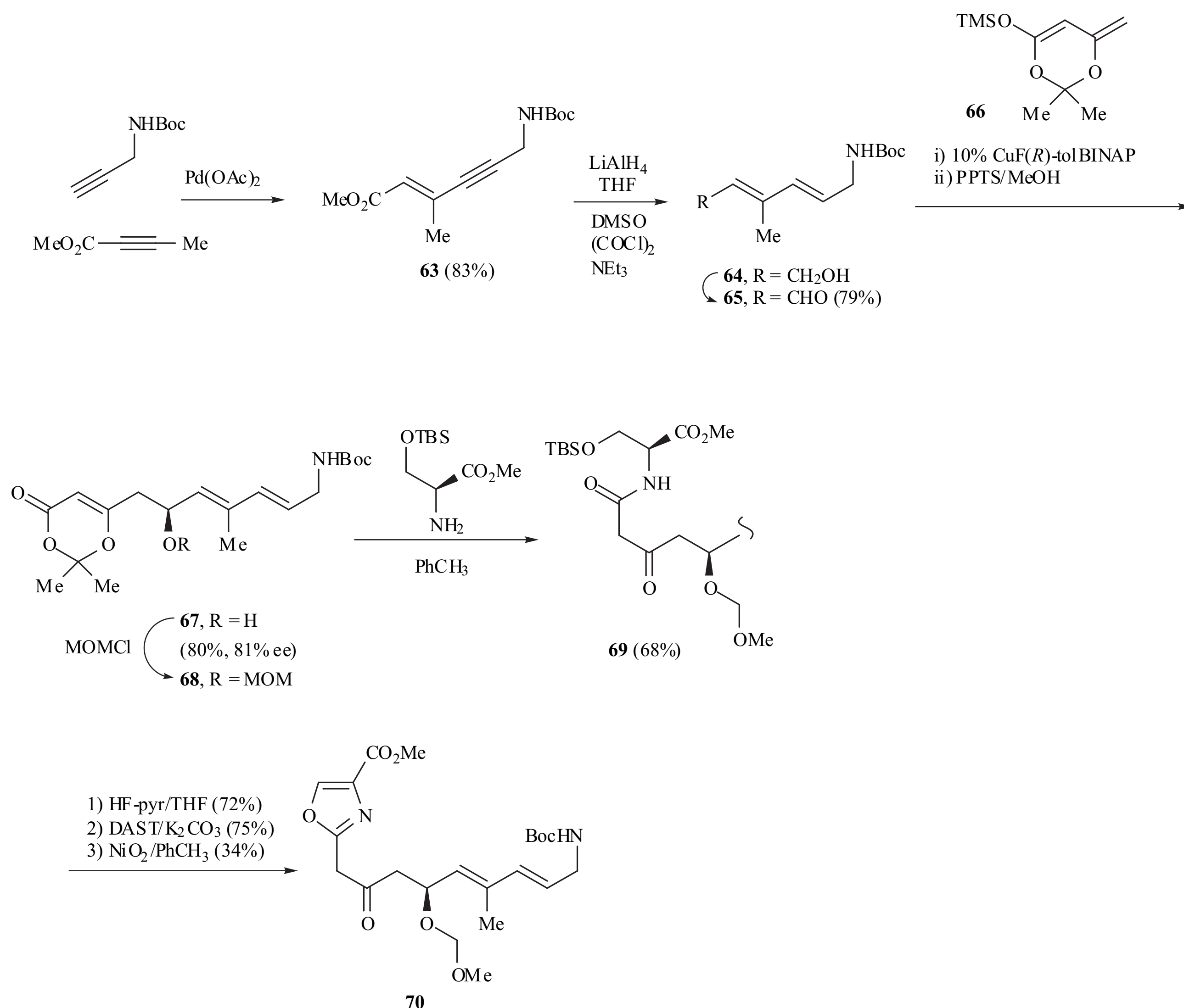


Scheme 9.

followed by Swern oxidation gave the dienal **58**. Asymmetric aldol condensation of **58** with lithium (*S*)-*N*-acetyl-4-isopropyl-2-oxazolidinone [34] yielded two separable diastereoisomers **59a**:**59b** (3:1 ratio, i.e. 50 % ee). The desired diastereoisomer (**59a**) was converted into the Weinreb's amide and the free hydroxyl group protected as its silyl ether.



Scheme 10.



Scheme 11.

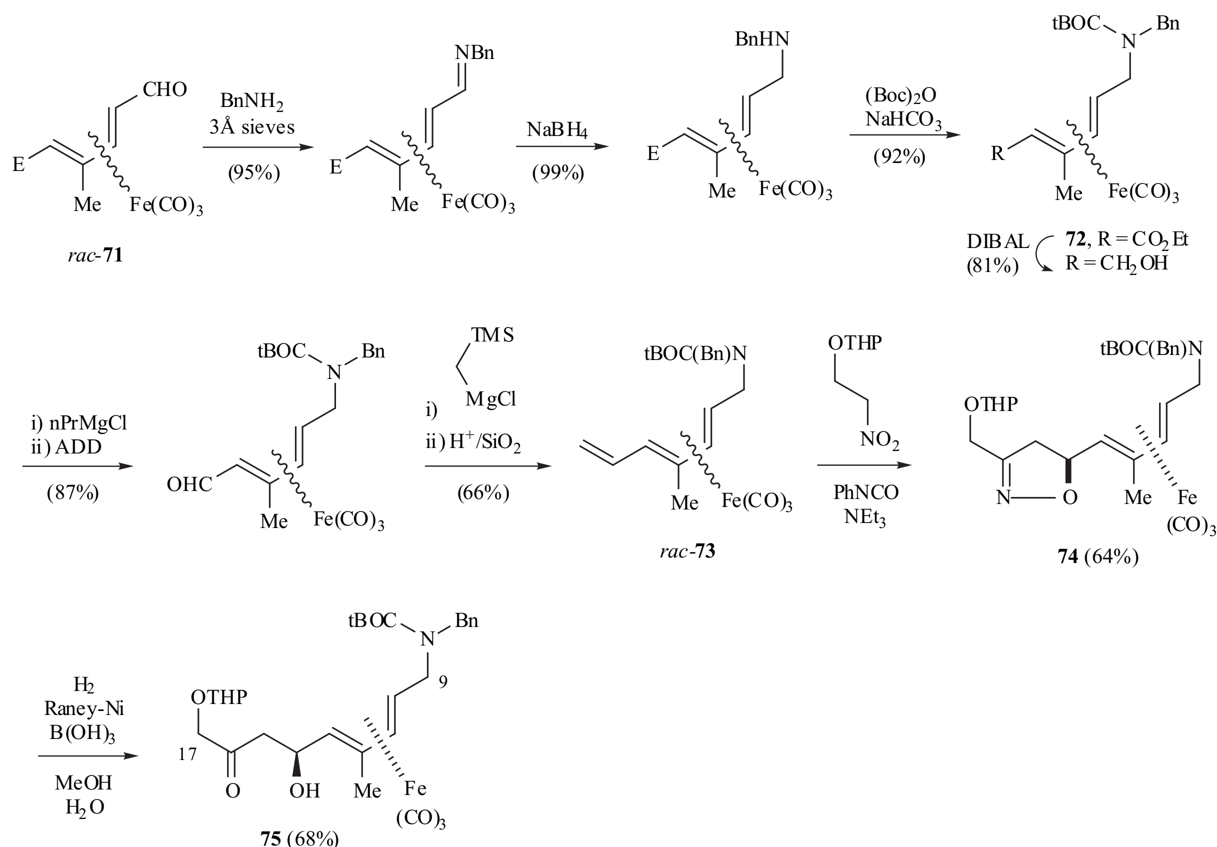
Reduction of the Weinreb's amide with DIBAL gave aldehyde **60**. Reaction of the zinc functionalized species derived from 2-bromomethyl oxazole **61** [31] with **60** gave a mixture of diastereomeric alcohols which upon oxidation resulted in a single protected β-hydroxy ketone **62**.

3.1.4 Brennan/Campagne Synthesis of C9-C22 Segment

Brennan and Campagne have prepared a similar C9-C22 segment of virginiamycin M_2 [35]. The synthesis begins with a palladium-catalysed coupling of *N*-Boc propargylamine and methyl 2-butynoate to yield **63** (Scheme **11**). Reduction of the alkyne and the methyl ester was carried out by treating **63** with $LiAlH_4$ to give the desired (*E,E*)-dienol **64**. Swern oxidation of **64** yields aldehyde **65**. An asymmetric acetoacetate vinylogous Mukaiyama-aldol reaction [36] of aldehyde **65** with the trimethylsilyloxydiene **66** in the presence of CuF(*R*)-TolBINAP followed by methanolysis of the TMS ether with PPTS yielded alcohol **67** (81% ee by chiral HPLC) which was protected as its MOM ether (**68**). Reaction of **68** with TBS protected serine methyl ester in toluene at elevated temperature gave amide **69**, which was deprotected by treatment with HF-pyridine. The resulting amido alcohol was cyclized with diethylaminosulfur-trifluoride (DAST) [37] under basic condition to afford an oxazoline. Dehydrogenation of the oxazolidine using NiO_2 proceeded in only 34% yield to give the oxazole **70**.

3.1.5 Ahmed/Cao/Donaldson Synthesis of C9-C17

Ahmed, Cao and Donaldson have prepared a C9-C17 segment of virginiamycin M_2 [38a]. Their synthesis begins with the known [39] *E,E*-dienal-iron complex **71** (Scheme **12**). Reaction of **71** with benzylamine followed by $NaBH_4$ reduction and protection gave the *N*-Boc derivative **72**. The ester complex was transformed into the triene **73** by reduction, Saigo-Mukaiyama oxidation [40], and finally Peterson olefination. Cycloaddition of **73** with the nitrile oxide derived from 2-(2-nitroethoxy)tetrahydropyran gave isoxazoline **74** as a mixture of diastereomers at the THP carbon. The diastereoselectivity of this cyclocondensation results from approach of the nitrile oxide to the complexed triene in the *s-trans* conformer on the face opposite to the bulky (tricarbonyl)iron group (Fig. **7**). The *s-trans* conformer is the predominant conformer in solution due to destabilizing steric interactions in the *s-cis* conformer. Reductive hydrolysis of isoxazoline **74** in the presence of commercially purchased Raney-Ni gave β-hydroxyketone **75** as a mixture of diastereomers at the THP carbon. While the diastereoselectivity of the intermolecular nitrile oxide-olefin



Scheme 12.

cycloaddition was demonstrated on a racemic (triene)iron complex, preparation of the precursor (**71**) in optically active form would lead to an enantioselective synthesis [38b].

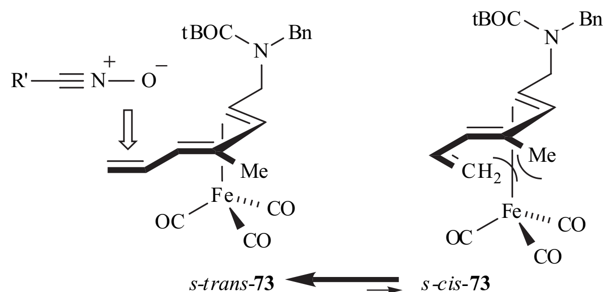


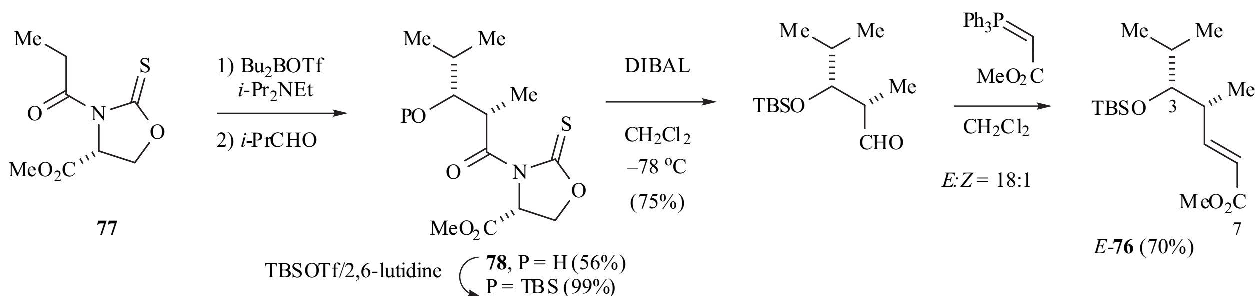
Fig. (7).

3.1.6 Helquist Route to the C3-C7 Segment of the Virginiamycins/Madumycins

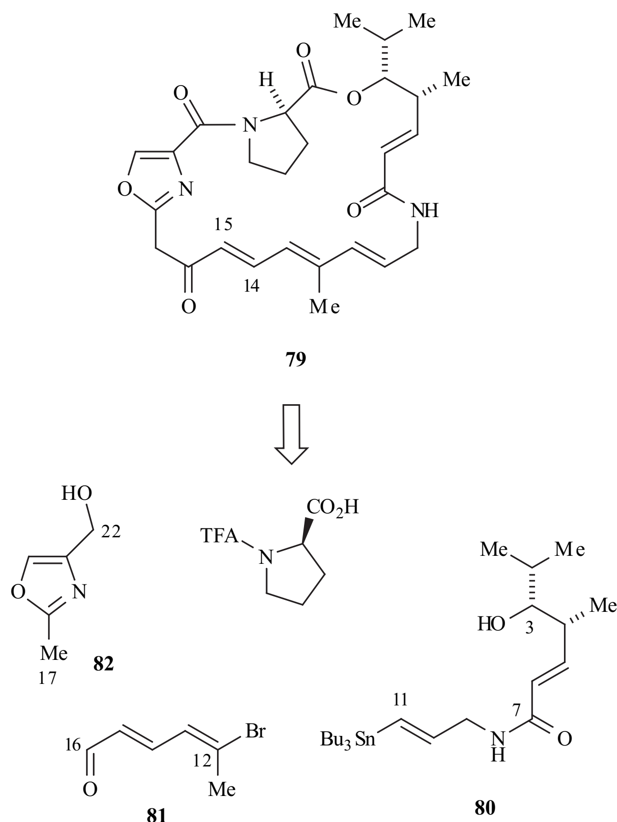
Helquist's group has described a short route to the C3-C7 segment **76** of the virginiamycins/madumycins [41]. This synthesis utilizes a diastereoselective aldol condensation between *N*-propionyl oxazolidinethione **77** and isobutyraldehyde to afford **78** (Scheme **13**). Protection of the C3 alcohol, reductive removal of the chiral auxiliary, and olefination complete the synthesis. The Wittig olefination proceeded with 18:1 E:Z selectivity, and the two geometrical isomers could be separated by column chromatography.

3.2 Synthesis of 14,15-Anhydropristinamycin II_B

14,15-Anhydropristinamycin II_B (**79**, Scheme **14**) is a streptogramin A antibiotic related to virginiamycin M_2; the dehydroproline derivative has been isolated from *S. olivaceus* ATCC53527 [42]. Pattenden's group has reported a total synthesis of **79** which relies on a Stille-type Pd-catalyzed vinyl-tin coupling [43] strategy for closure of the macrocyclic ring. Their retrosynthetic analysis dissects the target molecule into a vinyl-tin amide segment **80**, a dienal bromide **81**, and oxazole **82** (Scheme **14**) [44].



Scheme 13.



Scheme 14.

Preparation of the vinyl-tin amide segment (C3-C11) begins with a diastereoselective aldol condensation between the *N*-propionyl oxazolidinone **83** [34] and isobutyraldehyde to afford **84** (Scheme **15**). Reductive removal of the chiral auxiliary with Red-Al, followed by Horner-Emmons olefination gave the unsaturated ester **85**. Protection of the C3 alcohol, followed by amide formation with propargylamine gave **86**. The MOM protecting group was removed and replaced by an acetyl group. Hydrostannylation of the propargyl amide gave the vinyl-tin species **87**. Saponification of the acetyl group gave the alcohol **80**.

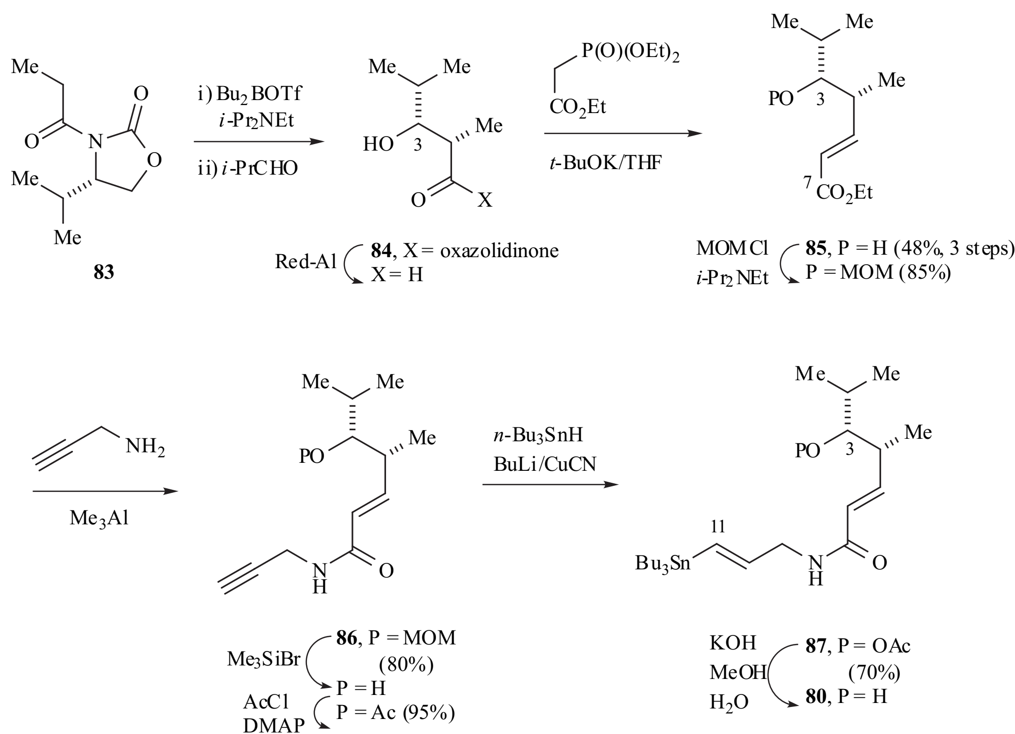
Preparation of the C12-C16 dienal bromide **81** began with oxidation of the known allylic alcohol **88** to afford the enal **89** (Scheme **16**). Horner-Emmons olefination, followed by reductive removal of the Weinreb's amide gave **81**. Reaction of the dianion generated from 4- hydroxymethylene-2-methyl-1,3-oxazole (**82**) with **81** gave the racemic dienol **90** in modest yield. Selective oxidation of the C23 hydroxymethylene group in the presence of the C16 dienyl alcohol was accomplished using MnO_2 to afford aldehyde **91**. The authors propose that this selectivity may be due to prior association of the C16 dienyl hydroxyl group with the oxazole nitrogen which protects this group from reaction. Oxidation of the oxazole carboxaldehyde gives carboxylic acid **92**.

Coupling of the C3-C11 alcohol **80** with *N*-trifluoroacetyl D-proline, followed by hydrolysis of the TFA group gave **93** (Scheme **17**). Further coupling of carboxylic acid **92** with **93** gave the vinyl stannane-vinyl bromide acyclic precursor **94** as a mixture of diastereomers at C16. Palladium catalyzed intramolecular Stille coupling [43] of **94** with $Pd_2(dba)_3$ and triphenylarsine afforded the macrocyclic trienol **95**, albeit in low yield. Oxidation of the alcohol completed the synthesis of anhydropristinamycin II_B. The synthesis proceeded in 14 steps, 1.3% overall yield from **83**.

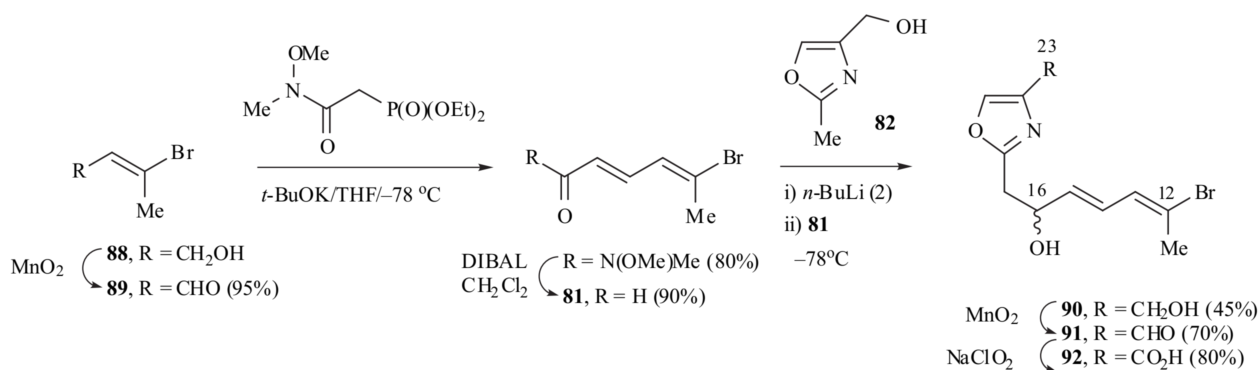
3.3 Syntheses/Synthetic Studies of Madumycin II_B

3.3.1 Meyers' Synthesis of Madumycin II

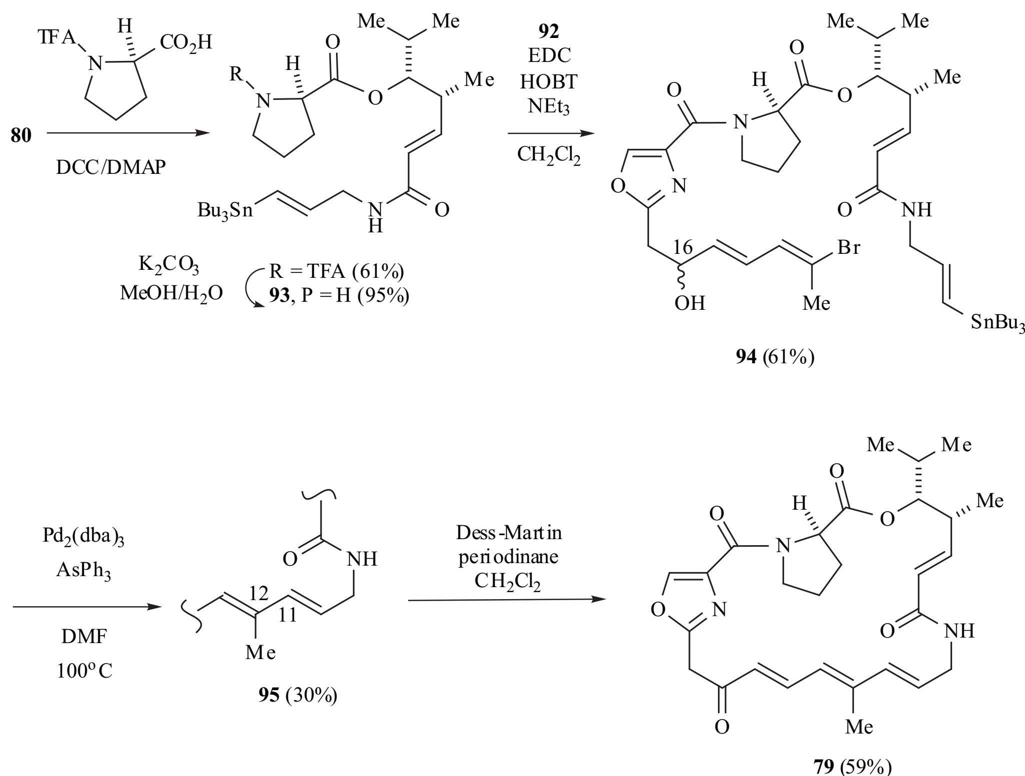
Meyers' group has reported a total synthesis of madumycin II_B [45]. Their strategy required dissecting **3** into two major



Scheme 15.

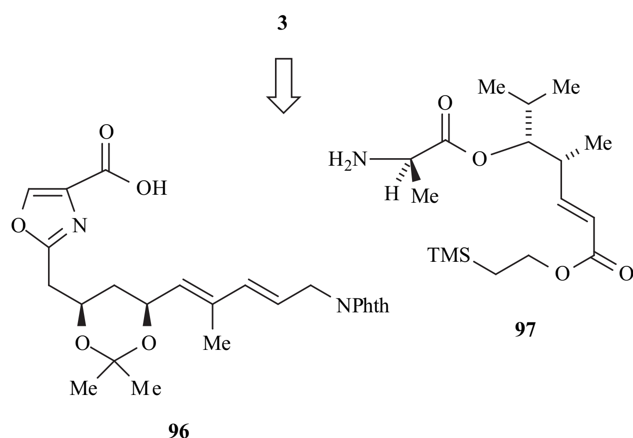


Scheme 16.



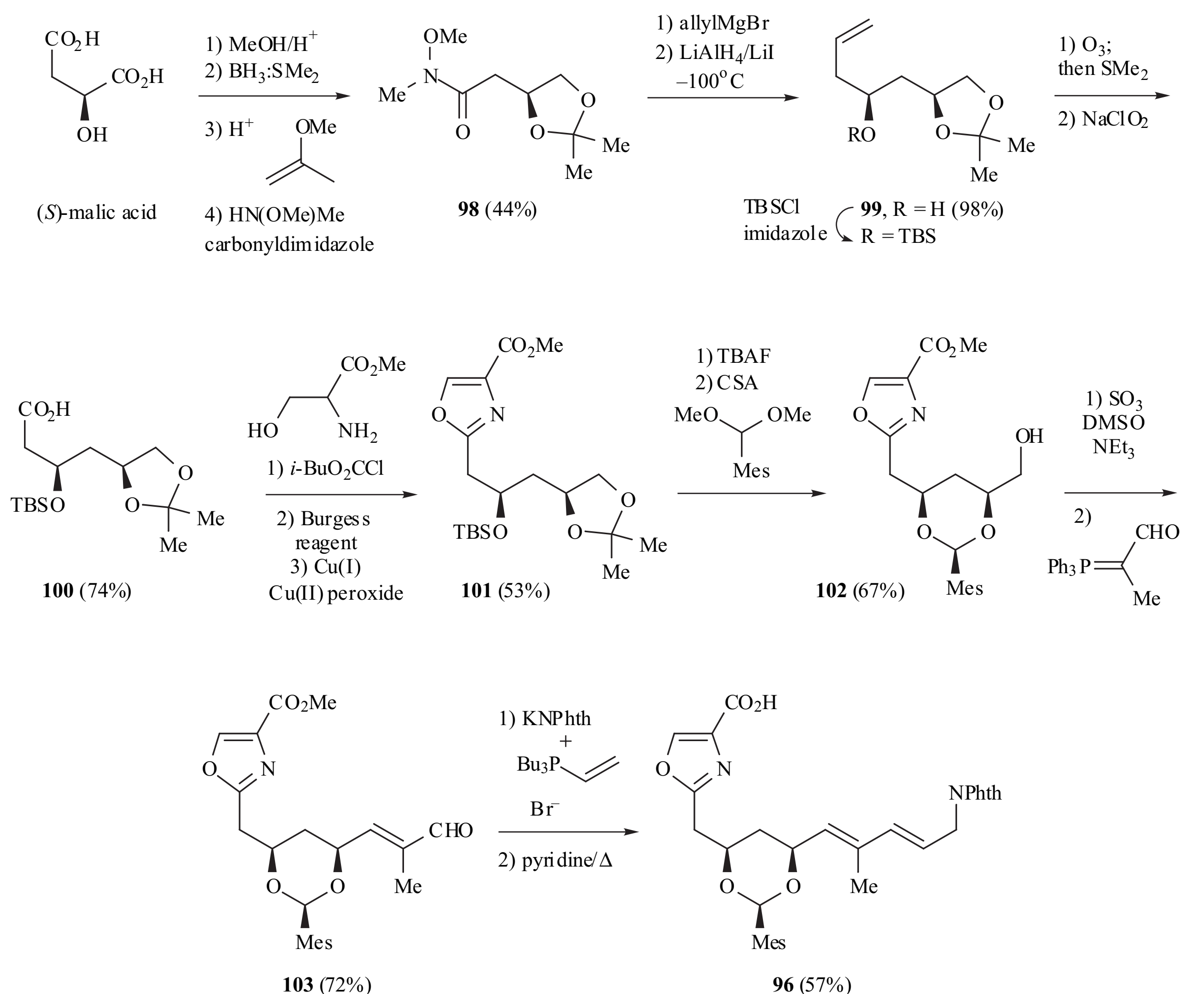
Scheme 17.

components **96** and **97** by disconnection at the two amide bonds (Scheme **18**).



Scheme 18.

Meyers route to the C9-C23 segment **96** began with transformation of (*S*)-malic acid into the Weinreb's amide **98** by 1) Fischer esterification, 2) chelation controlled borane reduction, 3) 1,2-diol protection, and 4) conversion to the amide (Scheme **19**). Reaction of **98** with allyl magnesium bromide generated the β,γ-enone which underwent stereoselective reduction (>99% de) with $LiAlH_4$ and LiI to afford the homoallylic alcohol **99**. Protection of the secondary alcohol, ozonolysis and chlorate oxidation yielded the carboxylic acid **100**. The carboxylic acid was converted into the requisite oxazole **101** by 1) generation of the mixed anhydride with isobutylchloroformate, and amide formation with (*S*)-serine methyl ester, 2) cyclization to the oxazoline with Burgess reagent [46], and 3) oxidation of the oxazoline to oxazole with Cu(II)-Cu(I) peroxide reagent [47]. Deprotection of the C16 TBS ether followed by reaction with the dimethyl acetal of (2-mesityl)formaldehyde in the presence of a catalytic amount of camphorsulfonic acid gave the acetal **102**. Swern oxidation of the 1° alcohol and Wittig olefination with α-formylethylidine

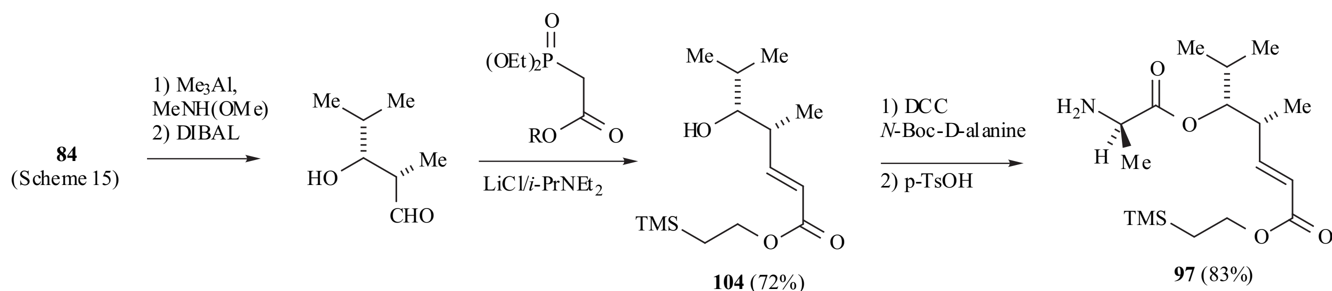


Scheme 19.

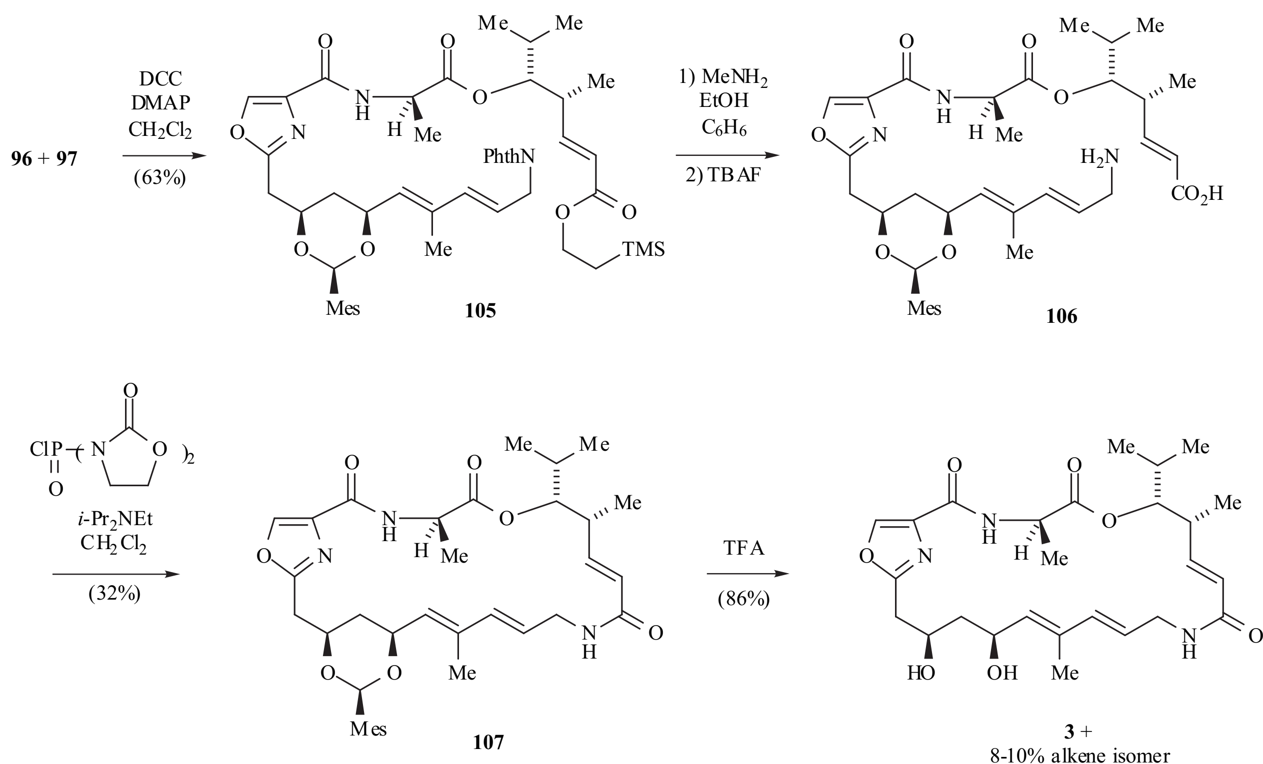
triphenylphosphorane afforded the (*E*)-α,β-unsaturated aldehyde **103**. Reaction of enal **103** with vinyl tributyl-phosphonium bromide and potassium phthalimide yielded the *E,E*-dienylamine, and removal of the methyl ester gave the oxazole carboxylic acid **96** (18 steps, 4.6 % overall yield).

Meyers' construction of the northern fragment of the macrolide utilized an Evans' diastereoselective aldol condensation, similar to that reported by Pattenden (c.f. Scheme **15**) to generate the alcohol **84**. The acyl oxazolidinone **84** was converted into its corresponding Weinreb amide which was reduced to the aldehyde (Scheme **20**). Olefination with diethyl 2-trimethylsilyl-ethyl phosphonoacetate gave **104** as the pure (*E*)- isomer. The resulting alcohol was coupled with *N*-Boc-D-alanine followed by toluenesulfonic acid mediated removal of the Boc protecting group afforded amino ester **97**.

Dicyclohexyl carbodiimide (DCC) mediated coupling of amine **97** with acid **96** afforded the amide **105** in good yield (Scheme **21**). Removal of the phthalimide protecting group was carried out by treating **105** with methylamine in ethanol-benzene mixture at 50 °C for 2 days. Cleavage of the β-silylethylester was accomplished by treating with TBAF to yield **106**. Finally coupling of the primary amine with the C7 carboxylic acid was carried out by treating **106** with *i*-Pr_2EtN and bisoxazolidinone phosphoryl chloride (BOPCl) to yield **107**. Hydrolysis of the acetal protecting group in **107** gave madumycin II (**3**) with 8-10 % of a double bond isomer



Scheme 20.

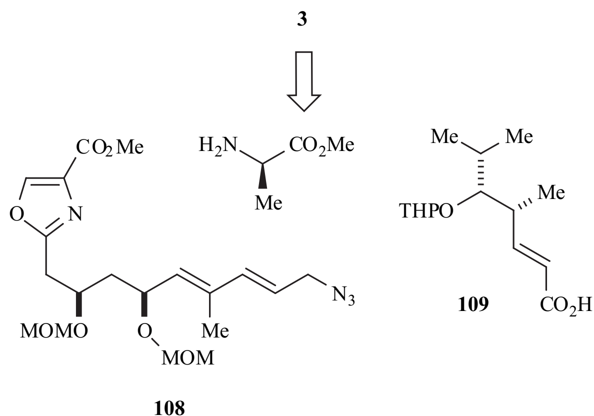


Scheme 21.

impurity. The Meyers synthesis requires 18 steps for the preparation of diene fragment **96** from (*S*)-malic acid and an additional 5 steps to couple **97** with **96** to form **3**.

3.3.2 Ghosh's Synthesis of Madumycin II

Ghosh's group adopted a linear synthesis strategy to make madumycin II. Their retrosynthetic strategy dissected the molecule into a dienyl azide (**108**) and the unsaturated carboxylic acid (**109**) (Scheme **22**) [48].



Scheme 22.

Desymmetrization of the *meso*-cyclopentane-3,5-diacetate **110** by enzymatic hydrolysis according to the procedure of Schefold [49], yielded alcohol **111** in 95% ee (Scheme **23**). Protection of **111** followed by ozonolysis and $NaBH_4$ reduction gave the diol **112**. Transesterification of the acetate with methanol and protection of the resultant 1,2-diol with 2,2-dimethoxypropane resulted in the formation of **113**. Oxidation and olefination, in a fashion similar to that of Meyers (c.f. **102** –> **103**, Scheme **19**), gave the enal **114**. Horner-Emmons olefination of **114** gave the *E,E*-dienoate **115**. Transformation into the dienyl azide **116** was accomplished by reduction with DIBAL, generation of the mesylate and subsequent S_N2 displacement with sodium azide. Selective removal of the acetonide in the presence of the MOM ether was accomplished by treatment with methanolic *p*-TsOH. Mesylation of the 1° alcohol followed by S_N2 displacement with cyanide gave nitrile **117** which was hydrolyzed to carboxylic acid **118**. Treatment with BOP and diisopropylamine in the presence of silyl protected L-serine methyl ester gave the amide, which upon protection of the C16 hydroxyl group with MOMCl furnished **119**. Conversion of **119** to the oxazole **108** required 1) silyl ether deprotection with fluoride ion, 2) Burgess reagent [46] mediated cyclization to an oxazoline, and 3) oxidation to the oxazole by treatment with $CuBr_2$, DBU, and HMTA [50].

Syn-homoallyl alcohol **120** was synthesised in >95% ee by reaction of the chiral (*Z*)-crotyl borane **121** [51] with isobutyraldehyde followed by oxidative workup (Scheme **24**). The terminal vinyl group of **120** was subjected to ozonolytic cleavage and subsequent Horner-Emmons olefination gave the α,β-unsaturated ester **85**. The secondary alcohol was then protected as the THP ether, followed by saponification to give carboxylic acid **109**.

Saponification of methyl ester **108** with aqueous LiOH followed by workup with dilute acid gave the corresponding carboxylic acid which was coupled with D-alanine methyl ester to afford **122** (Scheme **25**). Reduction of the azide functionality gave the primary amine **123**. Amine segment **123** and acid segment **109** were joined by amide formation to afford **124**. The THP protecting group was removed under acidic conditions followed by saponification of the C23 ester to afford **125**. Yamaguchi macrolactonization between the C2 hydroxyl group and the C23 carboxylic acid affords **126**. Exposure of **126** to

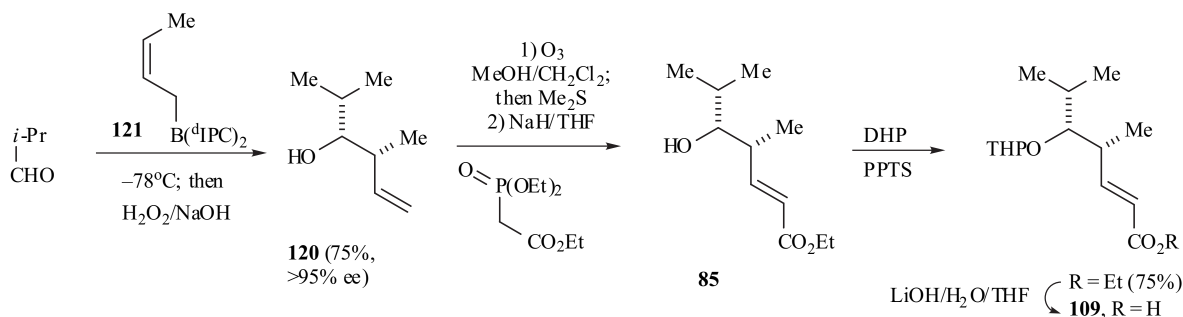
Scheme 23.

tetrabutylammonium bromide and an excess of dichlorodimethylsilane removes both of the MOM protecting groups of the 1,3-diol which concluded Ghosh's synthesis of madumycin II (**3**). The Ghosh synthesis requires 19 steps for the preparation of diene segment **108** from 3,5-diacetoxy cyclopentene and an additional 8 steps to complete the synthesis of **3** (0.68% overall yield).

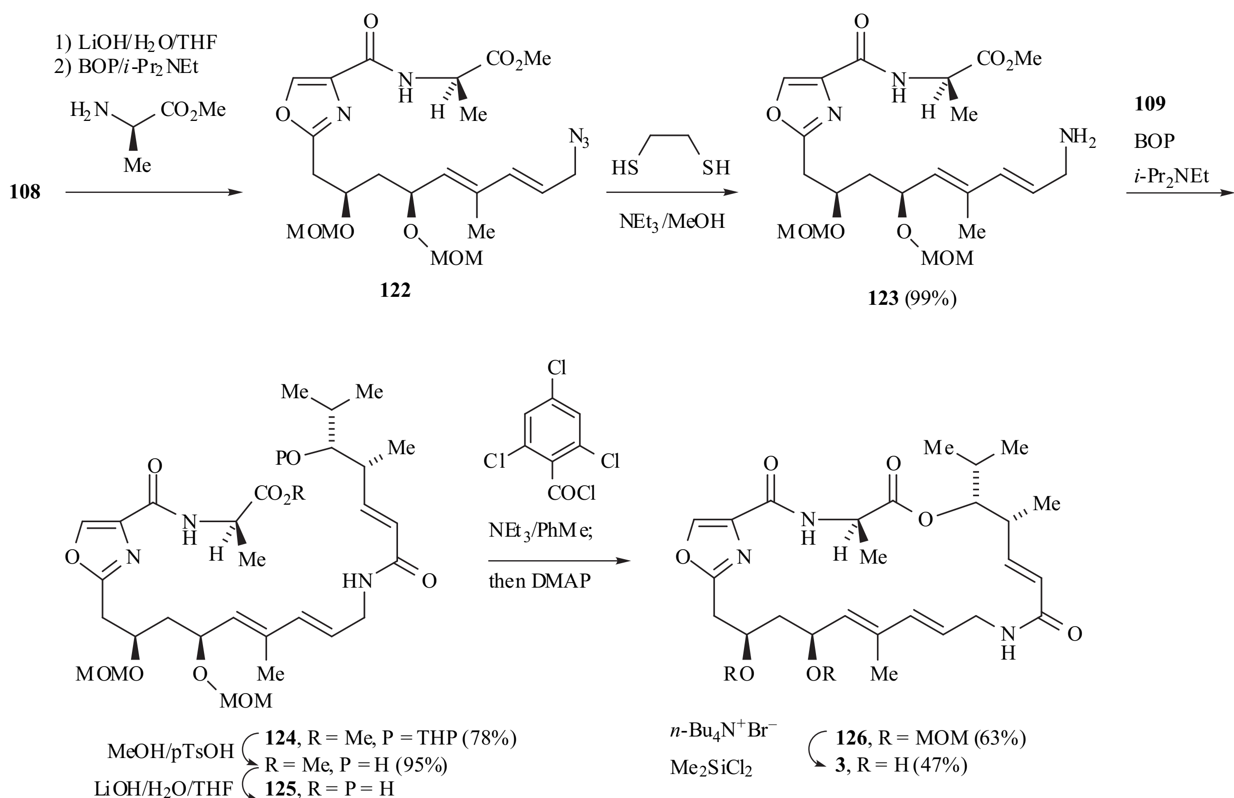
3.4 Syntheses/Synthetic Studies of Griseoviridin

3.4.1 Meyers' Synthesis

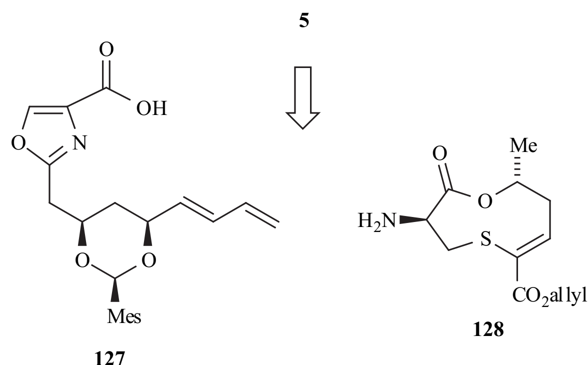
Meyers' group has reported the only total synthesis of griseoviridin [52]. Their retrosynthetic strategy divided the molecule **5** into a C11-C24 oxazole-diene **127** and the nine-membered vinyl sulfide macrolide **128** which would be joined using amide bond formation (Scheme **26**).



Scheme 24.



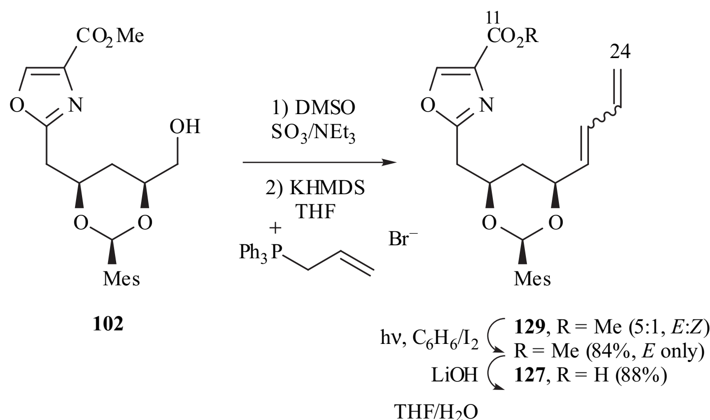
Scheme 25.



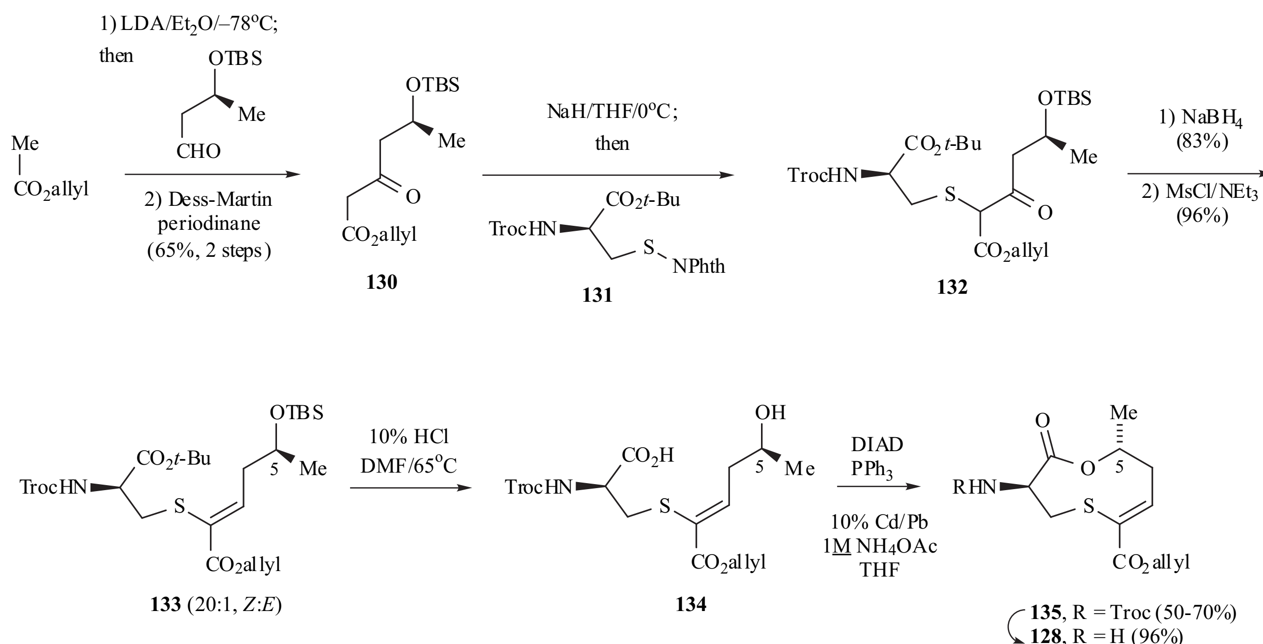
Scheme 26.

The preparation of diene segment began with the protected triol **102**, previously prepared from (*S*)-malic acid in the Meyers' synthesis of madumycin II_B (c.f. Scheme **19**) [47]. Oxidation of **102**, followed by Wittig olefination with allyltriphenylphosphonium bromide gave diene **129** as a mixture of *E*- and *Z*-isomers (5:1, Scheme **27**). Photolysis of this mixture in the presence of I_2 gave exclusively the *E*-isomer, which upon hydrolysis with LiOH gave the carboxylic acid **127**.

Condensation of the enolate anion from allyl acetate with (*S*)-3-*t*-butyldimethylsilyloxybutanal, followed by oxidation with Dess-Martin periodinane gave the β-ketoester **130** (Scheme **28**). Reaction of the anion of **130** with the electrophilic sulfur agent **131** proceeded with formation of the carbon-sulfur bond to give **132**. The configuration at this newly formed chiral center was irrelevant since reduction of the ketone functionality, mesylation of the resultant alcohol, and elimination gave the vinyl sulfide **133** (20:1, *Z*:*E*). Treatment of **133** with 10% HCl resulted in removal of both the TBS ether and



Scheme 27.



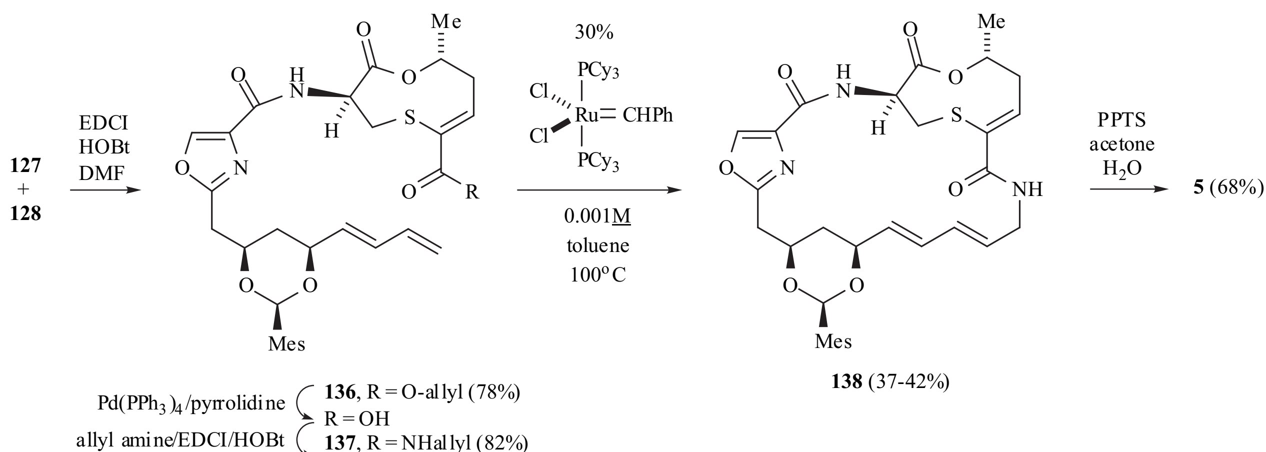
Scheme 28.

hydrolysis of the *t*-butyl ester. Cyclization of the hydroxy acid **134** was accomplished under Mitsunobu conditions [53] to give the macrolide **135** with inversion at C5. The trichloroethoxycarbonyl protecting group was removed by reduction over Cd/Pb to afford the amino lactone **128**. Many of these steps had been previously pioneered by Miller's group (c.f. Scheme **32**).

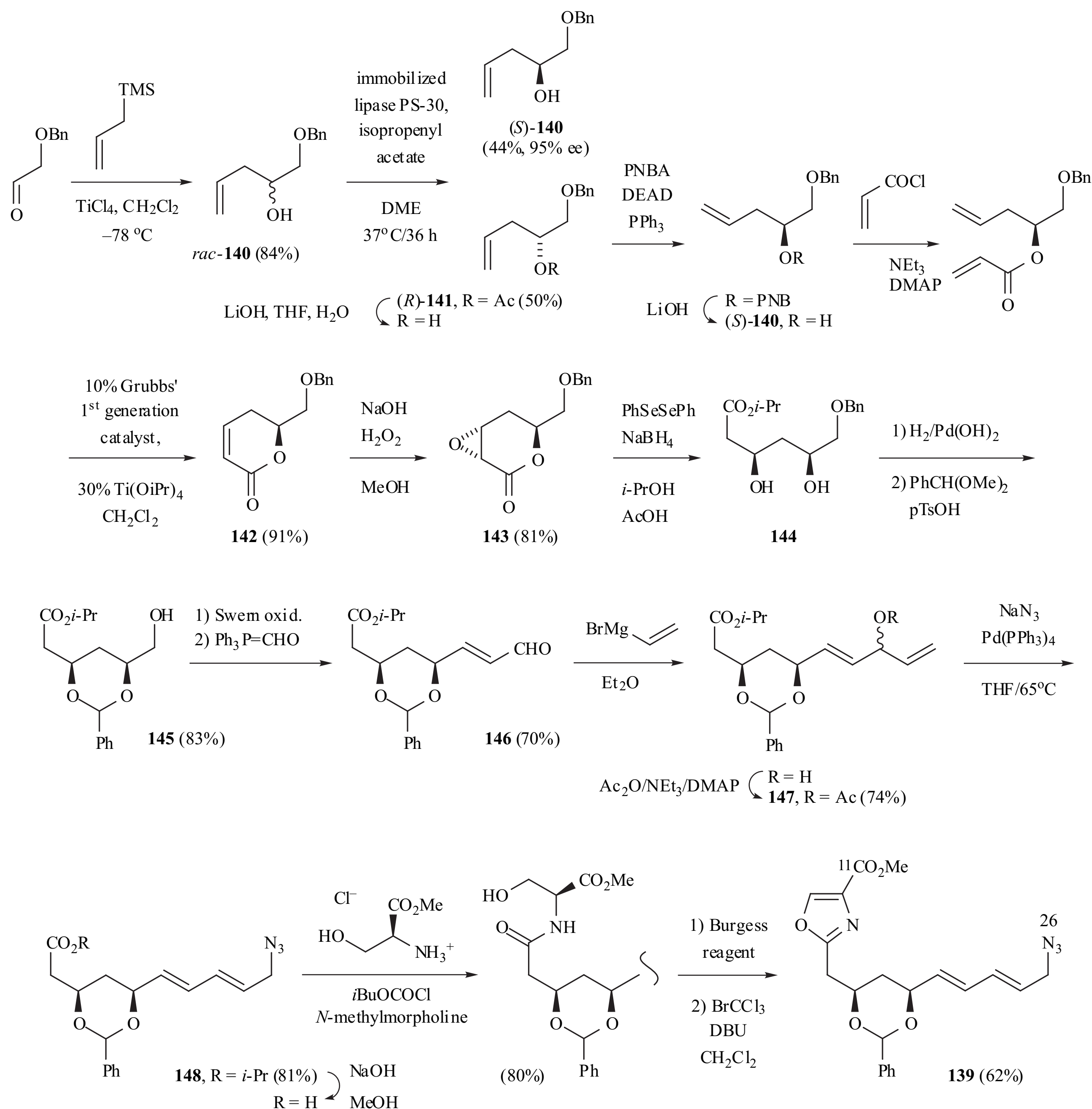
Coupling of amino lactone **128** with the oxazole carboxylic acid **127** gave the amide **136** (Scheme **29**). Conversion of the allyl ester to the carboxylic acid under Pd-catalysis, followed by amide bond formation with allyl amine gave the cyclization precursor **137**. Treatment of **137** with 30 mol % Grubbs' "1st generation catalyst" [54] proceeded with formation of the macrolide **138** as a single olefin stereoisomer. Attempts to optimize the RCM conditions resulted in yields in the 37-42% range. Hydrolysis of the mesityl acetal gave griseoviridin (**5**). The Meyers synthesis requires 17 steps from (*S*)-malic acid for the preparation of diene carboxylic acid **127** and an additional 5 steps to couple **127** with **128** to form **5**.

3.4.2 Ghosh/Lei Synthesis of C11-N26 Dienyloxazole Segment of Griseoviridin

Ghosh and Lei have reported a synthesis of the C11-N26 fragment (**139**, Scheme **30**) of griseoviridin [55]. Allylation of benzyloxyacetaldehyde gives racemic alcohol **140** which upon lipase catalyzed acylation afforded a separable mixture of unreacted (*S*)-**140** and the optically active acetate (*R*)-**141**. Conversion (*R*)-**141** into additional (*S*)-**140** was accomplished by: i) saponification, ii) Mitsunobu inversion [53] with *p*-nitrobenzoic acid, and iii) saponification. Esterification of (*S*)-**140** with acryloyl chloride and ring-closing metathesis with Grubbs' 1st generation catalyst in the presence of $Ti(OiPr)_4$ [56] gave the unsaturated lactone **142**. Epoxidation of **142** proceeded in a diastereoselective fashion, and the resultant epoxide **143** was reductively opened with diphenyl-diselenide/$NaBH_4$ in isopropanol to afford the ester **144**. Removal of the benzyl protecting group and selective protection of the 1,3-diol functionality gave **145**. The dienyl chain was installed by oxidation of the primary alcohol, Wittig olefination, addition of vinyl Grignard to the enal **146** and



Scheme 29.



Scheme 30.

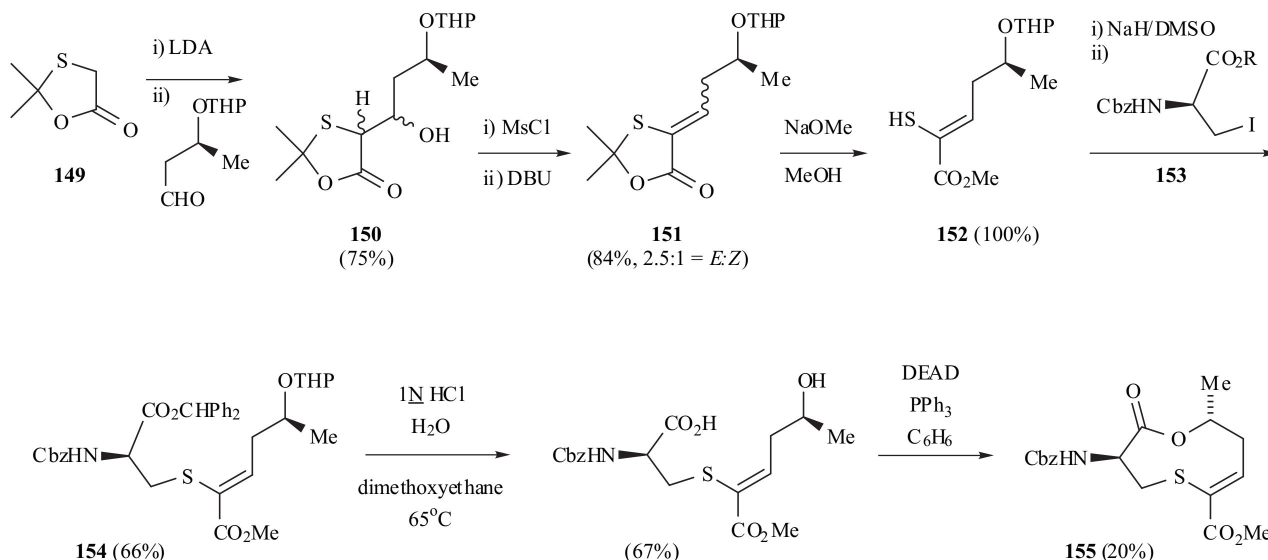
acylation of the resultant secondary alcohol to afford acetate **147** as a mixture of diastereomers. A palladium catalyzed dienyl acetate substitution with sodium azide gave **148** as the *E,E*-isomer. Conversion of the ester **148** into oxazole **139** was accomplished by a combination of methods used by Ghosh [48] and Meyers [45] in their syntheses of madumycin II (c.f. Schemes **19** and **22**). The preparation of **139** requires 17 steps from benzyloxyacetaldehyde.

3.4.3 Helquist Preparation of the Aminolactone Segment of Griseoviridin

There are many synthetic studies reported for the aminolactone segment of griseoviridin. Helquist's group reported a synthesis of the aminolactone segment in 1985 (Scheme **31**) [57]. Aldol condensation of 1,3-oxathiolanone **149** with (*S*)-3-tetrahydropyranyloxy-butanal gave a mixture of diastereomeric alcohols **150**. Mesylation followed by base mediated elimination gave **151** as a 2.5:1 mixture of *E*:*Z* isomers. Methanolysis of **151** gave the ester **152**, exclusively as the *Z*-isomer. Reaction of the anion from **152** with the protected (*S*)-iodomethyleneglycine **153** afforded the *S*-alkylation product **154**. Hydrolysis of the THP ether as well as the diphenylmethyl ester, followed by Mitsunobu cyclization [53] gave the aminolactone **155**.

3.4.4 Miller's Synthesis of a Diastereomeric Aminolactone

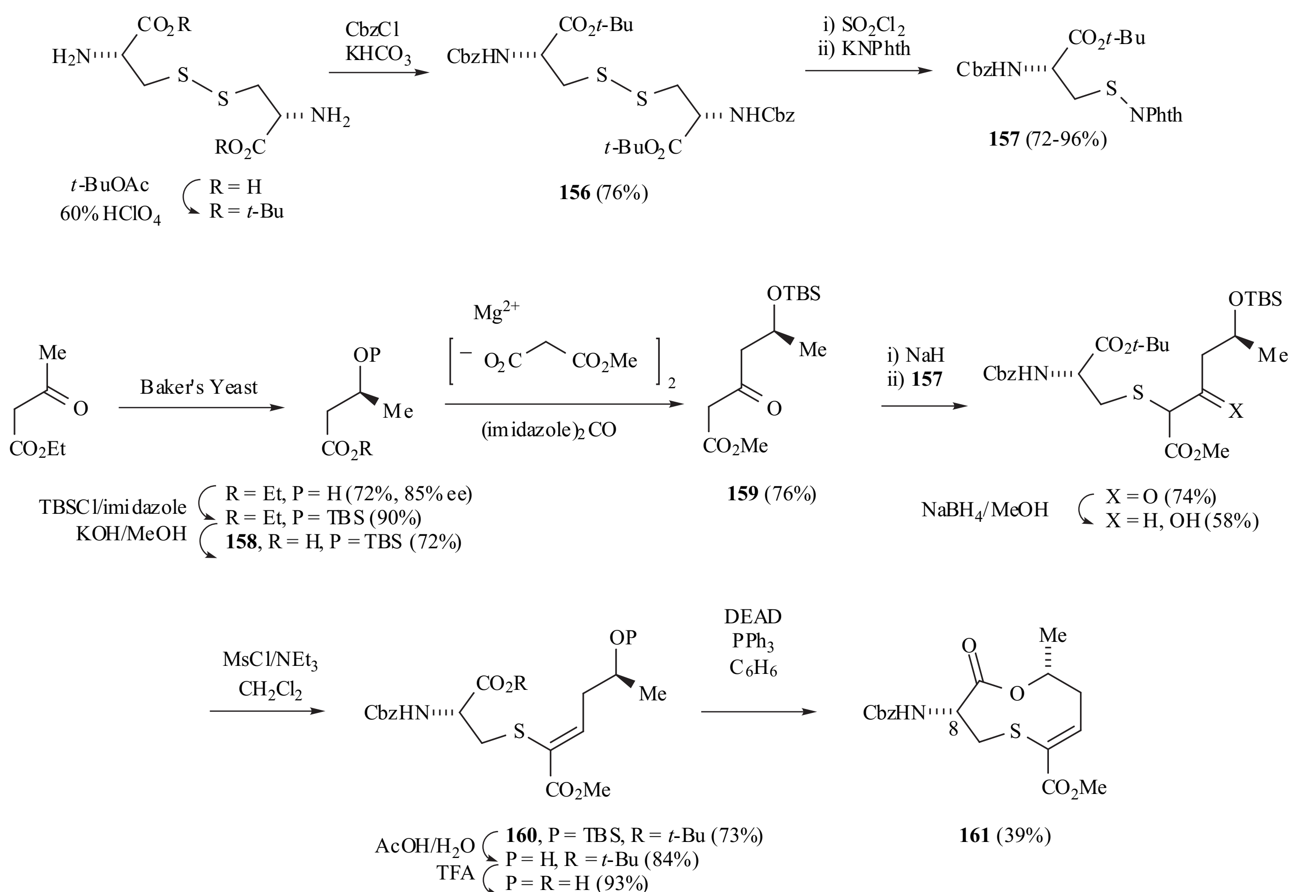
Miller's group reported a synthesis of an aminolactone diastereomeric at the C8 center with respect to griseoviridin (Scheme **32**) [58]. This difference in configuration is due to Miller's use of the less expensive L-cystine as a starting material. Esterification as the *t*-butyl ester and Cbz protection of the amino group gave **156**. Treatment of the protected cystine



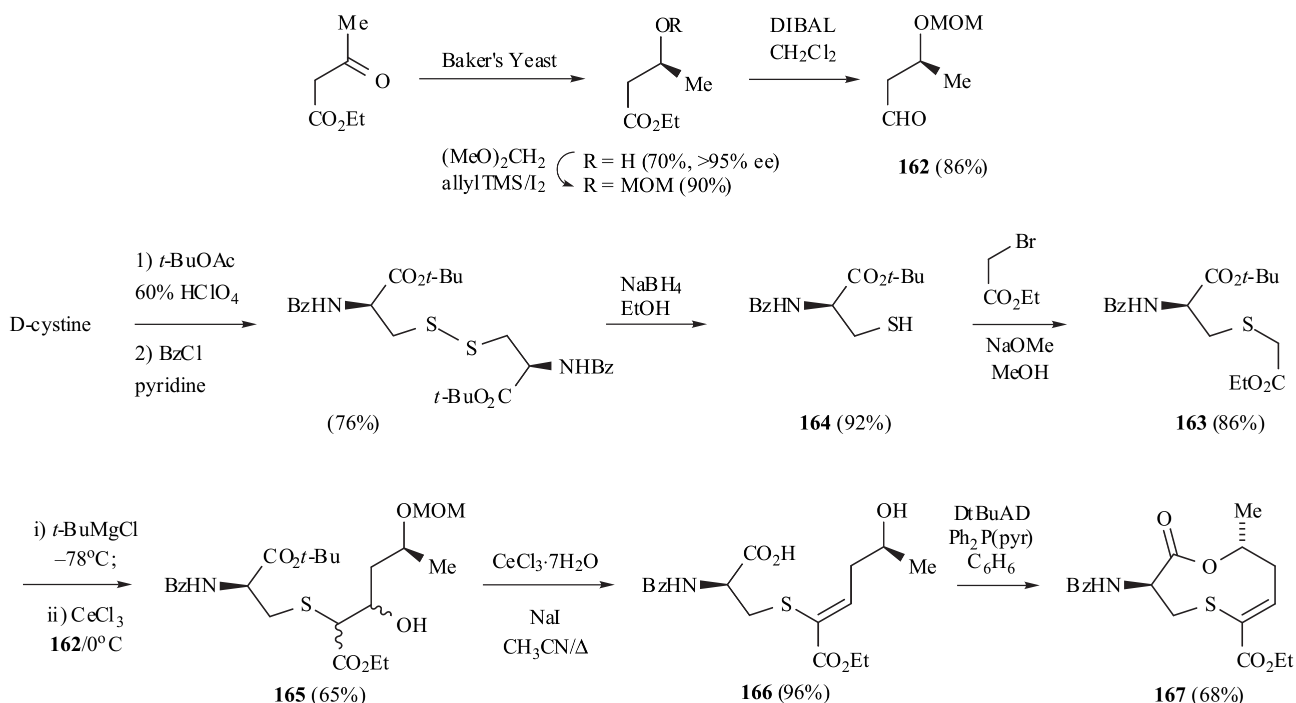
Scheme 31.

with sulfuryl chloride followed by reaction with potassium phthalimide gave an electrophilic sulfur transfer agent **157**.

Baker's yeast mediated reduction of ethyl acetoacetate gave ethyl (*S*)-3-hydroxybutanoate [59]. Protection of the alcohol and saponification of the ester gave the carboxylic acid **158**. Reaction of the carboxylic acid with carbonyldiimidazole and the magnesium salt of monomethyl malonate gave the β-keto ester **159**. Reaction of the anion of **159** with the electrophilic sulfur agent **157**, followed by ketone reduction, mesylation, and base mediated elimination afforded **160**. These steps were later utilized by Meyers' group in their synthesis of the correct diastereomer of the aminolactone segment (c.f. Scheme **28**). Hydrolysis of the TBS ether, followed by cleavage of the *t*-butyl ester and Mitsunobu cyclization [53] completed preparation of the diastereomeric aminolactone **161**.



Scheme 32.



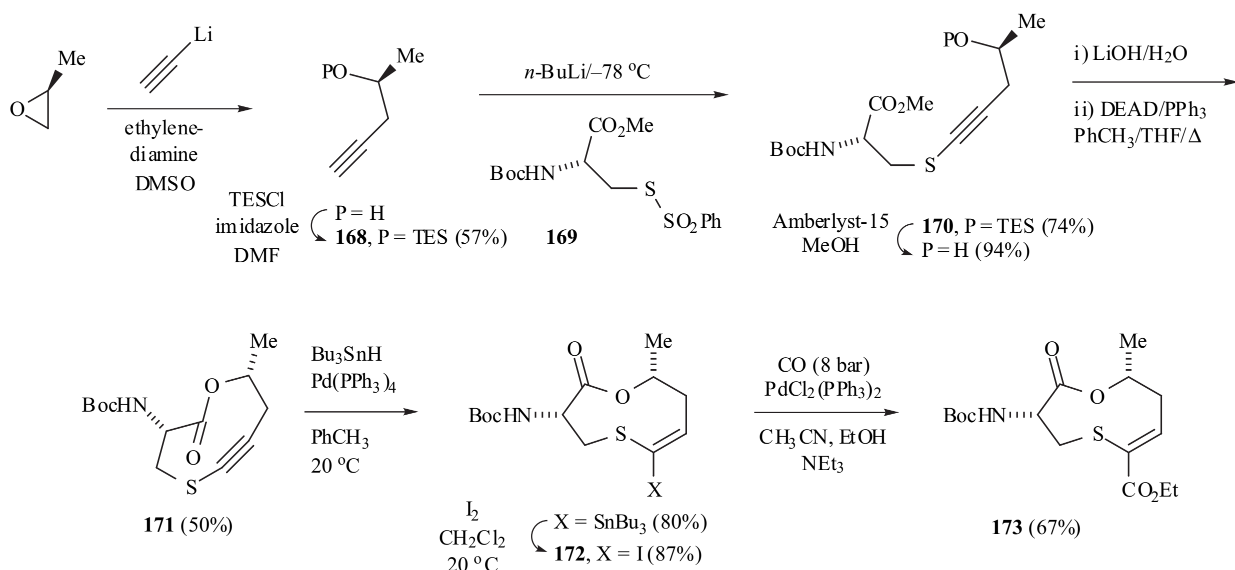
Scheme 33.

3.4.5 *Marcantoni/Bartoli Preparation of Aminolactone*

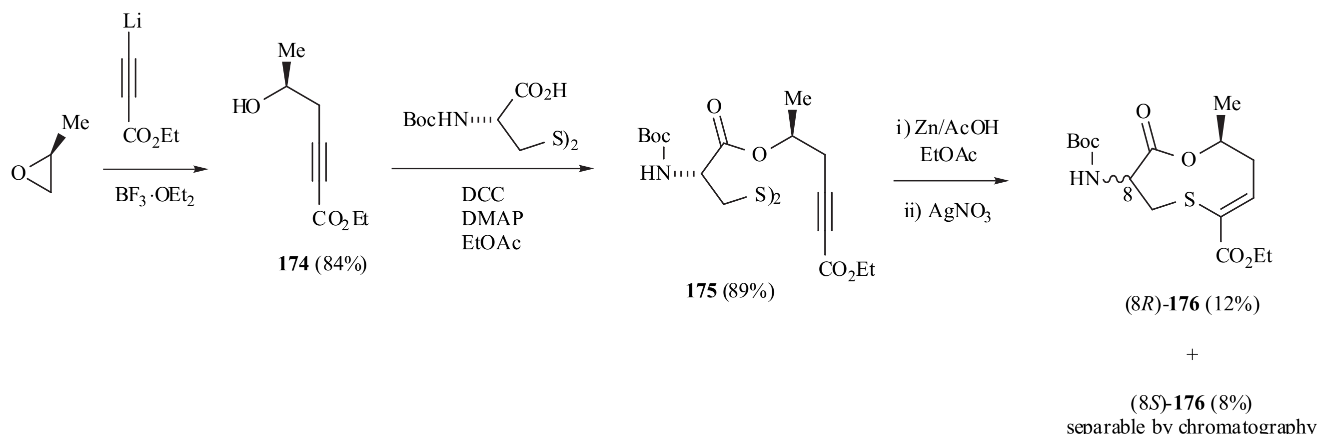
The groups of Marcantoni and Bartoli reported a synthesis of the aminolactone segment involving an aldol condensation between (*S*)-3-MOMO-butanal (**162**) and an S-alkylated 2-thioacetate (**163**) (Scheme **33**) [60]. The aldehyde segment was prepared by Baker's Yeast mediated reduction of ethyl acetoacetate [59]. In this case, the authors determined the enantiomeric excess to be 95.4% on the basis of Mischer's ester technique [61]. Protection of the secondary alcohol and DIBAL reduction of the ester gave **162**. Protection of D-cystine as its benzamide and *t*-butyl ester, followed by $NaBH_4$ reduction of the disulfide bond gave the protected D-cysteine **164**. Alkylation of **164** with ethyl bromoacetate afforded **163**. Generation of the magnesium anion of **163** and coupling with aldehyde **162** in the presence of $CeCl_3$ gave the alcohol **165** as a mixture of diastereomers. In this case, attempted mesylation/ elimination of **165**, in a fashion similar to that pioneered by Miller, (Scheme **32**) resulted in a "complex mixture of elimination products." This difficulty was eventually overcome by use of $CeCl_3$/NaI to give the vinylsulfide **166**. These reaction conditions also effected hydrolysis of the MOM ether and *t*-butyl ester. Mitsunobu cyclization [53] of **166** gave the aminolactone **167**.

3.4.6 *Ardisson's Preparation of a Diastereomeric Aminolactone*

Ardisson's group reported preparation of a diastereomeric aminolactone (Scheme **34**) [62] similar to that reported by



Scheme 34.



Scheme 35.

Miller. The French group however utilized a unique strategy compared to those outlined above. Reaction of (*S*)-propylene oxide with lithium acetylide gave (*S*)-1-pentyn-4-ol, which was protected as its triethysilyl ether (**168**). Deprotonation of **168** and reaction with the electrophilic sulfur agent **169**, derived from L-cystine, gave the alkynyl sulfide **170**. Removal of the TES protecting group, saponification of the methyl ester and Mitsunobu cyclization [53] gave the alkynyl lactone **171**. The requisite ester functionality was introduced by Pd-catalyzed hydrostannylation of **171**, followed by tin-halogen exchange to afford the vinyl iodide **172**. A Pd-catalyzed methoxy-carbonylation completed the synthesis of the diastereomeric aminolactone segment **173**.

3.4.7 Ardisson's Second Generation Approach to the Aminolactone Segment

More recently, Ardisson's group reported a very short, albeit non-stereoselective and lower yielding, approach to the aminolactone segment of griseoviridin (Scheme **35**) [63]. Reaction of (*S*)-propylene oxide with the anion derived from lithio ethyl propynoate gave alkynol **174**. Esterification of bis-*N*-Boc L-cystine with **174** afforded **175**; notably, both chiral centers are opposite in configuration to that required for naturally occurring griseoviridin. Zinc/acetic acid mediated reduction of the disulfide bond of **175** and work-up with silver nitrate gave the diastereomeric aminolactones (8*R*)-**176** and (8*S*)-**176** which were separable by column chromatography. Presumably, reduction of **175** proceeds with epimerization at the C8.

4. CONCLUSION

The streptogramin A macrolides are effective antibiotics, particularly when combined with the streptogramin B cyclic polypeptides. These agents act to halt protein synthesis against Gram-positive bacteria by binding to the 50S or 70S ribosomes. The complex structure of the streptogramin A antibiotics combined with their impressive biological activity has generated considerable synthetic interest, culminating in total syntheses of virginiamycin M_2 (**2**), madumycin II_B (**3**), 14,15-anhydropristinamycin (**81**), and griseoviridin (**5**). Additionally, due to the wide variety of chemical functionality present in these molecules, these synthetic studies have resulted in the development of methodology which can be applicable to a wide variety of naturally occurring targets.

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