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Recent Advances in the Chemistry and Biology of Naturally Occurring Antibiotics

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Lead-in

Ever since the world-shaping discovery of penicillin, nature's molecular diversity has been extensively screened for new medications and lead compounds in drug discovery. The search for anti-infective agents intended to combat infectious diseases has been of particular interest and has enjoyed a high degree of success. Indeed, the history of antibiotics is marked with impressive discoveries and drug development stories, the overwhelming majority of which have their origins in nature. Chemistry, and in particular chemical synthesis, has played a major role in bringing naturally occurring antibiotics and their derivatives to the clinic, and no doubt these disciplines will continue to be key enabling technologies for future developments in the field. In this review article, we highlight a number of recent discoveries and advances in the chemistry, biology, and medicine of naturally occurring antibiotics, with particular emphasis on the total synthesis, analog design, and biological evaluation of molecules with novel mechanisms of action.

Keywords

antibiotics; drugs; natural product; structure–property relationship; synthesis (org.)

1. Introduction

The advent of modern antibiotics, beginning with the discovery of penicillin, is undoubtedly one of the most significant developments of the twentieth century. With these medicines, bacterial infections are much more effectively treated, greatly enhancing the life expectancy and quality of life of people around the world. Modern antibiotics have saved uncounted millions of lives, and their role today is as important as ever. The worldwide sales of oral antibiotics totaled $25 billion USD in 2005.[1]

1.1. Historical Overview

The first general purpose antibiotic used in modern medicine was prontosil (**1**, Figure 1),[2] discovered by Gerhard Domagk in 1932, developed by the Bayer Laboratories, and launched in 1935 by the same company. Prontosil is a synthetic diazo dye containing a sulfonamide functionality, and the first member of a large class of antibacterial agents known as sulfonamides or sulfa drugs. Though largely supplanted by later antibiotics, sulfonamides still have some limited use today. Domagk was awarded the Nobel Prize in Physiology or Medicine

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in 1939 “for the discovery of the antibacterial effects of prontosil.” Another class of antibacterial agents of synthetic origin is the quinolones [see ciprofloxacin (**2**,Figure 1)],[3] first introduced in 1962. Interestingly, compounds structurally related to the quinolone antibiotics were later isolated from natural sources.[4] Almost four decades would elapse before the next synthetic antibiotic would be introduced. This would be the oxazolidinone linezolid (**3**,Figure 1),[5] whose approval by the U.S. Food and Drug Administration (FDA) came in 2000.

Though antibacterial agents of totally synthetic origin are important, they represent only a small fraction of the antibiotics in use today. Indeed, most antibiotics in the clinic can trace their development to the discovery of a natural product lead compound.[6] The history of naturally occurring antibiotics in modern medicine started in 1928 with the discovery by Alexander Fleming that *Penicillium notatum* inhibited bacterial growth around it.[7] The penicillins [see penicillin G (**4**,Figure 2)] saved the lives of countless soldiers during World War II, and afterward, they became available for civilian use. Penicillins belong to the large family of β-lactam antibiotics that also includes the cephalosporins and carbapenems. Ever since their launch, β-lactams have continuously represented the most widely used class of antibiotics. In 1945, Fleming, Chain, and Florey were awarded the Nobel Prize in Physiology or Medicine “for the discovery of penicillin and its curative effect in various infectious diseases.” In the two decades after World War II, several new classes of antibacterial agents were developed from naturally occurring antibiotics and brought to the clinic. Among them are the tetracyclines [see tetracycline (**5**,Figure 2)], the phenylpropanoids [see chloramphenicol (**6**,Figure 2)], the macrolides [see erythromycin A (**7**,Figure 2)], and the glycopeptides [see vancomycin (**8**,Figure 2)]. However, after this period of explosive growth in the development of antibiotics, the introduction of major new classes of natural product-based antibacterial agents stalled. The approval of the lipopeptide daptomycin (**9**,Figure 2)[8] in 2003 marked the launch of the first natural product-based antibiotic from a new structure class in 41 years.

The long pause in the introduction of new classes of antibacterial agents in recent times is partly due to a prevailing belief near the end of the period of rapid development that bacterial infections were more or less a solved problem.[9] However, in light of the growing problem of antibiotic resistance among clinically relevant pathogens, it soon became clear that this was not the case.[10] Even with careful use of antibiotics, the inevitable onset of bacterial resistance will demand the continued search for and development of new antibacterial agents. Indeed, resistance to antibiotics of last resort such as vancomycin is now a clinically significant problem,[11] and thus the need for new antibiotics is as urgent as ever. However, with few exceptions, new antibiotics have been next-generation versions of established drugs, and many structure classes are now in their third or fourth generation of development.[6b] While this phenomenon demonstrates the immense potential of the existing leads, it also points to a paucity of diversity within the arsenal of antibacterial agents used in modern medicine. This state of affairs leaves society vulnerable to the likelihood of highly resistant superbugs and the possibility of a dangerous outbreak.

Fortunately, developments in biology and chemistry have improved our ability to discover novel classes of antibiotics from natural sources.[6a,12] Furthermore, it is now easier than ever before to determine the mechanism of action of a newly discovered antibiotic. One can even screen for agents with a particular mechanism of action. Interestingly, progress in genomics has led to the identification of several highly conserved, essential bacterial genes, most of which have not yet been targeted as means to combat bacteria. Collectively, these advances are currently facilitating the discovery of new antibacterial agents with novel mechanisms of action.

From the beginning of the era of modern antibiotics, chemical synthesis has served an important role in the discovery and development of useful antibacterial agents.[6b] Thus, medicinal chemistry on naturally occurring antibiotics has yielded anti-infective agents with improved properties, and semisynthesis often offers a direct and cost effective process for the large scale production of next-generation compounds. And in some instances, such as in the manufacturing of chloramphenicol (**6**),[13] total synthesis is the preferred means to produce naturally occurring antibiotics due to the inefficiencies of the fermentation method. Even though few clinically used antibiotics are manufactured by total synthesis, the de novo synthesis of naturally occurring antibiotics and their analogs plays a critical role in understanding the mechanism of action and the Structure Activity Relationships (SARs) of many naturally occurring antibiotics.[6b] For example, research stemming from the total synthesis of vancomycin (**8**,Figure 2) has contributed significantly to the uncovering of its mechanism of action and led to the design and synthesis of improved analogs that are effective against vancomycin-resistant bacterial strains.[14]

1.2. Scope of Article

The body of work on the chemistry and biology of naturally occurring antibiotics is immense, and a comprehensive review of the subject is unrealistic and nearly impossible. Therefore, this review will limit its scope to works published since 2000, and highlights will be selected from classes of naturally occurring antibiotics for which total syntheses have been reported during this timeframe. Some antibiotics discussed in this review, such as tetracycline (**5**) and thiostrepton (**12**, Figure 3), have a history of extensive use in human and veterinary medicine stretching back in time for many decades. Others, such as pseudomonic acid A (mupirocin, **10**, Figure 3), have seen more limited use to date. Ramoplanin A2 (**13**, Figure 3) is currently in phase III clinical trials. Kinamycin C (**11**, Figure 3) has not been developed into a clinically useful drug, but controversy surrounding its molecular structure lasted for over two decades. The GE thiopeptides, lysobactin (katanosin B, **16**, Figure 3), abyssomycin C (**14**, Figure 3), platensimycin (**17**, Figure 3) and platencin (**18**, Figure 3) all represent new and exciting families of antibiotics that hold promise as novel therapeutic agents and leads for further optimization.

2. Tetracycline

The tetracyclines, originally discovered in 1945,[15] were the first broad spectrum antibiotics to be developed. Tetracyclines are effective against Gram-positive bacteria, Gram-negative bacteria, and bacteria lacking cell walls. Chlortetracycline (**19**,Figure 4) entered the clinic in 1948, followed by tetracycline (**5**) in 1953. The biology, medicine, and agricultural use of tetracyclines has been extensively reviewed,[16] and, therefore, only highlights will be presented here. To date, at least ten members of the tetracycline family have been used in human medicine. In addition, tetracyclines are heavily used in veterinary medicine, both for the treatment of bacterial infections and as feed additives.[16,17] The use of tetracyclines as feed additives was first reported in 1949,[18] and this usage was first approved by the FDA in 1951. Tetracyclines are also used to prevent and combat infections of commercially valuable fish, trees, and insects.[17] All told, an estimated 5000 metric tons of tetracyclines are consumed annually.[19] Given the pervasive use of tetracyclines for the last sixty years, it is not surprising that many resistant bacterial strains have emerged. This problem of growing bacterial resistance has no doubt contributed to the decline in the use of tetracyclines in human medicine. However, in view of their good safety profile, abundant supply, and broad spectrum activity, tetracyclines remain first line agents for a variety of indications, including acne vulgaris, cholera, Lyme disease, and pneumonia.[16d] Tetracyclines are also used as alternative agents for other indications, including the treatment of certain protozoan diseases such as malaria.[20]

Tetracyclines inhibit bacterial growth by reversibly binding to the prokaryotic 30S ribosomal subunit and blocking the interaction of the ribosome with aminoacyl-tRNA, thus inhibiting protein biosynthesis.[16d] By contrast, tetracyclines interact weakly with the eukaryotic 80S ribosomal subunit. However, tetracyclines do inhibit mitochondrial protein biosynthesis, and this accounts for some of their antiparasitic activity. Interestingly, some tetracycline-susceptible parasites do not possess mitochondria, and the mechanism of action of tetracyclines against such protozoa is not known. Tetracycline resistance rarely is the result of a mutation in the bacterial 30S ribosomal subunit, but, rather, is usually conferred by the acquisition of one or more resistance genes.[16d] These genes encode either an efflux pump or a ribosome-protecting protein, and over thirty such genes have been characterized.

Tetracycline (**5**) possesses a tetracyclic framework (ABCD, see Figure 4) containing a congested array of functionalities and six contiguous stereocenters. Semisynthetic tetracyclines [21] have been extensively investigated, and the recent development of the semisynthetic glycylglycines[16b,22] demonstrates the continued importance of studying semisynthetic analogs. However, de novo synthesis would ultimately provide access to a larger universe of analogs. Not surprisingly, the high level of molecular complexity within a deceptively simple carbon framework combined with the medically important broad spectrum antibacterial activity of the tetracyclines has attracted the attention of many synthetic organic chemists. Seminal works toward the total synthesis of the tetracyclines include those by the laboratories of R. B. Woodward,[23] H. Muxfeldt,[24] and G. Stork.[25] Also of note is a semisynthesis of tetracycline by H. H. Wasserman and coworkers.[26] The mechanism of tetracycline biosynthesis is well studied,[16a] but it provides little assistance to the synthetic chemist.

In 2000, Tatsuta and coworkers disclosed the first total synthesis of tetracycline.[27] As shown in Scheme 1, their synthesis featured a Diels–Alder cycloaddition[28] to forge the AB ring system and a Michael reaction Dieckmann condensation cascade to append the C and D rings. Thus, heating diene **20** and D-glucosamine-derived enone **21** to 170 °C afforded a Diels–Alder cycloadduct which was then subjected to Jones oxidation conditions to give the AB ring system **22**. The newly formed enone moiety was then reacted with the lithium anion of lactone **23** in a Michael reaction–Dieckmann condensation cascade to furnish tetracyclic compound **24**, possessing the entire tetracycline carbon framework, as an inconsequential mixture of diastereomers. A series of functional group manipulations provided anhydrotetracycline (**25**); and using the method described in the semisynthesis of tetracycline (**5**) disclosed by Wasserman and coworkers,[26] anhydrotetracycline (**25**) was photooxidized in the presence of molecular oxygen and tetraphenylporphine (TPP) as a sensitizer to yield hydroperoxide **26**. Platinum black-promoted hydrogenolysis of the crude hydroperoxide and concomitant reduction of the tetrasubstituted olefin completed the total synthesis of tetracycline (**5**).

Five years later, Myers and coworkers disclosed a second total synthesis of tetracycline[29] as part of a continuing program to develop next-generation tetracycline analogs.[30] The Myers synthesis featured a late-stage convergent assembly of the carbon skeleton via a Diels–Alder cycloaddition.[28] The AB ring system **34** (Scheme 2) was initially synthesized from benzoic acid,[30] but an improved synthesis of this compound[31] commenced with an enantioselective addition of divinylzinc to isoxazole aldehyde **27**, promoted by norephedrine-derived chiral auxiliary **28**,[32] to provide optically active alcohol **29** in 93 % *ee*. Alcohol **29** was converted into tertiary amine **30**, which was lithiated and trapped with furan aldehyde **31** to yield intermediate **32** as an inconsequential mixture of diastereomers. Compound **32** was heated to 105 °C in order to effect an intramolecular Diels–Alder reaction to furnish, after oxidation of the secondary hydroxyl group, intermediate **33**. The latter was smoothly converted by a sequence of functional group manipulations to AB ring system **34**.

A mixture of AB ring fragment **34** and excess cyclobutene derivative **35**[33] was heated neat to 85 °C to yield pentacycle **37** (Scheme 3). Presumably, thermal 4π ring opening of cyclobutene **35** generated transient diene **36**, which was trapped by a Diels–Alder cycloaddition with the enone moiety of **34**. Interestingly, the unprotected hydroxyl group of **34** appears to be a necessary feature of the dienophile for the success of this Diels–Alder reaction. Attempts to perform the reaction with hydroxyl-protected derivatives of **34**, with or without Lewis acid catalysis, did not yield the desired cycloadduct. Cleavage of the silyl ether within intermediate **37** and subsequent oxidation provided triketone **38**. The tertiary amine of **38** was protected by protonation, and then the sulfide moiety was oxidatively eliminated to generate naphthalene structure **39**. The latter intermediate was not isolated since it spontaneously oxidized upon exposure to air to afford hydroperoxide **40**. One possible explanation for this surprisingly facile autooxidation [compare with the sensitizer-promoted photooxidation of anhydrotetracycline (**25**,Scheme 1)[26,27]] is that the isoxazole ring system may serve as an internal sensitizer for this process. Subjecting the so-obtained hydroperoxide (**40**) to a hydrogen atmosphere and catalytic palladium black resulted in hydrogenolysis of the peroxide bond, hydrogenation of the tetrasubstituted alkene, and cleavage of the isoxazole N–O bond to complete the total synthesis of tetracycline (**5**).

The described total syntheses of tetracycline may facilitate the development of another generation of tetracycline-based therapeutics. Indeed, the Myers total synthesis was part of a program directed towards the development of new tetracycline-based antibiotics.[30] While de novo synthesis of tetracycline analogs may not match the low cost of fermentation, it allows access to analogs that are not obtainable by semisynthesis. Notable analogs designed, synthesized, and evaluated by the Myers laboratory include 6-deoxytetracycline (**41**, Figure 5) and pentacyclic derivative **42** (Figure 5). Antibacterial testing of these analogs (Table 1) revealed promising properties, including activity against pathogens that are resistant to tetracycline (such as *Staphylococcus aureus* ATCC 700699). No doubt, further research may uncover even more effective compounds within the tetracycline class, giving hope for the emergence of a new generation of antibiotics.

3. Thiopeptide Antibiotics

The thiopeptide family of antibiotics appeared on the scientific scene with the isolation of micrococcin (**43**, Figure 6) in 1948.[34] Since then, approximately thirty different sub-families spanning over 75 thiopeptide natural products have been discovered, including the flagship compound of this class, thiostrepton (**12**), in 1954.[35] The chemistry and biology of thiopeptide antibiotics has been well reviewed,[36] so only highlights will be presented here. Despite the broad diversity in their structural frameworks, nearly all of these secondary metabolites exert their biological activity through the inhibition of bacterial protein biosynthesis. Furthermore, they mainly target Gram-positive bacteria, and most are highly effective against methicillin-resistant *S. aureus* (MRSA), making them attractive potential drug leads in the face of growing bacterial resistance to existing antibiotics. Characteristic structural features of the thiopeptides include sulfur- and nitrogen-containing heterocycles, complex macrocyclic frameworks, indole structural motifs, tri- and tetrasubstituted pyridine cores, and unnatural amino acids. Thiostrepton is currently used as a topical antibiotic in animal health care,[37] but its low water solubility and poor bioavailability has precluded, so far, its use in humans.

While only a handful of thiopeptide antibiotics have been constructed by total synthesis, the continuous development of novel methods for heterocycle synthesis will fuel, no doubt, future synthetic undertakings in the field. Since 2000, amythiamicin D (**44**, Figure 6), thiostrepton (**12**), GE2270A (**45**, Figure 6), GE2270T (**46**, Figure 6), GE2270C1 (**47**, Figure 6), and

siomycin A (**48**, Figure 6) have succumbed to total synthesis. These synthetic endeavors will be discussed briefly below.

3.1. Amythiamicin D

Amythiamicin D (**44**) was isolated in 1994 from *Amycolatopsis* sp. MI481–42F4, and its structure was determined by degradative and spectroscopic techniques.[38] In addition to inhibiting the growth of Gram-positive bacteria, amythiamicin D also inhibits the action of elongation factor Tu (EF-Tu), a GTP-dependent translation factor associated with antimalarial activity in blood cultures of *Plasmodium falciparum* (the parasite responsible for human malaria).[39] These fascinating biological properties, the need to deduce the stereochemistry of the three chiral centers of the molecule, and the potential for a biosynthetically-inspired construction of the 2,3,6-trisubstituted pyridine core prompted the Moody group to embark on a total synthesis of amythiamicin D, which they completed in 2004.[40] This group had previously achieved the total synthesis of promothiocin A in 1998.[41]

The strategy devised by Moody et al. towards amythiamicin D (**44**) is shown retrosynthetically in Figure 7. Dissection of the structure at four amide bonds revealed four key building blocks (**49**–**52**), of which the trisubstituted pyridine core **49** presented the most significant synthetic challenge. The team opted to carry out a ring construction rather than functionalize a more readily available pyridine system. Additionally, they faced the task of installing orthogonal ester protecting groups at the thiazolyl carboxy termini of fragment **49** in order to avoid the potential complication of differentiating these two esters.

Thiazole building block **50** was constructed using Moody's rhodium carbene N–H insertion methodology.[42] Thus, as shown in Scheme 4, aspartic acid derivative **53** and diazo compound **54** underwent a chemoselective N–H insertion reaction in the presence of catalytic dirhodium tetraoctanoate (Rh_2Oct_4) to furnish an inconsequential mixture of β-ketoamide diastereomers (**55**). Exposure of **55** to Lawesson's reagent[43] and subsequent functional group manipulations provided thiazole building block **50**. This newly designed and productive method has already been adopted by others in the field and is a valuable addition to the commonly employed Hantzsch reaction[44] for the construction of thiazoles. Peptide coupling of intermediates **50** and **52** and subsequent acidic deprotection yielded dithiazole **56**.

Scheme 5 summarizes Moody's hetero-Diels–Alder based construction of the pyridine core of amythiamicin D (**44**), the assembly of the key building blocks, and the final stages of the synthesis. While the existence of Diels–Alderase enzymes is still being debated, there is no doubt about the usefulness of Diels–Alder based strategies inspired by biosynthetic considerations.[28] Such is the case with the proposal put forth originally by Bycroft and Gowland,[45] and subsequently by Floss and coworkers,[46] in which the 2,3,6-trisubstituted pyridine core of thiopeptide antibiotics such as amythiamicin D (**44**) [as well as the dehydropiperidine core of thiostrepton (**12**) and siomycin A (**48**)] is hypothesized to be constructed biosynthetically from serine-based dehydroalanine units. The syntheses of the corresponding core structures of amythiamicin D (**44**), thiostrepton (**12**), and the GE2270 compounds (**45**–**47**, see below) provide experimental support for this hypothesis.

The azadiene component (**59**, Scheme 5) for the synthesis of amythiamicin D was generated from the reaction of bisthiazole imidate **58** with amine hydrochloride **57**, followed by DBU-assisted elimination of the primary acetate from the condensation product. The biomimetic Diels–Alder reaction was then conducted in a microwave[47] at 120 °C in the presence of the dehydroalanine-like dienophile **60** to furnish the desired pyridine core (**49**) in 33 % yield. Subsequent elaboration of pyridine **49**, involving peptide couplings with protected glycine **51** and dithiazole fragment **56**, afforded macrocyclization precursor **61**. Simultaneous removal of the *tert*-butyl protecting groups and macrolactamization completed the synthesis of

amythiamicin D (**44**) in 73 % yield over the final two steps, and confirmed Moody's suspicion that the three stereocenters within the molecule were derived from naturally occurring amino acids.

3.2. Thiostrepton

Isolated in 1954 from *Streptomyces azureus* and subsequently from *Streptomyces hawaiiensis* and *Streptomyces laurentii*,[35] thiostrepton (**12**) is the flagship member of the thiopeptide antibiotics. Thiostrepton displays a remarkable biological profile, including potent activity against a broad spectrum of Gram-positive bacteria [including multiple drug resistant pathogens such as MRSA and VRE (vancomycin-resistant *Enterococcus*)],[37,48] micromolar activity against several tumor cell lines,[48,49] activity against *P. falciparum*,[50] and immunosuppressive properties.[51] Its mechanism of action, similar to that of many other thiopeptide antibiotics, involves binding to the 23S region of the bacterial ribosomal RNA and protein L11, thereby inhibiting the GTPase-dependent function of the 50S ribosomal RNA and thus inhibiting protein biosynthesis.[52] The biosynthetic origin of thiostrepton has been thoroughly investigated, and the hypothesized biogenetic Diels–Alder pathway[46b] inspired the Nicolaou laboratory's synthetic efforts[53] toward the construction of the dehyropiperidine nucleus of the molecule. These studies also shed considerable light on the biosynthetic origins of the quinaldic acid residue of thiostrepton.[54]

As shown in Figure 8, Nicolaou and coworkers envisioned thiostrepton (**12**) as arising from the convergent assembly of five building blocks (**63**–**67**). Six retrosynthetic disconnections were envisioned, namely four amide bond formations, one macrolactamization and one macrolactonization, as indicated on fully masked structure **62**. This disassembly provided a flexible and convergent approach to thiostrepton (**12**) since the chosen sites for ring closure could be altered if necessary. The overall complexity of thiostrepton, the acute sensitivity of its structural motifs such as the dehydropiperidine and thiazoline moieties and the dehydroalanine units, as well as the challenging task of installing and maintaining the seventeen stereogenic centers and the *Z*-trisubstituted olefin posed considerable challenges to its total synthesis. The Nicolaou laboratory's synthesis of thiostrepton was completed in 2004.

Prompted by the intriguing hypothesis of the natural origins of thiostrepton, [46b] the Nicolaou team adopted an aza-Diels–Alder dimerization strategy (Scheme 6) in which thiazolidine **68** would be utilized as the precursor for both the diene and the dienophile in their projected construction of the dehydropiperidine core (**65**) of the molecule. After extensive experimentation, it was found that exposure of thiazolidine **68** to a mixture of Ag_2CO_3, pyridine, DBU and BnNH2 at −12 °C furnished a ca. 1:1 inseparable mixture of C5/C6 dehydropiperidine diastereomers **65** and **65'** in 60 % total yield. The proposed mechanistic pathway for this cascade sequence commences with formation of the fleeting azadiene intermediate **69**, which spontaneously undergoes the dimerization illustrated in depiction **70** through an *endo* transition state to provide a mixture of imines (**71** + **71'**). A tautomerization can then occur to give, through enamines **72** and **72'**, stereoselective formation of bicyclic byproducts **73** and **73'** by an aza-Mannich cyclization (Path B). Alternatively, capture of the initially formed imine (**71** + **71'**) by $BnNH_2$ generates the desired mixture of products 65 and 65' after hydrolysis of intermediates 74 and **74'**, as well as aldehyde **75** as a recyclable byproduct (Path A). Water was initially used in place of $BnNH_2$, but the weaker nucleophilicity of water toward imine intermediates 71 and 71' favored formation of the undesired bicyclic products **73** and **73'**.

With the dehydropiperidine system in hand, the seemingly trivial task of coupling the mixture of primary amines **65** and **65'** with an appropriate carboxy donor proved to be problematic because of an undesired six- to five-membered imine ring contraction. A systematic investigation revealed that the use of a small electrophile such as **66** (Scheme 7) allowed direct

acylation without attendant isomerization to provide, after transesterification, the desired six-membered ring coupled products **76** and **76'**. Subsequent reduction of the azide functionality and separation of the diastereomeric mixture provided fragment **77**.

The quinaldic acid building block (**67**) was traced back to methyl ester **79**, prepared from commercially available 2-quinoline carboxylic acid (**78**, Scheme 8). A Boekelheide-type sequence[55] followed by dehydration with Burgess reagent[56] generated olefin **80**. Various diastereoselective epoxidation methods were tested, and it was found that the (*R,R*)-Katsuki manganese salen catalyst (**81**)[57] provided the desired epoxide **82** in 87:13 *dr*. Radical bromination and elimination of the so-formed bromide afforded **83**. Allylic epoxide **83** was then transformed into carboxylic acid **85** through a synthetic sequence that featured a regio- and stereoselective epoxide opening with L-Ile-OAllyl (**84**) as the key step. Carboxylic acid **85** was coupled with amine **86** to give, after allyl ester cleavage, quinaldic acid fragment **67**.

With gram-scale synthetic routes toward the required fragments secured, Nicolaou and coworkers proceeded to assemble them toward a total synthesis of thiostrepton. Thus, fragment **77** was transformed to amino alcohol **87** (Scheme 9), then coupled with thiazole acid **63**. The resulting diester was subjected to Me_3SnOH-mediated hydrolysis, producing an inseparable mixture of regioisomeric monoacids **88** and **88'**. The scope, selectivity, synthetic utility, and ability of the very mild reagent Me_3SnOH to hydrolyze epimerization-sensitive substrates has been demonstrated by the Nicolaou group,[58] and has found broad applicability in complex natural product total synthesis.[59] The mixture of monoacids **88** and **88'** underwent azide reduction and macrolactamization to provide the 26-membered macrocycle **90** after hydrolysis of **89**. As anticipated, the undesired monoacid **88'** did not macrolactamize, most likely due to unfavorable strain interactions as suggested by manual molecular modeling.

The next task, the preparation of the 27-membered quinaldic acid-containing macrocyclic intermediate **62** (Scheme 10), proved to be the most problematic. The primary obstacle encountered was the reactivity of the dehydroalanine moieties of thiostrepton, which were prone to palladium-mediated reduction, Et_2NH-mediated fragmentation, and addition of nucleophiles in a Michael fashion.[60] A solution was found by masking the dehydroalanine functionalities (as in dipeptide **64**) until the penultimate step. Thus, coupling of carboxylic acid **90** with **64** provided intermediate **91**. Alloc deprotection and coupling to fragment **67** afforded fluorenylmethyl ester **92**, which was deprotected and subjected to Yamaguchi macrolactonization conditions[61] to furnish macrolactone **62**, possessing the complete macrocyclic framework of thiostrepton. Gratifyingly, oxidative elimination of the three phenylseleno groups followed by simultaneous global desilylation and dehydration of the secondary TES-protected alcohol proceeded smoothly to furnish synthetic thiostrepton (**12**). The formation of the desired olefin geometry was rationalized as being due to an *anti*-periplanar elimination.

With the total synthesis of thiostrepton completed, the synthetic fragments and derivatives thereof were tested for biological activity. In these investigations, it was discovered that dehydropiperidine core analog **93** (Figure 9), despite its considerably reduced complexity to that of thiostrepton (**12**), maintained comparable antibacterial activity and surpassed the antitumor activity of the parent compound against several cancer cell lines.[48] Additionally, compound **93** showed a 30-fold difference in its ability to differentiate between human and bacterial cells, providing a promising therapeutic window for this potential drug lead. This unexpected discovery demonstrates the importance of natural product total synthesis as a tool in the investigation of biologically active substances.

3.3. Siomycin A

Isolated in 1961 from *Streptomyces sioyaensis*,[62] siomycin A (**48**) is almost structurally identical to thiostrepton (**12**), with the only difference being the dehydroalanine–valine unit connected to the quinaldic acid in siomycin A (**48**) rather than the alanine–isoleucine residues present in thiostrepton (**12**). Siomycin A is active against Gram-positive bacteria and mycobacteria,[62] and its structural elucidation was accomplished through extensive NMR spectroscopic analysis[63] and degradative studies.[64] The first total synthesis of siomycin A was reported in 2007 by Hashimoto, Nakata, and coworkers.[65] Their retrosynthetic analysis dissects a late-stage precursor to siomycin A (**94**) into five simplified fragments (**64**, **95–98**) as indicated by the peptide bond, ester, and macrolactamization disconnections shown in Figure 10. In examining the building block construction and subsequent assembly of siomycin A (**48**), the major differences that set this total synthesis apart from the thiostrepton synthesis discussed above are the differing strategies utilized for the synthesis of dehydropiperidine core **96** and the installation of the *Z*-trisubstituted olefin, the late-stage thiazoline formation, and the order in which the fragments were stitched together. Therefore, we will highlight the construction of dehydropiperidine **96** and its incorporation with the remaining fragments into the growing molecule that eventually yielded the natural product.

Hashimoto and Nakata's preparation of the dehydropiperidine core (**96**) commenced with a stereoselective 1,2-addition between chiral sulfinimine **100** and dehydropyrrolidine **99** to furnish addition product **102** in 71 % yield (Scheme 11). Both the (*R*)- and (*S*)- sulfinimine auxilliaries were investigated, and the stereochemistry of the major product was found to be controlled by the configuration of the sulfinimine group. The authors propose a transition state such as shown in depiction **101** to rationalize the observed stereochemical outcome. It is also possible that the reaction proceeds via a [3+2] dipolar cycloaddition mechanism, followed by fragmentation of the initially formed bicyclic aminal.[66] After desulfinylation of the 1,2-addition product with TFA to provide amine **103**, the resulting dehydropyrrolidine underwent equilibration with its six-membered ring relative **104**. Exposure of this mixture to $NaBH_3CN$ yielded piperidine **105** as the only isolated reduction product. The authors attributed this preference for reduction of the six-membered ring imine (**104**) to the steric hindrance around the imine functionality in dehydropyrrolidine **103**.[67] Piperidine system **105** was then transformed into intermediate **96** through functional group manipulations and coupling with Bpoc-L-Ala-OH (**106**).

The convergent fragment assembly process commenced with an intermolecular esterification between dehydropiperidine core **96** and quinaldic acid fragment **98** to yield ester **107** (Scheme 12). A series of deprotections and incorporation of bisphenylseleno amine **97** afforded intermediate **108**. Subjecting **108** to HATU-facilitated cyclization gave, after acid-induced *N*-Boc and mono-TBS cleavage, the 27-membered quinaldic acid-containing macrolactam **109**. After appending thioamide fragment **95** through another peptide coupling, a late-stage, DAST-mediated thiazoline formation was conducted to yield macrolactam precursor **110**. The decision to perform this transformation near the end of the synthesis was a witty strategic maneuver since the thiazoline moiety is prone to epimerization, and great care must be taken to avoid basic conditions in order to maintain its stereochemical integrity, as Nicolaou and coworkers also experienced in their thiostrepton synthesis.[53] Unable to differentiate between the two thiazolyl TMSE esters, Hashimoto and Nakata resorted to employing an excess of $ZnCl_2$, which resulted in hydrolysis of both esters as well as the rupture of both the *N*-Teoc and acetonide functionalities to give amino diacid **111**.

Maintaining optimism, this was viewed as an opportunity to attempt a one-pot macrolactamization–peptide chain elongation reaction. Thus, after examining a variety of peptide coupling conditions, Hashimoto and Nakata found that under high dilution conditions (1 mM solution) amino diacid **111** underwent the desired transformation in the presence of

HATU and bisphenylseleno fragment **64** (Scheme 13). The action of HATU presumably activated both carboxylic acid functionalities, resulting in formation of a macrolactam containing an activated ester (**112**). This activated ester then coupled with bisphenylseleno fragment **64** to give protected siomycin A (**94**). The crude product was then subjected to global desilylation and oxidative elimination of the five phenylseleno moieties to furnish synthetic siomycin A (**48**) in 7 % yield over four steps from **110** (along with the regioisomeric cyclization–elongation product in 8 % yield).

3.4. GE2270 Factors

The GE2270 factors were isolated in 1991 from the fermentation broth of *Planobispora rosea* ATCC53773.[68] This family of thiopeptide antibiotics consists of ten structurally related compounds. Their structural elucidation was a result of extensive spectroscopic[69] and degradation studies,[70] as well as the determination of the relative and absolute stereochemistry of the hydroxy phenylalanine domain by Heckmann and Bach.[71] Active against both Gram-positive and Gram-negative bacteria (including MRSA and VRE),[72] these antibiotics inhibit bacterial protein biosynthesis by acting on the elongation factor Ef-Tu[73] in a similar fashion to amythiamicin D (**44**). This segment of the review will focus on the recent synthesis of GE2270A (**45**), GE2270T (**46**), and GE2270C1 (**47**) in the Nicolaou–Chen laboratory in Singapore,[74] as well as the concise synthesis of GE2270A (**45**) that followed shortly thereafter by Bach and coworkers.[75] Recently, Nicoloau, Dethe, and Chen reported the total syntheses of amythiamicins A, B, and C using a similar strategy to that described here for the GE2270 factors.[40c]

The retrosynthetic analysis of GE2270A (**45**), GE2270T (**46**) and GE2270C1 (**47**) employed by the Nicolaou–Chen team[74] took advantage of the numerous sites for amide bond formation (**a**–**d**, Figure 11) as potential junctures for ring closure, allowing for considerable flexibility in the assembly process. The other two disconnection sites involve oxazoline/oxazole formation and L-prolinamide peptide coupling. The building blocks envisioned for this strategy (**51**, **113**–**118**, Figure 11) were comprised mainly of amino acid precursors, with the synthesis of 2,3,6-trisubstituted pyridine core fragment **114** being the most daunting. Since the three natural products (**45**–**47**) are closely related to one another, this strategy was expected to be applicable to the synthesis of all three antibiotics.

As shown in Scheme 14, the Nicolaou–Chen synthesis featured a key aza-Diels–Alder[28] dimerization cascade[76] similar to that previously optimized during the Nicolaou laboratory's thiostrepton total synthesis.[53] Thus, thiazoline intermediate **119** was subjected to the aza-Diels–Alder conditions and subsequent DBU-promoted deamination and aromatization to forge pyridine system **114** in 18 % overall yield. This key reaction presumably proceeded via a fleeting azadiene intermediate dimerizing in a Diels–Alder fashion through transition state **120**.

The four potential macrocyclization sites **a**–**d** (Figure 11) were evaluated, and it was determined experimentally that successful macrolactamizations could be carried out at sites **b–d**, but not at site **a**.[74b] The sequence involving macrolactamization at site **c** is shown in Scheme 15. Thus, tetrathiazole **114** was *N*-Boc deprotected and then coupled with Boc-Gly-OH (**51**) to provide amide **121**. A subsequent *N*-Boc deprotection and coupling with dithiazole **123** [synthesized by joining building blocks **113** and **117** (Figure 11)] furnished diester **124**. Unable to differentiate between the two thiazole methyl esters in **124**, the Nicolaou–Chen team resorted to Me_3SnOH hydrolysis,[58,59] which yielded a mixture of regioisomeric monoacids **125** and **125'**. After unmasking the free amine, FDPP-assisted macrolactamization under high dilution conditions afforded macrolactam **126** in 20 % overall yield from the mixture of monoacids **125** and **125'**. As with the 26-membered macrolactam formation in the thiostrepton

synthesis, the undesired monoacid did not macrolactamize. This is, again, most likely attributed to unfavorable strain interactions.

With the successful formation of macrolactam **126**, the first total synthesis of GE2270A (**45**) and GE2270T (**46**) was within reach. Thus, as shown in Scheme 16, peptide coupling of **126** with H-L-Ser-OMe (**115**) and oxazoline formation produced intermediate **127**. Diverging from this advanced material, Me_3SnOH hydrolysis and L-prolinamide (**116**) coupling furnished GE2270A (**45**), while oxazole formation followed by the same two transformations yielded GE2270T (**46**).

A superior route for the total synthesis of GE2270C1 (**47**, Scheme 17) was developed involving the peptide coupling of carboxylic acid **128** [differing from dithiazole **123** (Scheme 15) by the exclusion of the methoxymethyl group absent in GE2270C1] with the previously employed amine **122** to give diester **129**. After revealing the diacid and amino functional groups, a one-pot macrolactamization–peptide chain elongation was accomplished by subjection to HATU in order to promote ring closure, followed by addition of H-L-Ser-OMe (**115**) to furnish coupled macrolactam **131** in 35 % overall yield for the three steps. This sequence likely proceeds via presumed HOAt-activated ester intermediate **130**, and significantly improved the final approach to the GE2270 factors. The final operations needed to complete the first total synthesis of GE2270C1 (**47**) were oxazoline formation, hydrolysis to **132**, L-prolinamide (**116**) coupling, and desilylation.

Shortly after the disclosure of the Nicolaou–Chen synthesis of GE2270A (**45**) and GE2270T (**46**), Bach and coworkers published a remarkably concise synthesis of GE2270A (**45**).[75] As shown in Scheme 18, their synthetic route featured a unique approach which centered around three successive regioselective palladium-catalyzed cross-coupling reactions,[77] undoubtedly inspired by Bach's experience in this field,[78] to attach three advanced fragments onto the central pyridine core. This strategy was demonstrated initially in the same 2005 communication that included the elucidation of the previously unknown relative and absolute stereochemistry of the hydroxy phenylalanine domain by the de novo synthesis of a GE2270A degradation product.[71] Thus, a peptide coupling between carboxylic acid **134** and amine **133** provided iodide **135** (Scheme 18). Two sequential Negishi couplings[79] were then performed, first between **135** and organozinc reagent **136** to afford dibromo pyridine **137**, then a regioselective Negishi coupling with thiazolyl zinc reagent **138** to furnish bromo pyridine **139**.

To complete the total synthesis of GE2270A (**45**), Bach evaluated two potential macrocyclization strategies: a macrolactamization reaction at site **b** (Figure 11), as had been previously demonstrated by the Nicolaou–Chen group,[74] and an intramolecular Stille coupling.[80] The latter was ultimately chosen for implementation as the macrolactamization sequence suffered from low yields. Therefore, bromostannane **141** (Scheme 18), derived from the saponification of ester **139** and subsequent peptide coupling with amine **140**, underwent efficient intramolecular Stille coupling to afford macrolactam **142** in 75 % yield. Acidic cleavage of the *tert*-butyl ester, TOTU-mediated coupling with amine **143**, DAST cyclization, and desilylation completed the total synthesis of GE2270A (**45**) in 20 linear steps and 4.8 % overall yield.

4. Pseudomonic Acids

The pseudomonic acids [see for example pseudomonic acids A (**10**, Figure 12) and C (**144**, Figure 12)] were isolated from *Pseudomonas fluorescens*, and comprise a class of antibiotics with potent activity against Gram-positive bacteria and selected Gram-negative bacteria.[81] Due to the clinical importance of mupirocin (a mixture of pseudomonic acids containing 90 % pseudomonic acid A), the biology and medicine of the pseudomonic acids has been extensively reviewed.[82] Discovered in 1971,[81] pseudomonic acid A (**10**) is used in the clinic as a topical

disinfectant and antibiotic. However, its low bioavailability and metabolic instability (the ester moiety is readily hydrolyzed in vivo, resulting in an inactive metabolite) has hindered attempts to develop it as an oral antibiotic. The thiomarinols [see thiomarinol A (**145**, Figure 12)][83] and a related unnamed compound (**146**, Figure 12)[84] are rare marine natural products discovered in the 1990s with structures reminiscent of the pseudomonic acids, but possessing greater potency against both Gram-positive and Gram-negative bacteria.

The pseudomonic acids are competitive inhibitors of bacterial isoleucyl–tRNA synthetases (IleRSs).[82] These antibiotics inhibit protein biosynthesis by blocking formation of the enzyme–isoleucine complex that transfers the amino acid to tRNA. However, they bind only weakly to the corresponding eukaryotic IleRSs, minimizing eukaryotic toxicity. This unusual mechanism of action has resulted in a relatively slow emergence of resistant bacterial strains and minimal development of cross-resistance with other antibiotics.[85] Interestingly, it was recently found that the producing strain, *P. fluorescens*, possesses two different IleRSs, one of which is similar to eukaryotic IleRSs.[86] The presence of this eukaryotic-like IleRS allows protein biosynthesis to proceed in the producing strain even in the presence of high concentrations of pseudomonic acids.

The pseudomonic acids are polyketides, and their biosynthesis has been extensively studied.[87] The genetic machinery performing the biosynthesis of the pseudomonic acids, consisting of six proteins responsible for polyketide biosynthesis and 26 polypeptides performing tailoring functions, is well characterized. Recently, mutational analysis has determined that every open reading frame present in the 74 kilobase gene cluster is required for the biosynthesis of pseudomonic acid A, and has revealed the sequence in which many of these proteins function.[87]

In light of the recognized importance of mupirocin, it is not surprising that this class of compounds has received considerable attention from synthetic chemists. Extensive work on the preparation and evaluation of semisynthetic analogs in order to elucidate the SARs of this class of molecules has been performed, notably by researchers at SmithKline Beecham (now part of GlaxoSmithKline).[88] The company markets mupirocin as the topical antibacterial agent Bactroban®. The most notable structural motif of the pseudomonic acids from the chemical synthesis point of view is the densely functionalized tetrahydropyran core, and many strategies for its construction have been developed. The first total synthesis of pseudomonic acid C (**144**) was reported by Kozikowski and coworkers in 1980.[89] By 1995, at least fourteen total syntheses and formal total syntheses of pseudomonic acids had been published. These syntheses have been reviewed elsewhere.[90] Two more total syntheses, from the laboratories of Willis and Hall, have been disclosed since then and are discussed below.

In 2000, Willis and coworkers published a novel total synthesis of pseudomonic acid C (**144**) that featured two Baeyer–Villiger oxidations to prepare the tetrahydropyran core of the molecule (**151**, Scheme 19).[91] Dihydroxylation and subsequent silyl protection of optically active ketone **147** gave compound **148**, which was subjected to Baeyer–Villiger oxidation conditions to furnish lactone **149**. Reductive opening of the lactone and capping of the resulting primary hydroxyl group afforded secondary alcohol **150**, which was oxidized to the corresponding ketone and subjected to a second Baeyer–Villiger oxidation to give lactone **151**. Alkylation of the latter compound with allylic iodide **152** (Scheme 20) provided compound **153**, which was elaborated through a sequence of standard manipulations to furnish methyl ketone **154**. Horner–Wadsworth–Emmons olefination with phosphonoacetate derivative **155** gave, after desilylation, methyl pseudomonate C (**156**), which could be carefully hydrolyzed to yield pseudomonic acid C (**144**).

In 2005, Gao and Hall disclosed the first synthesis of the unnamed compound **146**.[92] Application of an inverse electron demand Diels–Alder cycloaddition[28] and allylboration sequence developed by the Hall and Carreaux laboratories[93] led to an efficient entry into the requisite core structure (**162**,Scheme 21). Thus, an enantioselective Diels–Alder cycloaddition of boronic ester **157** and vinyl ether **158** was promoted at room temperature by Jacobsen's chiral Cr(III) catalyst **159**.[94] It is interesting to note that vinyl ether **158** was difficult to obtain as a single isomer, and thus a mixture of isomers was employed. The desired *Z*-isomer was more reactive, and separation of isomers was unnecessary. After a quick filtration to remove the catalyst, the resulting cycloadduct (**160**) entered into a sluggish allylboration with aldehyde **161** to furnish key intermediate **162** in 76 % overall yield and with very high stereoselectivity (98 % *dr*, 95 % *ee*). This compound was elaborated to sulfone **163**, which was subjected to Julia–Kocienski olefination conditions with aldehyde **164** to produce ester **165**, as shown in Scheme 21. The ester moiety of **165** was hydrolyzed, and the so-revealed carboxylic acid was coupled to alcohol **166** to yield the protected natural product (**167**, Scheme 22). Fluoride-mediated desilylation and subsequent acid-promoted acetonide cleavage generated the natural product (**146**). This entire sequence was accomplished in an impressive 22 % overall yield from boronic ester **157**. The ability to produce pseudomonic acid analogs in high yield through a de novo synthesis is expected to enable SAR studies with analogs that are inaccessible from the natural substances.

5. Kinamycin C

The kinamycins [see kinamycin C (**11**, Figure 13)] are a class of antibacterial agents first discovered in 1970 by Omura and coworkers.[95] The kinamycins possess potent activity against Gram-positive bacteria, and kinamycin C also possesses modest cytotoxicity. On the basis of X-ray crystallographic analysis and chemical correlation, kinamycin C was originally assigned the cyanamide-containing structure **168** (Figure 13). In a long odyssey that has been reviewed elsewhere,[96] the structure of the kinamycins was the subject of investigation for many years. These studies culminated in revision of their originally assigned structures to the now accepted diazobenzofluorene compounds (as in **11**) as independently reported by the Gould[97] and Dmitrienko [98] groups in 1994.

Not surprisingly, the interesting biological profile and the novel and disputed structures of the kinamycins attracted the attention of several synthetic chemists. The first total synthesis of kinamycin C was completed by Lei and Porco in 2006.[99] The Porco total synthesis features a Stille cross coupling reaction[77,80] and a Friedel–Crafts acylation to assemble the kinamycin skeleton. Cross coupling partner **172** was prepared from phenol **169** as shown in Scheme 23. Thus, phenol **169** was oxidized to a partially protected quinone, and manipulation of the protecting groups provided compound **170**. A one-carbon unit was installed onto **170** under Baylis–Hillman conditions[100] to give, after an enantioselective epoxidation, epoxide **171**. Sharpless asymmetric epoxidation conditions[101] provided the epoxide in 85 % yield and 70 % *ee*. The low performance of this process prompted further studies that ultimately led to a tartrate-promoted asymmetric nucleophilic epoxidation,[102] which gave the desired epoxide in 94 % yield and 90 % *ee*. Epoxide **171** was then converted through a standard sequence of manipulations to vinyl bromide **172**. Stille cross coupling[77,80] of vinyl bromide **172** with aryl stannane **173** yielded coupled product **174** (Scheme 24), which was transformed into carboxylic acid **175** by standard chemistry. This set the stage for a critical intramolecular Friedel–Crafts acylation, which proceeded smoothly upon exposure of **175** to trifluoroacetic anhydride to furnish tetracyclic intermediate **176**. MOM deprotection and oxidation of the so-revealed dihydroquinone yielded quinone **177**. To complete the synthesis of kinamycin C (**11**), the diazo group was introduced by condensation of **177** with protected hydrazine **178** to afford the corresponding hydrazone, which was oxidized by the action of $PhIF_2$ to install the

diazo moiety.[103] Synthetic kinamycin C (**11**) exhibited indentical physical data to those of the natural substance, laying to rest any lingering doubts of the true structure of the kinamycins.

In 2007, Kumamoto, Ishikawa, and coworkers reported a synthesis of methyl kinamycin C (**186**, Scheme 26).[104] An intramolecular Friedel–Crafts acylation of carboxylic acid **179** (Scheme 25) provided a cyclic ketone, which was oxidized to enone **180** by the action of IBX.[105] Diels–Alder cycloaddition[28] of enone **180** with diene **181** furnished, after silyl deprotection, tetracyclic intermediate **182**. This intermediate was then oxidized by KF and air in DMSO to give tertiary alcohol **183**. This compound was elaborated in a sequence of standard manipulations to afford advanced intermediate **184** (Scheme 26). Exposure of **184** to Burgess reagent[56] then promoted dehydration of the unprotected tertiary alcohol, after which the acetonide moiety was cleaved and the resulting secondary alcohol was acetylated to give dienone **185**. Hydrazone formation and CAN-promoted oxidation to the required diazo moiety with concomitant oxidation of the protected dihydroquinone yielded methyl kinamycin C (**186**).

Shortly afterward, Nicolaou and coworkers reported a second total synthesis of kinamycin C (**11**),[106] featuring an Ullman coupling and a benzoin-type condensation. Starting with chiral enone **187** (Scheme 27), methyl cuprate addition and subsequent Saegusa–Ito oxidation[107] provided methylated compound **188**, which was dihydroxylated and protected to yield acetonide **189**. Another Saegusa–Ito oxidation and iodination of the resulting enone afforded vinyl iodide **190**. Ullman coupling[108] of iodide **190** with aryl bromide **191** furnished coupled product **192** (Scheme 28). Interestingly, the authors reported that the addition of catalytic CuI significantly improved the yield of this key step. The product was then exposed to the Rovis catalyst **193**[109] and triethylamine to yield pentacycle **194** in a benzoin-type condensation. The required migration of the olefinic bond was achieved through a three-step procedure. Thus, **194** was acetylated, and the resulting acetate was reductively cleaved with samarium(II) iodide.[110] Exposure of the resulting intermediate to triethylamine effected migration of the olefin into conjugation with the ketone. With the conjugated dienone moiety of compound **195** installed, a series of standard reactions provided advanced intermediate **196**. Hydrazone formation, oxidation to the corresponding diazo compound with concomitant oxidation of the protected dihydroquinone to a quinone moiety, and desilylation, yielded kinamycin C (**11**) as shown in Scheme 28.

6. Ramoplanin A2

Vancomycin and teicoplanin currently serve as drugs of last resort in the ongoing battle with pathogenic bacteria. However, bacterial resistance is inevitable,[10] and vancomycin resistance is now a clinically relevant problem.[111] Ramoplanin factors A1, A2 (**13**,Figure 14), and A3 were discovered in 1984 by Cavalleri and coworkers at Gruppo LePetit (now Biosearch Italia) in a screen for antibiotics that inhibit peptidoglycan biosynthesis in Gram-positive bacteria.[112] (Ramoplanins A1 and A3 differ only in the structure of the lipophilic domain and have virtually identical antibacterial properties.) Originally proposed to possess a (*Z*,*Z*) olefin geometry in the lipophilic side chain, the structure of ramoplanin A2 (**13**) was corrected by Kurz and Guba in 1996.[113] Ramoplanin A2 is more potent than vancomycin, and it is bactericidal at concentrations near its MIC.[112b] (In contrast, vancomycin is bacteriostatic at concentrations near its MIC.) It is also active against MRSA and VRE. Ramoplanin A2 is currently in phase III clinical trials for the prevention of VRE infections in hospitalized patients. The chemistry,[114] biology,[114] and clinical development[115] of ramoplanin have been recently reviewed.

Somner and Reynolds found in 1990 that ramoplanin A2 blocks the conversion of Lipid I into Lipid II, and proposed that it inhibits the MurG enzyme in peptidoglycan biosynthesis by

binding its substrate, Lipid I.[116] However, due to the lack of suitable MurG assays and the difficulty of studying Lipid I and Lipid II at the time, experimental support for this proposal was not firmly established. Walker and coworkers recently demonstrated in a series of experiments that ramoplanin A2 has a higher affinity for Lipid II, binding to Lipid II in a 2:1 stoichiometry to form insoluble fibrils, and this interaction is now believed to be responsible for the antibiotic activity of ramoplanin A2.[117] Inhibition of MurG may be a secondary mechanism of action, but contrary to the originally proposed model, binding of Lipid I was shown to be not required for MurG inhibition.

Ramoplanin A2 (**13**) is a large (molecular weight >2500) cyclic lipoglycodepsipeptide possessing a daunting array of synthetic challenges, including a mixture of D- and L-amino acids, multiple readily epimerizable arylglycine residues, a 49-membered macrocycle, and a hydrolytically labile lactone moiety. Having previously synthesized vancomycin aglycon [118,119] and teicoplanin aglycon,[118c,120,121] Boger and coworkers completed their total synthesis of the aglycon of ramoplanin A2 and ramoplanose (**197**,Figure 15), the latter having antibiotic activity equal to that of ramoplanin A2, in 2002.[118c,122] (Ramoplanose differs from ramoplanin A2 in the identity of the oligosaccharide domain.) Their retrosynthetic analysis of ramoplanin A2 aglycon (**197**) was designed around the known solution state structure of ramoplanin A2,[113,117b,123] and two potential macrocyclization sites **b** (Figure 15) were chosen in hopes that the formation of a beta sheet secondary structure would assist the critical macrolactamization step. Further retrosynthetic disconnections led to fragments **198**–**201**.

Boger and coworkers developed multiple successful syntheses of the requisite 49-membered macrocycle **204** (Scheme 29), and the route shown in Scheme 29 was ultimately selected as the most practical. DEPBT-promoted coupling of fragments **198** and **200** gave intermediate **202**. Selective Boc deprotection in the presence of trityl groups, promoted by bromocatecholborane, revealed a free amine, which was coupled with carboxylic acid **199** to provide macrocyclization precursor **203**. Sequential Boc and benzyl deprotection followed by EDC and HOAt-promoted macrocyclization afforded the key macrocyclic intermediate **204**. Selective Fmoc deprotection, amide coupling with carboxylic anhydride **201**, and global deprotection completed the total synthesis of ramoplanin A2 aglycon (**197**). By altering the choice of carboxylic anhydride, Boger and coworkers also prepared the aglycons of ramoplanins A1 and A3 by total synthesis.[124]

While hundreds of semisynthetic analogs of ramoplanin A2 have been studied,[115] the total synthesis devised by Boger and coworkers has allowed access to more varied modifications to the structure, enabling more precise probing of the biological properties of ramoplanin A2. [125] Notably, the laboratories of Boger and Walker demonstrated that [L-Dap^2]ramoplanin A2 aglycon (**205**,Figure 16), which replaces the unstable macrolactone functionality with a macrolactam of the same size, conferred improved hydrolytic stability with no loss of activity. [125b] More recently, Boger and coworkers performed an alanine scan on analog **205**, providing insight into the role and importance of each residue within the ramoplanin structure. [125c] No doubt, access to such a collection of analogs will assist further studies on the mechanism of action of ramoplanin A2 and enable the design of improved analogs.

7. Lysobactin

Lysobactin (katanosin B, **16**, Figure 17) is a depsipeptide antibiotic independently reported in 1988 by O'Sullivan and coworkers at Squibb[126] and Shoji and coworkers at Shionogi. [127] It is highly potent against Gram-positive bacteria (for example, MIC 0.06 μg mL^{-1} against *Streptococcus pneumoniae*; compare vancomycin, MIC 0.5 μg mL^{-1}) and possesses activity against strains resistant to a variety of other antibiotics (including vancomycin). For

example, lysobactin is up to 50-fold more potent against VRE than vancomycin, with MICs ranging from 0.4 to 0.8 μg mL^{-1}.[128] Like vancomycin, lysobactin inhibits peptidoglycan biosynthesis, but it appears to have a different mode of action that is not yet fully elucidated. In 2007, von Nussbaum and coworkers at Bayer reported an elegant total synthesis of lysobactin designed around knowledge gleaned from a crystal structure of the compound.[129] Shortly afterward, the VanNieuwenhze group reported another total synthesis which delivers this antibiotic in similar efficiency.[130] The biology and chemistry of lysobactin has been very recently reviewed.[131]

8. Abyssomicins

Abyssomicin C (**14**, Figure 18) is a polyketide antibiotic reported by Sussmuth and coworkers in 2004.[132] Isolated from the rare actinomycete *Verrucosispora* strain AB18-032, abyssomicin C blocks the growth of Gram-positive bacteria by inhibiting the synthesis of *para*-aminobenzoic acid (PABA) from chorismate, a key enzymatic step in the bacterial biosynthesis of tetrahydrofolate. The biosynthesis of PABA is essential for many microorganisms but absent in humans, making the responsible enzyme a highly appealing molecular target for an antibiotic.[133] Abyssomicin D (**206**, Figure 18) and other related natural products were found to be inactive, suggesting that the enone moiety of abyssomicin C (**14**) is an essential structural motif for its observed activity. Abyssomicin D (**206**) was proposed to be the product of a 1,4-reduction of the enone moiety of abyssomicin C (**14**) and addition of the resulting enolate into the unsaturated lactone moiety.

In light of the promising biological profile of abyssomicin C (**14**) and its intriguing molecular architecture, the molecule drew attention from several chemical synthesis laboratories. The total syntheses of abyssomicin C have recently been reviewed,[134] and thus only highlights will be presented here. One year after the disclosure of the structure of abyssomicin C, Sorensen and coworkers published the first total synthesis of this antibiotic.[135] As shown in Scheme 30, the synthesis featured a presumed biomimetic late-stage intramolecular Diels–Alder reaction.[28] Lithiation of lactone **208** and addition of the resulting species to aldehyde **207** provided, after oxidation, diketone **209**. The Sorensen group was able to eliminate the protected secondary hydroxyl moiety of **209** in order to reveal an electron-deficient conjugated triene (**210**) for an intramolecular Diels–Alder reaction to furnish advanced intermediate **211**. However, in order to avoid the requirement of handling the sensitive triene **210**, a one-pot elimination/Diels–Alder cascade was sought. It was found that lanthanum(III) triflate was a competent promoter of this cascade sequence, affording the desired product **211** in 50 % yield from diketone **209**. Epoxidation and methyl ether cleavage then led to epoxide **212**. All attempts at base-promoted intramolecular epoxide opening as a means to construct abyssomicin C (**14**) were met with failure. It was ultimately discovered that exposure of epoxide **212** to mild acidic conditions effected its quantitative conversion to abyssomicin C (**14**) and *iso*-abyssomicin C (ca. 1:1 ratio), an isomer of the natural product whose full structural characterization remained elusive until later (see below).

Concurrent with the Sorensen laboratory's publication, Snider and Zou disclosed a related Diels–Alder approach toward the abyssomicins (Scheme 31).[136] Thus, deprotonation of lactone **208** and addition of the resulting anion to aldehyde **213** gave, after oxidation, the same triene that the Sorensen group had prepared (**210**). A thermal Diels–Alder reaction (70 °C in chloroform) furnished compound **211** in 80 % yield, but Snider and Zou were unsuccessful in converting this advanced intermediate into abyssomicin C (**14**). However, the Sorensen laboratory's total synthesis of abyssomicin C (**14**) from the same advanced intermediate renders the Snider and Zou work a formal total synthesis. Interestingly, Snider and Zou discovered that upon conjugate addition of a thiolate into the enone moiety of **211**, compound **214**, possessing the abyssomicin D carbon skeleton, was obtained. This was the first synthetic entry into the

abyssomicin D ring framework, and it provided experimental support for the proposed biosynthesis of abyssomicin D (**206**).[132]

Shortly afterward, Couladouros and coworkers disclosed another formal total synthesis of abyssomicin C (**14**) based on the same Diels–Alder strategy (Scheme 32).[137] Thus, lactone **208** was lithiated and trapped with aldehyde **215** to provide compound **216**, which was transformed into triene **210** in a standard sequence of reactions. In the hands of Couladouros and coworkers, the requisite Diels–Alder cycloaddition was promoted by a catalytic amount of iodine to furnish advanced intermediate **211** in 50 % yield, thus completing their formal synthesis of abyssomicin C (**14**). Interestingly, the use of excess iodine resulted in formation of compound **217**, possessing the abyssomicin D carbon skeleton.

In 2006, Nicolaou and Harrison completed a conceptually different total synthesis of the abyssomicins.[138] An intermolecular Diels–Alder cycloaddition[28] was envisioned for the construction of the densely functionalized core of the abyssomicins, and it was proposed that a late-stage ring closing olefin metathesis[139] could forge the macrocyclic domain. Thus, chiral diene **218** (Scheme 33) was preorganized in a complex with the phenolate generated from the deprotonation of phenol **219** by MeMgBr, then Diels–Alder cycloaddition with methyl acrylate and spontaneous lactonization furnished lactone **221**, presumably via the intermediacy of complex **220**, in 80 % yield. Lactone **221** was converted in a series of standard manipulations to acetate **222**. Deprotonation of **222** resulted in a Dieckmann condensation to the non-isolated intermediate **223**, which, upon mild acidification and subsequent silyl protection, provided compound **224**. The latter compound was then lithiated and trapped with lactone **225** (Scheme 34) to yield, after masking of the ketone moiety as a dithiane, primary alcohol **226**. This compound was transformed into compound **227**, possessing two terminal alkene moieties, and setting the stage for the key ring closing metathesis reaction. Exposure to the Grubbs II olefin metathesis initiator (**228**)[140] then forged the required 11-membered ring, producing advanced intermediate **229**. Oxidation of the allylic alcohol moiety and dithiane cleavage afforded a compound whose spectroscopic data were very similar to that of abyssomicin C (**14**), but not a perfect match. Fortuitously, while characterizing this compound in $CDCl_3$ containing traces of acid, it was discovered that the unknown compound was equilibrating with abyssomicin C (**14**, Scheme 34). Chromatographic separation of the two isomers followed by X-ray crystallographic analysis of the unknown compound led to its identification as *atrop*-abyssomicin C (**15**, Scheme 34).

With the discovery of this unexpected atropisomerism, Nicolaou and Harrison proceeded to study the chemistry of the abyssomicins.[138b] They discovered that the thermal interconversion of the atropisomers of abyssomicin C (**14** and **15**,Scheme 35) required a surprisingly high temperature (180 °C). In contrast, this interconversion could be promoted at room temperature under acidic conditions. While a few possible mechanistic explanations have been put forth, it is as yet unclear why acids promote this interconversion. Interestingly, they demonstrated that the conditions of the final step in the Sorensen laboratory's synthesis of abyssomicin C (**14**) effected equilibration of the abyssomicin C atropisomers (**14** and **15**), suggesting the identity of the incompletely characterized *iso*-abyssomicin C as *atrop*-abyssomicin C (**15**). L-Selectride-promoted 1,4-reduction of both atropisomers yielded further insight into the chemistry of the abyssomicins. Thus, the conjugate reduction of abyssomicin C (**14**) did not afford abyssomicin D (**206**,Scheme 35), but rather, it provided a mixture of products, the major one of which was *iso*-abyssomicin D (**232**,Scheme 35), presumably via the intermediacy of *E*-enolate **230**. In contrast, the conjugate reduction of *atrop*-abyssomicin C (**15**) presumably generated *Z*-enolate **231**, transannular Michael addition of which provided abyssomicin D (**206**). Thus, abysomicin D (**206**) appeared to be the product of a bioreduction of the putative natural product *atrop*-abyssomicin C (**15**), not of abyssomicin C (**14**) as originally proposed. Kinetic studies in which both atropisomers of abyssomicin C (**14** and

15) were exposed to an analog of NADH further supported this conclusion. These studies also revealed that *atrop*-abyssomicin C (**15**) is more reactive than abyssomicin C (**14**). In an antibacterial assay against MRSA, *atrop*-abyssomicin C (**15**) was found to be somewhat more potent than abyssomicin C (**14**).[138] Together with the higher reactivity of *atrop*-abyssomicin C (**15**) towards an NADH analog, this observation supported the Sussmuth hypothesis[132] that the enone moiety of abyssomicin C (**14**) is responsible for its antibacterial activity.

As predicted by Nicolaou and Harrison, *atrop*-abyssomicin C (**15**) was discovered as a naturally occurring secondary metabolite in *Verrucosispora* strain AB18-032.[141]*atrop*-Abyssomicin C (**15**) was found to be the primary abyssomicin metabolite present, with abyssomicin C (**14**) representing a minor and less active byproduct. Sussmuth and coworkers recently disclosed that *atrop*-abyssomicin C (**15**) is a substrate mimetic that irreversibly binds to the thiol functionality of the Cys263 residue of the PabB subunit of 4-amino-4-deoxychorismate (ADC) synthase.[142] This fascinating tale and the still ongoing research on *atrop*-abyssomicin C (**15**) demonstrate the power of total synthesis; and the studies derived from unexpected discoveries along the way provide insight into the structure, biosynthesis, and mechanism of action of bioactive molecules.

9. Fatty Acid Biosynthesis Inhibitors

Fatty acids are biomolecules essential to biological membranes and involved in energy storage. In most eukaryotes, including mammals, fatty acid biosynthesis (FAS) is undertaken by a very large dimeric protein that is composed of several domains that together catalyze the entire repertoire of necessary reactions.[143] This process is known as the associated, or type I, fatty acid biosynthesis (FAS I) pathway. In contrast, prokaryotes employ a distinct pathway involving individual enzymes, each with a specific role, known as the dissociated, or type II fatty acid biosynthesis (FAS II) pathway.[144] The type II pathway also operates in plant [145] and parasite[146] plasmids and mammalian mitochondria,[147] as might be expected from the bacterial origin of these organelles.

The FAS II pathway is essential to bacterial viability and, since it differs significantly from the FAS I pathway of mammals, it is an attractive target for antibacterial chemotherapy.[148] Additionally, the pathway is now well understood at the molecular level, with three-dimensional structures available for many of the individual enzymes,[145] with many of the key components well conserved across important bacterial pathogens. The molecular biology of FAS II has been reviewed recently;[144] however, a brief description of the pathway and key steps is given here.

The best-characterized FAS II pathway is that of *Escherichia coli*. An overview of the key steps is shown in Scheme 36.[144] The first committed step of fatty acid biosynthesis, the conversion of acetyl-co-enzyme A (CoA) into malonyl-CoA, is mediated by acetyl-CoA carboxylase (Acc). Acc is a multi-subunit enzyme complex that catalyzes the carboxylation of acetyl-CoA in a two-step process. First, AccB is carboxylated on its biotin motif in an ATP driven process catalyzed by AccC. The AccA/D subunits then transfer the carboxyl group to acetyl-CoA to give malonyl-CoA.[144] The pseudopeptide naturally occurring antibiotics moiramide B (**233**, Figure 19) and andrimid (**234**, Figure 19)[149] have recently been shown to act through inhibition of the Acc complex.[150,151] The malonyl group is then transferred to the acyl carrier protein (ACP), which is a small (ca. 9 kDa) acidic peptide bearing a 4'-phosphopantetheine group (Scheme 36). Malonyl-CoA:ACP transacylase (FabD) catalyzes the transfer of the malonyl group from CoA to ACP to provide malonyl-ACP, the key feedstock of the FAS II cycle. Recently, a screen of natural products identified corytuberine (**235**, Figure 19), isolated from *Helicobacter pylori*, as an inhibitor of FabD.[152] FabD catalyzes the transesterification via the transient formation of a malonyl-enzyme intermediate, with malonyl-

CoA transferring the malonyl group to a serine residue in the active site (Ser92 in *E. coli*). Binding of ACP is followed by the transesterifaction step, with His201 activating the ACP thiol for attack on the acyl-enzyme ester.

Acyl chain formation is initiated by the action of the condensing enzyme β-ketoacyl- ACP-synthase III (FabH).[144] All the condensing enzymes catalyze the Claisen condensation [153] of an acyl primer with malonyl-ACP, with the loss of CO_2, but, unlike the elongation condensing enzymes (vide infra), FabH uses acyl-CoA primers, with high selectivity for short chains, primarily acetyl-CoA.[154] The reaction begins with the acetylation of the active site cysteine (Cys112 in *E. coli*) by acetyl-CoA to give an acyl-enzyme intermediate thioester (Scheme 37).[144] The active site cysteine is activated by its position at the end of a long α-helix, which lowers its pK_a significantly due to the strong helix dipole. Binding of malonyl-ACP then occurs. Decarboxylation of the malonyl group, assisted in the active site by hydrogen bonding to His254 and Asp274, generates a two-carbon nucleophile which attacks the acyl-enzyme thioester. The tetrahedral intermediate is stabilized by hydrogen bond donation from backbone N–H groups. The free enzyme is then regenerated, and the β-ketoacyl-ACP product is released. Variations in FabH selectivity between species determine the range of fatty acids produced. For example, the FabH enzymes of *Mycobacterium tuberculosis* and other mycobacteria accept long-chain acyl-CoA primers. Mycobacteria are unusual in that they have both FAS I and FAS II systems. The synthesis of C_{12}–C_{16} fatty acids is undertaken by a FAS I system similar to that in animals. These products are then converted into the very long chain fatty acids ($> C_{50}$) needed for mycolic acid synthesis by a FAS II system. Thus, mycobacterial FAS II does not undertake de novo fatty acid biosynthesis, and the initiation enzyme must accept longer chain primers.[155]

After Claisen condensation, the β-ketoacyl-ACP then progresses to β-ketoacyl-ACP reductase (FabG), an NADPH-dependent reductase that generates β-hydroxyacyl-ACP (Scheme 36). Only a single form of this enzyme has been isolated. It is essential for FAS II, and it is highly conserved throughout bacterial species,[144] but despite its promise as a target for antibiotics, there are very few known inhibitors of its action. Recently, a number of plant-derived polyphenols were found to inhibit FabG, including epigallocatechin gallate (**236**, Figure 19), but they did not exhibit potent antibacterial activity.[156]

Following reduction, the β-hydroxyacyl-ACP undergoes dehydration to form enoyl-ACP (Scheme 36). This process is catalyzed by one of two β-hydroxyacyl-ACP dehydratase enzymes in *E. coli*, FabA and FabZ. FabA also has the ability to catalyze isomerization of the *trans*-2,3-olefin to the *cis*-3,4-isomer, a key transformation in the synthesis of unsaturated fatty acids. FabA is limited to Gram-negative bacteria, whereas FabZ is found in all FAS II systems. [144,153] A second reduction step then converts the enoyl-ACP into a simple acyl-ACP intermediate, ready for the next round of elongation. There are three families of enoyl-ACP reductases: FabI, FabK, and FabL. The particular form(s) present and their cofactors vary with bacterial species. FabI is the only form present in *E. coli* and is dependent on NADH, whereas *S. aureus* FabI is dependent on NADPH. The tuberculosis treatment isoniazid (**237**, Figure 20) targets InhA, the enoyl-ACP reductase of *M. tuberculosis*, which is similar to *E. coli* FabI. Isoniazid undergoes enzymatic oxidation to form an active species that inhibits InhA by binding the InhA–NADH complex via a covalent bond. This important tuberculosis drug is the only clinically used antibiotic that targets bacterial type II FAS. FabI is the target of the important antibacterial agent triclosan (**238**, Figure 20), which is used widely in household items such as cleaners and fabrics. A number of important pathogenic bacteria utilize FabK, which shares no sequence similarity with FabI and is therefore unaffected by triclosan. FabK is NADH-dependent. The third form, FabL, is a distant homolog of FabI, NADPH-dependent, and present alongside FabI in *Bacillus subtilis*. The fact that several different enoyl-ACP reductases are

found across key pathogens makes this step less attractive as a target for developing broad spectrum antibiotics.[148c,e]

Enoyl-ACP reduction to acyl-ACP is the final step in the synthesis of fatty acids, and the acyl-ACP product is either taken off into other pathways or, if it is not yet long enough, enters into another cycle of elongation and reduction (Scheme 36). The elongation enzymes β-ketoacyl-ACP-synthases I and II, known as FabB and FabF, carry out the iterative carbon–carbon bond formations of the biosynthesis cycle.[144] FabB and FabF are closely related, sharing high sequence identity, and they carry out a very similar Claisen condensation to FabH.[153] Again, there is some variation between species, especially with regards to the FabB enzyme. Fab B is found alongside FabA only in Gram-negative bacteria, where it plays a key role in the elongation of unsaturated acyl-ACP primers. Both FabB and FabF have a conserved active site Cys–His–His catalytic triad, as compared with the Cys–His–Asn triad of FabH. The mechanism of the Claisen condensation is very similar to that described above for FabH, with the acyl-ACP primer transferring its acyl chain to the active site cysteine, followed by binding of malonyl-ACP in an adjacent pocket. Decarboxylation of the malonate group to generate an active two-carbon nucleophile is then followed by the Claisen condensation event, releasing a new β-ketoacyl-ACP product. The decarboxylation step in these enzymes is organized by the histidine residues and is thought to involve the participation of an active site water molecule, with the CO_2 leaving as bicarbonate. As in FabH, the active site cysteine is activated by a helix dipole effect, and backbone N–H groups provide an oxyanion hole to stabilize the tetrahedral intermediates in the two nucleophilic displacement steps.[144,153]

9.1. Cerulenin and Thiolactomycin

Cerulenin (**239**, Figure 21)[157] and thiolactomycin (**240**, Figure 21)[158] are two microbial metabolites that inhibit FAS II at the condensing enzyme stage. Cerulenin (**239**) was isolated from *Caephalosporium caerulens* in 1960 and contains a hydrophobic tail attached to a polar reactive head group bearing an epoxide.[157] Upon entering the active site of the FabB/F enzymes, the epoxide moiety of cerulenin is attacked by the active cysteine residue to form a covalent adduct, irreversibly inhibiting the enzyme. In *E. coli*, it inhibits FabB most potently (IC_{50} = 3 μM), and it also inhibits FabF (IC_{50} = 20 μM), but not FabH (IC_{50} > 700 μM).[159] This difference has been ascribed to the presence of a Cys–His–Asn triad in FabH, rather than Cys–His–His in FabB/F, which does not activate the epoxide electrophile strongly enough to encourage attack by the cysteine thiolate.[148a,d,159] Although cerulenin can inhibit bacterial growth, the reactivity of the epoxide and its lack of selectivity for FAS II over animal FAS I systems make it unsuitable for development as a drug. However, cerulenin has found utility as a biochemical tool.[160]

Thiolactomycin (**240**) was isolated from a *Nocardia* strain collected in Japan and reported in 1982.[158] It was found to be active against a range of bacterial species, and it protected mice challenged with various bacterial infections. Thiolactomycin was later shown to act on the fatty acid biosynthesis pathway, inhibiting all three β-ketoacyl-ACP-synthases, FabB, FabF, and FabH, with IC_{50}s of 6, 25, and 110 μM, respectively.[159] Thiolactomycin binds reversibly in the malonate binding pocket of the enzymes, with hydrogen bonding to the His–His active site residues of FabB and FabF being crucial interactions, endowing it with more potent inhibitory activity against FabB and FabF than against FabH (which has a His–Asn arrangement). In recent years, the search for novel antibiotics has led to a resurgence of interest in thiolactomycin, both as a biochemical tool[160] and a platform for drug discovery. The parent compound is not thought suitable for drug development due to synthesis and stability issues,[148] and studies have indicated that efflux and membrane permeability problems hamper its potential as an antibiotic.[161,162]

A number of groups have investigated thiolactomycin (**240**) as a potential anti-tuberculosis drug. As mentioned above, *M. tuberculosis* relies on a type II FAS system for the preparation of mycolic acids, and the success of isoniazid (**237**) validates the FAS II pathway as an antituberculosis target. Thiolactomycin inhibits the FAS II initiation condensing enzyme *mt*FabH[163] and the elongation condensing enzymes, known as KasA and KasB (equivalent to FabB and FabH in *E. coli*),[164] leading to the inhibition of mycolic acid biosynthesis.[165] The potential for thiolactomycin to inhibit multiple enzymes complicates the interpretation of SAR data and, with several conflicting results, a clear picture has yet to emerge. The Besra group has reported an analog series in which the thiolactomycin side chain was varied.[166] Analogs of general structure **243** (Scheme 38) were synthesized via alkylation of a dianion (**242**) derived from thiolactomycin core structure **241**, a modification of the first total synthesis of thiolactomycin by Wang and Salvino.[167] As such, all the analogs were tested as racemates. Tetrahydrogeranyl analog **244** (Scheme 38) showed improved activity against *M. tuberculosis* [MIC = 29 μM; compare (±)-thiolactomycin, MIC = 125 μM]. Later, the Besra group reported several series of analogs bearing C5 biphenyl and propargyl groups, leading to the discovery of analogs **245** and **246** (Scheme 38).[168] These analogs showed improved potency against *mt*FabH [IC_{50} = 3, 4 and 75 μM for **245**, **246** and (±)-thiolactomycin, respectively], but anti-mycobacterial activity against whole cells was either not reported or poor (MIC >250 μM against *Mycobacterium bovis* BCG).[168c] These results contrast those of Dowd and coworkers, who reported that the (5*R*)-isoprene side chain of thiolactomycin was necessary for activity against the condensing enzymes of *E. coli* (FabH, FabB) and *M. tuberculosis* (*mt*FabH, KasA and KasB), as well as whole-cell activity against both species.[169,170]

Thiolactomycin (**240**) has also been used as a scaffold for the development of anti-malaria drugs. FAS II has recently been identified as a potential target for anti-protozoan chemotherapy following the discovery of this pathway in a number of important pathogenic species, including *P. falciparum*, the parasite responsible for malaria; *Toxoplasma gondii*, the cause of toxoplasmosis, a neurological disease affecting infants and immunocompromised patients; *Trypanosoma brucei*, the causative agent of sleeping sickness; and *Trypanosoma curzi*, the parasite which causes Chagas' disease.[171] FAS II takes place in these eukaryotic parasites in their plasmid organelles, which are thought to be of bacterial origin.[172] Waller and coworkers identified a number of analogs of thiolactomycin with improved activity against *P. falciparum*.[173] They found that longer alkyl chains at C5 were more potent, with unsaturated chains giving better activity than the corresponding saturated systems. The most potent compounds (**247** and **248**,Figure 22) have geranyl and farnesyl groups at C5. Both compounds, which were tested as racemates, exhibited lethal activity against *P. falciparum* with an IC_{50} of 8μM [(±)-thiolactomycin, IC_{50} = 49 μM]. In contrast, saturated analog **244** (Figure 22) was tenfold less potent, with mono-unsaturated analog **249** (Figure 22) showing intermediate activity.[173] Gilbert and coworkers have also investigated thiolactomycin analogs as potential anti-malarial agents.[174] They investigated substitution at C3, C5, and the C4-hydroxyl, as well as substituting the heteroatom, and tested their analogs for inhibition of *P. falciparum*, *T. curzi*, and *T. brucei rhodesiense*, and for inhibition of *P. falciparum* KasIII (equivalent to FabH). Selected analogs are shown in Figure 22. Compound **250** (Figure 22), having a C3-propyl group and C5-hexadecyl side chain, was a potent inhibitor of *P. falciparum*, and a moderate inhibitor of *T. curzi* and *T. brucei rhodesiense* (IC_{50} = 6, 13, and 29 μM, respectively). A benzyl group at C3 (**251**,Figure 22) was also tolerated (IC_{50} = 7, 14, and 32 μM, respectively). Compounds **252** and **253** (Figure 22) were the most potent against *T. brucei rhodesiense* (IC_{50} = 6 and 7 μM), but were only weak inhibitors in the other species. The most potent compound against *P. falciparum* (IC_{50} = 1 μM) was **254**, bearing an allyl ether at C4. In comparison, thiolactomycin itself was a poor inhibitor of *P. falciparum*, *T. curzi*, and *T. brucei rhodesiense* (IC_{50} = 143, > 427, and 256 μM, respectively). As in the studies reported for

tuberculosis, little correlation could be made between the growth inhibition results and the results of *P. falciparum* KasIII inhibition studies.[173,174]

Finally, recent studies have identified thiolactomycin analogs active against type I FAS. Cancer cells are thought to be susceptible to FAS inhibitors since FAS is often subject to up-regulation in cancer cells. The FAS cycle generates NAD^+ from the two reduction steps, helping to offset the hypoxic nature of many cancer cells.[175] Townsend and coworkers found both cytotoxicity and weight loss activity amongst the analogs tested as part of a program directed towards FAS I inhibition, and were able to separate these activities. For example, compound **255** (Figure 23) did not kill cancer cells, but it induced 11 % weight loss when administered to mice. Conversely, compound **256** (Figure 23) is moderately active against a breast cancer cell line [IC_{50} = 17.6 μg mL^{-1} (73 μM)], without causing significant weight loss. Other analogs showed either one or both activities to varying degrees.[176] Similar results were reported by Ohata and Terashima, who tested a range of analogs for antibiotic activity and mammalian FAS I inhibition. Unusually, they prepared each analog in enantiomerically pure form and tested both enantiomers. They noted that while *ent*-thiolactomycin (*ent*-**240**) was inactive in the antibacterial assays, it was a weak inhibitor of FAS I [IC_{50} = 43.7 μg mL^{-1} (208 μM)]. The most potent compound (**257**,Figure 23) inhibited FAS I with an IC_{50} value of 8.8 μg mL^{-1} (44 μM). In general, they noted that the unnatural (5*S*) analogs were more potent than the natural (5*R*) series against FAS I.[177] While none of the thiolactomycin analogs studied against FAS I were highly potent, this potential crossover activity must be borne in mind when assessing such compounds as potential antibacterial agents.[147,176,177]

The interest in the medicinal chemistry of thiolactomycin (**240**) has been mirrored by the publication of a number of total syntheses in recent years. The first asymmetric synthesis of thiolactomycin (**240**), reported by Thomas and Chambers in 1989 (Scheme 39), established the absolute stereochemistry of the natural product as the (*R*)-enantiomer.[178] The key step in the synthesis is the [3,3]-sigmatropic rearrangement of an allylic xanthate[179] to generate the required chiral tertiary sulfide. Thus, distillation of xanthate **259**, derived from ethyl lactate (**258**), resulted in rearrangement to the dithiocarbonate **260** (Scheme 39). Carbonate removal and in situ protection of the thiol was followed by ozonolysis, which showed remarkable selectivity in the presence of the sulfide and electron rich arene. Olefination of **261** was achieved through the action of the lithium salt of α-silyl imine **262**. This reagent minimized deformylation through a retroaldol mechanism, a common problem in similar compounds. [180] The resulting enal was converted to diene **263**, but the diene side chain proved too labile to be carried intact through the remaining steps. Masking of the diene as a primary selenide (**264**) allowed assembly of the thiolactone ring in **265**. However, regeneration of the diene was troublesome, requiring base-mediated elimination of a methyl selenonium salt to produce (5*S*)-*ent*-thiolactomycin (*ent*-**240**).[178]

A second asymmetric approach to thiolactomycin (**240**, Scheme 40) was reported by the Townsend group in 2002,[181] in which they made use of Seebach's self-regeneration of chirality method[182] to install the required stereocenter. (*S*)-Thiolactic acid (**267**) was prepared in three steps from D-alanine (**266**) via chlorination with retention of stereochemistry under diazotization conditions, displacement with cesium thioacetate, and hydrolysis. Formation of the corresponding oxathiolanone resulted in a 2.5:1 ratio of diastereomers, with recrystallization giving **268** as a single compound in moderate yield. Aldol reaction of the lithium enolate of **268** with tiglic aldehyde provided allylic alcohol **269**, which was subjected to dehydration via sulfinic ester rearrangement (**270** to **271**) and sulfoxide elimination to yield diene **272**. Hydrolysis of the oxathiolanone, formation of thiopropionate **273**, and Dieckmann cyclization completed this concise approach to thiolactomycin (**240**).[181]

Ohata and Terashima developed the most efficient synthesis of thiolactomycin (**240**) reported to date as part of their analog program described above. Their strategy (Scheme 41)[183] featured a deconjugative asymmetric sulfenylation controlled by Evans' auxiliary.[184] Imide **275** was prepared in three steps from tiglic aldehyde (**274**). Treatment of **275** with NaHMDS generated an extended enolate which reacted at the α-position with thiosulfonate **276** to give sulfide **277** in 10:1 *dr*. With the chiral sulfide installed and the side chain in place, only four steps were required to complete the synthesis. Notably, a two-step removal of the thiol protecting group allowed for the direct coupling with propionyl chloride (**278** to **279**), obviating the need to isolate the free thiol. Again, a Dieckmann reaction was used to complete the total synthesis of thiolactomycin (**240**), in 22 % overall yield for the eight-step sequence.[183]

The Takabe group reported a chemoenzymatic approach to thiolactomycin (**240**).[185] Thiotetronic acid **241**, an intermediate from the Wang–Salvino route to (±)-thiolactomycin,[167] was protected as the methyl vinylogous ester under basic conditions and hydroxylmethylated to give (±)-**280** (Scheme 42). The primary alcohol was resolved by the action of *Candida antarctica*-derived lipase Chirazyme® L-2, which gave recovered **280** in 38 % yield as a single enantiomer. Lewis acid mediated crotylation of the corresponding aldehyde avoided deformylation, yielding homoallylic alcohol **281**. Bromination, elimination, and deprotection furnished thiolactomycin (**240**).[185,186]

Recently, Dormann and Bruckner reported an efficient and concise route to thiolactomycin (**240**, Scheme 43).[187] Their approach began from enal **282**, an intermediate in the BASF industrial synthesis of vitamin A. Wittig reaction followed by acetate cleavage gave allylic alcohol **283**, which was subjected to Sharpless asymmetric epoxidation;[101] in situ protection of the primary alcohol afforded epoxide **284** in 83 % yield and 93 % *ee*. Notably, this approach constitutes the first catalytic asymmetric approach to thiolactomycin. The tertiary sulfide was then installed via S_N2' addition[188] of thiopropionic acid promoted by trimethylaluminum, with addition occurring *syn* to the epoxide to afford **285**. Silyl deprotection and vicinal dideoxygenation[189] of the resulting diol installed the thiolactomycin side chain in **273**, and the now familiar Dieckmann cyclization then provided the natural product. This strategy provided thiolactomycin (**240**) in only seven steps and approximately 15 % overall yield, and was also applied to the first total syntheses of the related targets 834-B1 (**286**) and thiotetromycin (**287**).[187,190]

9.2. New FAS II Inhibitors

Recently, a team of researchers at Merck led by Singh and Wang published a series of studies aimed at the discovery of novel fatty acid biosynthesis inhibitors.[191] They developed a high-throughput screen for inhibitors of the elongation cycle of FAS II using ^{14}C-labelled malonyl-CoA and medium-length (C_8 and C_{12}) acyl-CoA substrates, thus eliminating the acetyl-CoA carboxylation and initial condensation reactions from the screen and simplifying analysis.[161] This assay, in combination with whole-cell phospholipid synthesis and MIC assays, allowed the correlation of activity in the biochemical study with whole cell antibacterial action. By screening a collection of natural product extracts, the team discovered the FAS II inhibitor bischloroanthrabenzoxocinone (BABX, **288**,Figure 24). BABX was shown to inhibit the FAS II elongation cycle and whole cell phospholipid biosynthesis, and was potent against permeable *E. coli* strains and *S. aureus* [MIC = 0.2–0.4 μg mL^{-1} (0.4–0.8 μM)]. BABX was not an inhibitor of FabD, but it did completely inhibit the uptake of ^{14}C-labelled malonyl-CoA, indicating that it acts by inhibiting the condensing enzymes FabB and FabF, as inhibition of either the reductase or dehydrase steps would allow incorporation of one malonyl unit in the first iteration. However, BABX was also found to inhibit DNA, RNA, and cell wall synthesis, so further study is needed to determine its primary target.[161,192] The potent FAS II inhibition of

Tu3010 (**289**,Figure 24),[193] a naturally occurring amide analog of thiolactomycin, was also discovered using this assay.[194]

Wang and coworkers have also described an antisense RNA approach for the high throughput screening of potential antibiotics.[194] Traditional high throughput screens fall into two categories. Screening whole cells in MIC assays ensures cell penetration and antibacterial action. However, it cannot distinguish selective inhibitors from toxic compounds, and the mechanism of action of the hits is unknown. Alternatively, screens may employ biochemical assays to determine activity against a known essential protein. While this yields hits with well-defined targets, activity against whole cells is often disappointing due to poor cell penetration and/or active efflux.[191] The Merck team used an engineered strain of *S. aureus* containing a xylose-inducible plasmid encoding antisense RNA corresponding to the gene enconding FabF and FabH. When cultured in the presence of xylose, this strain overexpresses antisense RNA for the connected gene encoding both FabF and FabH. This leads to destruction of the FabF/H mRNA transcript, thought to be due to formation of double-stranded RNA, which is degraded enzymatically. The result is the underexpression of the FabF and FabH enzymes, which increases the sensitivity of the strain to inhibitors of these enzymes. This allowed the design of a two-plate high throughput assay for FabF/H inhibitors. In this approach, two agar plates are prepared: one containing a control strain and one containing the sensitive strain. Potential antibiotics are then added to wells on each plate. Growth of the bacteria is inhibited in a zone around the wells containing active compounds as the antibiotic diffuses through the agar medium. If a well contains a FabF or FabH inhibitor, then the area of growth inhibition around that well will be greater in the sensitive strain than in the control. By comparing the zones of inhibition between the two plates, large numbers of samples can be assayed in a high throughput manner.[191,194]

9.2.1. Phomallenic acids—Following verification of the assay with compounds of known mechanism of action, the Merck team screened over 250,000 natural product isolates and discovered several substances with potent antibiotic activity, beginning with the phomallenic acids (**290**–**292**, Figure 25).[194,195] Phomallenic acids A–C inhibited *S. aureus* FAS II with IC_{50} values of 22, 3.4, and 0.77 μg mL^{-1} (89, 13, and 2.8 μM), respectively, and are thought to be dual inhibitors of *S. aureus* FabH and FabF. Though phomallenic acid A (**290**) was essentially inactive against *S. aureus* [MIC 250 μg mL^{-1} (~1 mM)], phomallenic acids B (**291**) and C (**292**) were active against *S. aureus* and MRSA with MICs of 12.5 and 3.9 μg mL^{-1} (48 and 14 μM), respectively. Phomallenic acid C (**292**) was also active against *Haemophilus influenzae* and *B. subtilis*, but did not show activity against enterococci.

The interesting acetylenic allene structure of the phomallenic acids inspired a total synthesis of phomallenic acid C (**292**) by the Wu group.[196] Their strategy included construction of the chiral allene group through an S_N2' reaction of a propargylic alcohol followed by a Negishi coupling. Their approach began from anhydride **293**, which was subjected to acetylene addition under Lewis acid catalysis to give acetylenic ketone **294** (Scheme 44a). Following MOM protection of the acid group, CBS reduction[197] of ketone **295** furnished propargylic alcohol **296** in 94 % yield and > 96 % *ee*. Removal of the acetylinic TMS group and activation of the alcohol as the tosylate provided the substrate for an S_N2' displacement. Treatment of the propargylic tosylate with CuBr and LiBr yielded bromo-allene **297** with efficient, but incomplete, transfer of central to axial chirality.[198] The coupling of an optically-enriched allene with an alkyne was investigated using model compound **298** (Scheme 44b), in which the adjacent stereocenter provided a means of monitoring the selectivity of the coupling reaction. Coupling of **298** with TMS-acetylene under Sonogashira conditions[77,199] led to substantial epimerization of the allene axis; however, the milder conditions of a Negishi coupling[77,79] gave allene **299** with clean inversion of the allene axis. This reactivity was replicated in the coupling of bromide **297** with 1,3-heptadiyne, with subsequent deprotection

affording phomallenic acid C (**292**) in excellent overall yield.[196] The Negishi coupling proceeded with complete inversion of the allene axis, as indicated by the *ee* of bromide **297** and phomallenic acid C MOM ester (88 % *ee*). Optical rotation comparisons indicated that the natural product was isolated at an *ee* of approximately 58 %. [195,196]

9.2.2 Platensimycin and Platencin—The Merck screening program led by Singh and Wang also discovered platensimycin (**17**, Figure 26)[200,201] and platencin (**18**, Figure 26). [202] These related natural products are characterized by a conserved polar aromatic group coupled through an amide linkage to a variable ketolide core. Both compounds were isolated from strains of *Streptomyces platensis* (Figure 27) and were found to be potent broad spectrum antibiotics. Platensimycin (**17**) was found to be a highly potent inhibitor of FAS II with an IC_{50} of 0.45 μM against the *S. aureus* FAS II enzyme system.[200a] Its potency in whole cell inhibition of lipid biosynthesis was in a similar range, indicating good access to the molecular target in a whole cell setting. Single enzyme assays indicated that platensimycin is a highly potent inhibitor of both *S. aureus* and *E. coli* FabF enzymes, with IC_{50} values of 48 and 160 nM, respectively, while activity against *S. aureus* FabH was significantly lower at 67 μM. Interestingly, the binding affinity of platensimycin for purified FabF was lower than expected from the potency of inhibition, and the Merck team discovered that platensimycin actually binds the acyl-enzyme intermediate formed during the condensing reaction. Thus, in the presence of lauryl-CoA to generate an acyl-enzyme species in situ, platensimycin was found to bind FabF with a binding IC_{50} of 19 nM.[200a] The short half-life of the acyl enzyme intermediate precluded successful crystallization of the acyl-enzyme-platensimycin complex. However, a mutant *E. coli* FabF with the active site cysteine replaced by a glutamine residue was used to mimic the acyl-enzyme intermediate. This was based on the observation that an analogous mutant of an animal-derived β-ketoacyl synthase domain converted the enzyme into a malonyl decarboxylase (i.e. the second stage of the elongation condensation reaction), indicating that this mutant may adopt a similar conformation to that of the acyl-enzyme intermediate.[203] Structural studies of the *E. coli* FabF(C163Q) mutant supported this supposition, indicating that the mutant had the essential features of an acyl-enzyme intermediate. Indeed, platensimycin showed excellent affinity with *E. coli* FabF(C161Q), allowing the generation of a high-resolution X-ray crystal structure of the bound platensimycin complex.

The X-ray crystal structure of the enzyme-platensimycin complex (Figure 28) indicated that platensimycin (**17**) binds in the malonyl binding site. The carboxylic acid of platensimycin interacts with the two active site histidine residues, the side chain of Phe400 makes an edge-to-face interaction with the aromatic ring, and the 5'-phenol makes a hydrogen bond to the periphery of the malonyl binding site through a water molecule. The amide of platensimycin is aligned perpendicular to the aromatic ring and makes two hydrogen bonds to threonines lining the cavity. The cage-like portion of the platensimycin molecule is positioned in the mouth of the malonyl binding pocket and masks 122 $Å^2$ of solvent-accessible surface, suggesting it makes a significant contribution to binding affinity. The enone carbonyl oxygen is hydrogen bonded to an alanine N–H, and the ether group engages in a hydrogen bond with a threonine side chain in a cleft on the protein surface. The enone olefin and the side of the cage unit that carries it are exposed to solvent.[200a]

Platensimycin (**17**) displays broad spectrum activity against Gram-positive bacteria, with MIC values as indicated in Table 2.[200a] As shown, the activity of platensimycin compared well with that of the clinical antibiotic linezolid. Notably, as expected due to its novel mechanism of action, no cross-resistance was observed with existing agents, and it is a potent inhibitor of a number of clinically important human pathogens, including MRSA, vancomycin-intermediate *S. aureus* (VISA), and vancomycin- and macrolide-resistant enterococci. In addition, no toxicity was observed towards HeLa mammalian cells. Platensimycin showed

promising in vivo activity in mice, with a parenteral dose of 100 –150 μg h^{-1} effectively suppressing a *S. aureus* infection after 24 h. Even at this rather high dose,[201] no toxic effects were observed in the test animals.[200a]

Platencin (**18**) shares a gross structural similarity with platensimycin, with the enone ring, linker section, and aromatic portion being completely conserved. The structures differ in their polycyclic domain, with platencin having a bicyclo[2.2.2]octane system in place of the ether-bridged [3.2.1] structural motif of platensimycin.[202] Despite this close structural relationship, examination of the mechanism of action of platencin indicated an important distinction to that of platensimycin. While the latter is a highly selective inhibitor of FabF, platencin is a dual inhibitor of FabF and FabH.[202a] Platencin binds the acyl-enzyme intermediate of FabF with an $IC5_0$ of 113 nM, reflecting a 5.9-fold lower affinity for this enzyme than platensimycin. Conversely, platencin has 4.1-fold greater affinity for FabH (IC_{50} = 16.2 μM) as compared to platensimycin. Although platencin has rather higher affinity for FabF than for FabH, it was shown to inhibit both enzymes with similar efficiency in multi-enzyme assays. The differences in binding affinities between the two compounds were rationalized after examination of the structures docked in the *E. coli* FabF(C163Q) and FabH active sites. Absence of the hydrogen bond made by the platensimycin ether group may account for the lower affinity of platencin for FabF. Unfavorable interactions between the ether and C17 methyl groups of platensimycin and residues on the surface of FabH might explain its much lower affinity for this enzyme, while the altered shape of platencin matches that active site better.[202]

As shown in Table 2, platencin (**18**) exhibited similar broad spectrum antibiotic activity, although there are slight differences in the profile of this compound. Similar in vivo results were also obtained in mice, albeit at a slightly higher dose, as expected from its lower potency against *S. aureus* in the presence of serum. The dual mechanism of action of platencin offers promise in combating the emergence of resistant bacterial strains through mutations, as two separate enzymes must undergo changes in order to render this compound ineffective.[202a]

Recent studies on the biosynthesis of platensimycin (**17**) have indicated that the non-mevalonate terpene pathway is responsible for the production of the ketolide-carboxylic acid motif (**303**, Scheme 45).[204] Formation of an *ent*-kaurane (**301**) or related (**302**) structure from geranylgeranyl diphosphate (**300**) followed by loss of the three terminal carbon atoms to form the carboxylic acid group accounts for the C_{17} skeleton.[201] Platencin (**18**) is proposed to arise from rearrangement of this skeleton.[202b] The Singh group at Merck have recently isolated platensic acid (**303**) along with its methyl ester (methyl platensinoate, **304**) from a strain of *S. platensis*, confirming that this acid is a natural product in its own right.[205] The also reported the isolation of two further natural products related to platensimycin. The first is platensimide (**305**, Figure 29), in which the aniline carboxylic acid motif of the parent compound is replaced by a 1,4-diaminobutyrate derivative.[205] They subsequently identified homoplatensimide (**306**) in cultures of the same strain.[206] In this species, the ketolide unit contains three further cabon atoms in the linking chain between the core enone and the carboxylic acid group, giving this region the C_{20} formula expected for a diterpene. Indeed, it is easy to envisage the biosynthesis of this structure from a species such as **302**, and this isolation can be taken as further evidence of the validity of the proposed biosynthesis hypothesis. In homoplatensimide (**306**), the ketolide makes an amide linkage to glutamine. The Singh group also undertook a semisyntheis of platensimide (**305**) in four steps from platensic acid (**303**), along with a number of other derivatives of the platensimide structure. None of these compounds (**303**–**306** and derivatives) retained the potent antibacterial activity of platensimycin and platencin, indicating the importance of the benzoic acid motif to the platensimycin pharmacophore.[205, 206]

Singh and coworkers have also reported some chemical studies on platensimycin (**17**).[206] Hydrogenation of the enone olefin was employed as a means to install a tritium label for direct binding studies. Dihydroplatensimycin (**307**,Scheme 46) was found to undergo an interesting condensation under mildly acidic conditions to form pentacyclic enamine **308**. Bromination of platensimycin (**17**) could be effected in high yield by treatment with NBS, giving 6'-bromoplatensimycin **309**, which allowed for assignment of the absolute stereochemistry of the natural product by X-ray crystallographic analysis.[200b,207] The 5'- and 6'-chloro derivatives and various *O*-methyl derivatives were also prepared. Although detailed biological data were not reported, the authors indicated that these compounds were all less active than the parent platensimycin.

The combination of a novel structural class, impressive biological activity, and the media attention surrounding its publication have made platensimycin an attractive target for total synthesis, and no fewer than ten distinct routes to this framework have appeared in the two years since its isolation was reported.[208] While there are similarities between some approaches, each also has important distinctions. The Nicolaou group reported a total synthesis of racemic platensimycin (**17**) in 2006, involving a SmI_2-mediated ketyl olefin cyclization as the key step.[209] Retrosynthetic disconnection of the amide bond followed by removal of the C18 methyl group and the propanoic acid side chain revealed ketolide **310** (Figure 30), representing the central challenge of the total synthesis. Rupture of the ether linkage gave tricycle **311**, which could be simplified to spirocyclic dienone **312** by an acyl–anion or ketyl–radical addition disconnection. This disconnection defined the character of this strategy, which relies on the local symmetry of the dienone to set the challenging C8 quaternary center.[210] Two routes were explored to assemble the key spirocyclic intermediate, one involving a potentially asymmetric enyne cycloisomerization (**313**) and the other a novel oxidative cyclization (**314**).[209,211]

To test the hypothesis that a spirocycle such as **312** could be converted into the platensimycin ketolide **310**, a synthesis of racemic platensimycin (**17**) was undertaken.[209] As shown in Scheme 47, vinylogous ester **315** was converted into compound **316** by a sequence of two sequential alkylations. Simple transformations gave 4,4-disubstituted enone **317**. Cycloisomerization of **317** was effected by exposure to catalytic $[CpRu(MeCN)_2]PF_6$,[212] providing spirocyclic silyl enol ether **318** as an inconsequential 1:1 diastereomeric mixture. Saegusa–Ito oxidation[107] followed by unmasking of the latent aldehyde group then led to **312**. Treatment of **312** with SmI_2 at low temperature resulted in an instantaneous reaction to form the desired tricyclic system **311** as a 2:1 mixture at the alcohol-bearing center.[110] The modest yield of this transformation is mitigated by the value obtained in terms of complexity; in addition to the C–C bond formation, three new stereocenters are established, of which two are completely controlled. The proximity of the secondary alcohol in the major diastereoisomer of **311** allowed for facile etherification, which completed the platensimycin cage structure **310**.

From intermediate **310**, installation of the side chains was achieved by successive alkylations with complete stereocontrol, presumably due to the steric influence of the adjacent polycyclic unit (Scheme 47). The second alkylation was limited to allylation, and, while hydroboration was not suitable for installing the required oxygenation, it was discovered that the olefin would undergo cross metathesis.[139] Thus, treatment of **319** with Grubbs' second generation olefin metathesis initiator (**228**)[140] in the presence of vinyl pinacol boronate[213] gave boronate **320** in high yield. Oxidation of the vinylboronate to the corresponding aldehyde was achieved under mild conditions using trimethylamine-*N*-oxide, with further oxidation providing carboxylic acid **303**. This mild two-step conversion of allyl units to aldehydes, originally exploited by Danishefsky and coworkers for the preparation of epothilone analogs, offered a functional group-tolerant alternative to hydroboration chemistry.[214] Coupling of carboxylic

acid **303** with aniline **321** (Scheme 48) followed by a one-pot deprotection sequence yielded (±)-platensimycin (**17**).[209]

Two routes have been reported for the synthesis of aniline fragment **321**. The first, which was employed in the Nicolaou group total synthesis, began with 2-nitroresorcinol (**322**, Scheme 48a), and proceeded in five steps.[209] Thus, the carboxylate functionality was introduced via directed *ortho*-lithiation[215] of intermediate **323**, and the carbamate removed by microwave irradiation[47] at 205 °C. In an alternative approach (Scheme 48b), Heretsch and Giannis reported the nitration of benzoate **324** to give **325** in modest yield, along with a similar quantity of its 5-nitro isomer.[216] The isomers were easily separable by precipitation of the unwanted isomer during work-up. MOM protection yielded intermediate **326**, and catalytic hydrogenation of the nitro group then provided aniline **321**. Although the overall yield of this sequence is lower than that of the Nicolaou approach, its operational simplicity and flexibility with regard to protecting group installation make it an attractive alternative.

Following their synthesis of (±)-platensimycin (**17**), the Nicolaou group turned their attention to developing an asymmetric total synthesis.[211] As indicated in Figure 30, two possibilities were envisaged for the asymmetric synthesis of spirocycle **312**, and these were investigated in parallel. A catalytic asymmetric cycloisomerization of **313** would provide spirocycle **312** by direct analogy with the route to the racemate. Such a process has not yet been reported using a ruthenium system,[212c] but the Zhang group has reported analogous reactions of internal alkynes using chiral rhodium complexes.[217] Investigation of an asymmetric reaction in the context of the approach to platensimycin (**17**) required introduction of the dienone system prior to the spirocyclization event. An ester group was used to cap the alkyne as the terminal alkyne proved unsuitable for use in the rhodium-catalyzed reaction. Thus, silylation of **317** (Scheme 49), introduction of the ester, oxidation with IBX,[218] and TBS deprotection gave enyne **327**. Treatment of **327** with the catalyst derived from $[Rh(cod)Cl]_2$, $AgSbF_6$, and (*S*)-BINAP [217] furnished spirocycle **328** in excellent yield and *ee*. Having served its purpose, the ester group had to be removed, which came at the price of a five-step sequence, with a Barton radical decarboxylation[219] responsible for the actual C–C bond cleavage. Interestingly, the decarboxylation resulted in isomerization of the olefin to the internal position (**329**). This was unexpected given the neutral reaction conditions and the fact that no such isomerization is observed under strongly acidic conditions (vide infra) (the mechanistic details await further investigation). In a final twist, the SmI_2-mediated cyclization of **329** proceeded in similar yield to that of the exocyclic olefin isomer **312**, but now gave complete stereoselectivity for the desired alcohol (**330**). This serves to underline the potential impact of subtle conformational and steric effects within the platensimycin framework. The endocyclic olefin **330** also underwent facile etherification, completing the synthesis of **310**, now as a single enantiomer. [211]

The other approach to enantiomerically pure platensimycin involved setting the absolute stereochemistry of **312** prior to the spirocyclization event, and made use of the hypervalent iodine-promoted oxidative dearomatization of phenols (Scheme 50).[220] The asymmetric alkylation of pseudoephedrine amides developed by the Myers group[221] provided a convenient means to install the required stereogenic center. Amide **331** was prepared from the corresponding carboxylic acid and alkylated with bromide **332** under Myers' standard conditions to give **333**. Although the selectivity was low for these systems (ca. 85 % *de*), the crystallinity of the pseudoephedrine derivative allowed for isolation of diastereomerically pure material in good yield. The amide group of **333** was efficiently transformed into the required allylsilane by way of intermediate **334**, providing dearomatization substrate **314** after deprotection of the phenol group. Treatment of **314** with bis(acetoxy)iodobenzene furnished dienone **335** in good yield, confirming that allylsilanes are competent nucleophiles in intramolecular dearomatization reactions.[222] Removal of the acetal under acid conditions

gave aldehyde **312** in enantiopure form, allowing the completion of the total synthesis of (–)-platensimycin (**17**) using the previously described route.[209]

The next approach to platensimycin ketolide **310** came from the Snider group, and, although **310** is formed as a racemate, this remains the most efficient preparation of this compound, proceeding in a remarkable 32 % overall yield from tetralone **338** (Scheme 51).[223] Thus, Birch reduction[224] and alkylation with **339** gave a mixture of diketones **337** and **340**. Equilibration of **340** under acidic conditions slightly favored **337**, allowing good material throughput. Radical cyclization of both diastereomers furnished tricycles **341** and **342** in high yield. In this case, base-catalyzed equilibration of undesired **342** provided some **341**, but favored **342**. Reduction of diketone **341** gave **336** with complete selectivity for the desired C10 secondary alcohol and an inconsequential 1:1 mixture at C7. Acid-catalyzed etherification served to differentiate the two hydroxyl groups (**343**) and was followed by dehydration to install the C6–C7 olefin of **344**. Finally, allylic oxidation of **344**, which was most efficient when carried out in two steps, yielded **310**, completing this short formal total synthesis of (±)-platensimycin (**17**).

An alternative strategy from the Nicolaou group bears similarities to both the earlier Nicolaou route and the Snider route. As shown in Scheme 52a, the retrosynthetic analysis includes a radical cyclization similar to that employed by Snider, and also incorporates a symmetrical dienone intermediate. In this case, however, the cyclization onto the dienone unit is a true desymmetrization in that the precursor is achiral (Scheme 52b).[225] Dienone **347** was constructed in a manner similar to that described above, beginning from **315** and by way of intermediate **346**. The key step was an intramolecular Stetter reaction[226] to form the requisite decalin system. This reaction was catalyzed by a carbene derived from heterocycle **193**[109] and provided **345** in good yield. However, the full potential of this reaction could not be realized as the substrate proved resistant to cyclization using chiral carbene catalysts. Following introduction of unsaturation in the new cyclohexanone ring to give **348**, the radical cyclization proceeded efficiently under standard conditions to afford **349**. While reduction of **341** (Scheme 51) with L-Selectride yielded a single diastereomer at C10, reduction of **349** under similar conditions gave **350** as a 1:1 mixture of secondary alcohols. Alternative conditions often provided high selectivity for the undesired isomer, indicating the influence of the pre-installed C6–C7 olefin on the conformation of the tricyclic system. As expected, etherification and thioacetal deprotection proceeded efficiently to give **310**.[225]

In a similar vein, Kaliappan and Ravikumar prepared an enantiopure surrogate for the platensimycin tetracyclic core[227] from the Wieland–Miescher ketone (**351**, Scheme 53). Transformation of **351** under standard conditions provided ketone **352**, reduction of which afforded secondary allylic alcohol **353**. Base-mediated addition to vinyl phenyl sulfoxide gave ether **354**, which, upon thermolysis, underwent a sulfoxide elimination to generate a vinyl ether followed by Claisen rearrangement to install the C8 quaternary center of **355**. A three-step sequence led to alkyne **356**, which underwent a similar radical cyclization to those described above. In this case it proceeded through stannylation of the alkyne; protodestannylation of the product proceeded on treatment with mild acid to yield ketone **357**. In this instance, L-Selectride again provided excellent stereoselectivity at C10, and etherification completed the synthesis of the platensimycin core (**358**).

Yamamoto and coworkers have reported a markedly different approach to platensimycin ketolide **310**,[228] involving an intramolecular Robinson annulation. The difference between this approach and those discussed above is evident from their retrosynthetic analysis, shown in Figure 31. The enone and pyran rings were formed last in the key Robinson annulation event. This disconnection revealed oxabicyclo[3.3.0]octane unit **359**, which was traced back to an asymmetric Diels–Alder reaction of a 2-substituted cyclopentadiene (**363**).[28] Although

reactions of 5-susbtituted cyclopentadienes are well established, reactions of 2-substituted isomers are frought with difficulty due to the facile [1,5]-sigmatropic rearrangement that renders them unstable even at ambient temperature.[229] The resulting mixture of 1- and 2-substituted dienes leads to product mixtures from the Diels–Alder reaction.

In an accompanying paper,[230] Payette and Yamamoto addressed this problem using a Brønsted acid activated Lewis acid catalyst[231] derived from chiral oxazaborolidine **365** (Scheme 54a). Addition of the C–H Brønsted acid **366** to **365** produces a highly active Diels–Alder catalyst. Steric bias generated by the catalyst structure disfavors reaction of the 1-substituted diene, giving selectivity for the 2-substituted reactants. Thus, treatment of methyl acrylate (**364**) with an excess of methyl cyclopentadiene (**363**, a mixture of 1- and 2-Me isomers) afforded norbornene derivative **367** in excellent yield with essentially total regio-, diastereo- and enantiocontrol. Interestingly, Payette and Yamamoto also reported a means to access Diels–Alder products from 1-alkyl cyclopentadienes. By employing a sacrificial acrylate dienophile, all the 2-alkyl diene in the mixture **370** (Scheme 54b) is consumed. At the reaction temperature (−78 °C), [1,5]-sigmatropic rearrangement does not occur, leaving the 1-alkyl isomer **371** unchanged. Addition of a more active quinone dienophile (**372**) allows reaction with the 1-alkyl diene **371** to provide **373**, again with excellent stereocontrol.

Progress towards the platensimycin ketolide from **367** began with oxidative decarboxylation via *N*-nitrosoaldol reaction and base-mediated hydrolysis (Scheme 54a).[228] Baeyer–Villiger oxidation of the resulting norbornenone (**362**) under basic conditions led to rearranged product **361**, possessing the required oxabicyclo[3.3.0]octane structure. An S_N2' addition[188,232] of a vinyl fragment was followed by re-lactonization of **368** under acid catalysis giving **369**, from which annulation substrate **359** was prepared in four steps through the intermediacy of nitrile **360**. The Robinson annulation process[233] was accomplished in two steps beginning with a Michael addition catalyzed by L-proline,[234] and completed by addition of NaOH to effect the aldol condensation step. The product (**310**) was obtained as a 5:1 mixture of C9 epimers, favoring the desired product. The use of a chiral reagent enhanced the intrinsic preference for this product, with D-proline giving the same major isomer but in only a 3:1 ratio.[228]

Ghosh and Xi have reported[235] a similar approach to the tetracyclic core of platensimycin to that reported by the Yamamoto group, using an intramolecular Diels–Alder reaction[28] rather than a Robinson annulation (Scheme 55). The oxabicyclooctane system was formed from carvone (**374**) via hydrative radical cyclization/reduction (**375**) and Baeyer–Villiger reaction/translactonization (**376**). Further transformations gave lactone **377**, which was converted into ketone **379** over five steps through the intermediacy of **378**. The use of chiral Horner–Wadsworth–Emmons reagent **380** allowed for stereocontrolled introduction of an olefin,[236] affording, upon further elaboration, compound **381**. Completion of the diene and installation of the dienophile provided Diels–Alder substrate **382**, which underwent cycloaddition with good stereocontrol on heating to 200 °C. Product **383** was isolated in only 39 % yield, largely because only the *E*-isomer of the 1:1 diene mixture reacted.

Another strategy is exemplified by the Tiefenbacher and Mulzer's approach to ketolide **310**.[237] Their retrosynthetic analysis (Scheme 56a) involved a unique ether disconnection revealing a tertiary alcohol (**384**) that was further disconnected to known tricyclic ketone **385**. This ketone was prepared previously by Mander and coworkers via the intramolecular alkylation of an aromatic precursor by a diazoketone group.[238]

Tiefenbacher and Mulzer prepared diazoketone **388** via hydrogenation of unsaturated carboxylic acid **387**,[237] prepared in three steps from tetralone **386** (Scheme 56b).[239] The reduction step was carried out under achiral conditions, providing **388** as a racemate, but, as the authors indicated, this step may be amenable to asymmetric induction. The dearomatization

was accomplished by treatment of **388** with TFA, giving dienone **385** in good overall yield. Addition of methyl Grignard reagent to **385** proceeded with excellent regio- and stereoselectivity to afford tertiary alcohol **389**. The platensimycin cage motif could then be completed via radical bromination (providing **384**) and intramolecular nucleophilic substitution. Hydrogenation of dienone system **390** using Crabtree's iridium catalyst[240] gave a 1.3:1 mixture of C9 diastereomers (**391**), reflecting the rather symmetrical nature of **390**. The required, but more accessible, C6–C7 olefin was also hydrogenated in the process, but it could be reinstalled in moderate yield by treatment with iodic acid•DMSO complex[241] to furnish **310**.

A related approach to the one described above was employed by Lalic and Corey in their enantioselective synthesis of enone **310**.[242] As seen in their retrosynthetic analysis (Scheme 57a), these investigators chose to carry out the key dearomatizing alkylation after construction of the tetrahydrofuran ring; the latter was disconnected according to a more conventional ether-forming reaction. Their synthesis began from naphthol **394**,[243] which was converted into quinone mono-acetal **395** (Scheme 57b). The stereochemistry at C12 in compound **396** was then set by a highly enantioselective rhodium-catalyzed conjugate addition[244] of 2-propenyl trifluoroborate.[245] This transformation was accelerated by the addition of triethylamine, allowing complete conversion at ambient temperature. The authors postulated that the amine base plays a role in the formation of the active monomeric Rh(I)-BINAP complex. The C10 stereocenter was set next through a stereoselective reduction of the carbonyl group, giving rise to **397** as a single isomer. Further elaboration, reduction at C13, and protecting group manipulations led to **393**, bromoetherification of which gave tetrahydrofuran **392** as a 10:1 mixture of diastereomers at the new tertiary chiral center. The remarkable stereoselectivity of this step was crucial, as it placed the allylic bromide in a suitable orientation for the following step. It was rationalized by a concerted mechanism, with simultaneous attack of the protected alcohol oxygen and bromine atoms on the olefin, which occupies a pseudodiaxial conformation. Treatment of TIPS ether **392** with TBAF at high temperature led to efficient alkylation of the aromatic ring to furnish dienone **390**. Lalic and Corey found that the reduction step could be achieved with excellent diastereoselectivity through the use of a chiral rhodium catalyst at high pressure, affording saturated ketone **391** in high yield. In this case, reintroduction of the C6–C7 olefin in **310** was accomplished via regioselective TMS enol ether formation using TMSOTf and trimethylamine, and oxidation using the IBX•MPO system.[218] Although this is a rather long sequence, the overall efficiency remains high due to the excellent yields and high diastereoselectivity obtained throughout.[242]

Nicolaou, Chen, and coworkers reported a chiral pool approach to the platensimycin ketolide (**310**),[246] starting from carvone and involving an alternative SmI2-mediated cyclization. Their retrosynthetic analysis (Scheme 58a) began with the now familiar ether disconnection (**398**), but was followed by a unique strategic disconnection of the cyclohexenone ring through the C4–C5 bond. This led back to an enone–aldehyde (**399**), which was hypothesized to be a substrate for a ketyl–olefin or Stetter cyclization. This substrate was then traced back to (*R*)-carvone (*ent*-**374**).

In the forward sense, the synthesis began with the conversion of (*R*)-carvone (*ent*-**374**) into (*S*)-carvone derivative **400** through 1,2-Grignard addition and oxidative rearrangement (Scheme 58b). Hydrative radical cyclization gave a 1:1 mixture of **401** and **402**, which were converted together into aldehyde **399**. The intramolecular Stetter reaction of **399** effected the required cyclization, but the diketone product was formed as a 5:1 inseparable mixture of diastereoisomers, favoring the undesired *trans*-decalin isomer, which was unstable to epimerization conditions. A SmI_2-mediated ketyl radical cyclization[110] gave hydroxy ketone **403** as a single diastereomer, again favoring the undesired stereochemistry at the C9 position. Although **403** was resistant to epimerization, conversion to an axial ester (**404**) by a

Mitsonobu reaction[247] allowed successful equilibration at C9 to afford, after base-promoted ester cleavage, **405** and **406** as a separable 1:1 mixture. Reduction of **406** with L-Selectride furnished the desired C10 secondary alcohol, which cyclized to yield ether **407** upon acidic workup. Oxidation of **407** followed by TMS enol ether formation and oxidation gave **310** as a 2:1 mixture of regioisomers, reflecting the selectivity of the silylation.[246]

The final approach to platensimycin reported to date is that by Eun Lee and coworkers,[248] based on a carbonyl ylid cycloaddition.[249] These researchers disconnected the enone ring **310** via aldol condensation and olefination reactions, leading back to ketonitrile **409** through **408** (Figure 32). Unravelling of the polycyclic cage motif along the lines of a carbonyl ylid cycloaddition led back to a diazoketone, such as **410**, and then to malononitrile **411**.

The quaternary chiral center of the cascade precursor was formed through an elegant diastereoselective double alkylation of malononitrile **411** (Scheme 59). Treatment of **411** with sodium hydride and enantiopure propylene oxide **412** led to lactone formation;[250] subsequent addition of iodide **413** to the reaction mixture gave a 63 % yield of lactone **414**, along with 13 % of the epimeric product. Ketothioester **415** was formed by lactone opening with thiol and oxidation of the secondary alcohol. Hydrolysis of the thioester and diazoketone formation gave the projected cascade substrate **416** in excellent overall yield. The generation of a metallocarbene from a substrate such as **410** or **416** can lead to several products,[251] and effective control of the cascade pathway is vital to the success of any such strategy.[249] When the simpler substrate **410**, which lacks the iodine residue, was exposed to catalytic rhodium acetate dimer, only a trace of the desired product was formed, with regioisomeric cage product **421** predominating, along with a small quantity of the cyclopropanation product (not shown). Use of rhodium trifluoroacetate dimer suppressed cyclopropanation, but it did not affect the cycloaddition regiochemistry. To overcome this problem, the iodide moiety of **416** was installed on the olefin partner in order to modify the HOMO coefficient of the dipolarophile. This proposal was borne out by the reaction of **416** with rhodium acetate dimer, which furnished the desired cage structure **418** via 1,3-dipole **417** in excellent yield, along with only traces of the regioisomeric product and cyclopropane. Reduction of the now redundant iodide and olefination of the ketone afforded enone **419**. Again, the issue of selective reduction of a fairly symmetrical C4–C9 enone group had to be addressed; and this obstacle was overcome using hydrosilylation with dimethylphenylsilane and Wilkinson's catalyst.[252] The temporary masking of the ketone as the silyl enol ether during the hydrosilylation reaction allowed Lee and coworkers to reduce the nitrile group in situ through the addition of DIBAL-H, which gave ketoaldehyde **420** in 59 % yield, after hydrolysis of the silyl ether. The C9 epimeric ketone was also formed in 23 % yield, reflecting the selectivity of hydrosilylation reaction. The formal asymmetric synthesis was completed by an efficient acid-catalyzed aldol condensation, which provided **310** in 96 % yield.[248]

Two bioactive analogs of platensimycin (**17**) have been reported by the Nicolaou group. Adamantaplatensimycin (**425**, Scheme 60)[253] was prepared via the rhodium-carbene C–H insertion reaction[254] of **422** (prepared from a commercially available adamantane precursor) to give **423**. Although the C–H insertion reaction was not amenable to asymmetric induction, adamantaplatensimycin (**425**) could be accessed as a single enantiomer by resolution of carboxylic acid **424** via the corresponding menthol ester.

Carbaplatensimycin (**430**, Scheme 61)[255] was prepared by modification of Nicolaou's asymmetric route to platensimycin (Scheme 49) by replacing the ketyl radical cyclization of **312** (Scheme 47) with an intramolecular cyanohydrin addition and the etherification employed in that scheme with a 5-*exo*-trig radical cyclization. Cyanohydrin **426** was synthesized in three steps from **312** and underwent smooth cyclization on treatment with KHMDS to afford α-alkoxy nitrile **427**, which was transformed into xanthate **428** in preparation for the radical

cyclization. Indeed, **428** cyclized under standard radical conditions to form carba-cage motif **429**. This intermediate was finally converted to (–)-carbaplatensimycin (**430**) by a sequence analogous to that used for platensimycin (**17**).

Both adamantaplatensimycin (**425**) and carbaplatensimycin (**430**) were found to be active against MRSA and vancomycin-resistant enterococci (VRE), with MIC values of 1.8–2.2 μg mL^{-1} (4–5 μM), as compared with platensimycin [0.4 and 0.8 μg mL^{-1} (0.9 and 1.8 μM) against MRSA and VRE, respectively, in parallel assays].[253,255] Although detailed SAR data have not been reported as yet, it seems that some variation in the structure of the cage portion is tolerated. The dual mechanism of action of platencin (**18**)[202] also raises the possibility that one or both of these analogs operates by such a mechanism, complicating any SAR interpretation at this time.

The novel molecular architecture and biological activity of platencin (**18**) have also prompted synthetic efforts, with the Nicolaou group reporting an asymmetric total synthesis in 2008.[256] Figure 33 depicts their retrosynthetic analysis. A similar final drive to that used for the total synthesis of platensimycin (see Scheme 47) was envisioned, revealing enone **431** as a key intermediate. Disconnection of the enone led to bicyclo[2.2.2]octane **432**, which could be converted retrosynthetically to bicyclo[3.2.1] system **433** through a homoallyl radical rearrangement.[257,258] This bicyclic system was further disconnected to reveal enone **434**, potentially available through asymmetric Diels–Alder chemistry.

In the forward sense (Scheme 62), enone **434** was accessed through a Rawal asymmetric Diels–Alder reaction between aminodiene **435** and enal **436** catalyzed by chromium salen complex **437**.[259] Standard transformations from **438** gave TIPS enol ether **439**, which cyclized efficiently on exposure to gold(I) catalysis, as reported by Toste.[260] The C9 stereochemistry was installed by conjugate addition to bicyclic enone **440**. Conversion of the ketone to the corresponding xanthate (**441**) set the stage for the key rearrangement. Toyota and coworkers had previously reported the rearrangement of similar systems for the formation of various terpene natural products,[257] and, under their reported conditions, xanthate **441** provided rearrangement product **432**. Notably, the 3-*exo*-trig cyclization step of the rearrangement (giving **442**) proceeded faster than the alternative cyclization onto the allyl group, with the 5-*exo*-trig product being isolated only as a minor byproduct. From **432**, Wacker oxidation, deprotection, and oxidation yielded **443**, which underwent smooth aldol condensation on treatment with ethanolic sodium hydroxide to afford enone **431**. Enone **431** was converted into carboxylic acid **444** using the same five-step sequence employed in the platensimycin synthesis. Coupling of **444** with aniline **445**, prepared by modification of the Giannis protocol [216] (see Scheme 48b), yielded amide **446**, which was deprotected under mild conditions to furnish platencin (**18**).

Hayashida and Rawal also reported a total synthesis of platencin in early 2008.[261] Their retrosynthetic analysis disconnected the target to reveal tricyclic enone **431** as a key intermediate. Their approach to this structure, shown in Figure 34, was conceptually distinct from that of Nicolaou et al., and involved a Ni-mediated reductive cyclization to form the core bicyclo[2.2.2]ocatane motif and a Diels–Alder reaction (to form **447** or a similar structure) between amino diene **449** and an equivalent of cyclohexadienone **448**.

The synthesis began with reductive alkylation of *ortho*-anisic acid (**450**) with 2,3-dibromopropene (**339**), followed by acid workup to effect hydrolsis and decarboxylation of the dearomatized material (Scheme 63).[261] Subsequent selenation gave **451**, a surrogate for the required cyclohexadienone moiety. Enone **451** underwent a smooth Diels–Alder cycloaddition with the highly reactive aminosilyloxy diene **449** at 40 °C under neat conditions, leading to *cis*-decalin enone **452** after hydrolysis/elimination upon treatment with HF. The

second enone group was unmasked through elimination of the selenoxide to give a decalin diene-dione. This species (not shown) was found to be a poor substrate for the key cyclization reaction, and reduction of the C5 enone group was investigated as means to bias the conformation of the decalin to favor cyclization. The reduction was accomplished in a highly regio- and stereoselective manner to afford enone **453**. Exposure of **453** to excess $[Ni(cod)_2]$ [262] led to efficient formation of the bicyclo[2.2.2]octane motif. This reductive Heck-type process provided **454** in good yield. Removal of the ketone group from **454** and re-oxidation of the allylic alcohol gave tricyclic enone **431**, the key intermediate for the total synthesis of platencin. Methylation of the enone proceeded smoothly and, in a variation to the procedure employed by Nicolaou et al., was followed by allylation with silicon-containing electrophile **455**. This allowed for facile oxidation of **456** to aldehyde **457** using a modified Tamao–Fleming protocol in which the addition of iodosobenzene proved crucial in effecting chemoselective silane oxidation in the presence of the enone group. Further oxidation of **457** and coupling of the resultant carboxylic acid **444** with fully-unprotected aniline **458**[216] gave platencin (**18**) directly, without the need for a final deprotection step.[261] Although this sequence furnished platencin as a racemate, the approach is notably concise, aided in part by the novel method for side-chain incorporation.

Very recently, a third route to the tricyclic core of platencin was reported by Daesung Lee and coworkers.[263] Their approach commenced from *meso* anhydride **459**, which was converted to racemic lactone **461** by treatment with DIBAL-H followed by acid-catalyzed lactonization in 92 % yield (Scheme 64). Alternatively, catalytic enantioselective desymmeterization of **459** using dimeric cinchona alkaloid catalyst $(DHQD)_2AQN$ according to the procedure of Deng et al.[264] gave monoester **460**, which was converted into highly enantioenriched lactone **461** in a three-step sequence. Stereoselective propargylation (giving **462**), reduction, and acetylation set the stage for the key step of this approach. Treatment of **463** with *n*-Bu_3SnH and AIBN resulted in addition of the tributyltin radical to the alkyne and a 5-*exo*-trig cyclization of the resulting vinyl radical to generate bicyclo[3.2.1]octyl radical **464**. This fleeting intermediate underwent a homoallyl radical rearrangement[257] (see Scheme 62 and relevant discussion above) to give vinylstannane **465**; addition of silica to the reaction mixture effected protodestannylation. It is instructive to compare the outcome of this process with those shown in Schemes 61 and 62, above. In the former cases, similar 5-*exo*-trig radical cyclizations onto enone acceptors resulted in the isolation of the bicyclo[3.2.1]octane system required for platensimycin. As indicated by the current example, the absence of a carbonyl group to stabilize the intermediate radical species clearly favors the rearrangement process, while in the former examples the 3-*exo*-trig/radical fragmentation equilibria must presumably favor the species with the radical stabilized by the adjacent carbonyl group.

In continuing towards the tricyclic enone core of platencin,[263] Lee and coworkers removed the acetate groups from **466** to give a diol, which was monoprotected by treatment with sodium hydride and TBSCl.[265] Although the protection was highly selective for the monoprotected products, the regioselectivity was only approximately 2:1. The major product (**468**) was converted through a seven step sequence to tricyclic enone **431** via diol **469** and an aldol condensation to form the enone ring. The minor TBS ether (**467**) was also progressed to enone **431** through an eight step sequence (not shown), with ring-closing metathesis as the key cyclization step.[263]

The striking biological activities of platensimycin and platencin highlight the value of targeting bacterial fatty acid biosynthesis as a strategy for antibiotic discovery and development. The manner of their discovery is testament to the continuing potential of natural product research in a medicinal chemistry setting, especially when coupled with sophisticated biochemical methods. Whether either of these compounds eventually reaches the market as an approved drug remains to be seen, but it seems likely that a compound from this class will eventually

give rise to an effective antibiotic treatment. The challenge of developing such drugs is supported by the efforts of chemical synthesis, and the variety of routes developed to both the thiolactomycin and platensimycin classes is indicative of the strength of the discipline. Each of the routes to platensimycin and platencin described above provide some insight into the chemistry of these fascinating structures, but none could yet be considered flawless. It will be interesting to chart future developments in this area, particularly with regard to investigation of SAR details, a task that will certainly demand more efficient and flexible synthetic routes.

10. Summary and Outlook

Following a brief history of antibiotics, this review highlighted recent advances in the chemistry, biology, and medicine in the field. The apparent surge in these investigations was prompted by the appearance and persistence of drug-resistant bacterial strains and the realization that a catastrophic outbreak of deadly infections due to such bacteria is not outside the realm of possibilities. As from the very beginning, natural products continue to be at the forefront of antibiotic research. Aided by new advances in biology and powerful screening and isolation techniques, this field is clearly back in favor, and further breakthrough discoveries should be expected. As demonstrated in this review, it does not take long for the synthetic chemists to follow suit once a new promising lead is discovered from nature. And given the awesome and constantly increasing power of chemical synthesis, such molecules and their analogs have become accessible for further study in the laboratory. To be sure, it is the combination of new discoveries from nature and their intelligent exploitation in the laboratory that will synergistically lead to the antibiotics of tomorrow. Such new drugs are certainly needed if we are to stay ahead of the never ending invasions by our fearful enemies, the superbugs.

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Abbreviations

Ac
: acetyl

Acc
: acetyl-CoA carboxylase

ACP
: acyl carrier protein

AIBN
: 2,2’-azobis(2-methylpropionitrile)

Ala
: alanine

Alloc
: allyloxycarbonyl

Asn
: asparagine

ATP
: adenosine triphosphate

BABX
: bischloroanthrabenzoxocinone

BAIB
: bis(acetoxy)iodobenzene

9-BBN
: 9-borabicyclo[3.3.1]nonane

BINAP
: 2,2’-bis(diphenylphosphino)-1,1’-binaphthalene

Bn
: benzyl

Boc
: *tert*-butoxycarbonyl

Bpoc

1-methyl-1-(4-biphenylyl)ethoxycarbonyl

brsm
based on recovered starting material

Bt
benzotriazol-1-yl

C
cysteine

CAN
ammonium cerium(IV) nitrate

cat
Catalytic

CBS
Corey–Bakshi–Shibata

Cbz
benzyloxycarbonyl

CIP
2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate

CoA
coenzyme A

cod
cyclooctadiene

Cp
cyclopentadienyl

CSA
camphorsulfonic acid

Cys
cysteine

DAST
(diethylamino)sulfur trifluoride

dba
1,5-diphenyl-1,4-pentadien-3-one

DBU
1,8-diazabicyclo[5.4.0]undec-7-ene

DCC
N,*N*’-dicyclohexylcarbodiimide

de
diastereomeric excess

DEPBT
3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one

DHP
3,4-dihydro-2*H*-pyran

DIAD
diisopropyl azodicarboxylate

DIBAL-H
diisobutylaluminum hydride

DIC
N,*N*'-diisopropylcarbodiimide

DIOP
4,5-bis(diphenylphosphino-methyl)-2,2-dimethyl-1,3-dioxolane

DIPT
diisopropyl tartrate

DMAP
4-dimethylaminopyridine

DMDO
dimethyldioxirane

DMP
Dess–Martin periodinane [1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one]

DMSO
dimethylsulfoxide

DNA
deoxyribonucleic acid

DPPA
diphenylphosphoryl azide

dr
diastereomeric ratio

EDC
N-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide

ee
enantiomeric excess

EE
1-ethoxyethyl

Fab
fatty acid biosynthesis enzymes

FAS
fatty acid biosynthesis

FDA
United States Food and Drug Administration

FDPP

pentafluorophenyl diphenylphosphinate

Fm
fluorenylmethyl

Gly
glycine

GTP
guanosine triphosphate

HATU
O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*’,*N*’-tetramethyluronium hexafluorophosphate

His
histidine

HOAt
1-hydroxy-7-azabenzotriazole

HOBt
1-hydroxybenzotriazole

HOMO
highest occupied molecular orbital

HMDS
hexamethyldisilazine

IBX
o-iodoxybenzoic acid

IC_{50}
inhibitory concentration 50 %

Ile
isoleucine

IleRSs
isoleucine–tRNA synthetases

KasA/B
ketoacyl synthase A/B

KHMDS
potassium hexamethyldisilazide

LDA
lithium diisopropylamide

LiHMDS
lithium hexamethyldisilazide

***m*CPBA**
m-chloroperbenzoic acid

MIC
minimum inhibitory concentration

MNBA
2-methyl-6-nitrobenzoic anhydride

MOM
methoxymethyl

MPO
4-methoxypyridine-*N*-oxide

mRNA
messenger RNA

Ms
methanesulfonyl

NCI
National Cancer Institute, U.S.A

NAD
nicotinamide adenine dinucleotide

NADH
reduced nicotinamide adenine dinucleotide

NADP
nicotinamide adenine dinucleotide phosphate

NADPH
reduced nicotinamide adenine dinucleotide phosphate

NaHMDS
sodium hexamethyldisilazide

NBS
N-bromosuccinimide

NMM
4-methylmorpholine

NMO
4-methylmorpholine-*N*-oxide

NMR
nuclear magnetic resonance

PABA
para-aminobenzoic acid

PCC
pyridinium chlorochromate

Phe
phenylalanine

pin
pinacol

Piv
trimethylacetyl

PMB *para*-methoxybenzyl

PPO pyrophosphate

PPTS pyridinium *para*-toluene sulfonate

***p*Tol** *para*-tolyl

py pyridine

Q glutamine

RNA ribonucleic acid

SAR Structure Activity Relationship(s)

SEM 2-(trimethylsilyl)ethoxymethyl

Ser serine

SES 2-trimethylsilylethanesulfonyl

TASF tris(dimethylamino)sulfonium difluorotrimethylsilicate

TBAF tetra-*n*-butylammonium fluoride

TBDPS *tert*-butyldiphenylsilyl

TBS *tert*-butyldimethylsilyl

Teoc 2-(trimethylsilyl)-ethoxycarbonyl

TES triethylsilyl

Tf trifluoromethanesulfonyl

TFA trifluoroacetic acid

TFAA trifluoroacetic anhydride

TFP
tri(2-furyl)phosphine

THP
tetrahydropyran-2-yl

TIPS
triisopropylsilyl

TMS
trimethylsilyl

TMSE
2-(trimethylsilyl)-ethyl

TOTU
O-[(Ethoxycarbonyl)cyanomethylenamino]-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate

TPAP
tetra-*n*-propylammonium perruthenate

TPP
5,10,15,20-tetraphenyl-21*H*,23*H*-porphine

Tr
trityl

Ts
4-toluenesulfonyl

tRNA
transfer RNA

VISA
vancomycin-intermediate *Staphylococcus aureus*

VRE
vancomycin-resistant *Enterococcus.*

Biographies

Professor K.C. Nicolaou, born in Cyprus and educated in England and the United States, is currently Chairman of the Department of Chemistry at The Scripps Research Institute where he holds the Darlene Shiley Chair in Chemistry and the Aline W. and L. S. Skaggs Professorship in Chemical Biology as well as Professor of Chemistry at the University of California, San Diego. The impact of his career on chemistry, biology and medicine flows from his contributions to chemical synthesis, which have been described in numerous publications and patents. His dedication to chemical education is reflected in his training of hundreds of graduate students and postdoctoral fellows. His books *Classics in Total Synthesis I* and *II*, and his book *Molecules That Changed the World*, which he has co-authored with his students Erik J. Sorensen, Scott A. Snyder, and Tamsyn Montganon, respectively, are used around the world as a teaching tool and source of inspiration for students and practitioners of the art of chemical synthesis.

Jason S. Chen was born in Taipei, Taiwan in 1979. He received his A.B. and A.M. degrees in 2001 from Harvard University, where he performed research under the supervision of

Professor Matthew Shair. He then joined Enanta Pharmaceuticals, where he was a medicinal chemist working on novel cyclosporine A analogs. In summer 2003, he joined Professor K. C. Nicolaou's laboratory at The Scripps Research Institute, where he is currently a graduate student. He was a member of a team that recently disclosed the total synthesis and biological evaluation of uncialamycin.

David J. Edmonds was born in Glasgow (UK) in 1980. He received his M.Sci. in chemistry with medicinal chemistry from the University of Glasgow in 2001. He was awarded a University Scholarship for postgraduate research, and carried out his Ph.D. work at Glasgow under the supervision of Dr. David J. Procter on the application of samarium(II)-mediated reactions to total synthesis. In early 2005, he joined Professor K. C. Nicolaou's group, supported by a European Merck Postdoctoral Fellowship, where he has continued to pursue his research interests in the total synthesis of natural products.

Anthony A. Estrada, born in Los Angeles, California in 1981, received his B.S. in chemistry from the University of La Verne in 2003 and his M.S. in chemistry from the University of California, San Diego in 2005. He is currently working towards his Ph.D. under the supervision of Professor K. C. Nicolaou where he has devoted his attention to the chemistry and biology of the thiopeptide antibiotics thiostrepton and the nocathiacins, as well as *N*-hydroxyindole and trimethyltin hydroxide synthetic methodologies. He has been the recipient of a NIH/UCSD pre-doctoral fellowship and an ACS Division of Organic Chemistry graduate fellowship sponsored by Boehringer Ingelheim.

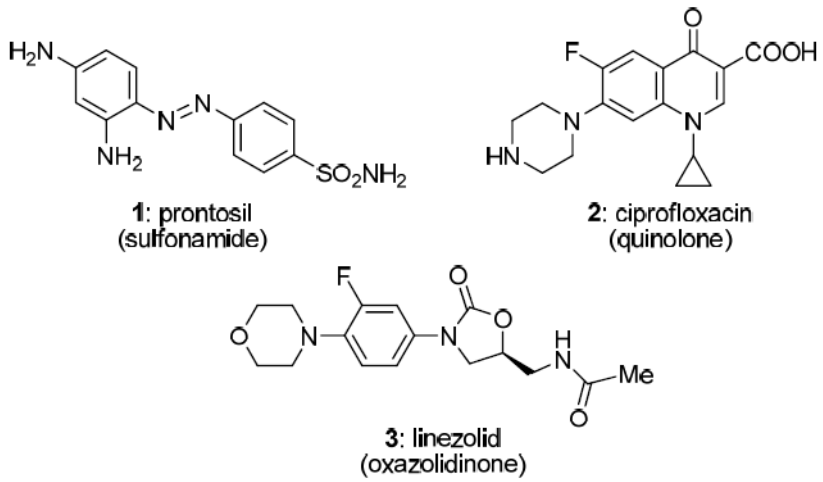


Figure 1.
Molecular structures of selected antibiotics of synthetic origin.

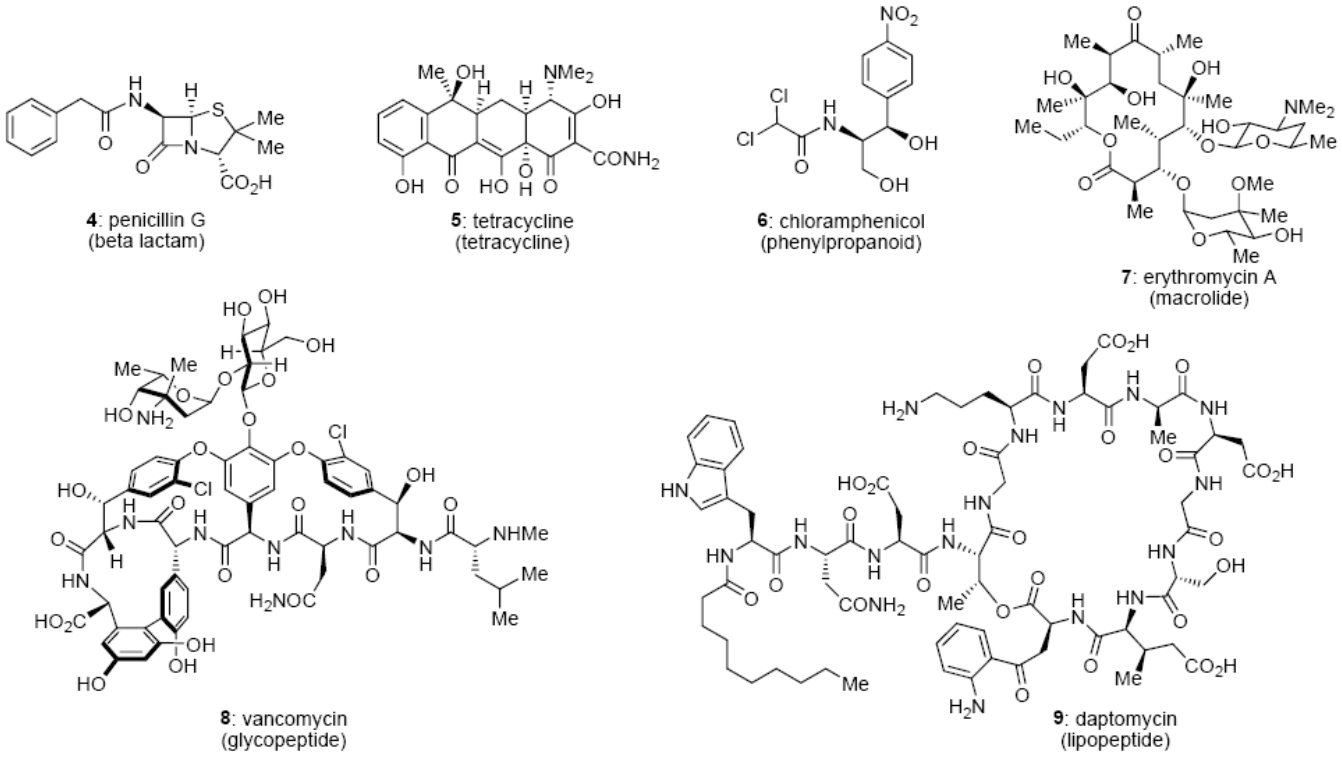


Figure 2.
Molecular structures of selected antibiotics derived from natural products.

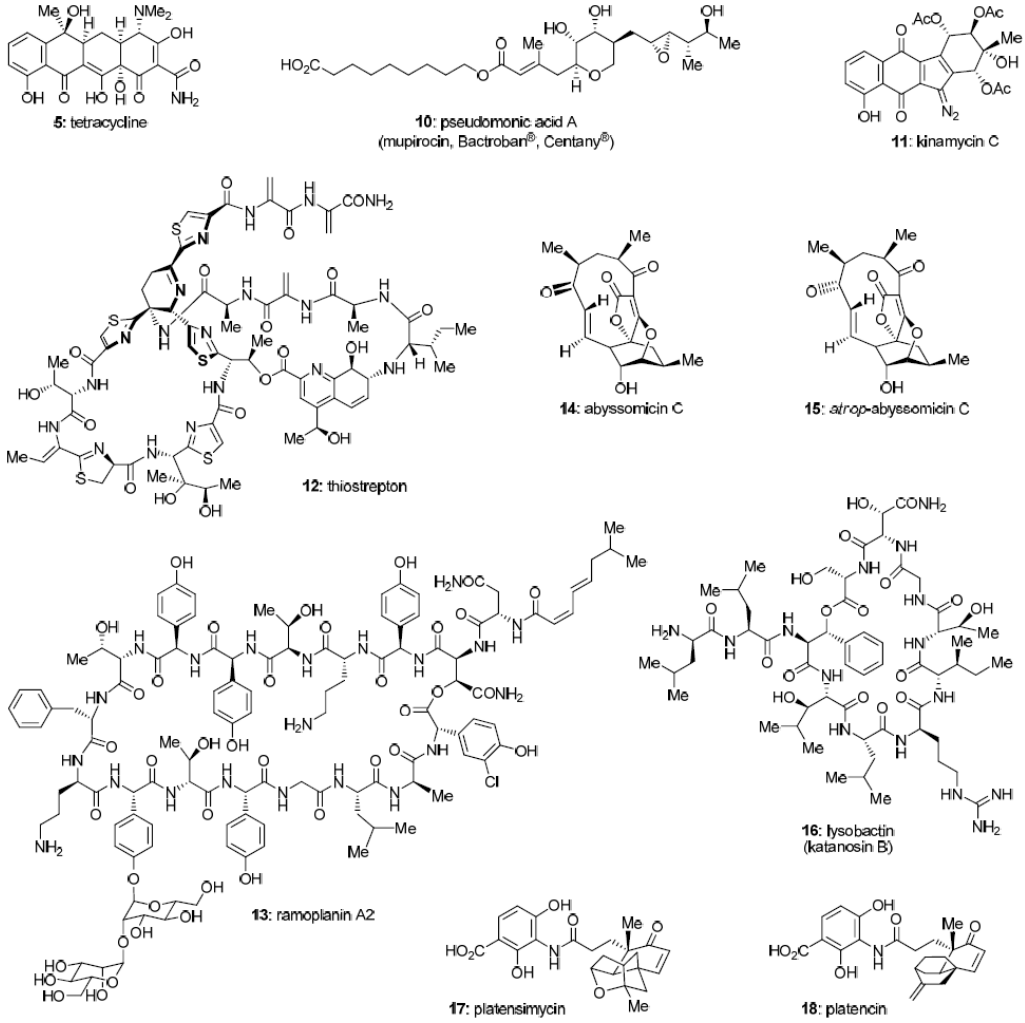


Figure 3.
Representative members of antibiotic classes discussed in this article.

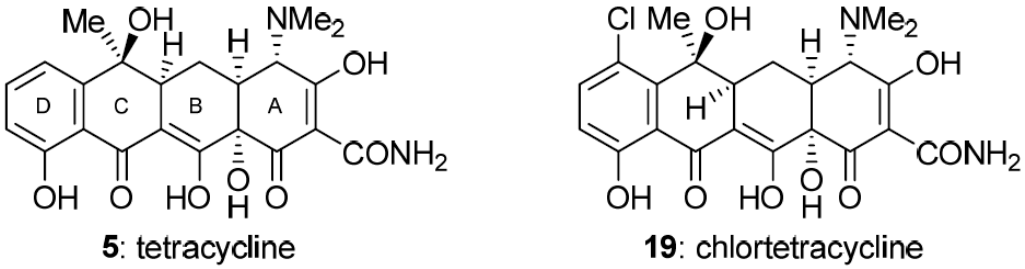


Figure 4.
Molecular structures of tetracycline (**5**) and chlortetracycline (**19**).

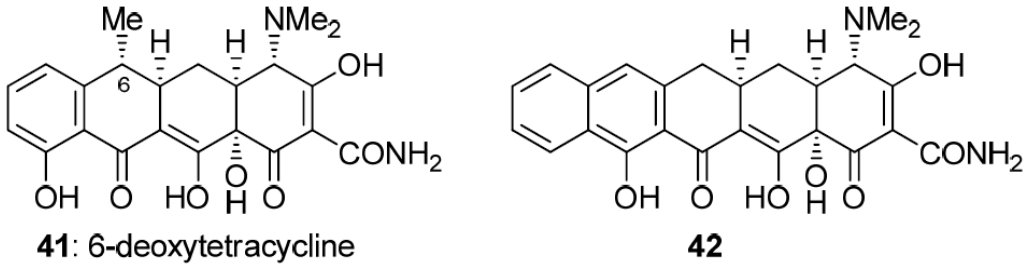


Figure 5.
Selected synthetic tetracycline analogs (Myers et al., 2005).[30]

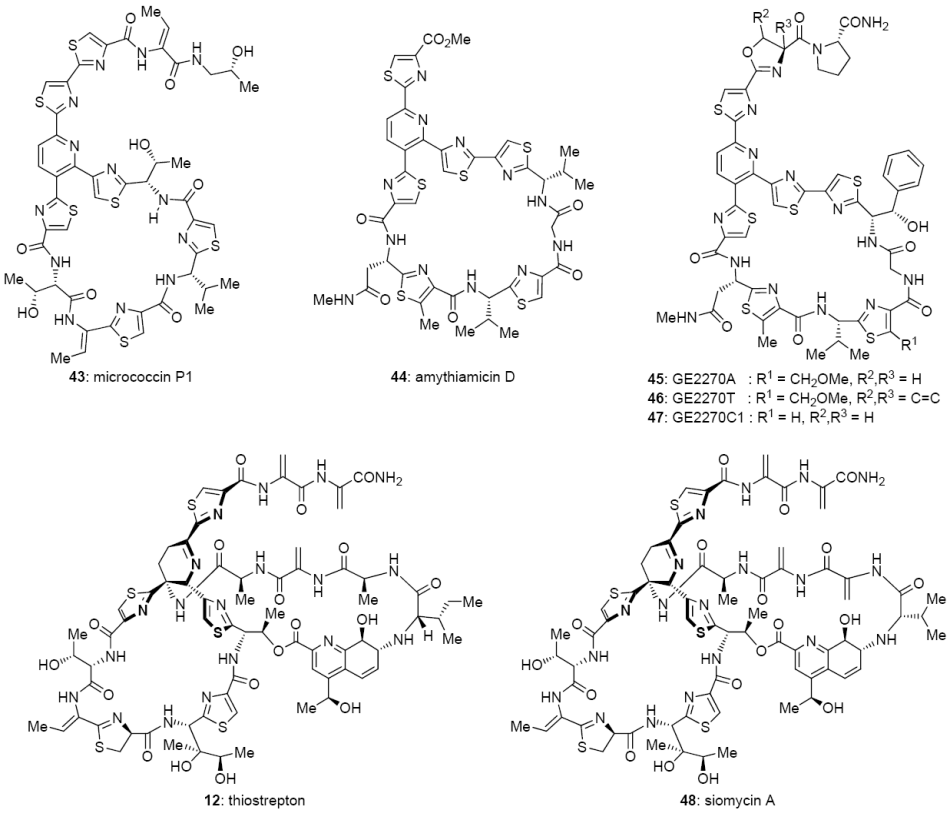


Figure 6.
Molecular structures of selected thiopeptide antibiotics.

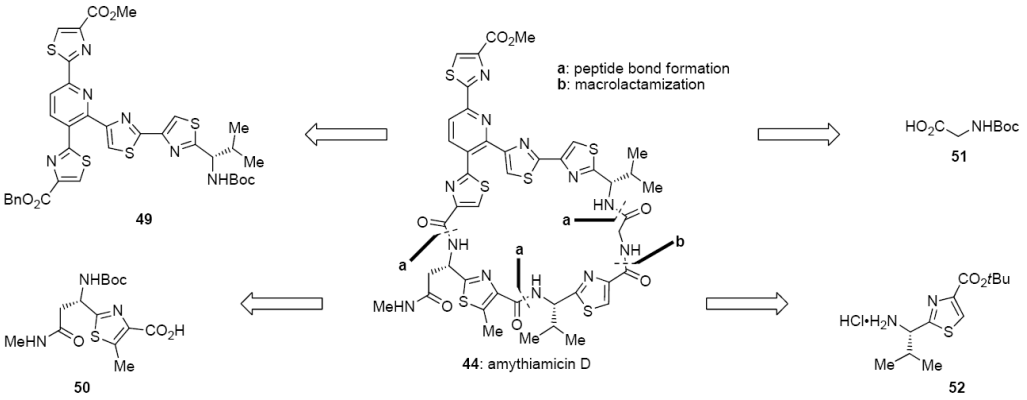


Figure 7.
Retrosynthetic analysis of amythiamicin D (**44**) (Moody et al., 2004).[40]

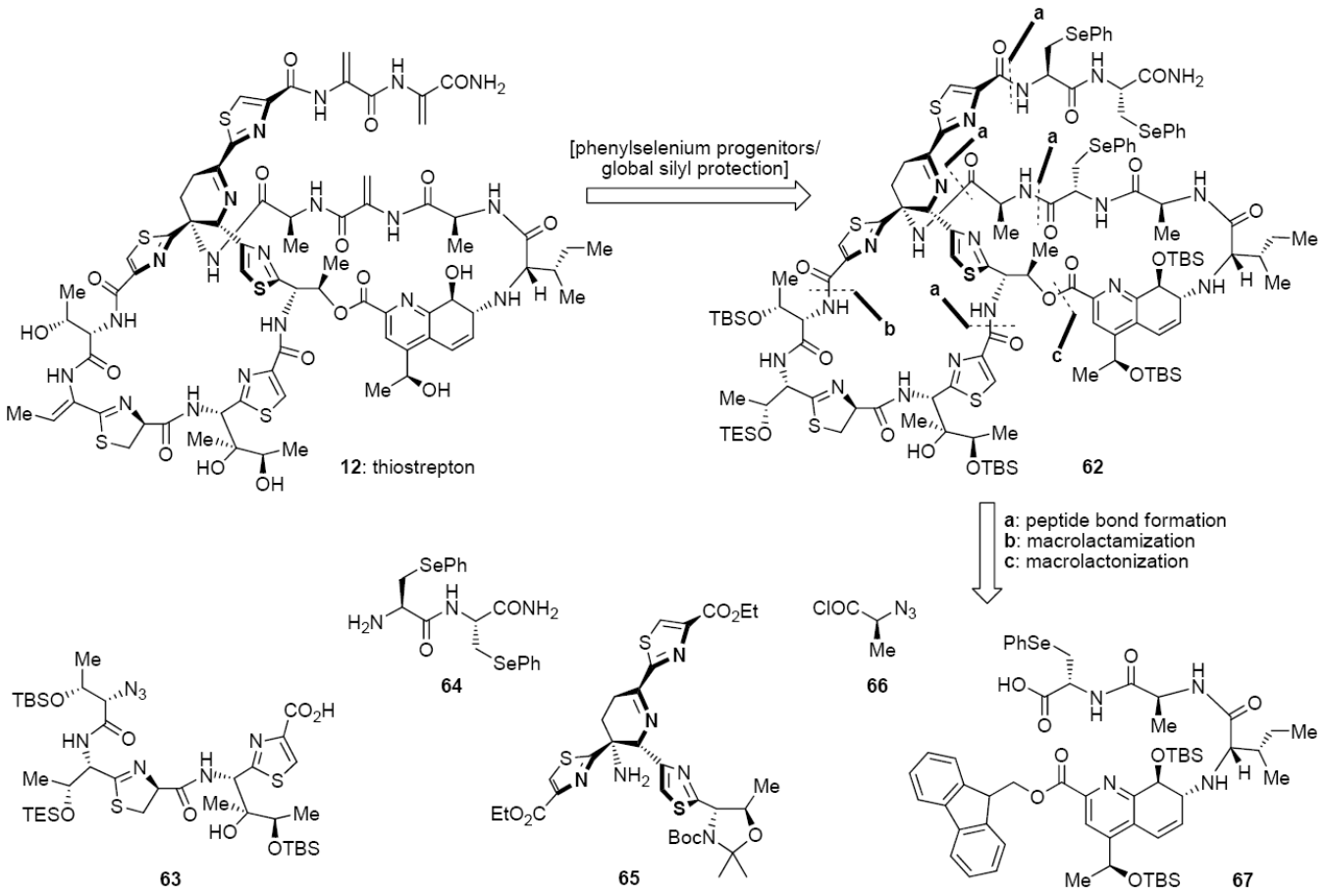
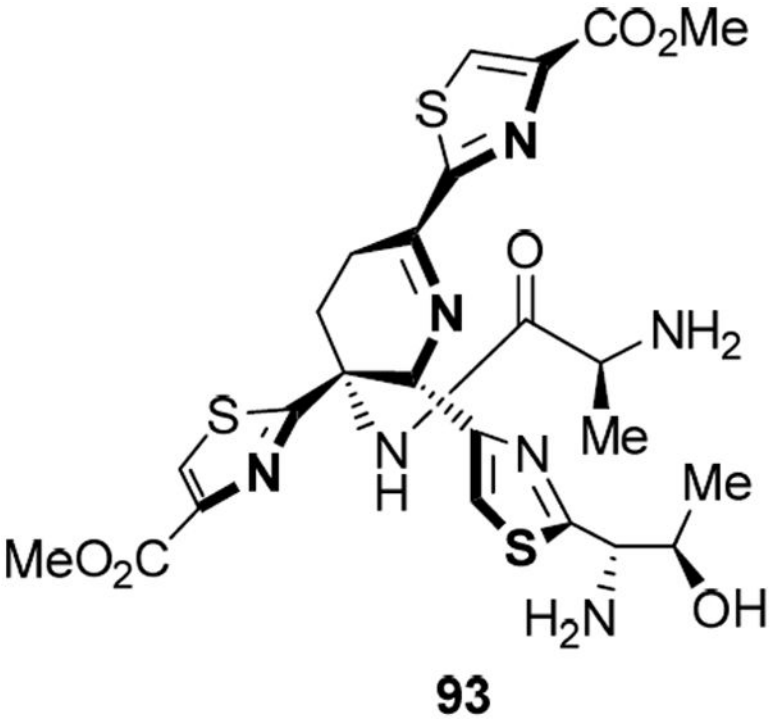


Figure 8.
Retrosynthetic analysis of thiostrepton (**12**) (Nicolaou et al., 2004).[53]



93

Figure 9.
Molecular structure of highly simplified thiostrepton analog **93** (Nicolaou et al., 2005).[48]

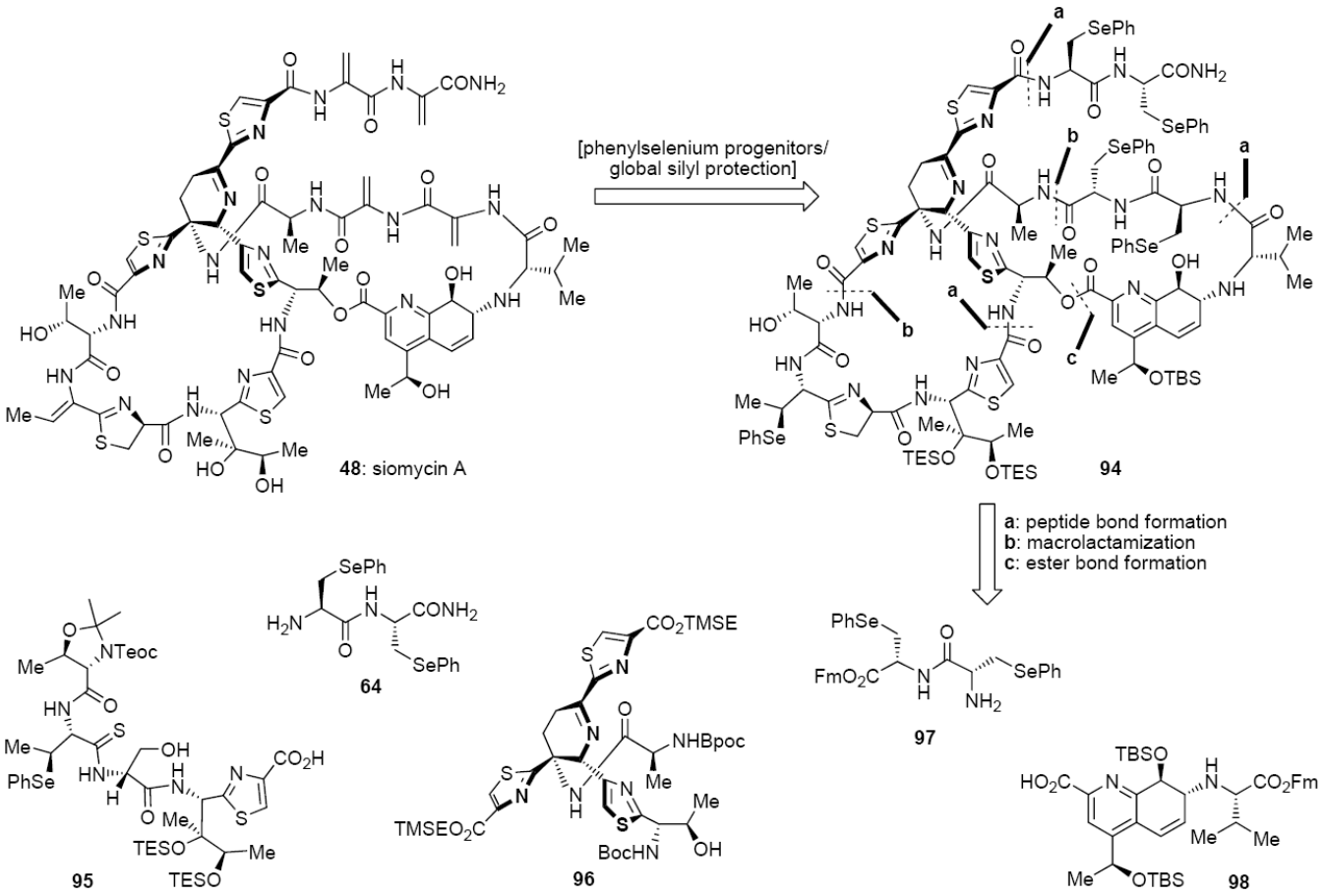


Figure 10.
Retrosynthetic analysis of siomycin A (**48**) (Hashimoto et al., 2007).[65]

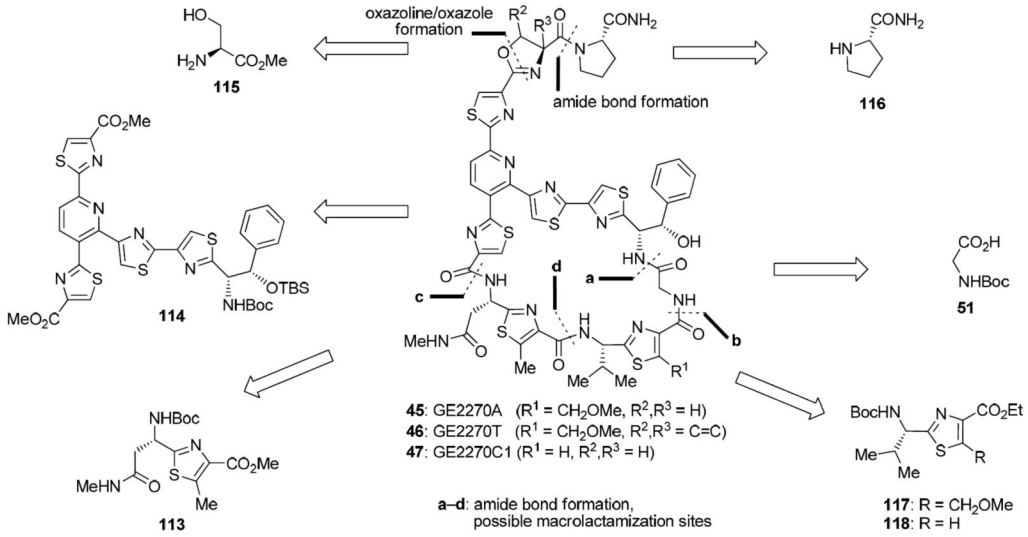


Figure 11.
Retrosynthetic analysis of GE2270A (**45**), GE2270T (**46**), and GE2270C1 (**47**) (Nicolaou, Chen et al., 2007).[74]

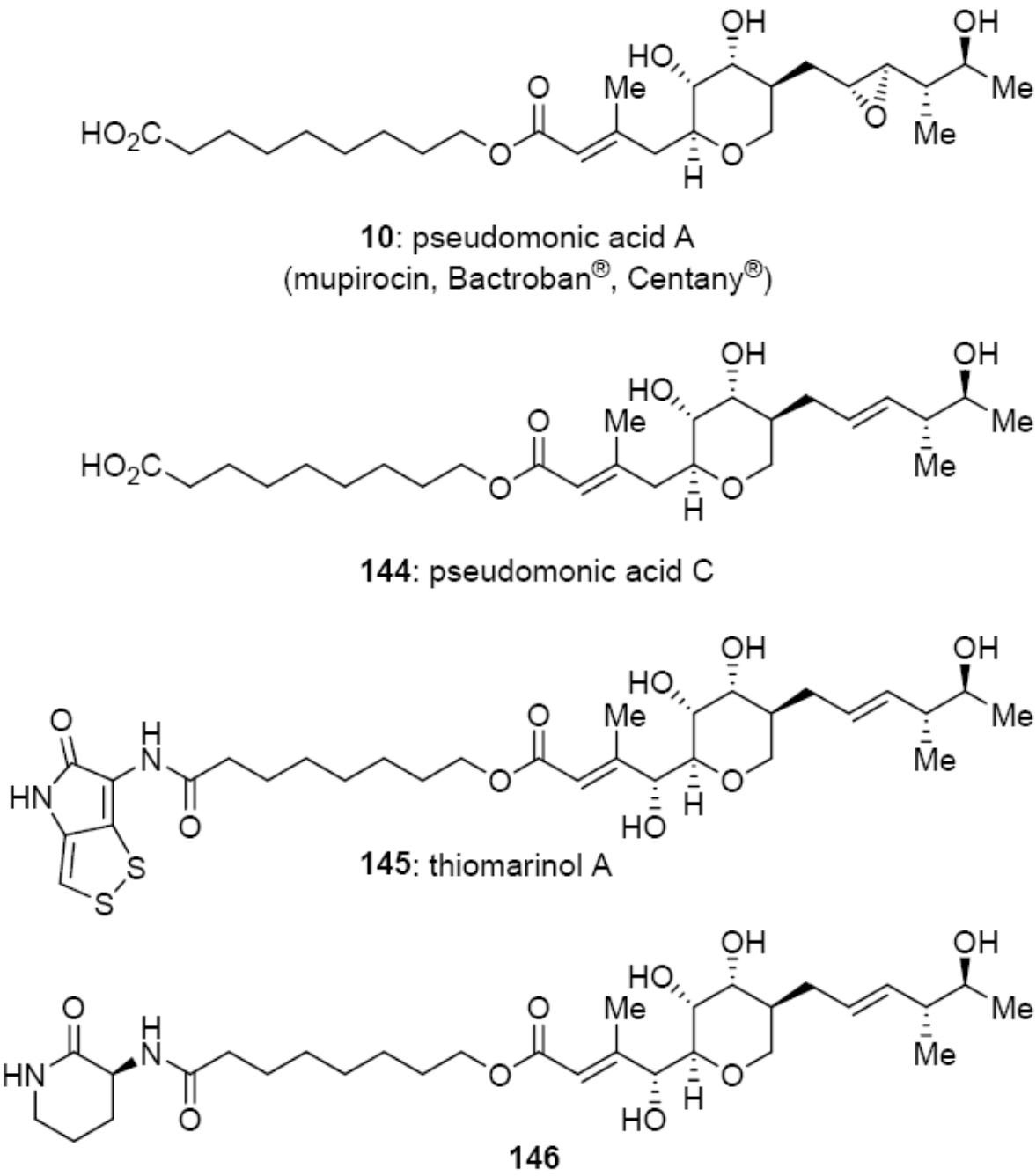


Figure 12.
Molecular structures of pseudomonic acid A (**10**) and related natural products.

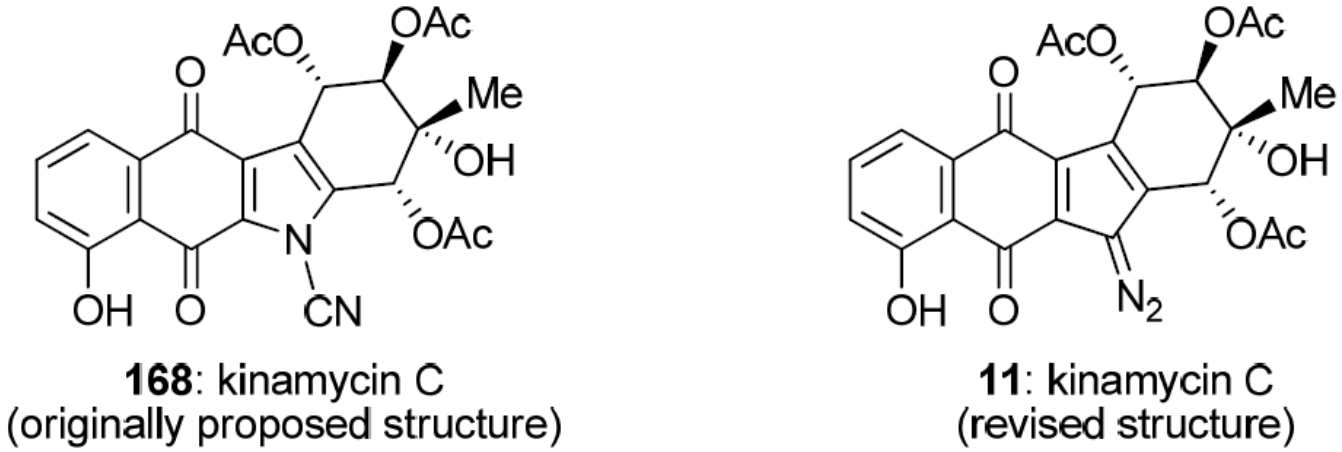


Figure 13.
Originally proposed (**168**) and revised (**11**) structures of kinamycin C.

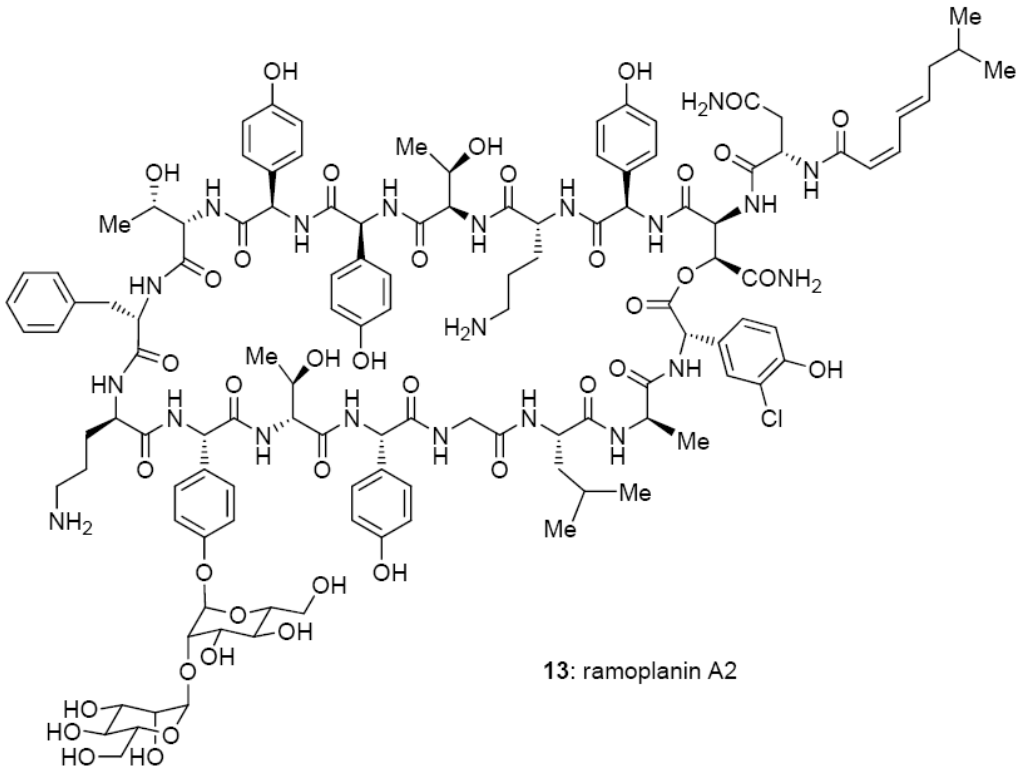


Figure 14.
Molecular structure of ramoplanin A2 (**13**).

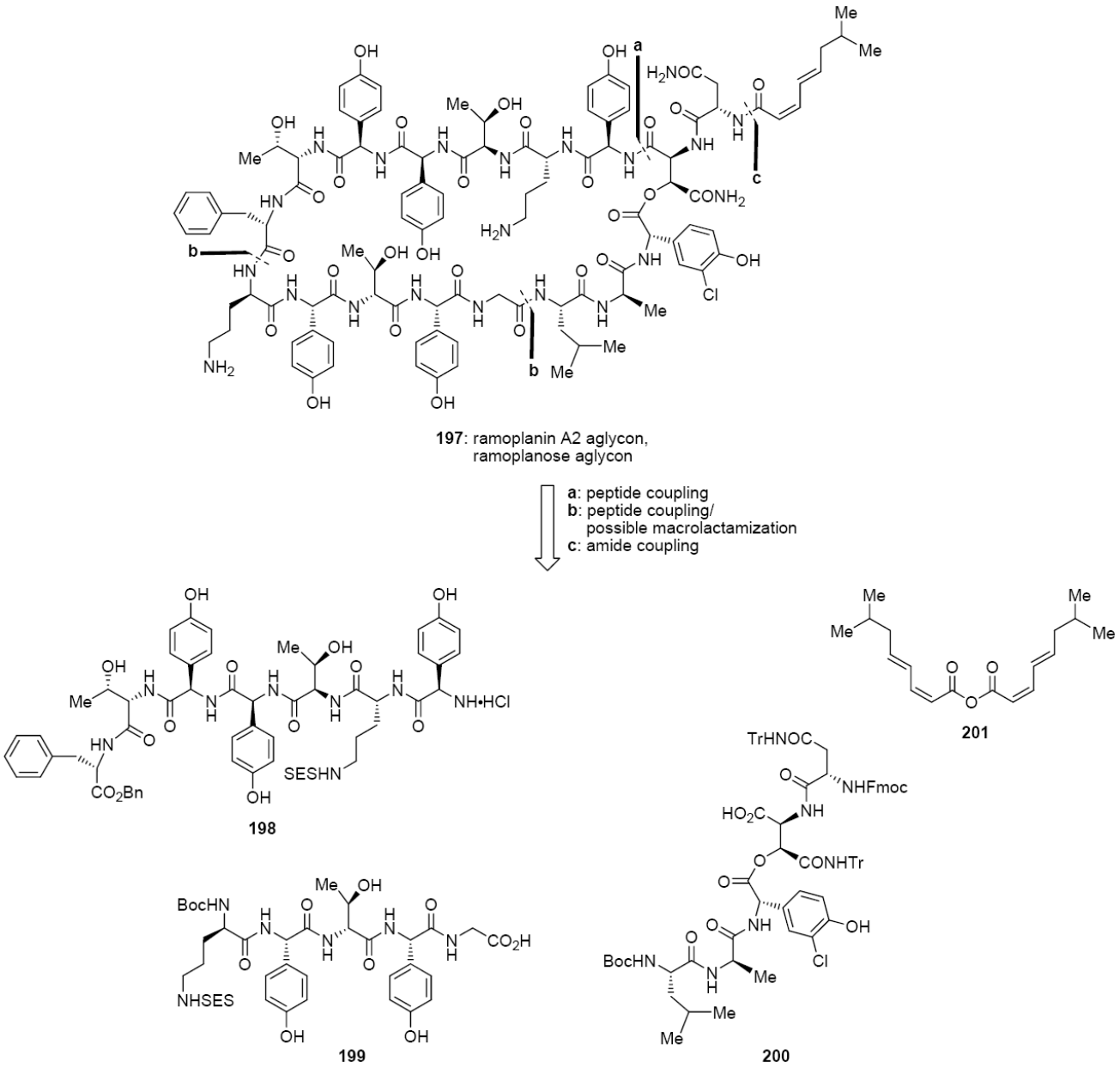


Figure 15.
Retrosynthetic analysis of ramoplanin A2 aglycon (**197**) (Boger et al., 2002).[122]

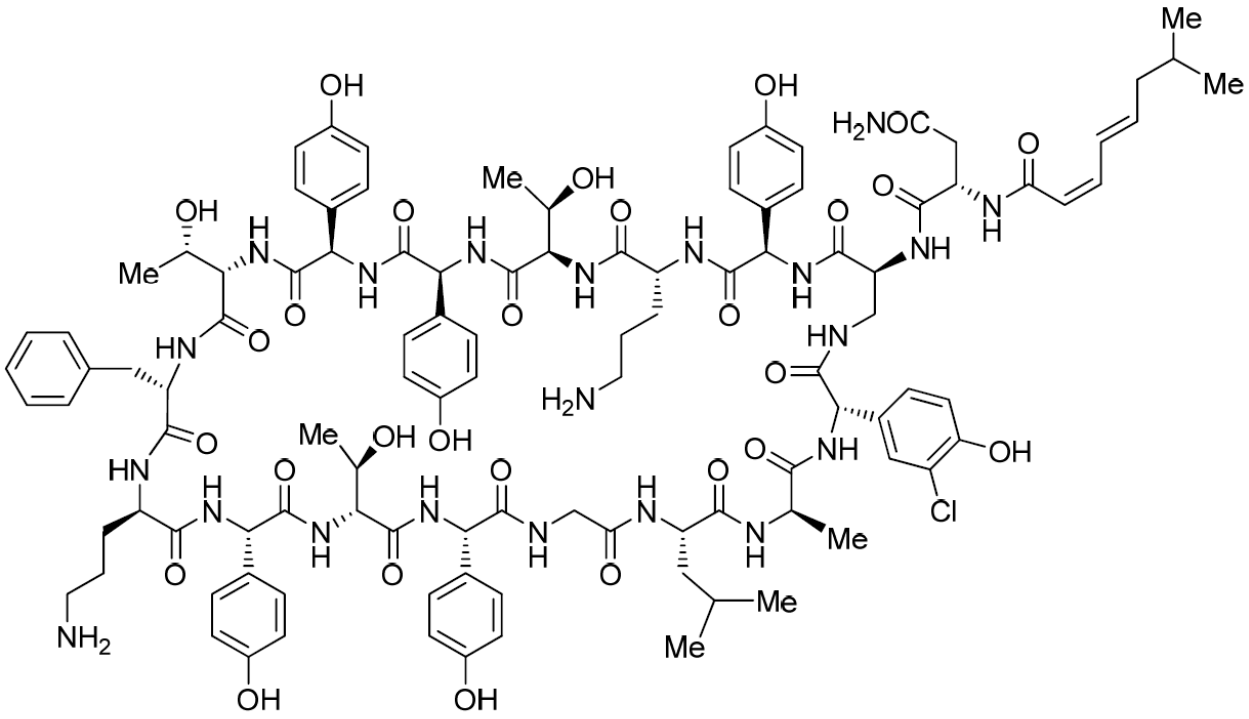


Figure 16.
Molecular structure of [L-Dap^2]ramoplanin A2 aglycon (**205**) (Boger et al., 2004).[125b]

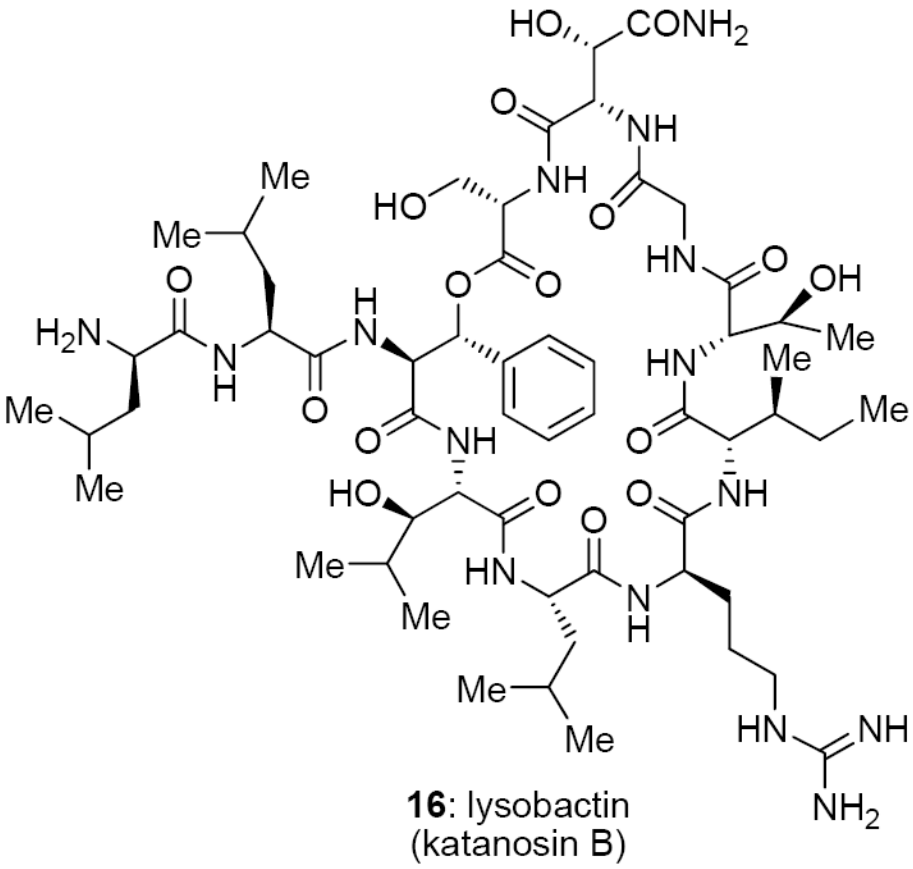
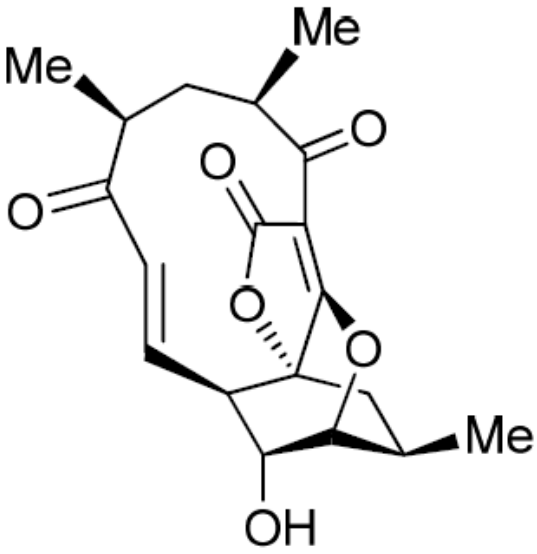
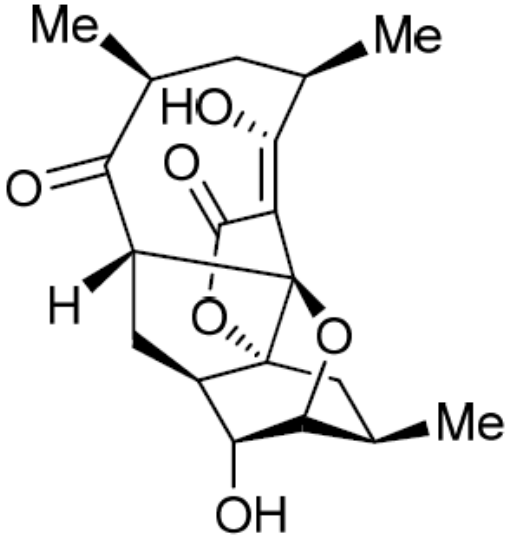


Figure 17.
Molecular structure of lysobactin (**16**).



14: abyssomicin C



206: abyssomicin D

Figure 18.
Molecular structures of abyssomicins C (**14**) and D (**206**).

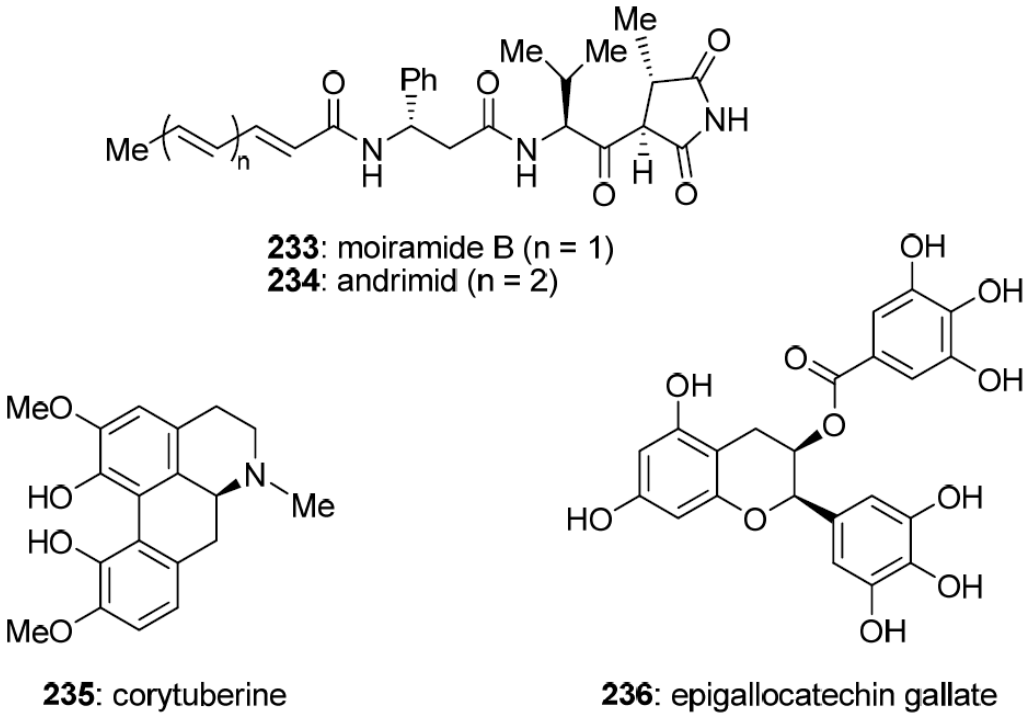
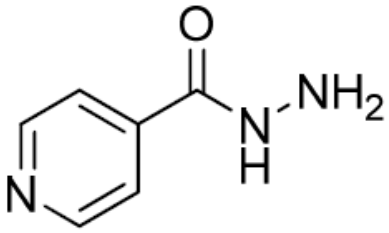
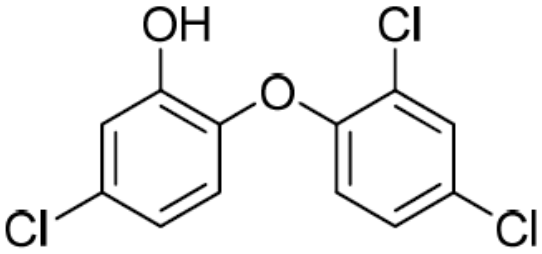


Figure 19.
Molecular structures of selected natural FAS II inhibitors.



237: isoniazid



238: triclosan

Figure 20.
Molecular structures of the clinical tuberculosis drug isoniazid (**237**) and the widely used antibacterial agent triclosan (**238**).

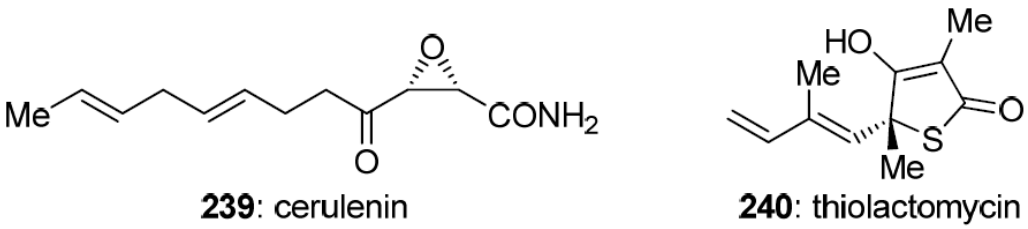


Figure 21.
Molecular structures of cerulenin (**239**) and thiolactomycin (**240**).

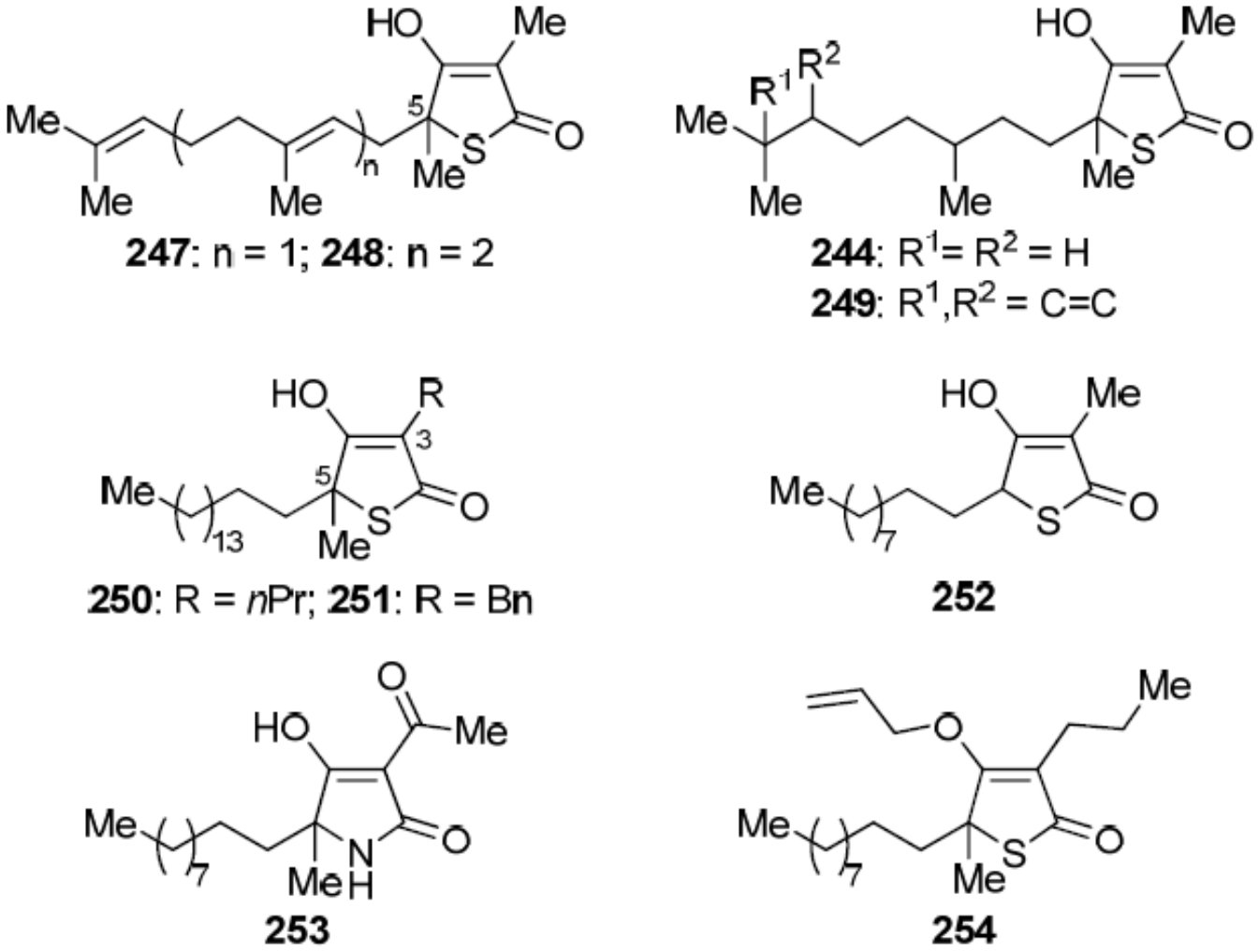


Figure 22.
Thiolactomycin analogs with activity against protozoan parasites (Waller et al., 2003;[173] Gilbert et al., 2004–2005[174]).

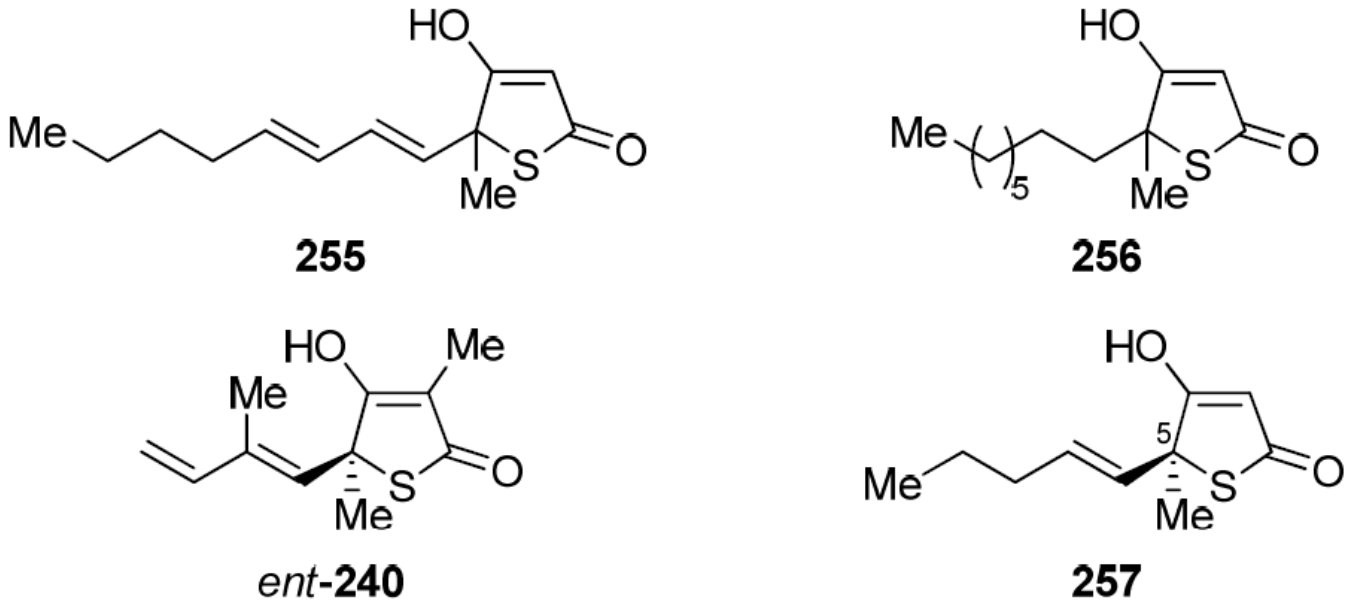
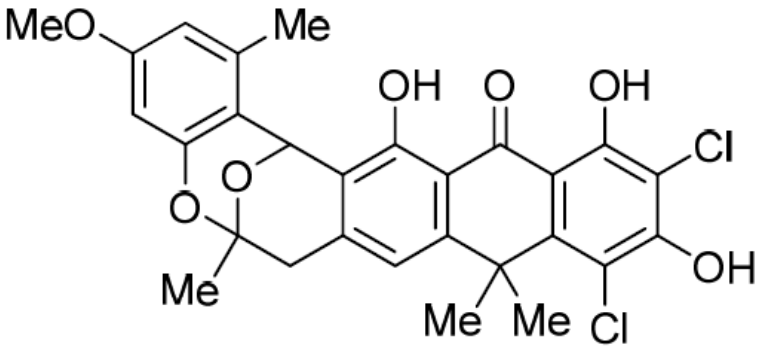
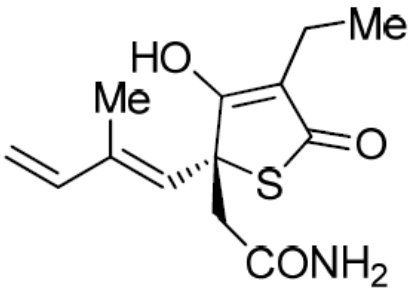


Figure 23.
Thiolactomycin analogs with activity against mamallian fatty acid biosynthesis (Townsend et al., 2005;[176] Ohata and Terashima, 2007[177]).



288: bischloroanthrabenzoxocinone



289: Tü3010

Figure 24.
Molecular structures of fatty acid inhibitors bischloroanthrabenzoxocinone (BABX, **288**) and Tü3010 (**289**).

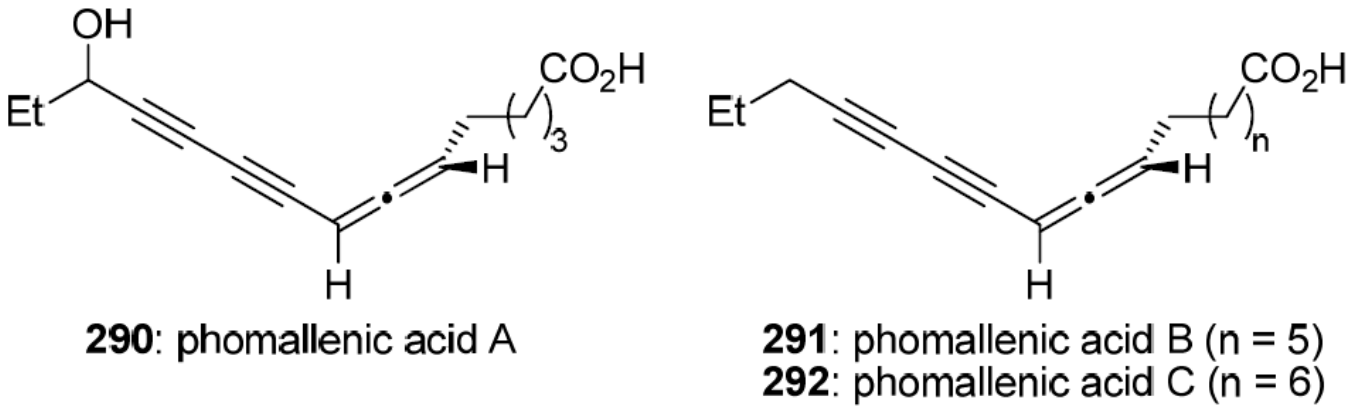


Figure 25.
Molecular structures of phomallenic acids A–C (**290**–**292**).

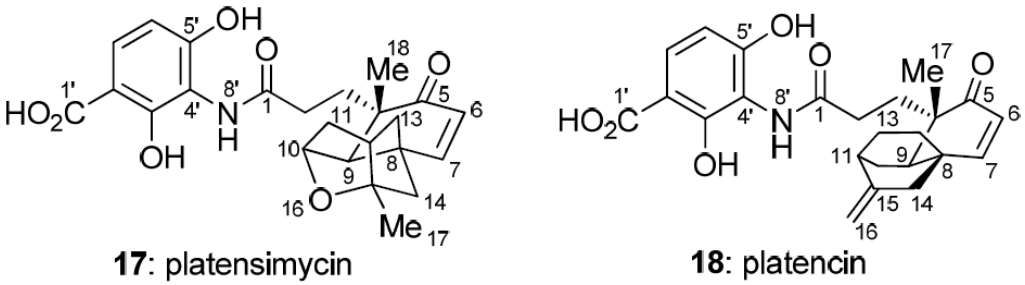


Figure 26.
Molecular structures of platensimycin (**17**) and platencin (**18**).

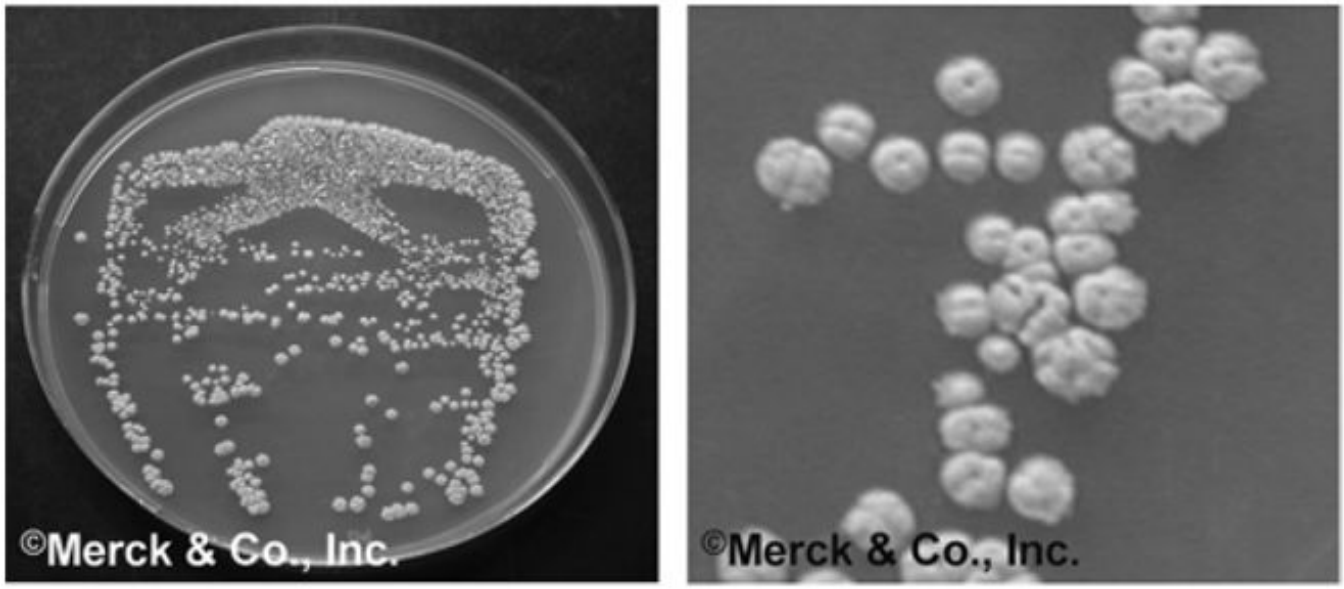


Figure 27.
Picture of *Streptomyces platensis*. (Copyright © 2007 Merck & Co., Inc., Whitehouse Station, N.J., U.S.A. All Rights Reserved.)

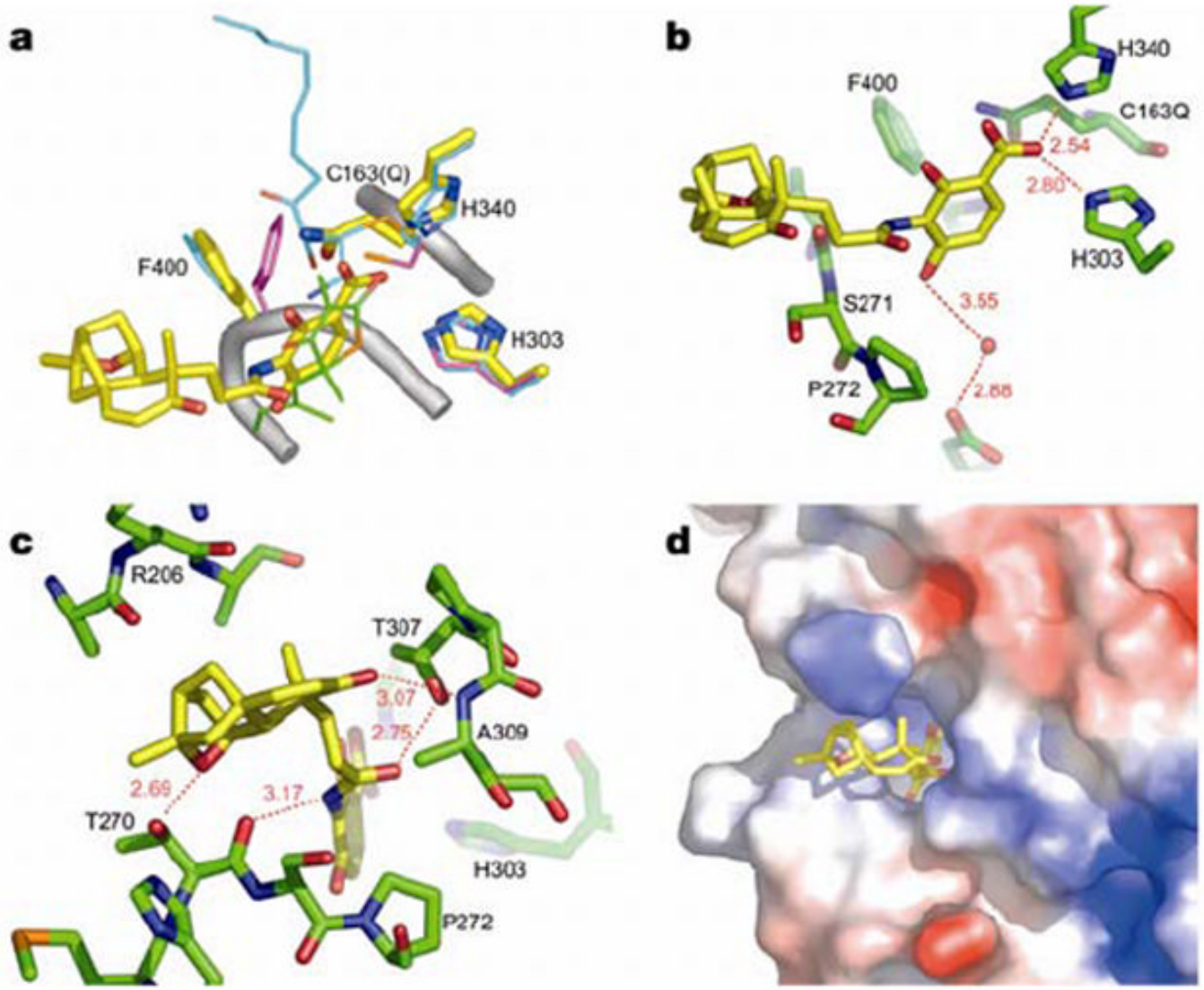


Figure 28.

Overlay of platensimycin (**17**), cerulenin (**239**), and thiolactomycin (**240**) bound to the active site of FabF (a). X-ray derived structures of platensimycin (yellow) bound in the malonate subsite of *E. coli* C163Q Fab F. Significant contacts to protein residues (green) are shown by dashed lines, with interatomic distances in Å (b and c). Solvent accessible surface of the C163Q Fab F–platensimycin complex showing platensimycin (yellow) partially exposed to solvent (d). Reprinted by permission from Macmillan Publishers Ltd: *Nature*, *441*, 358–361, **2006**.

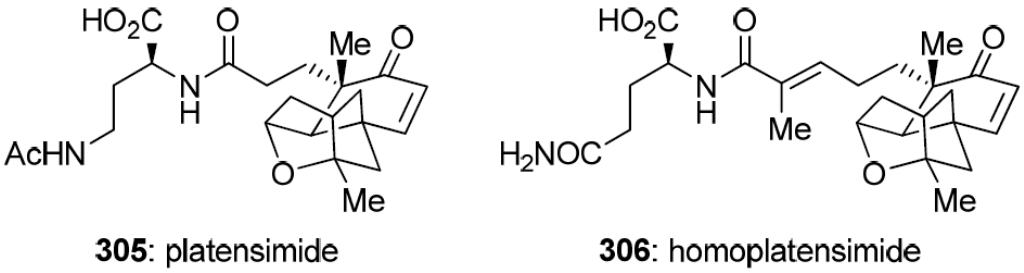


Figure 29.
Molecular structures of platensimide (**305**)[205] and homoplatensimide (**306**).[206]

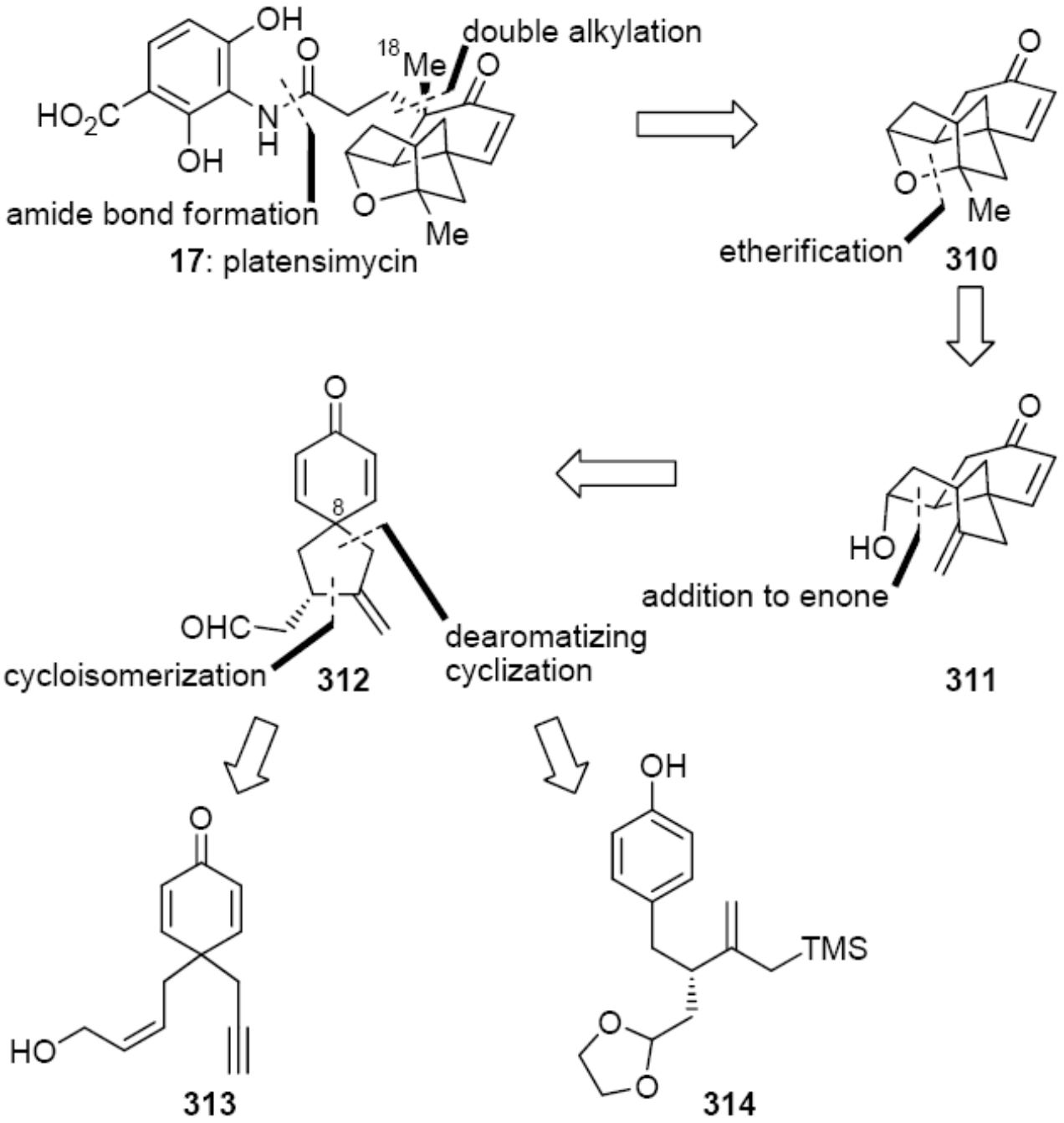


Figure 30.
Retrosynthetic analysis of platensimycin (**17**) (Nicolaou et al., 2006).[209]

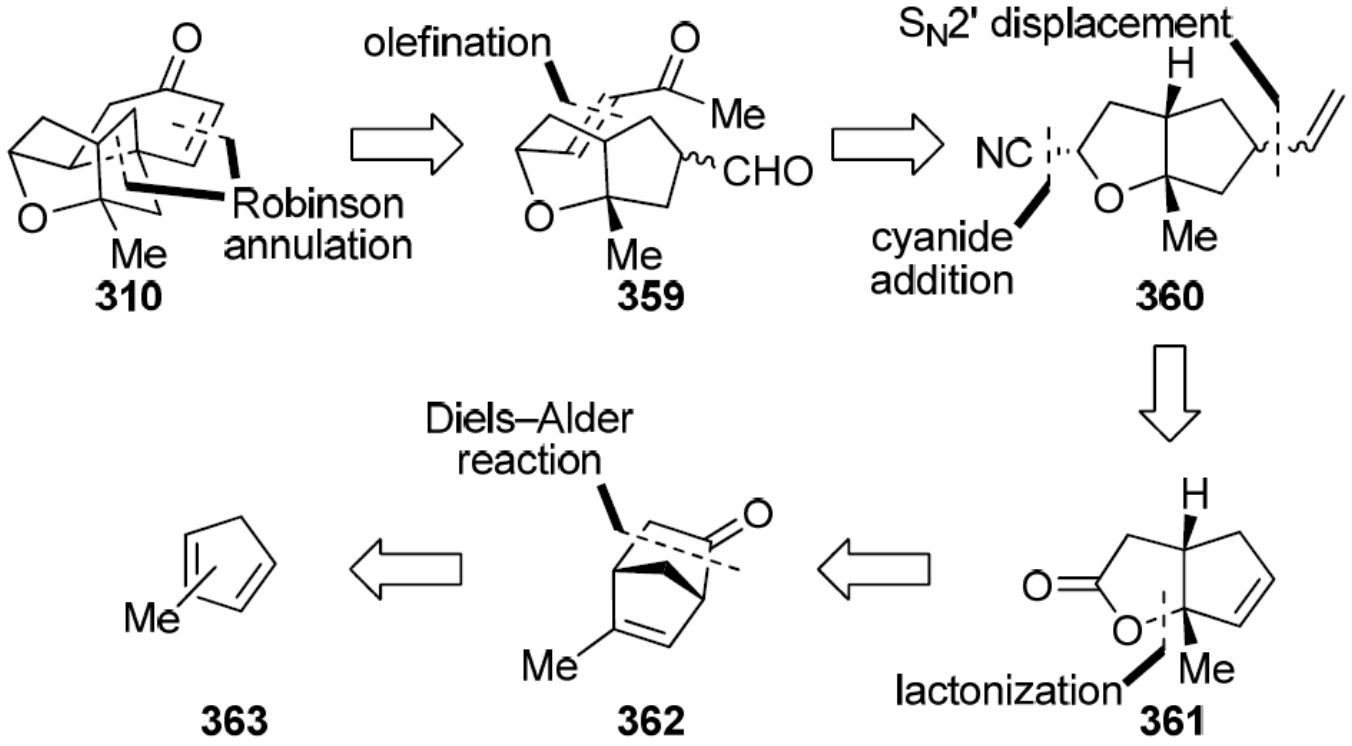


Figure 31.
Retrosynthetic analysis of the platensimycin ketolide (**310**) (Yamamoto et al., 2007).[228]

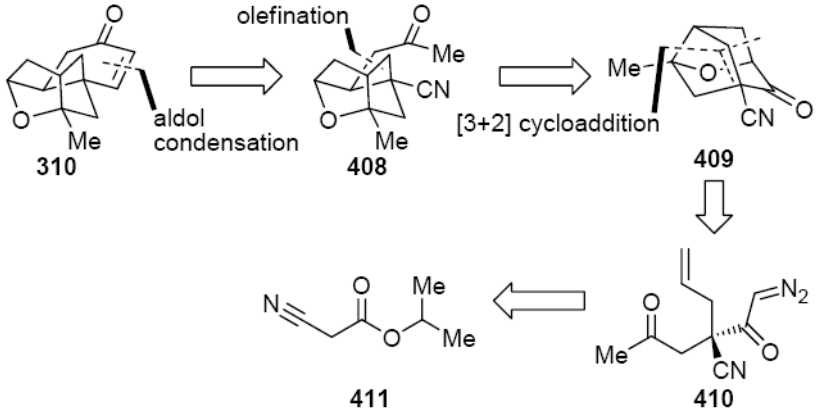


Figure 32.
Retrosynthetic analysis of **310** (Eun Lee et al., 2008).[248]

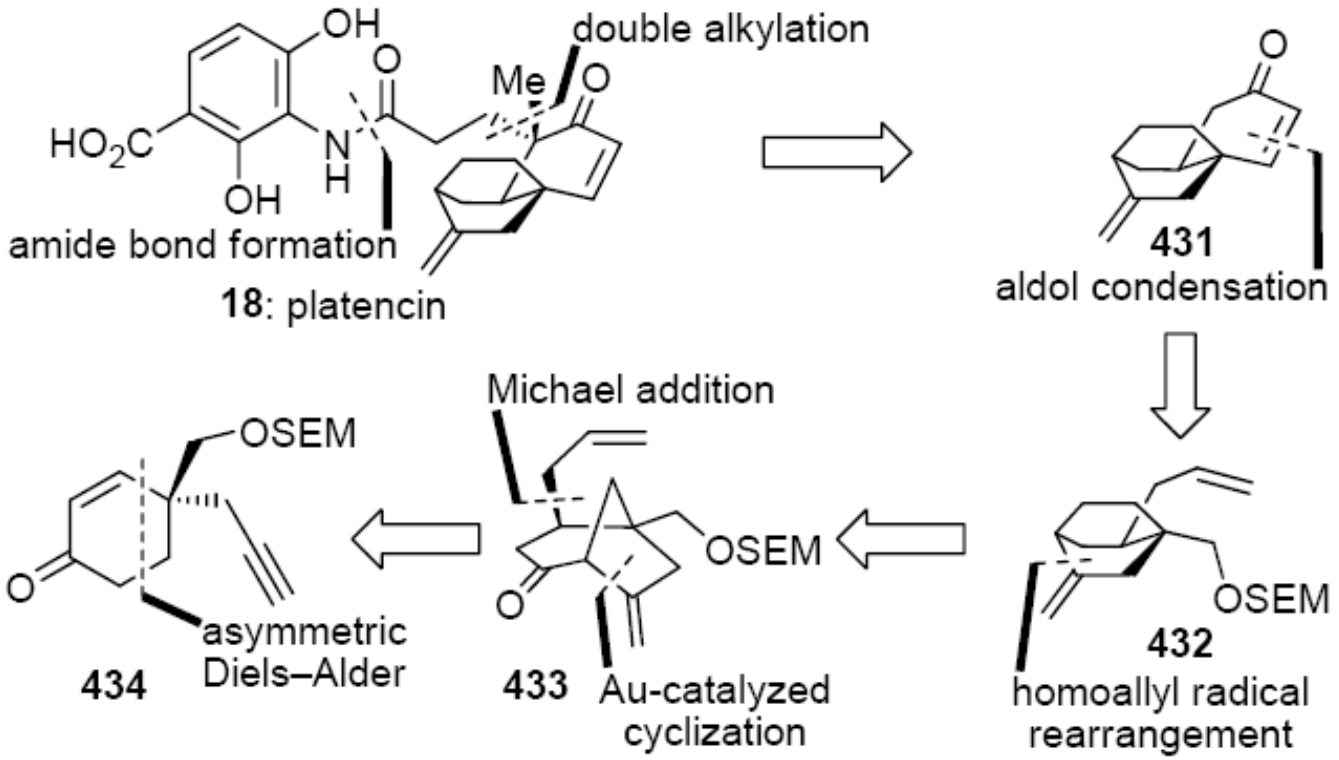


Figure 33.
Retrosynthetic analysis of platencin (**18**) (Nicolaou et al., 2008).[256]

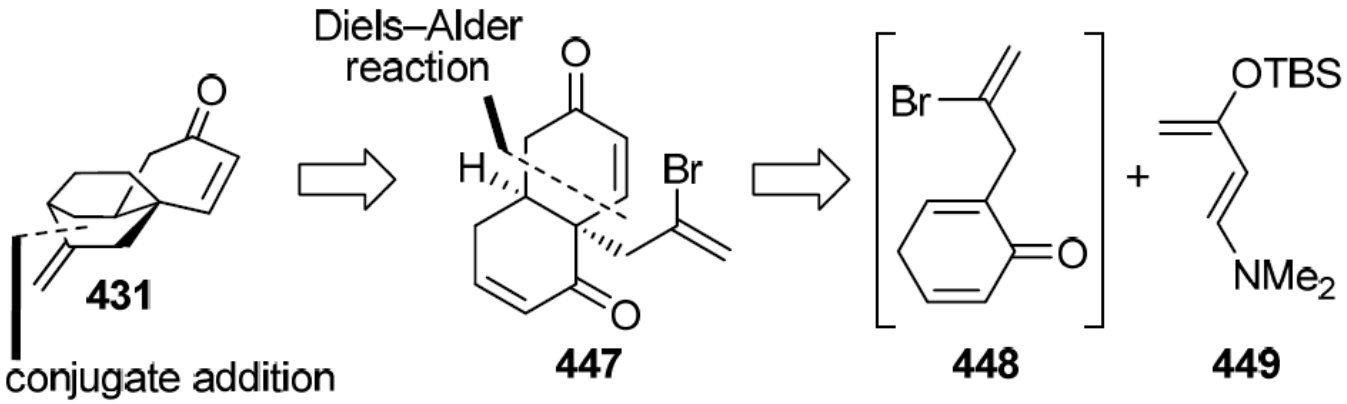
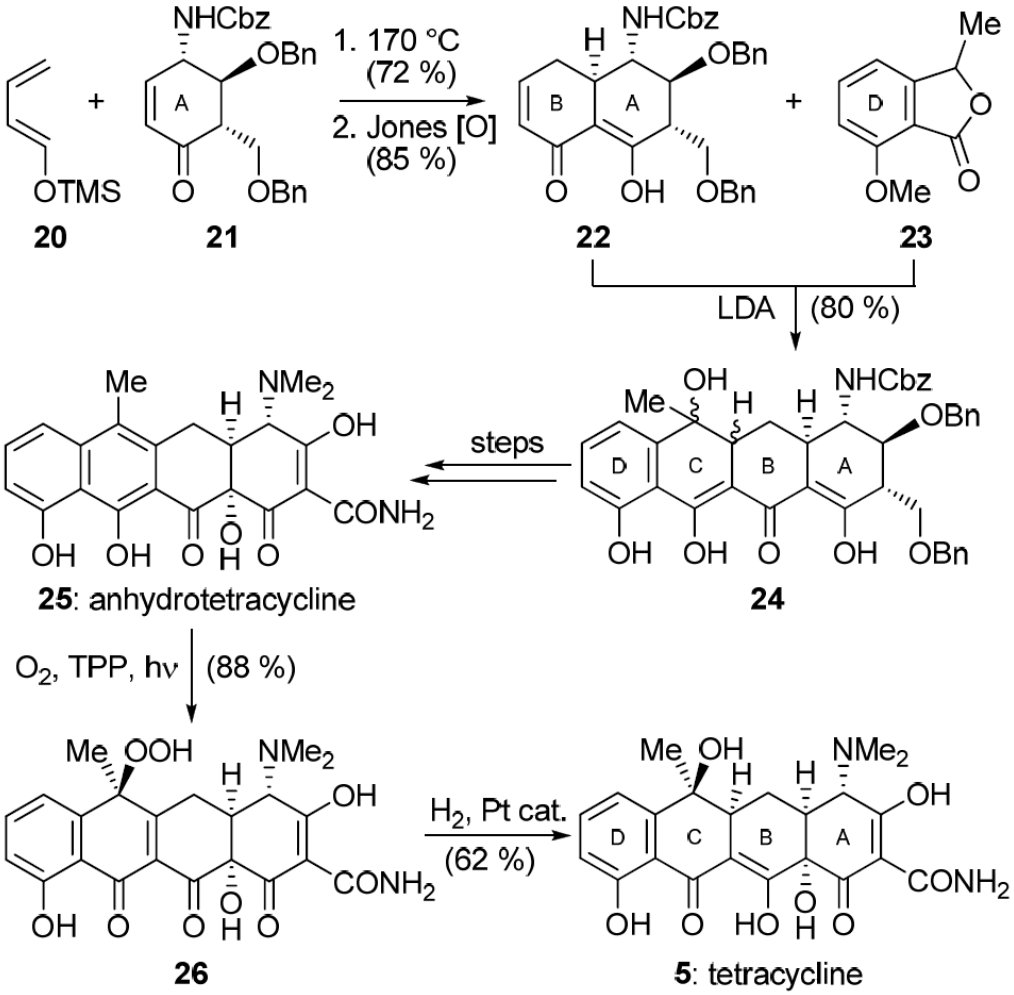
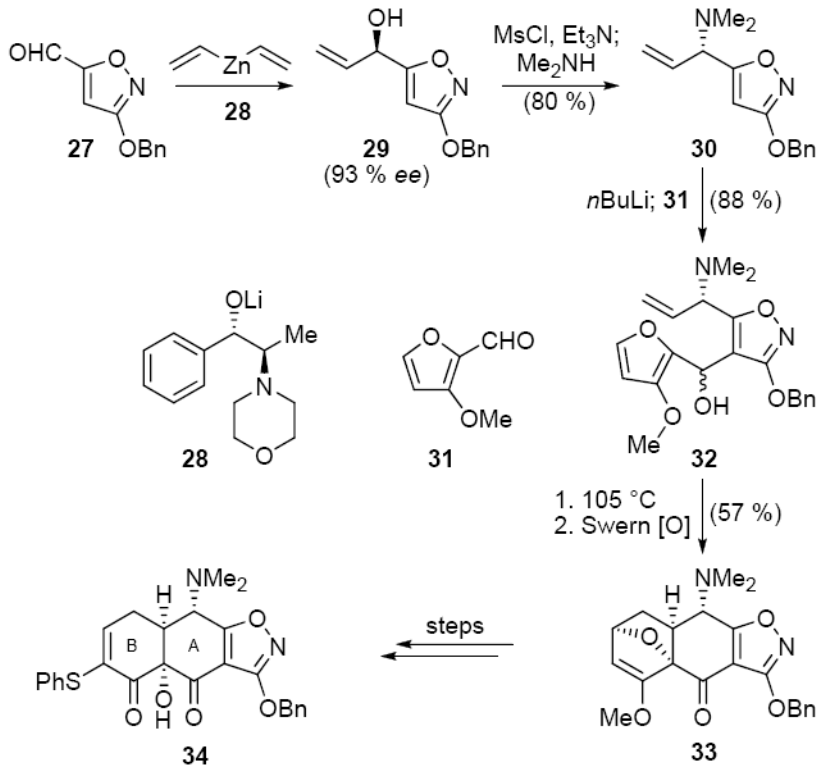


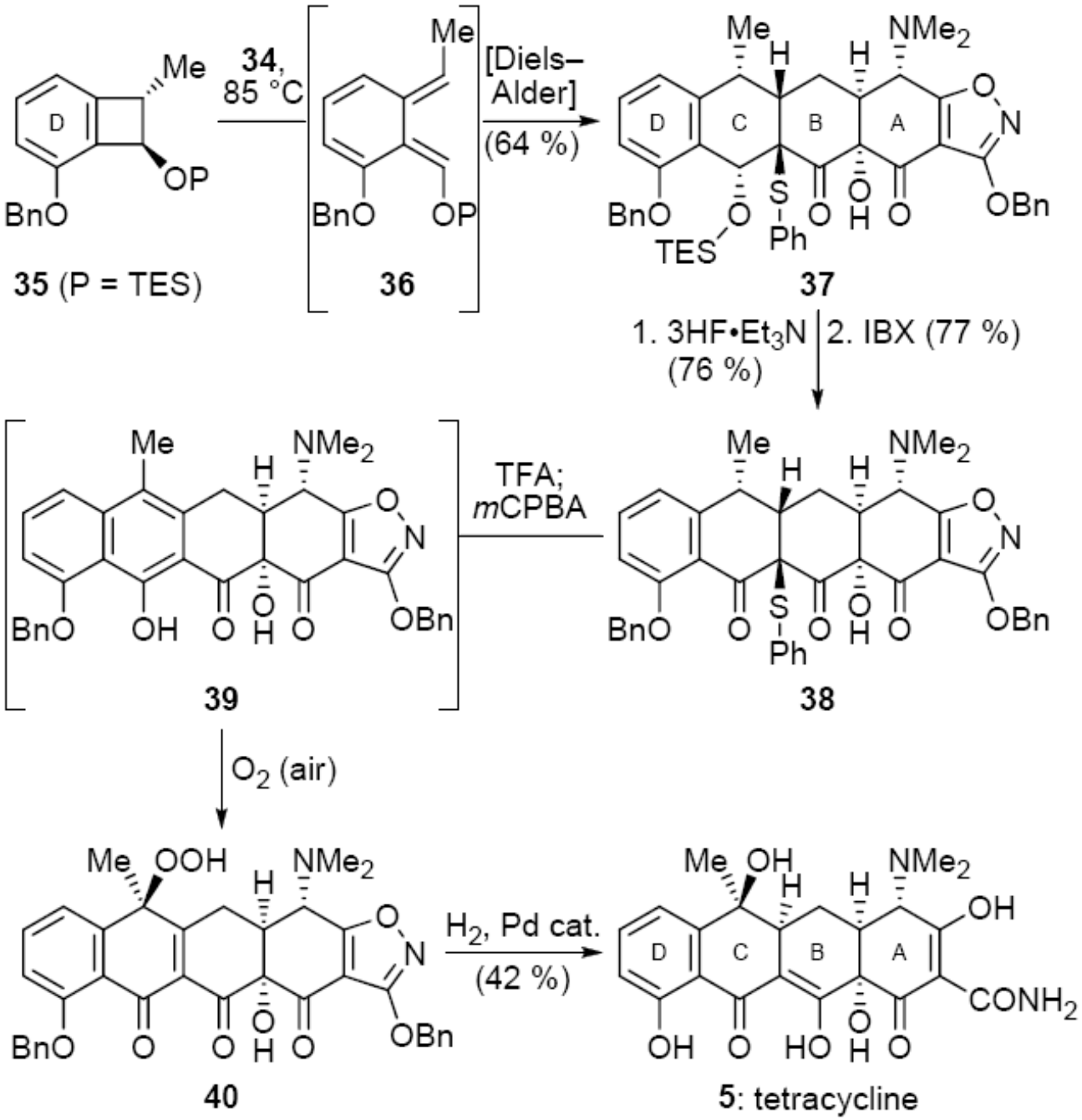
Figure 34.
Retrosynthetic analysis of platencin (**18**) (Hayashida and Rawal, 2008).[261]



Scheme 1.
Highlights of the first total synthesis of tetracycline (**5**) (Tatsuta et al., 2000).[27]

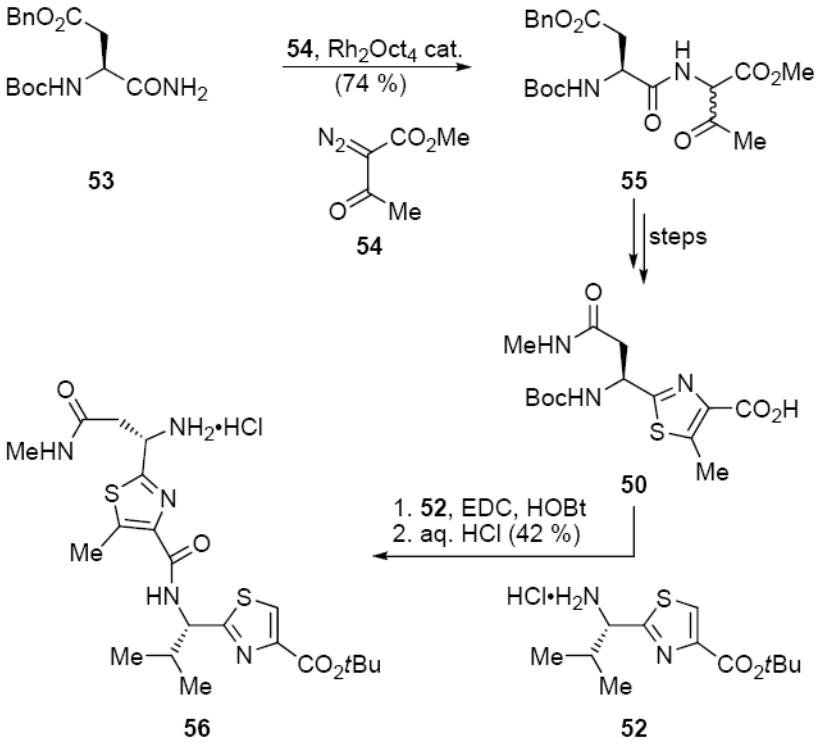


Scheme 2.
Highlights of the second generation synthesis of AB ring fragment **34** (Myers et al., 2007). [31]



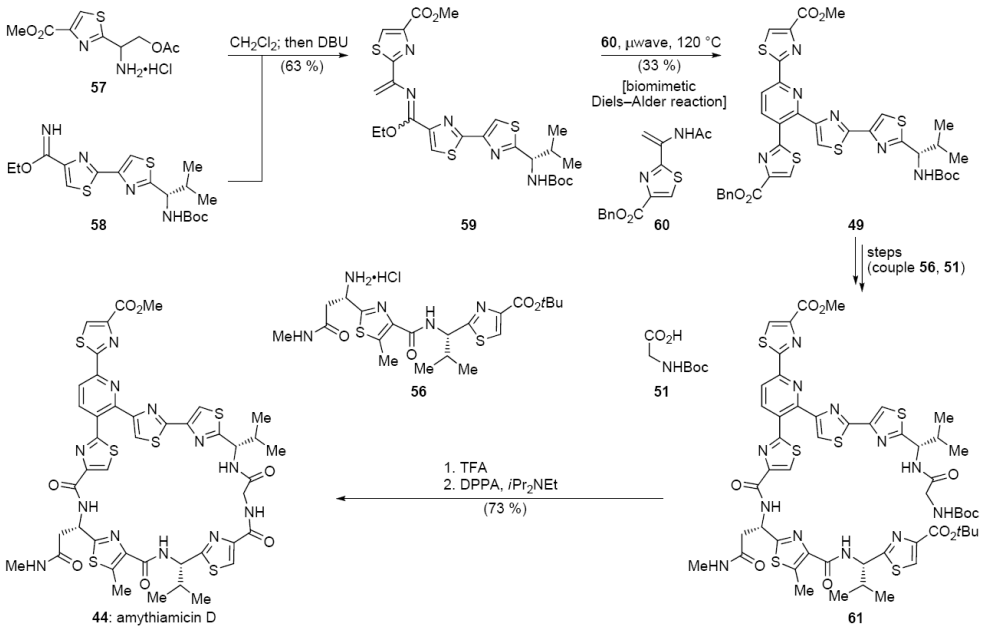
Scheme 3.

Completion of Myers' total synthesis of tetracycline (**5**) (Myers et al., 2005).[29]



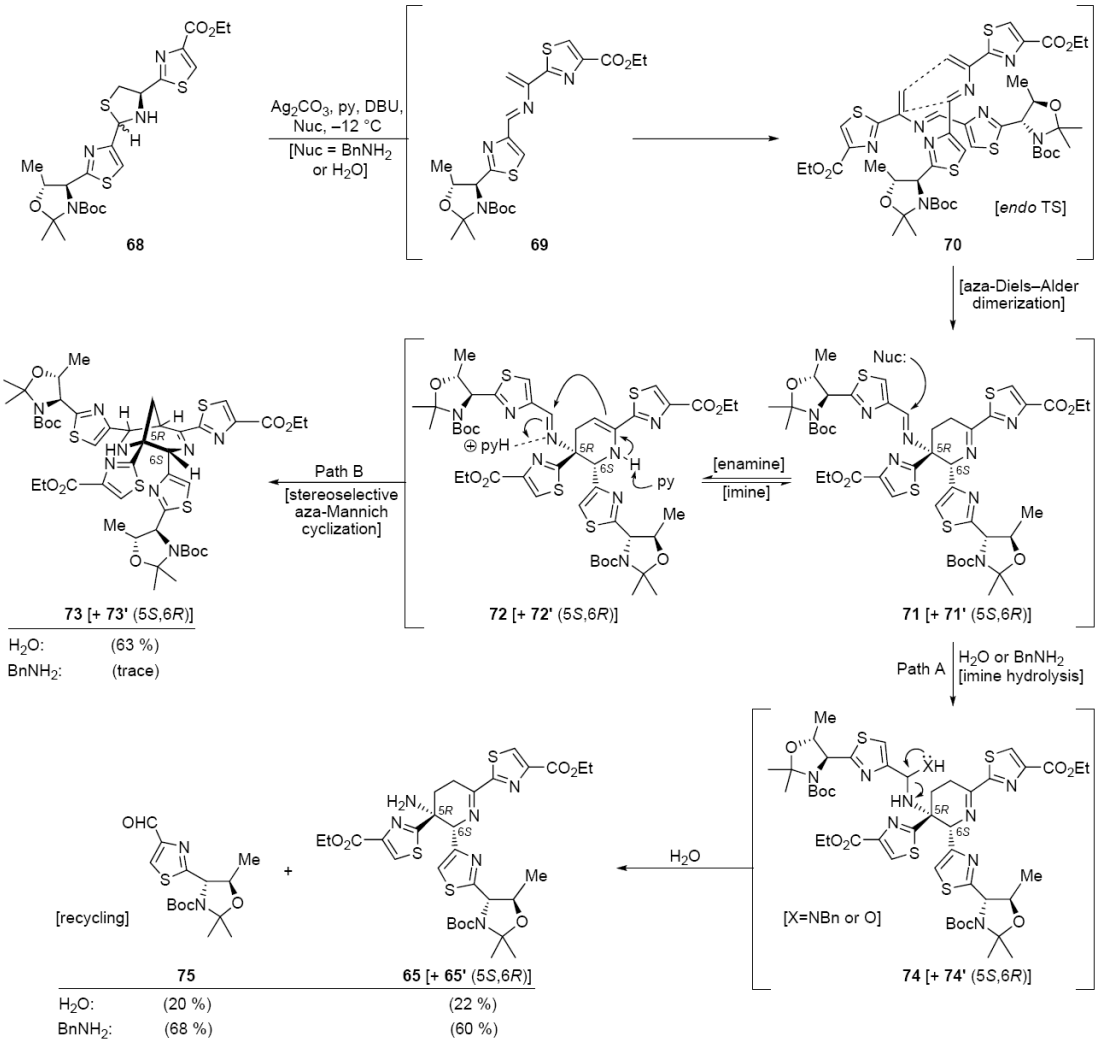
Scheme 4.

Application of rhodium carbene N–H insertion method to the construction of dithiazole **56** (Moody et al., 2004).[40]



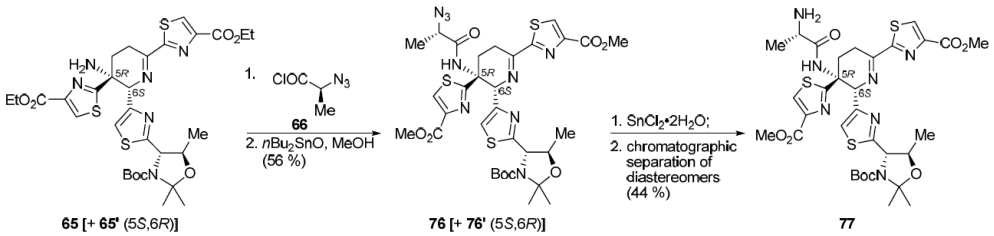
Scheme 5.

Biomimetic Diels–Alder approach to pyridine core **49** and completion of the total synthesis of amythiamicin D (**44**) (Moody et al., 2004).[40]

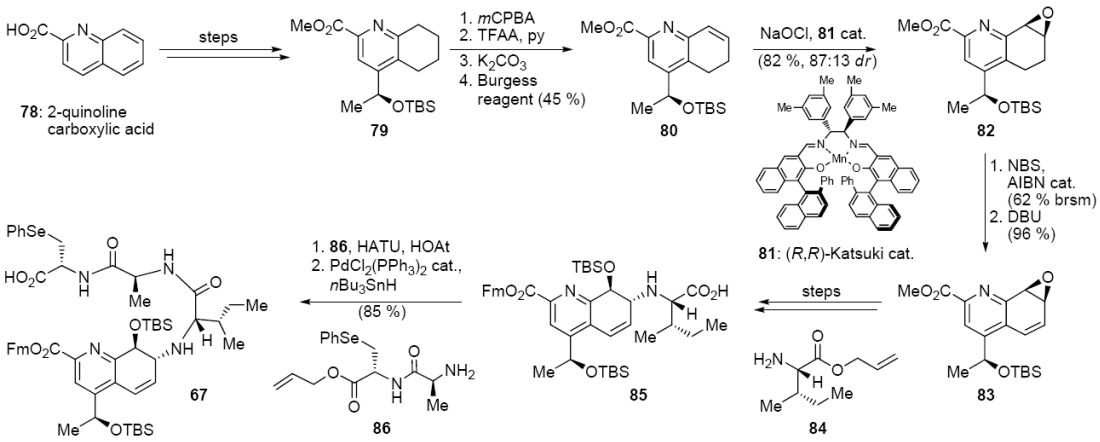


Scheme 6.

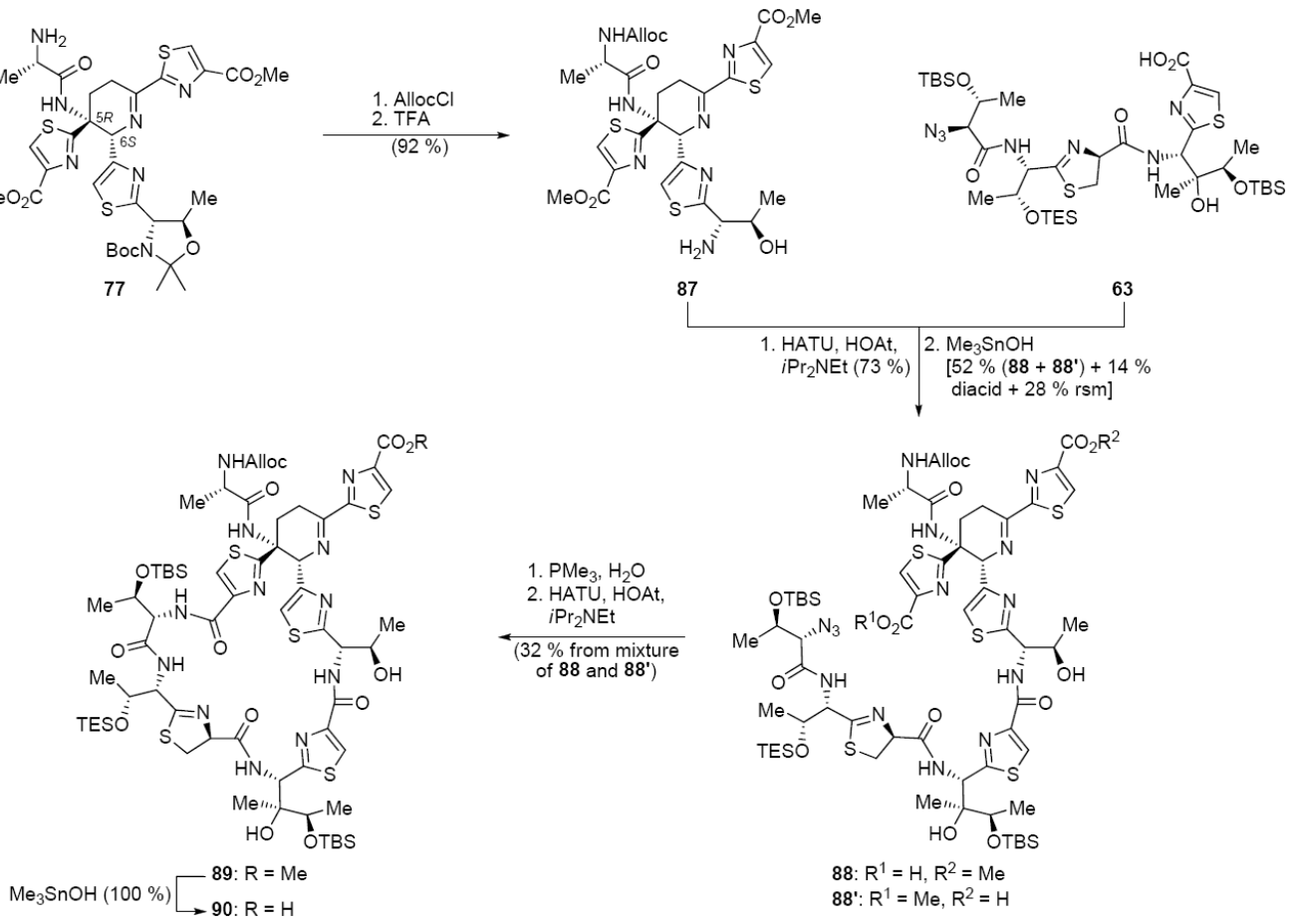
Construction of the dehydropiperidine core structure (**65**) of thiostrepton (**12**) through a biosynthetically inspired aza-Diels–Alder dimerization (Nicolaou et al., 2004).[53]



Scheme 7.
Acylation of dehydropiperidine core compound **65** (Nicolaou et al., 2004).[53]

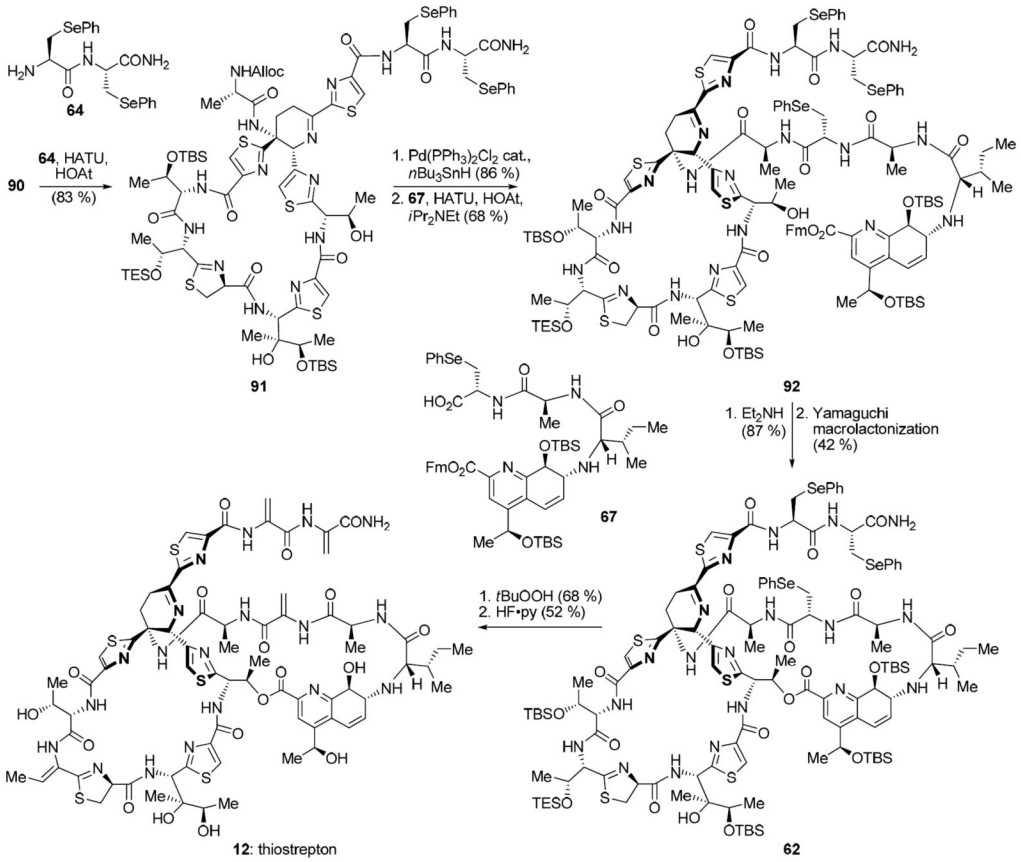


Scheme 8.
Synthesis of quinaldic acid fragment **67** (Nicolaou et al., 2004).[53]

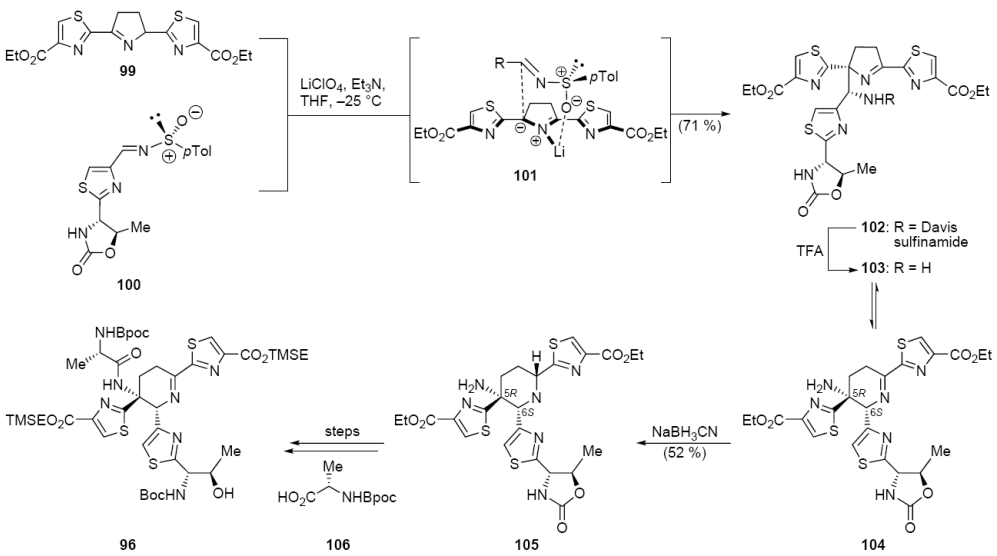


Scheme 9.

Synthesis of 26-membered tetrapeptide macrocycle **90** (Nicolaou et al., 2004).[53]

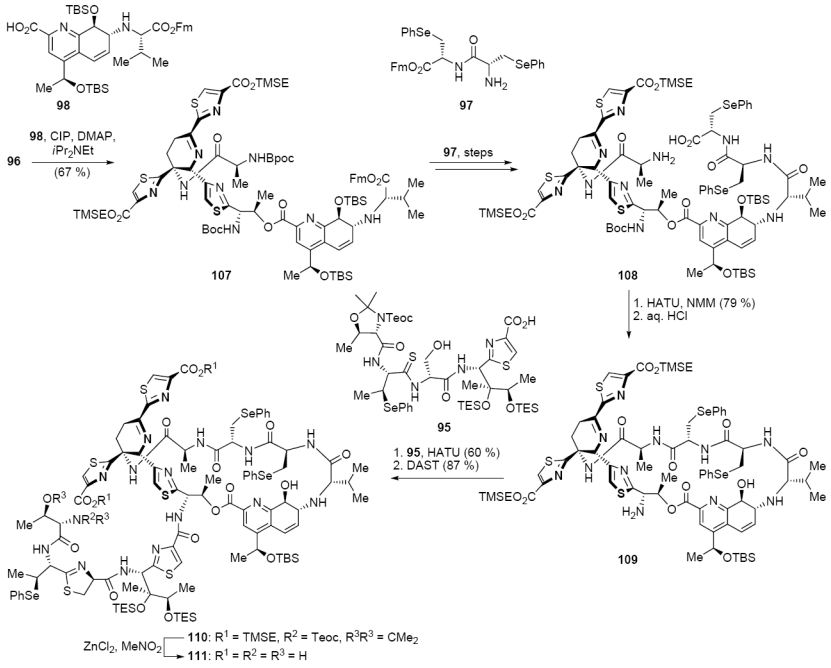


Scheme 10.
Completion of the total synthesis of thiostrepton (**12**) (Nicolaou et al., 2004).[53]



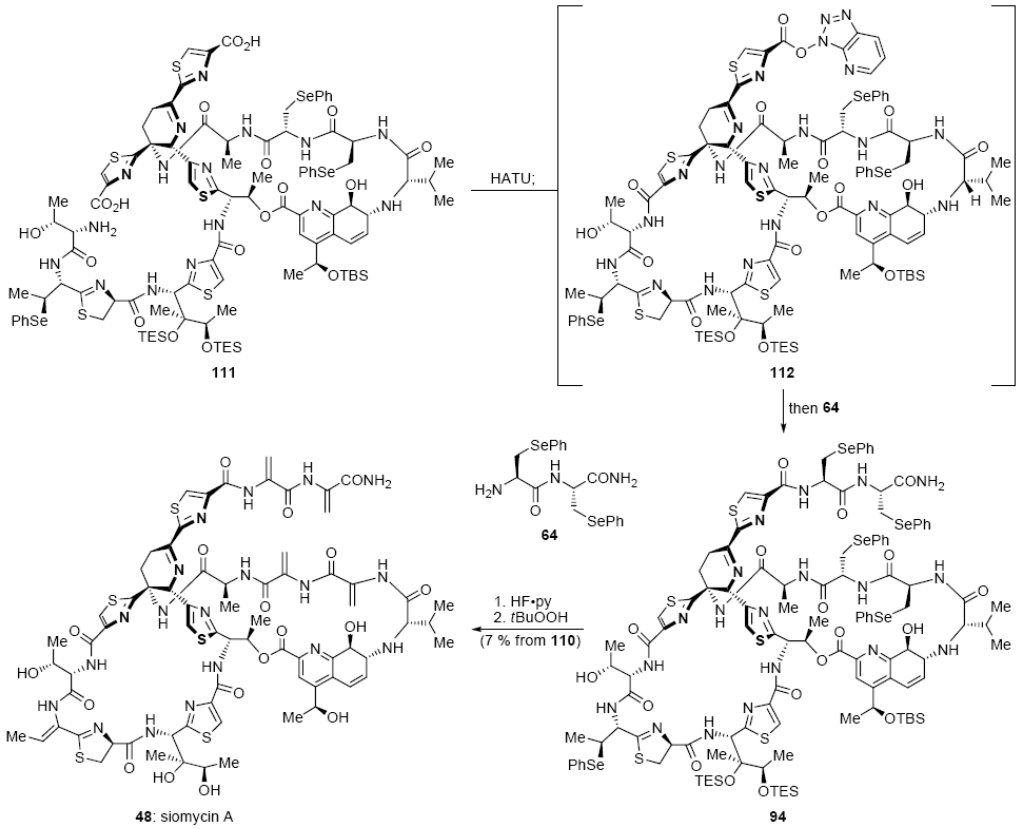
Scheme 11.

Synthesis of the dehydropiperidine core (**96**) via stereoselective 1,2-addition between chiral sulfinimine **100** and dehydropyrrolidine **99** (Hashimoto et al., 2007).[65]

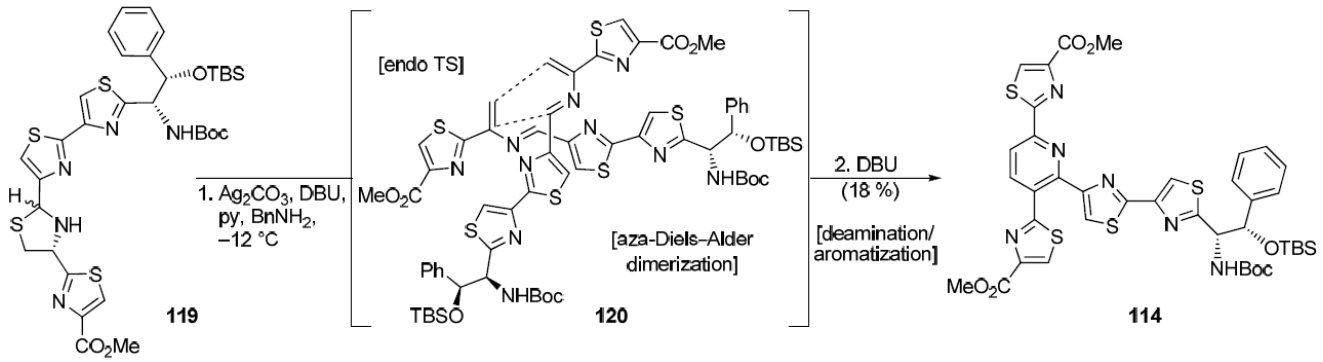


Scheme 12.

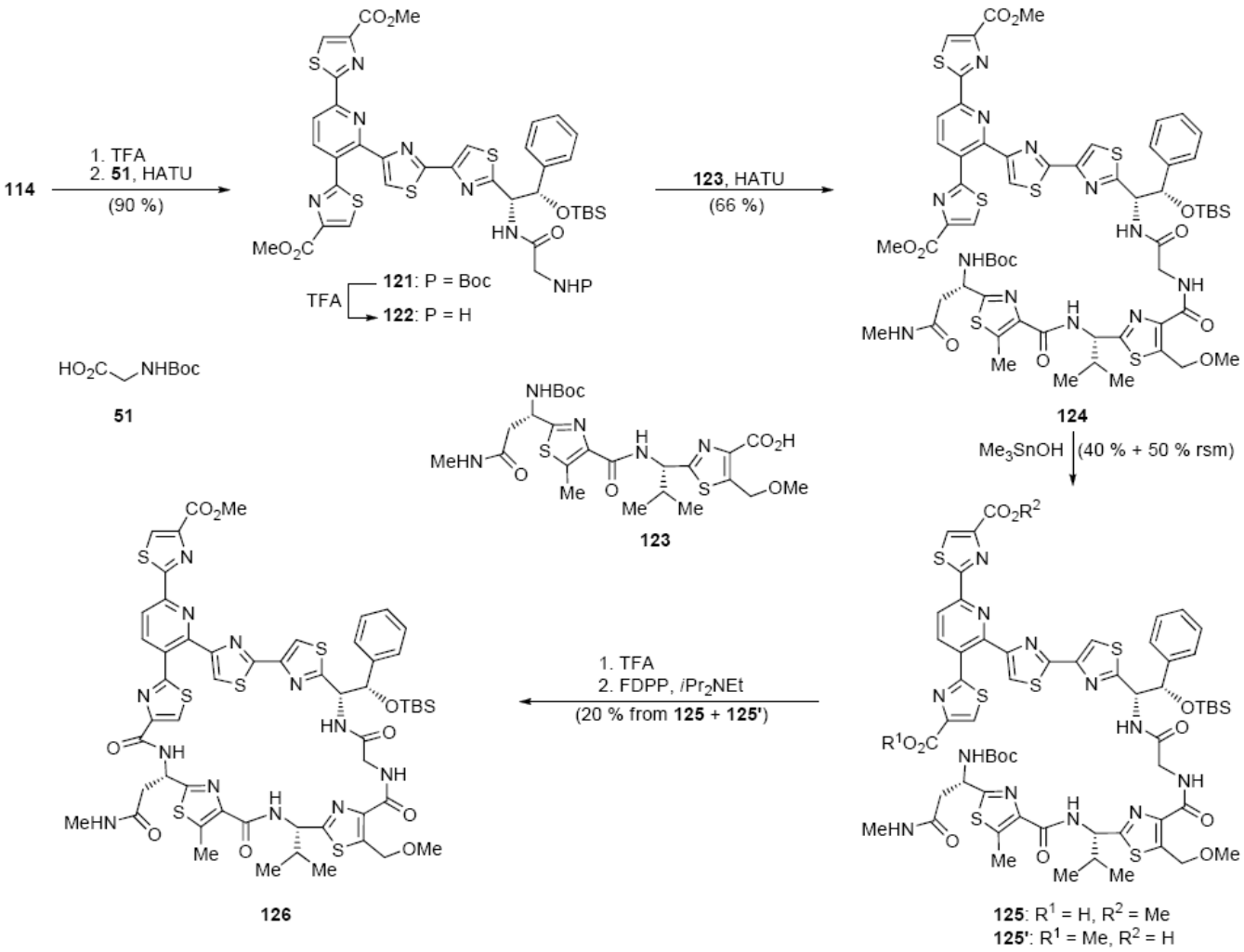
Fragment assembly and macrolactamization toward siomycin A (**48**) (Hashimoto et al., 2007). [65]



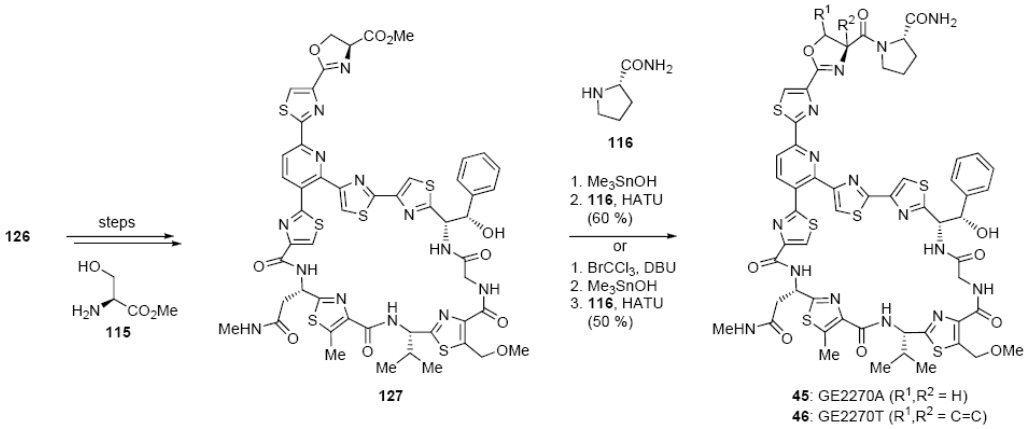
Scheme 13.
Completion of the total synthesis of siomycin A (**48**) (Hashimoto et al., 2007).[65]



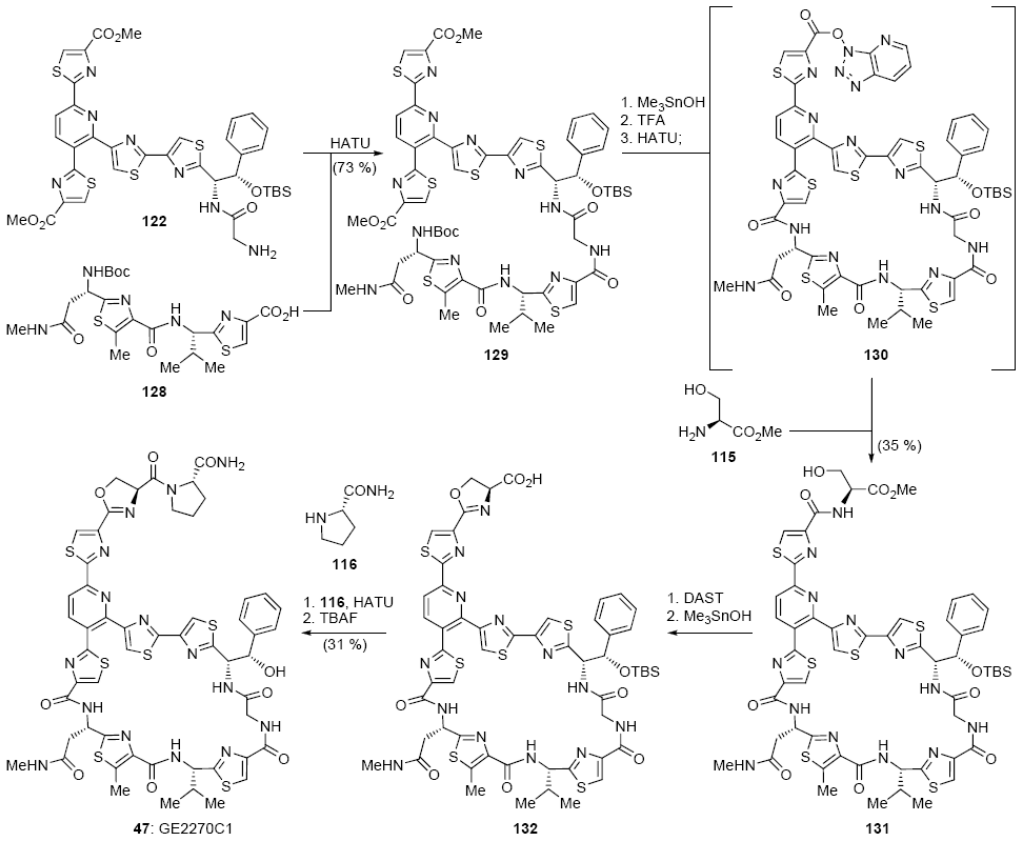
Scheme 14.
Synthesis of pyridine–bisthiazole intermediate **114** (Nicolaou, Chen et al., 2007).[74]



Scheme 15.
First-generation synthesis of macrolactam **126** (Nicolaou, Chen et al., 2007).[74]

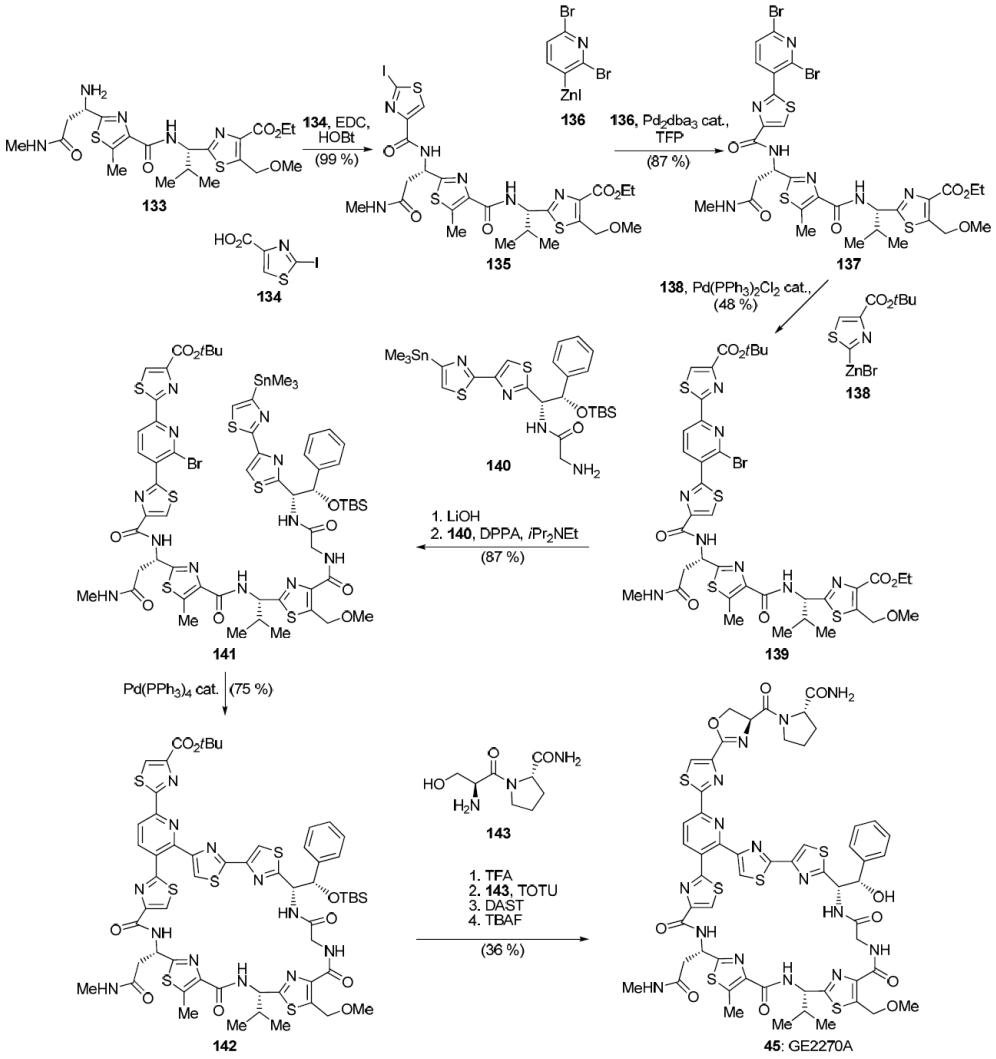


Scheme 16.
Completion of the total synthesis of GE2270A (**45**) and GE2270T (**46**) (Nicolaou, Chen et al., 2007).[74]

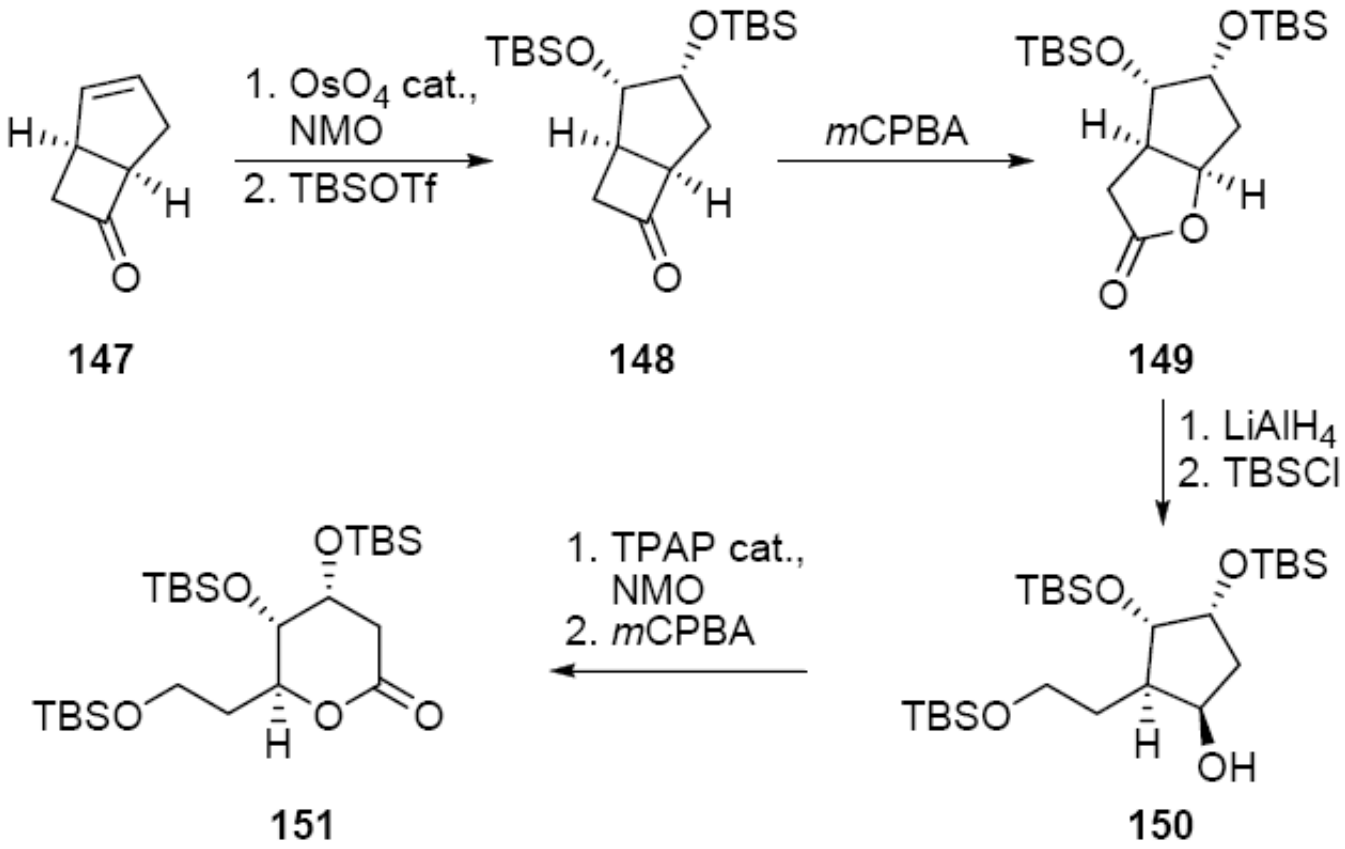


Scheme 17.

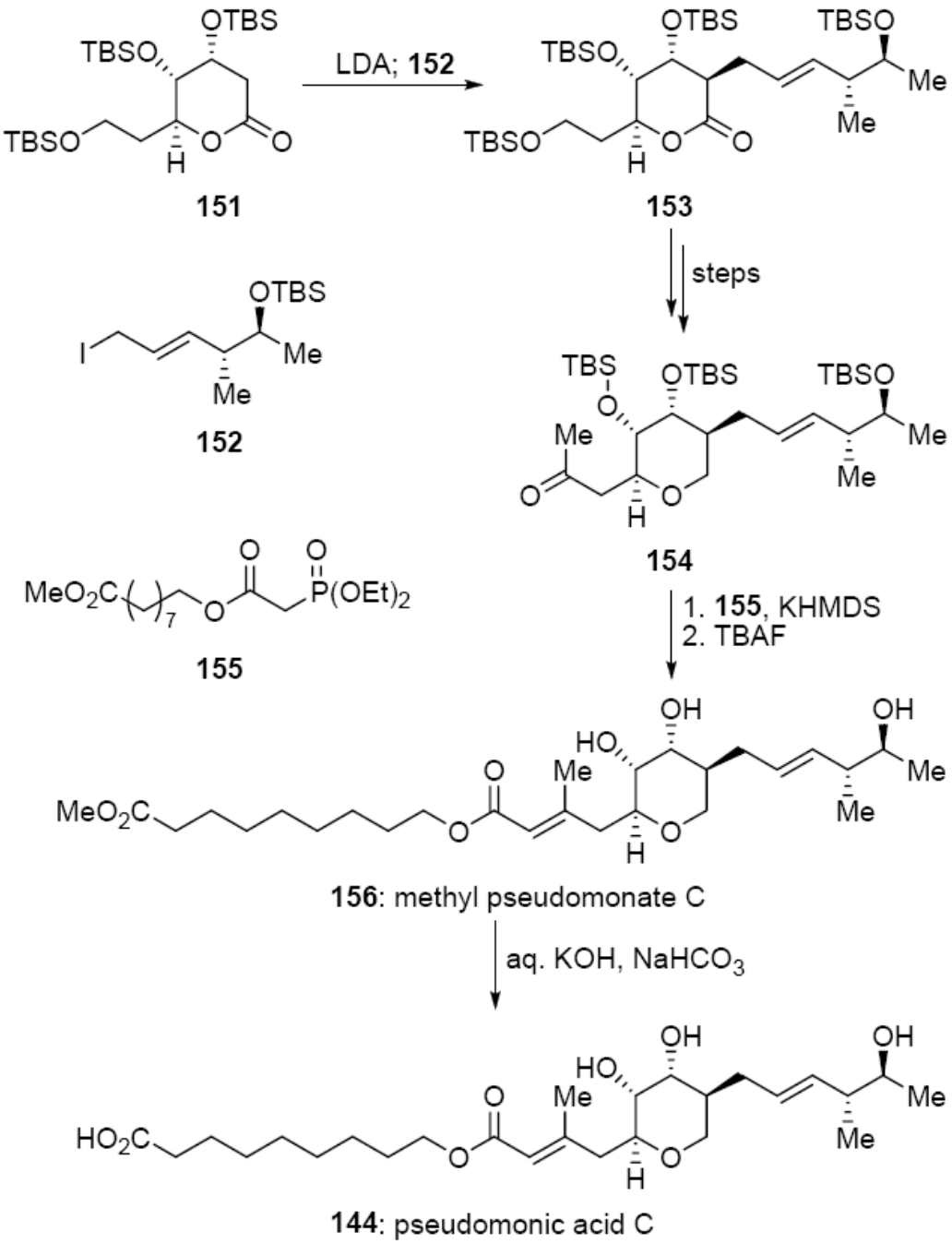
Second-generation macrocyclization applied to the total synthesis of GE2270C1 (**47**) (Nicolaou, Chen et al., 2007).[74]



Scheme 18.
Total synthesis of GE2270A (**45**) (Bach et al., 2007).[75]

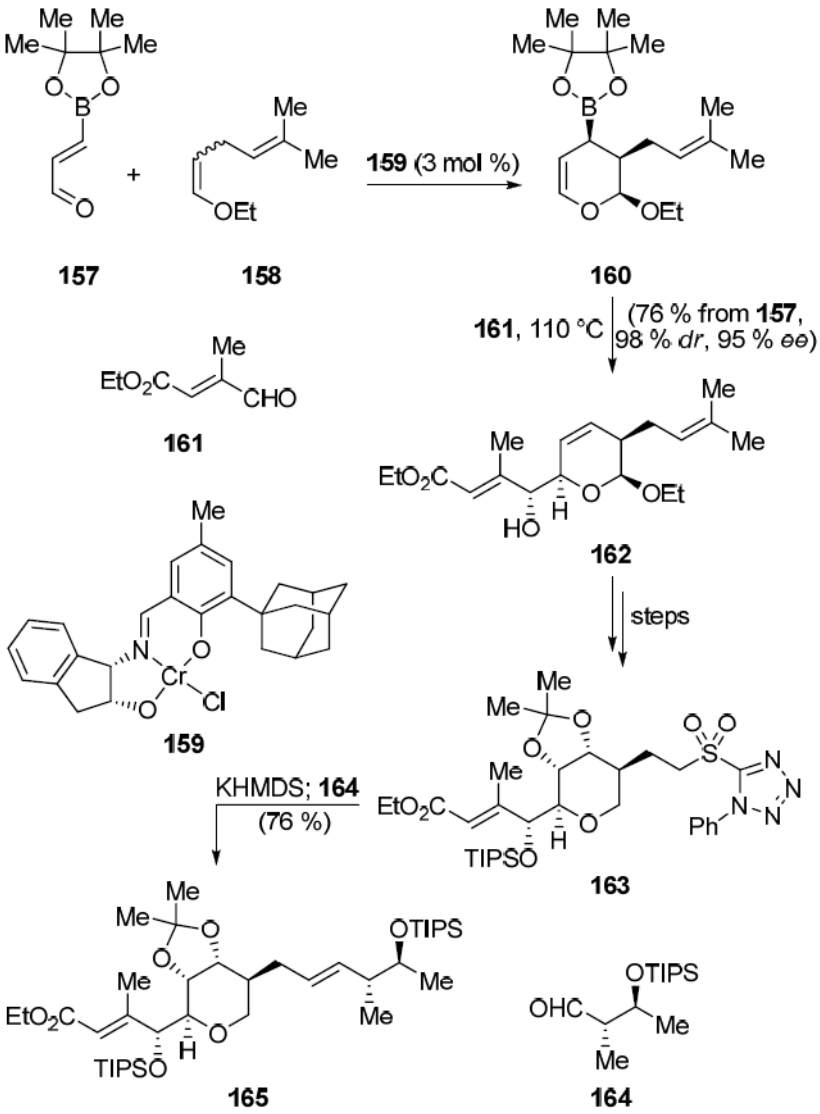


Scheme 19.
Baeyer–Villiger approach to the pseudomonic acid core (Willis et al., 2000).[91]

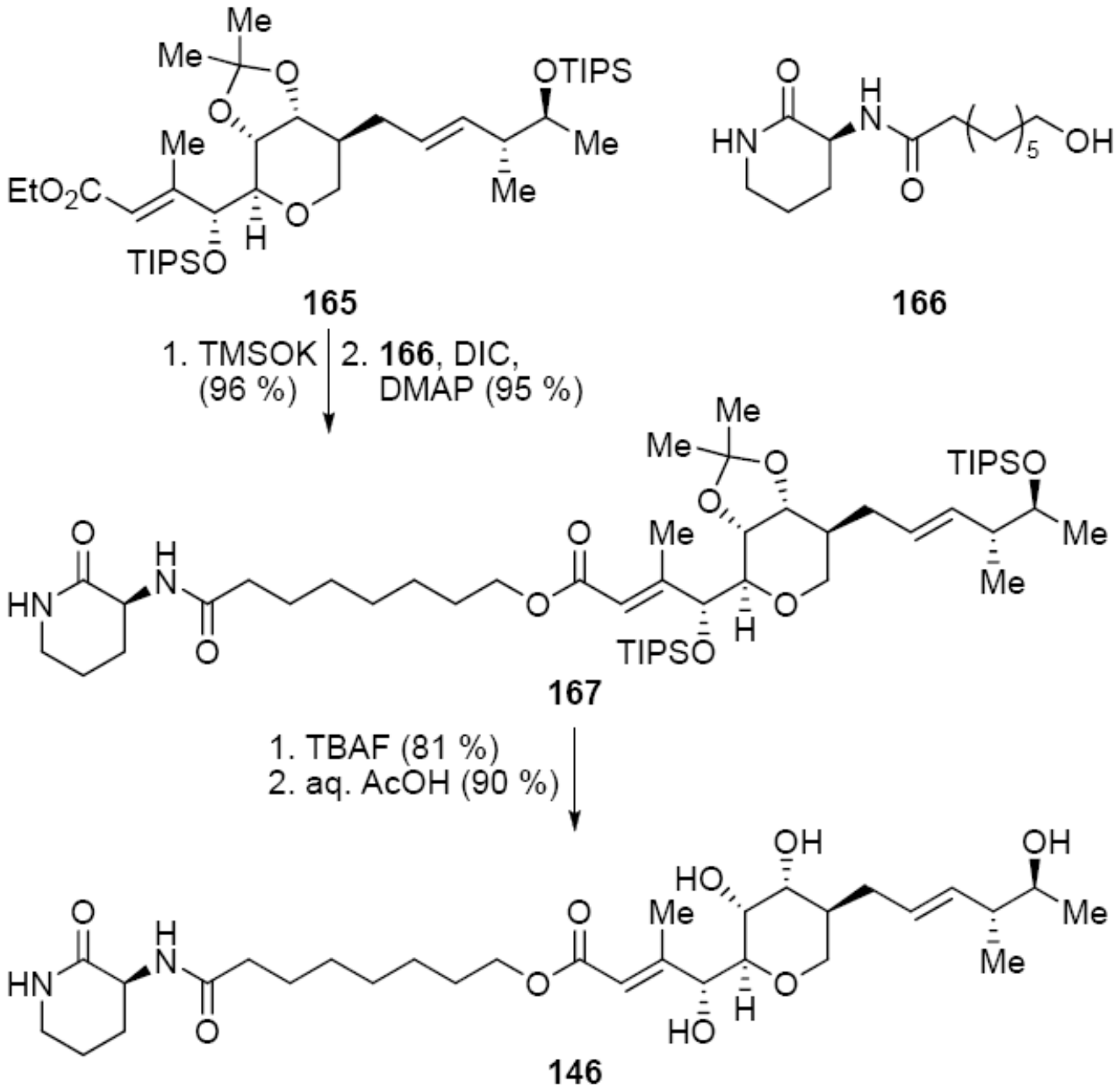


Scheme 20.

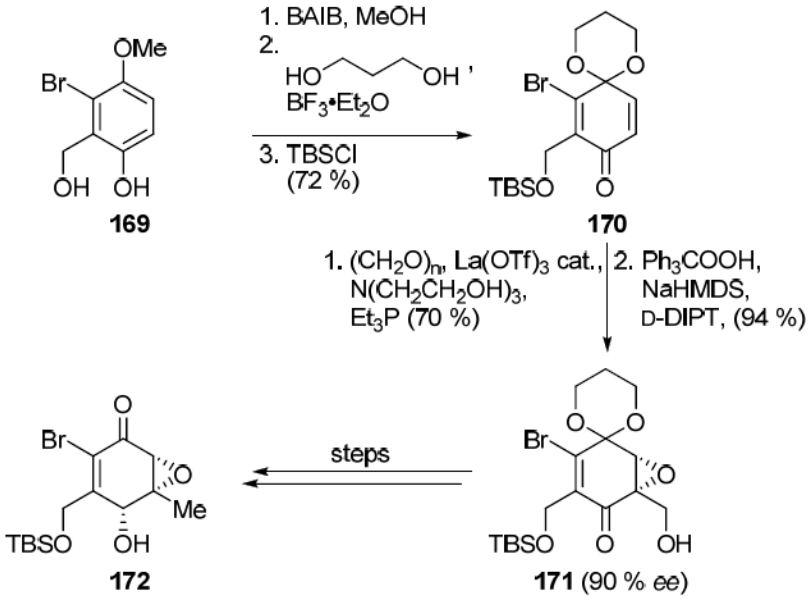
Highlights of the completion of the total synthesis of pseudomonic acid C (**144**) (Willis et al., 2000).[91]



Scheme 21.
Highlights of the synthesis of the thiomarinol core (Gao and Hall, 2005).[92]

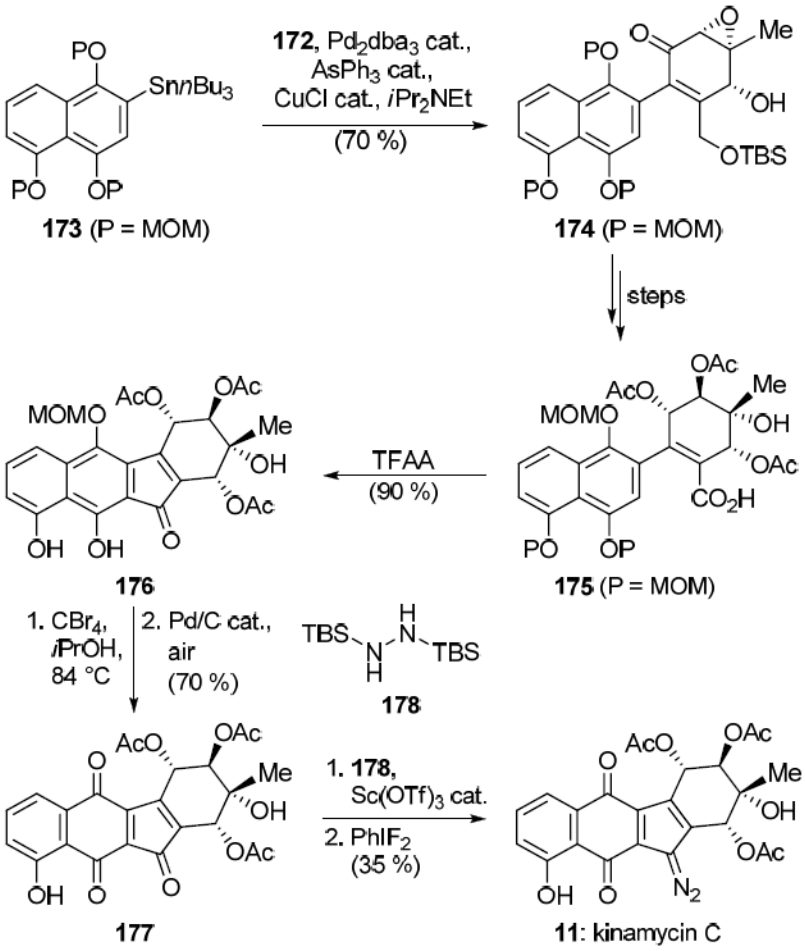


Scheme 22.
Completion of the total synthesis of thiomarinol derivative **146** (Gao and Hall, 2005).[92]



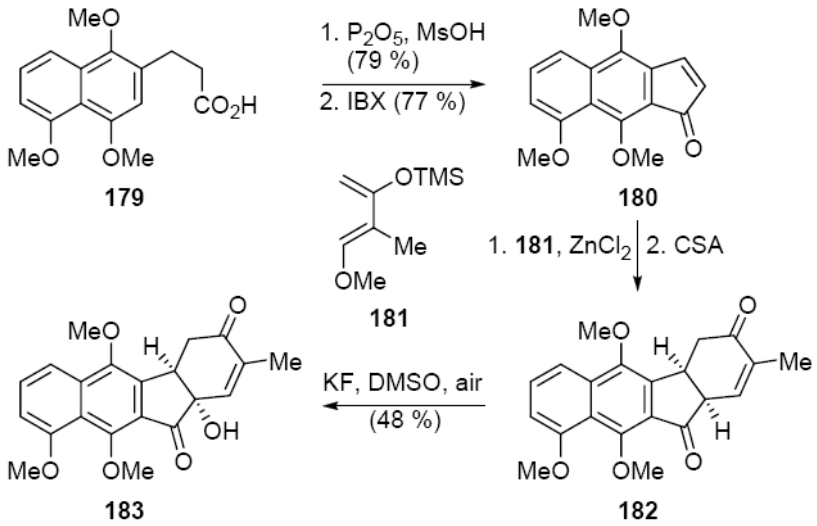
Scheme 23.

Highlights of the synthesis of vinyl bromide **172** (Lei and Porco, 2006).[99]

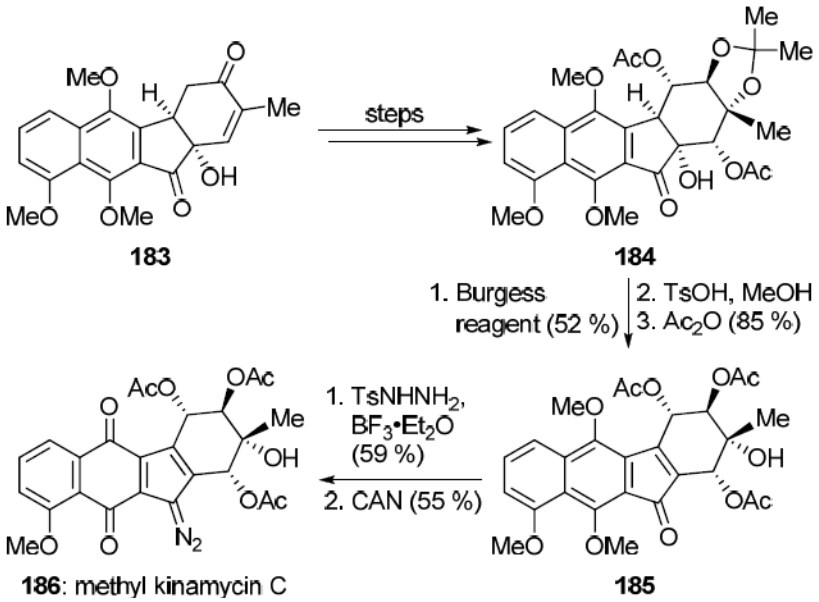


Scheme 24.

Highlights of the completion of the total synthesis of kinamycin C (**11**) (Lei and Porco, 2006). [99]

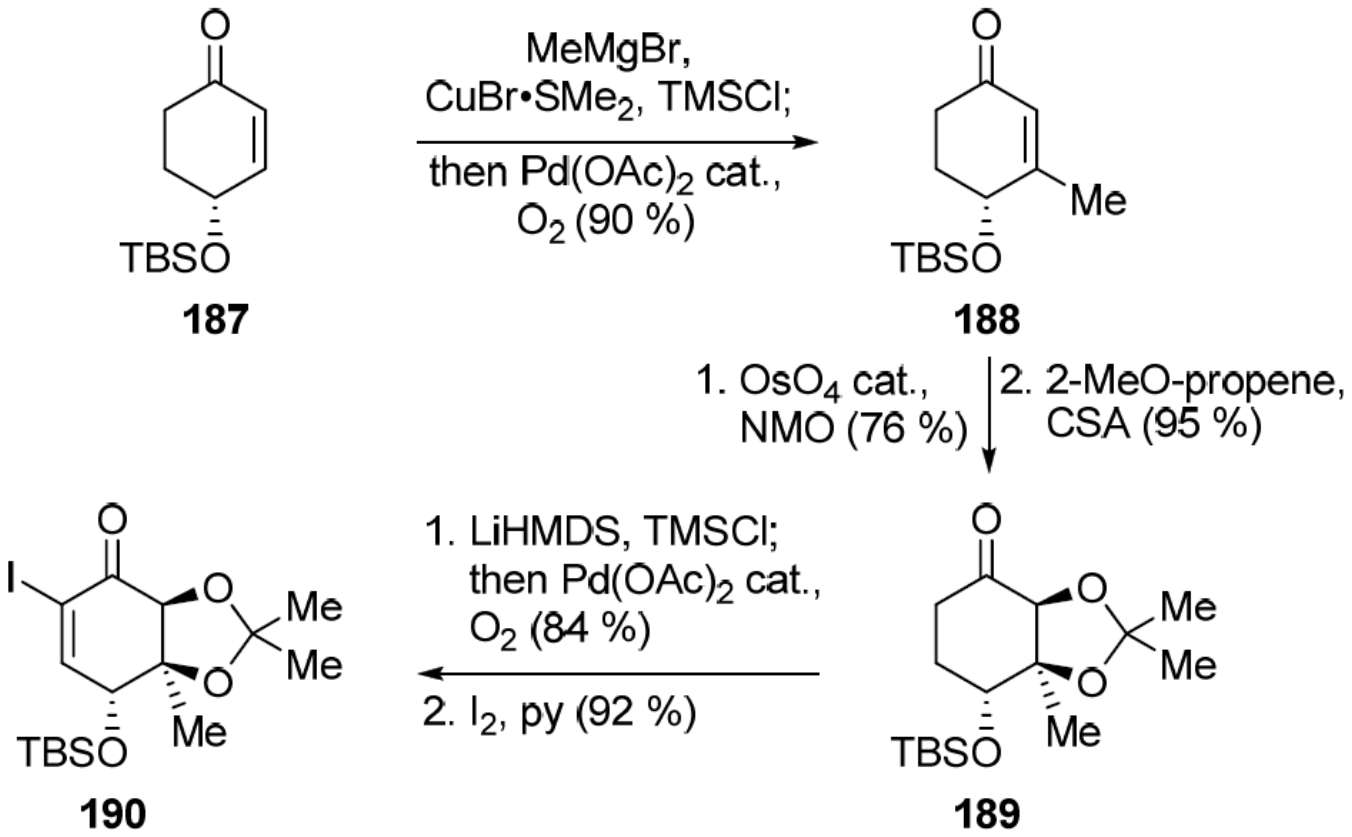


Scheme 25.
Synthesis of the kinamycin tetracyclic framework (Ishikawa et al., 2002).[104a]

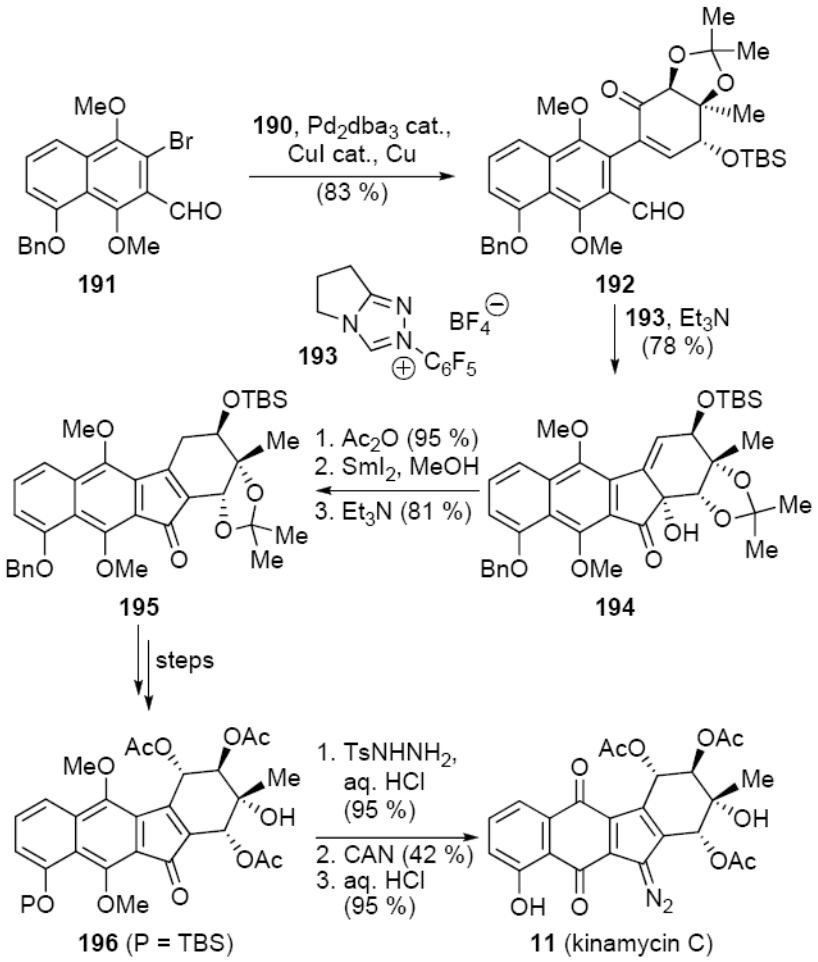


Scheme 26.

Highlights of the completion of the total synthesis of methyl kinamycin C (**186**) (Ishikawa et al., 2007).[104b]

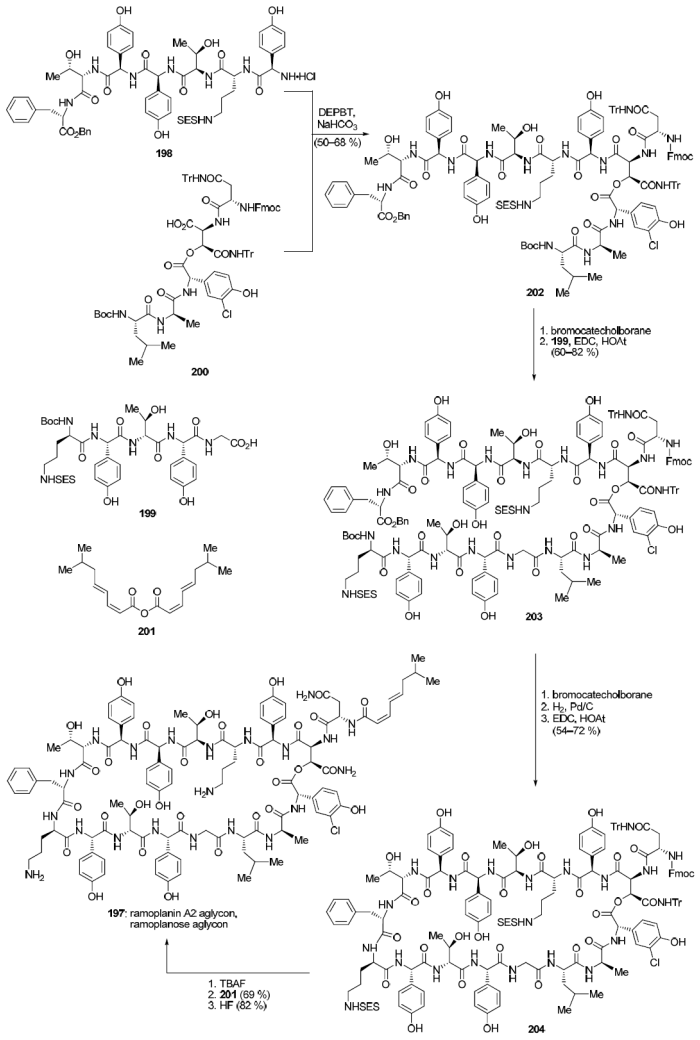


Scheme 27.
Synthesis of vinyl iodide **190** (Nicolaou et al., 2007).[106]

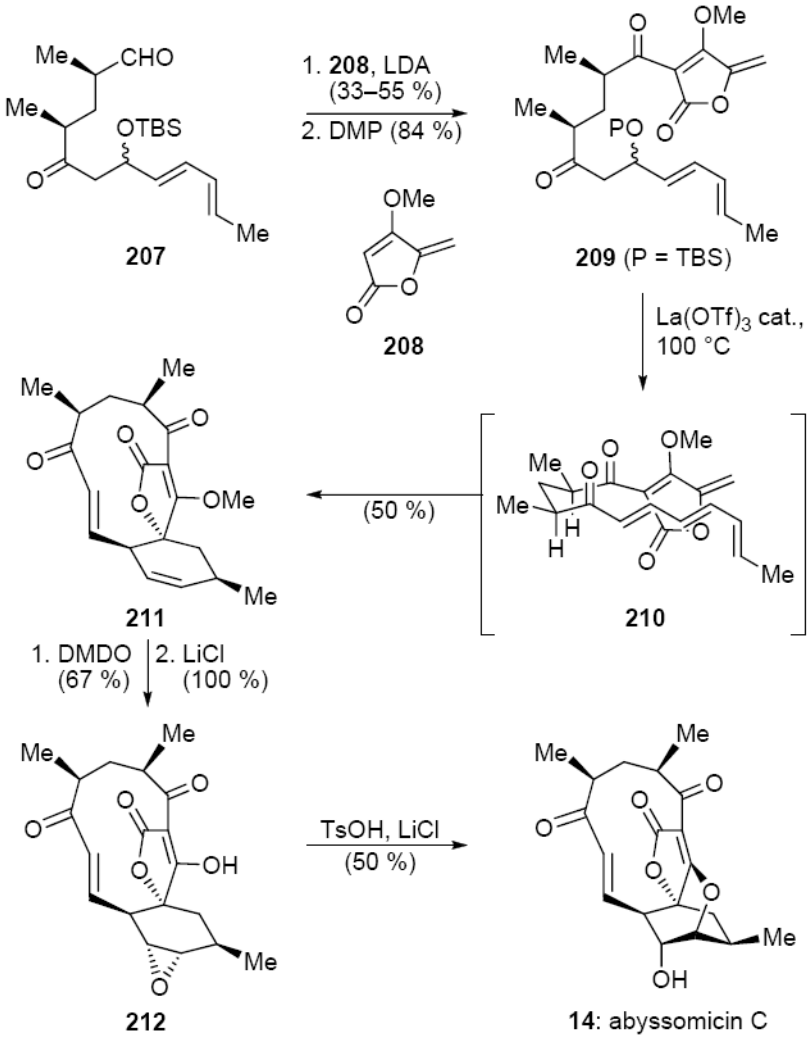


Scheme 28.

Highlights of the completion of the total synthesis of kinamycin C (**11**) (Nicolaou et al., 2007). [106]

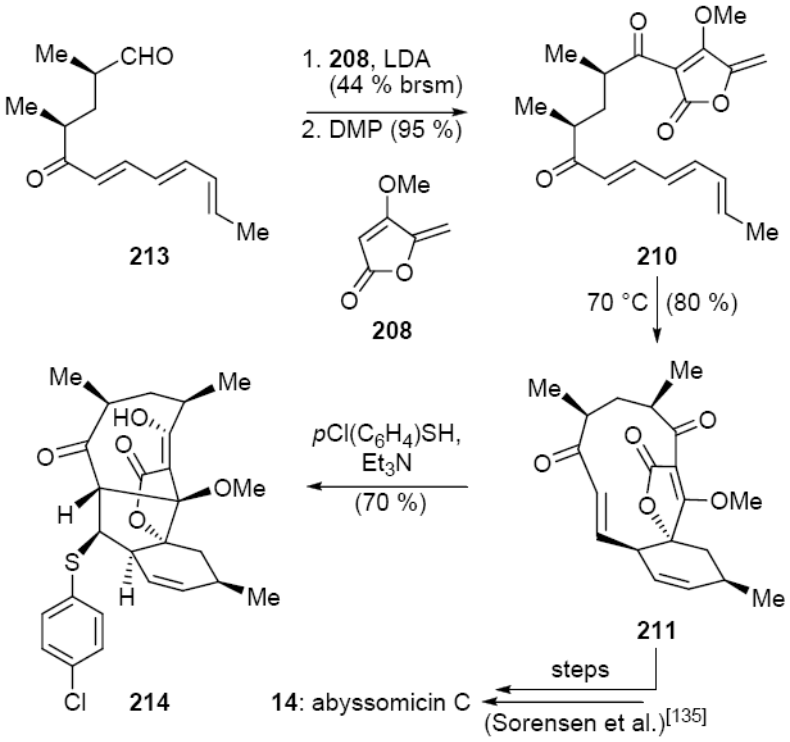


Scheme 29.
Total synthesis of ramoplanin A2 aglycon (**197**) (Boger et al., 2002).[122]



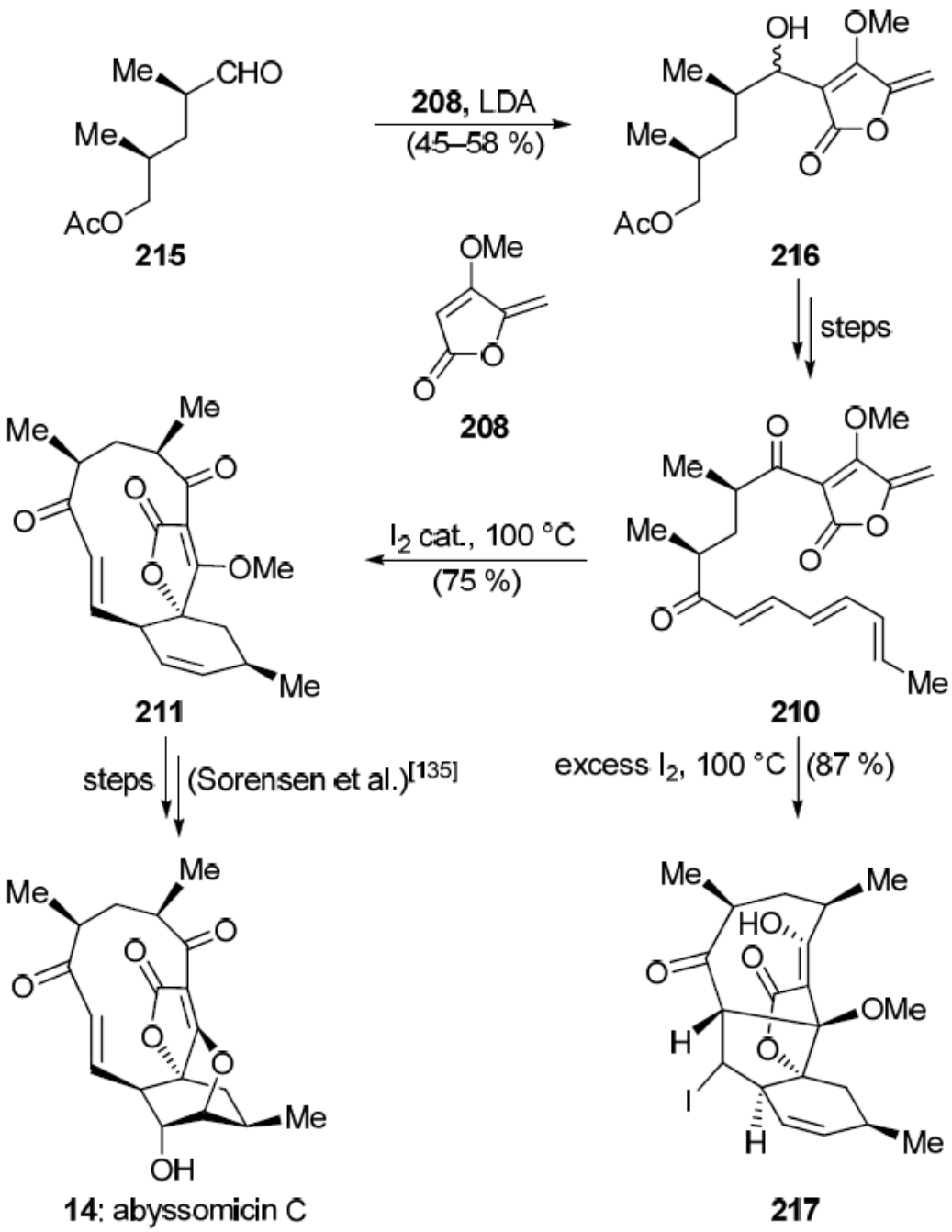
Scheme 30.

Total synthesis of abyssomicin C (**14**) (Sorensen et al., 2005).[135]



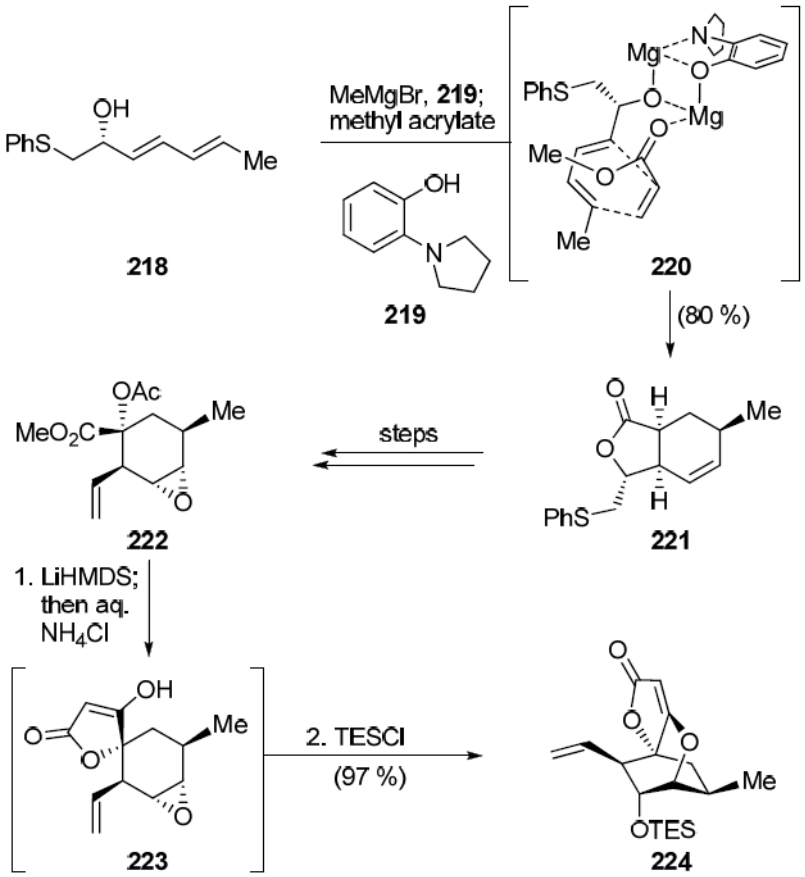
Scheme 31.

Formal synthesis of abyssomicin C (**14**) and entry into the abyssomicin D carbon skeleton (Snider and Zou, 2005).[136]



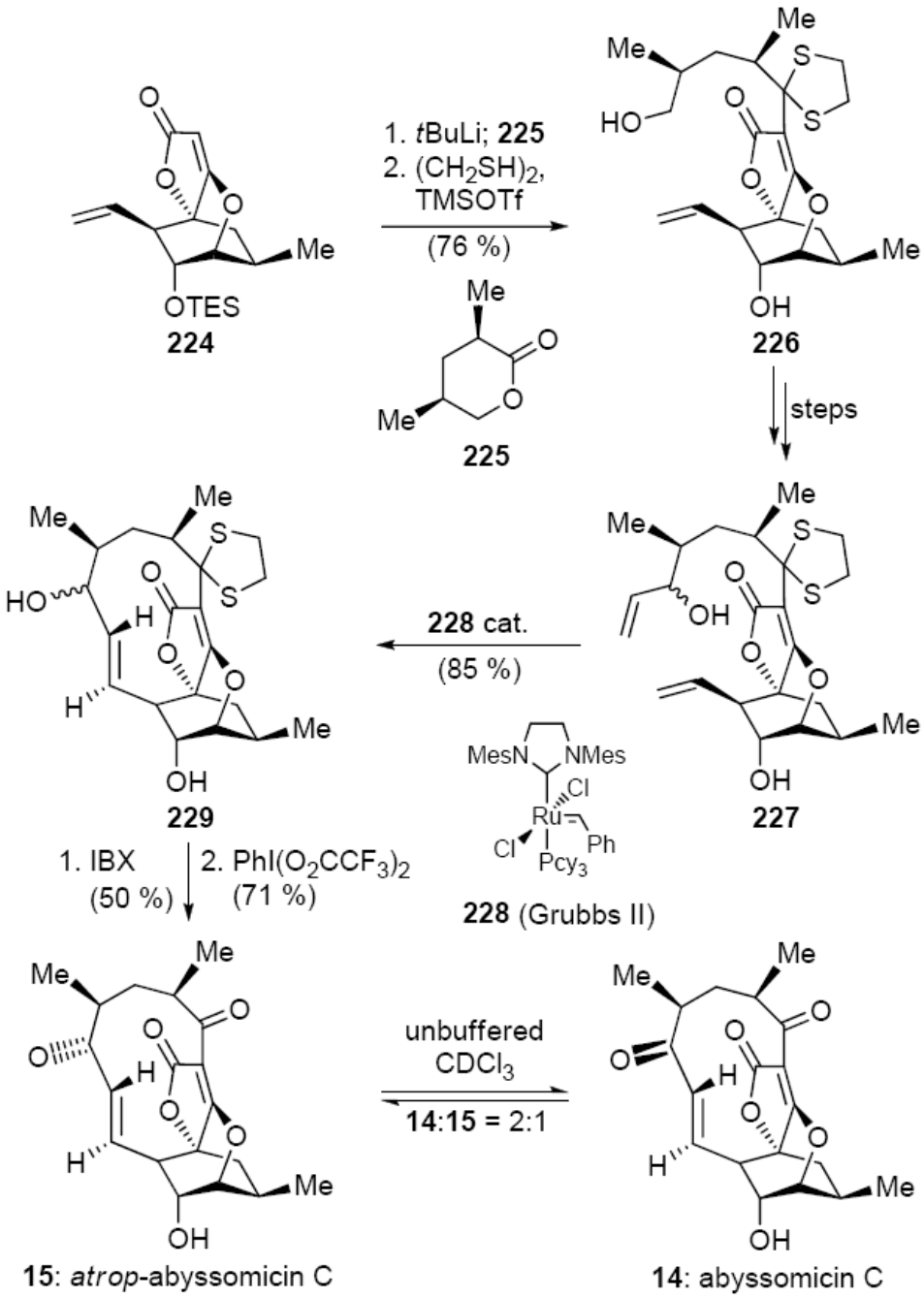
Scheme 32.

Formal total synthesis of abyssomicin C (**14**) and entry into the abyssomicin D carbon skeleton (Couladouros et al., 2006).[137]



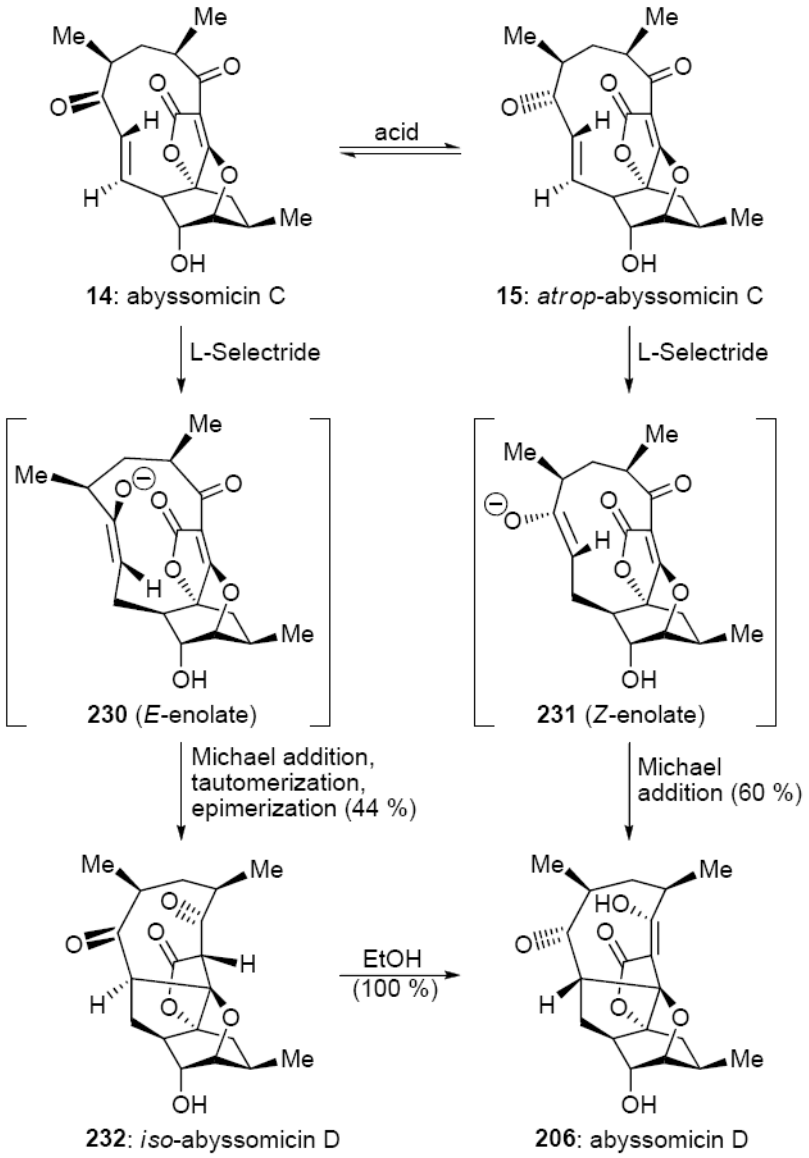
Scheme 33.

Highlights of the synthesis of the abyssomicin C bicyclic core **224** (Nicolaou and Harrison, 2006).[138]



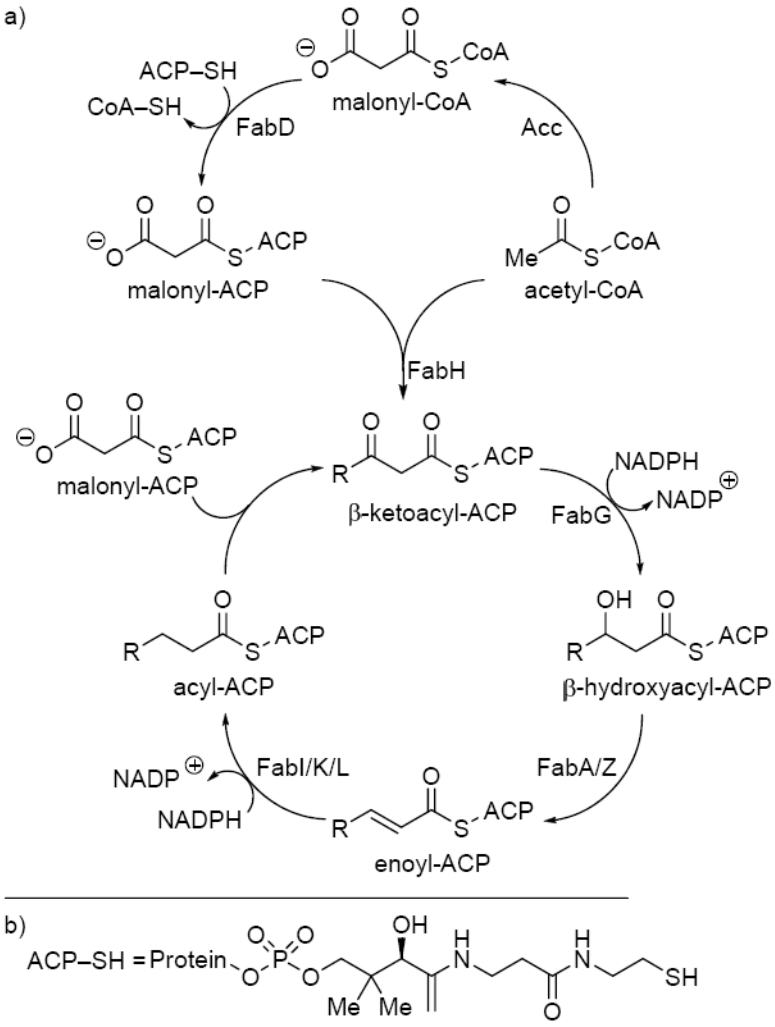
Scheme 34.

Highlights of the completion of the total synthesis of abyssomicin C (**14**) and *atrop*-abyssomicin C (**15**) (Nicolaou and Harrison, 2006).[138]



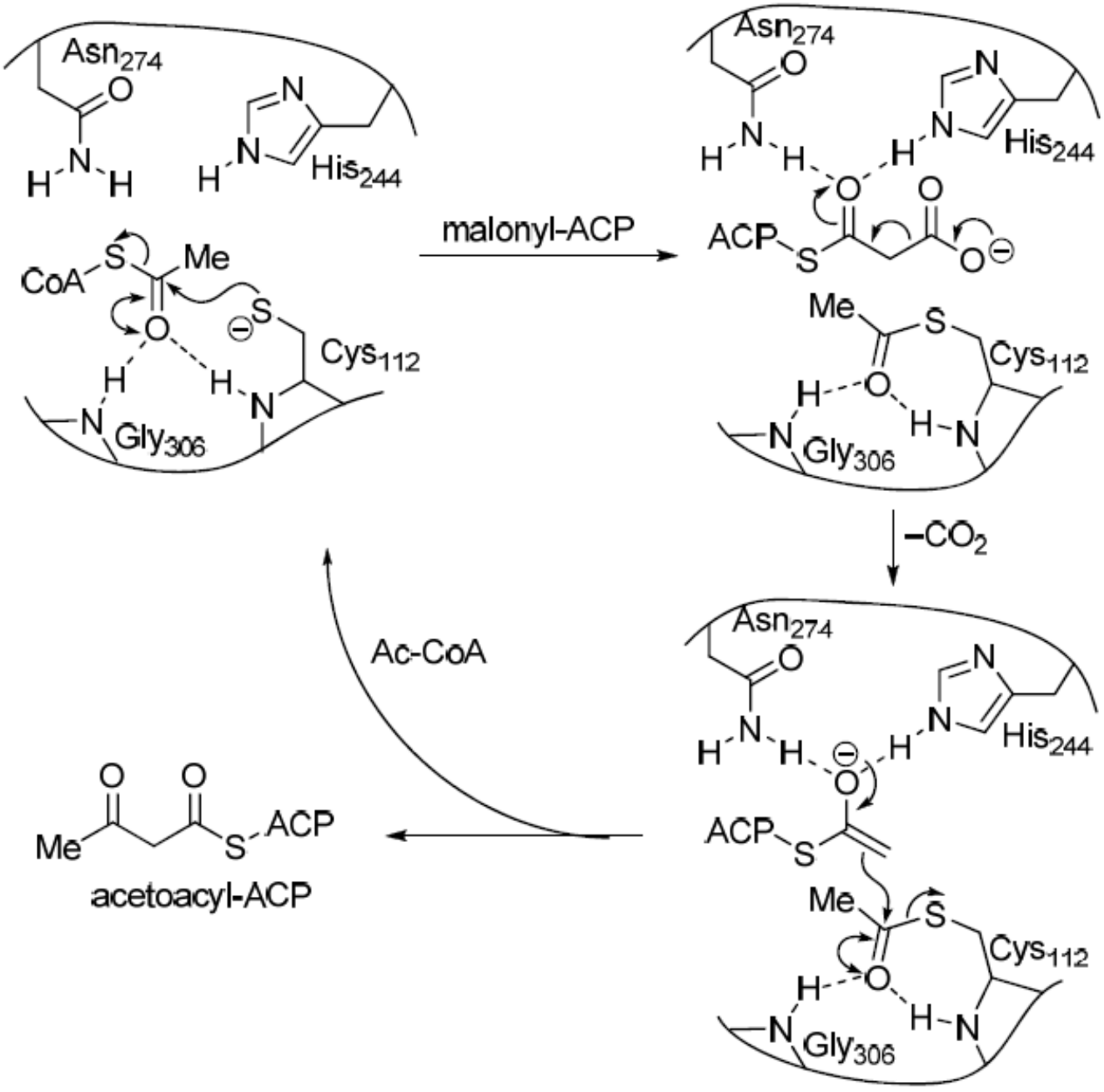
Scheme 35.

Synthesis of abyssomicin D (**206**) and *iso*-abyssomicin D (**232**) (Nicolaou and Harrison, 2007). [138b]

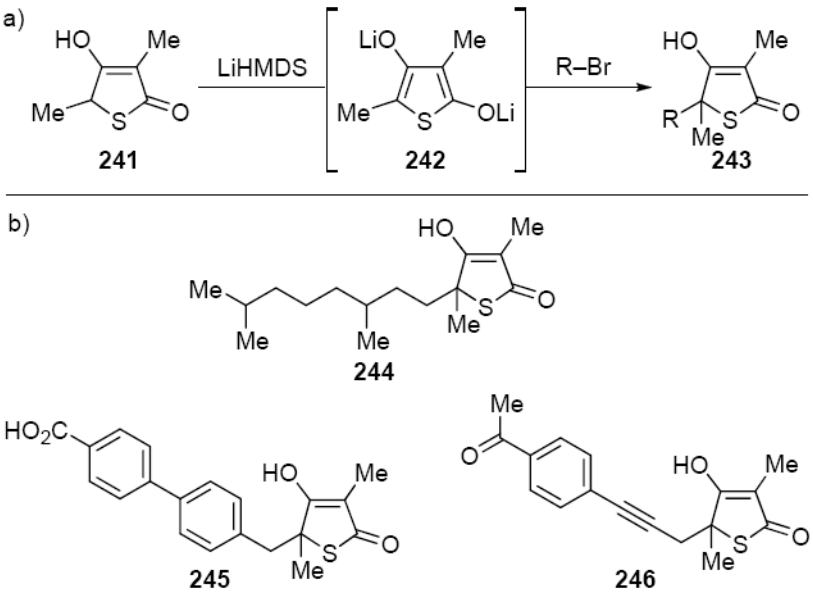


Scheme 36.

Bacterial fatty acid biosynthesis (FAS II) (a) and the structure of the acyl carrier protein (ACP) 4'-phosphopantotheine linker group (b).[144]

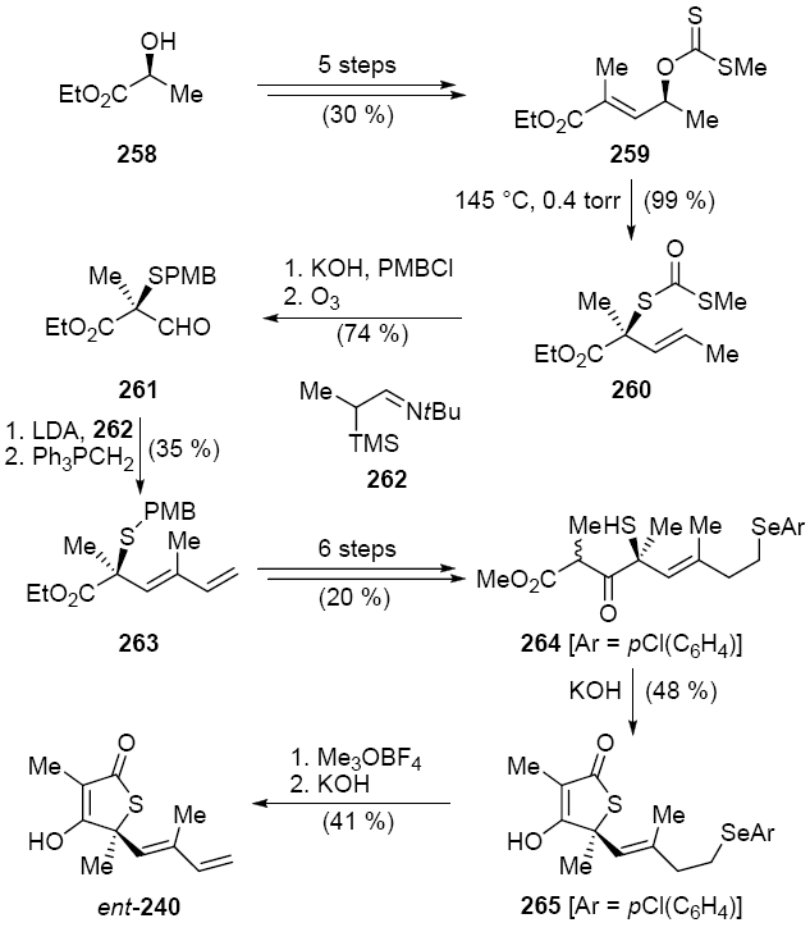


Scheme 37.
Mechanism of the FabH-catalyzed initial Claisen condensation reaction of FAS II.[144]



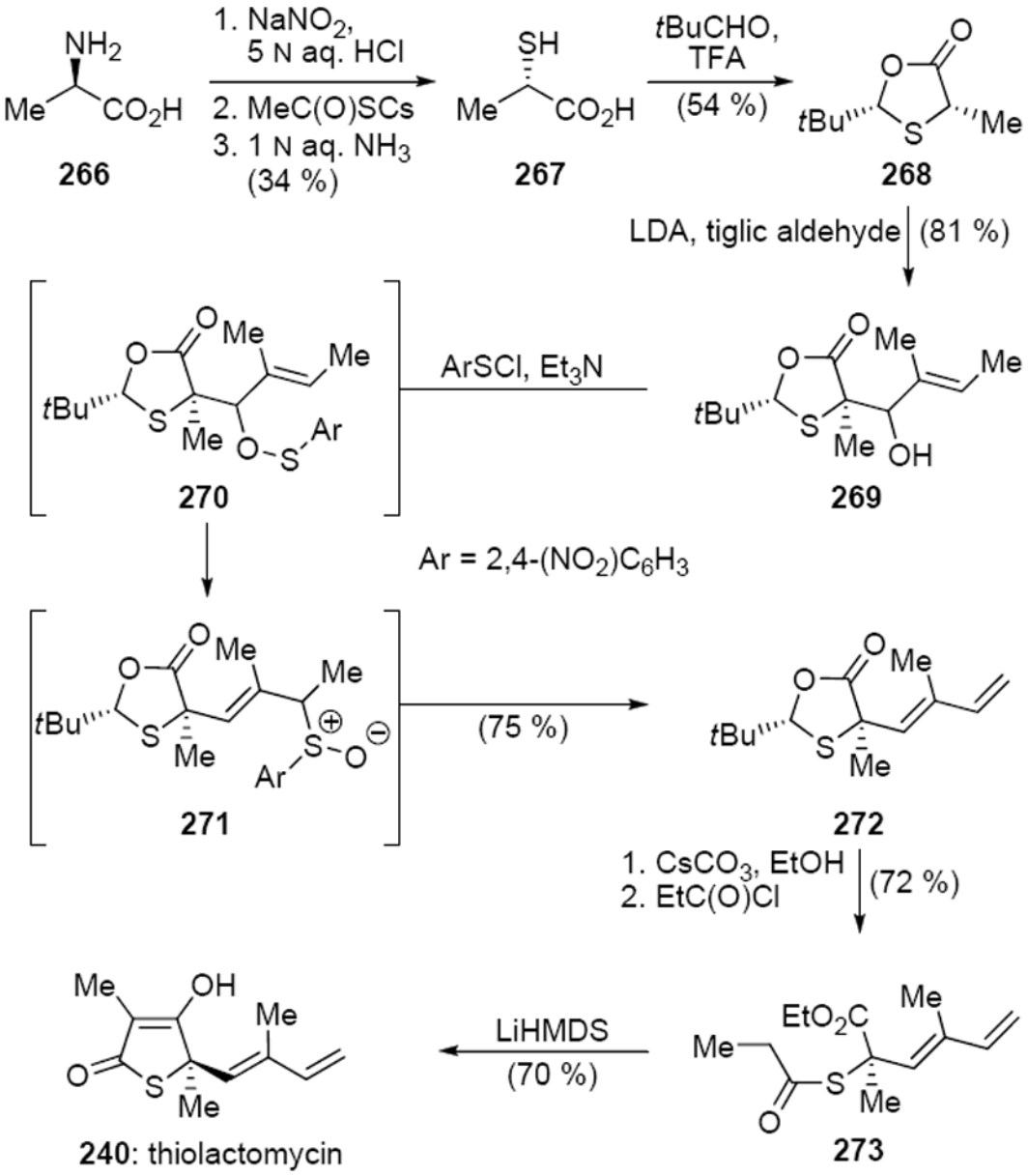
Scheme 38.

A widely used strategy for the synthesis of thiolactomycin analogs (a)[167] and molecular structures of selected thiolactomycin analogs with antitubercular activity (b) (Besra et al., 2002–2007).[166,168]

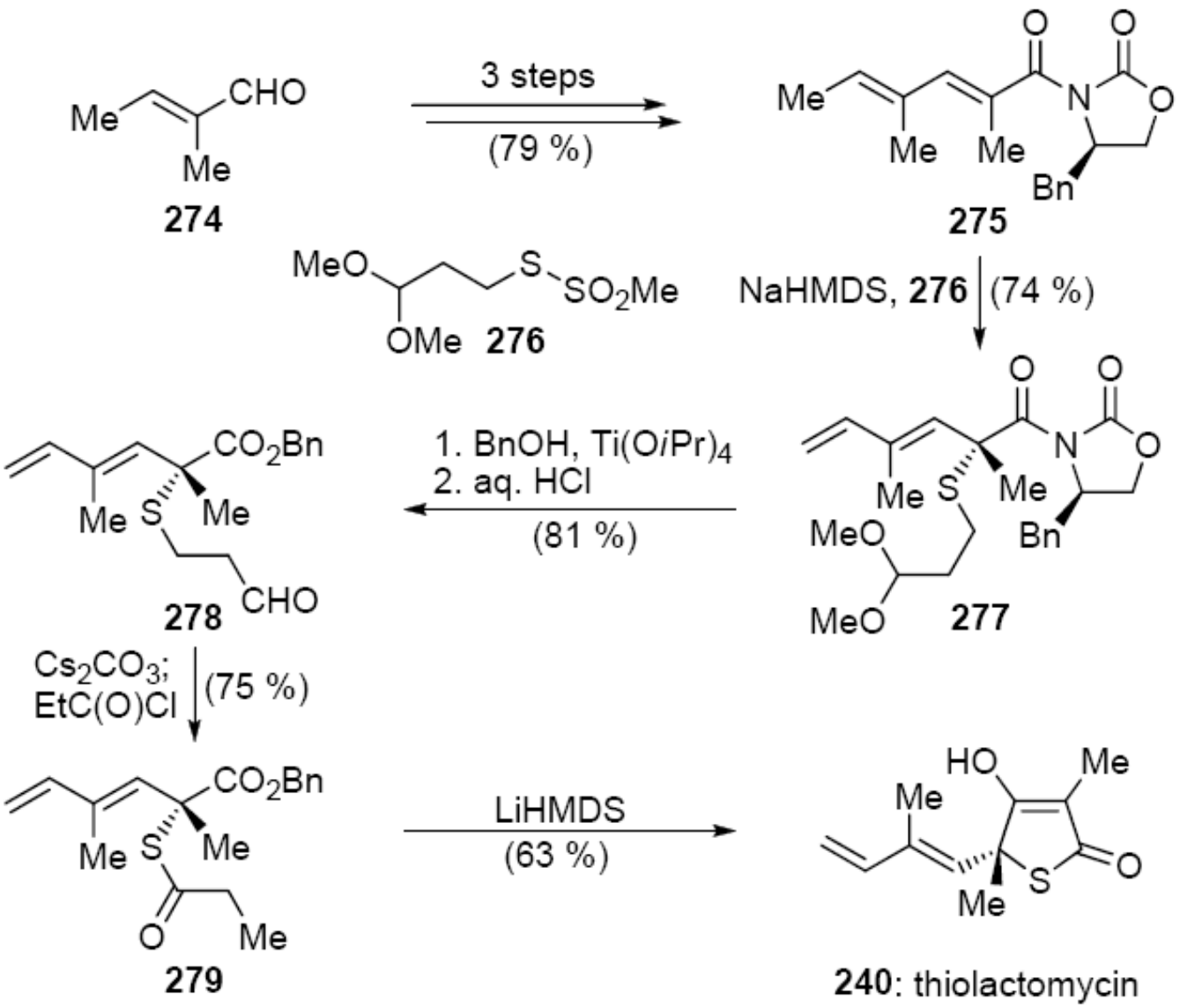


Scheme 39.

Total synthesis of *ent*-thiolactomycin (*ent*-**240**) (Chambers and Thomas, 1989).[178]

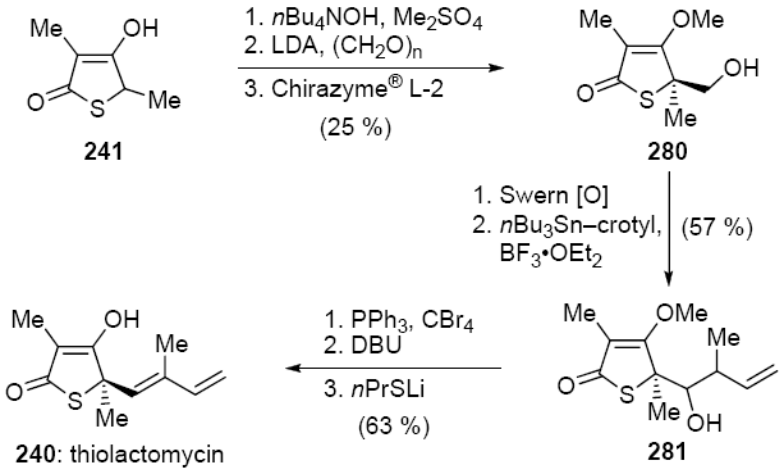


Scheme 40.
Total synthesis of thiolactomycin (**240**) using chiral relay (Townsend et al., 2002).[181]

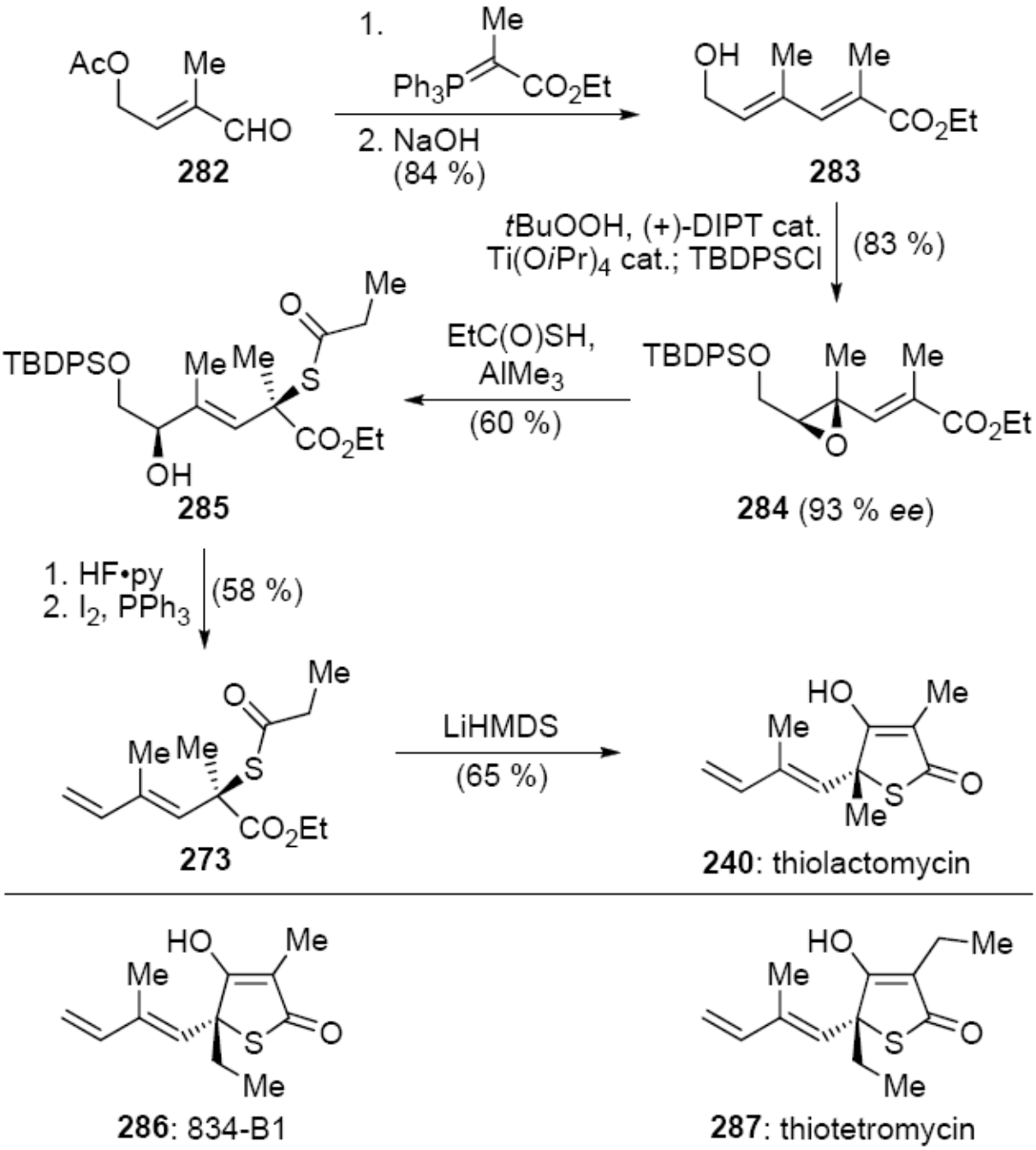


Scheme 41.

Total synthesis of thiolactomycin (**240**) through asymmetric sulfenylation (Ohata and Terashima, 2006).[183]

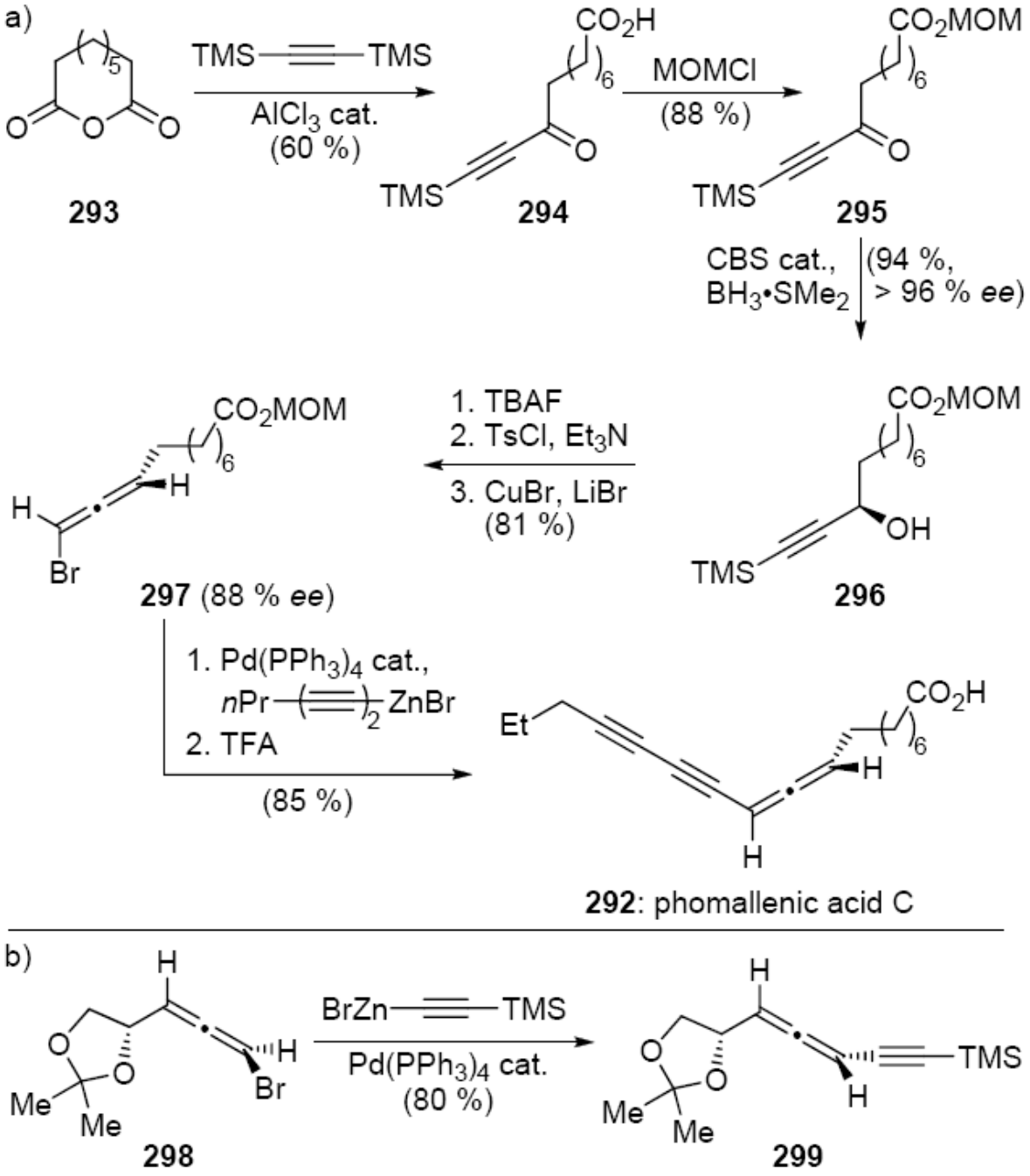


Scheme 42.
Chemoenzymatic total synthesis of thiolactomycin (**240**) (Takabe et al., 2006).[185]

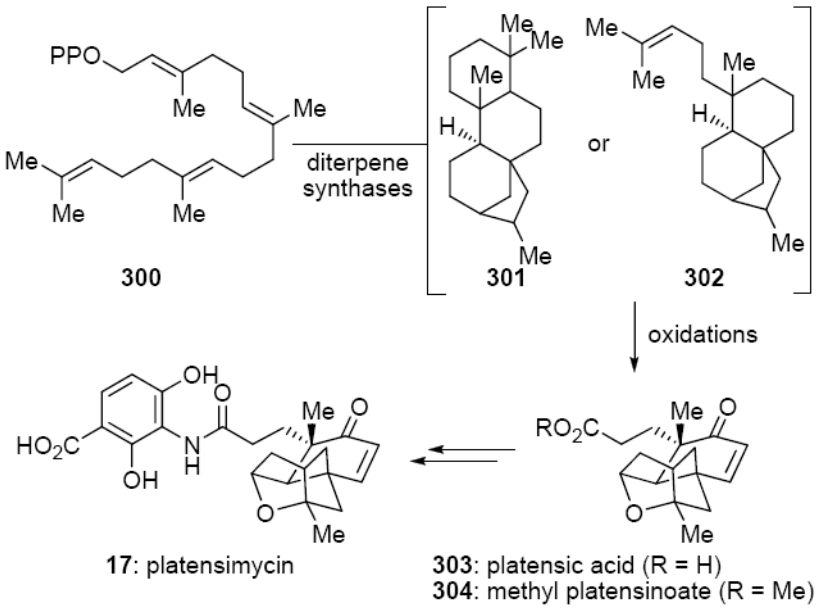


Scheme 43.

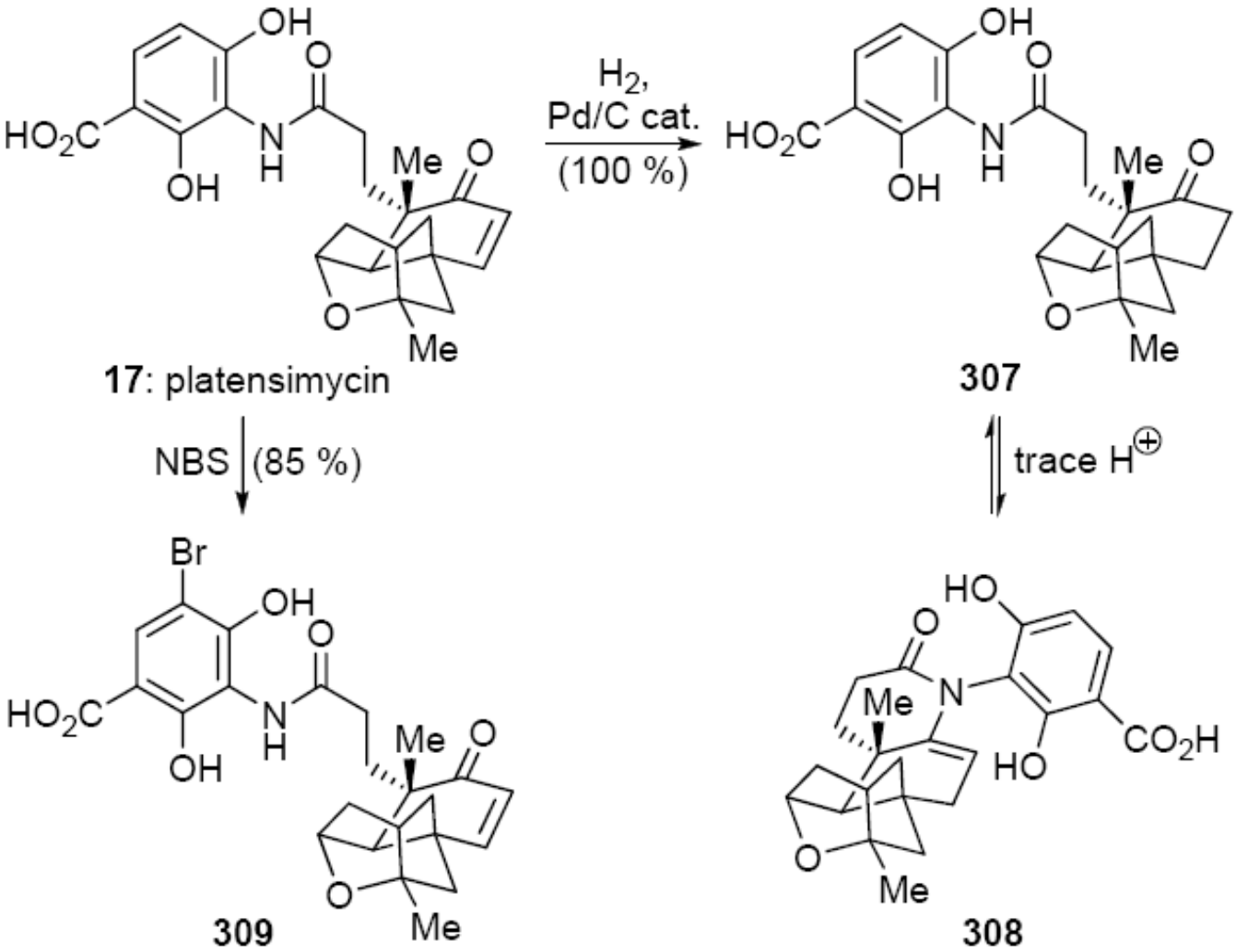
Catalytic asymmetric total synthesis of thiolactomycin (**240**) and the molecular structures of 834-B1 (**286**) and thiotetromycin (**287**) (Dormann and Bruckner, 2007).[187]



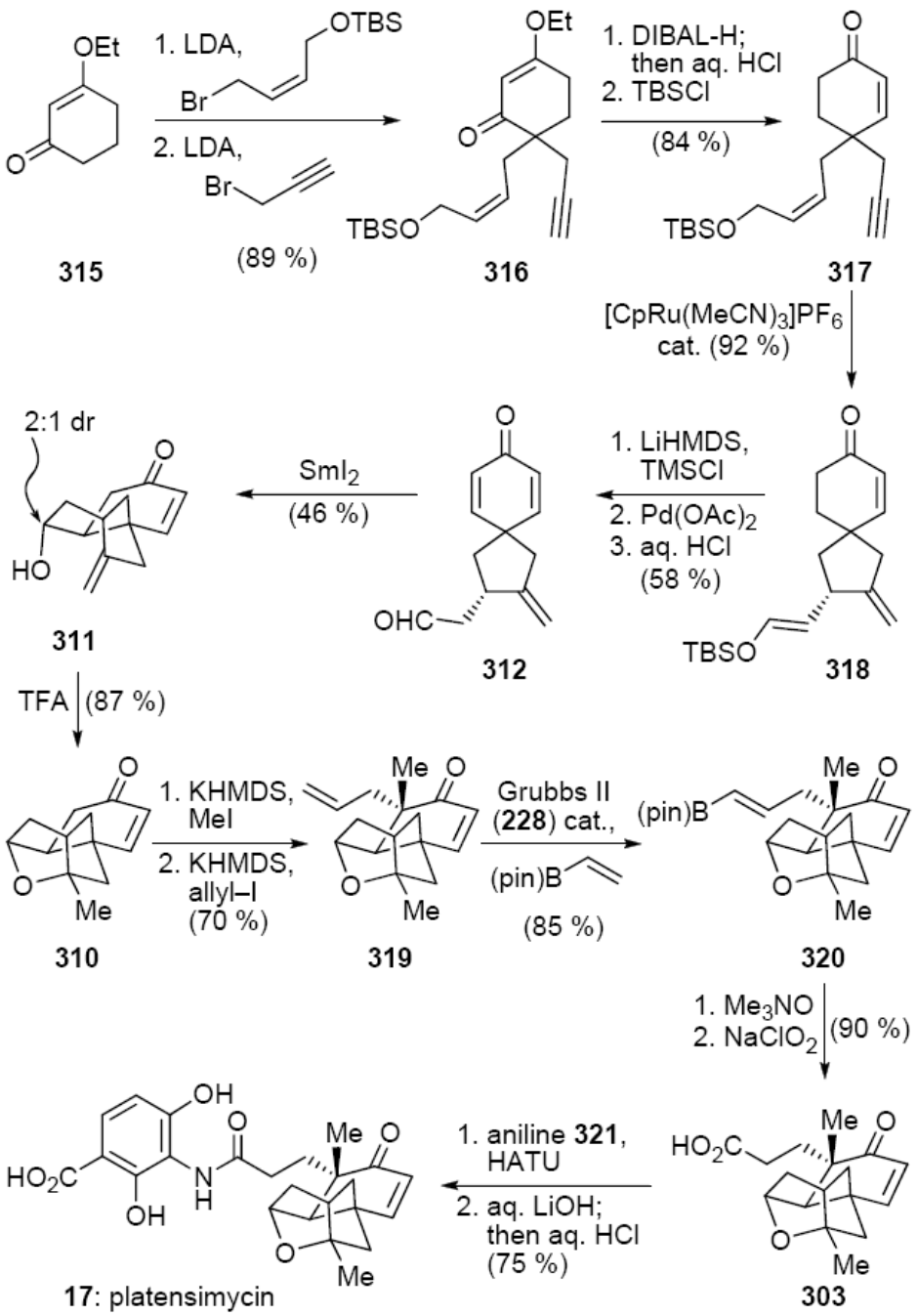
Scheme 44.
Asymmetric total synthesis of phomallenic acid C (**292**) (Wu et al., 2007).[196]



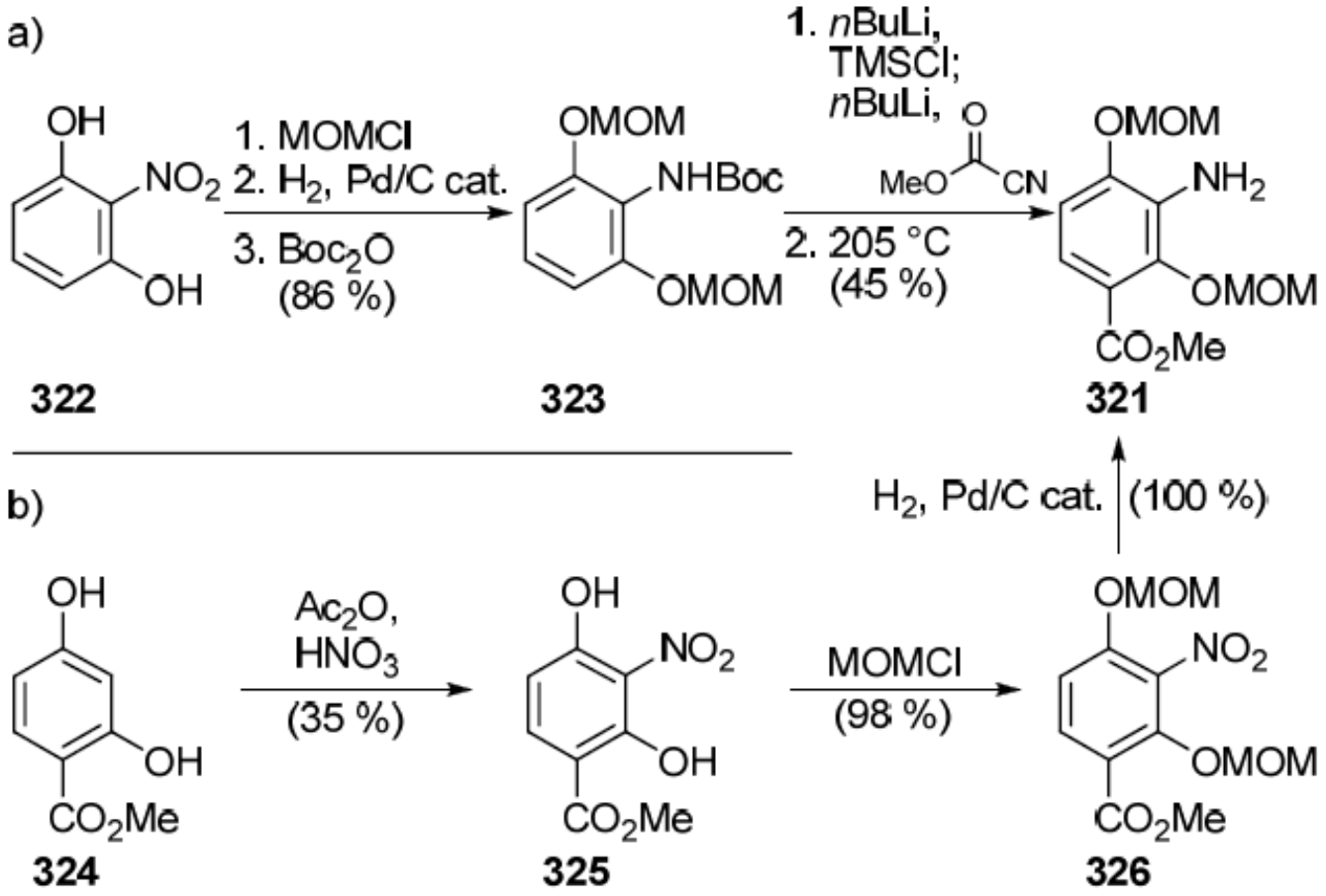
Scheme 45.
Highlights of the biosynthesis of platensimycin (**17**).[204]



Scheme 46.
Selected chemical transformations of platensimycin (**17**) (Singh et al., 2007).[200b,207]

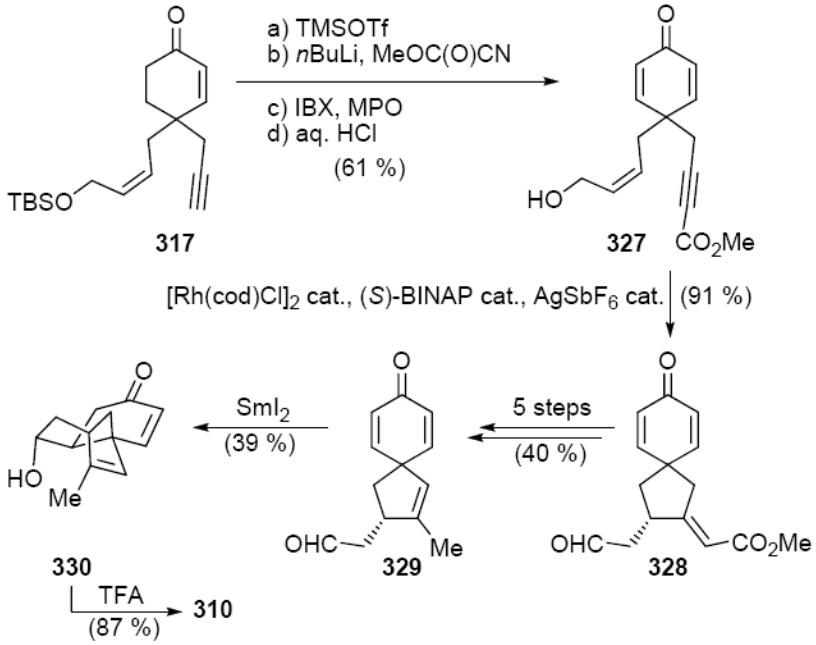


Scheme 47.
Total synthesis of (±)-platensimycin (**17**) (Nicolaou et al., 2006).[209]



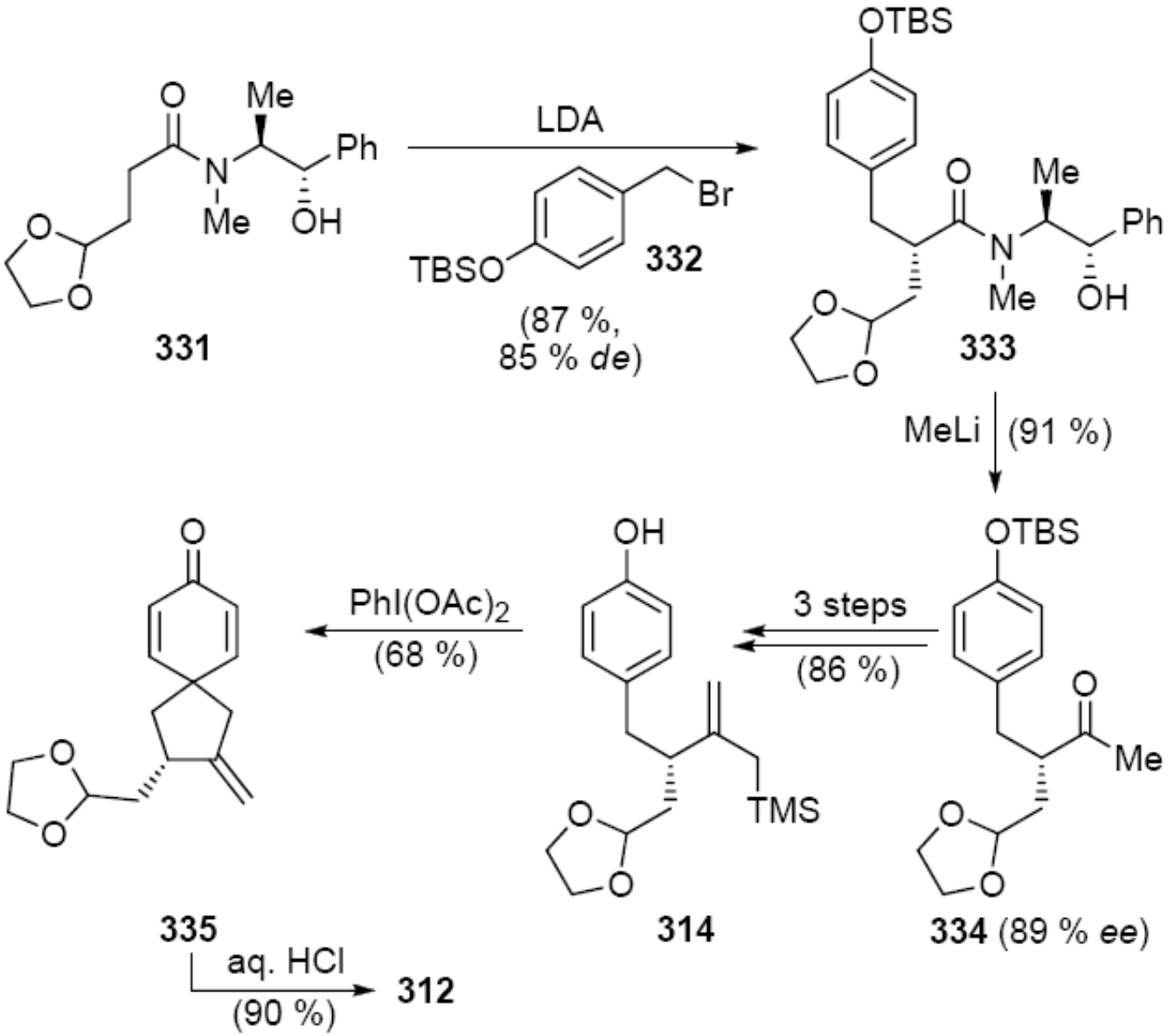
Scheme 48.

Synthesis of platensimycin aniline fragment **383** [a) Nicolaou et al., 2006;[209] b) Heretsch and Giannis, 2007[216]]

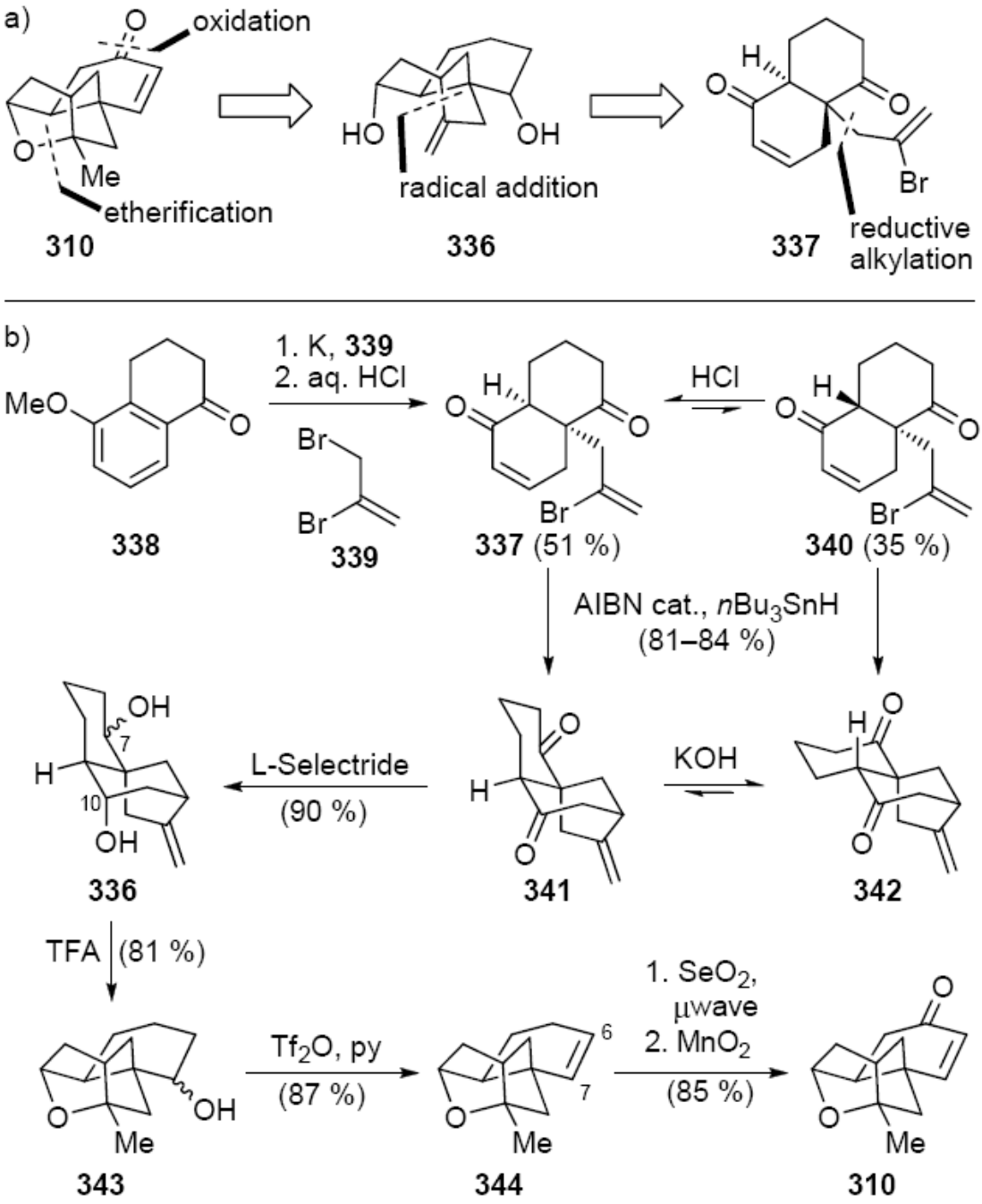


Scheme 49.

Asymmetric synthesis of (–)-**310** via Rh-catalyzed cycloisomerization (Nicolaou et al., 2007). [211]

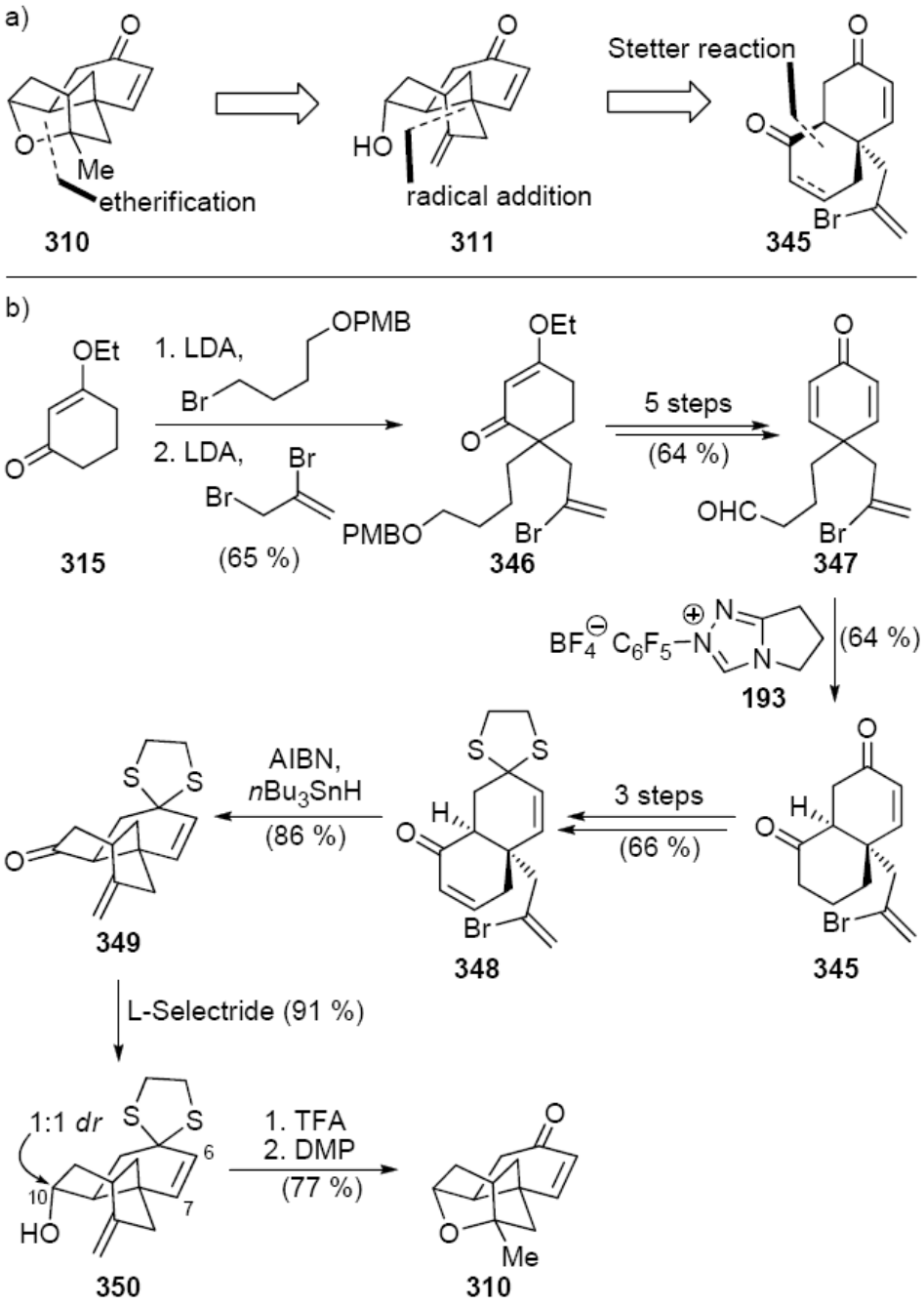


Scheme 50.
Asymmetric synthesis of (–)-**312** via dearomatization (Nicolaou et al., 2007).[221]



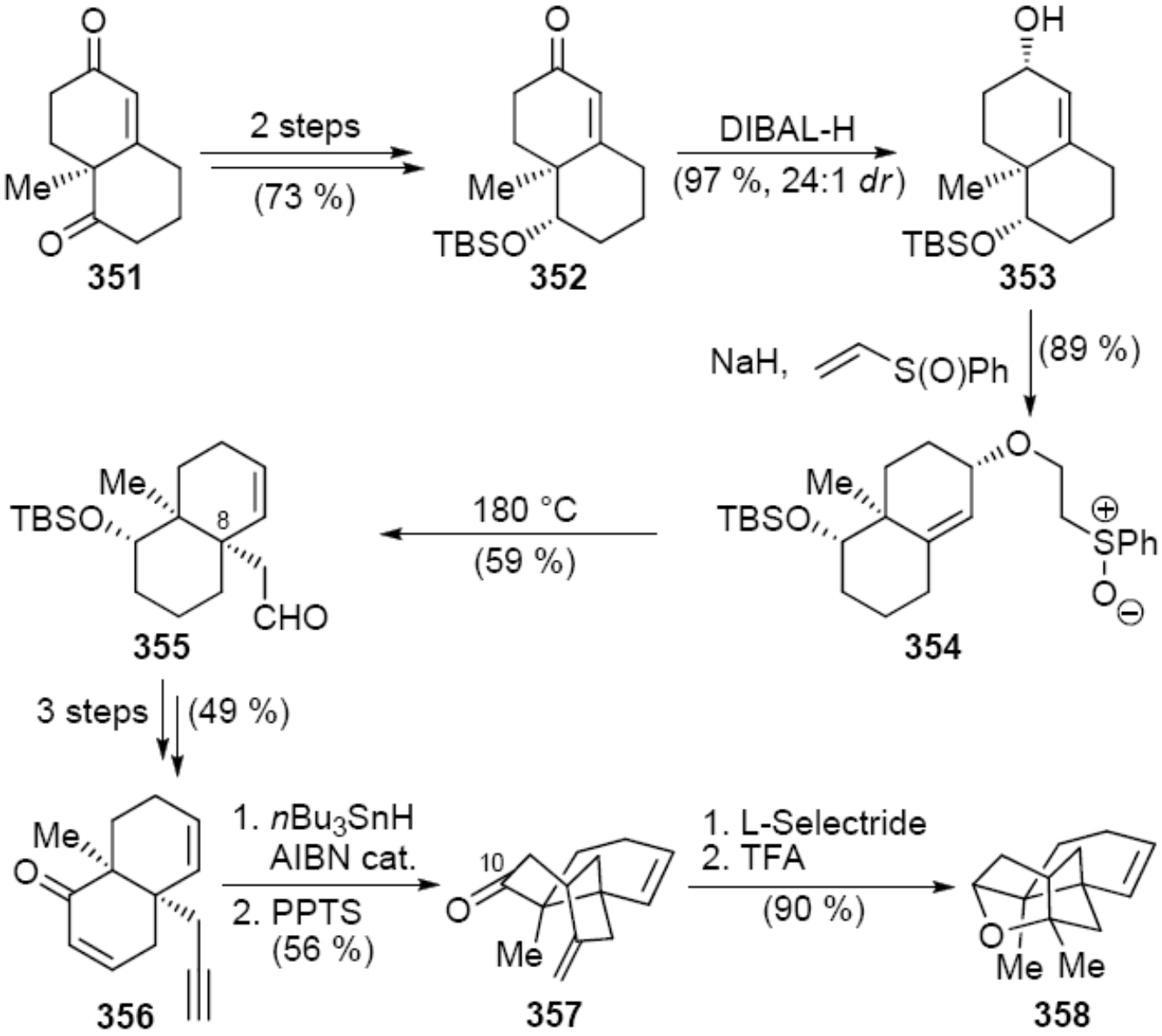
Scheme 51.

Retrosynthetic analysis (a) and synthesis (b) of (±)-**310** through a radical cyclization (Snider et al., 2007).[223]

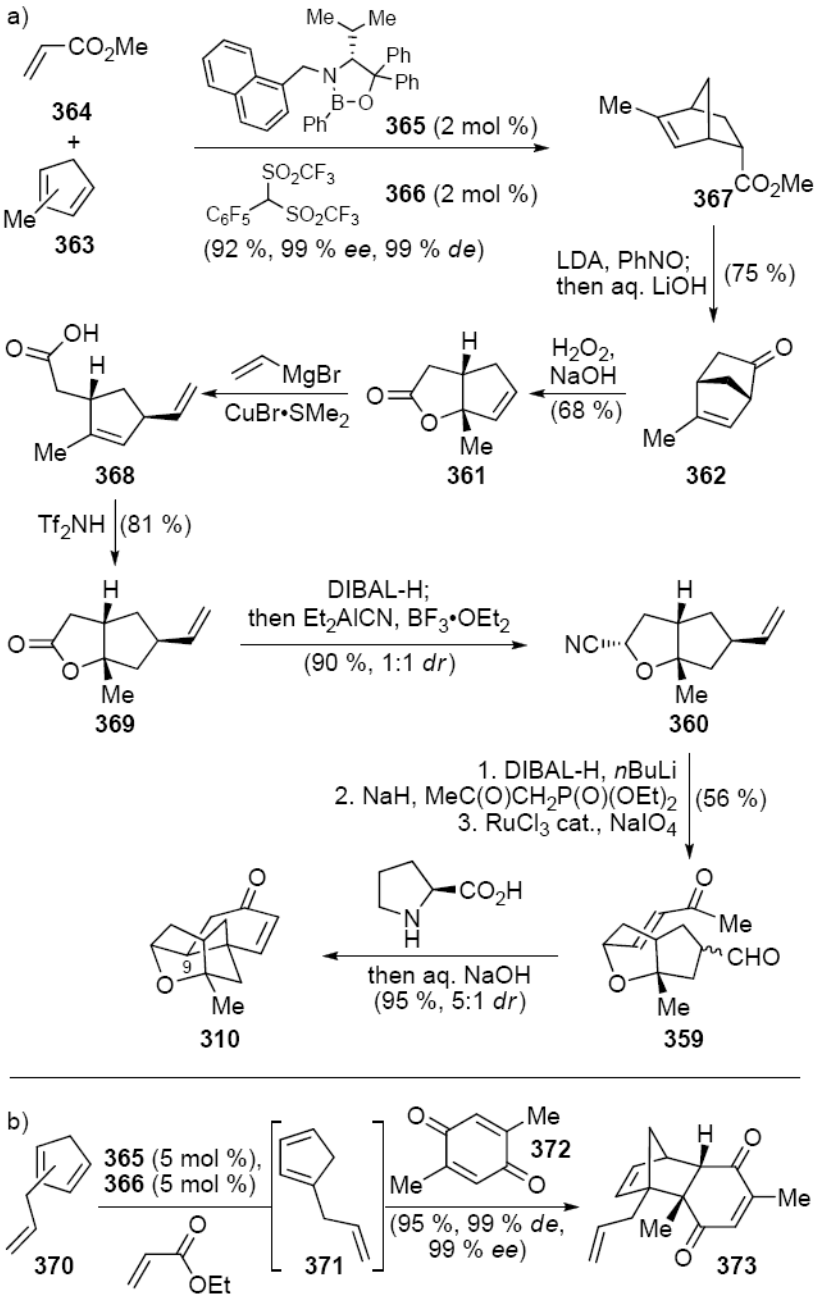


Scheme 52.

Retrosynthetic analysis (a) and synthesis (b) of (±)-**310** through desymmetrization and radical cyclization (Nicolaou et al., 2007).[225]

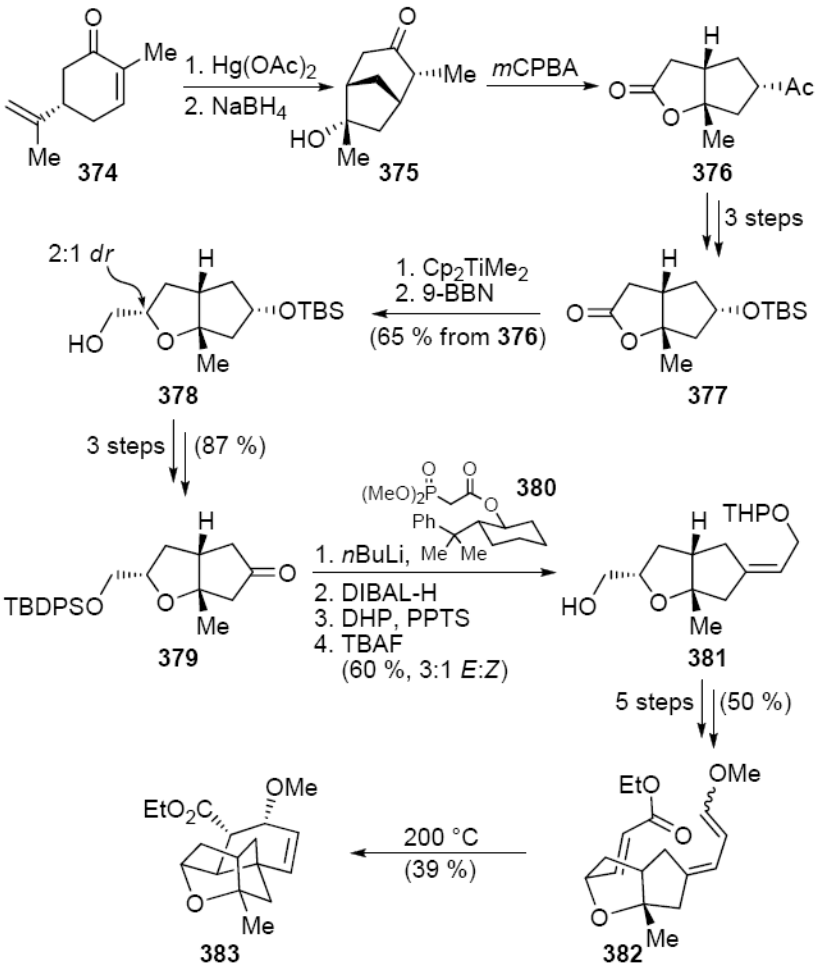


Scheme 53.
Synthesis of platensimycin core surrogate **358** (Kaliappan and Ravikumar, 2007).[227]



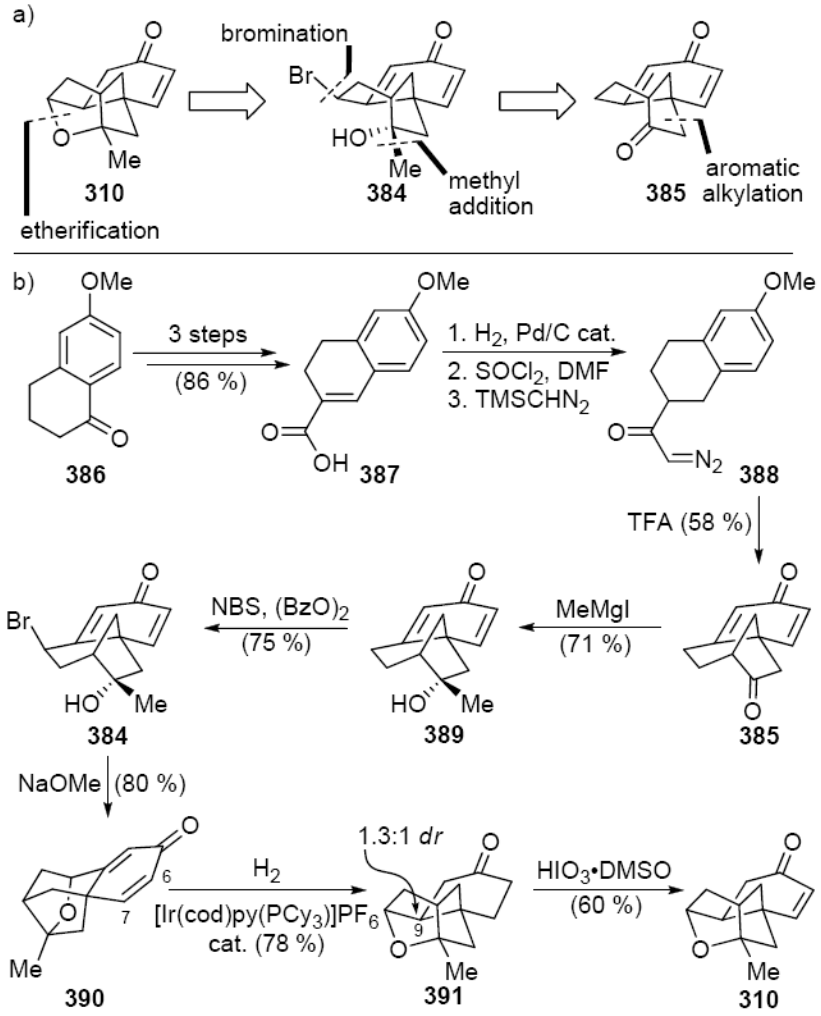
Scheme 54.

Synthesis of platensimycin core (**310**) (a) and asymmetric Diels–Alder reactions of 1-alkylcyclopentadienes (b) (Yamamoto et al., 2007).[228,230]



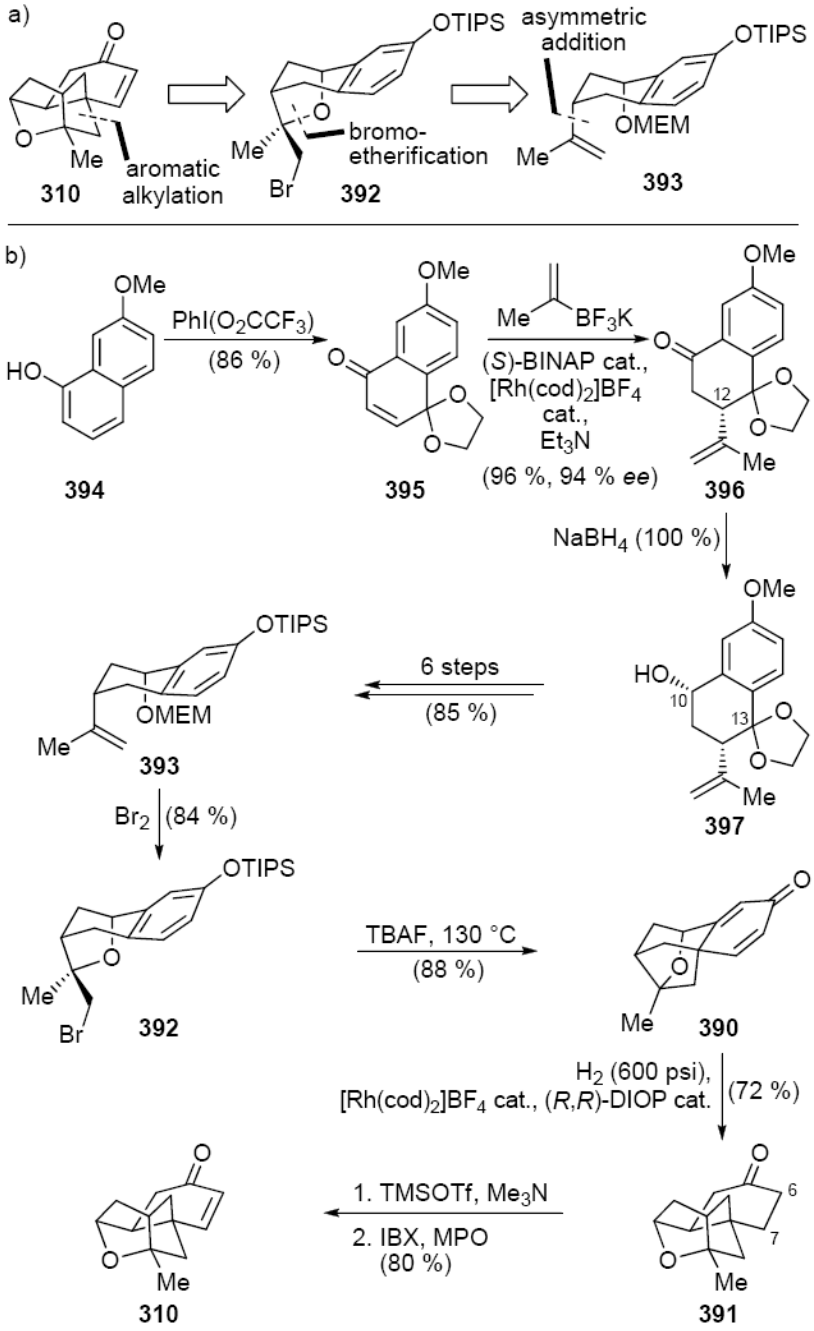
Scheme 55.

Synthesis of platensimycin core structure **383** via intramolecular Diels–Alder reaction (Ghosh and Xi, 2007).[235]



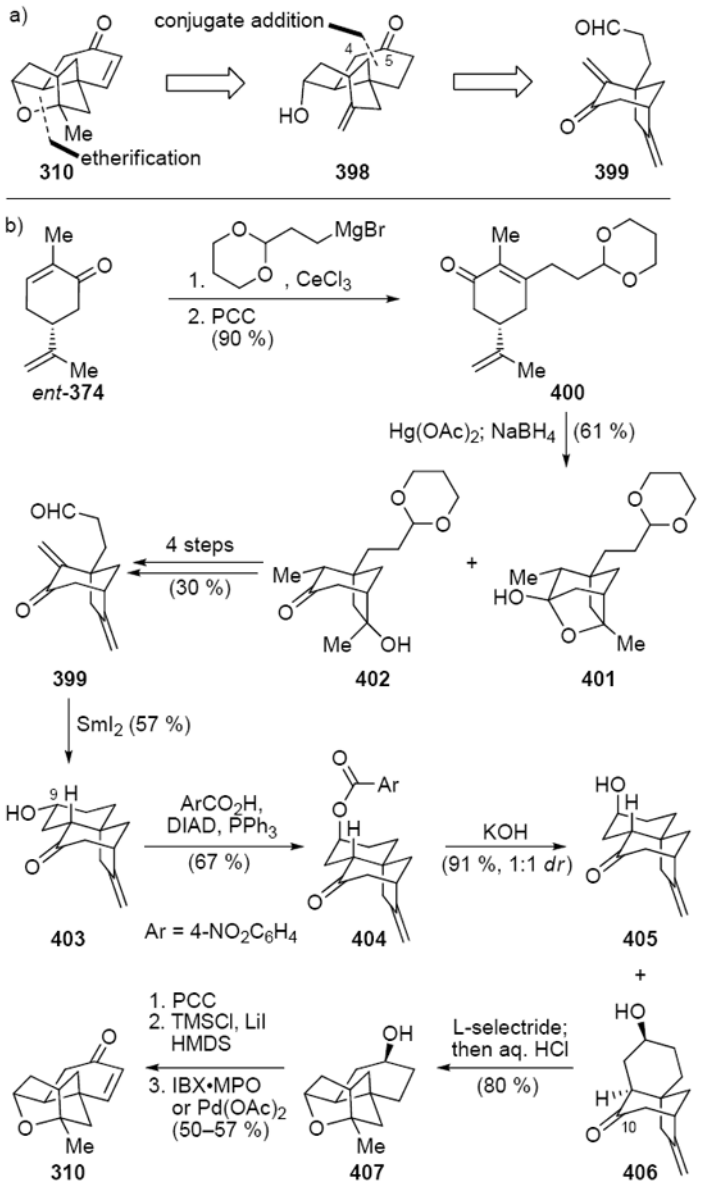
Scheme 56.

Retrosynthetic analysis (a) and synthesis (b) of (±)-**310** via dearomatizing alkylation (Tiefenbacher and Mulzer, 2007).[237]



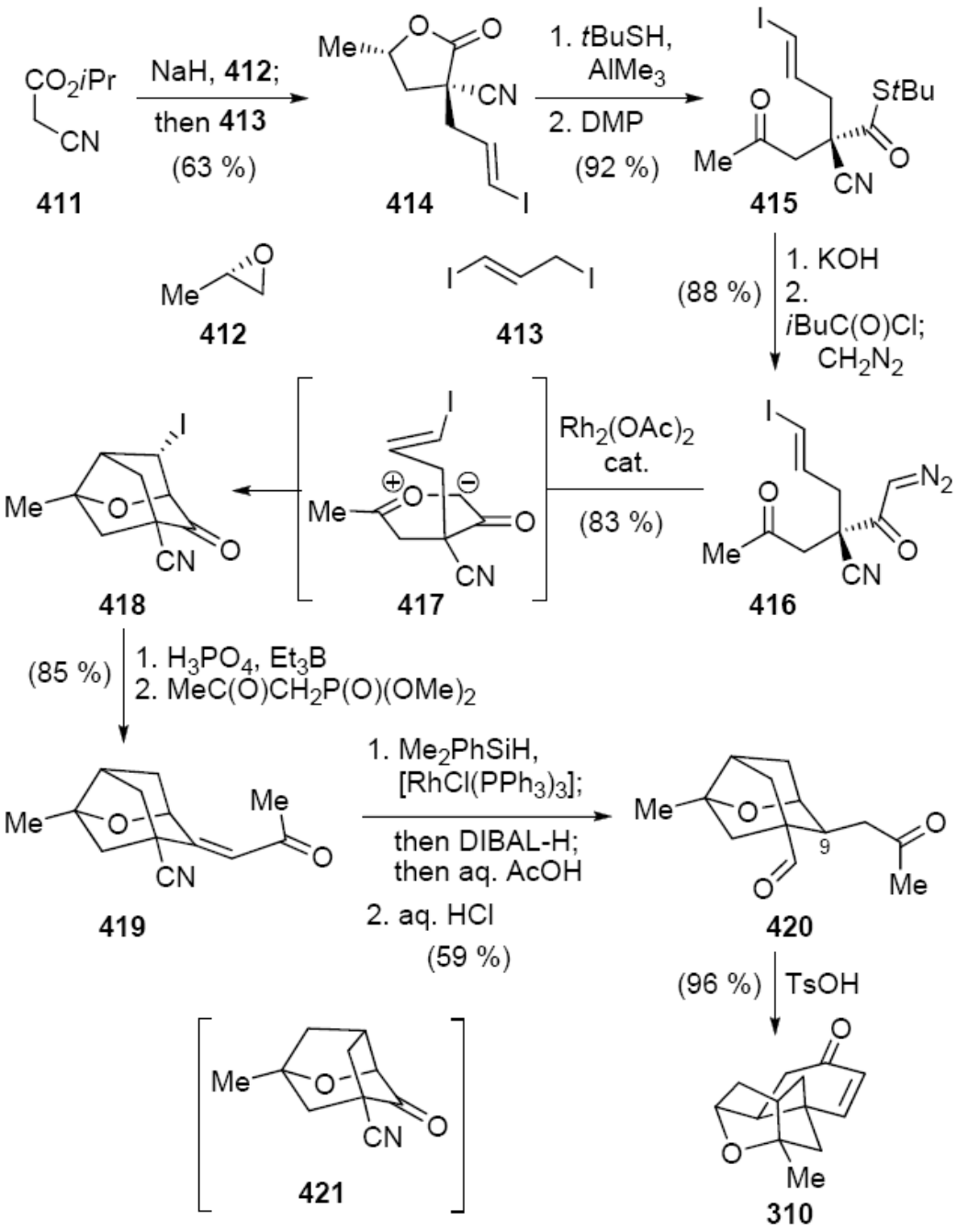
Scheme 57.

Retrosynthetic analysis (a) and enantioselective synthesis (b) of enone **310** via dearomatizing alkylation (Lalic and Corey, 2007).[242]

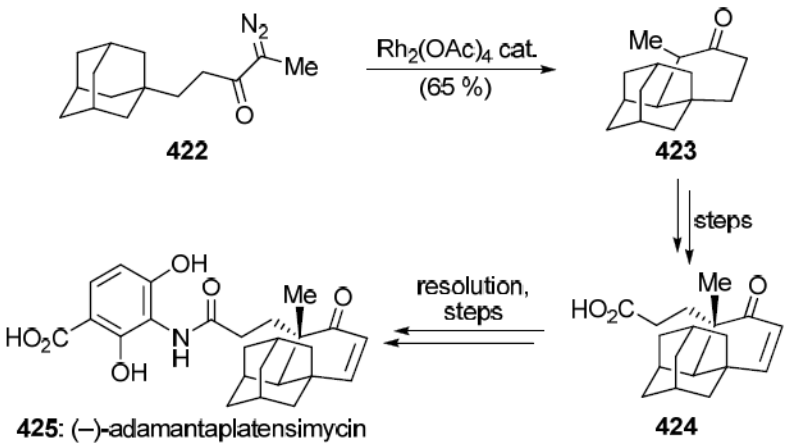


Scheme 58.

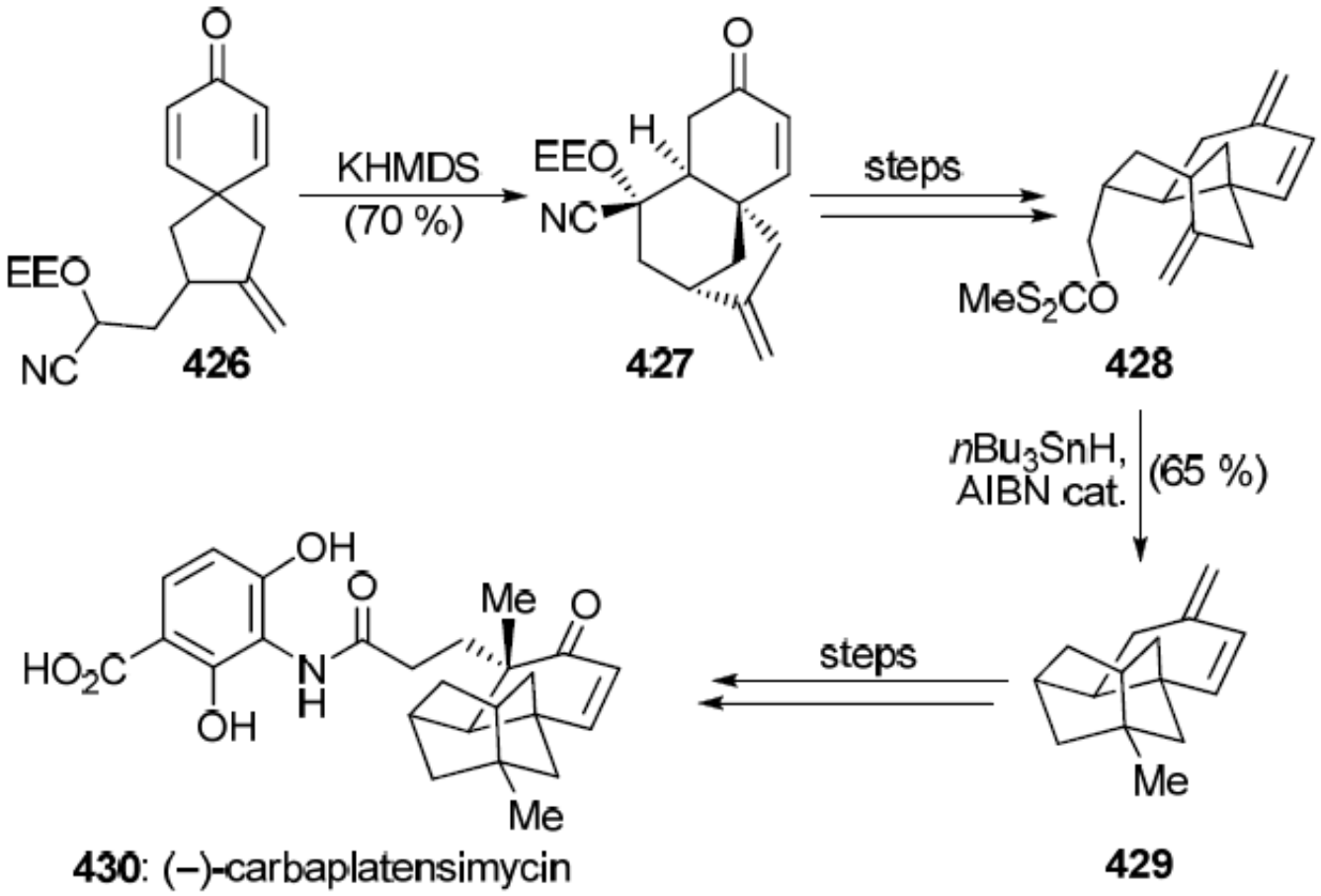
Retrosynthetic analysis (a) and synthesis (b) of **310** via ketyl–olefin cyclization (Nicolaou, Chen, et al., 2007).[246]



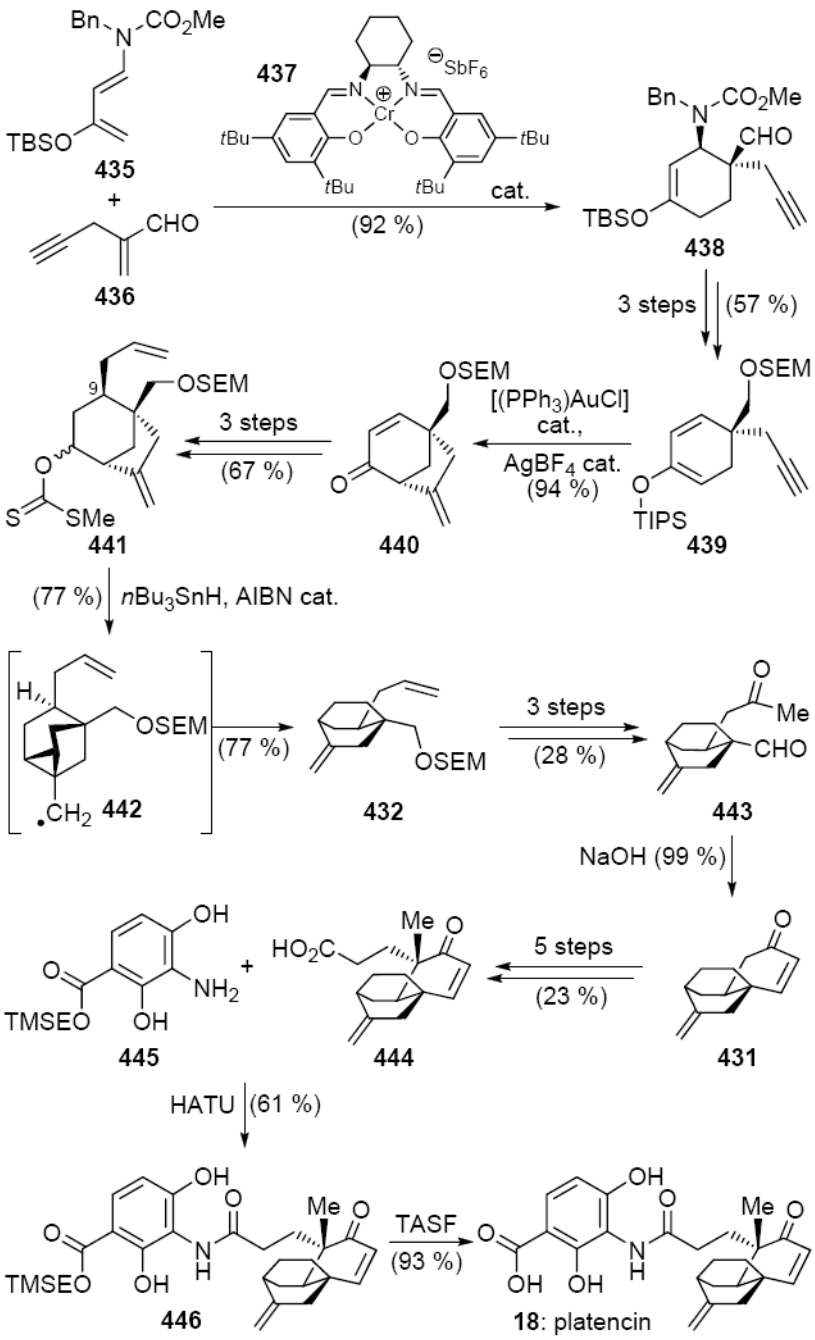
Scheme 59.
Enantioselective synthesis of **310** through a [3+2] cycloaddition (Eun Lee et al., 2008).[248]



Scheme 60.
Highlights of the synthesis of (–)-adamantaplatensimycin (**425**) (Nicolaou et al., 2007).[253]

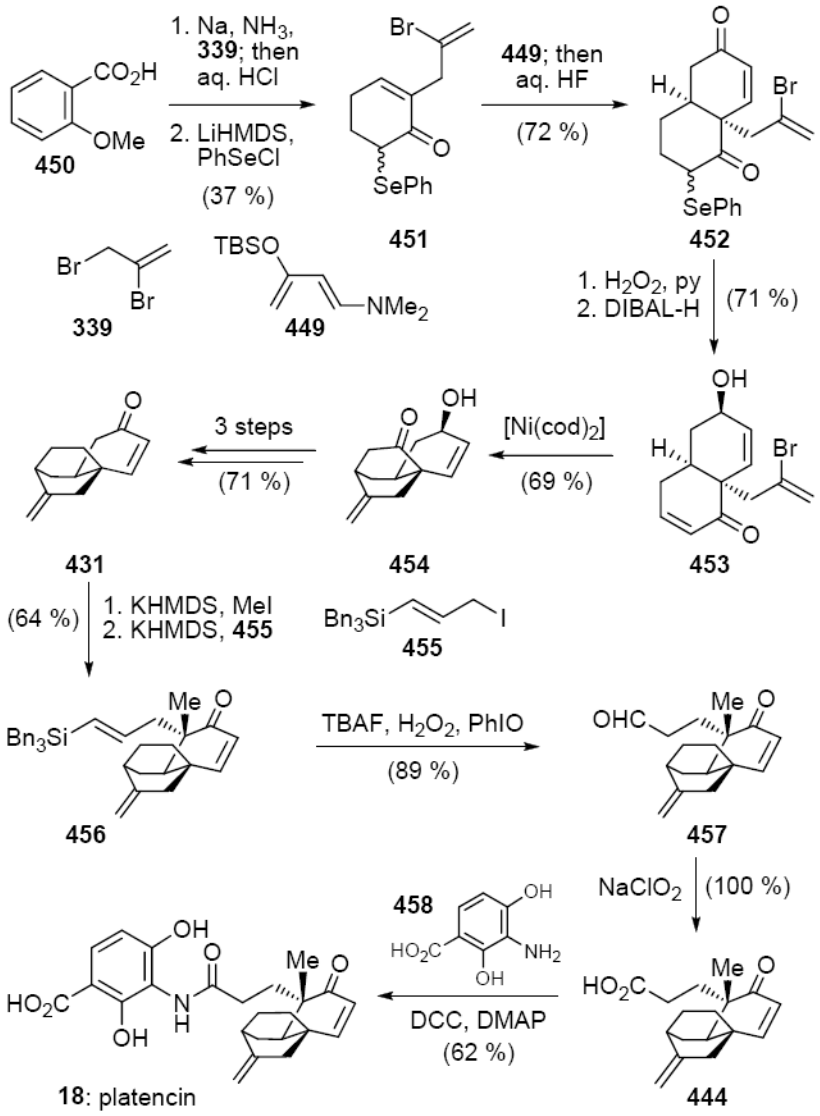


Scheme 61.
Highlights of the asymmetric synthesis of (–)-carbaplatensimycin (**430**) (Nicolaou et al., 2007). [255]



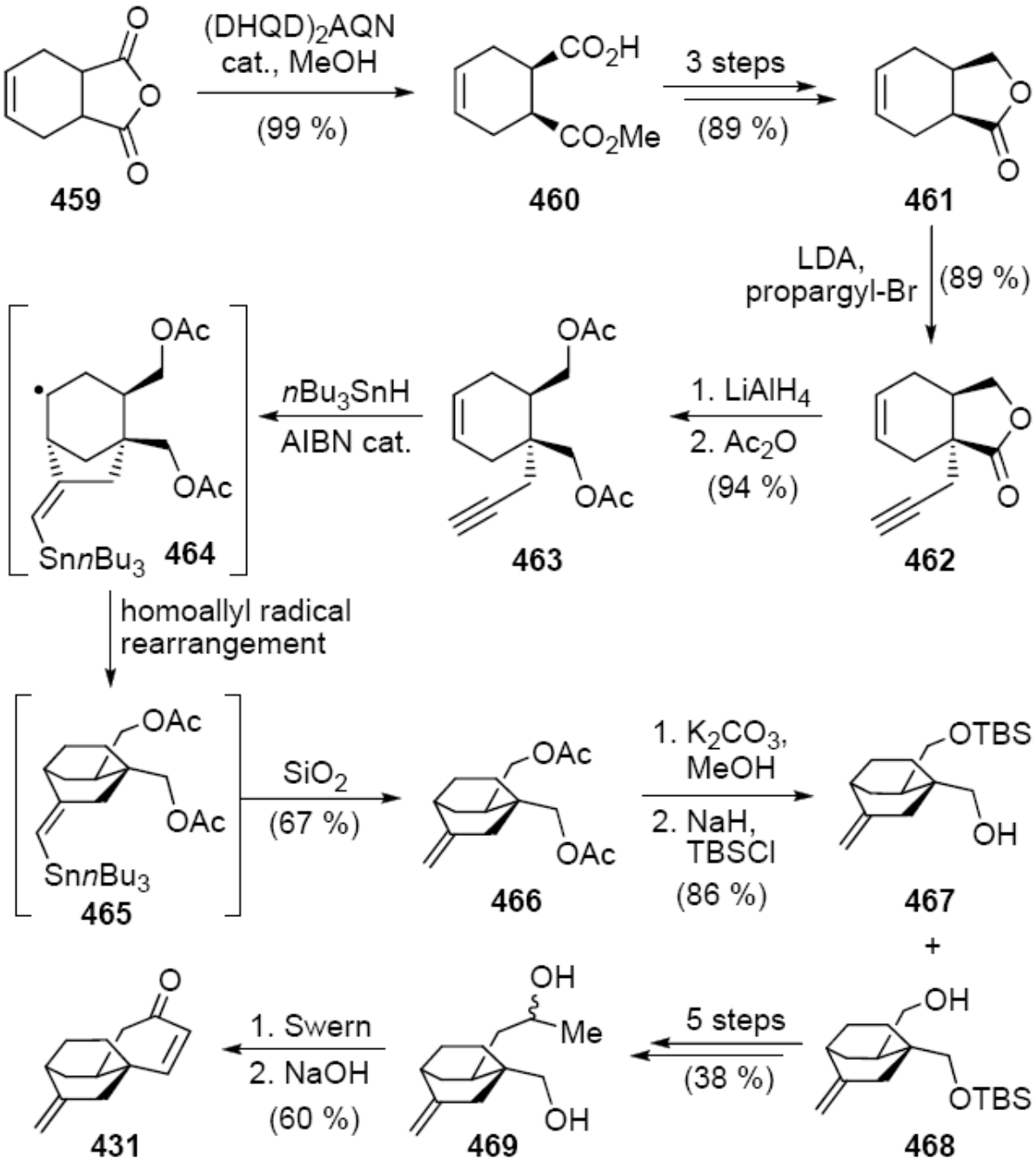
Scheme 62.

Enantioselective total synthesis of platencin (**18**) through a homoallyl radical rearrangement (Nicolaou et al., 2008).[256]



Scheme 63.

Total synthesis of (±)-platencin (**18**) via reductive cyclization and Diels–Alder reactions (Hayashida and Rawal, 2008).[261]



Scheme 64.

Formal total synthesis of platencin (**18**) using a radical addition/rearrangement cascade (Daesung Lee et al., 2008).[263]

Table 1

Antibiotic properties of selected tetracycline analogs against Gram-positive bacteria (Myers et al., 2005).[30]

Bacterial strain	**tetracycline (5) MIC (μg mL^{-1})**	**41 MIC (μg mL^{-1})**	**42MIC (μg mL^{-1})**
Staphylococcus aureus ATCC 29213	1	1	1
Staphylococcus epidermidis ACH-0016	1	0.5	0.5
Staphylococcus haemolyticus ACH-0013	8	2	1
Enterococcus faecalis ATCC 700802	1	0.5	1
Staphylococcus aureus ATCC 700699	> 64	2	1

Table 2

Antibiotic properties of platensimycin (**17**) and platencin (**18**) against selected bacterial strains (Wang et al., 2006–2007).[200a,202a]

Bacterial strain	**17**[a] **MIC (μg mL^{-1})**	**18**[a] **MIC (μg mL^{-1})**	**linezolid**[a] **MIC (μg mL^{-1})**
Staphylococcus aureus	0.5	0.5	4
Staphylococcus aureus plus serum	2	8	4
MRSA	0.5	1	2
MRSA (macrolide^{R})	0.5	1	2
MRSA (linezolid^{R})	1	1	32
VISA	0.5	0.5	2
Enterococcus faecalis (macrolide^{R})	1	2	1
Enterococcus faecium (vancomycin^{R})	0.1	< 0.06	2
Streptococcus pneumoniae	1	4	1
Escherichia coli	> 64	> 64	> 64
Candida albicans	> 64	> 64	> 64
HeLa MTT (IC_{50})	> 1000	> 100	> 100

[a] 1 μg mL^{-1} is equivalent to 2.27 μM for platensimycin (**17**), 2.35 μM for platencin (**18**), and 2.96 μM for linezolid.

^{R}indicates strain is resistant to the stated antibiotic(s).