REVIEW ARTICLE

A brief history of antibiotics and select advances in their synthesis

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The advent of modern antibiotics contributed enormously to the dramatic extension of human lifespan since their discovery by virtue of their lethal and selective action against pathogenic microbes. And yet despite our powerful arsenal of weapons against these pathogens, the war against them has not been won. And it may never be. Drug resistance is still menacing the society with many lives being lost due to deadly infections caused by continuously evolving strains spread beyond our means to eradicate them or prevent their spreading. Herein, the emergence and evolution of antibiotics is briefly reviewed, and a select number of total syntheses of naturally occurring antibiotics from the authors' laboratories are highlighted. The article concludes with a strong endorsement of the current efforts to intensify our fight against these dangerous pathogens with the hope that, this time, these initiatives will be sufficiently focused and serious enough so as to achieve our set goals of, at least, being prepared and ahead of them as part of our drive to improve humanity's healthcare and wellbeing.
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HISTORICAL PERSPECTIVE

The origin of the term 'antibiotic' can be traced back to the word *antibiose* first used as an antonym to symbiosis by Paul Vuillemin[1] in his 1890 publication to describe the antagonistic action between different microorganisms (for example, fungi vs bacteria; bacteria vs protozoa).[2,3] Later, the word antibiotic was used to describe naturally occurring secondary metabolites produced by bacteria and fungi possessing either growth inhibitory (bacteriostatic) or killing (bactericidal) activities against bacteria or fungi. Today the term has a broader meaning, in one sense to include designed molecules and a narrower definition, in another and with the terms antibacterial or antifungal, to designate their specific actions against bacteria and fungi, respectively, but not viruses.[2] The term antiviral is reserved for the latter. In the Middle Ages, the miasma (or miasmatic, from the Greek μίασμα, meaning pollution, fowl air or contaminated vapors) theory was used to explain the causes of various diseases. In 1546 the Italian scholar Girolamo Fracastoro (Hieronymus Fracastorius) proposed transmittable, imperceptible seed-like particles (*seminaria morbi*) as causative agents for the outbreak of certain diseases.[4] It took several centuries to prove that bacteria are one example of such 'particles'. In the meantime, the Hungarian physician Ignaz Semmelweis, also known as the 'savior of mothers', recognizing the importance of hygiene in hospitals suggested and enforced hand washing with chlorinated lime solutions before patient examinations, while the Scottish surgeon Sir Joseph Lister treated surgery wounds with phenol (carbolic acid) solutions to avoid infections. In the 1860s the French physician Casimir Davaine demonstrated that blood injections from animals infected with anthrax to healthy animals caused infection, providing further clues for the cause of disease. It was also in the

second half of the nineteenth century that the French chemist and bacteriologist Louis Pasteur contributed decisively to our understanding of the underlying causes of infectious diseases through his experimental studies with bacteria that culminated in his germ theory of disease. The subsequent contributions of the German physician Robert Koch also proved transformative. His discoveries, including the so-called four 'Koch postulates' establishing a causative relationship between microbes and disease (predicated on work of Jakob Henle,[5] and together with Friedrich Loeffler), propelled bacteriology toward its modern era.[6–8] In 1882 Koch, together with Bernhard Fischer and Georg Gaffky, isolated the *Mycobacterium tuberculosis* and in 1884 the *Vibrio cholerae* (a species first described in 1854 by Italian anatomist and pathologist Filippo Pacini),[9] the causative strains that lead to the corresponding diseases. These milestone discoveries earned Koch one of the first Nobel Prizes in Physiology or Medicine (1905).

The first antibiotic to be discovered from nature was mycophenolic acid (**1**, Figure 1). Reported by the Italian physician and microbiologist Bartolomeo Gosio in 1893, this antibiotic was isolated from *Penicillium glaucum* (*P. brevicompactum*) as a crystalline solid while he was studying pellagra.[10,11] At that time it was shown that mycophenolic acid inhibits the growth of *Bacillus anthracis*, and later that it also possess antiviral, antifungal, antitumor and anti-psoriasis properties.[12] This seminal discovery remained unnoticed (probably due to its publication in Italian) until mycophenolic acid was rediscovered in 1913 in the United States.[13] Its structure, however, remained unknown until 1952,[14] while its total synthesis was achieved in 1969.[15,16] It was not until 1995 that the 2-(morpholin-4-yl)ethyl ester of mycophenolic acid (a prodrug of **1**) was approved by the US Food and Drug Administration, although not as an antibacterial drug but rather as an
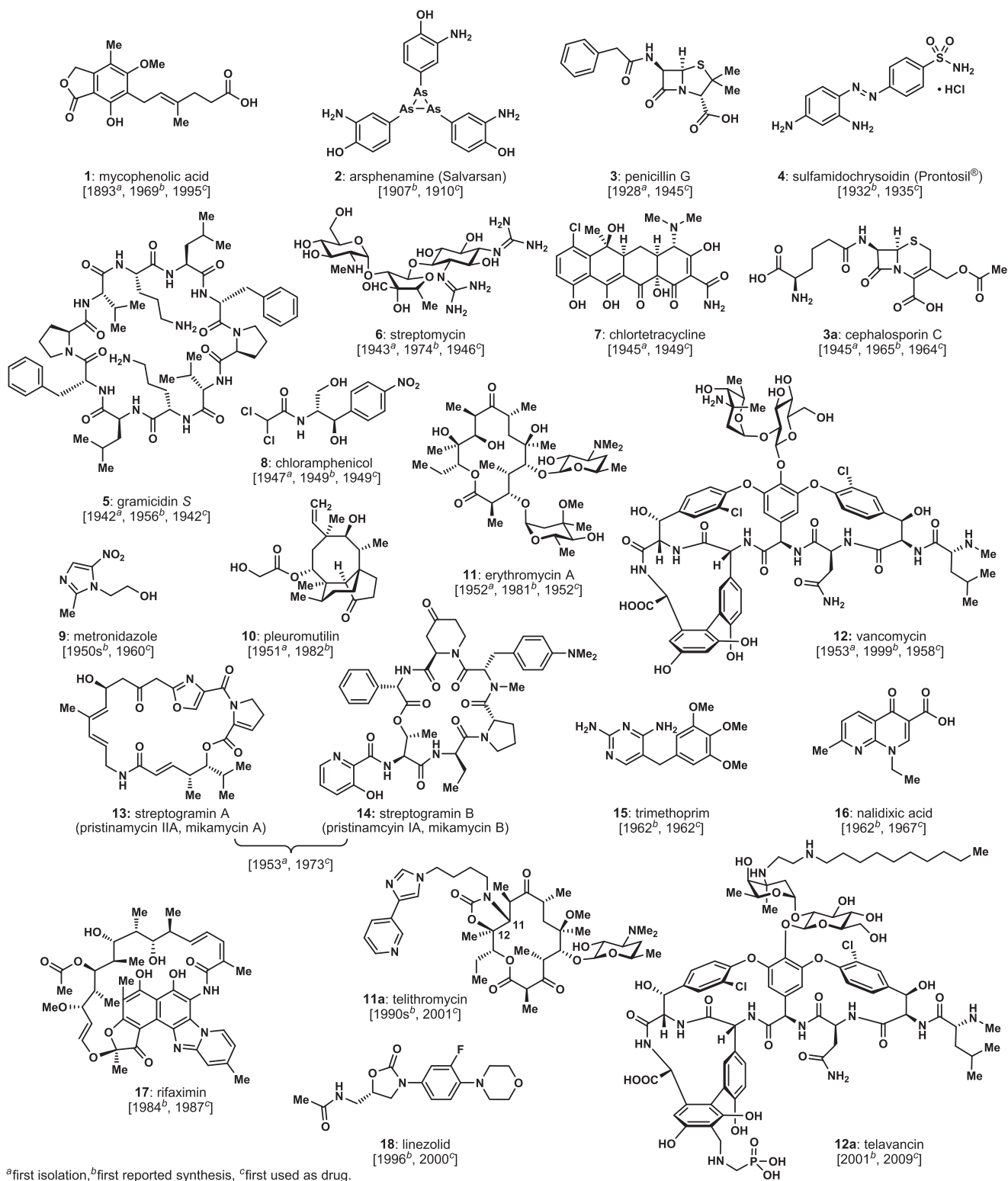
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Figure 1 Historic discoveries and developments of antibiotics as drugs.

[a]first isolation,[b]first reported synthesis, [c]first used as drug.

immunosuppressant to prevent transplant rejection (through a mechanism involving the inhibition of DNA biosynthesis).[17]

The first decade of the twentieth century witnessed the emergence of the first man-made antibacterial agent, arsphenamine (Salvarsan, **2**, Figure 1). Synthesized by chemist Alfred Bertheim in the laboratories of Paul Ehrlich and approved in 1910 as a drug,[18] the story of Salvarsan began when the immunologist Ehrlich was introduced to cell staining by his cousin Carl Weigert, who demonstrated that aniline dyes can be used for this purpose in histology.[19–22] Ehrlich was fascinated by the fact that selective staining of different cell types,

including bacteria, was possible, and this led him to contemplate the idea of *chemotherapia specifica* and to propose his famous concept of the *Zauberkugel* (magic bullet) that continues to inspire biologists and chemists alike today. Starting in 1906, Ehrlich and his group started to synthesize and test compounds derived from arsanilic acid (atoxyl) against bacterial strains. In 1909, a year after Ehrlich shared the Nobel Prize in Physiology or Medicine with Ilya Mechnikov for their work on immunology, he and his assistant Sahachirō Hata found that compound 606 was effective against bacterial strains of *Spirochaetes*, and against protozoa *Trypanosoma*, findings that led to clinical trials, and eventual marketing of the drug for the treatment of syphilis, a disease caused by bacterium *Treponema pallidum*. For nearly 40 years Salvarsan was the standard therapy for this disease, with new versions (Neosalvarsan and Solu-Salvarsan) being introduced later as improved drugs,[23–26] allowing for easier application and causing less side effects. Interestingly, the precise molecular structure of arsphenamine remained vague, with Ehrlich assuming it was dimeric in nature with the two As-atoms doubly bonded. A recent mass spectrometric investigation, however, revealed both trimeric (see **2**, Figure 1) and pentameric species.[27]

Staphylococci, a summer sojourn, and the serendipitous scrutiny of a Scottish scientist are the three ingredients that led to one of the most impactful discoveries in the history of medicine: penicillin (**3**, Figure 1). After returning from his vacation in September 1928, Alexander Fleming, a bacteriologist at St Mary's Hospital, went back to his laboratory in Paddington (Westminster, London) and found a *Staphylococcus aureus* colony he had left on his bench contaminated with a fungus (*Penicillium notatum*, now *P. chrysogenum*) in an intriguing pattern. This finding had occurred already to other scientists before him, but Fleming did not dispose of the contaminated petri dish without further examination. He realized that in proximity to the mold, the *Staphylococci* underwent lysis while colonies further away appeared to be normal and unaffected. Fleming went on to grow the fungus as a pure culture and to treat several pathogenic bacterial strains with its extract to descry similar effects as previously observed with the *Staphylococci*, especially for Gram-positive ones. He concluded that the fungus must have excreted a substance that killed the bacteria, and named it penicillin in March 1929.[28] Fleming attempted early on to collaborate with a number of researchers in an effort to isolate and purify the unknown substance, hoping to demystify the puzzle of penicillin, but without success. In 1939, pathologist Howard Walter Florey and biochemists Ernst Boris Chain and Norman Heatley at Oxford University started to work on the isolation of the mystery substance, and within a year managed to test the isolated compound in a mouse model, revealing phenomenal results. In early 1941, the first human, policeman Albert Alexander who was suffering from a severe face infection causing a sepsis, was treated with penicillin. His condition improved significantly during the first five days of therapy, but unfortunately the limited drug supply run out and the patient died from the prevailing sepsis. However, it became clear to the clinicians that penicillin was a powerful drug with auspicious properties. Later, and after painfully securing adequate supplies of the drug, several other patients were treated successfully and with full recovery. Out of necessity, and motivated by the outbreak of the Second World War, the collaborative Anglo-American penicillin project was launched. Its aim was to produce sufficient amounts of the new antibiotic for the needs of the allied forces fighting and dying from infections in the battle fields of Europe, Africa and Asia. In 1945, penicillin became available to the public and was no longer an exclusive medication for the military, consummating in the transformation of an allegedly failed experiment to a life-saving drug for millions. The same year,

the structure of penicillin was elucidated through X-ray crystallographic analysis by Dorothy Crowfoot Hodgkin,[29] allowing it to be classified as the first member of the β-lactam family of naturally occurring antibiotics. Later that year, Alexander Fleming, Ernst Boris Chain and Howard Walter Florey were jointly awarded the Nobel Prize in Physiology or Medicine for the discovery of penicillin and its curative effect in various infectious diseases. The first total synthesis of a member of the penicillin family (that is, penicillin V) was reported in 1957 by John Sheehan.[30,31] It featured five linear steps and resulted in 1.4% overall yield of the product. Even though not useful for industrial production, the synthesis provided the first opportunity to prepare analogs of penicillin from 6-aminopenicillanic acid, an intermediate that emerged from the endeavor. In contrast to the mode of action of the sulfonamides, penicillin and its other β-lactam siblings act bactericidally and, through a mechanism that involves inhibition of serine-type D-alanyl-D-alanine carboxypeptidase, an enzyme crucial to the peptidoglycan layer of the bacterial cell wall.

Exerting its antibiotic activities (bactericidal) through the same mode of action as penicillin, cephalosporin C (**3a**, Figure 1), the first member of the cephalosporins (a sub-class of β-lactams), was originally discovered in 1945 by Giuseppe Brotsu[32,33] from *Cephalosporium acremonium* (now *Acremonium chrysogenum*). Cephalosporin C was rediscovered in 1955[34] and structurally elucidated by chemical degradation studies[35] and X-ray crystallographic analysis in 1961.[36] Its first total synthesis was achieved by Robert B. Woodward in 1965 and reported in his Nobel lecture before it was published in 1966.[37] Although cephalosporin C did not become a clinical agent, its structure inspired numerous synthetic efforts that led to designed analogs from which emerged powerful antibacterial drugs, with cefalotin being the first clinically approved cephalosporin antibacterial agent.

The next advance in the antibiotics area was marked by the discovery and deployment of the sulfonamide drugs. First synthesized as a dye by Fritz Mietzsch and Josef Klarer at Bayer in December 1932, sulfamidochrysoidin (**4**, Prontosil, Figure 1) was recognized as an antibacterial agent by Gerhard Domagk,[38] a fortunate event that led to its marketing as a drug in 1935, and a Nobel Prize in Physiology or Medicine to him in 1939. Before the Nobel Prize and the approval of the drug, Domagk and his family were rewarded with the saving of the life of his 6-year-old daughter who was suffering from a life-threatening sepsis. He decided to use the then still experimental drug, code named D 4145 (Streptozon), to treat her, a decision that must have given him the most happiness of all his prizes. In the same year that Prontosil was approved, Jacques and Thérèse Tréfouël, Federico Nitti, and Daniel Bovet at the Pasteur Institute determined that sulfamidochrysoidin acts as a prodrug, releasing *in vivo* the active antibacterial agent *p*-aminophenylsulfonamide (through reductive cleavage of the diazo linkage).[39] The latter compound, however, had already been synthesized by the Austrian chemist Paul Gelmo in 1908,[40] and hence this molecular entity and compounds releasing it were not patentable. This predicament led to a surge of activities in the 1930s and 1940s, primarily in Europe and the USA, that resulted in the discovery and development of several new and patentable drugs. The sulfonamides are bacteriostatic agents, acting through a mechanism that involves inhibition of folic acid biosynthesis in bacteria, leaving normal human cells unharmed since the latter have no folic acid biosynthesis machinery.[41]

A new chapter on antibiotics was opened in 1939[42–44] when French microbiologist René Dubos isolated tyrothricin[45–47] from *Bacillus brevis*. It was later shown that tyrothricin was a mixture consisting of gramicidin D (itself a mixture of gramicidins $A_{1/2}$–$C_{1/2}$, all linear

pentadecapeptides differing at positions one and/or eleven of the amino acid sequence) and tyrocidine (a mixture consisting of tyrocidines A–D). In 1942, Soviet biologist Georgyi Frantsevich Gause and his wife Maria Brazhnikova discovered another gramicidin from the same bacterial strain (*Bacillus brevis*) and named it gramicidin S (**5**, Figure 1).[48] A symmetrical macrocyclic homodetic decapeptide [cyclo (D-Phe-Pro-Val-Orn-Leu-)$_2$], gramicidin S is also classified as a member of the polypeptide antibiotics mentioned above but differs from the polymyxins, another family of cyclic decapeptides, in that it lacks the characteristic extended lipophilic side chain of the latter. Gramicidin S was found to be active against Gram-positive and some Gram-negative bacteria. It was used for the first time in the year of its discovery (1942) in military hospitals, and starting in 1943 in the eastern front during the Second World War, making it the Soviet counterpart of penicillin.[49] And, interestingly just like penicillin, the structure of gramicidin S was solved in Great Britain, this time by Richard Synge who employed classical derivatization/degradation methods,[50–52] and Hodgkin who used X-ray crystallography to decipher the structure,[53] after the Red Cross brought a sample from Moscow.[49] In 1964, Hodgkin was awarded the Nobel Prize in Chemistry for her determinations by X-ray techniques of the structures of important biochemical substances. The total synthesis of gramicidin S was reported in 1957 by Robert Schwyzer[54,55] following previously published methods.[56] The clinical application of gramicidin S is limited to topical infections (for example, eye, ear) due to its undesired hemolytic properties originating from membrane lysis.[57] Its mechanism of action as a bactericidal antibiotic relies on its ability to form ion channels in the bacterial cell wall upon dimerization, causing collapse of the electrochemical gradient.[58,59]

Another important milestone in the history of antibiotics was the discovery of streptomycin (**6**, Figure 1) from *Actinomyces griseus* (now *Streptomyces griseus*), the first aminoglycoside antibiotic, in 1943 by Albert Schatz and Selman Waksman.[60,61] Significantly, it was shown that, in addition to being active against Gram-positive strains, the newly isolated antibiotic was also potent against multiple Gram-negative bacteria as well as against *Mycobacterium tuberculosis*.[62] Since the latter strain was not affected by penicillin, streptomycin was meeting an unmet medical need, offering physicians and patients suffering from tuberculosis hope for a potential cure for the first time.[63] The development of streptomycin as a powerful drug against this dreaded disease eventually led to the Nobel Prize in Physiology or Medicine to Waksman in 1952, but not without creating a bitter dispute between Waksman and Schatz over their individual contributions and the wealth of royalties from the streptomycin patent.[64,65] The first human cure of an infection by streptomycin was reported in 1944, and was followed by the successful treatment of a patient suffering from tuberculosis 2 months later.[65] Upon completion of successful clinical trials, the drug was approved for broad clinical use in 1946. After full structural elucidation of streptomycin,[66–68] the first total synthesis of the natural product was achieved in 1974 by Sumio Umezawa et al.,[69] the group having first completed the synthesis of dihydrostreptomycin.[70] The mode of action of streptomycin (bactericidal) involves inhibition of bacterial protein biosynthesis[71] through binding to the 30S subunit of the prokaryotic ribosome.[72]

The first member of one of the most important classes of antibiotics, that of the tetracyclines, was unearthed in 1945, being isolated from *Strep. aureofaciens* by American plant physiologist Benjamin M. Duggar. It was originally named aureomycin due to its golden color, but is known today as chlortetracycline (**7**, Figure 1).[73] In 1948, it was approved for clinical use as a broad spectrum antibiotic against both Gram-positive and Gram-negative bacteria.[74] Soon

thereafter, several other members of the tetracycline family were isolated at Pfizer (New York, NY, USA) by a group headed by Alexander C. Finlay, including oxytetracyclin (from *Strep. rimosus*) and tetracycline (from *Strep. aureofaciens*).[75] The gross structure of chlortetracycline was first determined by Woodward through chemical derivatization methods in 1954.[76] This was followed by X-ray crystallographic studies in 1959[77,78] and 1963[79] which led to the elucidation of the relative stereochemical structure of chlortetracycline. Although a total synthesis of chlortetracycline (**7**), oddly enough, has not been reported as yet, a formal total synthesis was reported in 1973 by Hans Muxfeldt et al.[80,81] The formal total synthesis of tetracycline (7-dechloro-**7**) itself was achieved by Mikhail M. Shemyakin in 1967[82–85] while Woodward had already succeeded in synthesizing the first biologically active tetracycline derivative in 1962.[86,87] Furthermore, several other tetracyclines have been synthesized over the years.[88–98] Like streptomycin, the tetracyclines exert their bacteriostatic properties through a mechanism involving inhibition of bacterial protein biosynthesis by binding to the ribosome at the 30S site.[74] Numerous tetracycline derivatives have been synthesized in efforts to overcome the emergence of resistance to the original drugs, including tigecycline (**7a**, Figure 2a), which was approved by the US Food and Drug Administration in 2005.[99]

Before the end of the decade of the 1940s, yet another original antibiotic made its entrance, chloramphenicol (**8**, Figure 1), a member of the phenylpropanoids. Discovered initially by John Ehrlich in 1947 (from *Strep. venezuelae*),[100] and shortly thereafter and independently by David Gottlieb et al.[101,102] and Umezawa et al.,[103] chloramphenicol proved to be a broad spectrum antibiotic and was used clinically for the first time, and with remarkable success during the 1947 typhus epidemic in Bolivia.[75] Its chemistry was investigated in 1948[104] and its structure was proposed[105] and confirmed by total synthesis[106] in 1949. Chloramphenicol was approved for clinical use as an antibacterial agent in the same year and became one of the best-selling drugs at the time. Its mechanism of action (bacteriostatic) involves binding to the 50S subunit of the bacterial ribosome, resulting in protein biosynthesis inhibition.[107,108] It is notable that chloramphenicol became the first naturally occurring antibiotic produced by chemical synthesis, rather than fermentation. This may be a reflection of a combination of factors, including its relative structural simplicity and the increasing capabilities of organic synthesis at the time.

Besides the rush for the discovery of antibiotics from nature triggered by penicillin's spectacular success, the 1950s saw the re-emergence of interest in synthetic designed antibacterial agents such as Salvarsan and Prontosil, two of the very first antibacterial agents to be introduced for clinical use. The opportunity arose when a rather simple natural antibiotic, azomycin (2-nitroimidazole) was originally discovered (1953)[109] and structurally elucidated (1954).[110] Azomycin proved too toxic for clinical use, but nevertheless inspired scientists at Rhône-Poulenc in France as a lead compound to design and synthesize analogs of it, from which metronidazole (**9**, Figure 1) was selected as a drug candidate for further development due to its high potency and low toxicity.[111–113] Metronidazole was approved as a clinical agent in France in 1960 and in the United States in 1963.[113] It exerts its antibacterial properties through a distinctively different mechanism than the other antibiotics discussed above in that it damages directly the genetic material of the bacteria through intracellular generation of nitroso radicals.[114] These reactive nitroso radicals are produced reductively through a single-electron transfer to the nitro group. This mechanism is expected to operate especially in anaerobic bacteria such as *Bacteroides*, *Clostridium*, *Helicobacter* or *Campylobacter*, but hardly in human cells, endowing the drug with the

desired bactericidal properties against bacteria without side effects to the patient.[114]

Another inspirational antibiotic that did not actually make it to the clinic is pleuromutilin (10, Figure 1).[115] Isolated in 1951 by Frederick Kavanagh from basidiomycetes *Pleurotus passeckerianus* (now *Clitopilus passeckerianus*) and *Pleurotus mutilus* (Fr.) Sacc (now *Clitopilus scyphoides*).[116,117] Found active predominantly against Gram-positive bacteria, but also against a number of Gram-negative, pleuromutilin was structurally elucidated in 1962 after extensive chemical studies[118] conducted independently at Manchester (UK)[119,120] and Zürich (Switzerland).[121,122] Its structure was confirmed by X-ray crystallographic analysis and ORD studies in 1968.[123] Pleuromutilin was synthesized first, in racemic form (1982),[124,125] and thence enantioselectively (2013) by David J. Procter.[126] Numerous semisynthetic analogs of pleuromutilin have been synthesized and tested, one of which, retapamulin (carrying a thiotropine moiety at the glycolic acid side chain), was approved as a clinical antibacterial drug in 2007 in the United States. The mechanism of (bacteriostatic) action of the pleuromutilin family of antibiotics is based on their ability to bind the 50S subunit of the bacterial ribosome.[127]

The 1950s would usher in a new crop of novel antibiotics, among the most prominent of which were the erythromycins. Endowed with complex 14-membered macrolide structures, erythromycins A and B were isolated by Eli Lilly (Indianapolis, IN, USA) scientists led by James M. McGuire in 1952 from *Saccharopolyspora erythraea*, found in a soil sample imported to the USA from the Philippines. Erythromycins A and B were marketed in the same year under the name Ilotycin[128,129] as a mixture of compounds. This mixture was later separated and the main components were renamed as erythromycins A–D, with A being the most abundant. The molecular structure of erythromycin A (11, Figure 1) was first determined in 1957[130–138] with the X-ray crystallographic analysis of the dihydrate reported in 1997.[139] The total synthesis of erythromycin A was accomplished and published by the Woodward group (posthumously for Woodward) in 1981.[140–142] It was preceded by the total synthesis of erythronolide B (the aglycon of erythromycin B) which was accomplished by the Corey group in 1978.[143,144] The mechanism of action of the erythromycins (bacteriostatic or bactericidal, depending on medicated strain and concentration) involves binding to the 50S subunit of the ribosome and inhibition of bacterial protein biosynthesis.[145,146]

Soon after the discovery of the erythromycins, another family of powerful antibiotics, that of the glycopeptides, was discovered. The first member of the class was isolated in 1953 from *Strep. orientalis* (now *Amycolatopsis orientalis*) found in a soil sample originating from Borneo.[147] Later named vancomycin (from its ability to vanish bacteria) (12, Figure 1), this legendary antibiotic was found to be especially active against Gram-positive bacteria, and most significantly against penicillin-resistant *Staphylococci*. Vancomycin was approved as a clinical agent for the treatment of bacterial infections in 1958. Its use
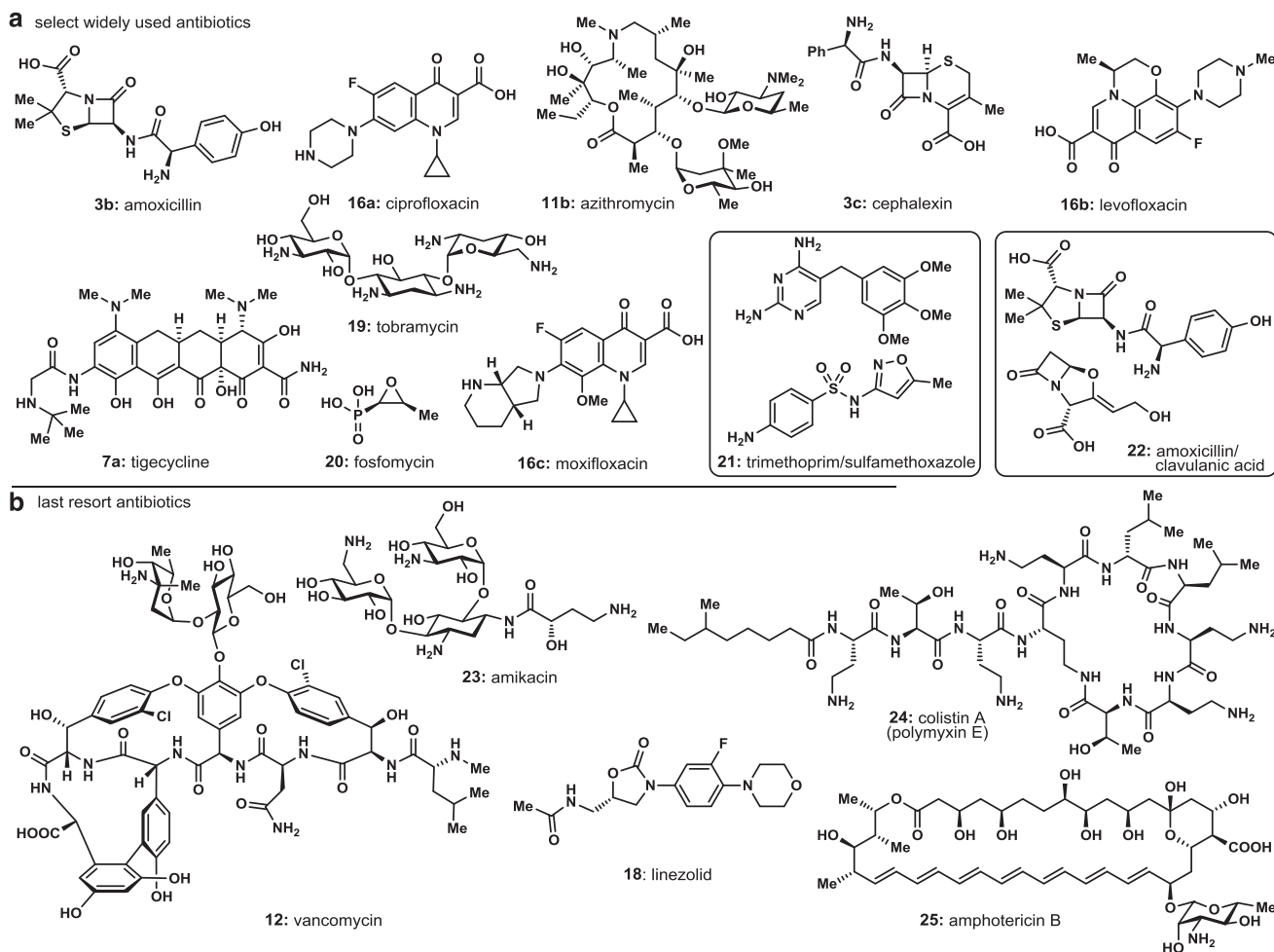

Figure 2 Select widely used (a) and last resort (b) antibiotics.

was later decreased in favor of other antibiotics for toxicity reasons,[148] although it continues to be employed in severe cases against drug-resistant bacteria. The quest for the structural elucidation of vancomycin involved chemical studies (1977)[149–151] and X-ray crystallographic analysis, first of its degradation product CDP-1 (1978)[152] and thence the natural product itself (1996).[153] The first total synthesis of the aglycon of vancomycin was accomplished in 1998 by the Evans group[154,155] and our group.[156–158] The total synthesis of vancomycin itself was achieved in 1999 by our group.[159] The mechanism of bacteriostatic action of vancomycin resembles that of the β-lactams in that it interferes with the construction of the bacterial cell wall. It exerts its disruptive activity by binding to the D-Ala-D-Ala unit of a pentapeptide moiety essential for the knitting of the peptidoglycan network of the cell wall, thereby hindering its proper formation.[160]

In the same year that vancomycin was discovered, another new antibiotic was isolated, ushering in the family of streptogramins. The eponymous compound, streptogramin was isolated as a secondary metabolite from a then unknown *Streptomyces* spp. (later named *Strep. graminofaciens*) and found to be especially active against Gram-positive bacterial strains.[161,162] It was subsequently found that streptogramin is a mixture of two distinct components, streptogramin A (also named pristinamycin IIA, virginiamycin M$_1$, ostreogrycin A, mikamycin A, **13**, Figure 1) and streptogramin B (also named pristinamycin IA, virginiamycin S$_1$, mikamycin B, vernamycin B$_\alpha$, **14**, Figure 1).[163] The structures of both components were elucidated during the mid-1960s[164–166] and confirmed by X-ray crystallographic analysis in 1974[167] (streptogramin A) and in 1990[168] (streptogramin B). Being comprised of two structurally unrelated, but concurrently produced compounds by a single species and classified as groups A and B, this paradigm represents a special case characteristic of the streptogramins. Substances of group A feature a 23-membered polyunsaturated macrolactone framework while members of group B possess a cyclic hexa- or hepta depsipeptide scaffold. Remarkably, the streptogramins demonstrated strong synergistic effects when administered in combination.[163,169] The mechanism of their antibacterial action relies on sequential binding of first streptogramin A, and then B to the 50S subunit of the bacterial ribosome, thus inhibiting protein biosynthesis. When applied as single substances, each compound acts bacteriostatically, but when used together they develop bactericidal activities.[170,171] For a long period of time, the streptogramins were mostly used in the agricultural sector as growth promoters. They were first launched in 1973 (as a 1:1 mixture of **13** and **14**) as pristinamycin in Europe for the treatment of infections caused by *Streptococci* and *Staphylococci*. Later, studies at Rhône-Poulenc Rorer directed toward improving the water solubility of streptogramins A and B led to the semisynthesis of quinupristin and dalfopristin, respectively, two analogs that were successfully developed in a 3:7 combination as an antibacterial drug[172] and approved by the US Food and Drug Administration in 1999. This combination medication is used especially in severe cases of infections associated with vancomycin-resistant *Enterococcus faecium*. Since their discovery several synthetic approaches toward the total synthesis of select members of the streptogramin family have been reported,[173–179] with some successfully reaching their targets.[180–185]

Trimethoprim (**15**, Figure 1) is another early unnatural antibiotic. Synthesized in 1962, this compound was found to exhibit strong antibacterial activities against both Gram-positive and Gram-negative strains.[186] In the same year, the first successful clinical data were reported,[187] and included synergistic effects when the drug was administered to patients together with sulfonamides.[188] Trimethoprim was marketed in 1974 as co-trimoxazole, a combination medication

consisting of one part trimethoprim to five parts sulfamethoxazole, and later also as a single molecular entity drug.[189] Trimethoprim acts bacteriostatically through inhibition of dihydrofolate reductase, an enzyme involved in the bacterial folic acid biosynthesis. It has the distinction of being the first member of the dihydrofolate reductase inhibitors.[190]

Nalidixic acid (**16**, Figure 1) was also synthesized in 1962 and found to be highly potent *in vitro* and *in vivo*,[191] its activity being most pronounced against Gram-negative bacteria such as *Escherichia coli*, *Proteus mirabilis* and *Shigella flexneri*, while exhibiting low toxicity.[191] This discovery turned out to be highly significant in that it led to the emergence of quinolones, an important family of synthetic antibiotics whose structures are related to quinoline.[192] Depending on the concentration, nalidixic acid can act as a bacteriostatic or bactericidal agent.[193] Its biological target is topoisomerase II,[194,195] an enzyme catalyzing the ATP-dependent negative supercoiling of double-stranded closed-circular DNA,[196] thus causing interruption of bacterial DNA biosynthesis.[197] Nalidixic acid was launched as a clinical antibacterial agent in 1967,[192] but was later replaced by fluoroquinolones like ciprofloxacin (**16a**, Figure 2a) which proved superior as drugs.

The ansamycins[198] are a group of macrolactam antibiotics whose first members were reported in 1959 by Piero Sensi, Maria T. Timbal and Pinhas Margalith.[199] Named rifamycins, these early ansamycins were isolated from *Strep. mediterranei* (now *Amycolatopsis rifamycinica*). The structures of a number of them were elucidated through chemical degradation studies in 1964,[200] while that of rifamycin B was determined in the same year by X-ray crystallographic analysis.[201,202] Naturally occurring rifamycin B failed to become a drug, but one of its slightly modified semisynthetic versions (that is, rifamycin SV) was approved as a clinical antibacterial agent especially effective against tuberculosis,[203] albeit intravenously delivered. Further studies led to improved and orally active drugs,[204] one of them being rifaximin (**17**, Figure 1).[205] The latter is specifically used to treat colon-related infections without significant systemic side effects due to its poor absorption properties upon oral administration,[204] and thus only effective in the intestinal lumen. The bactericidal action of the rifamycins originates from their ability to inhibit bacterial DNA-dependent RNA biosynthesis, which in turn inhibits protein biosynthesis.[206,207]

After the introduction of the quinolones in the 1960s, it took, surprisingly, more than two decades for the next class of antibiotics to be ushered into the clinic. The story of linezolid (**18**, Figure 1) goes back to at least the 1970s when certain oxazolidinones were recognized by DuPont scientists as possessing antibacterial properties.[208,209] It was, however, a group at the Upjohn pharmaceutical company (Kalamazoo, MI, USA)[210,211] that discovered and developed linezolid as a clinically used antibacterial agent,[212] approved in the United States in 2000.[210] Linezolid is particularly effective in treating infections caused by Gram-positive bacterial strains such as *Streptococci* and *Enterococci*, especially in cases where other antibiotics failed. The mechanism of action of this bacteriostatic last resort antibiotic[213] involves binding to the 50S subunit of the ribosome and inhibition of bacterial protein biosynthesis.[214]

The so-called ketolide family of antibacterial agents arose from the erythromycin class through semisynthetic studies. It was scientists at Roussel-UCLAF in France who prepared compound RU-66647 from erythromycin A (**11**, Figure 1) in 1997 and showed it to be active against bacteria, especially Gram-positive strains.[215] Later named telithromycin (**11a**, Figure 1), this first member of the ketolide family was successfully developed and launched as an antibacterial drug,

first in Europe (2001) and thence in the United States (2004).[216] Although derived from erythromycin A, telithromycin and its siblings structurally differ, significantly, from the latter in that they lack the L-cladinose sugar moiety at C3, exhibiting instead a keto group at that position and, thereby, improving the drug stability toward acidic conditions. In addition, the ketolides include in their structures a cyclic carbamate moiety fused onto the macrolide ring at C11 and C12, with the N-atom originating from replacement of the O-atom of the erythromycin precursor of the molecule. Telithromycin specifically includes an alkyl side chain on the carbamate nitrogen ending with two N-heterocyclic rings.[217] Its mechanism of action resembles its precursor compound, erythromycin A, namely inhibition of bacterial protein biosynthesis through binding to domain II of the 23S rRNA site of the ribosome.[218] Telithromycin generally acts bacteriostatically, but also shows bactericidal properties at higher dosings.[219]

Just like telithromycin, telavancin (12a, Figure 1) was derived semisynthetically from an abundant naturally occurring antibiotic, in this case vancomycin (12, Figure 1).[220] It is a newer antibacterial drug belonging to the family of lipoglycopeptides, the name being derived from the lipid chain attached on the glycopeptide domain. In addition to the lipophilic decylaminoethyl side chain attached onto the terminal carbohydrate moiety, telavancin also features a hydrophilic phosphonomethyl aminomethyl substituent on the biphenyl domain of vancomycin.[221] Its bactericidal properties toward several Gram-positive strains, including methicillin-resistant Staph. aureus (MRSA),[222] derive from a dual mechanism of action. On one hand, it hinders the peptidoglycan construction by binding to its D-Ala-D-Ala dipeptide terminus, thus weakening the bacterial cell wall, and on the other it interferes with the cell wall precursor lipid II, thereby causing membrane depolarization.[223] Telavancin was approved for clinical use in the United States in 2009.[223]

Today, more or less severe infections caused by microbes are alleviated with a variety of antibiotics, albeit not always successfully, from the large arsenal we have come to discover and develop from nature and the laboratory. Among the most prevalent of these drugs are amoxicillin (3b), ciprofloxacin (16a), azithromycin (11b), cephalexin (3c), levofloxacin (16b), tobramycin (19), tigecycline (7a), fosfomycin (20), moxifloxacin (16c), trimethoprim/sulfamethoxazole (21) and amoxicillin/clavulanic acid (22), all shown in Figure 2a. As a last line of defense, humanity has vancomycin (12, Figure 2b) and its analog telavancin (12a, Figure 1), amikacin (23, Figure 2b), linezolid (18, Figure 2b), colistin (polymyxin E, 24, Figure 2b), and amphotericin B (25, an antifungal agent, Figure 2b). Isolation and synthetic organic chemists have played a major role in the discovery and development of these life-saving antibiotics. To be sure they will continue to be protagonists in our seemingly never ending fight against pathogenic microbes.

ANTIBIOTIC RESISTANCE

Antibiotic resistance is apparently an inevitable consequence of the use of antibiotics against bacteria, a war waged against them by us but also, and for a much longer time, by bacteria against each other, ironically using the same weapons in both cases. That means that bacteria had the chance to develop resistance through various mechanisms to evade the action of these antibiotics which we isolated from them in the first place.[224] This explains the so-termed primary resistance of certain bacterial strains that are often unaffected by some antibiotics, whereas they are susceptible to others (for example, Gram-negative vs Gram-positive).[225] More dangerous is secondary resistance, the acquired ability of bacteria to withstand the action of antibiotics that were once effective against them. Such resistance may be developed through

mutations involving genetic changes that result in inactivation of the drug (for example, β-lactamases), modification of previously essential biosynthetic pathways, or alteration of the target site (cell wall construction, folic acid biosynthesis, protein biosynthesis). Expulsion of the drug from the cell (efflux) is another mechanism bacteria can use to evade the action of antibiotics. These genetic changes can later spread through lateral gene transfer via transformation, transduction or conjugation.[226–229] It was as early as the 1940s when the problem of resistance development and the problems of self-medication were discussed in public,[230] but even today in many countries antibiotics are available over the counter without prescription and are extensively used in veterinary context worldwide. Particularly dangerous are the drug-resistant bacterial strains collectively known as ESKAPE pathogens (vancomycin-resistant Enterococci, MRSA, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter spp.), which can cause difficult to treat nosocomial infections.[231] Although the development of resistance is inevitable, its spreading is not and that is where we can make a difference.

Bacteria surpass us massively in numbers, total mass, replication time, and time of existence on earth.[232] Our inability to eradicate their pathogenic strains is, therefore, not surprising. All we can do at present is to be vigilant and alert to stay ahead of them in our efforts to avoid catastrophic epidemics and deaths by them. Antibiotic resistance is a continuous threat to society as proven before and after penicillin's discovery, whose action on certain bacteria became obsolete even before its development as a drug during the Second World War. Certain dangerous bacterial strains developed resistance to almost all approved antibacterial drugs since (such as tetracyclines, erythromycins, methicillin, gentamicin, vancomycin, imipenem, ceftazidime, levofloxacin, linezolid, daptomycin and ceftaroline), either immediately or shortly after their approval.[233] And to exacerbate the situation, the number of new antibacterial drugs approved after the golden age of antibiotics (1940s to 1960s) has been steadily declining. It was only until recently, and after a lean time period of more than 30 years, that a new antibiotic, teixobactin (26, Figure 3), was discovered in 2015 and found to be impressively active against Gram-positive bacteria. Affecting the bacterial cell wall biosynthesis[234] and showing promising properties against resistance development, this new antibiotic was also accessed by total synthesis in 2016.[235] Even more recently, another new antibiotic, lugdunin (27, Figure 3), was isolated from Staph. lugdunensis and structurally elucidated,[236] revealing its macrocyclic peptide nature. Its total synthesis confirmed its thiazolidine-containing constitution. The prevailing doctrine of using overwhelming force of antibiotics (larger doses and prolonged times) to eradicate all pathogenic bacteria in the patent first introduced by Fleming has recently being challenged. The new theory suggests that just the opposite might by the right strategy, as lower doses may be a wiser tactic based on the competition of non-resistant bacteria and drug-resistant bacteria allowing the patient's immune system to finish the job of killing them both.[233] This may depend on the drug used, however, and the final verdict is not in yet as further research is on the way.

According to a recent review on resistance to antimicrobial drugs by O'Neil,[237] on behalf of the British government and the Wellcome Trust, 700 000 people die every year from infections caused by drug-resistant pathogens, and the number can reach 10 million by 2050 if nothing is done to stop the trend. According to a survey published in 2013[238] approximately one-fourth of the 40 million people with respiratory diseases were prescribed antibiotics between 2007 and 2009 in the United States, albeit only rarely indicated for their specific condition and in 78% of these cases broad spectrum

versions were recommended, despite the risk for more severe side effects.[239] Here lies the paradox: a chance to be healed or to heal compels the patient or the doctor to ask or prescribe an antibiotic to an individual for the possibility of a cure without concern of spreading drug resistance.

Improvements in this regard can be achieved with rapid testing first, and then deciding whether an antibiotic will help the patient or not. And it will be even more helpful if the on-the-spot testing could reveal the type of antibiotic to be used effectively. There is no question that we are in a saddle war with pathogenic bacteria, although we are cognizant that we need bacteria around us as essential symbiotic partners. A response is necessary in order to avoid major catastrophes from occurring in the future as multiple indicators predict they will. Remedies to stop the antibiotic resistance problem include: (a) stop the use of antibiotics as growth hormones in animals; (b) develop and use vaccines where appropriate for prophylaxis as opposed to treatment; (c) enforce better hygiene practices in clinics and hospitals; (d) stop the prescribing of antibiotics for viral diseases before proper diagnosis; and (e) encourage innovation to develop new antibiotics through incentives to academia and industry. Suggestions to achieve the latter initiative have been made not only for increased funding for research and development but also for 'entry rewards' that will guarantee to the investors substantial initial financial rewards in addition to sales.

HIGHLIGHTS OF SELECTED TOTAL SYNTHESES OF ANTIBIOTICS

The importance of natural products and their derivatives in medicine has been amply demonstrated through their direct clinical use, but also as biological probes that unravel biological pathways and targets for pharmacological intervention. The success of penicillin intensified the search for new antibiotics and other bioactive molecules from nature as evidenced from the postwar World War II surge in the discovery of such agents of which many became drugs to treat bacterial infections and cancer,[240] among other diseases. Many became challenging targets for synthetic organic chemists because of their unusual molecular architectures and the opportunities they presented for discovery and invention of new synthetic strategies and technologies for broader use. Figure 4 depicts a number of selected naturally occurring antibiotics synthesized in our laboratories during the last few decades. Herein, we highlight the total syntheses of some of these antibiotics [that is, antibiotic X-14547A (indanomycin, 28), efrotomycin (29), amphotericin B (25), vancomycin (12), everninomicin 13,384-1 (ziracin, 30), coleophomones B and C (31 and 32), thiostrepton (33), abyssomicin C and atrop-abyssomicin C (34 and 34′), marinomycins A, B and C (35, 36, 37), platensimycin (38), platencin (39), the alleged rugulin structure (40),

antibiotic BE-43472B (41), hirsutellone B (42), epicoccin G, 8,8′-epi-ent-rostratin B and emethallicin E (43, 44 and 45), viridicatumtoxin B (46), and antibiotic CJ-16,264 (47)].

Antibiotic X-14547A (indanomycin)

Isolated from Strep. antibioticus NRRL 8167,[241,242] antibiotic X-14547A (28, Figure 5a) belongs to the ionophore class of antibiotics and forms, interestingly, a 2:1 (acid:base) salt with (R)-(+)-1-amino-1-(4-bromophenyl)ethane. The latter yielded suitable crystals for X-ray crystallographic analysis that led to the complete structural elucidation of the molecule.[242] Its properties include antibacterial activities against Gram-positive bacteria, antihypertensive and antitumor activities and growth promotion in ruminants.[241–244] Its enantioselective total synthesis was achieved in our laboratories in 1981.[245–247] The employed retrosynthetic analysis is shown in Figure 5a, whereas highlights of the devised total synthesis are summarized in Figure 5b. The initial synthetic maneuvers were the conversion of (−)-diethyl tartrate (48) to (S,S)-epoxide 49 (chiral pool) and the asymmetric alkylation of SAMP-hydrazone 54 to afford aldehyde 55 (asymmetric synthesis). These two intermediates were converted to the required tetrahydropyran fragment 53 (through intermediates 50–52) and tetrahydroindan 58 (through intermediates 56–57), respectively. These intermediates were coupled to afford advanced precursor 59, which was converted to carboxylic acid 60. The latter was transformed to antibiotic X-14547A (28) through a sequence involving conversion to the corresponding 2-pyridinylthioester, its reaction with pyrrolylmagnesium chloride to install the 2-ketopyrrole system, and methyl ester hydrolysis. Several other synthetic approaches[248–250] and total syntheses[251–255] of antibiotic X-14547A have been subsequently reported.

Efrotomycin

Efrotomycin (29, Figure 6a) (isolated from Nocardia lactamdurans)[256] and its aglycon (aurodox or goldinomycin) are members of the elfamycin family of antibiotics. Their biological actions include activities against bacilli and dysentery, as well as growth promoting properties in ruminants.[257–259] The structure of efrotomycin contains two glycoside bonds, one amide linkage, a number of olefinic units, and several other interesting structural motifs. The devised total synthesis of this antibiotic was based on the retrosynthetic disconnections indicated in Figure 6a. It proceeded from key building blocks 61, 62, 64, 68 and 73 and through advanced intermediates 63, 66, 72, 74 and 75 as summarized in Figure 6b. Key steps in this synthesis[260–262] are the stereoselective glycosylation reactions of 61 and 62 to afford disaccharide 63, the cascade sequence involved in the conversion of diepoxide 69 to the tetrahydrofuran intermediate 70, the stereoselective coupling of aldehyde 72 with the phosphorane derived
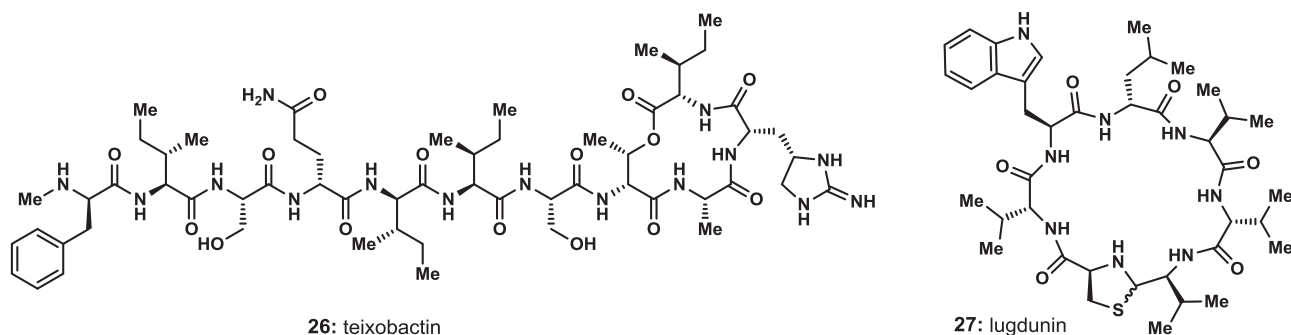

26: teixobactin

27: lugdunin

Figure 3 Recently discovered antibiotics.

from **74** to form the conjugated triene precursor of advanced intermediate **75**, and the final coupling of the latter with γ-lactone fragment **67**, which generated efrotomycin (**29**) and its acetate (**76**, for

final comparison with the acetate of the natural product), upon global deprotection and selective acetylation, respectively. This endeavor demonstrated the use of glycosyl fluorides and arylthioglycosides as
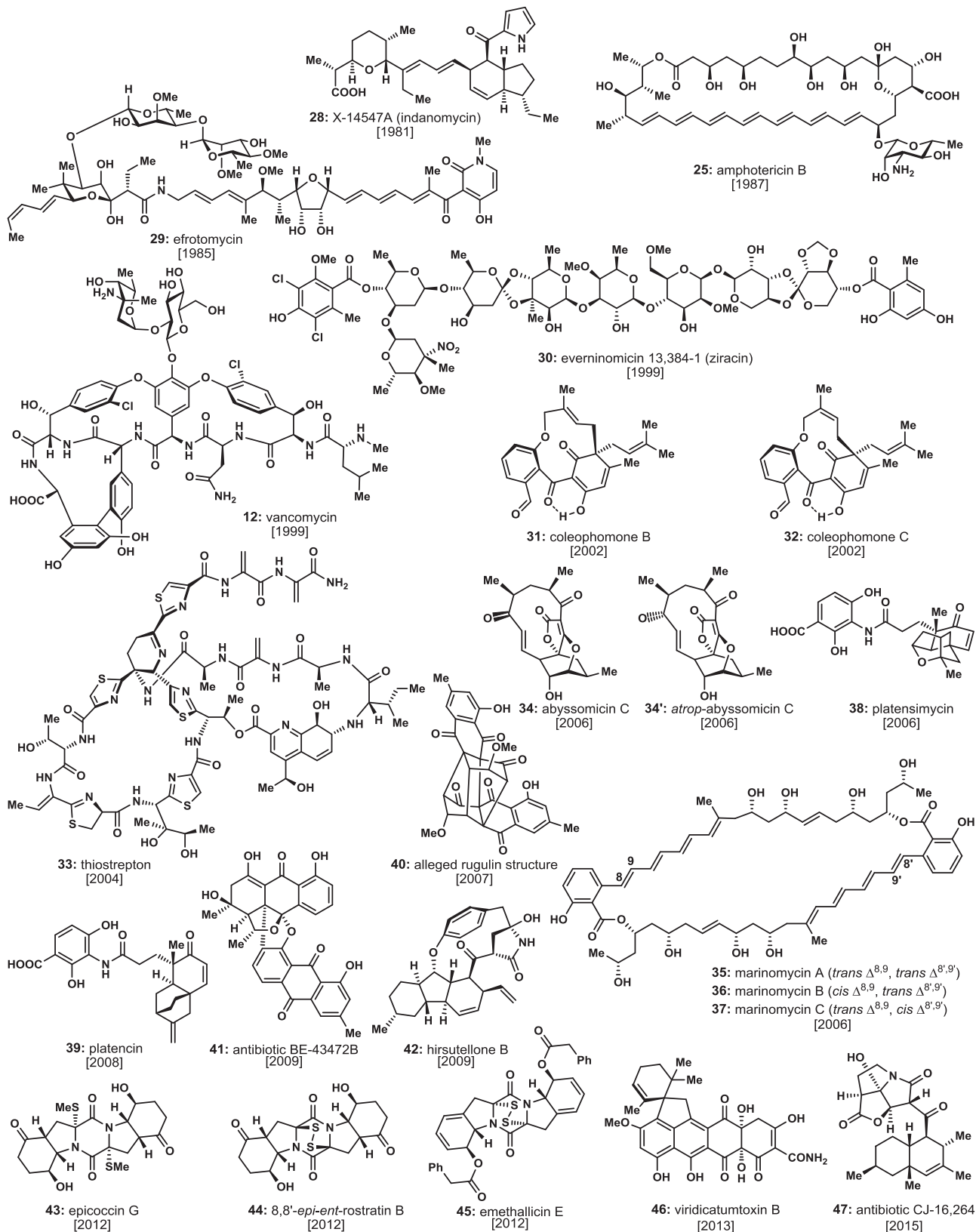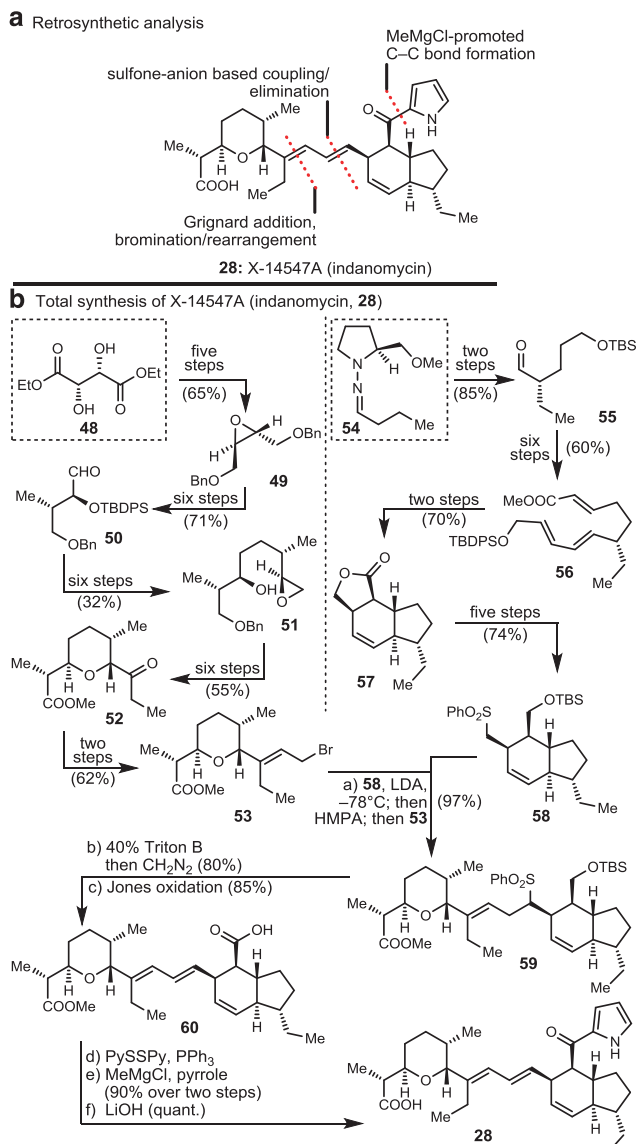

**Figure 4** Select antibiotics synthesized in the authors' laboratories.

Figure 5 Retrosynthetic analysis (**a**) and highlights of the total synthesis (**b**) of X-14547A (indanomycin, **28**).

glycosyl donors in complex molecule construction, pushed the frontiers of total synthesis to new levels of molecular complexity and diversity at the time, and provided opportunities for analog construction within the efrotomycin family of antibiotics.

Amphotericin B

A powerful antifungal[263,264] and antiprotozoal[265] drug, initially isolated in 1954 from *Strep. nodosus* Trejo,[266] amphotericin B (**25**, Figure 7a) possesses an imposing structure featuring a 38-membered macrolide ring, a conjugated heptaene system, an aminosugar, a host of hydroxyl groups and a carboxyl group. Its 19 stereogenic centers, β-glycoside bond and macrocyclic ring were the primary challenges from the synthetic point of view. Figure 7a presents the strategic bond disconnections that led to the definition of building blocks **77**, *ent*-**77**, **78**, *ent*-**49** and **92** as starting materials for its total synthesis.[267–270] As outlined in Figure 7b, the enantiomeric building blocks **77** and *ent*-**77** [(+)- and (−)-xylose, chiral pool approach] were selectively converted to key intermediates aldehyde **79** and ketophosphonate **80**. The same
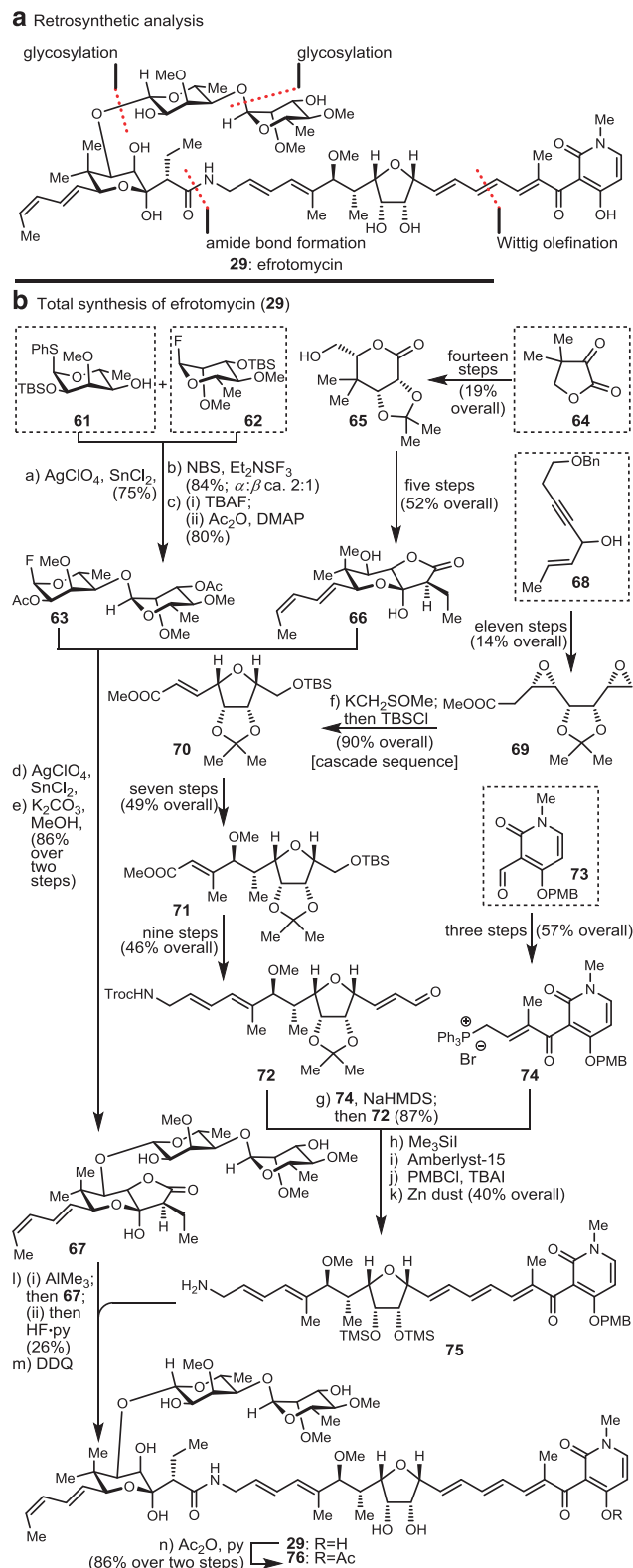
Figure 6 Retrosynthetic analysis (**a**) and highlights of the total synthesis (**b**) of efrotomycin (**29**).

building blocks were also synthesized from the prochiral allyl alcohol **78** through the then newly discovered catalytic asymmetric epoxidation reaction, furnishing epoxides **81** and *ent*-**81** in high
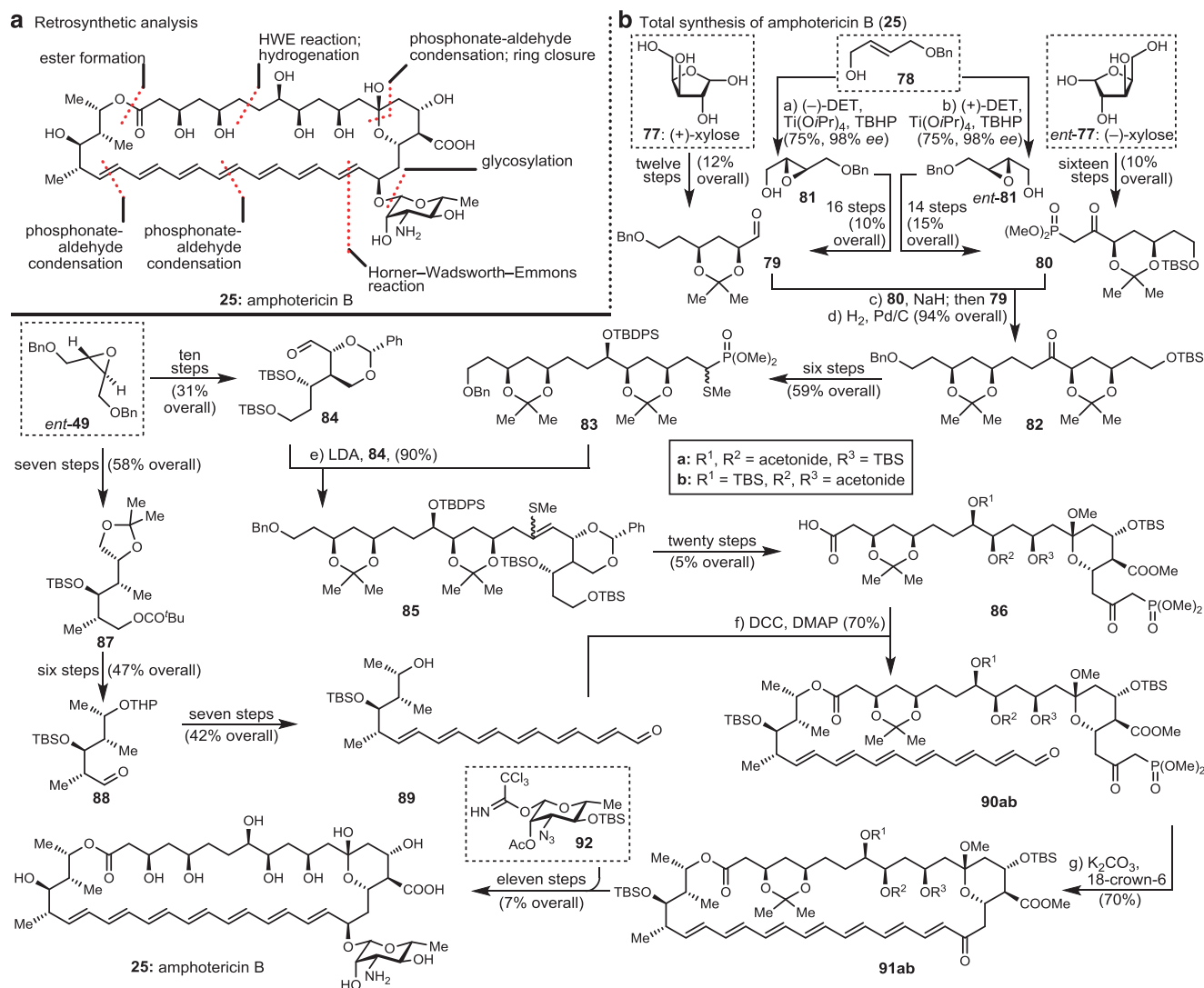
Figure 7 Retrosynthetic analysis (**a**) and highlights of the total synthesis (**b**) of amphotericin (**25**).

chemical yield and enantiomeric excess. Horner–Wadsworth–Emmons coupling of ketophosphonate **80** with aldehyde **79**, followed by reduction of the resulting enone led to ketone **82**. Further elaboration of the latter furnished methylthiophosphonate **83**, whose reaction with aldehyde **84** (obtained from tartaric acid-derived epoxide *ent*-**49**; as shown in Figure 5b) afforded methylthioenol ether **85**. This key intermediate was converted to ketophosphonate **86**. Coupling of the latter with conjugated aldehyde **89** (also obtained from epoxide *ent*-**49** through a different route through intermediates **87** and **88**) furnished ketophosphonate aldehyde **90ab**, which proved a worthy precursor to the coveted macrocyclic polyene **91ab** under carefully defined conditions (K$_2$CO$_3$, 18-crown-6). Impressively, polyene **91ab** was selectively reduced and glycosylated with carbohydrate donor **92** to afford, selectively, the desired β-glycoside, whose further elaboration led to amphotericin B (**25**). Featuring both the chiral pool (auxiliary based) and catalysis approaches to asymmetric synthesis and highlighting the power of the ketophosphonate/aldehyde macrolactonization, this total synthesis served as facilitator to further research on amphotericin B and related compounds that led to new insights into the mechanism of action of this important antifungal agent, and novel drug candidates for clinical development.[271–274] For decades the

presumed explanation for its antifungal action was that amphotericin B creates pores in the pathogen's outer membrane causing leakage of monovalent ions. The newly acquired information suggested a different mode of action, including the formation of extramembranous aggregates that extract ergosterol from the lipid bilayers in a sponge-like fashion.[274] Several other synthetic approaches to fragments and derivatives of amphotericin B have also been reported by other groups.[275–295]
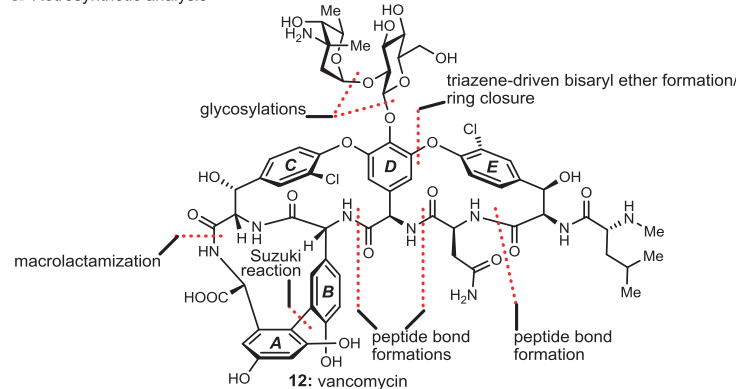
Vancomycin

Vancomycin (**12**, Figure 8a), known once as the last line of defense of humanity against bacteria, was not only a vanquishing agent for them, but also a demonic challenge to synthetic chemists for a long time, the latter designation being due to its unusual macrocyclic motifs and 20 stereogenic elements. The flagship of glycopeptide antibiotics, vancomycin was isolated from *Strep. orientalis* (later renamed, first to *Nocardia orientalis* and then to *Amycolatopsis orientalis*).[296–298] Its mechanism of action as mentioned in the previous section involves interference with the bacterial cell wall biosynthesis through binding to D-Ala-D-Ala structural motifs. Its total synthesis was reported from our laboratories in 1999.[159] Figure 8a indicates the strategic bond

disconnections of vancomycin that led to the devised synthetic strategy and defined key building blocks **93–99** as shown in Figure 8b. Figure 8c highlights the reactions employed for the assembly of these fragments and elaboration of the growing intermediates (**100–111**) into the final target. Among them are the palladium-catalyzed coupling of building block **93** and **94** to afford, upon further
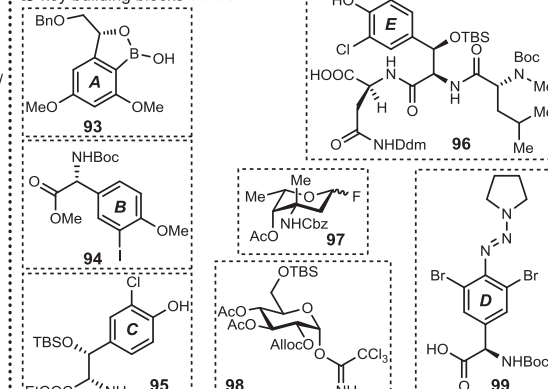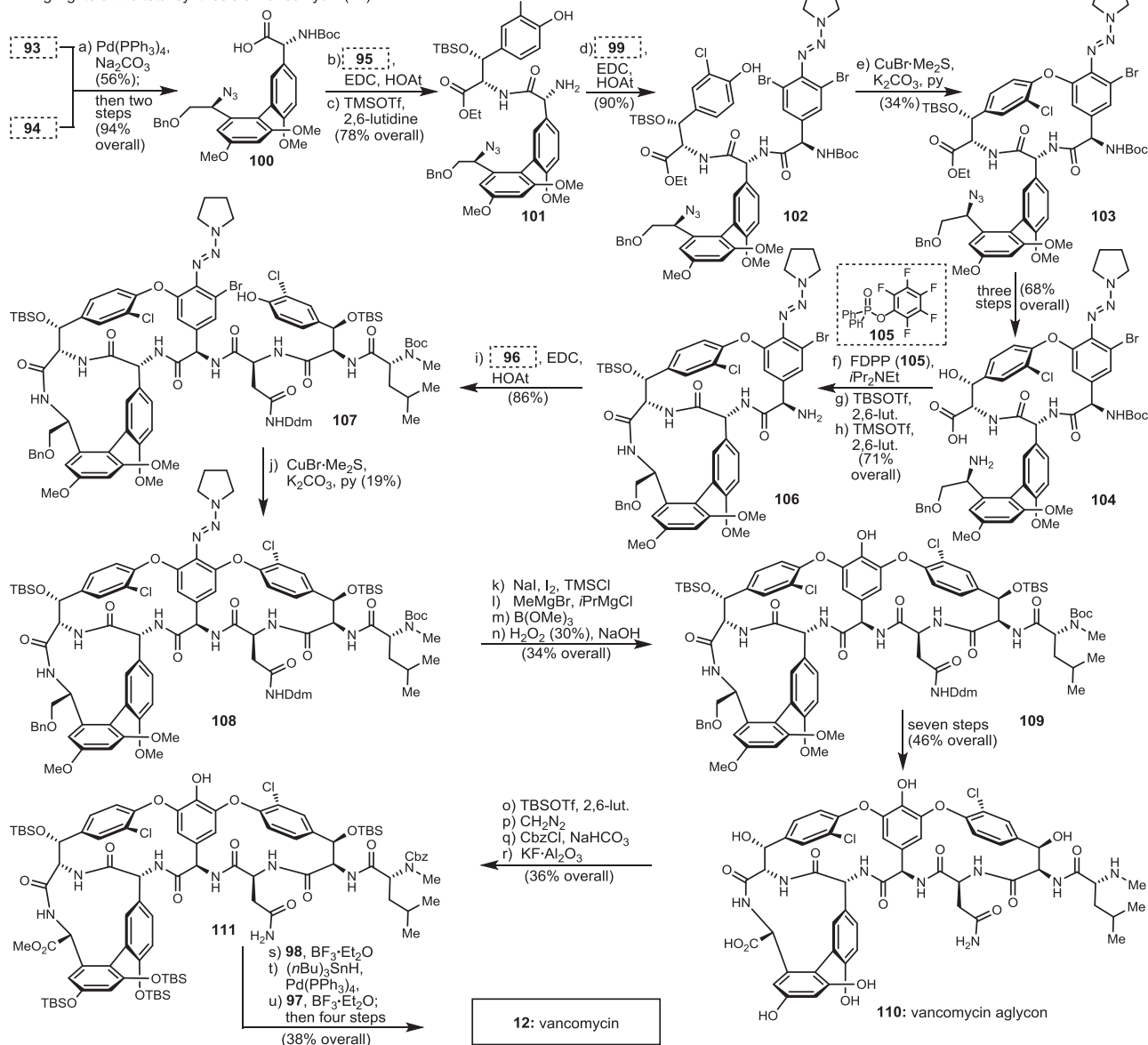
Figure 8 Retrosynthetic analysis (**a**), key building blocks (**b**), and highlights of the total synthesis (**c**) of vancomycin (**12**).

elaboration, azidobiaryl carboxylic acid **100**. The latter was coupled with aminoester fragment **95**, leading to the corresponding amide whose Boc group was removed to afford amine **101** in preparation for the next coupling. That step involved amide bond formation between carboxylic acid **99** and amino building block **101**, which furnished the desired precursor for the first macrocyclization reaction, phenolic dibromotriazine **102**. Intramolecular displacement of one of the two bromide residues by the phenolic hydroxyl group under the influence of CuBr·Me₂S led to the macrocyclic bis-aryl ether **103**, together with its atropisomer. The stage was then set for the next macrocyclization (**103**→**104**→**106**), and then the next (**106**→**107**→**108**), leading to complete vancomycin aglycon framework **109** upon further manipulation of the triazine moiety of **108** to the required phenolic group as summarized in Figure 8c. Vancomycin aglycon **110** was then generated from **109** via a seven-step sequence. Vancomycin itself was synthesized from its aglycon (**110**) via intermediate **111** by sequential glycosylations with glycosyl donors **98** and **97**, followed by deprotections and functional group adjustments as highlighted in Figure 8c. The vancomycin endeavor provided opportunities for new methodological advances, including the triazine-driven macrocyclic arylether forming reaction to cast the two bis-arylether domains of the molecule, as well as new solid phase combinatorial chemistry for analog construction. Significantly, a number of the analogs that emerged from these studies proved to be more potent than vancomycin against drug-resistant bacterial strains.[299–301]

Everninomicin 13,384-1 (ziracin)

Isolated from *Micromonospora carbonacea var. africana*, everninomicin 13,384-1 (**30**, Figure 9a)[302–306] is a member of the orthosomicin class of antibiotics.[307] It exhibited promising antibacterial properties against drug-resistant bacteria, including methicillin-resistant *Staphylococci* and vancomycin-resistant *Streptococci* and *Enterococci*.[308,309] Its bactericidal action[310] is based on its ability to inhibit protein biosynthesis by binding to the 50S subunit of the bacterial ribosome.[311] Contained within its structure are a number of novel and puzzling structural motifs, including two sensitive and synthetically challenging orthoesters, a 1,1′-disaccharide bridge (an oxygen bonded to two anomeric positions), a nitrosugar, and two aromatic esters situated at the two terminal loci of the molecule. In total, everninomicin 13,384-1 possesses 13 rings and 35 stereogenic centers, making its total synthesis a formidable task. Its total synthesis, featuring an array of new synthetic methods and tactics, was reported from our laboratories in 1999.[312–318] Figure 9a indicates the strategic bonds and their disconnections, defining key building blocks **112–121** (Figure 9b) that were used for the devised synthesis. Starting with commercially available and other readily prepared starting materials, these key intermediates were assembled orderly and the resulting products elaborated to advanced intermediates **126** (through compounds **122–125**), **130** (through compounds **127–129**) and **135** (through compounds **132–134**) as summarized in Figure 9c. Advanced intermediates **126** and **130** were then joint through a glycosylation reaction to afford polycycle **131**, after further elaboration (Figure 9c). Finally, the two penultimate advanced key building blocks, glycosyl fluoride **135** and hydroxyl octacycle **131**, were coupled through a SnCl₂-promoted α-selective glycosylation furnishing precursor **136**, whose conversion to everninomicin 13,384-1 (**30**) was achieved in four steps as summarized in Figure 9c. This total synthesis was notable, not only for the complexity of the target molecule but also because of its featuring of new synthetic strategies and tactics as well as new synthetic methods. The latter included a series of glycosylation reactions and 1,2-phenylthio- and -phenylseleno migrations.[318]

Coleophomone B and C

Coleophomones B (**31**) and C (**32**) were originally isolated from the fungus *Stachybothys cylindrospora* RF-5900 by a Shionogi group,[319] and subsequently from a *Coleophoma* sp. (MF6338) fungi by a Merck Sharp & Dohme group (Rahway, NJ, USA).[320] Their antibacterial action is partly based on their ability to inhibit the bacterial cell wall transglycosylase activity, thus disrupting peptidoglycan biosynthesis. Furthermore, the coleophomones inhibit RNA-, DNA- and protein biosynthesis.[320] Their antifungal, antibacterial and inhibitory activities against human heart chymase,[319,321] coupled with their novel molecular architectures were enticing, inspiring us to undertake their total synthesis.[322,323] The highly strained and compact nature of their 11-membered ring characterized by an (E)-olefinic bond (coleophomone B) or (Z)-olefinic bond (coleophomone C) and their unique polyoxygenated framework presented an intriguing synthetic challenge. Having attempted and failed to construct their unusual macrocycle structural motifs through traditional methods, the olefin metathesis reaction came to the rescue. As seen in Figure 10a, the retrosynthetic analysis improvised for a ring-closing metathesis reaction turned out to be pleasantly stereoselective in forming either the (E)- or (Z)-olefin within the macrocycle, depending on the exact structure of the precursor. Figure 10b highlights the total synthesis of both coleophomones B and C through an initially convergent strategy that led to advanced key intermediate **142** (from building blocks **137** and **140** and intermediates **138**, **139** and **141**), and which subsequently diverged to generate precursors **144** and **145** (in addition to compound **143**). The structural constitution of each substrate, **144** (exocyclic methoxy enone) and **145** (endocyclic methoxy enone), proved decisively influential in forming selectively, through the indented olefin metathesis reaction (cat. **146**), each desired product, **147** [(E)-olefin] and **148** [(Z)-olefin], respectively. From these precursors, the targeted natural products [coleophomones B (**31**) and C (**32**)] emerged through a short synthetic sequence as shown in Figure 10b. This achievement was a triumph for the metathesis reaction in that it demonstrated its unique power where other alternatives failed.[322,323]

Thiostrepton

As the flagship of the thiopeptide class of antibiotics due to its magnificent structure,[324] and because of its diverse and important biological properties[325,326] that include antibacterial, antimalarial, immunosuppressive and cytotoxic activities, and veterinary medical use, thiostrepton (**33**, Figure 11a) served as a challenge and inspiration to us in the early 2000s.[327–333] Thiostrepton was isolated from three different species of *Streptomyces* (*azureus* ATCC 14921, *hawaiiensis* ATCC 12236 and *laurentii* ATCC 31255).[334] Its mechanism of action is based on the inhibition of elongation factor G (translocase), a prokaryotic enzyme responsible for the translocation of the tRNA and mRNA down the ribosome.[335–337] We reasoned that although its total synthesis might not be of urgent need due to its natural abundance it would certainly be a playground for advancing the art of organic synthesis and a means to produce otherwise unavailable designed analogs for biological investigations. Besides, there were the elements of excitement, in breaking another glass ceiling of molecular complexity and diversity for total synthesis, and serendipity for discovering new chemistry and gathering useful intelligence for future explorations and applications. The most intriguing structural motif of thiostrepton is undoubtedly its dihydropiperidine structural moiety with its surrounding substituents, including the three thiazole rings and its tetrasubstituted carbon atom, not to mention that the entire structure is loaded with reactive and unpredictable functionalities in terms of their installment and chemical behavior. Figure 11a presents the

a Retrosynthetic analysis

30: everninomicin 13,384-1 (ziracin)
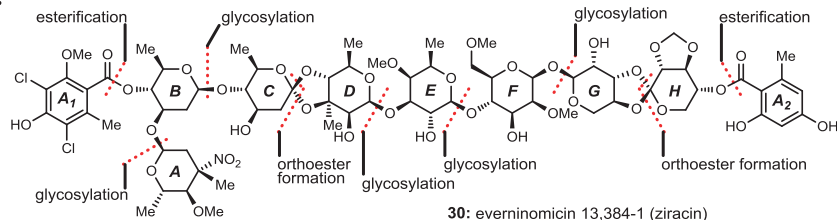
b required building blocks **112–121**
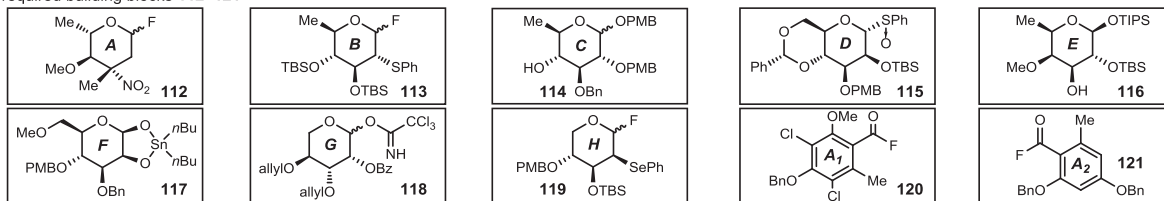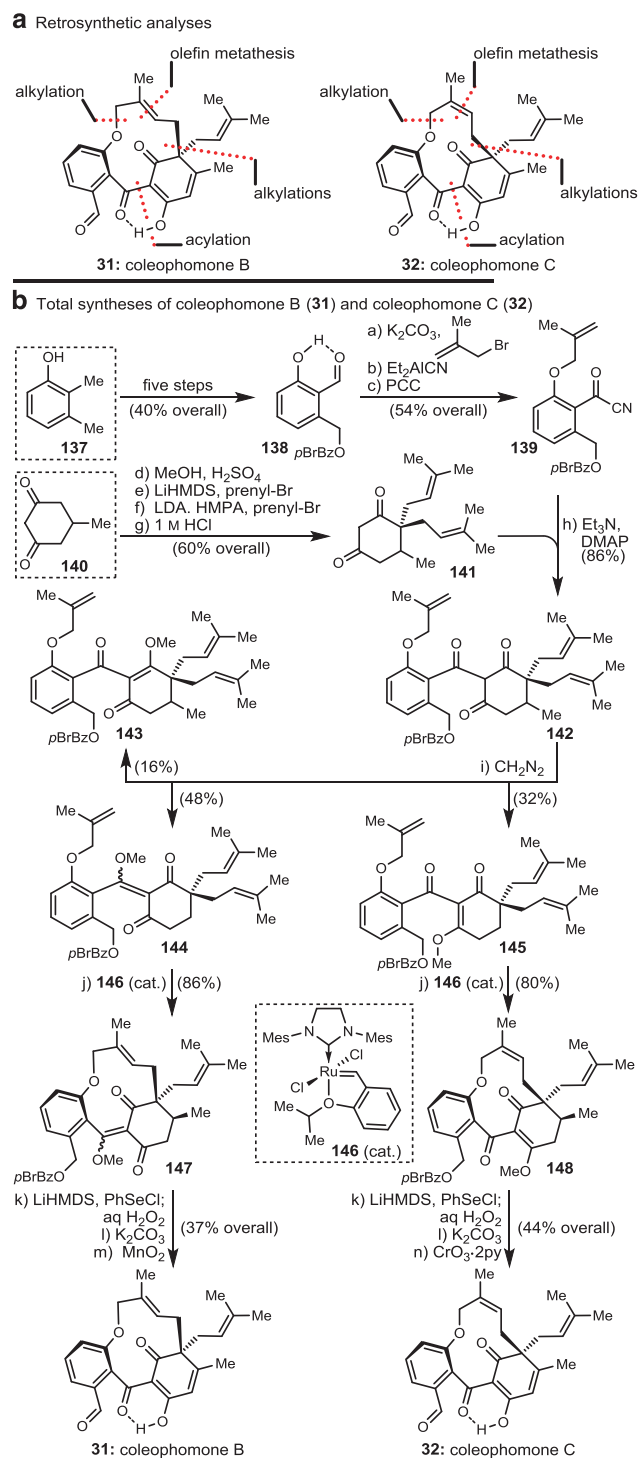

c Elaboration of building blocks **112–121** to fragents **126**, **130**, and **135** and highlights of the total synthesis of everninomicin 13,384-1 (**30**)

30: everninomicin 13,384-1 (ziracin)
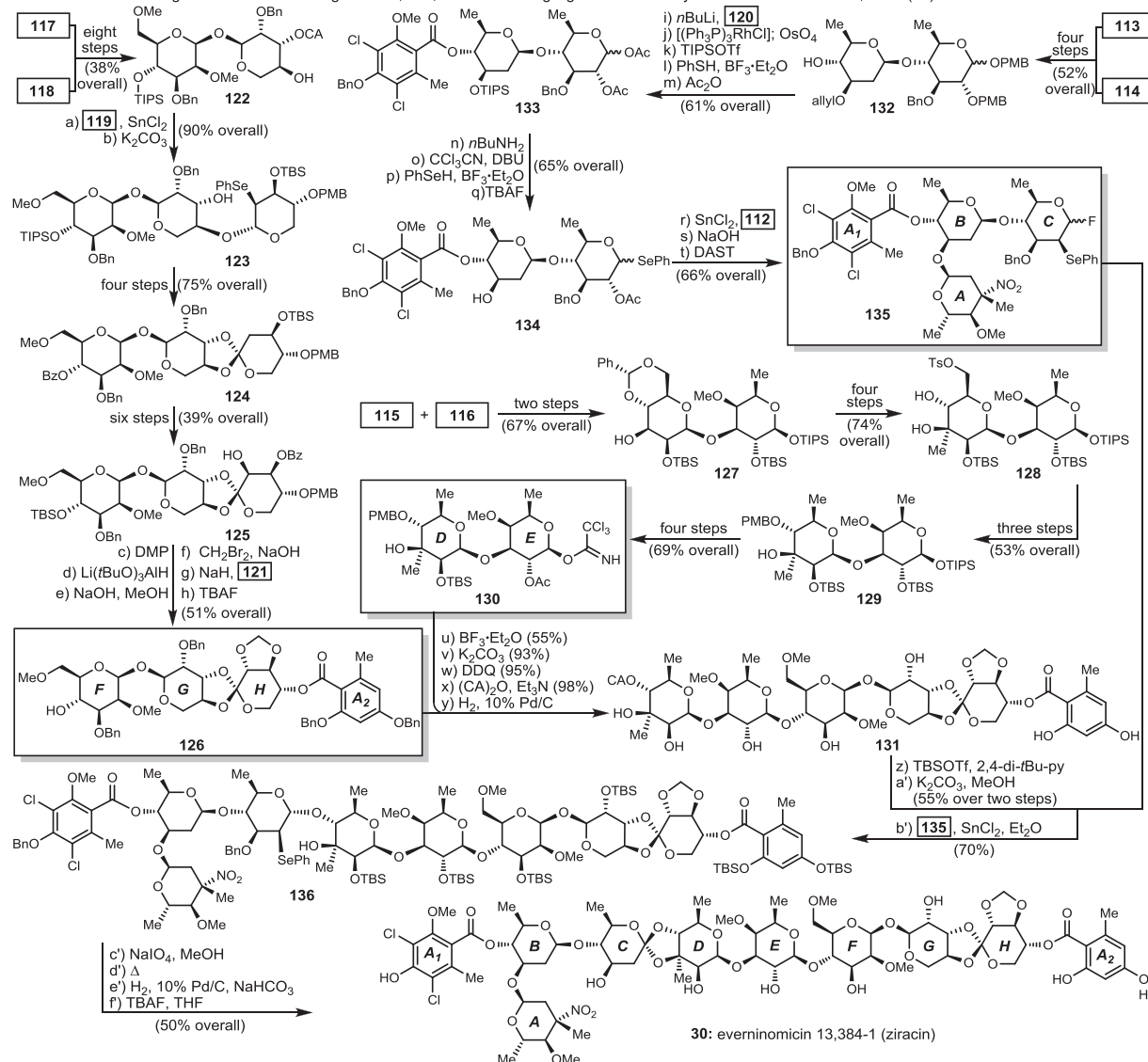
Figure 9 Retrosynthetic analysis (**a**), key building blocks (**b**), and highlights of the total synthesis (**c**) of everninomicin 13,384-1 (ziracin, **30**).

a Retrosynthetic analyses

31: coleophomone B

32: coleophomone C

b Total syntheses of coleophomone B (**31**) and coleophomone C (**32**)

Figure 10 Retrosynthetic analyses (**a**) and highlights of the total syntheses (**b**) of coleophomone B (**31**) and C (**32**).

employed retrosynthetic disconnections based on which the final strategy was devised for its total synthesis. Although details of the synthesis of thiostrepton can be found in our publications on the subject,[327–333] including a review,[338] its highlights can be seen in Figure 11b. Among them are the biomimetic aza-Diels–Alder-based construction of the tetrasubstituted dihydropiperidine structural motif from azadiene **154** (generated from precursor **153** whose preparation from building blocks **149** and **151** proceeded through intermediates

150 and 152, see Figure 11b). Azadiene **154** reacted spontaneously upon generation via *endo* transition stage **155** and through intermediate **156**, the latter collapsing under the reaction conditions to the desired product (**158**) through intermediate **157**. The crucial formation of the sterically challenging amide bond in the next advanced intermediate (**160**) was achieved through the use of azidoacid chloride building block **159**. The latter advanced intermediate was then grown to thiostrepton by crafting on it (that is, building block **160**) fragments **161**, **164** and **166** through a sequence of reactions involving intermediates **162**, **163**, **165** and **167**, as summarized in Figure 11b. It is of note that the three phenylseleno groups, introduced on the growing molecule as masking devices for the two reactive dehydroalanine structural motifs, had a crucial role in ensuring the survival and eventual emergence of these moieties in the final stages of the synthesis. Another worthy feature of the synthesis was the generation, in the final step and under the desilylation conditions (HF·py), of the olefinic bond conjugated to the thiazoline ring in its correct geometrical form. We would be remiss if we did not mention that it was during this endeavor that we discovered and developed the now popular method for selective hydrolysis of methyl esters using trimethyltin hydroxide.[339,340]

Abyssomicins

Abyssomicin C (**34**, Figure 12a) was originally isolated from the marine-derived actinomycete strain *Verrucosispora* AB-18-032 in 2004.[341,342] Its sibling, *atrop*-abyssomicin C (**34′**, Figure 12a) was subsequently discovered from the same species,[343] but not before it was synthesized in our laboratories.[344–346] Exhibiting potent antibacterial properties against drug-resistant strains due to its ability to inhibit the conversion of chorismate into *p*-aminobenzoic acid (thus blocking the tetrahydrofolate biosynthesis)[342] and because of its novel molecular architecture, abyssomicin C presented an irresistible challenge as a synthetic target. Our devised strategy for its total synthesis was based on the retrosynthetic analysis depicted in Figure 12a and featured a Diels–Alder reaction and a ring-closing metathesis as highlighted in Figure 12b. The synthetic sequence employed building blocks **168**, **171** and **175**, and ligand **170** needed for the success of the stereoselective Diels–Alder reaction of **169** with **171**, to afford product **173** via transition state **172**. Elaboration of bicyclic product **173** then furnished tricycle **174**, which was coupled under basic conditions with δ-lactone **175** to afford, upon dithioketal formation, intermediate **176**. Oxidation followed by vinyl Grignard addition to the resulting aldehyde then gave metathesis precursor **177**. The coveted ring-closing metathesis of precursor **177** was achieved through the use of ruthenium catalyst **178**, leading, after oxidation, exclusively to macrocycle **179**, from which *atrop*-abyssomicin C (**34′**, Figure 12b) was generated by exposure to phenyliodo bistrifluoroacetate. Finally, *atrop*-abyssomicin C was converted under acidic conditions into a separable mixture of abyssomicin C (**34**) and *atrop*-abyssomicin C (**34′**; **34**:**34′** ca. 2:1). Interestingly, in addition to being discovered in nature, *atrop*-abyssomicin C exhibited even higher potencies against bacteria than its sibling, abyssomicin C.[343] This endeavor demonstrated and expanded further the power of the Diels–Alder and metathesis reactions in total synthesis, provided useful insights and understanding of atropisomerism, especially as it pertains to naturally occurring molecules, and resulted in a number of structure-activity relationships within the abyssomicin family. It also led to the total synthesis of a natural product in the laboratory before its discovery from nature, a rare, but noteworthy contribution of the art and science of total synthesis. Besides our own work, other groups

a Retrosynthetic analysis

33: thiostrepton

• Diels–Alder reaction

• amide formation
• ester formation
• amino thiol/aldehyde condensation
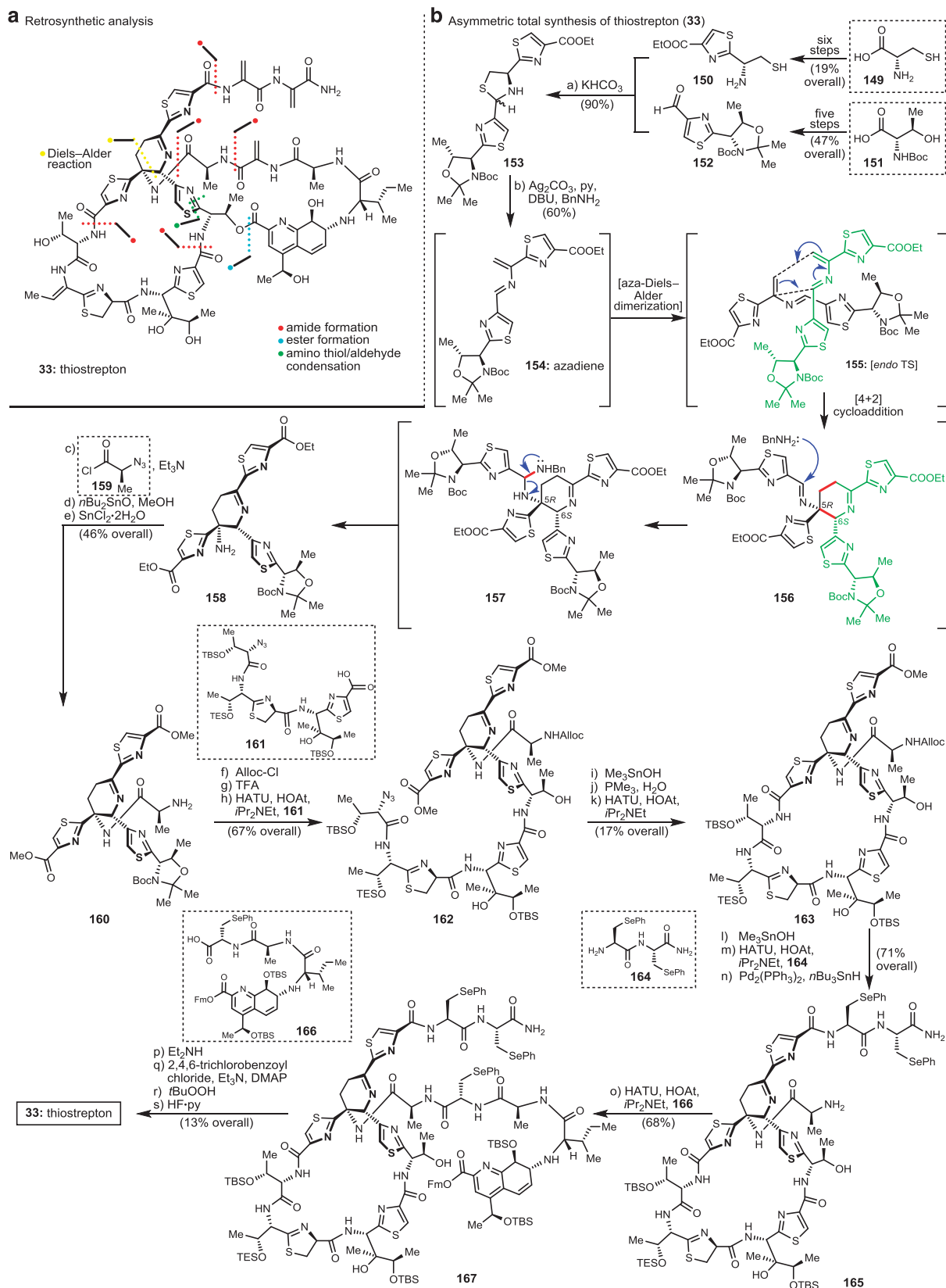
b Asymmetric total synthesis of thiostrepton (33)

Figure 11 Retrosynthetic analysis (a) and highlights of the total synthesis (b) of thiostrepton (33).

have also attempted[347–351] or completed the formal[352] and total synthesis of the abyssomicins.[353–355]

Marinomycins

Marinomycin A (**35**, Figure 13a) is the most prominent member of the marinomycin family of marine-derived natural products isolated from the actinomycete '*Marinispora*' CNQ-140.[356] Featuring a 44-membered dimeric macrolide ring and endowed with potent antibacterial and cytotoxic properties, these scarce molecules became synthetic targets in our group not only because of their biological properties but also due to their novel and synthetically challenging architectures. Our total synthesis of marinomycin A[357,358] is summarized in Figure 13a (retrosynthetic disconnections) and 13b (highlights). The sequence employed building blocks **180**, **181**, **185** and **189** and proceeded through intermediates **182–184** and **186–193** as outlined in Figure 13b. The key macrocyclization reaction involved conversion of acetylenic vinyl bromide **193** to afford the corresponding vinyl borane, which underwent intramolecular Suzuki coupling furnishing, upon global desilylation, the target molecule marinomycin A (**35**). Interestingly, the Heck, Stille and metathesis reactions failed to produce the corresponding macrocyclic products.
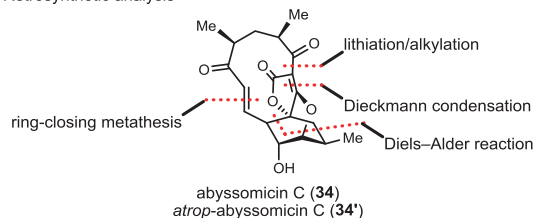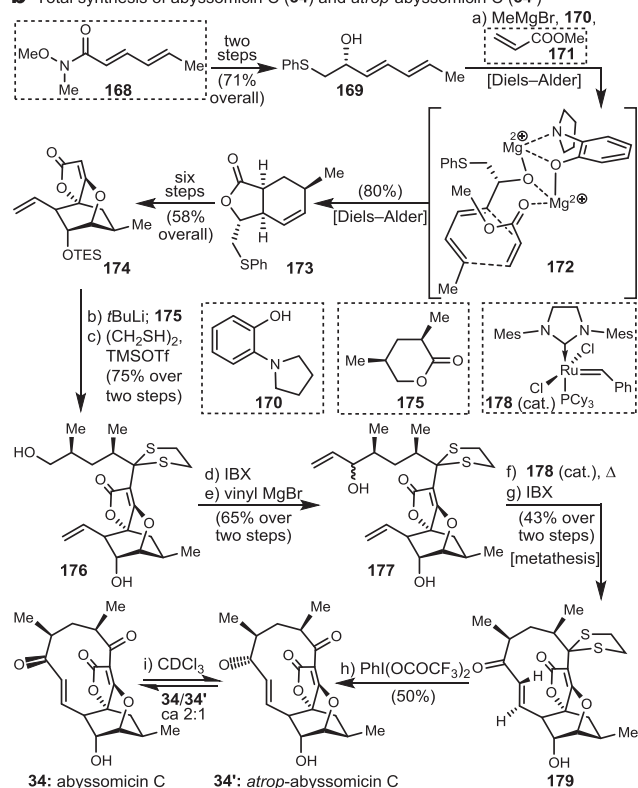
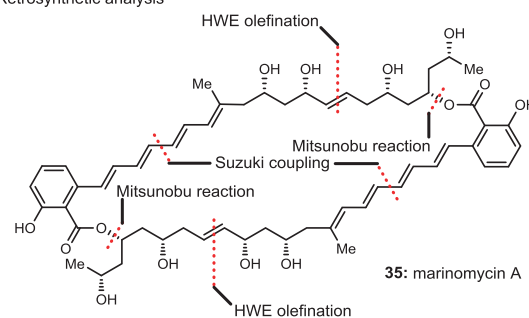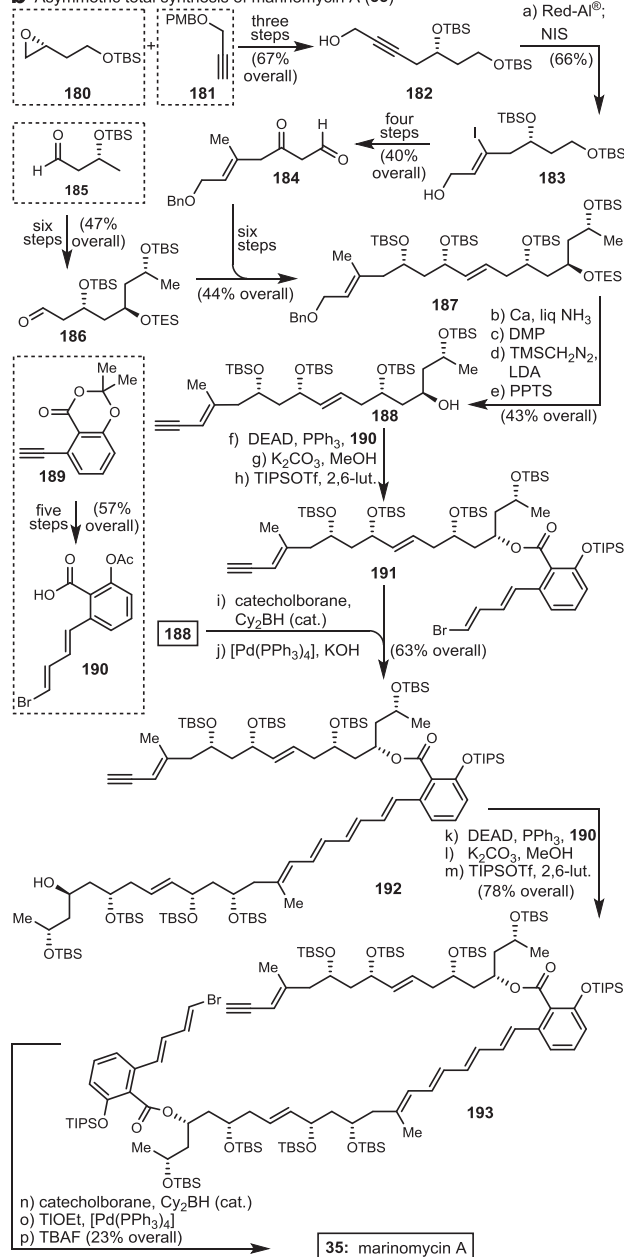**Figure 12** Retrosynthetic analysis (**a**) and highlights of the total syntheses (**b**) of abyssomicin C (**34**) and *atrop*-abyssomicin C (**34'**).
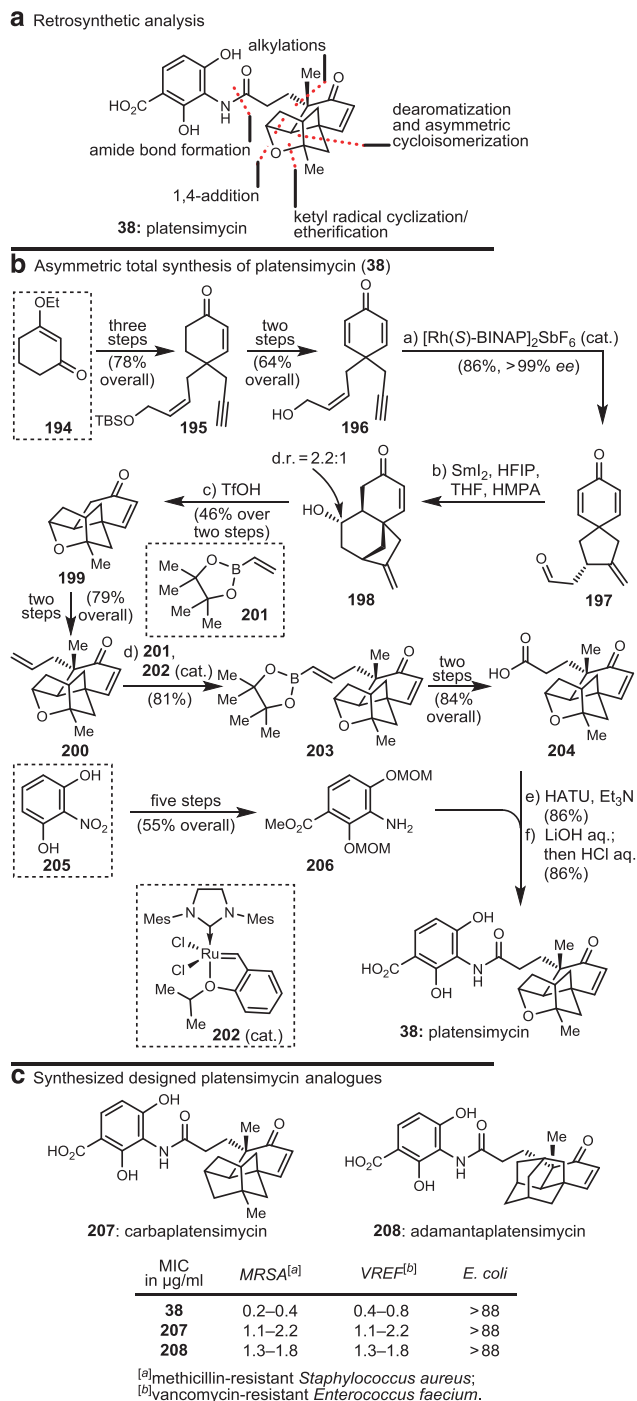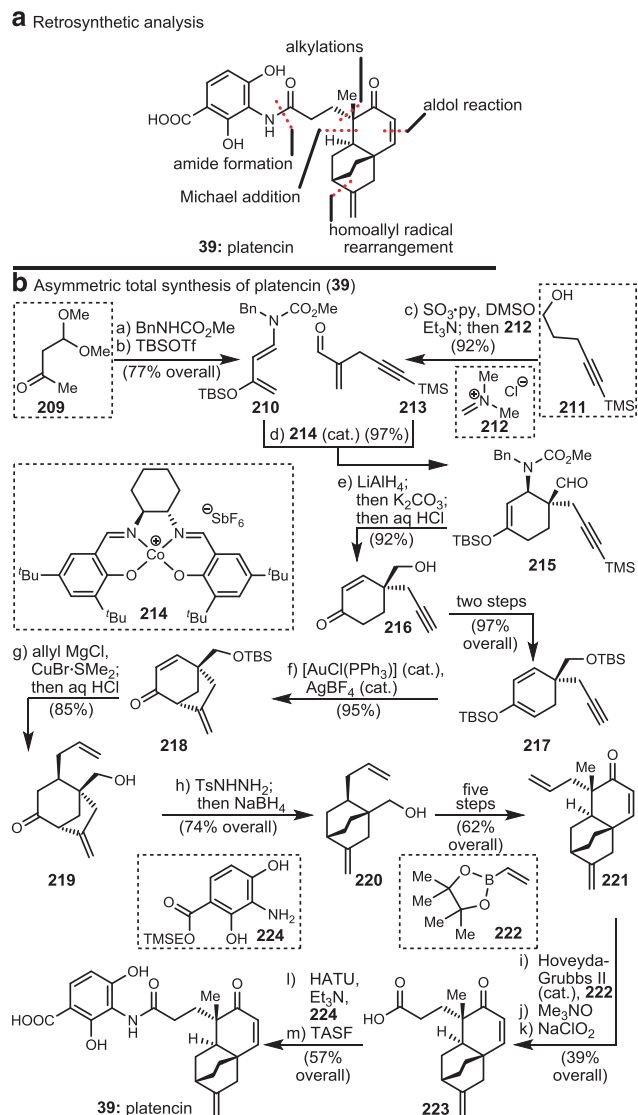

Figure 13 Retrosynthetic analysis (**a**) and highlights of the total synthesis (**b**) of marinomycin A (**35**).

a Retrosynthetic analysis

b Asymmetric total synthesis of platensimycin (**38**)

c Synthesized designed platensimycin analogues

207: carbaplatensimycin   **208**: adamantaplatensimycin

MIC in µg/ml	MRSA[a]	VREF[b]	E. coli
38	0.2–0.4	0.4–0.8	>88
207	1.1–2.2	1.1–2.2	>88
208	1.3–1.8	1.3–1.8	>88

[a]methicillin-resistant *Staphylococcus aureus*;
[b]vancomycin-resistant *Enterococcus faecium*.

Figure 14 Retrosynthetic analysis (**a**) and highlights of the total synthesis (**b**) of platensimycin (**38**), and select designed analogues and their biological activities (**c**).

Another interesting outcome of this project was the preparation of the 22-membered monomeric counterpart of marinomycin A, which proved inactive as compared to the natural product against the same bacterial strains. Furthermore, marinomycin A was transformed, upon photo-irradiation, to its geometrical isomers, marinomycins B and C (as a mixture with A), which were separated as individual compounds.[357,358] In 2007, the Cossy group published their work on the synthesis of the monomeric counterpart of marinomycin A.[359,360]

a Retrosynthetic analysis

b Asymmetric total synthesis of platencin (**39**)

Figure 15 Retrosynthetic analysis (**a**) and highlights of the total synthesis (**b**) of platencin (**39**).

Two other total syntheses of marinomycin A were more recently reported, one by the Evans group[361] and the other by the Hatakeyama group.[362]

Platensimycin

Aided by a new screening technique,[363,364] scientists at Merck Sharp & Dohme were able to isolate and characterize platensimycin (**38**, Figure 14a), a novel secondary metabolite from *Strep. platensis* that exhibited inhibitory activity against the FabH and FabF condensing enzymes of the fatty acid biosynthetic pathway crucial to bacteria.[365–367] Its unique mechanism of action, coupled with its unprecedented molecular architecture, propelled platensimycin to a priority status as a synthetic target and a potential new antibiotic for investigation and further development. From the several total syntheses we developed,[368–372] we present in Figure 14a (retrosynthetic disconnections) and 14b (highlights) an asymmetric version[373] that involved an enantioselective rhodium-catalyzed cyclization of a prochiral eneyne bis-enone (that is, **196**, obtained from building block **194** via **195**) to afford bicyclic aldehyde **197**. A samarium-

induced ring closure within the latter then led to tricyclic alcohol **198**, from which pentacycle **199** was formed through acid-catalyzed etherification, as shown in Figure 14b. Sequential bis-alkylation of ketone **199** then led to olefinic substrate **200**, whose cross metathesis reaction with vinyl boronate **201** under the influence of ruthenium catalyst **202** furnished advanced intermediate **203**, from which the coveted carboxylic acid **204** emerged in two steps. The required benzenoid domain (**206**) of the target molecule was secured from building block **205** through a high-yielding five-step sequence. Coupling of carboxylic acid **204** with aniline derivative **206** under the influence of HATU and Et₃N led to the corresponding amide, from which platensimycin (**38**) was derived upon deprotection, as shown in Figure 14b. This and the other synthetic strategies and technologies we developed during this program facilitated the design, synthesis and biological evaluation of numerous analogs of platensimycin. Among them, carbaplatensimycin (**207**)[374] and adamantaplatensimycin (**208**)[375] are notable for their comparable potencies against drug-resistant bacteria (see Figure 14c). Besides our initial total synthesis,[368] numerous other strategic approaches[376–380] and formal and total syntheses have been reported.[381–400]

Platencin

Isolated from *Strep. platensis* MA7339,[401,402] platencin (**39**, Figure 15a) is a relative of platensimycin (**38**) discussed above. Its antibacterial properties and mechanism of action are similar to those of platensimycin (**38**) and so is its molecular structure, except from its tricyclic domain. The latter structural site of platencin differs from that of platensimycin in that it includes a completely carbocyclic framework consisting of only three rings, instead of the tetracyclic cyclic ether-featuring framework of platensimycin. From the several strategies we developed toward platencin,[403–406] the one depicted in Figure 15a (retrosynthetic disconnections) and 15b (highlights) is distinguished for its enantioselectivity and novel carbocyclization to forge one of the rings of the molecule.[406] Starting with building blocks **209**, **211**, **222** and **224**, and using catalyst **214** and proceeding through intermediates **210**, **213**, **215–221** and **223** as shown in Figure 15b, this total synthesis of platencin delivered the natural product in its natural enantiomeric form. One of its most notable steps was the asymmetric, cobalt-catalyzed Diels–Alder reaction between diene **210** and dienophile **213** in the presence of catalyst **214** to afford cyclohexene **215**, whose one-pot conversion to hydroxyenone **216** proceeded in 92% yield and 98% *ee* (after recrystallization). Another pleasing step was the high-yielding (95%) gold-catalyzed cyclization of acetylenic enol ether substrate **217** to afford bicyclic system **218**. Several other elegant (formal) total syntheses of platencin and its analogs have been reported.[394,398,407–427]

Rugulin

There is a mystery surrounding the structure of rugulin, an alleged natural product isolated from *Penicillium rugulosum* in 1978 and claimed to possess structure **40** (Figure 16a)[428] and to exhibit antibacterial properties.[429] Its intriguing molecular architecture is characterized by a central core in the shape of a twisted cylinder defined by four five-membered carbocyclic rings, the latter in its naked hydrocarbon form termed 'skyrane'.[430–432] Its unusual and challenging structure, coupled with its reported biological properties, motivated us to undertake its laboratory synthesis. We achieved the total synthesis of the alleged structure of rugulin[432] following the novel strategy shown in Figure 16b, which employs the so-called 'cytoskyrin cascade' developed in our laboratories[430,431] for the purposes of synthesizing other members of the class, to which this structure belongs, along

a Retrosynthetic analysis

b Total synthesis of the alleged rugulin structure (**40**)
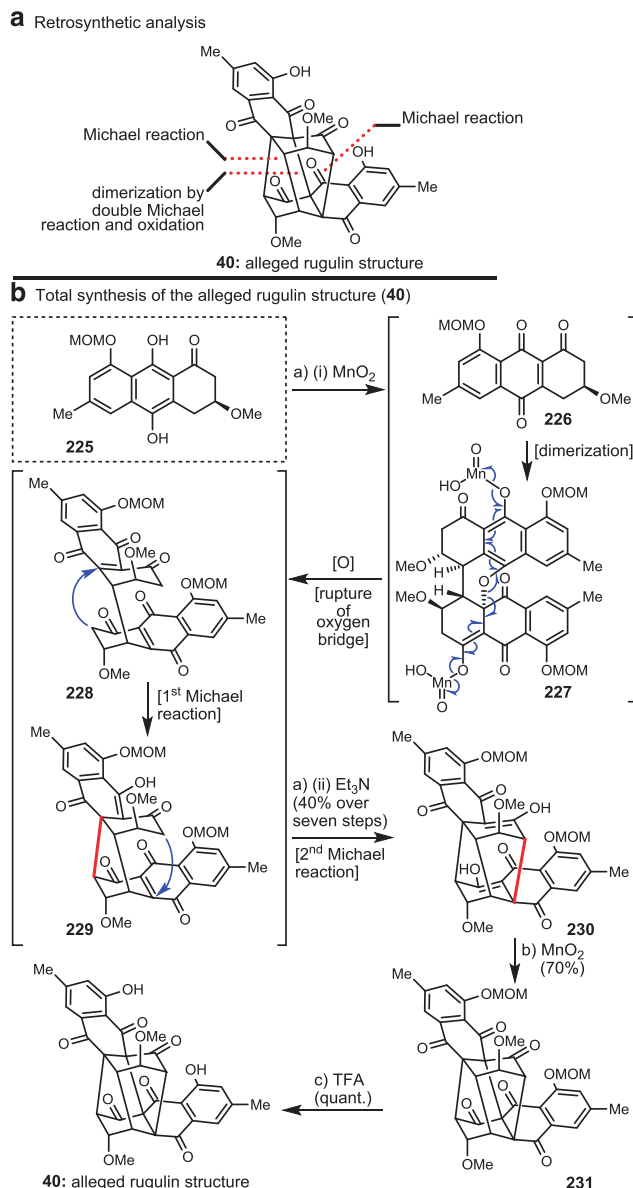
Figure 16 Retrosynthetic analysis (**a**) and highlights of the total synthesis (**b**) of the alleged structure of rugulin (**40**).

with cytoskyrin A[433] and 2,2′-*epi*-cytoskyrin A.[432,434] The developed synthetic strategy toward this novel structure involved two of the simplest reagents (that is, MnO₂ and CF₃COOH) and proceeded smoothly under thermal conditions (25–45 °C). Starting from dihydroanthracenone building block **225**, this rather stunning cascade sequence gave precursor **230**. It involved initial oxidation of the dihydroanthracenone **225** to the corresponding quinone (that is, **226**), which served as a substrate for the next step involving enolization/dimerization to afford bis-enol **227**. The latter underwent rapture of the oxygen bridge triggered by further MnO₂-induced oxidation to furnish the corresponding bis-anthraquinone system **228**, which entered an intramolecular Michael reaction to form the second required C–C bond of the skyrane cage, leading to intermediate **229**. Upon treatment with Et₃N in the same pot, this intermediate suffered a second intramolecular Michael reaction to
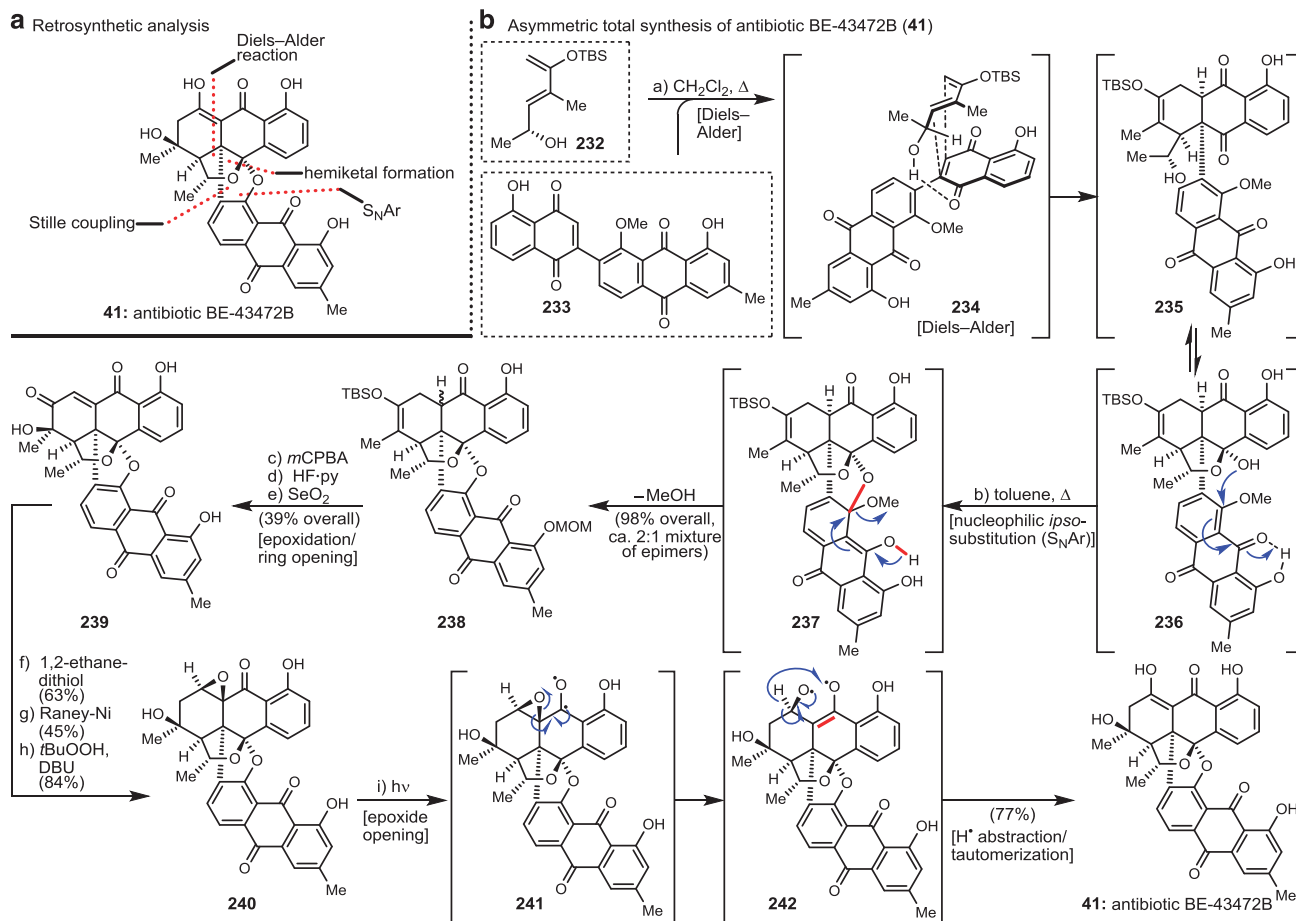
Figure 17 Retrosynthetic analysis (**a**) and highlights of the total synthesis (**b**) of antibiotic BE-43472B (**41**).

generate advanced intermediate **230**, missing only one of the four required C–C bonds to close the skyrane cage. This remaining objective was achieved by the addition of further amounts of MnO$_2$ in the same pot forming, upon exposure to CF$_3$COOH, the targeted rugulin structure **40**. As elegant as the synthesis was, it only proved that the originally assigned structure of rugulin was wrongly assigned, leaving the true structure of the natural product in a shroud of mystery and a continuing structural puzzle. This unfortunate mystery remains to this day, due to the fact that we were not able to obtain either a sample of the natural product or its full set of spectral data.

Antibiotic BE-43472B

The bis-anthraquinone antibiotic BE-43472B (**41**, Figure 17a) was isolated from *Streptomyces* sp. A43472 found in a blue-green algae associated with the ascidian *Ecteinascidia turbinate*.[435,436] This structurally novel antibiotic possesses, in addition to its two anthraquinone-type structural motifs, an unusual bicyclic core featuring an internal ketal functionality and a highly sterically hindered carbon-carbon bond. Its potent activities against drug-resistant bacteria such as MRSA and tetracycline-resistant *Staph. aureus* and vancomycin-resistant *Enterococcus faecium*,[437] coupled with its challenging molecular architecture prompted us to pursue its total synthesis.[438–440] Our motivation was to develop novel chemistry, determine its then unknown absolute configuration, and apply the developed synthetic strategies and technologies to the synthesis and

biological evaluation of designed analogs. Figure 17 displays the retrosynthetic analysis that guided the development of the devised strategy (panel a) and the highlights of the successful total synthesis of antibiotic BE-43472B (panel b) featuring two esthetically pleasing cascades. The first cascade sequence began with the Diels–Alder fusion of diene **232** and dienophile **233** (see transition state **234**) and proceeded through intermediates **235–237** [involving an *ipso* aromatic substitution reaction (S$_N$Ar) and expulsion of a molecule of MeOH] to afford octacycle **238**. The second cascade sequence involved the photo-induced rapture of epoxide **240** (prepared from **238** in six steps via intermediate **239**) to form diradical **241**, whose rearrangement led to isomeric radical **242**, from which antibiotic BE-43472B emerged after an intramolecular H-atom shift and tautomerization of the resulting keto-enol as indicated in Figure 17b. The developed synthetic strategy allowed the total synthesis of both enantiomeric forms [(+)-**41** and *ent*-(−)-**41**] of antibiotic BE-43472B, allowing its absolute configuration to be assigned as that depicted by **41** in Figure 17b. Interestingly, synthetic antibiotic BE-43472B (**41**) and its enantiomer (*ent*-**41**) exhibited essentially the same potencies against drug-resistant bacteria [that is, **41**: MIC = 0.083–0.166 µg ml^{-1} (methicillin-resistant *Staph. aureus*), 0.33–0.83 (vancomycin-resistant *Enterococcus faecalis*); *ent*-**41**: MIC = 0.055–0.11 µg ml^{-1} (MRSA), 0.17–1.1 (vancomycin-resistant *Enterococci*)].[439] In 2013, Keisuke Suzuki and his group reported a racemic total synthesis of antibiotic BE-43472B featuring an isoxazole-directed pinacol 1,2-shift.[441]

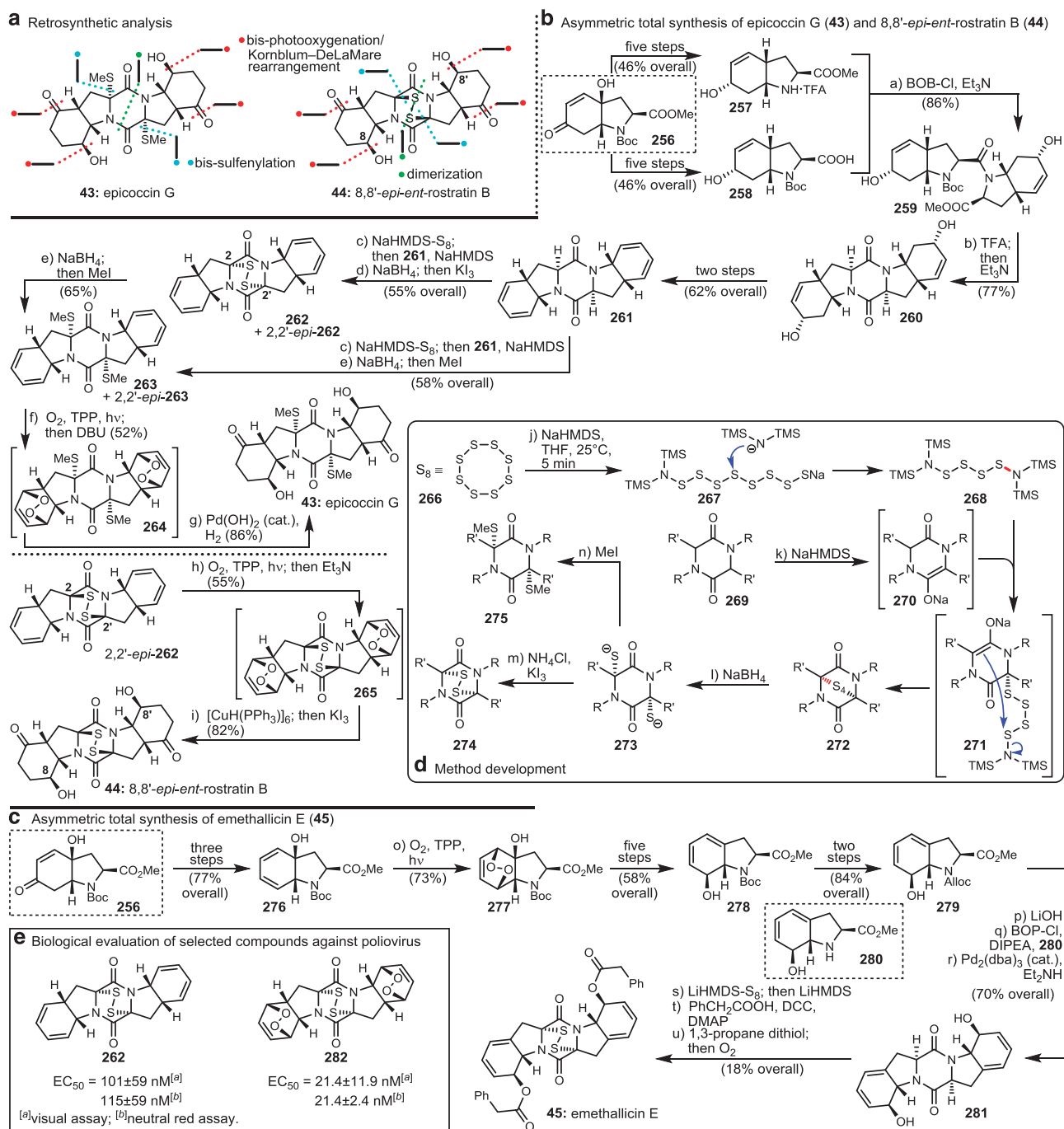**Figure 18** Retrosynthetic analysis (a) and highlights of the total synthesis (b) of hirsutellone B (42).
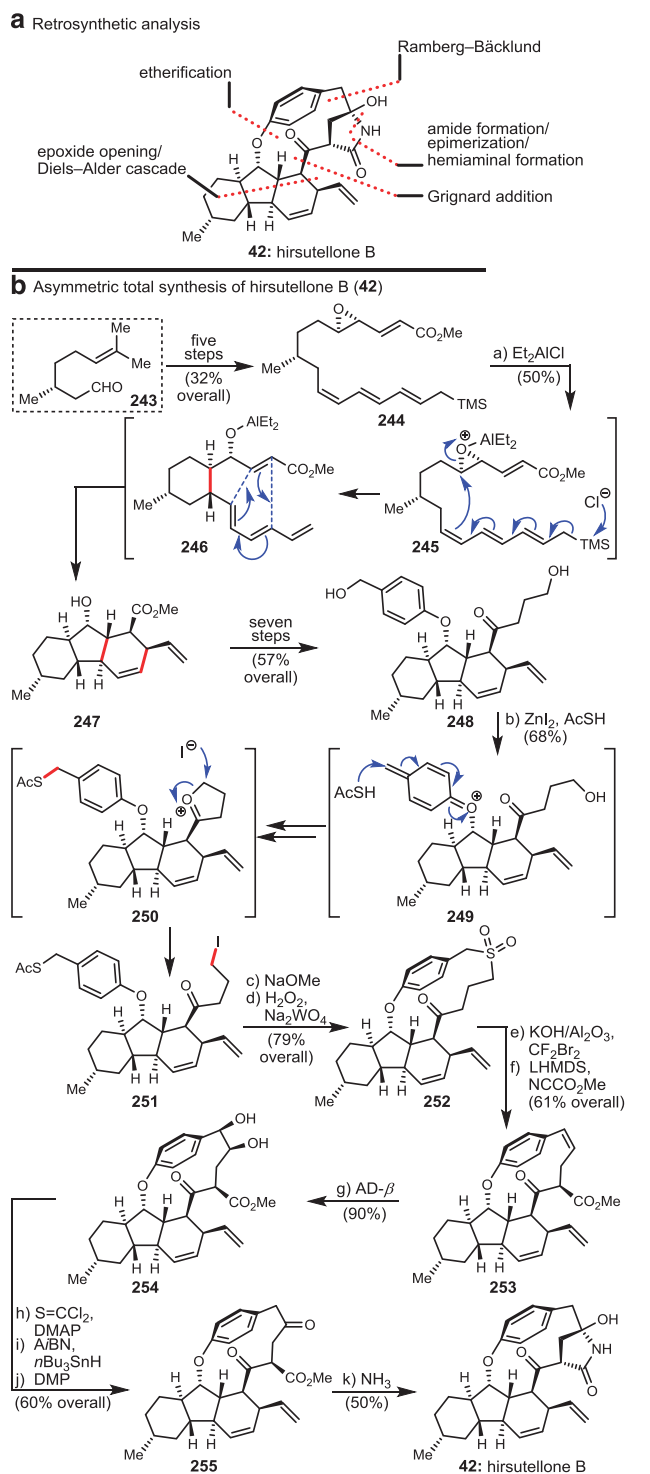
Hirsutellone B

A member of a large class of fungal metabolites, hirsutellone B (42, Figure 18a) rose to prominence due to its potent activity against *Mycobacterium tuberculosis*, the causative pathogen of tuberculosis. Isolated from fungus *Hirsutella nivea* BCC 2594,[442] hirsutellone B includes in its structure a 6,5,6-fused tricyclic core, a hydroxy γ-lactam, and a 13-membered *p*-cyclophane ring encompassing an

aryl ether bridge and five out of the ten stereogenic centers of the molecule. Its biological properties as a potential antituberculosis agent and novel molecular architecture elevated it to an opportunistic target molecule. Figure 18a indicates the disconnections of the identified strategic bonds onto which the devised synthetic strategy was based. A summary of the total synthesis of hirsutellone B, achieved in our laboratories in 2009,[443] is depicted in Figure 18b. Thus, starting from (R)-(+)-citronellal (243), polyunsaturated epoxide 244 was prepared and subjected to the influence of Et_2AlCl in CH_2Cl_2 at $-78 \to 25$ °C, conditions that allowed its stereoselective transformation to tricyclic system 247 through a cascade sequence featuring activation of the epoxide, a chloride-induced desilylation/ring closure/epoxide opening, and an intramolecular Diels–Alder reaction. Proceeding through transition states/intermediates 245 and 246, this cascade sequence delivered its product in 50% yield and with all eight stereocenters in their desired configurations. Product 247 was then converted to dihydroxyaryl ether 248, which, on exposure to ZnI_2 and AcSH, furnished in one step iodothioacetate 251 through presumed oxonium species 249 and 250. The latter intermediate was elaborated to macrocyclic sulfone 252 by sequential cyclization and oxidation. A Ramberg–Bäcklund rearrangement then led to olefin 253, from which hirsutellone B (42) was generated through intermediates 254 and 255 as shown in Figure 18b. This synthesis is marked by the elegance of its cascade reactions and its flexibility to deliver other members of the hirsutellone class[444] and analogs thereof. Besides our presented synthesis, a number of other conceptual studies[445–448] were pursued with two culminating in formal[449] and total syntheses.[450]

Epicoccin G, 8,8′-*epi*-*ent*-rostratin B and emethallicin E

Epidithiodiketopiperazines and bis-(methylthio)diketopiperazines are naturally occurring molecules whose biological properties include antiviral, antibacterial, antimalarial and cytotoxic activities.[451–463] Because of their biological actions, these natural products hold potential as drug candidates or lead compounds for drug discovery, but they are often scarce for thorough biological evaluation. Their synthesis and analogs are, therefore, of crucial importance for biological investigations and drug discovery initiatives. In an effort to improve the methods for their synthesis, often suffering from the key sulfenylation step (the installment of the two required sulfur atoms onto appropriate diketopiperazine scaffolds), and in order to render them readily available for further explorations, we initiated a program directed toward their total synthesis. Attracted by the molecular architectures and biological properties of certain members of this class, and aiming to develop a new sulfenylation method, we targeted for total synthesis[464] epicoccin G [43, Figure 19a, originally isolated from *Epicoccum nigrum* (XZC04-CS-302)],[465–467] 8,8′-*epi*-*ent*-rostratin B (44, Figure 19a; rostratin B was isolated from *Exserohilum rostratum*)[468] and emethallicin E (45, Figure 19c, isolated from *Emericella heterothallica* ATCC 16824).[469] Figure 19a shows the retrosynthetic disconnections that led to the development of the synthetic strategy toward these target molecules. Crucial to the success of these total syntheses, whose highlights are summarized in Figure 19b, were the bis-photo-oxygenation/Kornblum–DeLaMare rearrangement and the discovery of an improved method for the sulfenylation of diketopiperazines (Figure 19d, method developing box). The asymmetric synthesis of epicoccin G (43) started with the readily available building block 256 (from *N*-Boc-L-tyrosine), which was converted to diketopiperazine 261 through a series of synthetic steps involving intermediates 257–260 (Figure 19b). Having failed in our attempts to introduce the required sulfur atoms in the next step, we were motivated to improve existing methods previously employed

Figure 19 Retrosynthetic analyses (**a**) and highlights of the total syntheses of epicoccin G (**43**) and 8,8′-*epi-ent*-rostratin B (**44**) (**b**), and emethallicin E (**45**) (**c**) as well as the mechanistic rationale for the developed sulfenylation method (**d**), and select synthesized designed analogues and their biological activities (**e**).

in such operations.[470–483] We soon discovered that treating sulfur with NaHMDS in THF at ambient temperature for a few minutes produced a solution that contained reactive sulfur species capable of sulfenylating enolates generated from diketopiperazines (see **270 → 271**, Figure 19d, box) under the same basic conditions and in the same pot.[484] Consisting mainly of tetrasulfides, the generated products (for example, **272**, formed via **271**, Figure 19d, box) were easily converted to either epidithiodiketopiperazines (**274**) or bis-methylthio diketopiperazines (**275**) via dithiolate species **273** (formed by NaBH₄ reduction of **272**, see Figure 19d, box), as shown in

Figure 19. Applying the newly developed method to diketopiperazine **261** gave epidithiodiketopiperazine intermediate **262**, formed together with its 2,2′-epimer (2,2′-*epi*-**262**, see Figure 19b). The former was smoothly transformed to epicoccin G (**43**), whereas the latter was employed to synthesize 8,8′-*epi-ent*-rostratin B (**44**) as summarized in Figure 19b. The same key building block **256** was converted by similar chemistry to emethallicin E (**45**) through intermediates **276–281** as highlighted in Figure 19c. In addition to the benefit of developing the improved and valuable sulfenylation reaction, this project revealed, through biological testing, potent activities against the poliovirus of the

a Retrosynthetic analysis
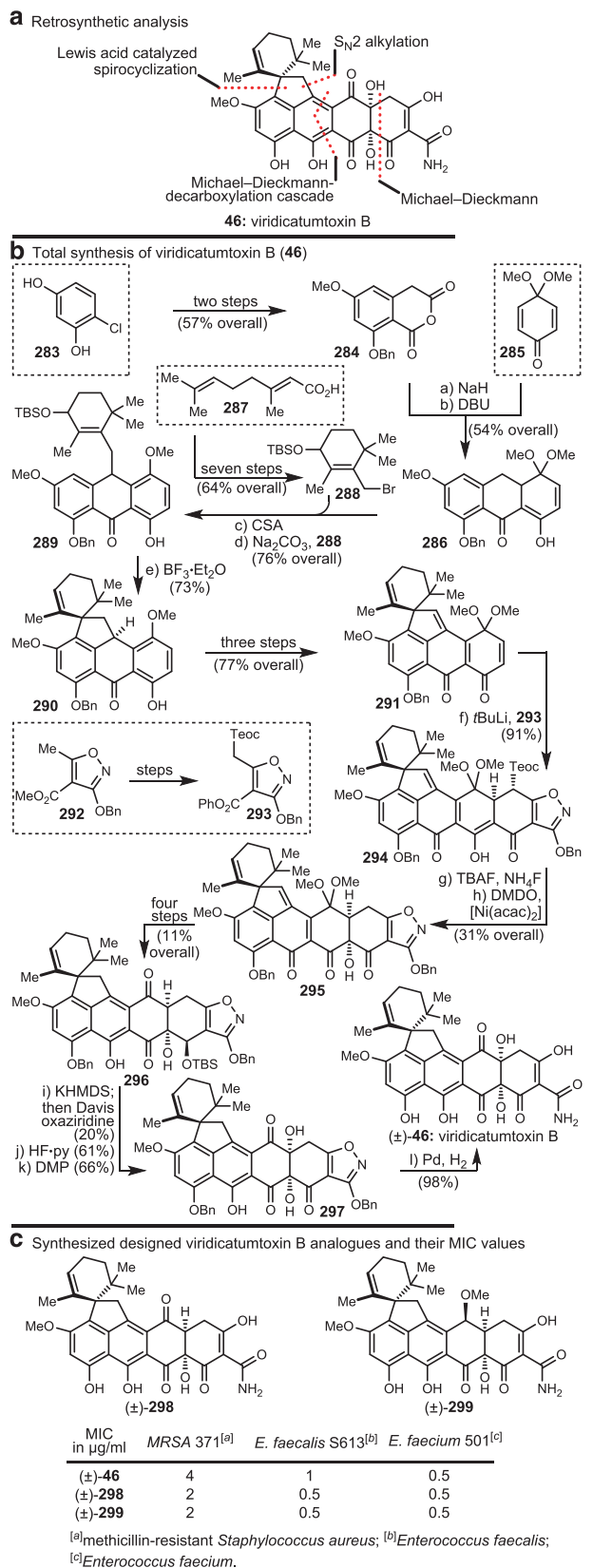
Figure 20 Retrosynthetic analysis (**a**) and highlights of the total synthesis (**b**) of viridicatumtoxin B (±-**46**), and select designed analogues and their biological activities (**c**).

encountered intermediates **262** and **282** (see Figure 19e, box). In addition to our own efforts several other laboratories reported on their progress toward or total syntheses of epicoccin G,[485,486] 8,8′-*epi-ent*-rostratin B,[487–490] and emethallicin E.[491]

Viridicatumtoxin B

Resembling but being more structurally complex than its siblings, viridicatumtoxin B (**46**, Figure 20a)[492] is loosely classified as a member of the tetracycline class of antibiotics due to its linear tetracyclic structural domain. Isolated from *Penicillium* sp. FR11 and possessing
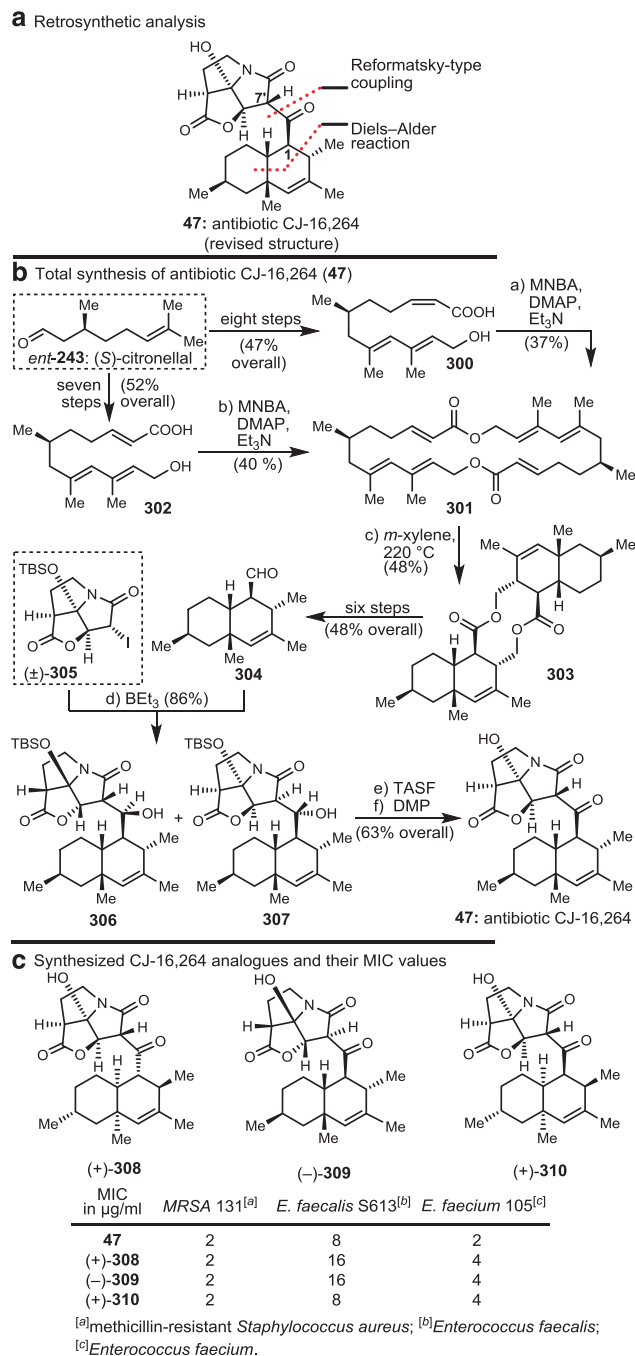

Figure 21 Retrosynthetic analysis (**a**) and highlights of the total synthesis (**b**) of antibiotic CJ-16,264 (**47**), and select designed analogues and their biological activities (**c**).

two additional rings than the traditional tetracyclines weaved in a spirocyclic structural motif, viridicatumtoxin B exhibits impressive antibacterial activities against drug-resistant bacteria, including Staph. aureus (MRSA).[492] The antibacterial properties of this impressive molecule presumably arise from its ability to inhibit UPP synthase, a key enzyme for bacterial peptidoglycan biosynthesis.[493,494] It became a synthetic target in our laboratories for its complexity and challenge, the appeal of its biological properties, and its potential as a lead compound for drug discovery. Figure 20a shows the strategic bond disconnections that guided the design of our synthetic strategy, which included two Michael–Dieckmann reactions, an S_N2-type alkylation, and a Lewis acid-catalyzed spirocyclization. Requiring building blocks 283, 285, 287 and 292 as starting materials, the synthesis proceeded along the pathway depicted in Figure 20b and through intermediates 284, 286, 288–291, 293–297. Noteworthy steps in this route, which in its original form delivered racemic viridicatumtoxin B,[97] included the alkylation of anthrone 286 under mild conditions, a step at which asymmetry could be introduced, in principle, in the growing molecule. Another remarkable step of this total synthesis is the final demasking of the distinguishing tetracyclic enolamide structural motif from its surrogate oxazoline functionality by hydrogenolysis, conditions that also led to the rapture of the two benzyl ethers of the ultimate precursor (297, Figure 20b). The total synthesis of viridicatumtoxin B not only rendered the racemic natural product readily available but also resulted in its structural revision.[97] Furthermore, an enantioselective total synthesis of viridicatumtoxin B (and decipherment of its absolute configuration) has been achieved in these laboratories employing phase-transfer catalysis.[495] Another important outcome of this total synthesis endeavor was the synthesis and biological evaluation of a series of simpler analogs of viridicatumtoxin B,[98] from which compounds (±)-298 and (±)-299 were notable for their potencies as compared to those of the racemic natural product [(±)-46] against drug-resistant bacteria (see Figure 20c).

Antibiotic CJ-16,264
A member of the pyrrolizidinone family of natural products, antibiotic CJ-16,264 (47, Figure 21a) was isolated from fungus CL39457.[496] It possesses a highly substituted decalin system and exhibits potent antibacterial properties against drug-resistant bacteria.[496] Its total synthesis from our laboratories rendered the natural product in its naturally occurring enantiomeric form readily available and led to its structural revision (configurations at C1 and C7').[497] Figure 21a summarizes our synthetic strategy, in retrosynthetic format, toward this target molecule which included a Reformatsky-type coupling and an intramolecular Diels–Alder reaction. The forward synthesis proceeded from citronellal (ent-243, also available in the other enantiomeric form) and racemic building block (±)-305[498] through intermediates 300 or 302 and 301, 303, 304 and 307 (Figure 21b). The availability of both enantiomers of these two building blocks was crucial for the final structural elucidation of antibiotic CJ-16,264. It provided several isomeric forms of the targeted molecule, allowing its structural identification as that depicted by structure 47. The most striking feature of this synthesis was the exclusive formation of diolide 303 incorporating two units of the desired decalin system from macrodiolide 301 through two consecutive, thermally induced, intramolecular Diels–Alder reactions. From the six isomers synthesized, the ones shown in Figure 21c proved the most active against methicillin-resistant Staph. aureus, Enterococcus faecalis S613 and Enterococcus faecium 105 (see Figure 21c). In addition to these CJ-16,264 isomers, the developed synthetic strategies and technologies made a number of structurally simpler analogs of this rather complex

antibiotic readily available (unpublished results), whose synthesis and biological evaluation will be reported in due course.

CONCLUSION
Microbes have been menacing society ever since the beginning of our existence. Empowering us to create new molecules in the laboratory, the advent of organic synthesis in the nineteenth century led to the introduction of the first antibacterial drugs. But it was not until we learned more about the pathogenesis of infectious diseases and the nature of microbes that we began to strategize against them in rational ways. Indeed, it was bacteria and fungi themselves that taught us how to fight them in the most effective ways: with the same weapons by which they have been waging war against each other and continue to do so today. Chemists were able to isolate an avalanche of powerful antibiotics from natural sources in a surge that climaxed into the antibiotic rush in the 1950s after the success of penicillin. And for a while it was perceived that the war against bacteria had been won. This is not so, as we came to know shortly thereafter. And we might not ever win it completely as we attempt to control the continuously emerging bacterial resistance, a phenomenon based on natural evolution. Ironically, it is human behavior and weakness that accelerate and spread bacterial resistance, whether it is through our medical, agricultural or psychological practices. Thankfully, the ever increasing power of our abilities to isolate new antibiotics from nature and to design and synthesize others like them in the laboratory provide us with the means to catch up with them, at least temporarily, by discovering and enlisting new weapons against them. The new antibiotics included in the last section and the synthetic work associated with them, for example, may hold the secrets to one or more new weapons to add to our arsenal—if only the funds were available to advance these investigations beyond the 'valley of death' where, unfortunately, so many academic discoveries remain buried.

The importance of continuous research and development for new antibiotics was furthermore highlighted by a press release from the World Health Organization (WHO) in February 2017.[499] It contains a list of the following 12 families of bacteria representing the greatest risk to human health.

WHO priority pathogens list for R&D of new antibiotics
Priority 1: (critical)[499]

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

  Priority 2: (high)

- *Enterococcus faecium*, vancomycin-resistant
- *Staph. aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

  Priority 3: (medium)

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

The severe threat emanating from these bacteria derives mainly from their resistance to known antibacterial drugs with the most dangerous strains being multidrug-resistant, and thus, capable of causing potentially untreatable, often deadly infections. The WHO urgently calls on governments worldwide to support research directed toward the discovery and development of new antibacterial agents against these dangerous strains. In parallel the organization also strongly recommends continuous improvements in preventing bacterial infections and strict enforcement of good practices in the application of currently used and to be discovered antibiotics as a means to prevent or at least curtail the emergence of resistance.[499]

The arms race against pathogenic microbes must continue with vigilance and prudency in order to avoid catastrophes of unpredictable and unimaginable proportions. At the same time we must restrict ourselves from practices that challenge their evolutionary instincts and propel them to develop resistance. It is this dual approach of wisdom and proactiveness that gives humanity hope to stay ahead of pathogenic microbes and, therefore, we must do what it takes to intensify our efforts in a focused and sustainable manner. We know what we have to do and how to do it. We must now gather the will and make the investment to implement our strategies to achieve the needed health security.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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