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From nature to the laboratory and into the clinic

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ABSTRACT

Natural products possess a broad diversity of structure and function, and they provide inspiration for chemistry, biology, and medicine. In this review article, we highlight and place in context our laboratory's total syntheses of, and related studies on, complex secondary metabolites that were clinically important drugs, or have since been developed into useful medicines, namely amphotericin B (**1**), calicheamicin γ_1^I (**2**), rapamycin (**3**), Taxol® (**4**), the epothilones [e.g., epothilones A (**5**) and B (**6**)], and vancomycin (**7**). We also briefly highlight our research with other selected inspirational natural products possessing interesting biological activities [i.e., dynemicin A (**8**), uncialamycin (**9**), eleutherobin (**10**), sarcodictyin A (**11**), azaspiracid-1 (**12**), thiostrepton (**13**), abyssomicin C (**14**), platensimycin (**15**), platencin (**16**), and palmerolide A (**17**)].

1. Introduction

The vast array of secondary metabolites found in nature provides a veritable treasure trove for drug discovery and development.[1,2] Natural products arise from a limited selection of simple building blocks and biosynthetic pathways, and yet the resulting diversity in both structure and function of these molecules far exceeds that found in synthetic compound libraries. Natural products are, therefore, a unique source of inspiration for chemists and biologists alike, and it is not surprising that they are the lead compounds for many drug discovery and development programs. Indeed, drugs developed from natural products are ubiquitous in modern medicine, particularly in the areas of anti-infectives, immunotherapy, and cancer chemotherapy.

We have had the opportunity and privilege to explore the chemistry and biology of several interesting secondary metabolites that were clinically important drugs, or have since been developed into clinically useful medicines. This review will highlight and put in a broader context our laboratory's work on these projects, namely the total synthesis of, and related studies on, amphotericin B (**1**, Fig. 1), calicheamicin γ_1^I (**2**), rapamycin (**3**), Taxol® (**4**), the epothilones [e.g., epothilones A (**5**) and B (**6**)], and vancomycin (**7**). Knowledge gleaned from these endeavors has advanced the understanding of the chemistry, biology, and medicine of these complex and structurally diverse molecules. The total synthesis of these secondary metabolites has led to the development of a range of useful synthetic strategies and technologies. Such studies have also enabled investigations into the biological function of these agents, resulting in the establishment of structure–activity relationships (SARs) within their classes and new insights into their mechanisms of action, and, in some cases, the discovery of potential drug candidates. Before concluding, we will also briefly highlight our studies with other selected bioactive natural products [i.e., dynemicin A (**8**, Fig. 2), uncialamycin (**9**), eleutherobin (**10**), sarcodictyin A (**11**), azaspiracid-1 (**12**), thiostrepton (**13**), abyssomicin C (**14**), platensimycin (**15**), platencin (**16**), and palmerolide A (**17**)] that provided useful insights into their chemistry and biology as part of our endeavors to develop useful biological tools and potential drug candidates.

2. Amphotericin B

Isolated from a strain of *Streptomyces nodosus* collected in 1955 from the Orinoco delta in Tembladora, Venezuela,[3] amphotericin B (**1**, Fig. 3) is the flagship member of the polyene macrolide family of natural products.[4] For nearly 50 years, amphotericin B as a deoxycholate complex has been, and continues to be, the gold standard for the treatment of life-threatening systemic fungal infections.[5] Despite its significant nephrotoxicity, the broad-spectrum activity and low incidence of fungal resistance after decades of use[6] has assured amphotericin B a continued and important role in modern medicine. Alternative formulations have been developed to address the observed nephrotoxicity of the deoxycholate complex, and some of these formulations are now in clinical use.[5a,7]

The mechanism of action of amphotericin B is not well understood. In a widely accepted model, several molecules of amphotericin B bind ergosterol and form an ion channel in the cellular membrane, disrupting potassium gradients.[8] However, amphotericin B appears to have multiple molecular functions, none of which is completely characterized.[7a] Recent findings by Burke and

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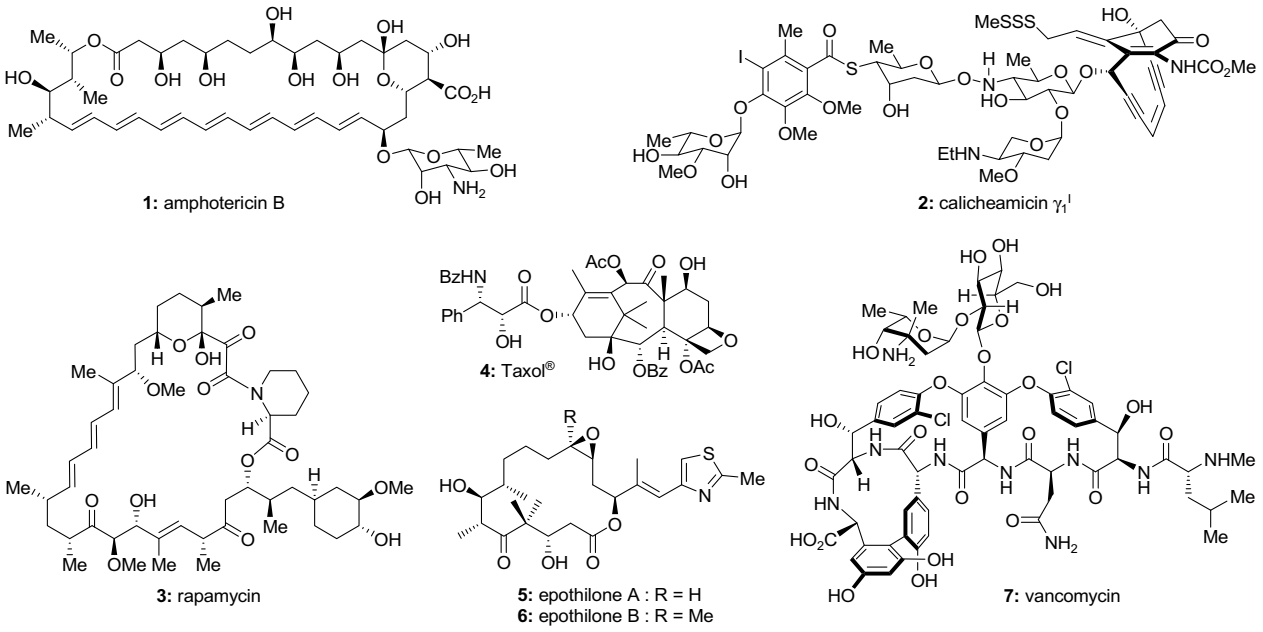


Figure 1. Molecular structures of selected natural product drugs and drug leads.

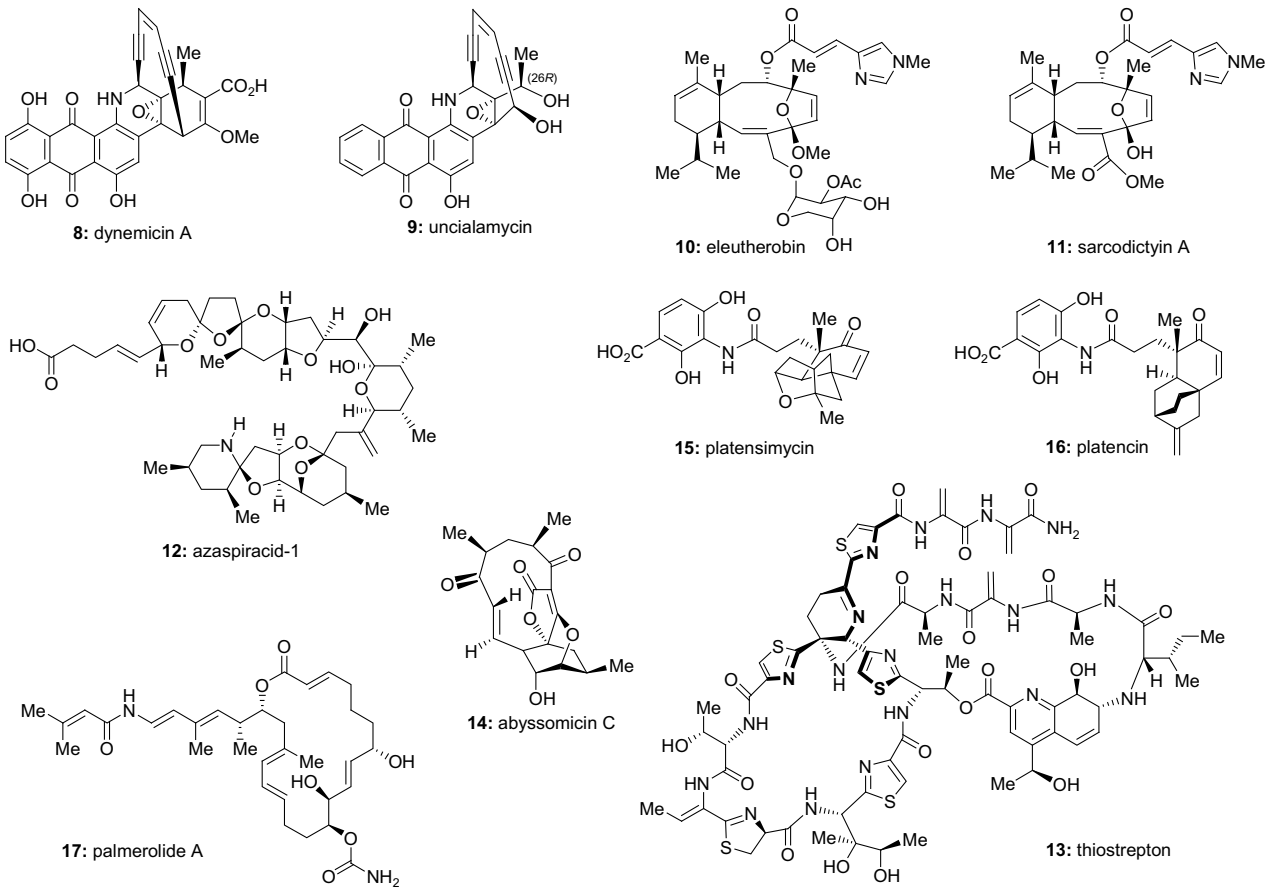


Figure 2. Molecular structures of selected bioactive natural products.

coworkers suggest either key details of the pore structure may be in error, or ion channel formation may not be essential for antifungal activity.[9] The chemical and photochemical instability of amphotericin B has impeded efforts toward elucidating its SARs and its mechanism of action. Hoping to enable investigations into the biology of amphotericin B and other polyene macrolide antibiotics, we embarked in the 1980s on a total synthesis of amphoteronolide B (**18**, Fig. 3) and amphotericin B (**1**).[10]

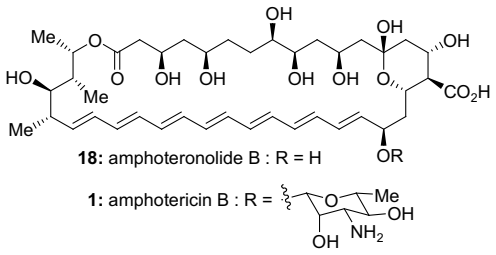


Figure 3. Molecular structures of amphoteronolide B (**18**) and amphotericin B (**1**).

The highlight of our total syntheses of amphoteronolide B (**18**) and amphotericin B (**1**), completed in 1987, was a macrocyclization process featuring a ketophosphonate–aldehyde condensation (Scheme 1). This strategy had been previously developed and deployed by us[11] and by others,[12] but this application remains to this day one of the most, if not the most, demanding tests of this macrocyclization technique. Pleasantly, the yellow-colored ketophosphonate **19** was converted into red/orange-colored 38-membered macrocycle **20** in 70% yield upon exposure to mildly basic conditions. Macrocycle **20** was then successfully transformed into amphoteronolide B (**18**) and amphotericin B (**1**), validating our synthetic strategy. Ketophosphonate–aldehyde macrocyclizations have since been successfully applied to many other total syntheses.[13]

3. Calicheamicin γ_1^I

The calicheamicins, reported in 1987,[14] are enediyne antitumor antibiotics[15] isolated from *Micromonospora echinospora* spp. *calichensis*, a bacterium residing in a rock (*caliche* in Greek) collected from Texas. Calicheamicin γ_1^I (**2**, Fig. 4), the most prominent member of the enediyne class of natural products, possesses phenomenal cytotoxicity against tumor cells. Although calicheamicin γ_1^I is too toxic and indiscriminant for use as a drug, gemtuzumab ozogamicin (Mylotarg®, **21**, Fig. 4), a derivative of calicheamicin γ_1^I conjugated to a humanized anti-CD33 antibody, was developed as an anticancer agent.[16] In 2000, Mylotarg® became the first antibody–drug conjugate to be approved for clinical use by the Food and Drug Administration (FDA) in the USA. It is indicated for the treatment of certain acute myeloid leukemias (AML).

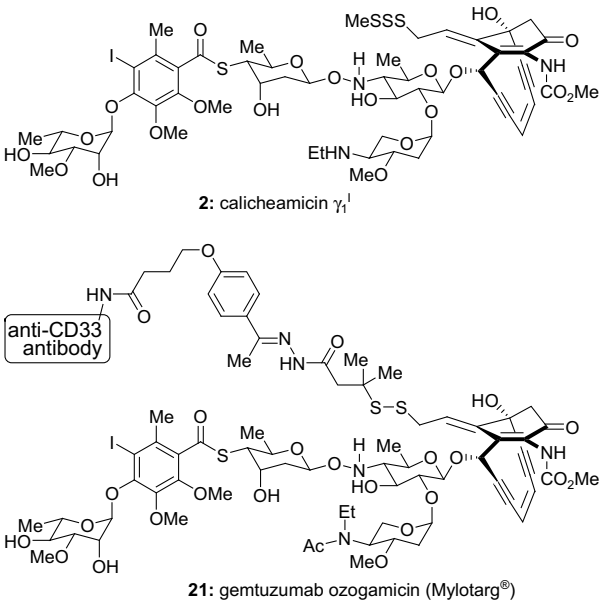
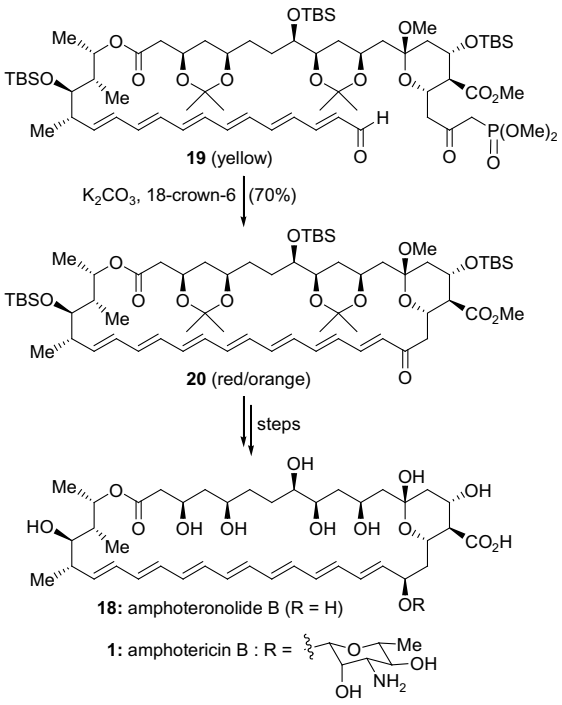


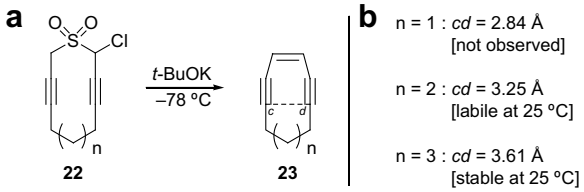
Figure 4. Molecular structures of calicheamicin γ_1^I (**2**) and gemtuzumab ozogamicin (Mylotarg®, **21**).

The complex structure of calicheamicin γ_1^I (**2**) possesses three distinct domains: an oligosaccharide chain, a trisulfide moiety, and an enediyne core. The oligosaccharide chain recognizes and targets selected base pair sequences in the minor groove of DNA. The trisulfide moiety then serves as a molecular trigger, and upon reductive activation, the resulting thiolate performs an intramolecular Michael addition onto the proximally positioned enone moiety to unlock the enediyne warhead. Bergman cycloaromatization[17] of the enediyne structural motif then generates a *para*-benzyne diradical,[18] which abstracts hydrogen radicals from the DNA backbone. Reaction of the so-formed DNA backbone radicals with molecular oxygen results in double strand cuts, leading to cell death. By virtue of this ingenious mechanism of action, the calicheamicins and other enediynes have been hailed as masterpieces of molecular design by nature that have captured the imagination of chemists and biologists alike.[15,16]

Intrigued by the structure and the mechanism of action of the calicheamicins, we set out on a study of enediyne reactivity.[19] Simple cyclic enediyne model systems **23** (Scheme 2) were prepared



Scheme 1. Application of the ketophosphonate–aldehyde macrocyclization to the total synthesis of amphoteronolide B (**18**) and amphotericin B (**1**) (Nicolaou et al., 1987).[10]

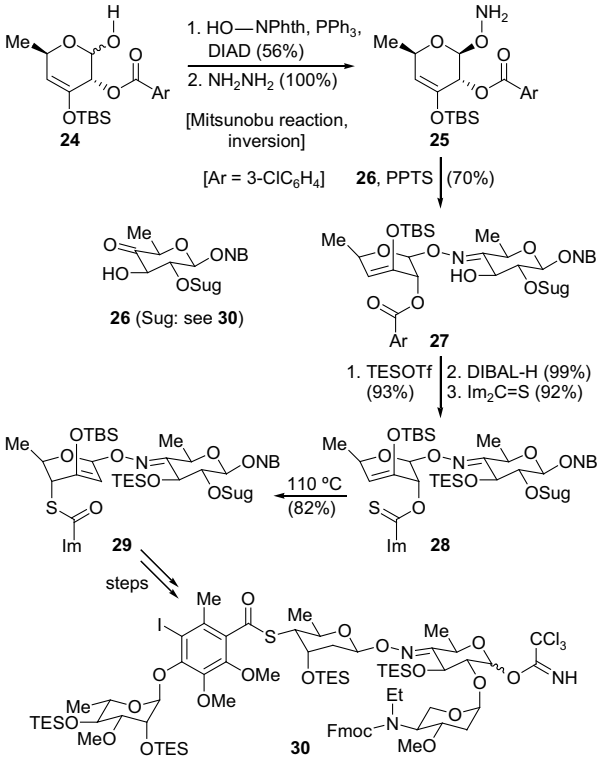


Scheme 2. (a) Application of the Ramberg–Bäcklund reaction to the preparation of simple enediyne model systems. (b) Calculated *cd* distances (Nicolaou et al., 1988–1992).[19]

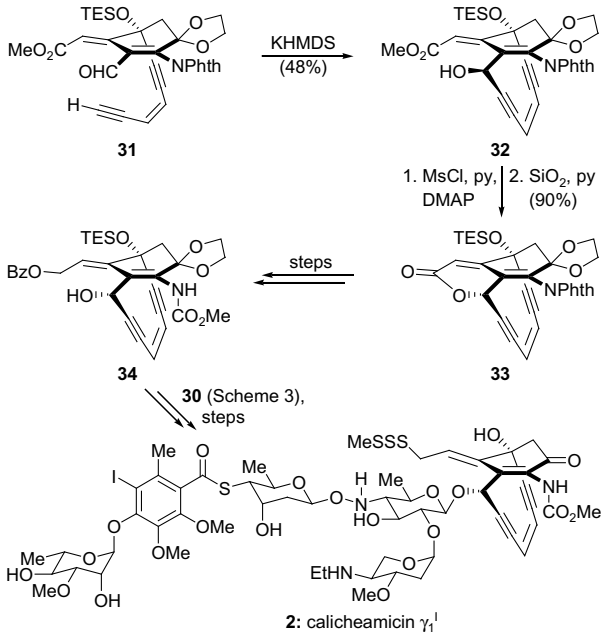
by the Ramberg–Bäcklund reaction[20] of halosulfones **22**, and by comparing the geometric parameters of these designed structures with their propensity toward Bergman cycloaromatization, we concluded that the *cd* distance (see structure **23**, Scheme 2) of an enediyne was well correlated with its propensity to undergo Bergman cycloaromatization. Thus, enediynes within this series with a *cd* distance greater than 3.31 Å were found to be stable at room temperature, whereas those predicted to have a *cd* distance below 3.20 Å could not be isolated, presumably because they rapidly underwent Bergman cycloaromatization. Ten-membered ring enediyne natural products have *cd* distances near this critical range, and thus are prone to cycloaromatization upon relatively minor structural changes within the molecule. Separately, our collaborative studies on the interaction of the oligosaccharide portion of calicheamicin γ_1^I with DNA led to interesting insights relating to DNA–carbohydrate interactions.[21]

As one might expect from the novelty and complexity of the target molecule, our campaign for the total synthesis of calicheamicin γ_1^I (**2**),[22] completed in 1992, was rich in chemical challenges and discoveries, a few of which are highlighted here. The unusual N–O glycoside linkage within the oligosaccharide domain was constructed through a Mitsunobu reaction[23] with hemiacetal **24** (Scheme 3). The neighboring ester did not control the stereochemistry of the newly formed acetal moiety, but rather, the stereochemical distribution of products was consistent with an S_N2 reaction. Condensation of the *N*-deprotected material (**25**) with ketone **26** completed the installation of the N–O linkage to give oxime ether **27**. This was converted into thiocarbonyl-containing intermediate **28**, which underwent a stereospecific [3,3]-sigmatropic rearrangement to give thioester **29**, an intermediate that was successfully elaborated into protected oligosaccharide fragment **30**.

The calicheamicinone core (**32**, Scheme 4) was constructed through an acetylene–aldehyde cyclization of precursor **31**. The



Scheme 3. Highlights of the synthesis of the calicheamicin γ_1^I oligosaccharide domain (**30**) (Nicolaou et al., 1990).[22a,22d]



Scheme 4. Highlights of the total synthesis of the calicheamicinone core and the total synthesis of calicheamicin γ_1^I (**2**) (Nicolaou et al., 1992).[22]

resulting propargylic hydroxyl group possessed the incorrect stereochemical arrangement, and all attempts at Mitsunobu inversion or similar reactions were unsuccessful. However, we discovered that formation of the corresponding mesylate and exposure to silica gel gave lactone **33** with clean inversion of stereochemistry. This material was elaborated to provide advanced intermediate **34**, which was coupled with oligosaccharide fragment **30** and successfully transformed into calicheamicin γ_1^I (**2**). A total synthesis of calicheamicin γ_1^I similarly rich in discoveries was later completed by the Danishefsky camp.[24]

4. Rapamycin

Rapamycin (sirolimus, **3**, Fig. 5)[25] was isolated in the early 1970s from *Streptomyces hygroscopicus*, a bacterium found on Rapa Nui (Easter Island).[26] First discovered as an antifungal agent, rapamycin was soon found to be too toxic for that purpose.[27] However, it was revisited because of its immunosuppressive properties, and,

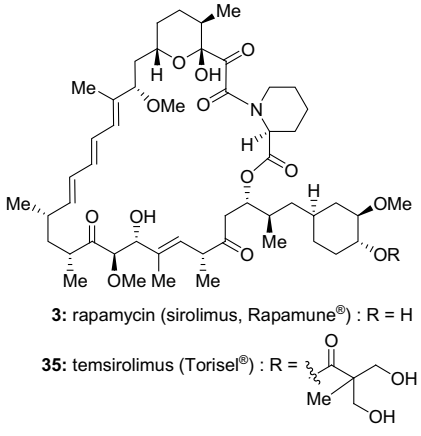


Figure 5. Molecular structures of rapamycin (Rapamune®, **3**) and temsirolimus (Torisel®, **35**).

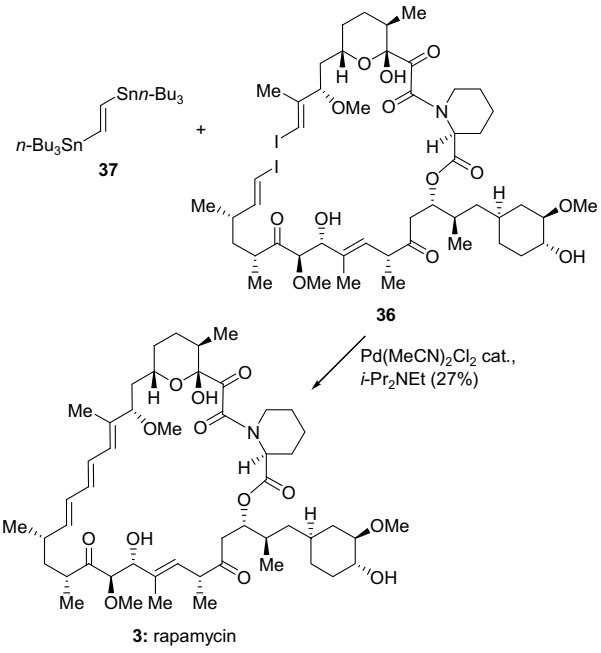
in 1997, rapamycin was launched as the immunosuppressant Rapamune®. A rapamycin-eluting stent was approved by the FDA in 2003. In 2007, the semisynthetic analog temsirolimus (Torisel®, **35**, Fig. 5) was approved by the FDA for the treatment of advanced renal cell carcinoma.

Rapamycin interacts with FK506 binding protein (FKBP) to form a protein–drug complex.[28] Despite sharing the same protein target, rapamycin's mechanism of action is different from that of FK506. Indeed, rapamycin and FK506 are competitive antagonists to each other.[29] The FKBP–rapamycin combination forms a ternary complex with the mammalian target of rapamycin (mTOR), and it is through this supramolecular assemblage that rapamycin exerts its biological properties, including immunosuppressive and cytostatic activity.[25,30] Rapamycin and other TOR ligands may play a role in a wide range of disease states and health conditions that are not yet fully explored.

The first total synthesis of rapamycin was reported from our laboratory in 1993.[31] Our synthetic strategy featured as final step a 'double stitching' cyclization, a concept first introduced specifically for this project. Thus, as shown in Scheme 5, diiodide **36**, free of protecting groups, was subjected to a double Stille coupling[32] with distannylethylene **37** to furnish rapamycin (**3**) in 27% yield. This strategy is notable for its brevity and affording the natural product directly and without further manipulations upon ring closure.[33] Subsequent total syntheses of rapamycin include those from the laboratories of Schreiber,[34] Danishefsky,[35] Smith,[36] and Ley.[37]

5. Taxol®

The toxic properties of yew trees have been recognized since ancient times. However, the modern story of Taxol® (paclitaxel, **4**, Fig. 6)[38] began in 1962 with the collection of bark from the Pacific yew tree *Taxus brevifolia*. The molecular structure of Taxol® was disclosed in 1971,[39] and its then novel mechanism of action was reported in the late 1970s.[40] Taxol® was launched in 1992 for the treatment of refractory ovarian cancer, and the semisynthetic taxoid docetaxel (Taxotere®, **38**, Fig. 6) in 1996 for certain



Scheme 5. Application of the 'double stitching' macrocyclization to the total synthesis of rapamycin (**3**) (Nicolaou et al., 1993).[31]

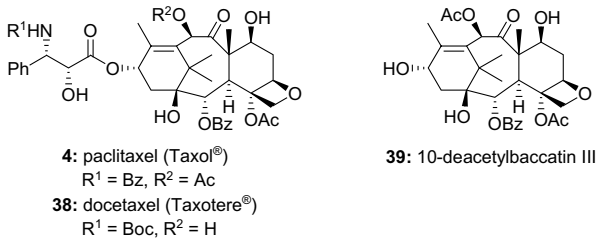


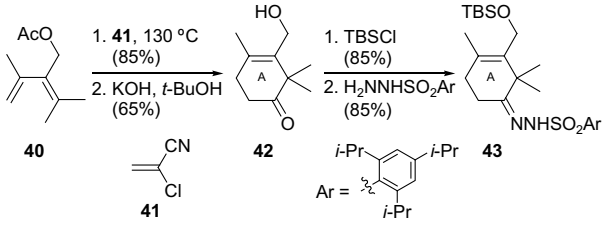
Figure 6. Molecular structures of paclitaxel (Taxol®, **4**), docetaxel (Taxotere®, **38**), and 10-deacetylbaccatin III (**39**).

breast cancers. Both anticancer agents have since been approved by the FDA for other indications. In 2004, the FDA approved the use of a paclitaxel-eluting stent. Abraxane®, a paclitaxel nanoparticle formulation, was approved in 2006.

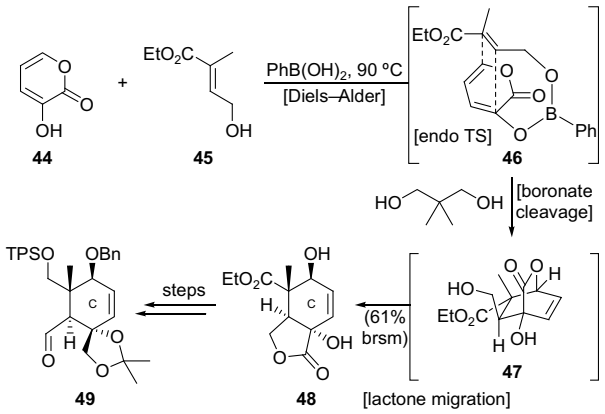
Taxol® exerts its cytotoxic effect by interacting with tubulin.[40] In contrast to other antimitotic anticancer drugs such as vinblastine, which act to inhibit microtubule formation, Taxol® acts by promoting microtubule formation and stabilizing microtubules. The disclosure of this mechanism of action ignited interest in this long-overlooked compound. In light of the importance of Taxol® in cancer chemotherapy, its SARs have been extensively studied.[41]

By the early 2000s, Taxol® (**4**) had become the best-selling anticancer drug of all time. However, there was a time when its development was in doubt because of the low availability from its natural source, the rare and slow-growing Pacific yew tree *T. brevifolia*. Indeed, the issues associated with Taxol® supply prompted the National Cancer Institute (NCI) to reevaluate its policies regarding the development of large-scale production methods for promising anticancer agents.[42] Fortunately, 10-deacetylbaccatin III (**39**, Fig. 6), readily available from the European yew tree *Taxus baccata*, was found to be a suitable precursor for industrial scale semisynthetic production of both Taxol® (**4**) and docetaxel (**38**),[43] and alternative methods of production have since been developed.[44] Before these discoveries, however, total synthesis was thought to be the only solution for the sustainable supply of Taxol®. The synthetic chemistry community responded, and several total syntheses have been disclosed.

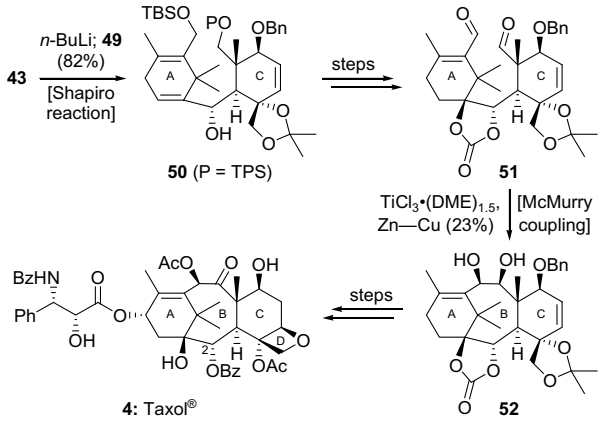
Completed in 1994, our total synthesis of Taxol®[45] featured two early-stage Diels–Alder cycloadditions[46] for the construction of the A- and C-ring equivalents. Heating diene **40** (Scheme 6) and ketene equivalent **41** afforded, after exposure to strong base, cyclohexene **42**, which was transformed into hydrazone **43**. The Diels–Alder based construction of the C-ring surrogate was originally problematic due to poor regioselectivity and low yield. However, taking inspiration from the work of Narasaka,[47] phenylboronic acid was used as a tether to preorganize pyrone **44** (Scheme 7) and dienophile **45** as shown in intermediate **46**, enhancing the propensity of the reactants toward a Diels–Alder cycloaddition and enforcing the desired regioselectivity. The boronate tether was then cleaved by the addition of a diol, providing lactone **48** (formed by sponta-



Scheme 6. Diels–Alder based construction of the A-ring fragment of Taxol® (Nicolaou et al., 1994).[45]



Scheme 7. Boron-tethered Diels–Alder based construction of the C-ring fragment of Taxol® (Nicolaou et al., 1994).[45]



Scheme 8. Highlights of the total synthesis of Taxol® (**4**) (Nicolaou et al., 1994).[45]

neous lactone migration of Diels–Alder cycloadduct **47**) in 61% yield. Lactone **48** was elaborated into C-ring fragment **49**, which also possesses the functionality required for installation of the oxirane ring.

A Shapiro reaction[48] converted the A-ring fragment **43** into a vinyl lithium species, which was trapped with C-ring aldehyde **49** to give intermediate **50** (Scheme 8) in 82% yield. The latter compound was converted into dialdehyde **51**, setting the stage for the critical 8-membered B-ring formation. The action of $TiCl_3{\cdot}(DME)_{1.5}$ and Zn–Cu couple effected an intramolecular McMurry coupling[49] on dialdehyde **51** and forged the strained B-ring to yield ABC-ring intermediate **52**. Further manipulations and side chain attachment then furnished Taxol® (**4**). The Holton group reported their total synthesis of Taxol®[50] at about the same time. Additional total syntheses of Taxol® followed in the next few years from the laboratories of Danishefsky,[51] Wender,[52] Kuwajima,[53] and Mukaiyama.[54]

Our Taxol® campaign yielded, in addition to its coveted target, a plethora of other discoveries. A practical avenue to C2 Taxol® analogs (see numbering on Scheme 8) was developed and exploited to construct numerous such taxanes.[45a,55] In addition, several water-soluble Taxol® prodrugs,[56] aromatic C-ring analogs,[57] and fluorescent Taxol® derivatives for use as biological probes[58] were designed and synthesized.

6. Epothilones

Epothilones A (**5**, Fig. 7) and B (**6**, Fig. 7)[59] were first discovered in the 1980s as novel antifungal agents.[60] They were soon recognized as potent antitumor agents, but they would not garner the attention they deserved until the compounds were rediscovered in the 1990s,[61] when their mechanism of action was determined. The epothilones have the same mechanism of action as Taxol®,[61,62] but with some improved properties, including the ability to overcome Taxol® resistance.[61–63] By 2007, at least seven epothilones, including the naturally occurring epothilone B, had been advanced to clinical trials. In October 2007, ixabepilone (Ixempra®, **53**, Fig. 7), a semisynthetic analog of epothilone B, was approved by the FDA for the treatment of certain advanced breast cancers. Ixempra® is the first epothilone to reach the clinic as an approved medication for cancer patients.

The epothilones bind to tubulin in the same protein pocket as Taxol®,[61] although apparently with different key interactions.[64] However, in contrast to most other antitumor agents, they show little susceptibility to phosphoglycoprotein-mediated drug efflux, giving them a distinctly different activity profile against multidrug-resistant (MDR) cancer cell lines.[61–63] Over 30 total syntheses of epothilones A (**5**) and B (**6**) have been reported,[39a,65] beginning with the pioneering syntheses by Danishefsky et al.,[66] us,[67,68] and Schinzer et al.[69] The development of flexible and efficient de novo syntheses of the epothilones has enabled detailed SARs investigations on all domains of the epothilone structure.[59,60,63,65]

In 1997, we disclosed the total synthesis of the epothilones by two distinct strategies: macrolactonization[67] and ring-closing olefin metathesis.[68] The latter strategy, as applied to the total synthesis of epothilone A (**5**), is shown in Scheme 9. Thus, triene **54** was exposed to catalytic ruthenium metathesis initiator **55**[70] to provide macrocycle **56** in 46% yield (plus 39% yield of the *E* isomer). While this was a relatively untested strategy at the time, its success on such a multifunctional substrate helped to propel olefin metathesis[71] to become a popular reaction in the total synthesis of complex molecules. Desilylation and epoxidation (promoted by dioxirane **57**) then completed the total synthesis of epothilone A (**5**).

Applying our solution and solid phase synthetic technologies, we synthesized hundreds of epothilone analogs and, through collaborative biological investigations, established useful SARs.[72] For example, we demonstrated that the presence and precise position of the basic nitrogen of the side chain is crucial for potent activity, and that analogs with cyclopropane moieties with *cis* or *trans* configurations [e.g., **58** (Fig. 8)] possess comparable potency to the natural epothilones.[72a] Based on these studies, later efforts focused

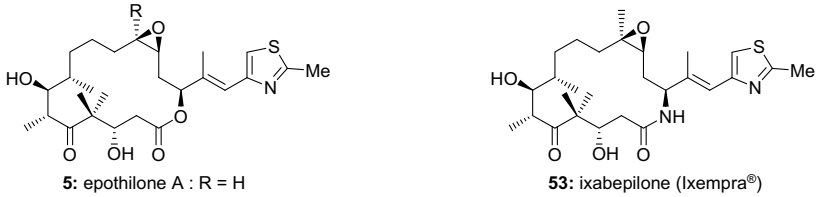
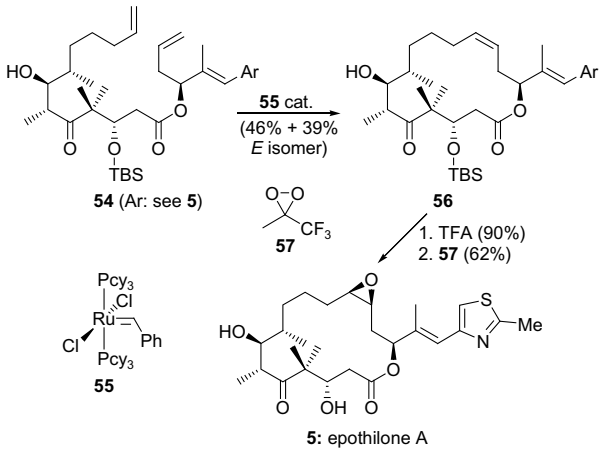
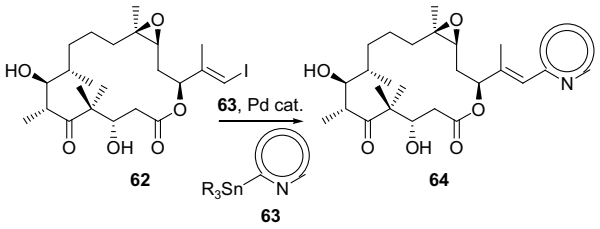


Figure 7. Molecular structures of epothilones A (**5**) and B (**6**) and ixabepilone (Ixempra®, **53**).



Scheme 9. Application of the olefin metathesis macrocyclization to the total synthesis of epothilone A (**5**) (Nicolaou et al., 1997).[68]



Scheme 10. General one-step synthesis of epothilone analogs with various heteroaromatic ring systems (Nicolaou et al., 2002).[73]

on analogs of general structure **64** (Scheme 10), possessing a heteroaromatic ring system with an *ortho*-positioned basic nitrogen.[73] These analogs were synthesized in one step by a Stille cross-coupling[32] reaction of vinyl iodide **62** with heteroaromatic stannanes of general structure **63**. Analogs containing pyridines, thiazoles, pyrazoles, imidazoles, triazoles, tetrazoles, and benzothiazoles were designed, synthesized, and evaluated for antitumor potency. Selected analogs (**59–61**)[72b,73] that display higher potency than the natural epothilones against a panel of tumor cell lines (including Taxol®- and epothilone-resistant strains) are shown in Figure 8. Thiazole analog **59** entered phase I clinical trials, and pyrazole analog **61** was recently licensed by a biotechnology company for further evaluation and development.

7. Vancomycin

Vancomycin (**7**, Fig. 9)[74] was discovered in 1956 from a soil sample collected in the jungles of Borneo.[75] Due to its unprecedented broad-spectrum activity against Gram-positive bacteria, the compound was renamed from O5865 to vancomycin (derived from 'to vanquish'), and was approved as an antibiotic by the FDA in 1958. Though vancomycin and its sister antibiotic, teicoplanin [see teicoplanin A_2-2 (**65**), Fig. 9], are not the most widely used antibiotics, they nonetheless are critical medications in our arsenal against drug-resistant Gram-positive bacteria because they serve as antibiotics of last resort when other drugs fail. With the growing problem of antibiotic resistance,[76] vancomycin has taken on an increasingly important role. However, no antibiotic can vanquish bacteria forever. With the discovery of vancomycin-resistant strains of methicillin-resistant *Staphylococcus aureus* (MRSA) in 1997,[77] the urgent need to develop new antibiotics effective against such superbugs became clearly evident.

Vancomycin and other glycopeptide antibiotics attack Gram-positive bacteria by binding to an L-Lys-D-Ala-D-Ala fragment of the peptidoglycan structure of their cell wall.[74,78] The disclosure of the molecular structure of vancomycin in the early 1980s[79] allowed this interaction to be studied in detail, and five important hydrogen bonding interactions between vancomycin and the bacterial cell wall have been identified.[78] In order to further the understanding of vancomycin's mechanism of action and possibly develop next-generation vancomycin-based antibiotics, synthetic chemists sought to construct vancomycin and to gain further insights into its structure and activity. The Evans laboratory[80] and our group[81] reported total syntheses of vancomycin aglycon simultaneously in 1998. In 1999, Boger and coworkers completed their total synthesis of vancomycin aglycon,[82] and our laboratory completed the total synthesis of vancomycin (**7**).[83] Since then, the Boger[82a,84] and Evans[85] groups have also prepared teicoplanin aglycon by total synthesis.

The first challenge addressed by our total synthesis of vancomycin was the atropselective construction of the axially chiral biaryl system. Diol **66** (Scheme 11) was monoprotected, and the resulting product was transformed into cyclic boronate monoester **67**. Suzuki cross-coupling[32] with aryl iodide **68** then furnished biaryl system **69** in 84% yield as a 2:1 mixture of atropisomers. The desired atropisomer was converted into triazine intermediate **70**, setting the stage for a triazine-driven bisaryl ether synthesis, which afforded macrocycle **71** (Scheme 12) in 67% yield and as a 1:1 ratio of atropisomers. Developed in response to the challenge presented by vancomycin,[81a,86] this reaction was facilitated by copper(I), which is thought to bind to the strategically placed triazine moiety, templating the substrate to bring about the desired macro-

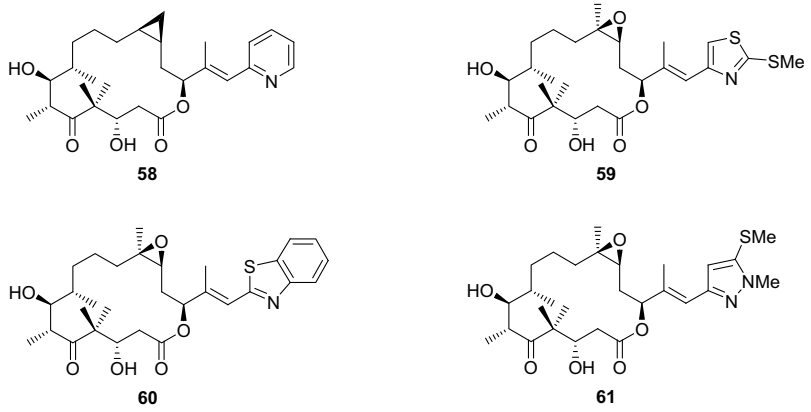


Figure 8. Molecular structures of selected highly potent epothilone analogs (Nicolaou et al., 1998–2006).[72,73]

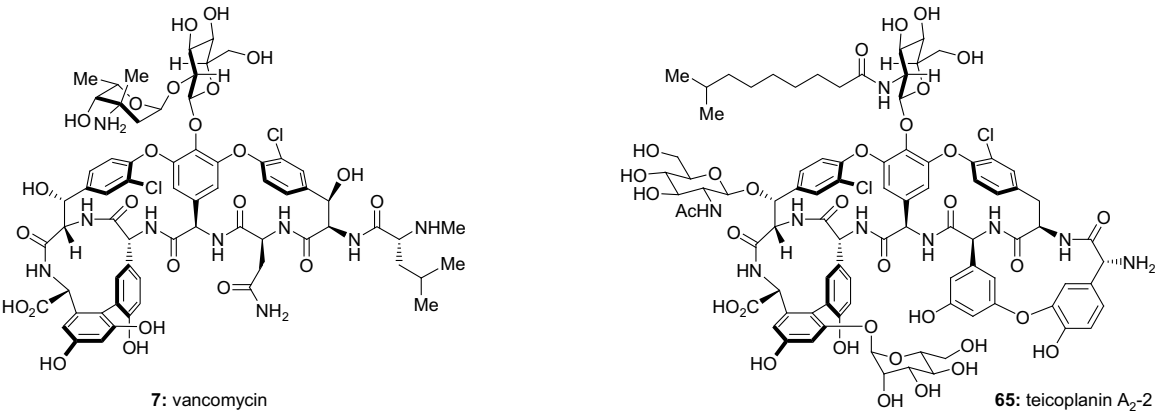
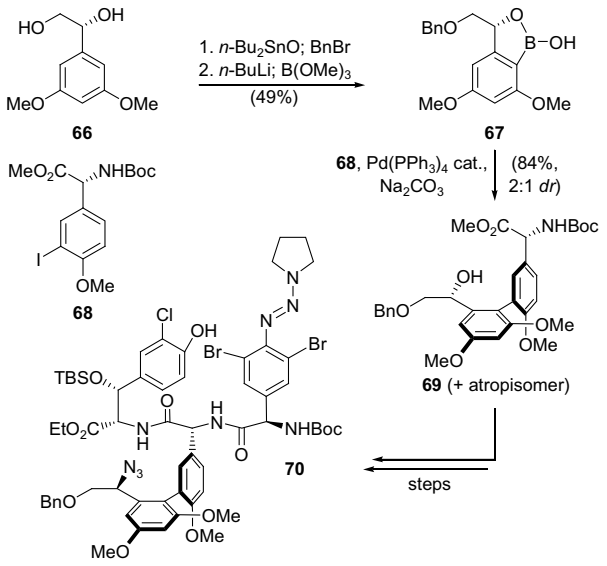


Figure 9. Molecular structures of vancomycin (**7**) and teicoplanin A_2-2 (**65**).



Scheme 11. Application of an atropselective Suzuki cross-coupling to the construction of triazine **70** (Nicolaou et al., 1998).[81]

cyclic bisaryl ether formation under exceptionally mild conditions while avoiding epimerization of the highly sensitive arylglycine groups. The desired atropisomer was then advanced to intermediate **72**, at which point a second triazine-driven bisaryl ether formation was employed to forge the remaining macrocyclic domain of the molecule, providing predominantly the undesired atropisomer (**73**). Thermal equilibration of **73** gave access to the desired atropisomer (**74**), which was then carried forward to complete the total syntheses of vancomycin aglycon and vancomycin (**7**). These highlights give a few examples of how natural product total synthesis can drive the development of synthetic technologies.

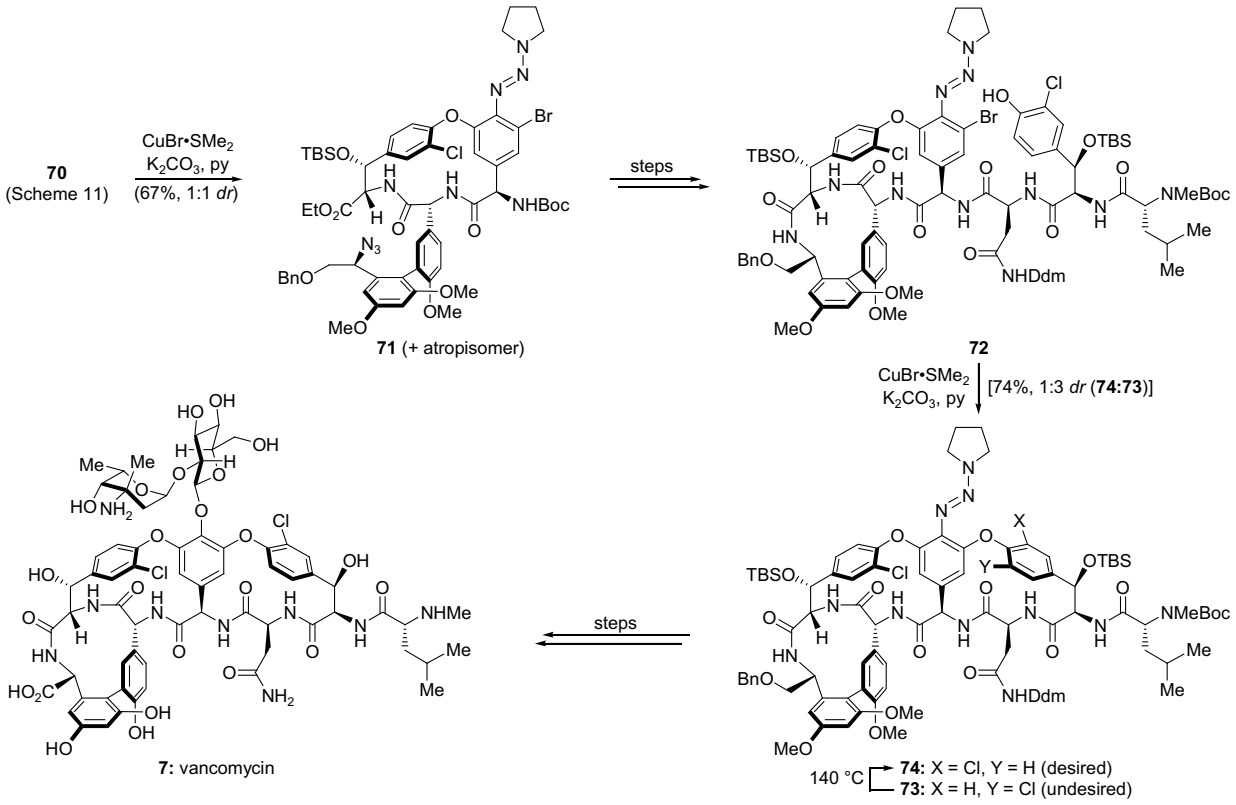
Having completed the total synthesis of vancomycin, we proceeded to design and synthesize a number of vancomycin structures for biological evaluation.[87] These studies culminated in the discovery of several vancomycin dimers, such as **75** (Fig. 10), that exhibited highly potent activity against drug-resistant bacteria, including vancomycin-resistant strains. Using dynamically generated virtual combinatorial libraries, a concept first introduced by Lehn and coworkers,[88] a greater number of potential dimeric pairs were evaluated than could readily be prepared individually. In short, mixtures of monomeric units were allowed to interact with a target containing an L-Lys-D-Ala-D-Ala moiety, and subsequent dimerization of the preorganized monomeric units preferentially dimerized the tightest-binding pairs. These dimeric compounds exhibited not only enhanced potency, but also the ability to overcome the most common mechanism of bacterial resistance to vancomycin.[89] Many resistant strains alter the vancomycin binding site into an L-Lys-D-Ala-D-Lac ester linkage, disrupting a critical hydrogen bond to vancomycin. The tighter binding of these dimeric analogs evidently allows them to retain high potency even against such strains. Therefore, vancomycin dimers such as **75** represent promising lead compounds for the development of next-generation vancomycin-based antibiotics.

8. Other promising bioactive molecules

The development of clinically useful drugs is a long and tedious process that can take many years to come to fruition. Experience, however, teaches us that today's basic discoveries may be the foundation of tomorrow's medicines. The sections above highlight our contributions to the chemistry and biology of some molecules successful in human medicine. This section will briefly highlight selected examples of our studies on a number of naturally occurring substances that possess promising biological activities but are not, at least as yet, in the clinic.

Following our research on calicheamicin γ_1^I, our work on enediynes expanded to include investigations of the chemistry and biology of other enediyne natural products and designed analogs. During the 1990s, a series of analogs of dynemicin A (**8**, Fig. 11)[90] were designed and synthesized, and their biological properties evaluated.[91,92] Dynemicin analog **76** was especially interesting, exhibiting potent broad-spectrum activity against tumor cells, in particular leukemia cell lines. In 2007, we accomplished a racemic synthesis and stereochemical assignment of uncialamycin (**9**, Fig. 11),[93,94] an enediyne recently discovered in minute quantities from an incompletely characterized strain of Streptomycete. Our subsequent enantioselective synthesis of uncialamycin (**9**) and 26-*epi*-uncialamycin (**77**, Fig. 11) enabled extensive in vitro biological investigations of these molecules, which we demonstrated to be highly potent DNA cleaving agents with promising antibiotic and antitumor properties.[95]

Eleutherobin (**10**, Fig. 12)[96] is a cytotoxic microtubule stabilizing agent isolated from an *Eleutherobia* species of soft coral collected from a coastal area of western Australia and disclosed in 1995. Because of the limited supply of this promising but extremely scarce bioactive substance and of the closely related natural products eleuthosides A (**78**, Fig. 12) and B (**79**, Fig. 12)[97] and sarcodictyins A (**11**, Fig. 12) and B (**80**, Fig. 12)[98] and their perceived importance as potential anticancer agents,[99] we set out to



Scheme 12. Application of the triazine-driven bisaryl ether synthesis to the total synthesis of vancomycin aglycon and vancomycin (**7**) (Nicolaou et al., 1998–1999).[81,83]

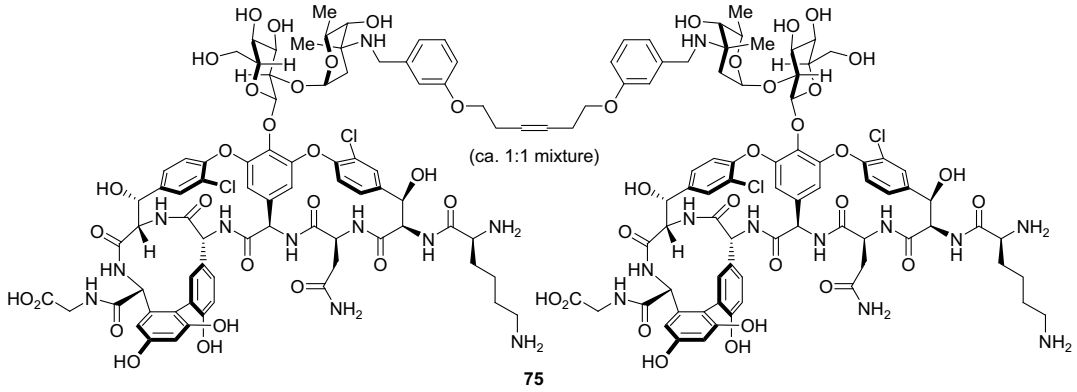


Figure 10. Molecular structure of a highly potent dimeric vancomycin analog active against vancomycin-resistant bacteria (Nicolaou et al., 2001).[87]

synthesize them in the laboratory, a goal that was achieved in 1997.[100,101] In addition to supplying enough material for further biological evaluation, the synthetic technology that was developed was also adapted to the solution and solid phase synthesis of a combinatorial library of these novel structures.[102] The evaluation of these analogs defined the SARs for this class of molecules and identified compound **81** (Fig. 12) as a potent cytotoxic agent that retains activity against Taxol®-resistant cell lines.

Azaspiracid-1 (**12**, Fig. 13) is a marine toxin found in contaminated mussels. Isolated in 1998,[103] it is responsible for a toxic syndrome known as azaspiracid poisoning (AZP).[104] Because of the importance of this toxin in human health, we pursued the total synthesis of the published structure of the azaspiracid-1 (four possible isomers were proposed, one of which was structure **82**, Fig. 13) only to find, in 2003, that none of the proposed structures were correct.[105] Careful investigation of the structural discrepancies and de novo synthesis of multiple fragments and analogs for spectroscopic comparisons with the natural substance and its degradation products ultimately revealed the true structure of azaspiracid-1 to be **12** (Fig. 13).[106,107] An improved synthesis of this molecule[108] also provided access to its siblings, azaspiracids-2 and -3, which enabled biological investigations that were previously unattainable due to the natural scarcity of these neurotoxins.[109]

Discovered in 1954, thiostrepton (**13**, Fig. 14)[110] is the flagship member of the thiopeptide class of antibiotics.[111] Thiostrepton possesses antibacterial, antiparasitic, and immunosuppressant activities. Though it has not been used in human medicine, thiostrepton is used as a veterinary antibiotic. In 2004, we completed a total synthesis of thiostrepton featuring a biomimetic aza-Diels–Alder cycloaddition to forge the dehydropiperidine core of the molecule.[112,113] Subsequent chemical biology studies revealed

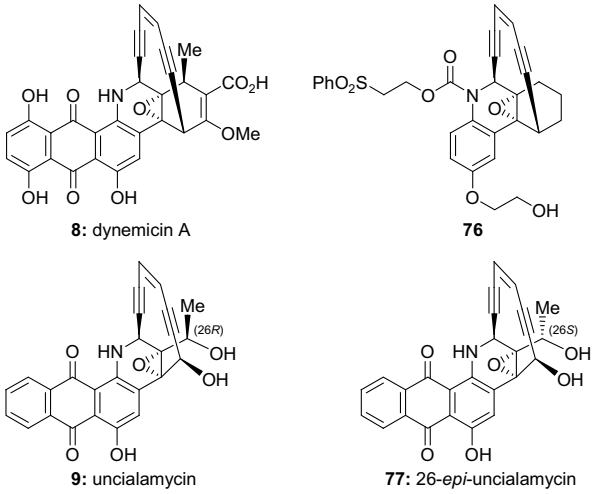


Figure 11. Molecular structures of selected natural and designed enediyne compounds (Nicolaou et al., 1990–1992, 2007–2008).[91,94,95]

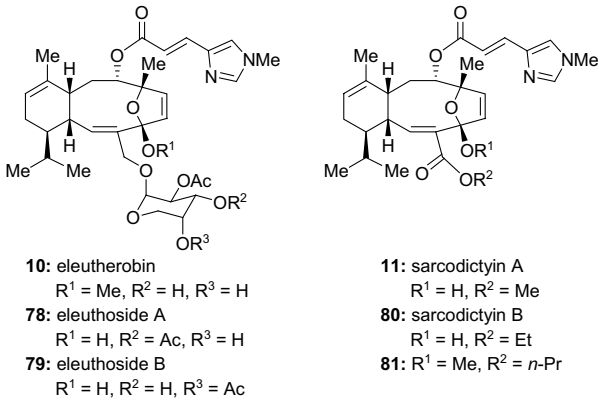


Figure 12. Molecular structures of eleutherobin (**10**) and related compounds (Nicolaou et al., 1997–1998).[100,102]

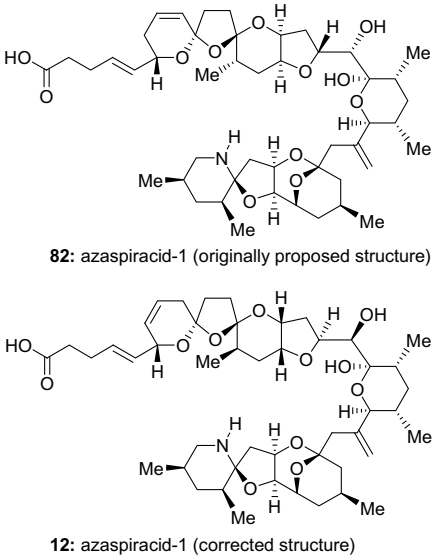


Figure 13. Originally proposed (**82**) and corrected (**12**) molecular structures of azaspiracid-1 (Nicolaou et al., 2003–2004).[105,106]

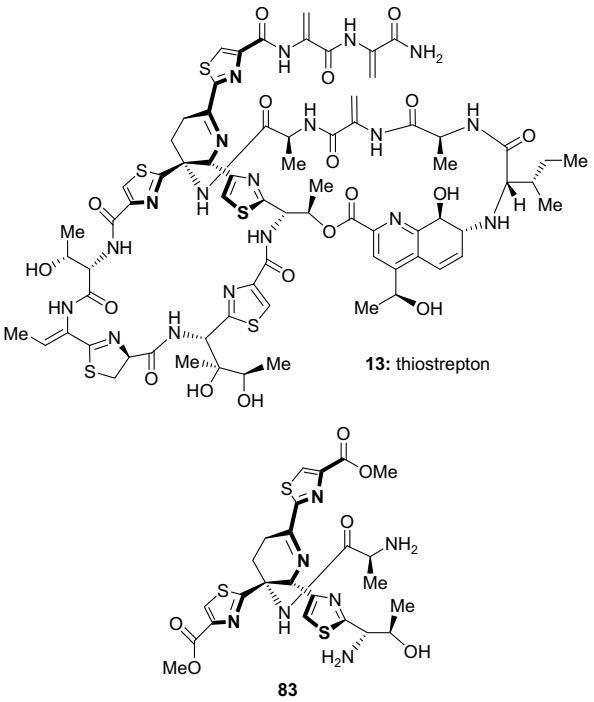
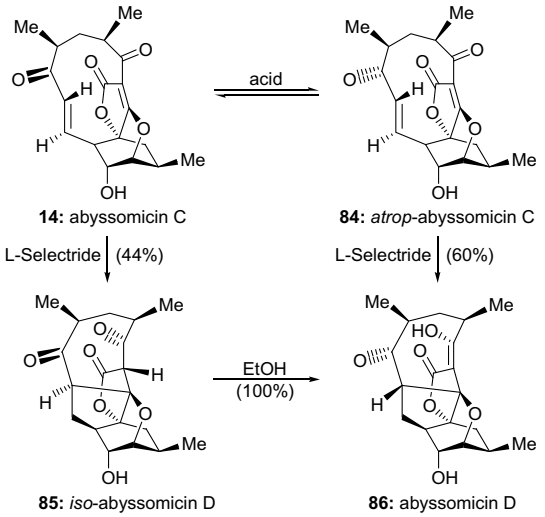


Figure 14. Molecular structures of thiostrepton (**13**) and a simplified bioactive analog (**83**) (Nicolaou et al., 2004–2005).[112,114]



Scheme 13. Highlights of selected reactions of the abyssomicins (Nicolaou and Harrison, 2006–2007).[117]

significant antibacterial and cytotoxic properties for the simplified compound **83** (Fig. 14).[114]

Reported in 2004 from the rare actinomycete *Verrucosispora* strain AB18-032, abyssomicin C (**14**, Scheme 13) is the first natural product discovered to inhibit the biosynthesis of *p*-aminobenzoic acid.[115] This enzymatic pathway is essential to many microorganisms, but absent in humans, making it an attractive target for intervention as a means to develop new antibiotics.[116] Our total synthesis of abyssomicin C[117,118] resulted in the serendipitous discovery of the more potent *atrop*-abyssomicin C (**84**, Scheme 13) and a facile acid-promoted interconversion between the two atropisomers (**14** and **84**). Careful investigation of the chemistry of abyssomicin C and *atrop*-abyssomicin C also shed light on the pos-

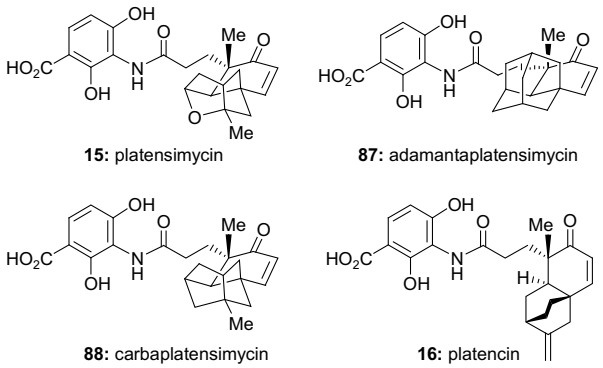


Figure 15. Molecular structures of platensimycin (**15**), platencin (**16**), and designed platensimycin analogs (Nicolaou et al., 2007–2008).[123,124,126–128]

sible biosynthetic origin of abyssomicin D (**86**, Scheme 13) and uncovered the previously undescribed *iso*-abyssomicin D (**85**, Scheme 13). Interestingly, *atrop*-abyssomicin C (**84**) was subsequently identified as the primary abyssomicin metabolite of *Verrucosispora* strain AB18-032.[119]

Platensimycin (**15**, Fig. 15)[120] and platencin (**16**, Fig. 15)[121] were reported in 2006 and 2007, respectively, as novel fatty acid biosynthesis inhibitors.[122] Platensimycin is a selective inhibitor of FabF, and platencin is an inhibitor of FabF and FabH, enzymes in the bacterial type II fatty acid biosynthesis (FAS II) pathway. These antibiotics display broad-spectrum activity against Gram-positive bacteria, including MRSA and vancomycin-intermediate *S. aureus* (VISA). We reported the first total synthesis of racemic platensimycin[123] as well as the first asymmetric synthesis of both platensimycin[124,125] and platencin.[126] Our laboratory also designed and synthesized the platensimycin analogs adamantaplatensimycin (**87**, Fig. 15)[127] and carbaplatensimycin (**88**, Fig. 15),[128] and reported their potent antibacterial properties.

Isolated from the Antarctic tunicate *Synoicum adareanum* and disclosed in 2006, palmerolide A (**17**, Fig. 16) was claimed to possess potent cytotoxicity against melanoma cell lines and impressive selectivity in the National Cancer Institute (NCI) 60 human tumor cell line assay.[129] Prompted by this promising biological profile, the Nicolaou–Chen group in Singapore developed an enantioselective synthesis of palmerolide A which not only contributed

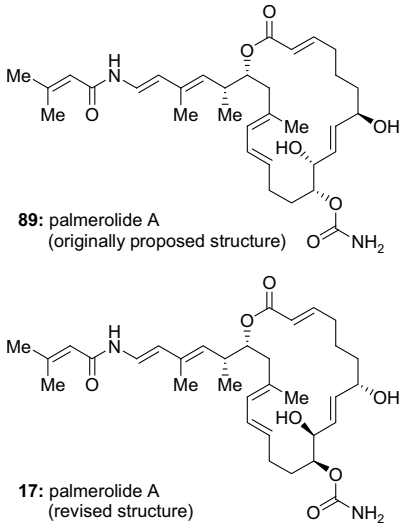


Figure 16. Originally proposed (**89**) and revised (**17**) molecular structures of palmerolide A (Nicolaou et al., 2007).[130]

to the structural revision of this natural product from **89** (Fig. 16) to **17** (Fig. 16), but also rendered palmerolide A and several of its analogs readily available for biological investigations.[130,131]

9. Conclusion and future perspectives

As demonstrated in this article, chemistry not only plays an important role in isolating and structurally characterizing bioactive secondary metabolites, but also contributes decisively to understanding and further developing these natural products into useful drugs. In particular, chemical synthesis, whether semi-synthesis or total synthesis, often plays a pivotal role in supplying the natural substance in large amounts and in delivering novel analogs for biological investigations, clarifying the mechanism of action, and providing useful intelligence on their SARs. In addition, these studies frequently provide useful insights into the intrinsic chemical and physical properties of such molecules that enable their eventual development as medicines. The story of Aspirin®[2,132] continues to be a brilliant paradigm for drug discovery, demonstrating the value of folk medicine, isolation and structural chemistry, medicinal chemistry on the originally-isolated molecule, and chemical synthesis as a means to manufacture the active ingredient of the drug. The intervening successes since the introduction of this important medication bode well for further discoveries in the future through the same avenue, the one that starts with nature.

Acknowledgments

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