



Building trans-bicyclo[4.4.0]decanes/decenes in complex multifunctional frameworks: the case for antibiotic development

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Building *trans*-bicyclo[4.4.0]decane/decene in complex multifunctional frameworks: the case for antibiotic development

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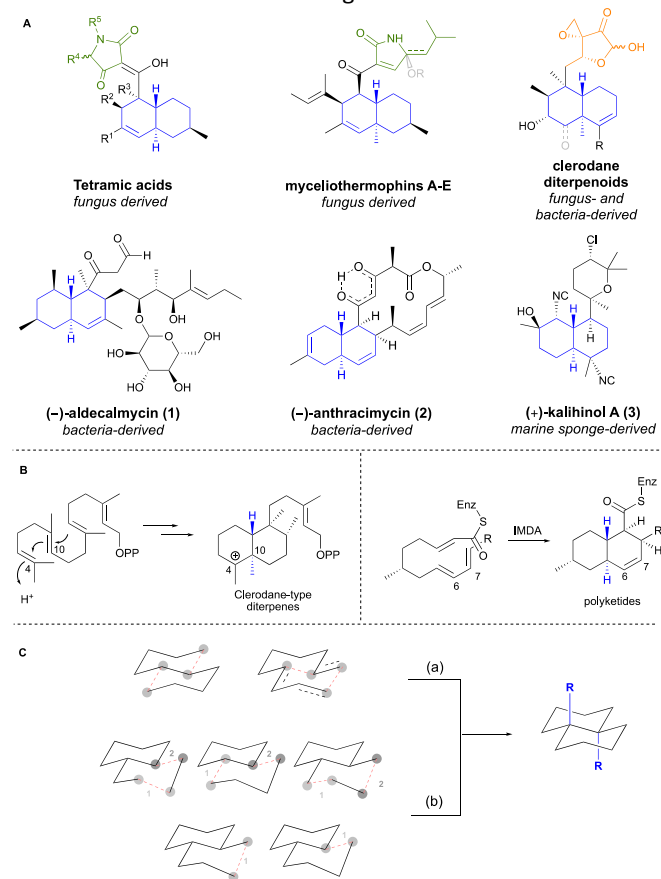
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Trans-bicyclo[4.4.0]decane/decene (such as *trans*-decalin and *trans*-octalin)-containing natural products display a wide range of structural diversity and frequently exhibit potent and selective antibacterial activities. With one of the major factors in combatting antibiotic resistance being the discovery of novel scaffolds, the efficient construction of these natural products is an attractive pursuit in the development of novel antibiotics. This highlight aims to provide a critical analysis on how the presence of dense architectural and stereochemical complexity necessitated special strategies in the synthetic pursuits of these natural *trans*-bicyclo[4.4.0]decane/decene antibiotics.

Introduction

Antibiotics have played an integral role in treating bacterial infections for thousands of years; Alexander Fleming's discovery of penicillin in 1928 marked the beginning of a revolution in modern medicine, known as the "Golden Age of Antibiotics".¹ During this time, mankind's arsenal against pathogenic bacteria grew exponentially, whereby the discovery of a diverse array of antibiotics, including vancomycin, ciprofloxacin, and doxycycline, enabled the treatment of severe, and in some cases, previously untreatable bacterial infections.² Although these monumental discoveries have saved innumerable lives, this success may be short-lived. Our ability to treat bacterial infections has been compromised by the increasing prevalence of antibiotic-resistant pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA), which kills 19,000 patients per year in the United States alone.³ This issue is further exacerbated by the misuse and overuse of antibiotics.⁴ The structural homogeneity of current antibiotics is further hindering our ability to combat resistant pathogens. In fact, the majority of antibiotics currently prescribed are derived from scaffolds introduced between 1935 and 1967,⁵ with just four of these classes – penicillins, cephalosporins, quinolones, and macrolides – comprising 73% of the new antibacterial compounds filed for patent protection between 1981 and 2005.² The compounding effect of increasing resistance to

antibiotics alongside the declining discovery of novel antibiotics means we are now encountering the



Scheme 1 a) Representative examples of TBD-containing antibiotic natural products (TBD motifs highlighted in blue); b) Common biosynthetic pathways to TBDs; c) General approaches to the synthesis of TBD skeletons; path (a) designates the simultaneous construction of TBD scaffolds and path (b) designates their stepwise construction

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post-antibiotic era head-on, and are thus faced with the daunting task of developing efficacious new therapies based on novel antibiotic scaffolds.

The *trans*-bicyclo[4.4.0]decane/decene (TBD) motifs (including, but not limited to, *trans*-decalins, *trans*-octalins, *trans*-hexahydronaphthalenes and *trans*-octalones) (Scheme 1a, blue) are found in a variety of natural products which often display promising antibiotic activity and are derived from a wide range of producing organisms.⁶ Several fungal species produce TBD antibiotics decorated with a tetramic acid motif (Scheme 1a, green), including (–)-equisetin,⁷ (–)-hymenosectin,⁸ and (–)-myceliothermophins,⁹ all of which exhibit differing levels of potency against (methicillin-resistant) *S. aureus* and *Bacillus subtilis*. Fungus and bacteria-derived clerodane diterpenoids (Scheme 1a, orange) such as clerocidin,¹⁰ and (–)-terpentecin¹¹ display broad-spectrum antibiotic activity as well as antitumor activity. In addition, recent work by Quave and Melander showed that a natural product containing this scaffold plays a critical role in resensitizing MRSA to β -lactam antibiotics.¹² (–)-Aldecalmycin (**1**)¹³ and (–)-anthracimycin (**2**)¹⁴, both derived from *Streptomyces* sp., exhibit potent activity against MRSA as well as *Bacillus anthracis*, a major threat as a bioterrorism agent.¹⁵ Also active against these two species is (+)-kalinol A (**3**), isolated from the marine sponge *Acanthella* sp.¹⁶ The diversity in both origin and functionalization of these TBD antibiotics highlights the importance of Nature as a source of inspiration in the search for novel antibiotic scaffolds.

Diterpene skeletons like those found in clerodane diterpenoids are thought to form biosynthetically through cationic polycyclizations followed by C10 and C4 methyl migration,¹⁷ while the bicycle of polyketide secondary metabolites are widely thought to originate from intramolecular Diels-Alder cycloadditions (IMDA) (Scheme 1b).¹⁸ Indeed, the prevalence of C6-C7 unsaturation in many such natural products would appear to corroborate the IMDA proposal.⁶ Enzyme-mediated IMDA processes have been identified, for example in the case of lovastatin,¹⁹ while other naturally occurring bicyclic terpenoids are postulated to undergo spontaneous (i.e. via non-enzymatically assisted) IMDA reactions when still bound to the polyketide synthase (PKS) machinery.²⁰ It must be stated that additional mechanistic pathways, particularly nonenzymatic, for formation of TBD frameworks should not be excluded.

Syntheses of the TBD scaffold generally employ one of two key approaches: (a) establishing two rings simultaneously and stereospecifically; and (b) establishing each ring in a stepwise fashion, relying on the thermodynamic stability of equatorial substituents on the bridgehead carbons to guide the formation of the *trans* isomer (Scheme 1c). The TBD skeletons of the aforementioned natural products are characteristically multifunctional with various complex pendant moieties that pose unique synthetic challenges. Thus, devising new and efficient strategies for selectively constructing these highly decorated TBD systems has been important in their pursuit by synthetic chemists.

Previous reviews have specifically discussed annulation approaches to TBDs, the syntheses of *cis*-

bicyclo[4.4.0]decane/decenes, and the construction of bicyclo[4.4.0]decane/decene containing natural products with a focus on isolation or specific functionalities.^{6,21-25} However, there are no reviews primarily focused on the diverse synthetic approaches required to access the complex scaffolds of TBD containing natural products. The focus of this review is to highlight the strategies utilized to access densely functionalized naturally occurring TBD antibiotics. The target natural products assessed in this review occupy very similar chemical space, and their complex frameworks contribute to the bottleneck in their development as novel therapeutics. By shedding light on the various methods that have been successfully employed to access these TBD scaffolds, we hope to inspire further use of these established methods to construct more TBD containing antibiotics and analogous, as well as the development of new methods to efficiently access TBD frameworks. If these scaffolds can be constructed in a more efficient manner, then this will allow a for more streamlined discovery of their mechanism of action and potentially new antibiotic targets, which has been a major bottleneck in the development of effective new antibiotics.

Recent strategies utilized to synthesize the densely substituted TBD scaffold in naturally occurring antibiotics have been primarily limited to two main strategies, namely, IMDA cyclizations and nucleophilic cyclizations, with several miscellaneous approaches also being reported. These strategies will be further elaborated on in the following sections.

IMDA Cycloadditions

Introduction

Since its discovery by Otto Diels and Kurt Alder in 1928,²⁶ the Diels-Alder cycloaddition has proven to be a robust method to assemble polycyclic systems efficiently, and with high chemo-, regio-, and stereoselectivity.²⁷ The relative configuration of the TBD system is dictated by the transition state through which the IMDA reaction proceeds. While the thermodynamically favored *exo*-transition states deliver corresponding *cis*-octalin products, **A** and **B**, the kinetically favored *endo*-transition states afford *trans*-octalin products, **C** and **D** (Scheme 2). Additional considerations surrounding substrates and/or reaction conditions can be made to enhance facial selectivity and afford a single enantiomer of these four possible products. This powerful, bioinspired methodology has seen numerous applications for TBD complex syntheses.

Substrate-Controlled IMDA Syntheses

Inspired by Nature, substrate-controlled IMDA reactions are a powerful technique used to rapidly build complexity in natural product systems when the inherent preference of the substrate complements the desired configuration of the TBD motif. These reactions are particularly useful, as they can set up to four stereocenters in a single step. The power of this methodology has been exemplified by the recent syntheses of the naturally occurring antibiotics (–)-hymenosectin (**4**) and (+)-apiosporamide (**5**).

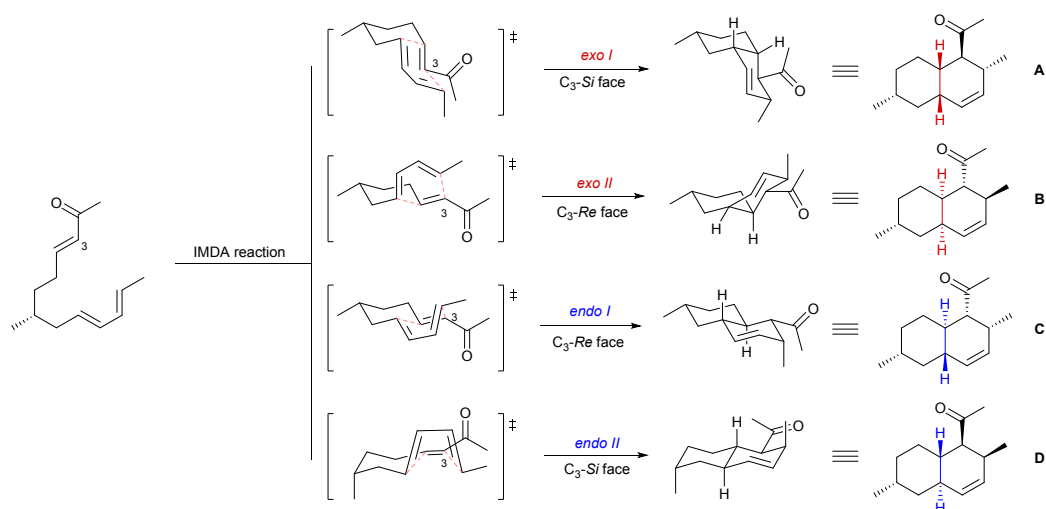
(-)-Hymenoseetin (**4**), containing the aforementioned tetramic acid moiety, was isolated in 2014 from a virulent strain of the ash dieback fungal pathogen, *Hymenoscyphus pseudoalbidus*.⁸ It displayed strong activity against a series of Gram-positive bacteria, including *Micrococcus luteus* (DSM 20030, MIC 1.0 $\mu\text{g}/\text{mL}$), *Nocardioides simplex* (DSM 20130, MIC 0.52 $\mu\text{g}/\text{mL}$), and MRSA (N315, MIC 0.83 $\mu\text{g}/\text{mL}$).⁸ In 2015, the Opatz group reported the first total synthesis of (-)-**4**, featuring an IMDA reaction to construct the TBD motif (Scheme 3a).²⁸ Tetraene **6**, accessed in four steps from (+)-citronellal, was subjected to the key IMDA reaction, utilizing $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -78°C . The facial selectivity of the IMDA reaction was controlled by the preference for the chiral methyl substituent to position pseudo-equatorially in the IMDA transition state **7**, giving rise to TBD **8** with a high degree of diastereoselectivity ($\text{dr} > 10:1$). A subsequent series of 11 steps, including a Reformatsky reaction and Lacey-Dieckmann cyclization yielded the target tetramic acid, (-)-hymenoseetin (**4**).

(+)-Aposporamide (**5**), containing a unique scaffold in which a 4-hydroxy-2-pyridone moiety is appended to the TBD fragment, was isolated from the coprophilous fungus *Apiospora montagnei* in 1994.²⁹ While preliminary investigations were motivated by its antifungal properties, it was also found to have antibacterial activity against *B. subtilis* (ATCC 6051, 32 mm zone of inhibition at 200 $\mu\text{g}/\text{disk}$) and *S. aureus* (ATCC 29213, 21 mm zone of inhibition at 200 $\mu\text{g}/\text{disk}$).²⁹ The total synthesis of (+)-apiosporamide (**5**) was completed by the Williams group in 2005,³⁰ and an IMDA reaction was used to construct the TBD core (Scheme 3b). The desired TBD framework was accessed from triene **9**, which was obtained from (-)-citronellol in 6 steps. Studies of the key cyclization step revealed that higher temperatures significantly diminished stereocontrol. Thus, the Lewis-acid mediated IMDA reaction of **9** was conducted at -78°C , proceeding through *endo II* transition state **10**. The diene approached from the C_3 -*Si* face of the dienophile, guided by the single methyl stereocenter, similar to (-)-hymenoseetin (**4**), to provide the target TBD **11** with excellent stereoselectivity ($\text{dr} > 97:3$). Six additional transformations were performed to afford (+)-**5**.

The importance of substituents on the linear IMDA substrates in controlling the facial selectivity of IMDA reactions has been highlighted by the syntheses of macrolides (+)-tubelactomicin A (**12**) and (-)-chlorotonil A (**13**). In these examples, the IMDA substrates were fine-tuned to obtain the desired the TBD diastereomer.

(+)-Tubelactomicin A (**12**), isolated in 2000 from a culture broth of actinomycete MK703-102F1 collected in Suwashi (Japan), is a 16-membered macrolide natural product bearing an appended TBD ring system.³¹ (+)-Tubelactomicin A (**12**) was found to display potent and genus-specific activity against numerous *Mycobacterium* strains, including *M. smegmatis* (ATCC607, MIC 0.10 $\mu\text{g}/\text{mL}$), *M. vaccae* (MIC 0.10 $\mu\text{g}/\text{mL}$) and *M. phlei* (MIC 0.20 $\mu\text{g}/\text{mL}$).³¹ Importantly, (+)-**12** was active against drug-resistant *Mycobacterium* strains, with no cross-resistance to other anti-tuberculosis drugs observed, suggesting a novel mechanism of growth inhibition.³¹ In 2005, the Tadano group reported the total synthesis of **12**, noting that the TBD unit, bearing six contiguous stereocenters, presented a particularly formidable synthetic challenge (Scheme 3c).^{32,33} Their strategy utilized an IMDA reaction to forge the complex bicyclic system, leveraging an important benzylidene acetal ring appendage to enforce π -facial stereocontrol. Heating **14** to 80°C facilitated the intramolecular cycloaddition via transition state **15**, to provide TBD **16** with high diastereoselectivity (8:1 *endo:exo*). It was proposed that the high π -facial control and *endo*-selectivity arose from minimization of nonbonding interactions in transition state **15** through the conformational restraint imposed by the benzylidene acetal ring. 13 additional transformations including a Stille coupling and Mukaiyama macrolactonization afforded (+)-tubelactomicin A (**12**).

Isolated from myxobacterium *Sorangium cellulosum*, So ce1525, (-)-chlorotonil A (**13**) was characterized as a TBD-fused 14-membered macrolide bearing a *gem*-dichloride moiety.³⁴ (-)-Chlorotonil A (**13**) exhibited strong antibiotic activity against a series of Gram-positive bacteria including *M. luteus* (DSM-1790, MIC 0.0125 $\mu\text{g}/\text{mL}$), *B. subtilis* (DSM-10,



Scheme 2 Possible diastereomeric octalin products produced by IMDA reactions

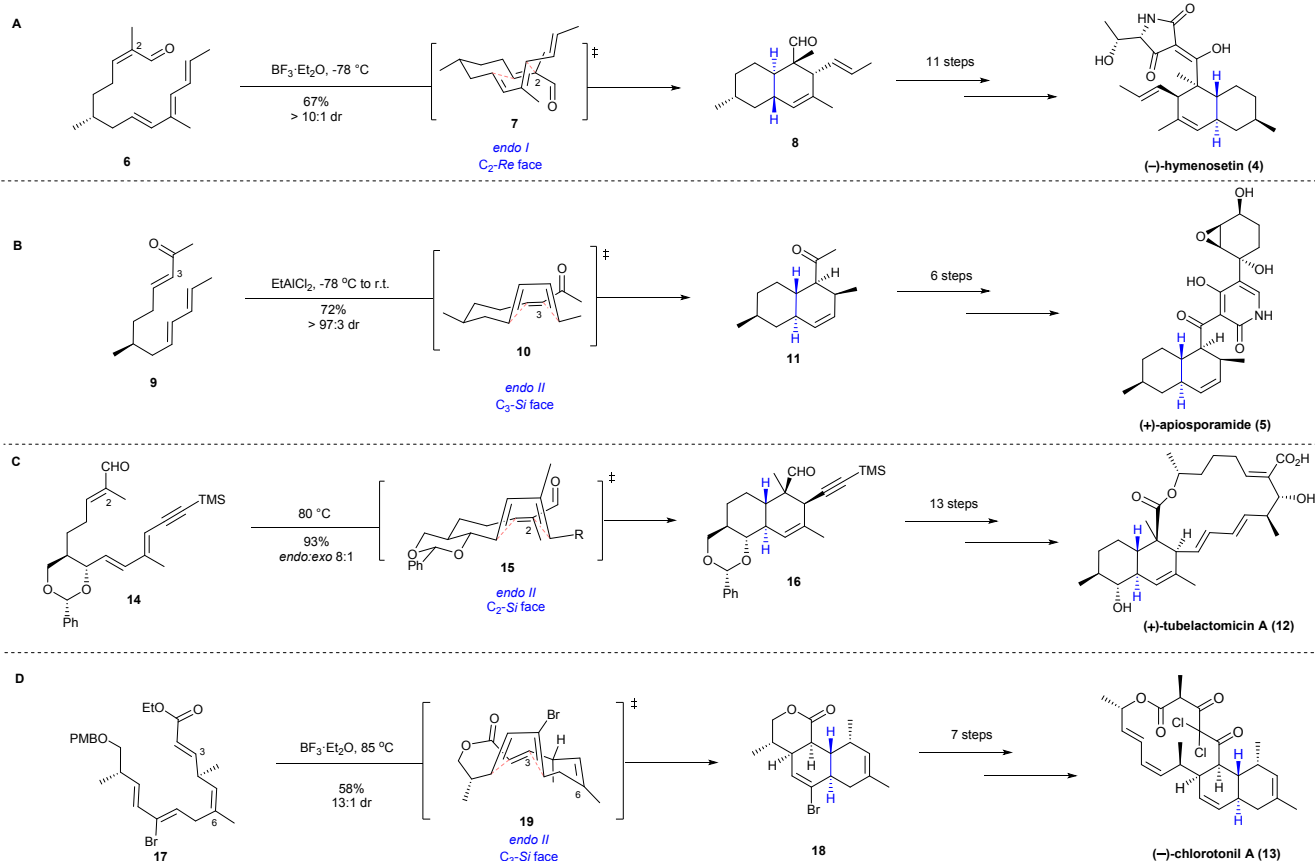
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MIC ≤ 0.003 $\mu\text{g/mL}$), and *S. aureus* (Newman, MIC 0.006 $\mu\text{g/mL}$).²⁰ The total synthesis of (–)-**13** was realized by Kalesse and coworkers in 2008, utilizing a strategic IMDA reaction of **17**, which promoted formation of the desired TBD adduct **18** through a halogen-directing effect (Scheme 3d).³⁵ Accessed in 10 linear steps from (*R*)-Roche ester, tetraene **17** was treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at 85 °C to facilitate the IMDA cyclization simultaneously with PMB removal and transesterification to afford **18** with high diastereoselectivity (dr 13:1). Analysis of the proposed cyclic reaction intermediates uncovered the significant effect of steric repulsion between the bromide and C6 methyl group, thereby favoring intermediate **19** with the diene approaching the C_3 -Si face of the dienophile, leading to predominant formation of **18**. With the desired TBD scaffold **18** formed, an additional 7 steps completed the total synthesis of (–)-chlorotonil A (**13**).

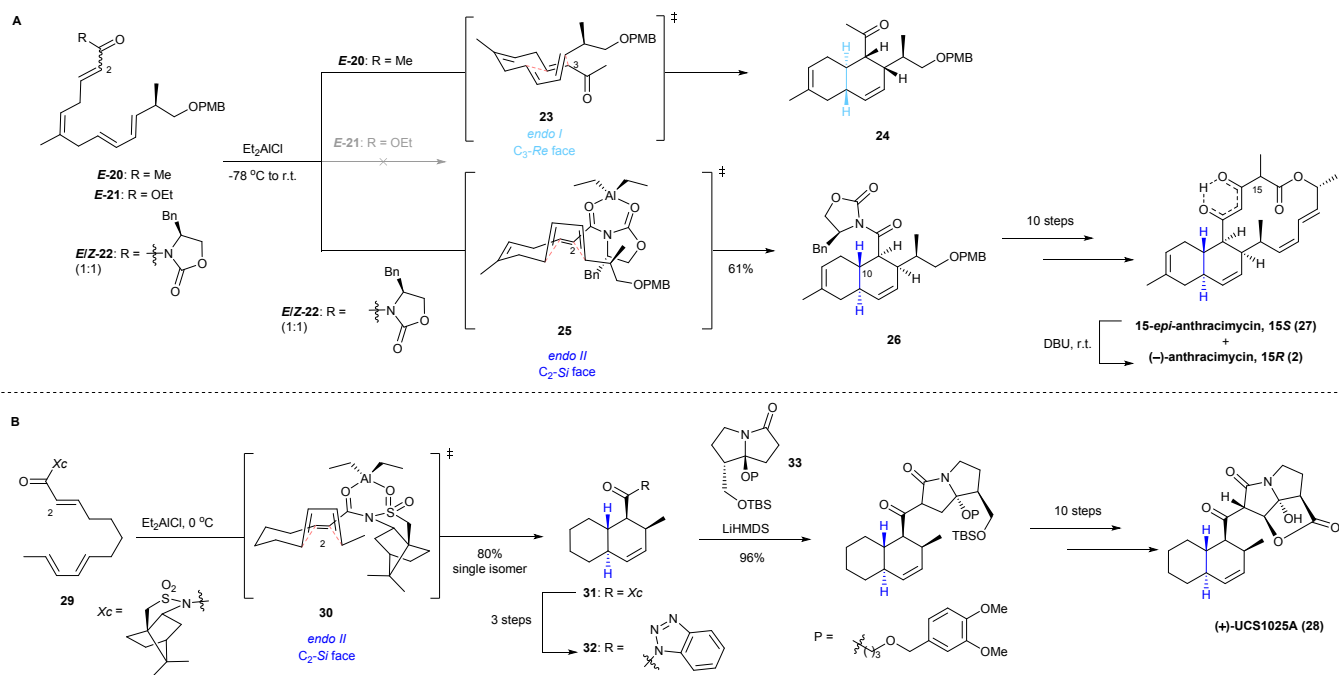
Chiral auxiliary-controlled IMDA Syntheses

In many cases, the structure of the substrate does not lend itself to favorable facial control and *endo* selectivity required to construct the desired *trans*-bicyclic systems through an IMDA approach. In many cases, chiral auxiliaries are useful pendant moieties which are applied to invert the inherent undesirable facial selectivity of certain substrates in the formation of complex TBDs using IMDA reactions.

The tricyclic macrolide (–)-anthracimycin (**2**) was isolated from *Streptomyces* sp. CNH365 in 2013.¹⁴ (–)-Anthracimycin (**2**) shows remarkable structural similarities to the aforementioned (–)-chlorotonil A (**13**). (–)-Anthracimycin (**2**) demonstrated potent *in vitro* activity against a series of MRSA strains (MIC 0.03–0.0625 $\mu\text{g/mL}$), and exhibited *in vivo* protection against MRSA-induced mortality in mice (single dose, 1 mg/kg).³⁶ Significant activities were also found against the bioterrorism agent *B. anthracis* (UM23C1-1, MIC 0.031 $\mu\text{g/mL}$) as well as against *M. tuberculosis* (H37Ra, MIC 1–2



Scheme 3 Substrate-Controlled IMDA Syntheses: a) Opatz's total synthesis of (–)-hymenosetin (**4**);²⁸ b) Williams' total synthesis of (+)-apiosporamide (**5**);³⁰ c) Tadano's total synthesis of (+)-tubelactomicin A (**12**);^{32,33} d) Kalesse's total synthesis of (–)-chlorotonil A (**13**).³⁵



Scheme 4 Auxiliary controlled IMDA Syntheses a) Evans' oxazolidinone facilitated IMDA based total synthesis of (-)-anthracimycin (**2**);^{37,38} b) Oppolzer's camphor sultam enabled IMDA approach to (+)-UCS1025A (**28**).⁴⁰

$\mu\text{g/mL}$).^{14,36} The minimal toxicity of (-)-**2** to human cells (IC_{50} 70 mg/L) makes it a valuable lead in the development of novel antibiotics to combat MRSA.³⁶ The first total synthesis of this potent naturally occurring antibiotic has recently been realized through a collaborative effort between the Brimble and Wuest groups (Scheme 4a).^{37,38} A series of tetraene substrates (**20-22**), accessed in 8 steps from (*S*)-Roche ester, were tested in the key IMDA reaction. Cyclization of ester IMDA substrate, *E-21*, similar to that reported by Rahn and Kalesse during their aforementioned synthesis of (-)-**13**, proved unproductive. Enone *E-20* proceeded through the *endo I* transition state **23**, affording the undesired diastereomer **24** as the major IMDA adduct under all conditions tested. However, the inherent facial selectivity of the cycloaddition can be inverted through application of a chiral auxiliary. Lewis acid mediated IMDA reaction of tetraene **22** (1:1 mixture of *E/Z*-isomers) proceeded through the *endo II* transition state **25** and yielded IMDA adduct **26**, possessing the desired stereochemistry, albeit as a 1:1 mixture with its C10 epimer (resulting from cycloaddition of C2-*Z-22* via the same transition state). These epimers were separated following PMB deprotection, which was followed by an additional 9 steps, affording **2** as a 1:1 mixture with 15-*epi*-anthracimycin (**27**). Base-mediated epimerization of the mixture provided (-)-anthracimycin (**2**) as a single diastereomer.

(+)-UCS1025A (**28**), comprised of a TBD skeleton linked to a pyrrolizidine motif by an acyl bond, was isolated from the fungus *Acremonium* sp. KY4917 in 1999.³⁹ (+)-UCS1025A (**28**) displayed micromolar antibiotic activities against Gram-positive *S. aureus* (ATCC 6538P, MIC 1.3 $\mu\text{g/mL}$), *B. subtilis* (No. 10707, MIC 1.3 $\mu\text{g/mL}$), *Enterococcus hirae* (ATCC 10541, MIC 1.3

$\mu\text{g/mL}$), and Gram-negative *Proteus vulgaris* (ATCC 6897, MIC 5.2 $\mu\text{g/mL}$). In 2012, Kan and coworkers reported the second total synthesis of (+)-**28**⁴⁰ (the first of which will be discussed in the next section). Triene **29**, bearing a chiral Oppolzer's sultam auxiliary underwent Lewis acid-mediated cycloaddition via transition state **30** to afford desired TBD **31** as a single diastereomer (Scheme 4b). Blocking of the C₂-*Re* face of the dienophile by the sultam auxiliary promoted cycloaddition at the opposite face leading to high stereoselectivity. Further transformations, including coupling of benzotriazole **32** with pyrrolizidinone **33** provided (+)-UCS1025A (**28**).

Miscellaneous IMDA Syntheses

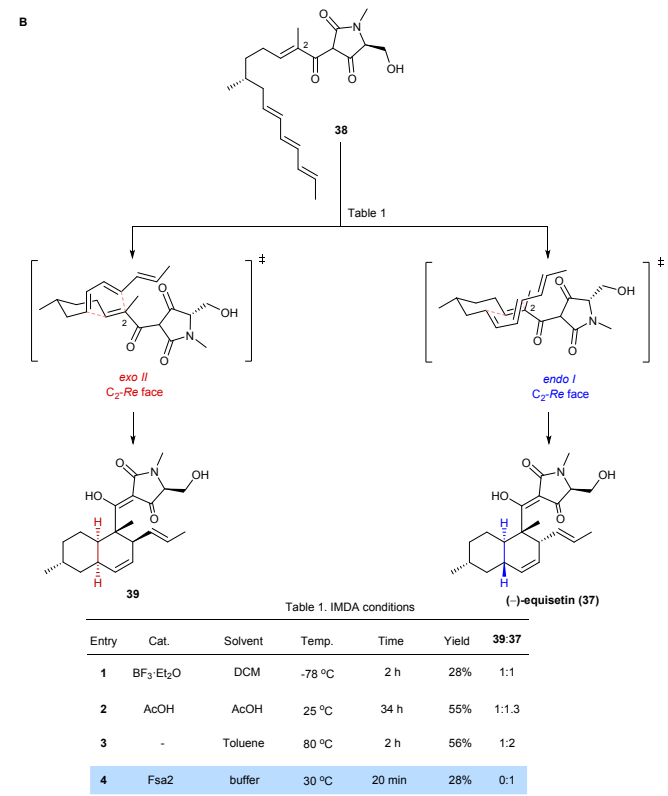
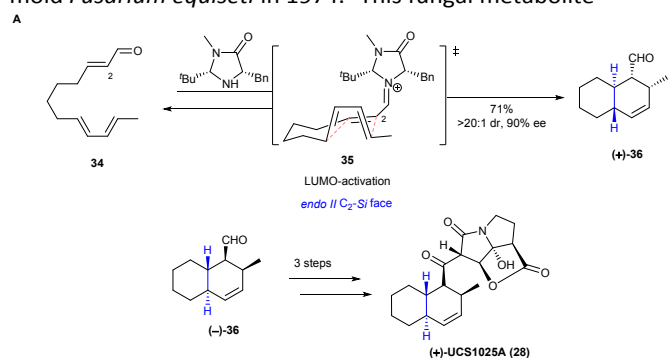
While auxiliary-controlled IMDA reactions have proven extremely useful in the stereoselective construction of complex TBD systems in natural products, removal of the auxiliary can sometimes be problematic. As such, organocatalyzed IMDA reactions are emerging as an attractive alternative, as aldehyde substrates can be activated chemoselectively, and the directing group established *in situ* is also cleaved after promoting the desired transformation.

The efficiency of this methodology was highlighted in the first total synthesis of (+)-UCS1025A (**28**) by the Danishefsky group in 2005,⁴¹ who utilized an enantioselective IMDA reaction promoted by an organocatalyst developed by MacMillan and coworkers⁴² (Scheme 5a). Reversible condensation of the imidazolidinone catalyst with aldehyde **34** formed iminium ion **35** *in situ*, (lowering the LUMO energy to activate the dienophile), which underwent Diels-Alder cyclization through *endo II* transition state **35**, followed by iminium hydrolysis, to afford TBD (+)-**36**.⁴² Importantly, all four stereocenters were set

in a single step with excellent stereoselectivity. Using this same methodology, the Danishefsky group prepared the enantiomer (–)-**36**, which was transformed in 3 additional steps, including incorporation of the pyrrolizidine moiety, to the natural product (+)-**28**.

Chemo-enzymatic IMDA reactions are valuable in the late-stage construction of densely functionalized TBD systems. This methodology provides a high degree of stereoselectivity without the need for directing groups, and has the additional benefit of elucidating elements of the biosynthetic pathway to the desired natural products, as exemplified by the recent synthesis of (–)-equisetin (**37**) by Gao and coworkers.

(–)-Equisetin (**37**) was originally isolated from the white mold *Fusarium equiseti* in 1974.⁷ This fungal metabolite



Scheme 5 Miscellaneous IMDA Syntheses: a) Organocatalytic synthesis of (+)-UCS1025A (**28**) by Danishefsky;⁴¹ b) Chemo-enzymatic IMDA synthesis of (–)-equisetin (**37**) by Gao and coworkers.⁴³

displayed potent antibiotic activity (*B. subtilis* B-543, MIC 0.5 µg/mL, and *S. aureus* B-313, MIC 0.5 µg/mL).⁷ In 2017, Gao and

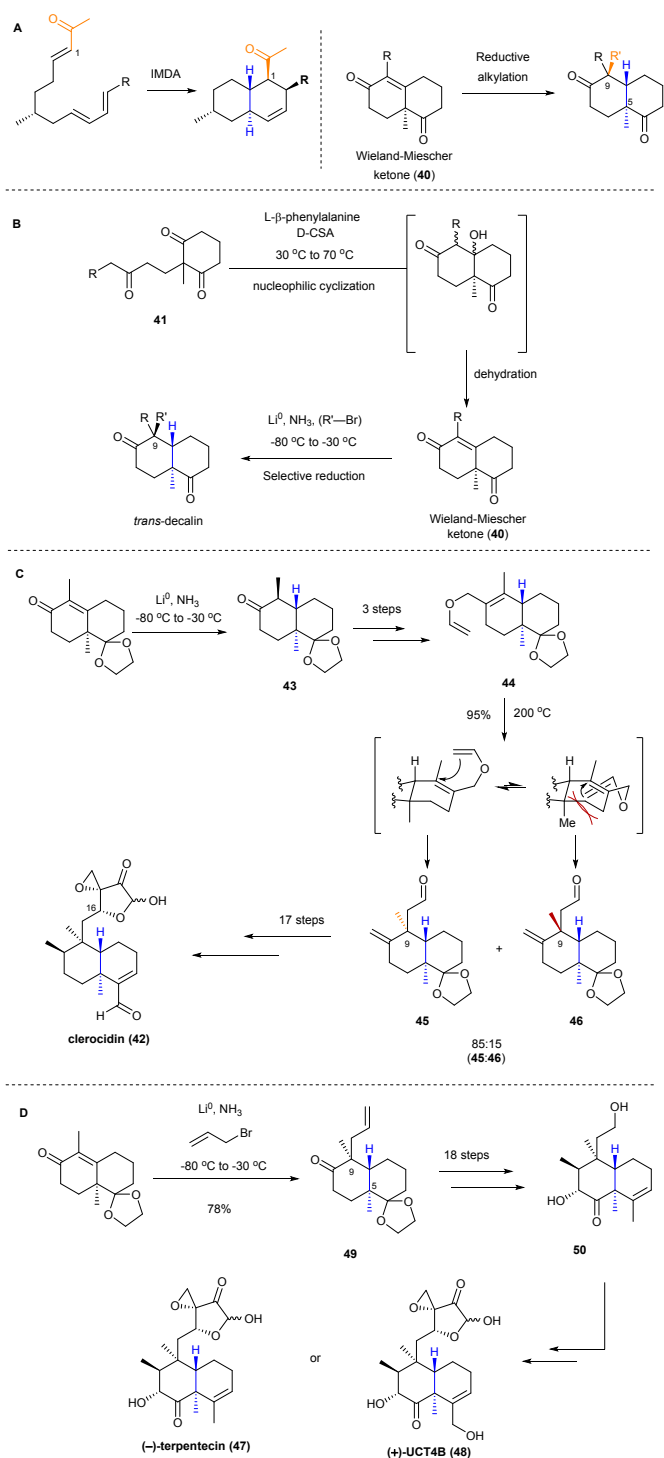
coworkers reported the chemo-enzymatic synthesis of **37** employing the Diels-Alderase enzyme Fsa2 to selectively form the TBD moiety (Scheme 5b).⁴³ Tetraene **38**, obtained in 7 steps from (+)-citronellal, was subjected to a series of conditions in an attempt to access (–)-**37**. Both Lewis acid-catalyzed and thermally-promoted Diels-Alder conditions failed to facilitate stereoselective conversion of **38** to the desired TBD natural product (Table 1, Scheme 5b). Lewis acid-mediated IMDA reaction of **38** delivered (–)-**37** and its *cis*-fused epimer **39** in a 1:1 ratio (entry 1). Marginal improvements in this ratio were observed upon treatment of **38** with AcOH or simply heating **38** in toluene (entries 2 and 3). Opportunely, treatment of **38** with the Diels-Alderase enzyme, Fsa2, expressed and purified from *E. coli*, resulted in complete conversion of **38** to (–)-**37** with no detectable formation of epimer **39** (entry 4). This bioinspired synthesis showcases the power of enzymatic catalysis in conducting late-stage diastereoselective Diels-Alder cyclizations for the construction of TBD scaffolds.

Nucleophilic cyclizations

Wieland-Miescher Ketones

As illustrated herein, IMDA cycloadditions have seen wide usage in the pursuit of TBD systems, and this methodology provides these bicyclic motifs with a reactive pendant carbonyl moiety at C1 for further functionalization (Scheme 6a). However, the bicyclic ring structures of clerodane diterpenoids possess additional structural elements that are poorly accessible through this methodology, in particular, the congested C5 quaternary center. The Wieland-Miescher ketone (**40**) is accessed through a nucleophilic cyclization/dehydration sequence of tricarbonyl **41**, to forge this C5 quaternary center (Scheme 6b).^{44,45} The different reactivity of the two carbonyls in **40** can then be exploited for the selective incorporation of various structural moieties at positions such as C9 (Scheme 6a, b).

The clerodane diterpenoid clerocidin (**42**), previously called PR-1350, was isolated in 1983 from the fungus *Oidiodendron truncatum*, and displays a wide range of activity against Gram-positive (*M. luteus* 2495, MIC < 0.05 µg/mL, and *S. aureus* 1276, MIC 0.1 µg/mL) and Gram-negative bacteria (*Bacteroides fragilis* 9844, MIC < 0.05 µg/mL, and *Pseudomonas aeruginosa* 9545, MIC 0.8 µg/mL).⁴⁶ Further biological studies elucidated DNA topoisomerase II inhibition as the mechanism by which this natural product exerts its antibacterial and antitumor effects.⁴⁶ Intrigued by its unique biological activity, Theodorakis and coworkers embarked on the first total synthesis of **42** in 1998 (Scheme 6c).⁴⁷ Stereoselective construction of the *trans*-decalin framework was achieved *via* the aforementioned Robinson annulation-dehydration-stereoselective reduction sequence and site-selective acetalization to give TBD **43**, which was then converted to allyl vinyl ether **44** in 3 steps.^{48,49} Claisen rearrangement was then



Scheme 6 Use of Wieland-Miescher ketone (**40**) in the synthesis of TBD natural products: a) Incorporation of reactive functionalities at different positions on the TBD scaffold; b) General construction of TBD scaffolds through Robinson annulation; c) Theodorakis's total synthesis of clerocidin (**42**);⁴⁷ d) Theodorakis's formal synthesis of (-)-terpentecin (**47**) and (+)-UCT4B (**48**)⁵¹

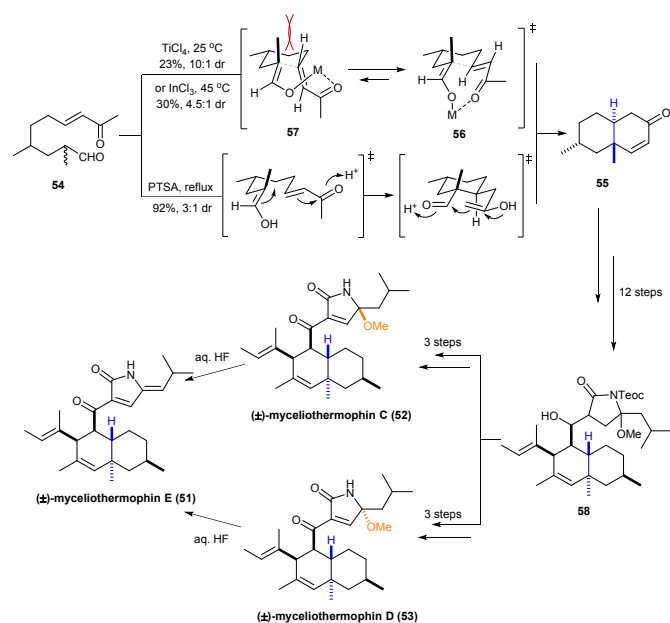
performed to stereoselectively install the C9 quaternary center. Facial preference for top face attack was derived from the steric repulsion between the angular methyl and vinyl group on the bottom face, thus predominant formation of aldehyde **45** was observed (85:15, **45:46**). An additional 17 steps, including a novel asymmetric homoallenylboration reaction to install the

C16 chiral alcohol, were undertaken, affording **42** as a single enantiomer.

The highly oxygenated natural product, (-)-terpentecin (**47**) bears significant structural similarity to clerocidin (**42**), and was originally isolated in 1985 from the bacteria *Kitasatosporia* sp. MF730-N6,¹¹ and again from *Streptomyces* sp. along with (+)-UCT4B (**48**) in 1992.⁵⁰ Akin to the biological profile of (-)-clerocidin (**42**), these two compounds displayed broad-spectrum antibiotic activity ((-)-**47**: *B. subtilis* PCI 219, MIC < 0.05 µg/mL; *S. aureus* Smith, MIC < 0.05 µg/mL; *E. coli* K-12, MIC 3.12 µg/mL; *Shigella dysenteriae* JS 11910, MIC < 0.05 µg/mL. (+)-**48**: *B. subtilis* No. 10707, MIC 8.3 µg/mL; *S. aureus* ATCC 6538, MIC 4.1 µg/mL; *K. pneumonia* ATCC 10031, MIC 2.1 µg/mL).^{11,50} Similar to clerocidin, these two compounds also captured the attention of the Theodorakis group, however, a more direct approach was taken to set the C9 stereocenter and construct the TBD core of (-)-**47** and (+)-**48** (Scheme 6d).⁵¹ Stereoselective Birch reductive alkylation of Wieland-Miescher ketone with allyl bromide afforded the desired TBD **49**. The stereoselectivity was proposed to arise from the steric clash with the C5 methyl group rendering bottom-face approach of the electrophile unfavorable, thus resulting in predominant formation of **49**. The fully functionalized core fragment **50** was afforded after 18 additional steps. Core fragment **50** could then feasibly be elaborated to both (-)-**47** and/or (+)-**48** using established protocols.⁴⁷

Nucleophilic cascade sequences

Five tetramic acid polyketide natural products, myceliothermophins A-E were originally isolated from the thermophilic fungus *Myceliophthora thermophila* in 2007.⁹ Although these natural products are more potent against various cancer lines, (-)-myceliothermophin E (**51**) has moderate antibacterial activity against MRSA (MIC 15.8 µM).⁵² The first total synthesis of myceliothermophins C-E (**51-53**) was accomplished by Uchiro and coworkers in 2012 utilizing an IMDA approach to construct the *trans*-octalone framework.⁵³ Recognizing the challenges arising from construction and reaction of the complex polyene IMDA substrates, Nicolaou and coworkers sought an alternative approach, employing what they termed an "unusual cascade sequence of reactions" to access the TBD system (Scheme 7).⁵⁴ Ketoaldehyde **54**, synthesized from (±)-citronellal over 3 steps (although both enantiomers are commercial available, the authors commenced the synthesis from racemic materials for cost effectiveness), was extensively screened under a variety of reaction conditions to access octalone **55**. This led to the initial discovery that Lewis-acidic conditions, namely TiCl₄ and InCl₃, favored formation of the desired octalone **55** with good diastereoselectivity (dr 10:1 and 4.5:1, respectively). The presence of these metals enhanced preference for transition state **56**, wherein favorable overlap of the enolate HOMO and enone LUMO are observed, compared to the unfavorable steric clash between the methyl group and the vinylic proton in transition state **57**. Significantly higher yields for the



Scheme 7 Nicolaou's divergent total synthesis of (±)-myceliothermorphins C-E (**51-53**).⁵⁴

biscyclization cascade were observed using catalytic *p*-toluenesulfonic acid (PTSA), albeit with decreased diastereoselectivity (dr 3:1). With the desired TBD **55** in hand, an additional 12 steps gave intermediate **58** (as a mixture of diastereomers), which was then further elaborated to (±)-**51-53**. This synthesis highlights the importance of developing novel methods of TBD construction when access to suitable IMDA substrates is challenging.

Miscellaneous reactions

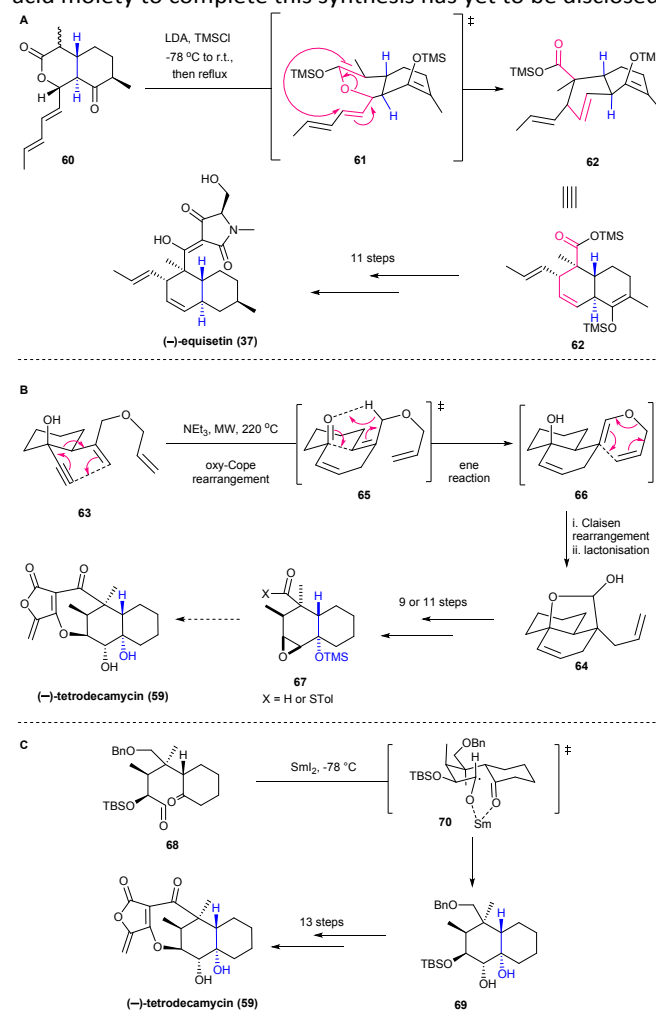
Sigmatropic rearrangements

Sigmatropic rearrangements have found use in the efficient construction of some of the most densely functionalized TBD natural products, such as (–)-tetrodecamycin (**59**) and (–)-equisetin (**37**), making it an important method for synthesizing these particularly formidable targets.

Danishefsky employed an intramolecular lactonic Claisen rearrangement for the formation of the TBD system of aforementioned natural product (–)-equisetin (**37**) (Scheme 8a).⁵⁵ Treatment of **60** with lithium diisopropylamide (LDA) and trimethylsilyl chloride (TMSCl) gave the corresponding silyl dienol ether, which then underwent intramolecular lactonic Claisen rearrangement. Due to the constrained nature of the cyclic system, stereospecific [3,3]-rearrangement through boat-like transition state **61** occurred, furnishing the desired TBD **62** as the major product.⁵⁶ Conversion of **62** to (–)-**37** was then accomplished in 11 additional steps.

(–)-Tetrodecamycin (**59**), an antibiotic compound featuring a 6,6,7,5-tetracyclic skeleton, was isolated from the culture broth of *Streptomyces* sp. MJ885-mF8 in 1994.⁵⁷ Along with its moderate activity against several Gram-positive (*S. aureus* FDA 209P, MIC 6.25 μg/mL; *B. anthracis*, MIC 6.25 μg/mL) and Gram-negative pathogens (*Xanthomonas oryzae*, MIC 12.5 μg/mL), it

exhibited distinct activity against *Pasteurella piscicida* (sp. 6395, MIC 1.56 μg/mL), a pathogen responsible for causing pseudotuberculosis in cultured fish. A key challenge in the synthesis of (–)-**59** is accessing its densely substituted central cyclohexane ring, containing two quaternary centers, a *trans*-fusion in the *trans*-decalin scaffold and six contiguous stereocenters. In 2005, Barriault and coworkers reported the synthesis of the TBD scaffold of (–)-**59** through a tandem oxy-Cope/ene/Claisen rearrangement (Scheme 8b).⁵⁸ The oxy-Cope precursor **63**, obtained in 5 steps from cyclohexene oxide, was subjected to microwave irradiation, affording **64** in excellent yield and stereoselectivity. The transformation was proposed to occur *via* initial oxy-Cope rearrangement to intermediate **65**, followed by ene reaction to **66**, then a Claisen rearrangement and lactonization to furnish the desired TBD **64**. This was then further elaborated to **67**, however incorporation of the tetrionic acid moiety to complete this synthesis has yet to be disclosed.



Scheme 8 Miscellaneous approaches to the synthesis of naturally occurring TBD antibiotics a) Danishefsky's intramolecular lactonic Claisen rearrangement enabled total synthesis of (–)-equisetin (**37**);⁵⁴ b) Barriault's oxy-Cope/ene/Claisen rearrangement approach to the TBD framework of (–)-tetrodecamycin (**59**);⁵⁸ c) Tatsuta's Sml_2 -mediated radical cyclization process to (–)-tetrodecamycin (**59**).⁵⁹

Radical cyclizations

Radical cyclizations offer an attractive alternative reactivity mode by which to access sterically congested products, such as those commonly seen in TBD systems. In 2006, Tatsuta and coworkers became the first group to complete the total synthesis of (–)-tetrodecamycin (**59**) utilizing a stereoselective SmI_2 -mediated pinacol cyclization to construct the TBD core (Scheme 8c).⁵⁹ Ketoaldehyde **68**, derived from (S)-(–)-5-hydroxymethyl-2(5H)-furanone in 13 steps was treated with SmI_2 , promoting the critical pinacol cyclization and affording the desired TBD **69** as a single isomer. The excellent stereoselectivity was believed to arise from the preference for the more stable chair-like transition state **70** through O-Sm chelation. Further manipulations, including formation of the tetronic acid motif, ultimately completed the synthesis of (–)-**59** in a total of 27 steps.

Conclusions

The significance of TBD containing natural products as inspiration in the development of novel antibiotics is made evident through the diversities in their chemical structures and often potent biological activities. Synthetic pursuits have led to the construction of several promising antibiotics containing these densely functionalized scaffolds. Many top synthetic groups have achieved elegant syntheses of these compounds utilizing a variety of approaches to access the TBD motif.

IMDA reactions continue to be the most robust and frequented method to access densely substituted TBD scaffolds, as has been made evident through the successful syntheses of a plethora of complex TBD-containing natural products. While substrate controlled-IMDA reactions are appealing for the inherent simplicity of the reaction, the application of chiral auxiliaries is a useful means for reversing undesired facial selectivities in these reactions. The use of organocatalysts and enzymes are also attractive alternatives since they enable the stereospecific synthesis of TBD scaffolds without the necessary appendage of chiral auxiliaries which are frequently difficult to remove. The use of Cope and Claisen rearrangements and Wieland-Miescher-type ketones demonstrate the significant value of classical chemical reactions in forming TBDs possessing strategically placed functional handles and congested quaternary centers. Finally, Tatsuta's synthesis of (–)-tetrodecamycin (**59**) displayed the value of radical cyclizations in the assembly of densely functionalized TBD systems.

We encourage the readership to consider two paths forward when pursuing these scaffolds to combat antibiotic resistance. The first is the continued development of new methods to enable the construction of these densely functionalized scaffolds. For example, in a recent review, Baran and coworkers highlighted the potential of radicals as reactive intermediates in the stereoselective construction of complex natural products,⁶⁰ Electrochemical, photochemical, and other radical-based methods indeed hold a great deal of potential in the construction of TBD systems. This bolsters the case for syntheses like that of (–)-tetrodecamycin (**59**). Additionally, arene dearomatization could be further developed to access structurally complex *trans*-fused bicycles.⁶¹ The second involves

a collaborative effort between synthetic chemists and biologists, wherein efficient access to these TBD systems will enable more comprehensive biological studies including SAR, target identification, and deducing mechanism of action. The latter approach will hopefully inform the rational design of more potent derivatives unavailable in Nature. Nevertheless, with the plethora of powerful synthetic tools available to chemists, the synthesis of novel TBD antibiotics and derivatives is a promising and powerful pursuit for the development of next-generation antibiotics.

Conflicts of interest

There are no conflicts to declare.

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