Published in final edited form as:

European J Org Chem. 2012 April ; 2012(11): . doi:10.1002/ejoc.201101609.

Biosynthesis and Total Synthesis Studies on The Jadomycin Family of Natural Products

Ehesan U. Sharif and George A. O'Doherty

Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA, 02115,
Homepage: <http://nuweb9.neu.edu/odoherty/>

George A. O'Doherty: G.O'Doherty@neu.edu

Abstract

Jadomycins are unique angucycline polyketides, which are produced by soil bacteria *Streptomyces venezuelae* under specific nutrient and environmental conditions. Their unique structural complexity and biological activities have engendered extensive study of the jadomycin class of natural compounds in terms of biological activity, biosynthesis, and synthesis.

This review outlines the recent developments in the study of the synthesis and biosynthesis of jadomycins.

Keywords

Jadomycin; Biosynthesis; Phenanthridine Ring System; Digitoxose; Carbasugar; Total Synthesis

1. Introduction

Nature provides us with ample sources of therapeutically useful molecules. Often the natural products are derivatized to modulate their activity in order to achieve specificity and selectivity. In fact, more than half of the drugs on market today are derived from natural products.¹ The necessity to discover and develop new and potent therapeutic agents, to address a wide array of disease and health-related conditions, has encouraged scientists to discover versatile and efficient routes for the biosynthesis and synthesis of new biologically active natural products.

Jadomycins are novel angucycline polyketide natural products composed of an unusual 8H-benzo-[b]-phenanthridine backbone with variously fused nitrogen and oxygen containing heterocycles (e.g., oxazolidine, pyrimidine, oxazinane). With the exception of jadomycin A (aka, jadomycin B aglycon), all the jadomycins are glycosylated with a L-digitoxose sugar unit (Figure 1).² This sugar moiety plays a key role in the bioactivity exhibited by these compounds (e.g., jadomycin B exhibits anti-yeast activity whereas jadomycin A is inactive).³ Jadomycins are active against gram-positive and gram-negative bacteria and shows anti-cancer activity, which has tentatively been attributed to aurora-B kinase inhibition and/or DNA cleaving capacity.⁴ These secondary metabolites are produced by gram-positive soil bacteria *Streptomyces venezuelae* ISP5230 (ATCC10712) under nutrient limitation along with additional stress (e.g., heat shock, phase infection or exposure to toxic concentration of ethanol).^{5,6} In contrast, chloramphenicol is the only antibiotic currently characterized from *Streptomyces venezuelae* under normal growth conditions.⁷

2. Jadomycin Biosynthesis

2.1. Regulatory genes for jadomycin biosynthesis

Since the early isolation work of Ayer,⁵ the unique structure of the jadomycins has inspired extensive study of their biosynthesis. These initial studies ultimately led to the discovery of related jadomycin secondary metabolites. In 1994, Vining was the first to clone and characterize the polyketide synthase (PKS) genes responsible for jadomycin B biosynthesis in *Streptomyces venezuelae* ISP5230.⁸ Later, more detailed investigations of the gene clusters were carried out by Yang.⁹ A schematic diagram depicting an organizational map of the jadomycin gene cluster is shown in Figure 2. The genome sequence of *Streptomyces venezuelae* ISP5230 (ATCC10712) was recently reported.^{6b} AntiSMASH analysis of the genome sequence identified 26 natural product biosynthetic gene clusters along with four additional polyketide synthase clusters and an independent lantibiotic biosynthetic cluster. Although, production of the lantibiotic was not observed in *Streptomyces venezuelae*.¹⁰

2.2. Sequencing region upstream of PKS-II

The need for both nutrient depletion and environmental stress on *S. venezuelae* to induce jadomycin production is quite unique, which suggests the existence of a control mechanism.¹¹ In contrast, most other streptomycetes produce type-II PKS antibiotics under normal growth conditions⁷ and modulate the antibiotic production upon physiological imbalance.¹² Evidence for this control mechanism can be found in the genetic code for jadomycin. An Open Reading Frame (ORF) upstream of type-II PKS encodes for a 196 amino acid sequence (*jadR*₂). This amino acid sequence resembles known proteins (*e.g.*, MtrR, AcrR, TetC and TcmR) that regulate resistance to xenobiotic exposure. Thus, when the nucleotide sequence of the *jadR*₂ repressor gene in *S. venezuelae* was disrupted,¹³ jadomycin B was produced under normal growth conditions, and overproduction was observed when these mutants were exposed to ethanol stress. This findings point to the conclusion that *jadR*₂ negatively regulates the expression of biosynthetic genes of jadomycin B.¹¹

In 2001, a second regulatory gene (*jadR*₁) with 234 amino acids was identified by Vining.¹⁴ The gene was located immediately upstream of the repressor gene (*jadR*₂) and resembles sequences for two component regulator systems.¹⁵ The mutants generated by disruption or deletion of *jadR*₁ did not produce jadomycin B, implying that the gene functions as a positive regulator in the antibiotic biosynthesis. When a disrupted chromosomal copy of *jadR*₁ was complemented with a cloned gene, recovery of the wild-type phenotype was observed. Also, a negative effect on the growth of *S. venezuelae* occurred upon increasing the copy number of *jadR*₁ in the plasmid. This investigation by Vining led to the conclusion that both *jadR*₁ and *jadR*₂ form an interacting stress-responsive regulatory system for the biosynthesis of jadomycin B.¹⁴

2.3. Sequencing region downstream of PKS-II

In 1996, Vining and co-workers cloned and sequenced DNA from a region downstream of an overlapping PKS gene cluster in *S. venezuelae* (ISP5230), which is responsible for jadomycin B biosynthesis.^{6a} Their analysis of the nucleotide sequence located one complete ORF (ORF6) and two incomplete ORFs (ORF4 and ORF7). The amino acid sequence for ORF6 and ORF7 resembles oxygenase. Transformation of *S. venezuelae* with an ORF6 disruption vector¹⁶ gave a mutant, which blocked jadomycin B biosynthesis. Instead, the mutant accumulated a non-nitrogenous secondary metabolite (rabelomycin **4**), which is also produced by *Streptomyces olivaceus* (Scheme 1).¹⁷ This suggests that rabelomycin **4** is an intermediate¹⁸ in the biosynthesis of jadomycin, where ORF4, ORF6 and ORF7 encodes for oxygenases that are involved in the oxidative cleavage of the B ring in angucycline **4** to

aldehyde **6** All that remains for the biosynthesis of jadomycin B is A-ring dehydration/aromatization, isoleucine incorporation, oxazoline ring formation and glycosylation. However, the specific order of these sequences is still in doubt. Left of *jadR*₂, a cluster of three other regulatory genes (*jadW*₁, *jadW*₂ and *jadW*₃) were identified by Vining *et al.* (2003).¹⁹

Subsequently, another ORF was found (*jadJ*) between *jadR*₁ and *jadI*.²⁰ The gene *jadJ* encodes for proteins that are homologous to the biotin carboxylase (BC) and biotin carboxyl carrier protein (BCCP) components of acyl-coenzyme A carboxylase. The mutants produced by disruption of *jadJ* significantly reduced jadomycin production, without negative effects on the growth or morphology of the mutants. Thus Vining *et al.* concluded that *jadJ* is not essential for fatty acid biosynthesis, but rather responsible for supplying malonyl-coenzyme A for the synthesis of polyketide intermediate. Later, several more genes were identified for the biosynthesis of jadomycin, by Vining.²¹ Three complete ORF (*jadM*, *N* and *X*) and one incomplete ORF (*jadO*) were found. The later (*jadO*) relates to the biosynthesis of the sugar portion of jadomycin (Scheme 7). Although the role of *jadX* could not be identified, the roles *jadM*, *N* and *O* were assigned by homology to known proteins. The other two complete ORFs were assigned as a holo-ACP synthase (*jadM*), and acyl-coenzyme A decarboxylase (*jadN*), respectively. The incomplete ORF (*jadO*) showed strong similarities with to NDP-hexose-2,3-dihydratase, indicating it's role in the synthesis of L-digitoxose sugar unit in jadomycin B.

2.4. UWM6 a new intermediate in jadomycin biosynthesis

A new gene (*jadI*), upstream of *jadA* was characterized by Hutchinson *et al.*²² *JadI* has homology to a related cyclase responsible for the biosynthesis of the ABCD rings of jadomycin in combination with the minimal PKS genes (*jadABC*), a cyclase (*jadD*), and a keto reductase (*jadE*). When these genes are expressed in *Streptomyces lividans*, rabelomycin **4** is produced along with a new angucycline UWM6 **12** (Scheme 2). When this experiment was run with an incomplete *jadI* shunt, products with out C-ring (SEK43 **14** and UWM4 **15** were obtained), thus suggesting the role of *jadI* in ABCD-ring construction and the potential of UWM6 **12** and/or rabelomycin **4** as being an intermediate in the biosynthesis of jadomycin B.²³

2.5. Proposed ring opening mechanism of UWM6

Initial biosynthetic studies suggested that rabelomycin is the intermediate in jadomycin biosynthesis and *jadF* catalyzes the oxygenation of rabelomycin leading to B-ring opening.^{6a} However, subsequent work discovered other intermediates in the pathway, including UWM6 (**12**) and prejadomycin (**16**), which suggested that rabelomycin is not an actual intermediate in the pathway of jadomycin B biosynthesis.^{24,25} The most recent studies by Yang *et al.*²⁶ suggests that *jadF* is a bifunctional enzyme that catalyzes the dehydration of UWM6 (**12**) to prejadomycin (**16**), and oxygenation at C-12 to form (**17**) which spontaneously air oxidizes to form dehydrorabelomycin (**18**) (Scheme 3). Although the exact identity of the enzyme responsible for the B-ring opening of dehydrorabelomycin (**18**) is still unknown, it is assumed that some combination of *jadF*, *jadH* and *jadG* is responsible for this reaction (**18** to **19**).²⁴ Rohr *et al.* have proposed a mechanism for the C-C bond cleavage of B-ring by a Baeyer-Villiger type mechanism (**20** to **21**). Subsequent hydrolysis of lactone intermediate **22** by *jadK* would give aldehyde **19**. However, at that time, the C-12 oxygenation was incorrectly assigned as performed by *jadG* (Scheme 3).²⁵

3. Amino acid incorporation in jadomycin biosynthesis

Regardless of the pathway of its formation, aldehyde **19** is believed to be the intermediate that incorporates the amino acids. Initial amino-acid condensation followed by a series of decarboxylation and ring closing sequences to form the pentacyclic skeleton of jadomycin. Early on, Vining *et al.*^{6a} suggested that isoleucine incorporation begins with an intermolecular 1,4-addition across the quinone enone (**6** to **7**), which is followed by a decarboxylation (**7** to **8**). A subsequent intramolecular addition to the aldehyde and lactonization should give the pentacyclic core (*i.e.*, **8** to **9**, Scheme 1). Considering the presence of excess amino acid nucleophile (*e.g.*, isoleucine) and the relative reactivity of the functional groups, Rohr *et al.* proposed an alternative mechanism. Their mechanism begins with the amine of isoleucine condensing with the aldehyde to form intermediate imine **23**. A subsequent cascade cyclization (carboxylate addition to the imine and amine addition to the quinone)²⁷ and decarboxylation leads to the pentacyclic core of jadomycin (Scheme 4).

It is still an open question as to where the amino acid incorporation proceeds through an enzymatic or spontaneous process. To date, no enzyme has been isolated in the jadomycin gene cluster that is responsible for the process. Rohr *et al.* suggested the possibility of a non-enzymatic incorporation of amino acid based on the fact that jadomycin occur as an inseparable mixture of diastereomers.²⁷ They synthesized a range of jadomycin B analogues using different amino acids in the culture medium. A careful NMR analysis of the jadomycin analogues and molecular modelling studies suggested that the jadomycin is a mixture of diastereomers at the aminal position. They propose that the mixture of diastereomers equilibrate via an undetected zwitterionic intermediate (Scheme 5). A recent total synthesis of jadomycin A and carbasugar analogue of Jadomycin B by O'Doherty *et al.* (see synthetic approach to jadomycin) supports the proposal that amino acid incorporation is indeed a non-enzymatic process.²⁸

3.1. Alternative mechanism of ring opening in jadomycin B

Jakeman proposed an alternative mechanism for the inter-conversion of the jadomycin diastereomers.²⁹ His proposal was based on the isolation of an aldehyde intermediate (~pH 11) as a mixture of conformational isomers about the aldehyde C-C bond, **27** and **28**. They suggested that these two conformational isomers can selectively cyclize into the two corresponding diastereomeric forms of jadomycin B upon acidification (~pH 4). Interestingly, Dalomycin T **30** (which has an oxazolidine ring and the same angucycline framework as of jadomycin B) was not responsive to the same acid-base treatment. This led to the conclusion that the carbonyl group of the oxazolone ring is essential for ring opening. They suggest that the aldehyde intermediate **27** is formed by nucleophilic attack of hydroxide ion at the carbonyl carbon of the oxazolone ring, subsequent opening of the oxazolone give aldehydes **27/28**. Not surprisingly, Dalomycin T **30**, which lacks the required carbonyl group, does not undergo a similar isomerization and exists as a single diastereomer (Scheme 6).

3.2. Incorporation of non-natural/non-proteogenic amino acids

Jadomycin analogues can be obtained by using different amino acids in the growth medium. Doull *et al.* was the first to observe this phenomenon.^{4a} Differently colored pigments were observed in the culture medium when L-isoleucine was replaced with other nitrogen sources. But no effort was made to isolate or characterise these compounds. Rohr and Jakeman were the first to characterize and report novel jadomycin analogues by the fermentation of *Streptomyces venezuelae* in the presence of excess amino acids.^{4d,27,30} The new jadomycin analogues that were produced using different amino acids are listed in Table 1. jadomycin N with a unique six-membered ring containing two nitrogens was obtained when L-asparagine

was used as a nitrogen source. It is probably formed by the cyclization of the primary amine side chain of L-asparagine rather than ring closure through a carboxylic acid.^{30b} Jakeman *et al.* have reported spectroscopic evidence suggesting that, jadomycin analogues can also be obtained from the non-natural D-amino acids and non-proteogenic/synthetic amino acids. The size of the oxazolone ring in jadomycin analogues can also be expanded by using β -amino acids, thus, if β -alanine or racemic-3-aminoisobutyric acid is used as the only nitrogen source in *Streptomyces venezuelae* culture, derivatives containing six-membered oxazinanone rings are produced.^{30a,c,d} These efforts lead to the first systematic study of structure activity relationships associated with jadomycins. For instance, substitution of the alkyl side chain on the oxazolone ring of jadomycin B resulted in changes to the bioactivity (antibacterial and DNA cleaving properties), whereas the two analogues with no alkyl side chain on the oxazolone ring were significantly less active.^{2,30b,d}

4. Biosynthesis of the L-digitoxose sugar unit

The biosynthesis of the sugar portion of jadomycin has also attracted significant attention. In the jadomycin gene cluster, immediately downstream of *jadN*, eight structural genes, *jadX*, *O*, *P*, *Q*, *S*, *T*, *U* and *V* are located, which are involved in the biosynthesis of the carbohydrate portion of jadomycin B. The specific functions of the corresponding proteins from seven of these genes (*jadO*, *P*, *Q*, *S*, *T*, *U* and *V*) were assigned by sequence analysis and comparisons to the related genes involved in deoxy sugar biosynthesis (2,6-dideoxy sugar L-digitoxose). To carry out sequence analysis, the genes were cloned and propagated in *Escherichia coli*.³¹ Analysis of the intermediates produced by the mutants and the sequence similarities to genes described in other species producing deoxysugar derivatives confirmed that these seven genes (*JadO*, *P*, *Q*, *S*, *T*, *U* and *V*) were responsible for the dideoxy sugar biosynthesis and attachment to the aglycone (jadomycin A). In contrast to the other seven, *jadX* is not essential for jadomycin B biosynthesis. However, the presence of *jadX* improves the yield for the production of jadomycin B. Based on these results, Vining *et al.* have proposed a biosynthetic pathway for the production of L-digitoxose sugar unit from glucose-1-phosphate **32** (Scheme 7).³

jadQ encodes glucose-1-phosphate nucleotidyltransferase that activates glucose to nucleotide diphosphate (NDP) derivative **33**. A 4,6-dehydratase encoded by *jadT* converts this NDP-glucose **33** to NDP-4-keto-6-deoxy-D-glucose **34**. An NDP-hexose 2,3-dehydratase encoded by *jadO* converts **34** to a ketoenol intermediate **35**, which exists in equilibrium with the diketone intermediate **36**. This diketone intermediate is transformed to NDP-2,6-dideoxy-D-threo-4-hexulose **37** by an oxidoreductase encoded by *jadP*. Isomerization of this D-threo hexulose **37** to L-erythro form **39** occurs by the *jadU* product (NDP-4-keto-2,6-dideoxy-5-epimerase) via intermediate **38**. Finally the ketone group of NDP-4-keto hexulose **39** is reduced by NDP-4-keto-2,6-dideoxyhexose 4-ketoreductase, encoded by *jadV* to give the L-digitoxose moiety **40** in jadomycin B biosynthesis. It is unclear whether glycosylation occurs on jadomycin A or other intermediates prior to the formation of the oxazolone ring by incorporation of amino acid. Comparison of the amino acid sequence encoded by *jadS* shows resemblance to deoxy-glycosyltransferase. So, it was proposed that *jadS* is involved in installing the L-digitoxose sugar unit onto the jadomycin B.

4.1. Substrate flexibility of 2,6-dideoxyglycosyl transferase

The function of *jadO* as a nucleoside diphosphate (NDP)-hexose 2,6-dehydratase was confirmed by Jakeman *et al.*³² The jadomycin analogue ILEVS 1080 was reported after a careful analysis of the natural products formed by using a previously developed *S. venezuelae* strain (VS 1080).³ NMR and MS/MS analysis showed that the sugar unit in

ILEVS 1080 differs from the L-digitoxose in case of jadomycin B. The new sugar replaces the axial hydrogen at the C-2 position with an axial hydroxyl group. The disrupted *jadO* could not dehydrate at C-2 position of NDP-4-keto-6-deoxy-D-glucose **34** (Scheme 7), thus the biosynthetic mechanism produced the sugar unit having C-2-hydroxyl functionality. This unnatural 6-deoxy sugar is then transferred to phenanthroviridin by *jadS* (a 2,6-dideoxyhexosyltransferase) to produce ILEVS 1080 (Scheme 8). It is worth noting that this is the first report of a 2,6-dideoxysugar-*O*-glycosyltransferase with substrate flexibility at C-2-position. The yield of ILEVS 1080 production (2.6 mg/3L)³² is significantly lower than jadomycin B (12 mg/L).²⁷ The low yield of ILEVS 1080 is likely the result of alteration in kinetic parameters of the enzymes downstream of *jadO* as they are processing a non-natural substrate.

5. Biosynthetic improvements for jadomycin B production

Effects of heat shock, ethanol treatment and phase infection on the production of jadomycin B by *Streptomyces venezuelae* have been studied extensively by the groups of Doull,^{4a} Rohr²⁷ and Jakeman.³³ Initial studies on *S. venezuelae* ISP5230 in galactose-isoleucine medium and corresponding media with different amino acids replacing isoleucine lead to isolation and characterization of jadomycin B analogues with modified oxazolone ring substituents.^{2,3,4a} Rohr's fermentation procedure differs from that of Doull *et al.* only in the starting culture volume and the volume and time of ethanol shock.^{4a,27} A more robust and efficient culture condition was developed by Vining and Jakeman where glucose was used as the carbon source instead of galactose, MOPS was employed as the buffer along with low concentration of phosphate and immediate ethanol shock. This altered media can render jadomycin B/anologue production in a time efficient and cost effective manner.³³

Yang *et al.*⁹ has reported a genetically modified strain of *Streptomyces venezuelae* that exhibits a two fold increase in the production of jadomycin B compared to the wild type. Four regulatory genes (3' end 272 bp of *jadW2*, *jadW3*, *jadR2* and *jadR1*) and the negative promoter upstream of *jadJ* (*P_J*) were replaced with promoter sequence ermEP*. The promoter sequence ermEP* can derive the expression of jadomycin biosynthetic genes from *jadJ* and is able to produce jadomycin without ethanol shock in contrast to the wild type.

6. Synthetic approaches

6.1. Benzo-[b]-phenanthridine synthesis

The benzo-[b]-phenanthridine containing natural products are structurally unique angucyclines isolated from different species of *Streptomyces*.³⁴ Despite many synthetic efforts, there has only been a limited number of successful total syntheses of this type of angucycline antibiotics. This lack of successful syntheses can be attributed to both the structural complexity and instability associated with these structures, particularly with the glycosidic bond. In contrast, there have been several successful approaches to the phenanthridine core.

Gould³⁵ reported the first synthesis of the naturally occurring benzo-[b]-phenanthridine aglycon in 1991. The A, C and D rings were constructed by coupling of cyanophthalide **42** with substituted bromocinnamate **41** followed by air oxidation to give quinone **43**. This was then converted to amide **45** by reduction/methylation of quinone **43** followed by deprotection of TMSE. The C-5 carbon was installed by formylation to give desired product **46** along with dehalogenated product **47** and fluorenone **48**. Finally the B ring was installed in phenanthridine **50** by Hoffmann reaction followed by hydrolysis/imine formation (Scheme 10).

In 1997, Valderrama *et al.* reported a synthesis of the benzo[*b*]phenanthridine framework by employing a hetero Diels-Alder reaction (Scheme 11).³⁶ The angular tetracyclic system was synthesized by an A plus CD to ABCD strategy. The B ring was constructed by a regioselective 4+2 cycloaddition of 5-hydroxy-1,4-naphthaquinone **51** and *N,N*-dimethylhydrazine **52** followed by spontaneous air oxidation/aromatization. The high regioselectivity of cycloaddition can be attributed to polarization of the azadiene **52** and directing effect of the C5 hydroxy group on juglone **51**. The regioselectivity of cycloaddition of juglone and azadienes was previously established by Potts³⁷ and Fillion.³⁸ Although a higher degree of regioselectivity was achieved, the reaction was slow at room temperature and was associated with the formation of minor bi-products (*e.g.*, regioisomer **54** and addition/oxidation products **55** and **56**).

The most common method for constructing the phenanthridine B ring has been by the condensation of 3-amino quinones with aryl aldehyde at the 3-position of quinone.^{39,40,41} In 1997, Snieckus reported the synthesis phenanthrovirdin aglycone **50**. The ACD rings were constructed by Suzuki-Miyaura coupling of bromojuglone **59** and oxaborole **58**. The 3-amino functionality was introduced by a 1,4-addition on to the quinone **60**. The B ring was then constructed by condensation of the amine and the aldehyde after MnO₂ oxidation of allylic alcohol **61**. Subsequent removal of methyl protection gave desired phenanthrovirdine aglycone **50** (Scheme 12).³⁹

Echavarren *et al.* have also reported the synthesis of phenanthrivirdine aglycone **50** following the same cyclization procedure. They constructed the ACD ring system by Stille coupling of bromo juglone **59** with aryl stannane **63**. A 1,4-addition of ammonia onto the quinone followed by subsequent deprotection of the acetal and subsequent condensation gave the B ring of the tetracycline **65**. MOM and methyl protections were removed to obtain **50** (Scheme 13).⁴⁰

Construction of the B ring of phenanthrivirdine by amine condensation with the aldehyde has also been achieved by Ishikawa (see total synthesis of dimethyl Jadomycin A).⁴¹ Although the B ring has been successfully constructed by the intramolecular condensation of an amine to the C3 aryl aldehyde of juglone, 1,4-addition of the aryl amine/imine at the C3 position of juglone does not give the desired B-ring of benzo-[*b*]-phenanthridine **68**. Instead, it undergoes a 6-*exo-dig* cyclization by condensing with C1 carbonyl of juglone **67** to form benzo-[*c*]-phenanthridine **66** (Scheme 14).⁴⁰

A solution to this problem came in 2010 from the synthesis of jadomycin A by O'Doherty. They showed that the B ring in the benzo-[*b*]-phenanthridine skeleton could be constructed regioselectively by changing the mechanism to circumvent the issues associated with a 6-*endo-dig* cyclization. Specifically, they decided to use a 6- π -electrocyclic ring closure instead of 1,4-addition of an amine to the quinone (see total synthesis of jadomycin A and carbasugar analogue of jadomycin B).²⁸

6.2. Synthesis of L-digitoxose sugar unit

In contrast to syntheses of the aglycon, there have been many approaches to the synthesis of L-digitoxose sugar. In 1982, Fronza *et al.* reported a stereospecific synthesis of L-digitoxose by addition of diallylzinc on to chiral aldehyde **73**. The stereochemistry of addition is controlled by steric interaction of the chiral α,β -dialkoxy aldehyde. Deprotection and ozonolysis gave L-digitoxose **75**.⁴² Three years later, Fujisawa *et al.* discovered a highly stereospecific and scalable synthesis of the key intermediate (glyceraldehyde derivative **73**) by diastereoselective reduction of α,β -diketodithiane with baker's yeast and subsequent

protection of the diol (Scheme 15).⁴³ Other related approaches to the sugar have been achieved by isoxazoline anion chemistry.^{44,45}

Braun *et al.* (1991) synthesized L-digitoxose from *O*-silylated lactal **77**. Lactal **77** can be obtained from optically pure/commercially available *S*-lactate. The sugar C3 and C4 stereocenters were installed by the sequential diastereoselective addition of anions (**78** to **79**) and (**79** to **71**). Finally L-digitoxose **75** was obtained by reducing mixture of lactones **82** and **83** with disiamylborane followed by hydrolysis and silica gel chromatography (Scheme 16).⁴⁶

In the same year, Tatsuta *et al.* reported the synthesis of L-digitoxose **75** from a glucose sugar **84**. Key to their approach was the use of a highly stereocontrolled hydride addition to a carbonyl group at the C-3 position of 2,6-anhydro-2-thiosugar **85**. The structure of 2,6-anhydro-2-thiosugar and configuration of the anomeric methoxy group directs the incoming nucleophile in a stereoselective manner. The unfavorable 1,3-diaxial interaction overrules the lone-pair repulsion from the sulfur and thus the hydride is delivered from bottom face. The key intermediate **85** was prepared in 10 steps starting from methyl α -L-glucopyranoside **84** (Scheme 17).⁴⁷

In 2005, Wang *et al.* reported a synthetic strategy for optically pure L-digitoxose sugar unit by employing kinetic resolution followed by ring closing metathesis. The synthesis began with commercially available acyclic trans-4-phenyl-3-buten-2-one **88**. Reduction of the α,β -unsaturated carbonyl followed by enzyme-metal catalysed dynamic kinetic resolution to obtain optically pure allylic alcohol **90**. Mitsunobu esterification of **90** followed by Grubb's ring closing metathesis and subsequent epoxidation/epoxide opening gave the key intermediate **94**. This α,β -unsaturated lactone **94** (Osmundalactone) can be transformed to L-digitoxose **75** by hydroxyl directed epoxidation/reductive epoxide opening strategy.⁴⁸ Zhang *et al.* in 2007 has also reported the synthesis of the L-digitoxose sugar unit from Osmundalactone, following Wang's procedure. However lactone **94** was synthesized from commercially available peracetyl L-rhamnal **95** by employing $\text{BF}_3 \cdot \text{OEt}_2$ induced epoxidation (Scheme 18).⁴⁹

In 2007, Jakeman reported synthesis of the L-digitoxose sugar unit based on a method developed by Brimacombe and co workers (1982). Their approach utilized a Klemmer and Rodemeyer⁵⁰ elimination on fully protected L-rhamnopyranoside **102**.⁵¹ The stereoselectivity was based on preferential deprotonation of the quasi-axial hydrogen which cleaves the benzyldiene acetal protection forming 2-deoxy-3-ketosugar **101**. The ketone of **101** was stereoselectively reduced with NaBH_4 to give the desired L-digitoxose stereochemistry. The major drawbacks to this method were the formation of side products from the $\text{S}_{\text{N}}2$ reaction of *n*-BuLi at the anomeric position and deprotonation at C-2 and the benzyldiene ring. Jakeman and Timmons improved the yield of the Klemmer-Rodemeyer elimination reaction by changing the base to *s*-BuLi and switching to an isopropylidene protecting group.⁵² They also reported a new method with improved yield to obtain the key intermediate, 2-deoxy-3-ketosugar **101** from L-rhamnose **98** (Scheme 19).

In contrast to traditional approaches to carbohydrates from carbohydrates with pre-existing stereocenters, the O'Doherty group has been interested in the synthesis of carbohydrates from achiral starting materials.⁵³ These *de novo* asymmetric approaches have been developed from both achiral furans⁵⁴ and dienones.⁵⁵ In 2010, they reported a *de novo* synthesis of L-digitoxose from the achiral and inexpensive acyl furan **104**. Asymmetric Noyori reduction and Achmatowicz rearrangement gave pyranoside **105**. The diastereomers **106** and **107** were separated after Boc-protection. Stereoselective palladium glycosylation of **106**, followed by Luche reduction and NIS mediated iodo-carbonate formation installed the

digitoxose stereochemistry in **110**. Radical deiodination using tris(trimethylsilyl)silane (TTMSS) gave the desired L-digitoxose glycosyl donor **111** (Scheme 20).²⁸

7. Total synthesis of jadomycin

To date, there have been only two synthetic efforts reported towards the total synthesis of jadomycins. In 2010, Ishikawa *et al.*⁴¹ reported the synthesis of dimethyl-protected jadomycin A. Their route used α -spirolactonyldihydroquinone **113** as the key intermediate for construction of the jadomycin ring system. Retrosynthetically, they envisioned construction of the jadomycin skeleton by imine cyclization followed by oxazolone formation of an amino-aldehyde **112**. This cyclization precursor was obtained from the spiro lactone intermediate **113**, which in turn was prepared from bromobenzene derivative **115** and tetralone **116** (Scheme 21).

Palladium-catalyzed coupling of *O*-bromobenzoate **115** and 5-methoxy tetralone **116** gave enol-lactone **117**. A subsequent dihydroxylation and rearrangement produced α -spirolactonyltetralone **118**. Benzylic bromination and S_N2 displacement was followed by allylic oxidation to give the masked naphthoquinone **113**. As a model study to form the phenanthroviridin skeleton, **113** was treated with methylamine to form 2-amino quinone **119**, which upon thermolysis generated **120**. Unfortunately, under identical conditions when methyl isoleucinate was used instead of methylamine as a nitrogen source, the desired dehydrative cyclization did not proceed. The most likely reason for this is the unfavorable steric interaction between the carboxyl and amino-acid fragment in **121**. Because of the free rotation around C-C bond, **121** obtains an energetically more stable conformation where carboxyl and amino functional groups are not in close proximity to undergo dehydration/cyclization (Scheme 22).

Ishikawa next decided to investigate the use of Snieckus's oxidative cyclization procedure³⁹ involving the intramolecular condensation of an amine and aldehyde to construct the B ring. The carboxyl group on the masked naphthoquinone **113** was reduced with BH₃•THF complex and the isoleucine methyl ester was hydrolyzed by lithium hydroxide to give **123**. Allylic oxidation of **123** with MnO₂ to aldehyde promotes condensation of the secondary amine with aldehyde forming iminium. This iminium intermediate is then trapped by carboxylate to form the pentacyclic ring system in jadomycin (**124**). Unfortunately, all attempts to remove the methyl protecting groups were unsuccessful (Scheme 23).

That same year O'Doherty *et al.* reported a successful synthesis of jadomycin A and the carbasugar analogue of jadomycin B.²⁸ The key transformation utilized to construct the B-ring in jadomycin was a 6- π -electrocyclic ring closure. Retrosynthetically it was envisioned that the B-ring in the phenanthridine core could be obtained by a 6- π -electrocyclic ring closure and the oxazolone ring could be constructed by an acid promoted cyclization reaction (Figure 4). The connection between C-7a and C-7b could be formed by Stille coupling of aryl stannane **127** and bromojuglone **128**. These stannane and bromojuglone can be obtained from commercially available starting materials **125** and 5-hydroxy-bromojuglone respectively.

The stannane **127** was prepared by directed ortho-metallation of **126** using MOM or BOM ether as the *O*-directing group. These metallation precursors were prepared from commercially available phenol **125**. The other coupling partner **128** was prepared by benzylation of commercially available bromojuglone. Stille coupling was carried out with stannane **127** and unprotected or protected bromojuglones, **128** to give tricyclic adduct **129** (Scheme 24).

The acetal protection on **129** was selectively removed with aqueous THF to generate aldehyde **131**. This aldehyde was then converted to 6- π -electrocyclic ring closure precursor **136** by condensation with *t*-butyl isoleucinate **133**. Unfortunately **136** did not undergo the expected electrocyclic ring closure. This unexpected result was attributed to the unfavourable alignment of the π -electrons due to steric congestion of the nitrogen substituent, which could lead to unfavourable alignment for the electrocyclic ring closure. Fortunately, when the MOM or BOM group was removed, the 6- π -electrocyclic ring closure readily occurred to give jadomycin precursor **135**. Finally acid promoted formation of oxazolone ring with simultaneous debenzoylation yielded jadomycin A as a 6:1 diastereomeric mixture (Scheme 25).

The authors assert that the removal of the offending protecting group benefited the cyclization beyond the removal of a negative steric interaction. They suggest that the presence of H-bonding between C-7 hydroxyl and the C-8 carbonyl of **134** preferentially aligned the cyclization precursor in proper orientation, thus promoting electrocyclic ring closure to **138**. Once the B ring in **138** is formed, a subsequent 1,3-proton transfer forms intermediate **139**, which undergoes hydration under the reaction condition to form quinol **140**. Quinol **140** undergoes air oxidation to give **135** (Scheme 26).

After a successful synthesis of jadomycin A, total synthesis of jadomycin B was attempted by the direct installation (Schmidt glycosylation, S_N2 alkylation, Pd-catalyzed glycosylation and Mitsunobu conditions) of a suitably protected sugar moiety (**106**, **140**, **141** and **142**). The required L-digitoxose sugar units were synthesized by the route in Scheme 20. Despite numerous attempts of jadomycin A and **129**, they were never able to isolate a product of glycosylation. The failure to successfully glycosylate the jadomycin aglycon was attributed to the acid sensitivity of the glycosylated products, both to the reaction conditions and silica gel chromatography. This acid sensitivity has also been seen in jadomycin B (Scheme 27). In fact, only tangential signs (a distinctive wine-red color) of glycosylation between **129** and **140** could be seen under the Mitsunobu glycosylation conditions.

With the acid sensitivity precluding the total synthesis of jadomycin B, they decided to investigate the synthesis of a less acid labile cyclitols (5a-carbasugar) analogue of jadomycin B. Following a previously reported method,⁵⁶ quinic acid **143** was converted to dihydroxy ketone **144** in nine steps. Enone **145** was obtained by Boc-protection of **144** followed by base mediated elimination. This enone was selectively reduced to **146** using $LiAlH_4$ at low temperature. Myers rearrangement of allylic alcohol gave alkene **147**. Stereoselective dihydroxylation and diol protection gave **148**. Removal of Boc-protection with $LiAlH_4$ to obtain the Mitsunobu glycosylation precursor **149** (Scheme 28).

Mitsunobu glycosylation was first attempted with cyclitol donor **149** and jadomycin A as the acceptor. Unfortunately, only a complex mixture was obtained, which was attributed to the sensitive oxazolone ring. Successful glycosylation occurred when cyclitol acceptor **150** was used forming stable acetal **151**. Global deprotection with aqueous HCl removed all the protecting groups affording **152**. This set the platform for introduction of amino acid and successive ring closure. Condensation of *t*-butylisoleucinate **133** with aldehyde **152** promotes 6- π -electrocyclic ring closure forming the B ring **153**. Finally an acid catalyzed lactonization was used to install the oxazolone ring and the carbasugar analogue of jadomycin B was synthesized as 2.5:1 diastereomeric mixture (Scheme 29).

8. Conclusions

A detailed account of the jadomycin biosynthesis and synthetic studies has been reviewed. These biosynthetic studies have lead to a better understanding of the biosynthetic pathway,

which has led to the discovery of new analogues and improved production of various jadomycins for further biological evaluation. Similarly, the synthetic contributions have shed light on the reactivity and stability of the jadomycin ring system and natural product. In this regard, the access to the cyclitol analogue of jadomycin B allows access to stably analogues for further structure activity relationship (SAR) studies.

Acknowledgments

We would like to thank Prof. Penny Beuning at Northeastern University for her helpful discussions regarding the genomic data. We are also grateful to NIH (GM090259 and GM088839) and NSF (CHE-0749451) and the Department of Chemistry and Chemical Biology at Northeastern University for supporting of this research.

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Figure 1.
Jadomycin A and its structural diversified congeners

Figure 2.
Organizational map of jadomycin gene cluster

Figure 3.
Phenanthridine core in natural products

Figure 4.
Retrosynthetic analysis of jadomycin

Scheme 1.
First hypothesis of the jadomycin biosynthetic pathway

Scheme 2. Polyketides produced from *jad* PKS gene cassettes in *S. lividans*

Scheme 3.
Proposed ring opening of UWM6

Scheme 4.
Proposed non-enzymatic incorporation of isoleucine

Scheme 5.
Proposed mechanism of diastereomeric interconversion

Scheme 7.
Proposed biosynthesis of L-digitoxose sugar unit.

Scheme 8.
Effect of *jadO* on sugar unit

Scheme 10.
Synthesis of phenanthridine ring.

Scheme 11.
DA approach to phenanthridine ring

Scheme 12.

Construction of B ring by condensation of amine and aldehyde

Scheme 13.

Construction of B ring by condensation of amine and aldehyde

Scheme 14.
Regioselectivity of B ring formation

Scheme 15.

Synthesis of L-digitoxose employing baker's yeast reduction

Scheme 17.
Synthesis of L-digitoxose from L-glucose

Scheme 18.
Synthesis of L-digitoxose via Osmundalactone

Scheme 19.
 Synthesis of L-digitoxose from L-rhamnose

Scheme 20.
de novo synthesis of L-digitoxose sugar

Scheme 21.
Retrosynthetic analysis of jadomycin A

Scheme 22.
Synthesis of key intermediate α -spiro lactonyltetralone **113**

Scheme 23.
Synthesis dimethyl jadomycin A

Scheme 24.
Stille coupling; synthesis of intermediate **129**

Scheme 25.
Synthesis of jadomycin A

Scheme 26.
Plausible mechanism of ring closure

Scheme 27.
Attempted glycosylations

Scheme 28.
Synthesis of cyclitol equivalent of L-digitoxose

Scheme 29.
Synthesis of carbasugar analogue of jadomycin B

Table 1

Jadomycin analogues produced using different amino acids

Amino acids used	Analogues produced	R =	n =
L-isoleucine	jadomycin B		0
D-threonine	jadomycin DT		0
L-serine	jadomycin S		0
L-phenylalanine	jadomycin F		0
Alanine	jadomycin Ala		0
Glycine	jadomycin G		0
L-leucine	jadomycin L		0
D-serine	jadomycin DS		0
D-methionine	jadomycin DM		0
L-threonine	jadomycin T		0
L-tyrosine	jadomycin T		0
DL-4-fluoro-phenylalanine			0
β-alanine			1
DL-aminoiso-butyric acid			1
L-asparagine	jadomycin N