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First Total Synthesis of Jadomycin A and Carbasugar Analogue of Jadomycin B **

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Abstract

The first syntheses of Jadomycin A and the carbasugar analogue of Jadomycin B have been achieved in 6 and 20 longest linear steps respectively. The key ring system of the aglycone was prepared by a 6π -electron electrocyclic ring closure and subsequent hemi-aminal ring closure. Acid sensitivity of the glycosidic bond in Jadomycin B precluded its synthesis but led to the synthesis of the carbasugar analogue.

Keywords

Jadomycin; 6π -electrocyclic ring-closure; de novo synthesis; carbasugar

Jadomycins A & B are unique members of the angucycline family of natural products with the unusual 8H-benz[*b*]oxazolo[3,3-*f*]-phenanthridine ring system. Both Jadomycins A & B are produced by the Gram-positive soil bacteria *Streptomyces venezuelae* ISP5230 under specific nutrient and environmental stress.^[i] They display important bioactivities, including antitumor, antimicrobial, anti-viral, as well as, aurora-B kinase inhibition and DNA-cleaving capacity.^[ii,iii,iv]

There has been no total synthesis of Jadomycin A or B, although libraries of Jadomycin analogues have been produced through fermentation approaches.^[v] Several approaches to the benzo[*b*]-phenanthridine ring system have been developed (Scheme 1).^[vi,vii] From these studies one can conclude that for stereoelectronic reasons the B-ring is best constructed by a cyclization of a 2-amino-3-phenylnaphthoquinone (e.g., **6** to **5**), rather than an amine cyclization onto the 2-position of an anthroquinone (e.g., **8** to **5**). However, these results stand in contrast to the proposed biosynthetic route (e.g., **1/2** via **4**, Figure 1).

Our ongoing interest in the synthesis and study of biologically active carbohydrate containing natural products,^[viii] along with these biosynthetic questions, made us interested in this class of natural products. Specifically, we were interested in testing our hypothesis that by employing an 6π -electrocyclic ring closure for the B-ring construction, one could skirt the stereoelectronic disadvantages of the 6-endo-dig ring closures (**10** to **9**).^[ix] To the best of our knowledge this is the first time that switching to an electrocyclic ring closure was used to change the regioselectivity for ring closure. This may also be the biosynthetic mode

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of ring closure and thus implying that the B-ring cyclization step doesn't need enzyme mediation to control the regioselectivity of cyclization.

Retrosynthetically, we envisioned **1** and **2** arising from the condensation of a protected aminoacid **11** and aldehyde **4** to form imine **10**. A 6π -electron electrocyclic ring closure would form the desired benzo[*b*]-phenanthridine **9** after hydration and oxidation. Finally an acid catalyzed deprotection/dehydration would install the final oxazolone ring in Jadomycin (Scheme 2). Following precedent, a Stille coupling could be employed to prepare **4**.^[vi] In accordance with the proposed biosynthetic pathway,^[v] the L-digitoxose could be incorporated earlier (e.g., **4**) or on Jadomycin A, this would depend on the stability of the glycosidic bond to these acid catalyzed transformation.

Our synthesis began with commercially available phenol **12**,^[vi] which was then protected as MOM and BOM ethers **13a** (68%) and **13b** (70%). Ortho-metalation of **13a/b** gave stannanes **14a** (68%) and **14b** (49%) in modest yields along with some recovered starting material (~30%). The other coupling partner **16** was prepared by benzylation of commercially available bromojuglone **15** (Scheme 3).^[x]

Coupling between stannane **14a** and juglone **16** gave **17a** in 73% yield (5 mol% Pd₂(dba)₃•CHCl₃, 20 mol% PPh₃ and 20 mol% CuI co-catalyst in THF, 75 °C for 12 h) (Scheme 4). Under identical conditions, unprotected juglone **15** was coupled with **14a** and **14b** to similar yields of **17b** (76%) and **17c** (54%). Selective acetal cleavage on **17a** (TFA_(aq)/THF, 10 min, 86%) gave the desired cyclization precursor aldehydes **19**. Unfortunately, when **19** was subjected to condensation conditions with protected isoleucine **11** no products of cyclizations were detected (e.g., **20**). We surmised that replacing the MOM-ether with a phenol would turn the negative ortho-ortho steric interaction into a positive hydrogen-bonding interaction.

Turning to an unselective acetal cleavage conditions (2.4 M HCl in CH₃CN, 4–8 min, 59–90%)^[xi] acetals **17a–c** were converted into aldehydes **18a/b**. To our delight, when aldehyde **18a** was condensed with **11** a smooth imine formation and cyclization occurred to give hemi-aminal **21a** (91%), which when treated with neat TFA underwent a *t*-butyl ester hydrolysis, oxazolone ring formation and benzyl ether cleavage to give the natural product Jadomycin A (74%, dr = 6:1).

The discovery of the surprising acid sensitivity of the benzyl ether in **21a**, led us to our optimal synthesis of Jadomycin A. Thus exposure of **18b** to the previous imine formation/electrocyclic ring closure conditions cleanly gave **21b** mixture of diastereomers (55%) and subsequent exposure of **21b** to neat TFA gave Jadomycin A (**1**) in 50% yield. This optimized route allowed for the formation of Jadomycin A in 6 steps from both commercially available **12** and **15** in 17% overall yield. A plausible mechanism for this key ring closure is outlined in Scheme 5.

We next decided to undertake a chemical glycosylation using our *de novo* carbohydrate approach as a part of our effort to study SAR of Jadomycin B. The synthesis of glycosyl donor **27**, **31**, **32** and **33** were achieved by a *de novo* asymmetric synthesis with achiral acyl furan as the starting material.^[xii] Following a procedure we previously disclosed for its enantiomer, acylfuran **26** was enantioselectively converted into *t*-butyl carbonate **28** in six steps via α -pyranone **27**.^[xiii] An NIS promoted iodo-carbonate cyclization installed the desired digitoxose stereochemistry in **29** and a radical TTMSS deiodination gave **30**, which could be debenzylated to give **31**.^[xiv] The anomeric alcohol in **31** could be activated for a Schmidt glycosylation^[xv] as an unstable trichloroacetimidate **32**, which was used *in situ*.

Simply switching the cyclic carbonate protecting group of **30** to an acetonide and debenzoylation gave another potential glycosyl donor **33** (Scheme 6).^[xvi]

We primarily focused on the installation of the L-digitoxose onto the aglycon employing mild Mitsunobu conditions to construct Jadomycin B (e.g., **31** or **33** and **17b/c** or **1** with DIAD/PPh₃, -78 °C to rt).^[xvii] While these reaction conditions had TLC evidence consistent with the formation of the desired glycosidic bond (a distinctive wine-red spot),^[xviii] unfortunately, none of the desired products could be isolated from these reaction mixtures. Changing of solvent and/or order of addition did not seem to have any significant affect, whereas, raising the temperature above -20 °C caused the *in situ* formed wine-red product to disappear. Schmidt glycosylation using **32** failed to produce the desired *in situ* product as determined by TLC.^[xv] The acid sensitivity of the glycosylated hydroxylquinones was evident by the fact that even our non-Lewis acidic Pd-catalyzed glycosylation of **1** and **17b/c** with pyranone **27** also failed. This instability of Jadomycin B precluded a practical SAR type studies and thus, we decided to investigate the synthesis of a less acid sensitive cyclitol analogue **3**.

The synthesis of carbasugar glycosyl donor equivalent of L-digitoxose starts from quinic acid (Scheme 7). Following a known procedure, D-(–)-quinic acid was converted into dihydroxyketone **35** in nine steps.^[xix] Boc protection followed by base mediated elimination resulted enone **36** (88%, two steps). A diastereoselective substrate controlled reduction of ketone **36** afforded **37** (94%). A Myers reductive rearrangement (NBSH/DIAD/PPh₃) cleanly gave alkene **38** (87%).^[xx] Stereoselective dihydroxylation using OsO₄ and subsequent diol protection gave acetonide **39** (80%, two steps). Finally, our proposed Mitsunobu type cyclitolization precursor **40** was prepared by a low temperature LiAlH₄ removal of the Boc group (97%).

With the cyclitol donor **40** in hand, we employed the proposed Mitsunobu cyclitolization with Jadomycin A **1**, unfortunately no cyclitol product **41** was observed (Scheme 8). Success occurred when we performed the Mitsunobu on oxazolone precursors (e.g., **17b** and **17c**). As before these reactions TLCs had the tell-tell sign of the wine-red spots, which this time did not disappear upon warming to rt. More convincingly, stable products **42a** and **42b** were isolated in excellent yields (84% and 91% respectively) when the reactions were run at rt. These acid stable products **42a** and **42b** could be globally deprotected upon exposure to aqueous acid (2.4 M, HCl/MeCN) giving moderate yield of **43** (59% from **42a**, 56% from **42b**).

As before with the aglycone, the cyclitol analogues **43** could be annulated with Boc-isoleucine **11**. Thus, condensation of aldehyde **43** with amino-ester **11** followed by a 6 π -electrocyclic ring closure resulted in the formation of the desired ring system **44**. Finally acid catalyzed trans-esterification leads to the formation of carbasugar analogue of Jadomycin B as an inseparable mixture of 2.5:1 diastereomers (Scheme 8).

In conclusion, the first total synthesis of Jadomycin A was accomplished in 6 longest linear steps in 17% overall yield. A cyclitol analogue of Jadomycin B has been successfully achieved in 20 longest linear steps in a 5% overall yield.^[xxi] A 6 π -electrocyclic ring closure was used to obtain the Jadomycin ring system, which should be compatible with the incorporation of various other amino acids for rapid synthesis of analogues. This synthesis supports the conclusions by Rix et al. that the isoleucine incorporation and consequent formation of the oxazolophenanthridine system occur non-enzymatically.^[vb] The application of this methodology for further analogue synthesis and biological testing is ongoing.

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- xxi. The route is 20 longest linear steps from quinic acid but only 9 steps from known starting materials, 36.

Figure 1.
Jadomycin A, B and its analogue

Scheme 1.
Retrosynthetic comparison for phenanthridine B-ring formation

Scheme 2.

Our biomimetic approach toward the Jadomycins

Scheme 3.

Synthesis of the desired coupling partners: MOM = methoxymethyl, BOM = benzyloxymethyl, DIPEA = *N,N*-diisopropylethylamine.

Scheme 4.

Synthesis of Jadomycin A: dba = dibenzylideneacetone, TFA = trifluoroacetic acid.

Scheme 5.

A plausible mechanism for ring closure

Scheme 6.

De Novo synthesis of glycosyl donors: NIS = *N*-iodosuccinimide, AIBN = azobisisobutyronitrile, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

Scheme 7.

Asymmetric synthesis of a cyclitol donor: Boc = *t*-butyl carboxylate, DIAD = diisopropyl azodicarboxylate, NBSH = *o*-nitrobenzenesulfonylhydrazide, NMO = *N*-methylmorpholine *N*-oxide, DMP = 2,2-dimethoxypropane, TsOH = *p*-toluenesulfonic acid.

Scheme 8.
 Synthesis of Jadomycin B carbasugar analogue