Synthetic Methods

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

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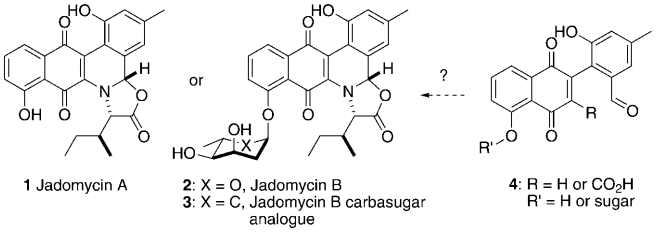
Jadomycins A and B are unique members of the angucycline family of natural products with the unusual 8*H*-benz[*b*]oxazolo[3,3-*f*]-phenanthridine ring system (Scheme 1). Both jadomycins A and B are produced by the Gram-positive soil bacteria *Streptomyces venezuelae* ISP5230

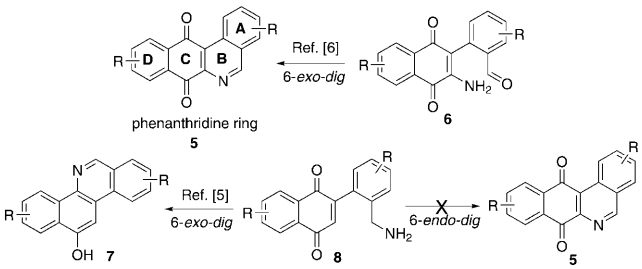


Scheme 1. Jadomycin A, B and its analogue.

under specific nutrient and environmental stress.[1] They display important bioactivities, including antitumor, antimicrobial, anti-viral, as well as, aurora-B kinase inhibition and DNA-cleaving capacity.[2–4]

There has been no total synthesis of jadomycin A or B, although libraries of jadomycin analogues have been produced through fermentation approaches.[5] Several approaches to the benzo[*b*]-phenanthridine ring system have been developed (Scheme 2).[6,7] 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** through **4**, Scheme 1).

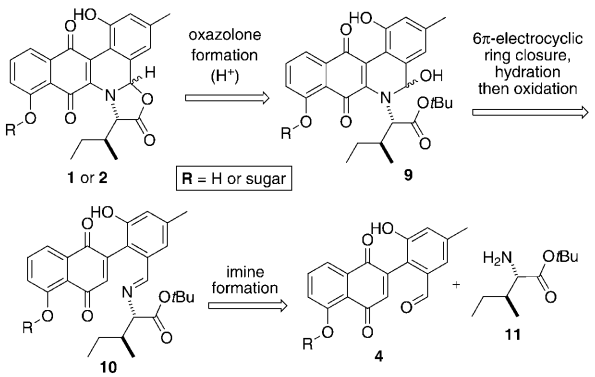
Our ongoing interest in the synthesis and study of biologically active carbohydrate containing natural products,[8] along with these biosynthetic questions, made us interested in this class of natural products. Specifically, we were interested in testing our hypothesis that by employing a 6π-electrocylic ring closure for the B-ring construction, one



Scheme 2. Retrosynthetic comparison for phenanthridine B-ring formation.

could skirt the stereoelectronic disadvantages of the 6-*endo-dig* ring closures (**10** to **9**).[9] 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 of ring closure and thus implying that the B-ring cyclization step does not need enzyme mediation to control the regioselectivity of cyclization.

Retrosynthetically, we envisioned **1** and **2** arising from the condensation of a protected amino acid **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 3). Following precedent, a Stille coupling could be employed to prepare **4**.[6] In accordance with the proposed biosynthetic pathway,[5] 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 the required acid-catalyzed transformations.



Scheme 3. Our biomimetic approach toward the jadomycins.

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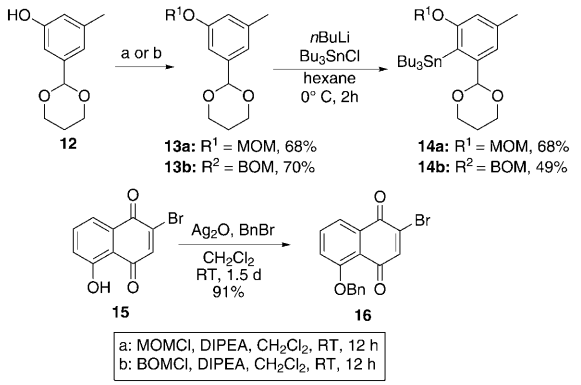
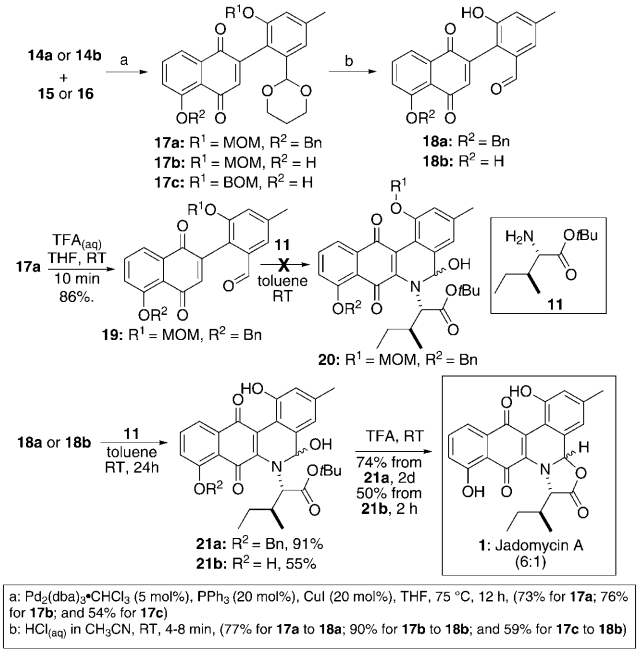
Our synthesis began with commercially available phenol **12**,[6] which was then protected as MOM and BOM ethers **13a** (68%) and **13b** (70%). *ortho*-Metalation of **13a/b** gave stannanes **14a** (68%) and **14b** (49%) in modest yields along with some recovered starting material (ca. 30%). The other coupling partner **16** was prepared by benzylation of commercially available bromojuglone **15** (Scheme 4).[10]



Scheme 4. Synthesis of the desired coupling partners: MOM = methoxymethyl, BOM = benzyloxymethyl, DIPEA = *N*,*N*-diisopropylethylamine.

Coupling between stannane **14a** and juglone **16** gave **17a** in 73% yield (5 mol% $[Pd_2(dba)_3]\cdot CHCl_3$, 20 mol% PPh_3 and 20 mol% CuI co-catalyst in THF, 75 °C for 12 h) (Scheme 5). 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

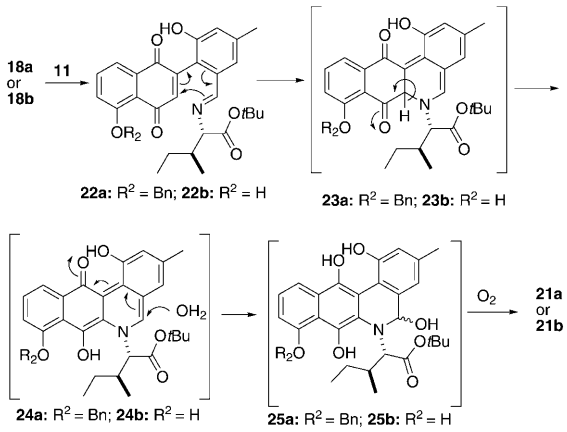


Scheme 5. Synthesis of jadomycin A (**1**): dba = dibenzylideneacetone, TFA = trifluoroacetic acid.

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.

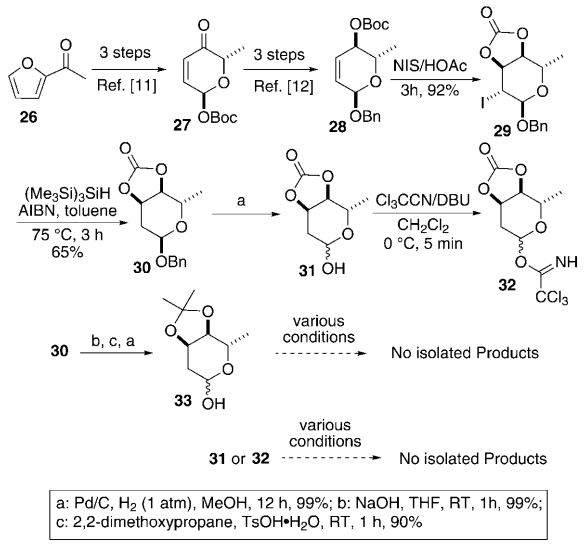
Turning to an unselective acetal cleavage conditions (2.4 M HCl in CH_3CN, 4–8 min, 59–90%)[11] acetals **17a–c** were converted into aldehydes **18a/b**. To our delight, when aldehyde **18a** was condensed with **11** a smooth imine formation and cyclization occurred to give hemiaminal **21a** (91%), which when treated with neat TFA underwent a *tert*-butyl ester hydrolysis, oxazolone ring formation, and benzyl ether cleavage to give the natural product jadomycin A (74%, d.r. = 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 six steps from both commercially available **12** and **15** in 17% overall yield. A plausible mechanism for this key ring closure is outlined in Scheme 6.

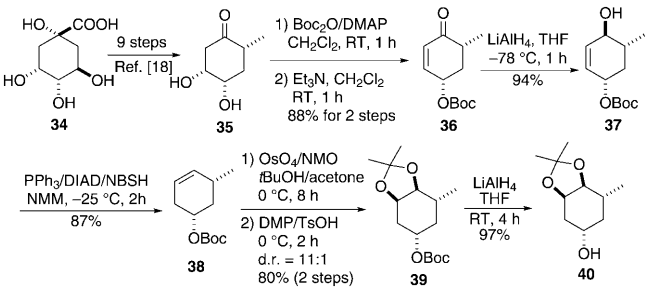


Scheme 6. A plausible mechanism for ring closure.

We next decided to undertake a chemical glycosylation using our carbohydrate approach as a part of our effort to study structure–activity relationships (SARs) of jadomycin B (**2**). The synthesis of glycosyl donors **27**, **31**, **32**, and **33** was achieved by a asymmetric conversion with achiral acylfuran as the starting material (Scheme 7).[12] Following a procedure we previously disclosed for its enantiomer, acylfuran **26** was enantioselectively converted into *tert*-butyl carbonate **28** in six steps through α-pyranone **27**.[13] An NIS-promoted iodocarbonate cyclization installed the desired digitoxose configuration in **29** and a radical TTMSS ($(Me_3Si)_3SiH$) deiodination gave **30**, which could be debenzylated to give **31**.[14] The anomeric alcohol in **31** could be activated for a Schmidt glycosylation[15] as an unstable trichloroacetimidate **32**, which



Scheme 7. Synthesis of glycosyl donors: NIS = *N*-iodosuccinimide, AIBN = azobisisobutyronitrile, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



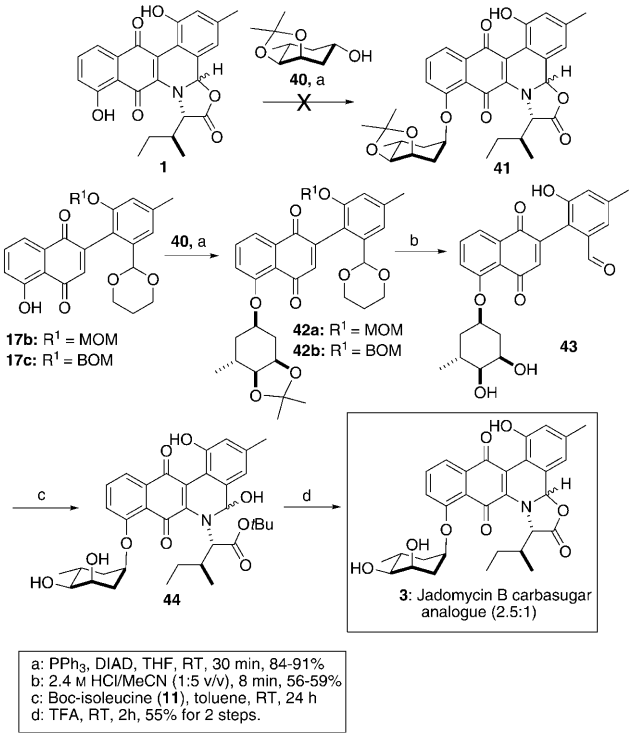
Scheme 8. Asymmetric synthesis of a cyclitol donor: Boc = *tert*-butyl carboxylate, DIAD = diisopropyl azodicarboxylate, NBSH = *o*-nitrobenzenesulfonylhydrazide, NMO = *N*-methylmorpholine *N*-oxide, DMP = 2,2-dimethoxypropane, TsOH = *p*-toluenesulfonic acid.

was used in situ. Simply switching the cyclic carbonate protecting group of **30** to an acetonide and debenzylation gave another potential glycosyl donor **33** (Scheme 7).[16]

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/PPh_3, −78 °C to RT).[17] While these reaction conditions had TLC (thin-layer chromatography) evidence consistent with the formation of the desired glycosidic bond (a distinctive wine-red spot),[18] 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 effect, 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.[15] The acid sensitivity of the glycosylated hydroxyquinones 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 study 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 8). Following a known procedure, D-(−)-quinic acid was converted into dihydroxyketone **35** in nine steps.[19] Boc protection followed by base mediated elimination resulted in enone **36** (88%, two steps). A diastereoselective substrate-controlled reduction of ketone **36** afforded **37** (94%). A Myers reductive rearrangement (NBSH/DIAD/PPh_3) cleanly gave alkene **38** (87%).[20] Stereoselective dihydroxylation using OsO_4 and subsequent diol protection gave acetonide **39** (80%, two steps). Finally, our proposed Mitsunobu-type cyclitolization precursor **40** was prepared by a low-temperature $LiAlH_4$ removal of the Boc group (97%).

With the cyclitol donor **40** in hand, we employed the proposed Mitsunobu cyclitolization with jadomycin A (**1**), but unfortunately no cyclitol product **41** was observed (Scheme 9). Success occurred when we performed the Mitsunobu reaction on oxazolone precursors (e.g., **17b** and **17c**). As before these reactions' TLCs showed the characteristic wine-red spots, which this time did not disappear upon warming to room temperature. More convincingly, stable products **42a** and **42b** were isolated in excellent yields (84% and 91% respectively) when the reactions were run at room temperature. 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**).



Scheme 9. Synthesis of jadomycin B carbasugar analogue **3**.

As before with the aglycone, the cyclitol analogues **43** could be annulated with isoleucine *tert*-butyl ester **11**. Thus, condensation of aldehyde **43** with aminoester **11** followed by a 6π-electrocyclic ring closure resulted in the formation of the desired ring system **44**. Finally acid-catalyzed transesterification leads to the formation of carbasugar analogue of jadomycin B as an inseparable mixture of 2.5:1 diastereomers (Scheme 9).

In conclusion, the first total synthesis of jadomycin A (**1**) was accomplished in six longest linear steps in 17% overall yield. A cyclitol analogue of jadomycin B (**2**) has been successfully achieved in 20 longest linear steps in a 5% overall yield.[21] A 6π-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 ring system occur non-enzymatically.[5b] The application of this methodology for further analogue synthesis and biological testing is ongoing.

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