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Total Synthesis of Jadomycins B, S, T, and ILEVS1080

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Jadomycins are a unique family of angucycline antibiotics featuring an 8*H*-benzo[*b*]phenanthridine skeleton fused with an amino acid unit.[1] With the exception of jadomycin A (**7**, which is the aglycon of jadomycin B (**1**))[2] and ILEVS1080 (**2**, which bears a 6-deoxy-α-L-altrose group),[3] all of the jadomycin congeners bear an α-L-digitoxose unit at C12-OH. The biosynthesis of the jadomycins is intriguing, involving an oxidative cleavage of the angucycline B ring[4] and subsequent nonenzymatic incorporation of the amino acid residue.[5] In fact, all of the jadomycins are produced upon feeding *Streptomyces venezuelae* under stress conditions with an amino acid (including non-natural amino acids) as the nitrogen source.[2,3,5] These compounds show potent antitumor activities,[5d–h] which may be due to their ability to inhibit the Aurora-B kinase[6] and induce DNA cleavage.[7] Antibacterial activity and activity against yeast are also reported for jadomycins.[2c,5h,8] The sugar unit is found to be critically important to these activities, since no activity has been observed for the aglycon jadomycin A.[2c,5,8] The side chain of the amino acid unit significantly modulates the activities.[5d–h,7a] Thus, jadomycins S (**3**) and T (**4**), embedded with L-serine and L-threonine, respectively, are among the most active antitumor congeners.[5e]

Chemical synthesis of jadomycin A was achieved in 2010 by O'Doherty and co-workers, but installation of an L-digitoxose unit onto the relevant aglycons did not succeed under various conditions.[9] Recently, Ishikawa et al. reported the synthesis of jadomycin A together with a few of the jadomycin aglycons.[10] They found that the proposed aglycons of jadomycins S and T, which contain the 4-(hydroxymethyl)-1,3-oxazolidin-5-one moiety, could not be accessed; instead the corresponding 1,3-oxazolidin-4-carboxylic acid derivatives were detected. These results suggest that the proposed structures of these two jadomycin congeners should be revised accordingly (Figure 1). Herein, we report the first total syntheses of jadomycins B, S, T, and ILEVS1080 (**1**–**4**).

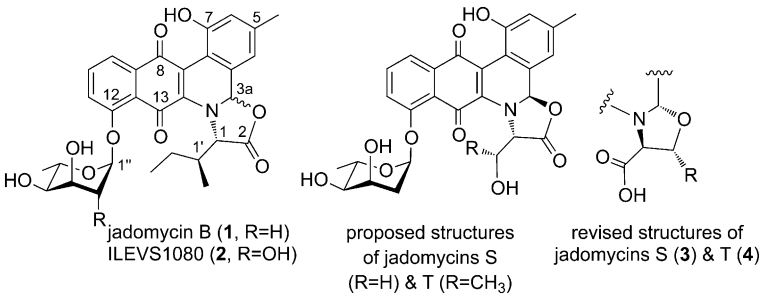

Figure 1. Structures of jadomycin B and ILEVS1080 and the proposed and revised structures of jadomycin S and T.

Inspired by biosynthetic transformations, O'Doherty et al. condensed a 2-(2-benzyl aldehyde)-1,4-naphthoquinone (**5**) with *tert*-butyl isoleucinate to obtain jadomycin A (**7**) through a cascade of imine formation, 6π-electrocyclic ring closure, hydration and air oxidation, cleavage of the *tert*-butyl group (upon treatment with CF_3COOH), and oxazolone-ring formation.[9] Alternatively, Ishikawa et al. introduced the amino acid unit onto a 2-[2-(hydroxymethyl)aryl]-1,4-naphthoquinone moiety through Michael addition and air oxidation. Subsequent oxidation of the benzyl alcohol and spontaneous isoquinoline–oxazolidone formation, followed by deprotection, furnished jadomycin A and the other jadomycin aglycons.[10b]

Herein, we describe a protecting-group-free biomimetic synthesis of jadomycin A (**7**) through direct condensation of naphthoquinone aldehyde **5** with sodium L-isoleucinate **6** (Table 1). Thus, a solution of aldehyde **5**[9,11,12] in toluene was charged with solid **6**; a red precipitate appeared slowly over 2 d. Washing a solution of the resulting solid in EtOAc with 1 N HCl, in an effort to remove excess **6**, resulted in a dark-green solution. Chromatography of the concentrated residue on silica gel provided jadomycin A (**7**) in 25% yield (Table 1, entry 1). The same reaction in THF, in which isoleucinate **6** has better solubility, proceeded better; the reaction mixture turned purple after 3 h and became dark green upon treatment with H^+ resin for 15 min, and the yield of **7**

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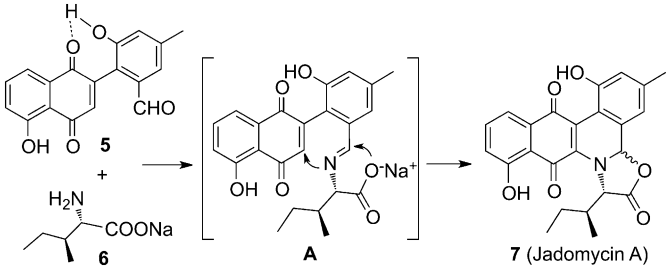
Table 1. Protecting-group-free biomimetic synthesis of jadomycin A (**7**).



Entry	Conditions	Yield [%]
1	1) toluene, RT, 2 d; 2) 1 N HCl	25
2	1) THF, RT, 3 h; 2) H^+ resin	51
3	1) THF/MeOH or THF/H_2O, RT; 2) H^+ resin	complex mixture
4	1) DMF, RT; 2) H^+ resin	complex mixture
5	1) CH_2Cl_2/H_2O, RT; 2) H^+ resin	34
6	1) $CHCl_3/H_2O$, 45 °C; 2) H^+ resin	50

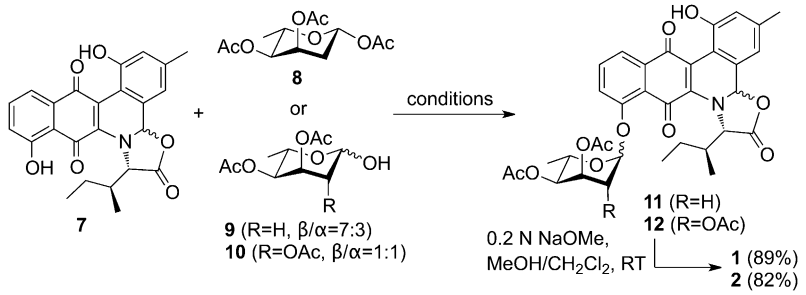
(d.r. = 7:1 at C3a) was improved to 51 % (Table 1, entry 2). More polar solvents such as THF/MeOH, THF/H_2O, and DMF were also used for the condensation reaction; however, these reactions resulted in complex mixtures of products (Table 1, entries 3 and 4).

To mimic a biogenetic environment, we carried out the condensation reaction under biphasic conditions. Although the reaction in CH_2Cl_2/H_2O at RT produced jadomycin A (34 %), the reaction in $CHCl_3/H_2O$ at 45 °C led to a better yield (50 %; Table 1, entries 5 and 6). The less polar solvent was found to be crucial to the condensation reaction in that formation of an intramolecular hydrogen bond between C7-OH and the quinone in **5** forces the aldehyde residue to take the orientation necessary for the cascade cyclization reaction.[9] The red intermediate before treatment with acid showed a pair of ^{1}H NMR spectroscopic singlets at $\delta = 8.05$ and 8.10 ppm, supporting the previous proposal that aldimine A (in a *Z*/*E* mixture),[5a] rather than the corresponding amine (derived from Michael addition),[4a] is involved in the biogenesis of jadomycins.

Installation of an L-digitoxose unit onto the poorly nucleophilic C12-OH group in jadomycin A (or its precursors) has been tried by O'Doherty et al. under a variety of Mitsunobu conditions, as well as under the Schmidt glycosylation conditions and Pd-catalyzed glycosylation conditions with a pyranone derivative as the donor.[9] Unfortunately, no glycosylation product could be isolated. However, the Mitsunobu condensation of a cyclitol derivative with a 2-aryl-1,4-naphthoquinone precursor was successful, leading finally to a carbasugar analogue of jadomycin B.[9] Previously, we have carefully studied the glycosylation of a similar angucycline phenol in landomycins and solved the problem by S_N2 substitution of a glycosyl α-iodide with the angucycline phenolate.[13] Thus, we attempted the glycosylation of **7** with 3,4-di-*O*-acetyl-L-digitoxosyl iodide, which was prepared in situ from the corresponding acetate **8** (TMSI, CH_2Cl_2, 0 °C),[12,14,15] in the presence of KHMDS and [18]C-6 in THF. The reaction led to a complex mixture of products (Table 2, entry 1); detection of glycal derivatives in the mixture indicated the vulnerability of the digitoxosyl iodide to decomposition under the reaction conditions. In fact, the stability of the glycosyl iodide (which contains an electron-withdrawing substituent at C6) has been found to be crucial to the successful glycosylation in the landomycin synthesis.[13] We therefore attempted the glycosylation with the more stable glycosyl bromide (derived in situ from acetate **8** with TMSBr).[12] Indeed, the desired glycoside **11** was isolated, albeit in only a moderate yield of 25 % with no α/β selectivity (Table 2, entry 2).

Mitsunobu condensation of **7** with 3,4-di-*O*-acetyl-L-digitoxose (**9**) was also examined.[12,14] Under conventional conditions (PPh_3 (2 equiv), DEAD (2.5 equiv), 4 Å MS, toluene),[16] the reaction at 0 °C led to a complex mixture of products; fortunately, at −78 °C, the reaction proceeded smoothly to furnish the desired glycoside **11** in 45 % yield in favor of the α anomer (α/β = 3:1; separable on silica gel) with 43 % of the starting material (**7**) being recovered. The yield of **11** was further increased to 64 % (with 31 % of **7** recovered) and the α/β ratio to 6:1 when the amount of donor **9** was increased to 3.0 equivalents (Table 2, entry 5). Applying these optimized conditions to the coupling of **7** with 2,3,4-tri-*O*-acetyl-6-deoxy-L-altrose (**10**)[12,17] provided the desired α-glycoside **12** in a satisfactory 78 % yield without

Table 2. Glycosylation of jadomycin A and synthesis of jadomycin B (**1**) and ILEVS1080 (**2**).[a]



Entry	Donor ([equiv])	Conditions	Results (yield [%], α/β)
1	**8** (1.5)	1) **8**, TMSI, CH_2Cl_2, 0 °C; 2) KHMDS, [18]C-6, 4 Å MS, THF, 0 °C	complex mixture
2	**8** (1.5)	1) **8**, TMSBr, CH_2Cl_2, 0 °C; 2) KHMDS, [18]C-6, 4 Å MS, THF, 0 °C	**11** (25, 1:1)
3	**9** (1.5)	PPh_3, DEAD, 4 Å MS, toluene, 0 °C	complex mixture
4	**9** (1.5)	PPh_3, DEAD, 4 Å MS, toluene, −78 C	**11** (45, 3:1); **7** (43)
5	**9** (3)	PPh_3, DEAD, 4 Å MS, toluene, −78 °C	**11** (64, 6:1); **7** (31)
6	**10** (3)	PPh_3, DEAD, 4 Å MS, toluene, −70 °C	**12** (78, 1:0)

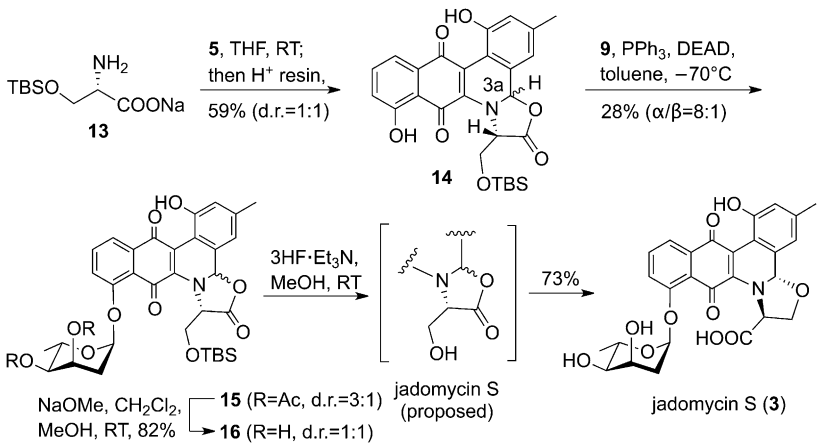
[a] TMS = trimethylsilyl, KHMDS = potassium hexamethyldisilazide, [18]C-6 = 1,4,7,10,13,16-hexaoxacyclooctadecane ([18]Crown-6), DEAD = diethyl azodicarboxylate, MS = molecular sieves.

detection of the β anomer. In contrast, the rigid L-digitoxose donors that are installed with 3,4-*O*-carbonate or 3,4-*O*-isopropylidene could not be coupled with **7** under Mitsunobu conditions, as reported by O'Doherty et al.[9] Finally, removal of the acetyl groups on glycosides **11α** (3a*S*/3a*R*=3:2) and **12** (d.r.=1:1) with NaOMe afforded jadomycin B (**1**, 3a*S*/3a*R*=3:2) and ILEVS1080 (**2**, d.r.=3:2), respectively, in high yields. The analytical data for the synthetic compounds **1** and **2** are in full agreement with those reported for the natural products.[3,5a,12]

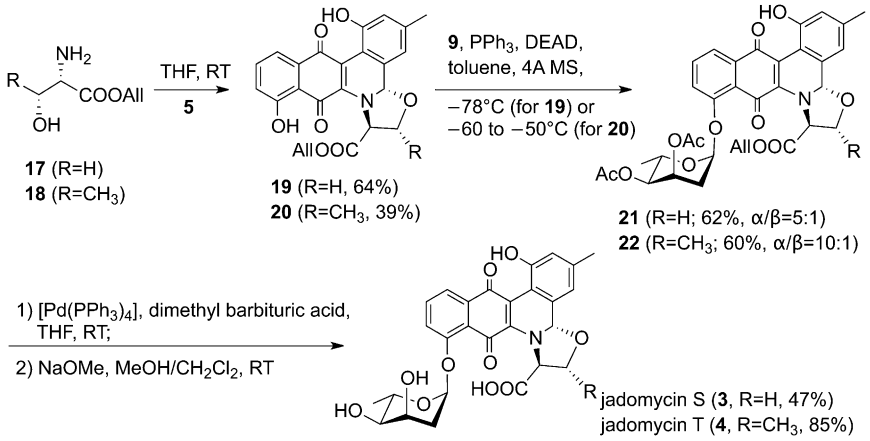
Considering the ambiguity in the structure of jadomycin S, we devised an unambiguous synthesis by condensing naphthoquinone aldehyde **5** with sodium *O*-TBS-L-serinate **13** (Scheme 1). Thus, treatment of **5** and **13** under the optimized conditions (Table 1, entry 2) gave 1,3-oxazolidin-5-one **14** in 59% yield (d.r.=1:1). Coupling of **14** with L-digitoxose donor **9** under the previously optimized Mitsunobu conditions provided a complex mixture due to the unexpected cleavage of the TBS group. Reducing the amounts of **9** (1.2 equiv) and PPh_3/DEAD (1.2 equiv) in the reaction led to the desired glycoside **15** in 28% yield (α/β=8:1; d.r.=3:1). Removal of the acetyl groups on **15** led to **16** (82%; d.r.=1:1), which was then subjected to cleavage of the TBS group to furnish the proposed structure of jadomycin S. Treatment of **16** with tetra-*n*-butylammonium fluoride (TBAF) or TBAF/HOAc led to decomposition of the oxazolone ring, as indicated by the color change from purple to yellow; however, with 3HF·Et_3N in MeOH, the final product **3** was obtained in good yield (73%), the analytical data of which match reasonably well with those reported for natural jadomycin S.[5a,12] The structure of **3** was assigned to be the 1,3-oxazolidin-4-carboxylic acid based on the facts that 1) the H-3a NMR spectroscopic signal of **3** appears at 5.73 ppm, whereas for **16** it appears at 6.56 and 6.37 ppm; 2) the IR absorption at 1621 cm^{-1} in **3** is in accord with a carboxylic group, whereas that at 1808 cm^{-1} for **16** implies an ester group; and 3) compound **3** is obtained as a single isomer from a 1:1 C3a diastereoisomeric mixture of **16**.

To further confirm the structure of jadomycin S, we carried out a synthesis directed specifically towards the revised structure (Scheme 2). Thus, L-serine allyl ester **17** was used in the condensation reaction with aldehyde **5**, to provide the 1,3-oxazolidine **19** in good yield (64%). In this case, only one isomer was isolated, which was determined to be the *S* isomer at C3a based on the absence of a NOSEY signal between H-1 and H-3a. Mitsunobu glycosylation of **19** with L-digitoxose **9** led to glycoside **21** in good yield (62%; α/β=5:1, easily separable). Cleavage of the allyl ester group in **21α** with $[Pd(PPh_3)_4]$ in the presence of dimethyl barbituric acid gave the corresponding acid in 73% yield,[18] which was then subjected to the conditions for removal of the acetyl groups to furnish the desired compound **3** (64%). Similarly, starting from the condensation of L-threonine allyl ester **18** with aldehyde **5**, the revised structure of jadomycin T (**4**) was obtained concisely (Scheme 2), the analytical data of which agree reasonably well with those reported for the natural product.[5a,12]

In conclusion, the total syntheses of jadomycins B, S, T, and ILEVS1080 (**1**–**4**) have been achieved, in that the challenging glycosylation of jadomycin aglycons was realized for



Scheme 1. Synthesis of the proposed structure of jadomycin S (TBS=*tert*-butyldimethylsilyl).



Scheme 2. Synthesis of the revised jadomycins S (**3**) and T (**4**) structures.

the first time by resorting to Mitsunobu condensation with sugar lactols bearing the proper protecting-group patterns. The protecting-group-free biomimetic condensation of a 2-aryl-1,4-naphthoquinone (i.e., **5**) with the sodium salts of amino acids (e.g., **6**) to furnish the unique 8*H*-benz[*b*]oxazolo[3,3-f]phenanthridine jadomycin aglycons is also hightlighted. This synthesis has unambiguously confirmed that the originally assigned structures of jadomycins S and T should be revised from containing a 4-(hydroxylmethyl)-1,3-oxazolidin-5-one unit to containing a 1,3-oxazolidin-4-carboxylic acid unit. This structural revision explains the fact that jadomycins S and T are the jadomycin congeners which occur as single isomers, with no epimerization occurring at the aminal C3a, supporting the conclusion that the carbonyl group of the oxazolone unit is essential for ring opening of jadomycins.[19] The unique carboxylic acid side residue in jadomycins S and T also rationalizes their stronger antitumor activities than the other congeners. The present concise approach could be easily adapted to the synthesis of various jadomycin congeners, thus in-depth studies on their activities is now a feasible task.

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Keywords: amino acids · antibiotics · glycosylation · jadomycins · Mitsunobu condensation · natural products · total synthesis

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