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Synthetic studies on jadomycins: synthesis of dimethyljadomycin A

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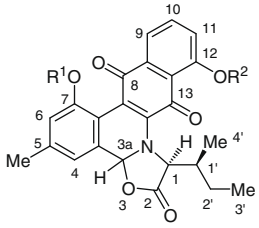
ABSTRACT

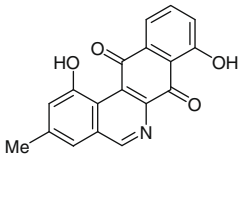
Dimethyljadomycin A was synthesized as the first example for the construction of 8*H*-benzo[*b*]oxazolo[3,2-*f*]phenanthridine skeleton.

Jadomycins A (**1**) and B (**2**) are unique 8*H*-benzo[*b*]-oxazolo[3,2-*f*]phenanthridine polyketide antibiotics containing isoleucine unit in the oxazolidinone ring, isolated from *Streptomyces venezuelae*[1]

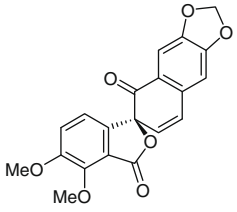
In this Letter we report the synthesis of dimethyljadomycin A (**4**) as the first example for the construction of 8*H*-benzo[*b*]oxazolo[3,2-*f*]phenanthridine skeleton.



jadomycin A (**1**: $R^1 = R^2 = H$)
jadomycin B (**2**: $R^1 = H$; R^2 = digitoxose)
dimethyljadomycin A (**4**: $R^1 = R^2 = Me$)



phenanthroviridin aglycon (**3**)



arnottin II (**5**)

together with phenanthroviridin aglycon (**3**). Biogenetically, jadomycins and gilvocarcins come from the related precursors, UWM6 for jadomycins and MM2002 for gilvocarcins.[2] It was reported that jadomycin B (**2**) and the biosynthetic analogs with different amino acid units from isoleucine show cytotoxic activity against several cell lines;[1e,g,h] however, the jadomycin skeleton with five ring systems has never been synthesized until now. We have synthesized the related polyketide kinamycin antibiotics.[3]

Although fully aromatized phenanthroviridin aglycon (**3**) had been prepared by three groups,[4] these approaches look hard to be simply expanded to the synthesis of jadomycin skeleton. We recently achieved the enantioselective synthesis of (−)-arnottin II (**5**) with the α-spirodehydrotetralone system by palladium-catalyzed α-arylation of 1-tetralone.[5] Thus, a synthetic route for the jadomycin skeleton using an α-spirolactonyltetralone (see, **9** in Scheme 1) as a key synthetic intermediate was designed.

o-Bromobenzoate **6** as an aryl unit for palladium-catalyzed coupling reaction with tetralone **7** was prepared from 3,5-dimethylanisole through a known 2-bromo-3-methoxy-5-methylbenz

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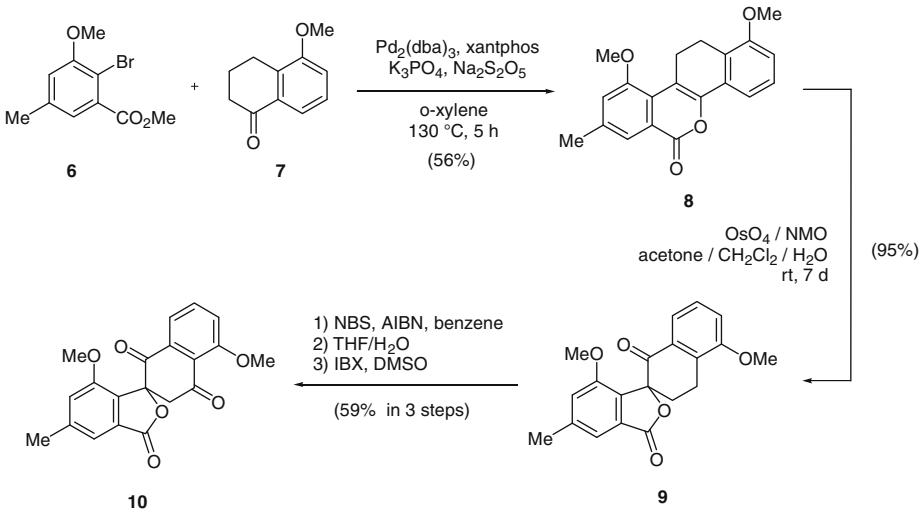
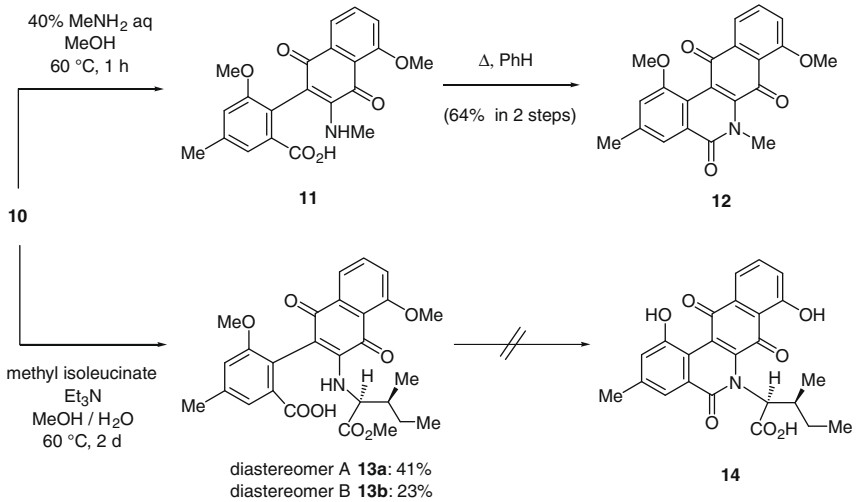


Scheme 1.

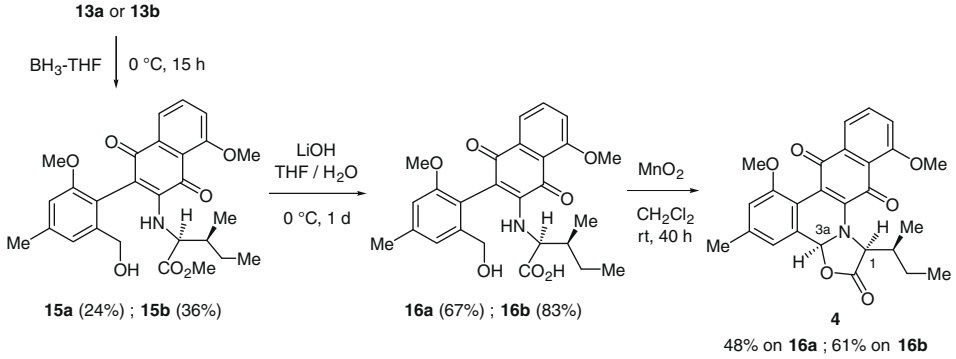
aldehyde[6] by successive reactions of benzylic bromination, the Sommelet reaction,[7] regioselective aromatic bromination, the Pinnick oxidation, and methylation. Coupling reaction between **6** with 5-methoxy-1-tetralone (**7**) under the reported conditions[5] afforded an expected enol-lactone **8** in 56% yield, which was easily oxidized with a catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine N-oxide to give a key intermediate α-spirolactonyltetralone **9** in 95% yield. Although direct introduction of an oxygen function to the benzylic position of the tetralone unit using conventional reagents such as 2,3-dichloro-5,6-dicyanobenzoquinone, chromium(VI) oxide, pyridinium dichromate, potassium permanganate, and ceric ammonium nitrate failed, conversion to a masked naphthoquinone system **10** was accomplished by stepwise reactions of bromination with *N*-bromosuccinimide, displacement with hydroxyl group, and oxidation with *o*-iodoxybenzoic acid (IBX) (Scheme 1).

Treatment of **10** with methylamine followed by thermal dehydration reaction of 2-(aminonaphthoquinonyl)benzoic acid **11** gave the phenanthroviridin skeleton **12** in good yield. On the other hand, in the use of methyl isoleucinate as a nitrogen source the second cyclization step of **13**–**14** failed even in reactions using dehydration reagents such as *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (Scheme 2). The naphthoquinone carrying isoleucine unit obtained in the first step was produced as a chromatographically separable mixture of diastereomers **13a** ($[\alpha]_D^{17}$ +37) and **13b** ($[\alpha]_D^{18}$ −156) in 41% and 23% yields, respectively, the structures of which were determined by application of 2D NMR experiments. These isomers show quite similar signal patterns in NMR spectra, except the chemical shifts of 6′-methoxy substituent on the phenyl pendant and the isoleucine unit in the ^{1}H NMR spectra (see, Supplementary data). Slow partial isomerization of the major isomer **13a** to the minor **13b** was observed in the ^{1}H NMR measurement, in which ca. 2:1 equilibrium mixture was obtained when **13a** was kept to stand in deuteriochloroform for 10 days. This phenomenon strongly suggests that these diastereomeric isomers were due to the restriction of rotation of the naphthoquinone–aryl bond. Trials for the structural assignment of these diastereomers were unsuccessful because of decomposition during purification.

Sniekus et al.[4c] reported a smooth isoquinoline construction in the synthesis of phenanthroviridin aglycon (**3**) by oxidative cyclization of 2-amino-3-(2-hydroxymethyl-phenyl)-1,4-dihydroxynaphthalene derivative. Thus, the carboxyl function in **13** was reduced to an alcoholic one. Treatment of each isomer **13a** and **13b** with borane-tetrahydrofuran complex solution followed by hydrolysis with lithium hydroxide gave the corresponding naphthoquinone derivatives **16a** ($[\alpha]_D^{23}$ +186) and **16b** ($[\alpha]_D^{23}$ −279) carrying both *o*-hydroxymethylphenyl and amino acid functionalities, which could be expected to simultaneously construct an oxazolid-



Scheme 2.



Scheme 3.

inylisoquinoline ring leading to an 8*H*-benzo[*b*]oxazolo[3,2-*f*]phenanthridine skeleton, albeit in unsatisfactory yield at the first reduction step.[8] Independent treatment of **16a** and **16b** with manganese oxide, as expected, afforded the same single product in the NMR spectra, in spite of the possible construction of diastereoisomers at the stereogenic benzylic acetal position (C3a) (Scheme 3).

The spectral data indicated that the product was an expected dimethyljadomycin A (**4**) and that absolute configuration at the 3a position was deduced to be *S* due to positive NOE enhancement between the 3a-H and the 1-H. Jadomycin A (**1**) was firstly isolated with 1–5% impurity[1a] and then identified to be a 10:1 diastereomeric mixture of 3a*S* and 3a*R* isomers.[1f] On the other hand, it was reported that jadomycin B (**2**) was determined to be a 67:33 diastereomeric mixture containing a major 3a*S* isomer.[1d] Preferential formation of the 3a*S* isomers in both natural jadomycin A (**1**) and synthetic dimethyljadomycin A (**4**) indicated that they are thermodynamically stable isomers. Unfortunately demethylation with boron tribromide[4c] afforded an inseparable mixture of a desired jadomycin A (**1**) and 11-bromojadomycin A albeit using HPLC.[9] Trials with boron trichloride and lithium iodide-2,6-lutidine resulted in no reaction and the formation of complex mixture, respectively.

In conclusion, dimethyljadomycin A (**4**) was synthesized through α-spirolactonyltetralone **9**. Difficult demethylation of dimethyljadomycin A (**4**) has made us examine a more general synthetic approach to jadomycin A (**1**) itself and the related compounds with a variety of amino acid residue by the use of more readily cleavable phenol protecting groups for structure–activity relationship experiments of bioactive jadomycins.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.014.

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8. Trials for other conditions such as hydride reduction after conversion to acid halide resulted in the decomposition of starting material.
9. The ratio of **1** and its brominated product is estimated to be ca. 3:2 by ^{1}H NMR spectrum. Formation of a brominated product under the similar condition has been reported: Knölker, H.-J.; O'Sullivan, N. *Tetrahedron* **1994**, *50*, 10893–10908.