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Total Synthesis of 8-Deshydroxyajudazol B

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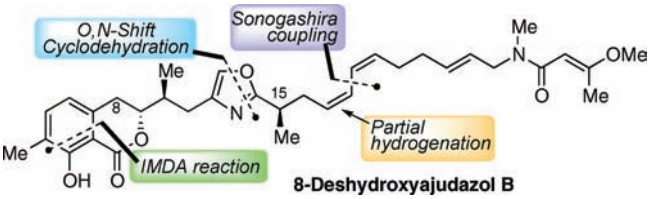
ABSTRACT



The total synthesis of a stereoisomer of 8-deshydroxyajudazol B (4), the putative biosynthetic intermediate of the ajudazols A (1) and B (2), is described. The key steps in the synthesis included an intramolecular Diels–Alder (IMDA) reaction to secure the isochromanone fragment, a novel selective acylation/*O,N*-shift to give a hydroxyamide which was cyclized to the oxazole and a high yielding Sonogashira coupling to form the C18–C19 bond. Partial alkyne reduction then afforded the target 4.

Myxobacteria are a rich source of potentially useful secondary metabolites with about 80 different basic compounds characterized so far.[1] A chemical investigation of the myxobacterium *Chondromyces crocatus* Cm c5 resulted in the isolation of two oxazole-containing compounds ajudazols A (**1**) and B (**2**) (Figure 1).[2] The ajudazols contain an isochroman-1-one, an oxazole, and a *Z*,*Z*,*E*-triene terminating in a 3-methoxybutenamide. Ajudazol A (**1**) has an exo methylene group at C15 while **2** possesses a methyl group with unknown stereochemistry. The relative configuration of the isochromanone core and the stereochemistry of the *Z*,*Z*,*E*-triene were assigned from NOESY and $^{1}H-^{1}H$ coupling constant analysis; however the absolute configuration remains to be determined.

Both ajudazols were identified as inhibitors of the mitochondrial respiratory energy metabolism of beef heart submitochondrial particles (SMP). NADH oxidation in SMP was inhibited at an IC_{50} of 13.0 ng/mL (22.0 nM) for ajudazol A (**1**) and 10.9 ng/mL (18.4 nM) for ajudazol B (**2**).[3]

Müller and co-workers have proposed that the biosynthesis of ajudazols A (**1**) and B (**2**) involves a series of post-PKS (PKS, polyketide synthase) P450 mediated late stage oxidations/desaturation of the putative intermediate 8-deshydroxyajudazol B (**4**).[4] This proposal was based on analysis of extracts from *C. crocatus* Cm c5 mutants in which the genes *ajuI* and *ajuJ* that encode for post-assembly-line P450 enzymes were inactivated by insertional mutagenesis. HPLC-MS analysis of the extracts from the *ajuI* knockout showed the absence of ajudazol A (**1**) and an increase in the production of ajudazol B (**2**) while the *ajuJ* knockout produced neither **1** nor **2** but afforded

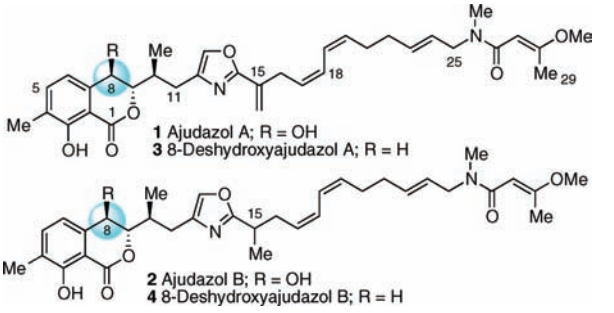


Figure 1. Structures of the ajudazols A (**1**) and B (**2**) and 8-deshydroxyajudazols A (**3**) and B (**4**).

(1) (a) Reichenbach, H *J. Ind. Microbiol. Biotechnol.* **2001**, *27*, 149. (b) Weissman, K. J.; Müller, R. *Biorg. Med. Chem. Lett.* **2009**, *17*, 2129.

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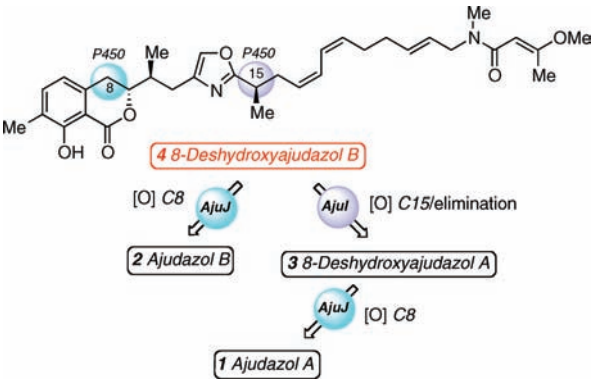
Scheme 1. Proposed Biosynthesis of the Ajudazols

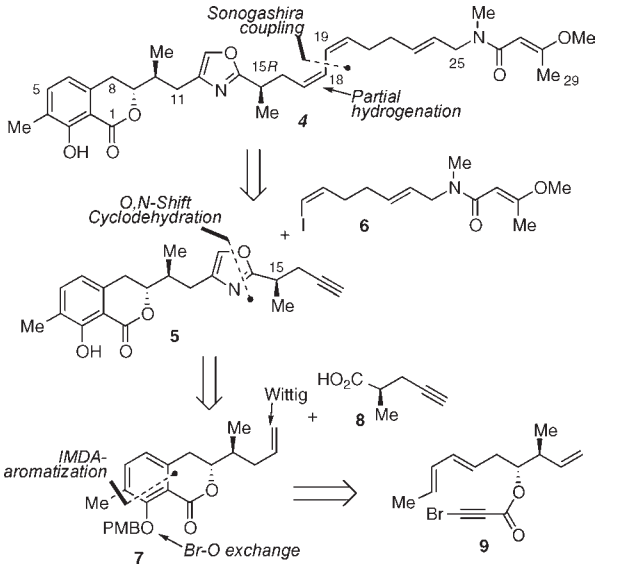


8-deshydroxyajudazol A (**3**), which was characterized by NMR, and what was proposed to be 8-deshydroxyajudazol B (**4**) by MS analysis. Close examination of the extracts from the wild type showed the presence of all four metabolites although **3** and **4** were in much smaller quantities. Thus, the post-PKS biosynthesis begins with 8-deshydroxyajudazol B (**4**) as shown in Scheme 1. More recently, it has been suggested that the rare isochromanone residue is produced by an unusual thioesterase and not a terminal cyclase.[5]

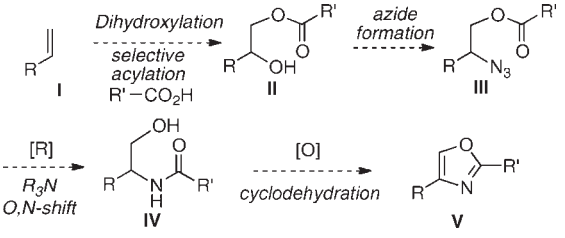
Several synthetic approaches to the polyene/oxazole 'eastern fragment' of the ajudazols have been reported[6] along with an approach to the isochromanone fragment.[7] In this paper, we report the synthesis of a stereoisomer of the proposed intermediate trace natural product 8-deshydroxyajudazol B (**4**) which utilizes a convergent strategy that can afford all members of this family and a modified oxazole synthesis from a terminal alkene.

The retrosynthetic analysis of the 15*R* isomer of 8-deshydroxyajudazol B (**4**) is shown in Scheme 2. The key final steps are the formation of the C18−C19 bond by a Sonogashira coupling[8] between alkyne **5** and vinyl iodide **6**[6b] followed by partial reduction to secure the *Z*,*Z*-diene. The 2,4-disubstituted oxazole in **5** could be formed by cyclodehydration of an amide precursor synthesized from alkene **7** and known optically pure acid *R*-**8** or *S*-**8**.[9] In this way, either stereoisomer of **4** could be produced in an efficient manner. The isochromanone **7** would be formed

Scheme 2. Retrosynthetic Analysis of 8-Deshydroxyajudazol B (**4**)



Scheme 3. Proposed Modified Synthesis of 2,4-Disubstituted Oxazoles from a Terminal Alkene



by the intramolecular Diels−Alder (IMDA)[10] reaction of tethered dienyne **9** and subsequent aromatization, bromide−oxygen exchange, and Wittig extension.

Details of the modified 2,4-disubstituted oxazole synthesis from a terminal alkene is shown in Scheme 3. Dihydroxylation of an alkene **I** followed by selective acylation of the resultant primary alcohol would provide the monoester **II**. Mitsunobu displacement of the hydroxyl group to give azide **III** and subsequent reduction to the amine along with a base induced *O*,*N*-shift of the acyl group[11] gives the hydroxy amide **IV**. Oxidation and cyclodehydration using the Wipf protocol[12] would then form the desired 2,4-disubstituted oxazole **V**. This proposed synthesis of the 2,4-disubstituted oxazole would circumvent the need for production of an amino alcohol precursor. Furthermore, a

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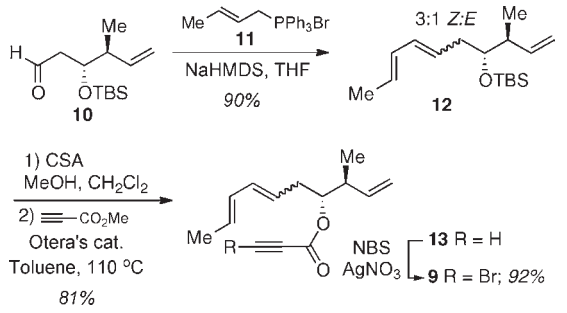
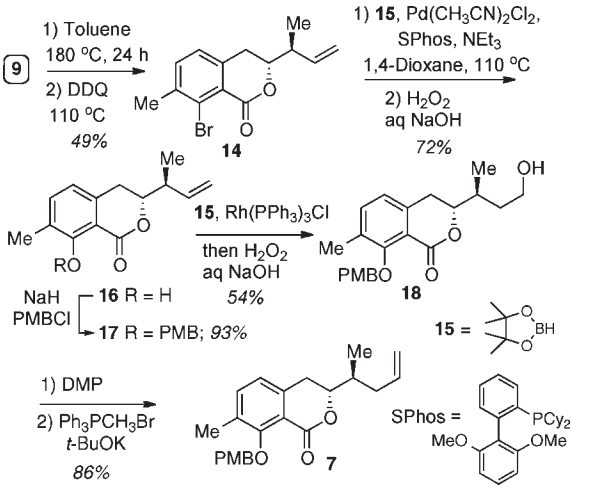
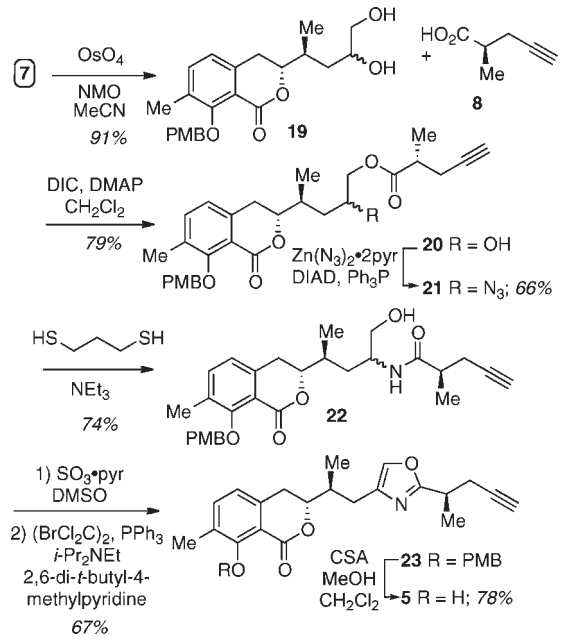
Scheme 4. Synthesis of the Diels–Alder Precursor **9**



Scheme 5. Diels–Alder Synthesis of the Isochromanone **7**



Scheme 6. Synthesis of the Oxazole Fragment **5**



^{13}C label for subsequent biosynthetic studies could be easily introduced at C5 of the oxazole by a Wittig extension.

The synthesis of the Diels–Alder precursor began with the known optically pure aldehyde **10** (Scheme 4).[13] Wittig olefination with the ylide derived from phosphonium salt **11**[14] afforded triene **12** as a 3:1 mixture favoring the *E*,*Z*-diene. Acid induced TBS group removal and ester exchange with excess methyl propiolate mediated by Otera's catalyst[15] formed ester **13**. Alkyne bromination[16] gave IMDA precursor **9**.

The IMDA reaction was effected upon heating a dilute solution of **9** in a sealed tube at 180 °C for 24 h (Scheme 5). Addition of DDQ caused aromatization[10a] to afford the isochroman-1-one **14**. The Br–O exchange was best achieved in a two-step sequence. Palladium-catalyzed borylation of the bromide with pinacol borane (**15**) using Buchwald's conditions,[17] followed by oxidation and hydrolysis, gave phenol **16**. Reproducible yields were only obtained when the stable intermediate borane was purified by silica gel chromatography prior to hydrolysis. Protection of the phenol to give the PMB ether **17** proceeded in excellent yield. Hydroboration of the alkene in **17** proved troublesome, with BH_3•Me_2S or BH_3•THF giving poor yields while 9-BBN failed to react, so we turned to a Rh-catalyzed method.[18] Treatment of alkene **17** with pinacol borane (**15**) and Wilkinson's catalyst followed by oxidative workup gave primary alcohol **18** in a reproducible yield. Oxidation and Wittig extension afforded oxazole precursor **7**.

Dihydroxylation of alkene **7** under Upjohn conditions[19] gave diol **19** as a mixture of diastereoisomers which was selectively acylated with *R*-acid **8**[9] to give the hydroxy ester **20** (Scheme 6). Conversion of **20** into **21** was achieved by a Mitsunobu reaction with the stable ZnN_3•2pyr. complex.[20] The azide **21** was obtained in 52% yield for the two-step process. After some experimentation, we found that the azide could be reduced in high yield with propane-1,3-dithiol[21] and an *O*,*N*-shift was promoted by

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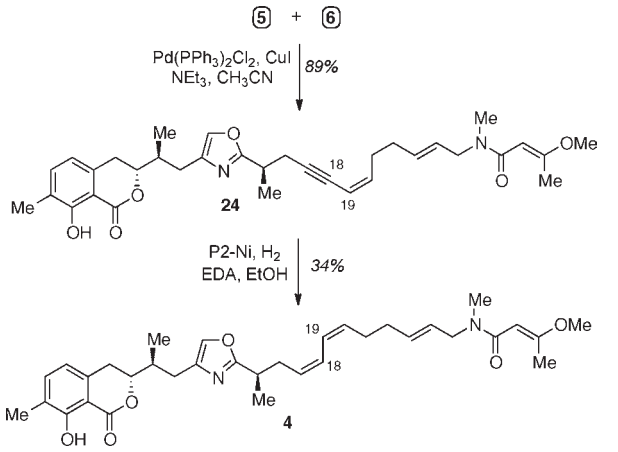
Scheme 7. Synthesis of 8-Deshydroxyajudazol B (**4**)



triethylamine[11] to give hydroxyamide **22**. The hydroxyamide diastereoisomers were separated by flash chromatography and characterized, but for convenience, the mixture was subjected to Parikh−Doering oxidation and cyclization was effected by treatment with 1,2-dibromotetrachloroethane and Ph_3P in the presence of hindered base 2,6-di-*tert*-butyl-4-methylpyridine.[12b] The use of Dess−Martin periodinane for the oxidation of alcohol **22** was less effective.[12a] Dehydrohalogenation was then induced in one pot by addition of a hindered amine base to give the oxazole fragment **23** in good yield. The PMB group was then removed to circumvent any problems with late stage deprotection in the presence of the acid labile 3-methoxybutenamide. Exposure of **23** to camphor sulfonic acid in methanol gave phenol **5** ready for the coupling reaction.

The Sonogashira coupling between **5** and iodide **6**[6b] was particularly effective in forging the key C18−C19 bond providing enyne **24** in excellent yield (Scheme 7). The challenging partial reduction of **24** could only be achieved using P2−Ni in the presence of hydrogen gas and ethylenediamine[22] as was found in our earlier studies on the eastern fragment synthesis.[6b] This gave the 15*R* diastereoisomer of 8-deshydroxyajudazol B (**4**) in a modest yield; however, little over-reduction occurred and unreacted starting enyne could be recovered from the reaction by preparative HPLC. Key changes in the ^{1}H NMR spectrum were the shift for H19 (5.77 ppm in **24** to 6.21 ppm in **4**) and the appearance of two new alkene signals for H17 and 18 at 5.45 and 6.24 ppm. Synthetic **4** also showed a doubling/broadening of some signals in its ^{13}C NMR spectrum at 25 °C due to restricted rotation about the tertiary amide.

Since no NMR data for natural **4** were available for direct comparison, we compared the NMR spectroscopic data for synthetic 8-deshydroxyajudazol B (**4**) with literature data for both ajudazol B (**2**) and 8-deshydroxyajudazol A (**3**). All the key signals compared favorably with our synthetic material supporting the assigned structure.[23]

In conclusion, we have completed the synthesis of the 9*R*,10*S*,15*R* stereoisomer of the postulated putative biosynthetic intermediate and trace natural product 8-deshydroxyajudazol B (**4**). Current studies toward the synthesis of 8-deshydroxyajudazol A (**3**) and the ajudazols A (**1**) and B (**2**) using this approach are underway.

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Supporting Information Available. Experimental details as well as characterization data and copies of the NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) See Supporting Information for full details.