

## Total Synthesis of 8-Deshydroxyajudazol B

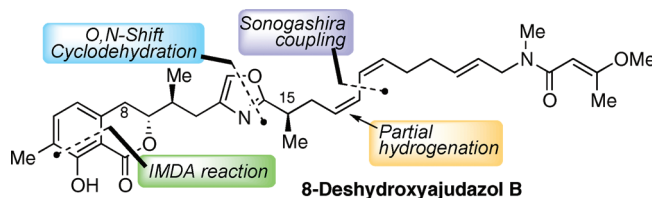
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Received February 3, 2011

## ABSTRACT

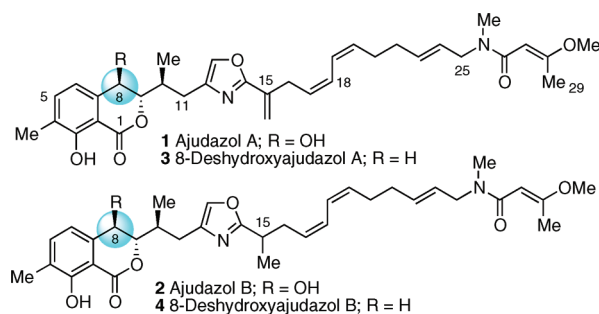


The total synthesis of a stereoisomer of 8-deshydroxyajudazol B (4), the putative biosynthetic intermediate of the ajudazols A (1) and B (2), is described. The key steps in the synthesis included an intramolecular Diels–Alder (IMDA) reaction to secure the isochromanone fragment, a novel selective acylation/O,N-shift 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.<sup>1</sup> 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).<sup>2</sup> 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 <sup>1</sup>H–<sup>1</sup>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<sub>50</sub> of 13.0 ng/mL (22.0 nM) for ajudazol A (1) and 10.9 ng/mL (18.4 nM) for ajudazol B (2).<sup>3</sup>

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



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

oxidations/desaturation of the putative intermediate 8-deshydroxyajudazol B (4).<sup>4</sup> 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

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Chemical reaction scheme showing the biosynthesis of Ajudazol A from 8-Deshydroxyajudazol B. The scheme starts with a chemical structure of 8-Deshydroxyajudazol B, highlighting the P450 8C8 site (C8) and the P450 15C15 site (C15). The reaction proceeds through two steps: 1) 8-Deshydroxyajudazol B is converted to 2 Ajudazol B by the P450 8C8 site. 2) 2 Ajudazol B is converted to 3 8-Deshydroxyajudazol A by the P450 15C15 site. Finally, 3 8-Deshydroxyajudazol A is converted to 1 Ajudazol A by the P450 15C15 site.

Several synthetic approaches to the polyene/oxazole ‘eastern fragment’ of the ajudazols have been reported<sup>6</sup> along with an approach to the isochromanone fragment.<sup>7</sup> 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.

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The reaction scheme illustrates the synthesis of compound **9** from compound **4** through several steps:

- Compound 4** (a substituted coumarin) undergoes **Sonogashira coupling** and **Partial hydrogenation** to form **Compound 5** (a coumarin with an alkyne side chain).
- Compound 5** undergoes **O,N-Shift Cyclodehydration** to form **Compound 6** (a pyridine derivative).
- Compound 6** reacts with **Compound 7** (a substituted coumarin with a PMBO group) via **Wittig** reaction and **Br-O exchange** to form **Compound 8** (a coumarin with a PMBO group and a bromine atom).
- Compound 8** undergoes **IMDA-aromatization** to form **Compound 9** (a coumarin with a PMBO group and a bromine atom).

I  $\xrightarrow[\text{selective acylation, } R^1-\text{CO}_2\text{H}]{\text{Dihydroxylation}}$  II  $\xrightarrow{\text{azide formation}}$  III

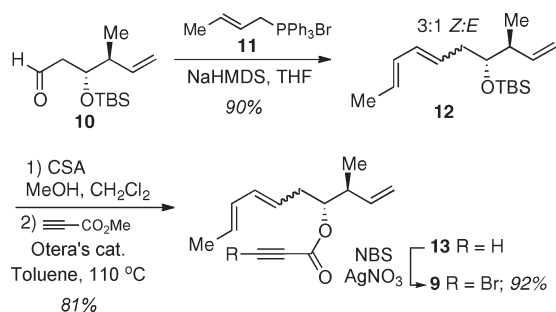
I  $\xrightarrow[\text{O,N-shift, } R_3\text{N}]{[R]}$  IV  $\xrightarrow[\text{cyclodehydration}]{[O]}$  V

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<sup>11</sup> gives the hydroxy amide **IV**. Oxidation and cyclodehydration using the Wipf protocol<sup>12</sup> 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**

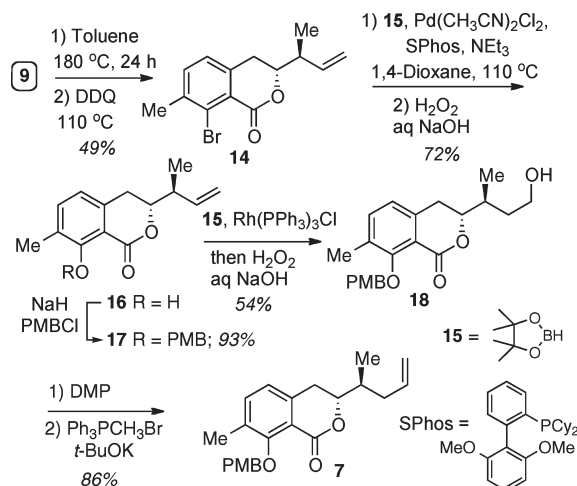


$^{13}\text{C}$  label for subsequent biosynthetic studies could be easily introduced at C5 of the oxazole by a Wittig extension.

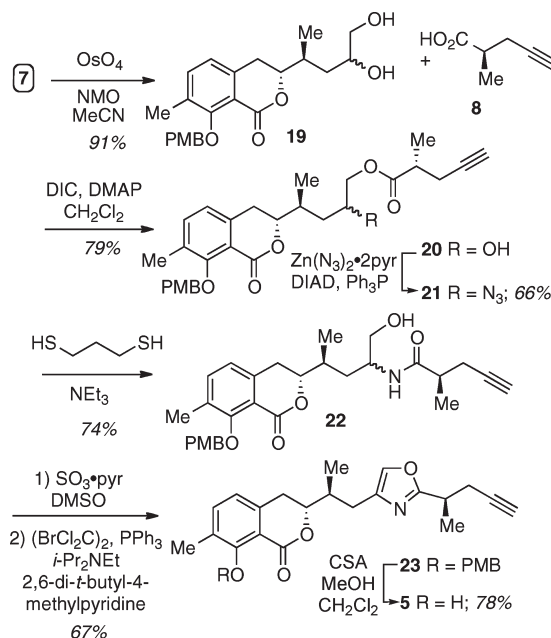
The synthesis of the Diels–Alder precursor began with the known optically pure aldehyde **10** (Scheme 4).<sup>13</sup> Wittig olefination with the ylide derived from phosphonium salt **11**<sup>14</sup> afforded triene **12** as a 3:1 mixture favoring the *E*,*Z*-diene. Acid induced TBS group removal and ester exchange with excess methyl propiolate mediated by Otera's catalyst<sup>15</sup> formed ester **13**. Alkyne bromination<sup>16</sup> 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<sup>10a</sup> 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,<sup>17</sup> 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  $\text{BH}_3\cdot\text{Me}_2\text{S}$  or  $\text{BH}_3\cdot\text{THF}$  giving poor yields while 9-BBN failed to react, so we turned to a Rh-catalyzed method.<sup>18</sup> 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**.

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



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



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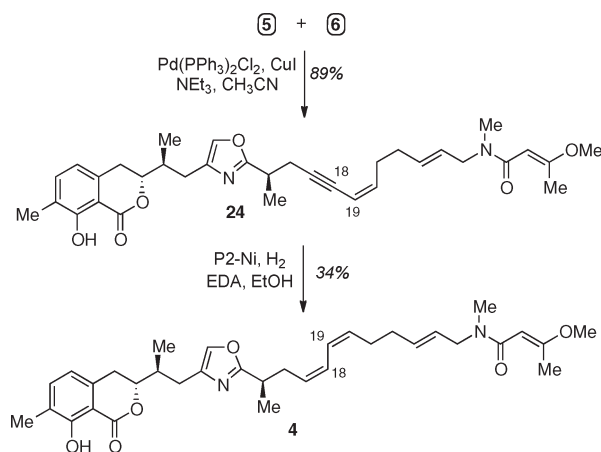
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Dihydroxylation of alkene **7** under Upjohn conditions<sup>19</sup> gave diol **19** as a mixture of diastereoisomers which was selectively acylated with *R*-acid **8**<sup>9</sup> to give the hydroxy ester **20** (Scheme 6). Conversion of **20** into **21** was achieved by a Mitsunobu reaction with the stable  $\text{ZnN}_3\cdot 2\text{pyr}$  complex.<sup>20</sup> 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<sup>21</sup> and an *O,N*-shift was promoted by

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



triethylamine<sup>11</sup> 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  $\text{Ph}_3\text{P}$  in the presence of hindered base 2,6-di-*tert*-butyl-4-methylpyridine.<sup>12b</sup> The use of Dess–Martin periodinane for the oxidation of alcohol **22** was less effective.<sup>12a</sup> 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**<sup>6b</sup> 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  $\text{P2-Ni}$  in the presence of hydrogen gas and ethylenediamine<sup>22</sup> as was found in our earlier studies on the eastern fragment synthesis.<sup>6b</sup> 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  $^1\text{H}$  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  $^{13}\text{C}$  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.<sup>23</sup>

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.

**Acknowledgment.** We thank the Australian Research Council-Discovery Grants Scheme for financial support.

**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.