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Synthesis of the C9–C29 fragments of ajudazols A and B

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Abstract—The syntheses of both C9–C29 fragments **3** and **4** of the myxobacteria metabolites ajudazols A (**1**) and B (**2**) are described. The key steps were a cyclodehydration to form the oxazole, Sonogashira coupling to form the C18–C19 bond and a P-2 Ni mediated partial alkyne hydrogenation to install the C17–C18 *Z*-alkene. The C15 alkene in the ajudazol A fragment **3** was introduced in the final steps by elimination of the corresponding primary alcohol.

Myxobacteria are a life form at the interface between single and multicellular organisms and are a rich source of potentially useful secondary metabolites with about 80 different compounds characterized so far.[1] The ajudazols A (**1**) and B (**2**) are novel isochromanone containing natural products isolated from the myxobacterium *Chondromyces crocatus*.[2] These molecules also contain an oxazole moiety connected to a *Z*,*Z*,*E*-triene sidechain and terminate in an *E*-3-methoxybutenamide. Ajudazol A (**1**) has a methylene group at C15 whilst the co-metabolite **2** possesses a methyl substituent at C15 creating an asymmetric center. The relative configuration of the isochromanone core and the stereochemistry of the *Z*,*Z*,*E*-triene was determined from NOESY and ^{1}H–^{1}H coupling constant analysis, however, the absolute stereochemistry remains to be determined. In addition, the configuration at the isolated stereocenter at C15 in **2** was also not determined. The ajudazols were identified as inhibitors of the mitochondrial respiratory energy metabolism of beef heart sub-mitochondrial 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]

Taylor and Krebs have reported an approach to the eastern fragment of ajudazol A (**1**) in which the C14–C15 bond was constructed by a Stille cross-coupling reaction between 2-tributyltin oxazole and a vinyl iodide triene to afford a model C12–C29 ajudazol A fragment.[4] We envisaged a convergent approach in which ajudazols A and B could arise from common late intermediates and our retrosynthetic approach to both **1** and **2** is shown in Scheme 1. The key step in the proposed routes is the formation of the C18–C19 bond by a Sonogashira cross-coupling reaction[5,6] between the oxazole-isochromanone fragment alkynes **5** or **6** and common vinyl iodide **7**. Partial hydrogenation should introduce the C17–C18 *Z*-alkene in a stereoselective manner. The synthesis of the ajudazol A alkyne fragment **5** would require amide formation between isochromanone-amine **8** and acid **9** followed by oxazole formation using the modified Wipf protocol.[7] The C15 primary alcohol could then be eliminated to introduce the C15 alkene. On the other hand, the ajudazol B alkyne fragment **6** could be obtained by coupling between the same isochromanone fragment **8** and either enantiomer of the known chiral acid **10**[8] followed by cyclodehydration. In this Letter, we report the synthesis of the model C9–C29 fragments **3** and **4** of ajudazols A (**1**) and B (**2**).

The synthesis of the C9–C29 segments of the ajudazols began with the production of the common vinyl iodide fragment **7** as outlined in Scheme 2. The known alcohol **11**[9] was oxidized and subjected to Wittig homologation to give diene **12**. Ester reduction followed by bromide formation and displacement with methylamine gave the secondary amine **13**. Peptide coupling of **13** with the acid **14**[4,10] then afforded the common vinyl iodide **7**.

We next utilized a surrogate for the isochromanone/oxazole fragment and the synthesis of the ajudazol B model oxazole **15** is shown in Scheme 3. Racemic alcohol **16**[11] was converted into amine **17** by mesylation, azide displacement, and Staudinger reduction. Peptide coupling

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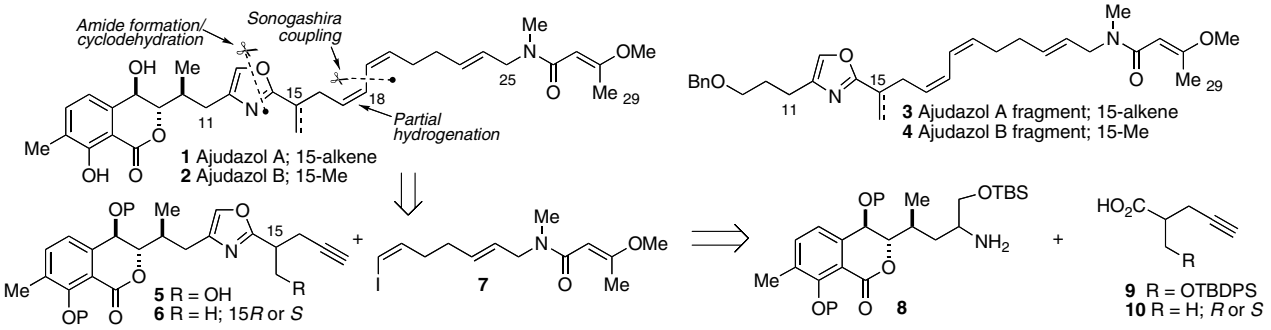
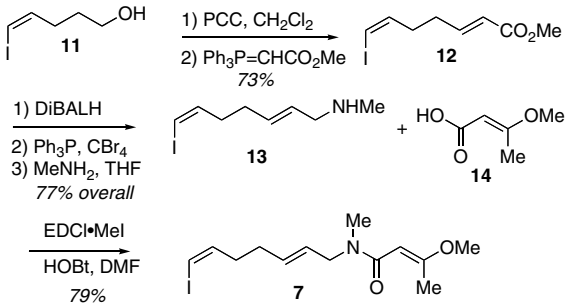
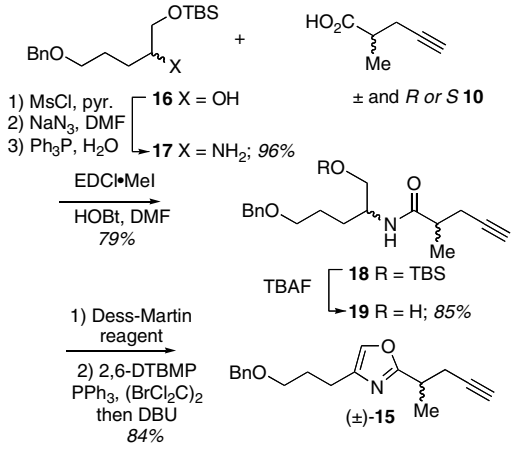


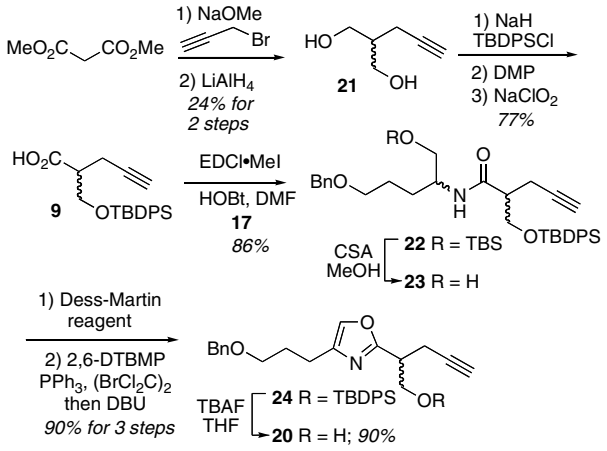
Scheme 1. Retrosynthetic analysis of ajudazols A (**1**) and B (**2**).



Scheme 2. Synthesis of vinyl iodide **7**.



Scheme 3. Synthesis of ajudazol B model oxazole **15**.



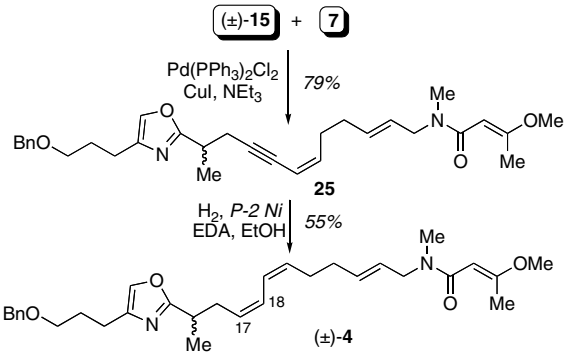
Scheme 4. Synthesis of ajudazol A model oxazole **20**.

of **17** with racemic acid **10**[8] gave amide **18** as a mixture of diastereoisomers. Silyl group removal afforded alcohol **19** and Dess–Martin oxidation followed by cyclodehydration using a hindered base[7] and dehydrobromination gave the model oxazole (±)-**15** in high yield. Both enantiomers of **15** were also synthesized in homochiral form using either *R*- or *S*-**10**[8] and chiral HPLC analysis indicated that no racemisation had occurred during the oxazole synthesis.

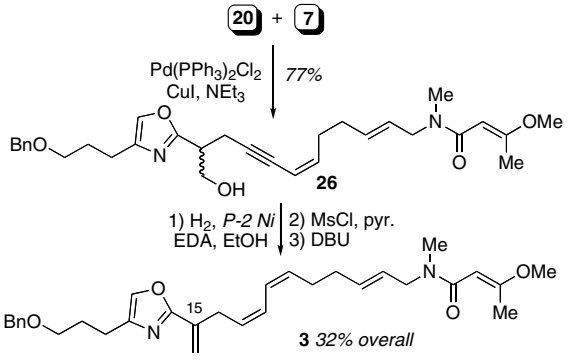
Oxazole **20** required for the production of the ajudazol A model system **3** was synthesized as shown in Scheme 4. Preliminary experiments suggested that introduction of the C15 alkene in the ajudazol A system was best left until a later stage in the synthesis. The route began with the alkylation of dimethyl malonate with propargyl bromide.[12] Subsequent reduction afforded diol **21**, which was easily separated from the bis-alkylated by-product by flash chromatography. Monosilylation[13] of **21** and two step oxidation gave acid **9**. Peptide coupling between **9** and amine **17** proceeded in high yield and selective removal of the TBS group in **22** was achieved using CSA in methanol. Dess–Martin oxidation of the resultant alcohol **23** gave an intermediate aldehyde, which was smoothly cyclized to oxazole **24** in a high overall yield.[7] Silyl group removal then gave the model ajudazol A oxazole precursor **20**. With each of the alkynes in hand, we next examined the Sonogashira coupling-partial hydrogenation protocol for the production of **3** and **4**.

The synthesis of the model C9–C29 ajudazol B fragment **4** is outlined in Scheme 5. Sonogashira coupling between racemic **15** and iodide **7** gave the enyne **25** in good yield. Partial hydrogenation of the C17–C18 alkyne in **25** proved challenging. Exposure of **25** to hydrogen gas in the presence of Lindlar catalyst resulted in no reaction while prolonged treatment resulted in some formation of the desired diene **4** in low yield accompanied by a substantial amount of C17–C18 fully saturated product. The use of catalyst poisons did not improve the yield of **4** and usually resulted in no reaction at all.

At this stage we turned to the P-2 nickel (P-2 Ni) catalyst as reported by Brown.[14] This catalyst can be applied to the partial reduction of alkynes to *Z*-alkenes in the presence of ethylenediamine[15] and we have successfully



Scheme 5. Synthesis of the C9–C29 fragment **4** of ajudazol B.



Scheme 6. Synthesis of the C9–C29 fragment **3** of ajudazol A.

utilized P-2 Ni for the partial hydrogenation of a skipped diyne to afford a *Z*,*Z*-diene.[16] The catalyst can be generated by the $NaBH_4$ mediated reduction of $Ni(OAc)_2$ in ethanol under a hydrogen atmosphere.[14,15] Partial hydrogenation of alkyne **25** proceeded well in the presence of P-2 Ni and ethylenediamine to afford the desired ajudazol B side-chain **4**[17] in 55% yield along with a small amount of the C17–C18 fully saturated product. This produced racemic **4**, however, it should be noted that both enantiomers of the real alkyne fragment **6** could be synthesized as demonstrated in the synthesis of both *R* and *S*-**15**.

The synthesis of the ajudazol A fragment **3** is outlined in Scheme 6. Sonogashira coupling between **20** and iodide **7** proceeded smoothly to afford enyne **26** in good yield. Partial hydrogenation with P-2 Ni as catalyst followed by mesylation of the primary alcohol and DBU induced elimination[18] afforded the target compound **3**.[19] Attempts at introducing the C15 alkene prior to coupling and hydrogenation failed to afford **3**.

In conclusion, we have developed a route to the C9–C29 fragments **3** and **4** of ajudazols A (**1**) and B (**2**). The key steps involve a high yielding Sonogashira coupling and P-2 Ni mediated partial hydrogenation. The synthesis of the isochromanone fragment of **1** and **2** is currently underway in our laboratories.

Acknowledgment

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17. *Data for compound* **4**: IR ν_{max} (film): 2918, 2851, 1738, 1647, 1601, 1459, 1238, 1104 cm^{-1}; ^1H NMR (800 MHz, acetone-d_6) δ 1.27 (d, $J = 7.0$ Hz, 3H), 1.88–1.91 (m, 2H), 2.14 (m, 2H) 2.14 (br s, 3H), 2.26 (dt, $J = 7.4$, 7.4 Hz, 2H), 2.49 (m, 1H), 2.55 (td, $J = 7.5$, 1.0 Hz, 2H), 2.61 (m, 1H), 2.84 and 2.85 (br s, 3H), 2.99 (m, 1H), 3.51 (t, $J = 6.2$ Hz, 2H), 3.59 (br s, 3H), 3.92 (dd, $J = 6.0$, 1.0 Hz, 2H), 4.50 (s, 2H), 5.32 and 5.35 (each br s, 1H), 5.42 (dt, $J = 10.0$, 7.9 Hz, 1H), 5.48 (dt, $J = 9.5$, 8.1 Hz, 1H), 5.51 (m, 1H), 5.60 (m, 1H), 6.28 (ddd, $J = 11.3$, 11.3, 1.0 Hz, 1H), 6.32 (t, $J = 11.1$ Hz, 1H), 7.26–7.36 (m, 5H), 7.49 (t, $J = 1$ Hz, 1H); ^{13}C NMR (200 MHz, acetone-d_6) δ 18.3, 18.7, 23.6, 27.9, 29.3, 32.8, 33.4, 33.5, 34.6, 49.2 and 52.4 (br), 55.3, 70.1, 73.2, 92.2, 124.7, 126.2, 126.9, 128.1, 128.2, 128.9, 129.0, 132.3, 132.7, 134.6, 140.0, 141.0, 167.6, 167.7 and 167.9 (br), 168.81 and 168.83 (br); HRMS (ESI) Calcd for $C_{31}H_{43}N_2O_4$ [M+H^+]: 507.3223. Found: 507.3225.
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19. *Data for compound* **3**: IR ν_{max} (film): 2925, 2856, 1723, 1646, 1605, 1455, 1248, 1107 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 85 °C): δ 1.83–1.90 (m, 2H), 2.08 (s, 3H), 2.10–2.13 (m, 2H), 2.22–2.27 (m, 2H), 2.54 (t, $J = 7.2$ Hz, 2H), 2.84 (s, 3H), 3.33 (d, $J = 7.6$ Hz, 2H), 3.50 (t, $J = 6.4$ Hz, 2H), 3.56 (s, 3H), 3.87 (d, $J = 5.2$ Hz, 2H), 4.47 (s, 2H), 5.28 (s, 1H), 5.37 (s, 1H), 5.35–5.61 (m, 4H), 5.87 (s, 1H), 6.33 (m, 1H), 6.35 (m, 1H), 7.24–7.35 (m, 5H), 7.69 (s, 1H); ^{13}C NMR (200 MHz, DMSO-d_6 55 °C): δ 18.6, 22.8, 26.8, 27.2, 28.4, 30.4, 31.6, 33.3 and 35.0 (br), 48.5 and 51.8 (br), 55.3, 69.2, 72.2, 92.0, 117.5, 124.1, 125.6, 126.2, 126.3, 127.7, 128.0, 129.0, 132.1, 134.4, 135.3, 139.1, 141.5, 161.2, 166.9, 167.3. HRMS (ESI) Calcd for $C_{31}H_{40}N_2O_4Na$ [M+Na^+]: 527.2886. Found: 527.2882.