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Total Synthesis of the Proposed Structure of 8-Deshydroxyajudazol A: A Modified Approach to 2,4-Disubstituted Oxazoles†

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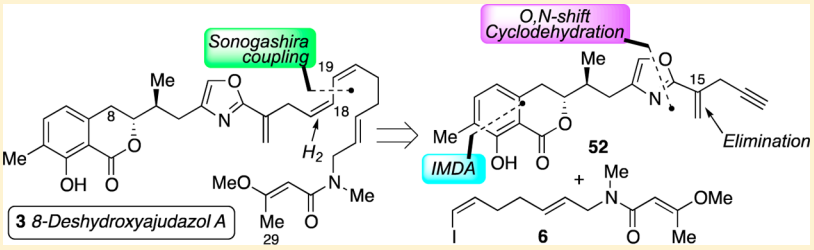
Supporting Information



ABSTRACT: The total synthesis of the proposed structure for the minor myxobacterial metabolite 8-deshydroxyajudazol A (**3**) is described. The isochromanone moiety present in the eastern fragment was constructed by an intramolecular-Diels–Alder (IMDA). Difficulties were encountered with the formation of the 2,4-disubstituted oxazole, so this was synthesized via a modified approach. This involved selective acylation of the diol **7** with acid **8**, azide displacement of the secondary alcohol, and subsequent azide reduction in the presence of base which induced an *O,N* shift to give the hydroxyamide **23**. Cyclodehydration then gave the desired oxazole **24** and deprotection followed by mesylation and elimination produced the C15 alkene **5**. Sonogashira coupling with the eastern fragment vinyl iodide **6** and partial reduction yielded 8-deshydroxyajudazol A (**3**).

INTRODUCTION

Myxobacteria are a life form at the interface between single and multicellular organisms. They live in places that are rich in organic matter and are otherwise known as gliding bacteria owing to the fact that they move by gliding over a solid surface.[1] These microorganisms have astonishing life cycles culminating in multicellular fruiting body formation upon starvation and are a rich source of potentially useful secondary metabolites.[2] Indeed, myxobacteria produce an amazing array of natural products with structural diversity not seen in other single-celled organisms. This could be due to a combination of their organic rich living environments as well as the sophisticated enzyme machinery. For example, the myxobacterium *Sorangium cellulosum* produces the potent anticancer compounds the epothilones,[3] the isochromanone-containing icumazols,[4] as well as the complex spiroketal natural product spirangien A.[5] *S. cellulosum* has the largest bacterial genome sequenced to date (>13 Mb),[6] much of which is dedicated to regulation to support the complex lifecycle of this organism. In addition, there are 17 secondary metabolite loci,[6] which explains the array of natural products isolated from this species. Extracts of *Chondromyces crocatus* have also afforded a number of diverse compounds including the crocacins[7] and the ajudazols.[8] Ajudazol A (**1**) (Figure 1) possesses a novel structure that includes an isochromanone fragment, a 2,4-disubstituted oxazole, and a polyene chain terminating in a tertiary enamide moiety. Ajudazol B (**2**) differs from compound **1** at C15 whereby a methyl group and additional asymmetric center is present rather than the 1,1-disubstituted alkene; however, the absolute configurations of **1** and **2** were not determined. The ajudazols are inhibitors of the mitochondrial respiratory energy metabolism of beef heart submitochondrial particles (SMP). For ajudazol A (**1**), NADH oxidation in SMP was inhibited at an IC_{50} of 13.0 ng/mL (22.0 nM), while ajudazol B (**2**) had an IC_{50} of 10.9 ng/mL (18.4 nM).[9]

Müller and co-workers have proposed that the final stages of the biosynthesis of ajudazols A (**1**) and B (**2**) involve a series of post polyketide synthase (PKS) cytochrome P450 mediated oxidations of the putative biosynthetic precursors 8-deshydroxyajudazol A (**3**) and B (**4**).[10] Two mutant forms of *C. crocatus* were produced in which the genes that encode for the P450 enzymes AjuJ (C8 oxidation) or AjuI (C15 oxidation/elimination) were removed by mutagenesis. The AjuI knockout produced only ajudazol B (**2**), while the AjuJ knockout produced deshydroxyajudazol A (**3**). Thus, the final stages of the biosynthesis of **1** and **2** begin with the post-PKS tailoring of deshydroxyajudazol B (**4**) by P450-mediated oxidations to produce either ajudazol B (**2**) (AjuJ) or deshydroxyajudazol A (**3**) (AjuI) (Figure 1). Further oxidation of deshydroxyajudazol A (**3**) by AjuJ then gives ajudazol A (**1**). However, it appears that ajudazol B (**2**) is not a substrate for AjuI-mediated desaturation to form ajudazol A (**1**). This accounts for the presence of both ajudazols A (**1**) and B (**2**) and the higher proportion of **1** is presumably because AjuI is a more efficient

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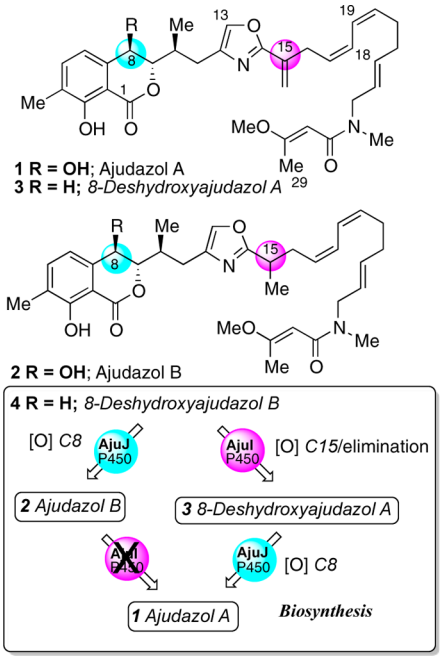


Figure 1. Structures of the ajudzols A (**1**) and B (**2**) and 8-deshydroxyajudzols A (**3**) and B (**4**) and the proposed final stages of the biosynthesis.

catalyst than AjuJ for the selective oxidation of deshydroxyajudazol B (**4**). Both 8-deshydroxyajudazols A (**3**) and B (**4**) were detected in small amounts in the extracts of wild type *C. crocatus* and deshydroxyajudazol B (**4**) is present in trace amounts in both AjuI and AjuJ mutants.[10] However, only compound **3** had it is structure assigned by NMR analysis while the structure of 8-deshydroxyajudazol B (**4**) was inferred by MS analysis. Müller and co-workers have also investigated the biosynthesis of the unusual isochomanone moiety and have suggested that this is produced by an unusual thioesterase and not a terminal cyclase.[11]

A number of synthetic approaches to the C12−C29 fragment of ajudazol A (**1**)[12,13] and (**2**) have been reported as well as an approach to the isochromanone fragment.[14] We have recently reported the total synthesis of a the minor metabolite and putative biosynthetic precursor to the ajudazols, 15*R*-8-deshydroxyajudazol B (**4**)[15] and now describe the first total synthesis of the structure proposed for 8-deshydroxyajudazol A (**3**) which utilizes a modified approach to the 2,4-disubstituted oxazole.

RESULTS AND DISCUSSION

Retrosynthetic Analysis of 8-Deshydroxyajudazol A (3). Our initial retrosynthetic analysis of the 15*R* isomer of 8-deshydroxyajudazol A (**3**) is shown in Scheme 1. It was envisaged that the C18−19 bond could be formed by an efficient Sonogashira coupling[16] between the alkyne−oxazole western fragment **5** and labile vinyliodide eastern fragment **6**.[13] Partial reduction of the resultant enyne would then form the *Z,Z*-diene and yield 8-deshydroxyajudazol A (**3**).

The alkyne−oxazole **5** would arise from ester formation between diol **7** and the acid **8** followed by *O,N*-shift, oxidation, and cyclodehydration,[17] while the 1,1-disubstituted alkene could be formed by elimination of a mesylate derived from the alcohol arising from acid **8**. The isochromanone in fragment **7** can be formed by an intramolecular Diels−Alder (IMDA)[18] cyclization followed by aromatization and bromine−oxygen exchange.

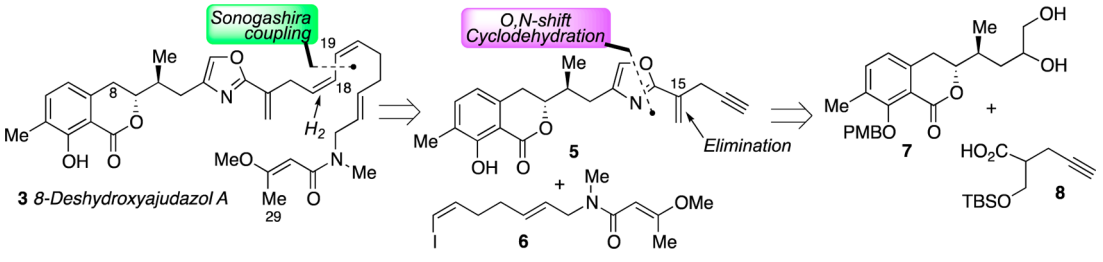
This approach to deshydroxyajudazol A (**3**) is based on our synthesis of 15*R* deshydroxyajudazol B (**4**), which is summarized in Scheme 2.[15] Compound **10** was secured by a IMDA reaction of dienyne **9**, which on aromatization afforded the isochromanone. Br−O exchange via Pd-mediated cross-coupling[19] with pinacol borane and oxidative workup gave the phenol **11**. Further functionalization gave diol **7**, which was then converted into the oxazole **12** using a modified protocol (see below). Sonagashira coupling with iodide **6** followed by partial reduction the P2−Ni gave 15*R* deshydroxyajudazol B (**4**).

Since no NMR data were measured for deshydroxyajudazol B (**4**), we compared data for the synthetic material with that reported for the C1−10 western fragment of deshydroxyajudazol A (**3**)[10] and the C11−29 eastern fragment of ajudazol B (**2**).[7b] Because of the possible effects of conjugation of the *exo*-methylene at C15 on some of the chemical shifts, C11−C14 were included in the eastern fragment for the purpose of this analysis. These compared very well with our synthetic material but since no chiroptical data was available, we were unable to confirm the C15 stereochemistry or the absolute configuration.

Eastern Fragment Vinyl Iodide Synthesis. The full detail of the synthesis of the required vinyl iodide fragment **6** is shown in Scheme 3.[13] This began with the known volatile alcohol **13**[20] (Scheme 2). PCC oxidation and Wittig extension gave the α,β-unsaturated ester **14** with high *E* selectivity in 73% yield for the two steps. DIBAL-H reduction of ester **14** gave allylic alcohol **15**, which was converted into the bromide **16**. Treatment of bromide with methylamine in THF gave the secondary amine **17** which was coupled with the known unsaturated acid **18**[12,21] to give the vinyl iodide fragment **6** in good yield. Key to the success of this peptide coupling was the use of EDCl·MeI and 20 mol % HOBt in DMF solvent.

Modified Approach to the 2,4-Disubstituted Oxazole. The failure to produce a protected amino alcohol from diol **7** required for amide formation and cyclodehydration to the oxazole in our original approach to the deshyroxyajudazols

Scheme 1. Retrosynthetic Analysis of 8-Deshydroxyajudazol A (3)



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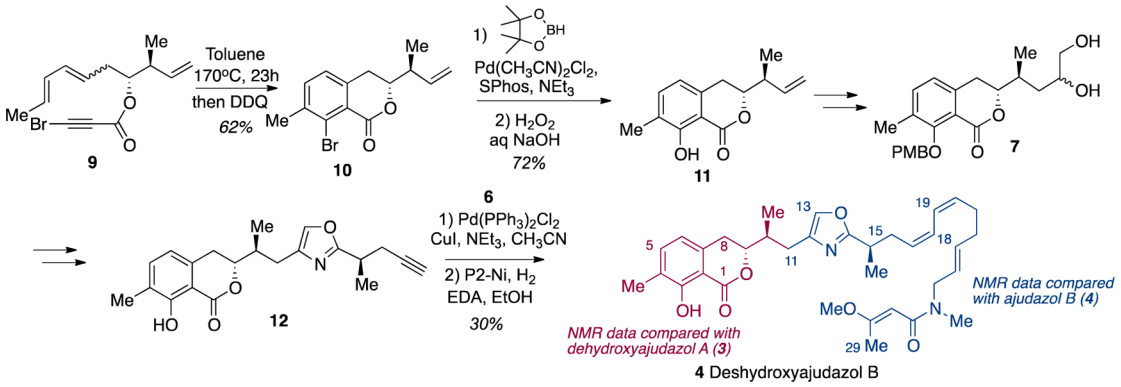
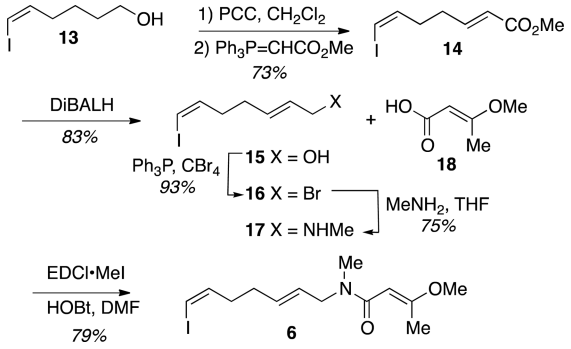
Scheme 2. Total Synthesis of 8-Deshydroxyajudazol B (4)[15]



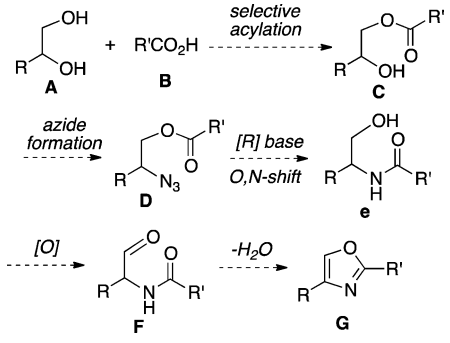
Scheme 3. Synthesis of Vinyl Iodide 6



forced us to reconsider a modified protocol.[15] 2,4-Disubstituted oxazoles are present in a number of myxobacteria metabolites[2] and a synthetic approach to this functionality from a *non-amino acid* precursor, especially in the present case, would be desirable.[22] The focus in the present case would be on the synthesis of this system, which circumvents the need for the isolation of an amine but could be adaptable to the construction of 2,4-disubstituted oxazoles with a wide variety of substituents.

This modified approach is detailed in Scheme 4 and begins with selective acylation of a vicinal diol **A** with acid **B** to give a

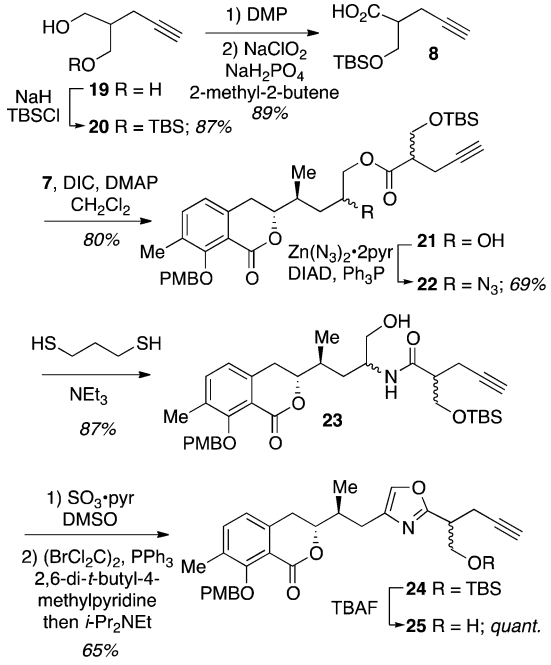
Scheme 4. Modified Approach to 2,4-Disubstituted Oxazoles



monoester **C**. Azide displacement[23] of the secondary alcohol affords an azide which upon reduction under basic conditions would induce a *O,N* acyl shift[24] to form the hydroxyamide directly without the need for isolation of an amine intermediate and subsequent peptide coupling. Oxidation give the aldehyde ready for cyclodehydration to give a 2,4-disubstituted oxazole. This approach is an alternative to the aza-Wittig type approaches to oxazolines and oxazoles[25] and allows for the formation of 2,4-disubstituted oxazoles from alkenes via dihydroxylation with a wide array of substituents.

Western Fragment Oxazole Synthesis. The synthesis of the acid coupling partner and oxazole for the production of deshydroxyajudazol A (**3**) is detailed in Scheme 5. Mono-

Scheme 5. Synthesis of the Western Fragment Oxazole 25 via a Modified Approach



silylation[26] of the known diol **19**, readily available via alkylation of dimethylmalonate with propargyl bromide followed by reduction,[27] gave the alcohol **20**. Oxidation with Dess–Martin periodinane followed by Pinnick oxidation then afforded racemic acid **8** in high yield and selective acylation of the primary alcohol in diol **7**[15] with **8** gave ester **21** which was transformed to the azide **22** by a Mitsunobu reaction using $Zn(N_3)_2$·pyridine as a stable azide source.[23] Reduction and *O,N* shift was best achieved with 1,3-propanedithiol[28] to give hydroxyamide **23** as a complex mixture of four diastereoisomers. Dess–Martin periodinane oxidation of the hydroxyamide **23** resulted in some over oxidation so we resorted to a Parikh–Doering oxidation to the aldehyde and subsequent cyclodehydration using the Wipf protocol[18b] to give the oxazole **24** in a serviceable yield as a mixture of two inseparable

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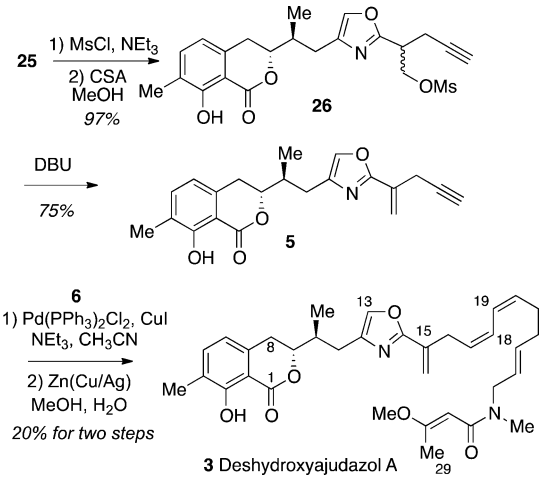
diastereoisomers. Desilylation then yielded alcohol **25** ready for elimination to produce the C15 alkene.

Total Synthesis of Deshydroxyajudazol A (3). In our early model studies,[13] the C15 1,1-disubstituted alkene was installed after the Sonogashira coupling and partial reduction; however, for a more convergent approach, we elected to form this double bond prior to coupling. Mesylation of alcohol **25** followed by removal of the PMB ether under acidic conditions gave the mesylate **26** in high yield (Scheme 6). Immediate

Scheme 6. Completion of the Total Synthesis of 8-Deshydroxyajudazol A (3)



DBU-mediated elimination[29] of **26** smoothly formed the 1,1-disubstituted alkene **5**. This compound proved to be reasonably stable, however acidic conditions or prolonged exposure to silica gel resulted in substantial isomerization to the conjugated enyne.

Sonagashira coupling of alkyne **5** with iodide **6** produced the coupled product, but unfortunately, this could not be separated from the excess **6** used in the reaction by chromatography so we proceeded with the mixture. Partial reduction proved challenging and we eventually resorted to exposure of the mixture to Cu/Ag activated Zn[30] which gave deshydroxyajudazol A (**3**) after purification by HPLC. These partial reduction conditions proved superior to the P2−Ni/H_2/EDA[31] procedure utilized for dehydroxyajudazol B as over reduction was completely suppressed.

The ^{1}H and ^{13}C NMR spectral data for **3** in methanol-d_4 were compared to that quoted for natural material[10] (Table 1). The ^{1}H and ^{13}C NMR spectra matched very well with those reported; however, a few exceptions were observed. Most notable were the signals in the unsaturated amide C25−C29 region especially for NCH_3, 28-OCH_3, and H25 which appeared slightly further downfield than reported,[10] although these resonances were significantly broadened due to restricted rotation. These minor discrepancies between synthetic and natural **3** values could be due to concentration and/or temperature effects.[32] In addition, as can be seen in Table 1, there are some missing peaks in the quoted spectra as well as misassigned resonances for NCH_3, C7, and C10. Thus, the only major difference is the ^{13}C NMR chemical shift for 28-OCH_3. Unfortunately, due to the small amount of natural **3** isolated, an authentic sample was not available for direct comparison and no copies of the original spectra were provided in the Supporting Information of the original publication.[10] Further confirmation of the structure for synthetic **3** was achieved through examination of the 2D spectra for synthetic **3** (COSY, gHSQC and gHMBC), but at this stage, confirmation of the composition of natural material remains to be achieved beyond reasonable doubt.

■ CONCLUSION

In conclusion, we have completed the first total synthesis of the reported structure for the minor metabolite 8-deshydroxyajudazol A (**3**), the proposed biosynthetic precursor to ajudazol A (**1**). Key steps included an IMDA reaction and subsequent aromatization to construct the isochromanone western fragment, late stage installation of the sensitive 1,1-disubstituted alkene and a Sonagashira coupling to form the C18−C19 bond. In addition, a modified approach to the 2,4-disubstituted oxazole was developed which utilized a selective acylation and *O,N* shift to form a hydroxyamide which could be oxidized and cyclodehydrated to the oxazole. Experiments directed toward the application of synthetic **3** for the investigation of the interesting biogenesis of these compounds as well as the total synthesis of ajudazols A (**1**) and B (**2**) using a similar approach are underway.[33]

■ EXPERIMENTAL SECTION

General Methods. Proton nuclear magnetic resonance spectra (^{1}H NMR, 400 MHz, 500 MHz, and 600 MHz) and proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR, 100 MHz, 125 MHz, and 150 MHz) were obtained in deuterochloroform with residual chloroform as internal standard unless otherwise noted. COSY, gHMQC, and gHMBC spectra (^{1}H 500/^{13}C 125 MHz) were recorded in methanol-d_4. Chemical shifts are followed by multiplicity, coupling constant(s) (*J*, Hz), integration, and assignments where possible. Optical rotations were recorded for a 1 mL solution, and units are deg cm^2 g^{-1}. Flash chromatography was carried out on silica gel 60. Analytical thin-layer chromatography (TLC) was conducted on aluminum-backed 2 mm thick silica gel 60 GF_{254}, and chromatograms were visualized with 20% w/w phosphomolybdic acid in ethanol. High-resolution mass spectra (HRMS) were obtained by ionizing samples via electron spray ionization (ESI) on a Finnigan LTQ Fourier transform hybrid linear ion trap ICR mass spectrometer. Anhydrous THF and CH_2Cl_2 were used from a solvent cartridge system. Dry methanol was distilled from magnesium methoxide. All other solvents were purified by standard methods. Petrol used refers to petroleum ether 40−60 °C boiling range. All other commercially available reagents were used as received. The standard workup refers to extraction with a particular solvent (3×), washing with water and brine, drying with $MgSO_4$, and concentration under reduced pressure.

*(2E,6Z)-Methyl 7-iodohepta-2,6-dienoate (**14**).* To a solution of the alcohol **13**[19] (7.0 g, 33.01 mmol) in CH_2Cl_2 (160 mL) was added PCC (17.30 g, 82.53 mmol), and the resulting mixture was stirred at rt under Ar for 2 h. The mixture was filtered through Florisil, and the solvent was carefully removed under reduced pressure to give the volatile crude aldehyde (6.50 g), which was dissolved in CH_2Cl_2 (200 mL). To this solution was added (triphenylphosphoranylidene)-propionaldehyde (25.87 g, 77.39 mmol), and the resulting mixture was stirred at rt under Ar for 24 h. The solvent was concentrated under reduced pressure, and the crude mixture was filtered through a plug of silica gel with 10% EtOAc/petroleum ether. Purification of the residue left on evaporation of the solvent, by flash chromatography eluting with 2.5% EtOAc/petroleum ether gave the methyl ester **14** (6.0 g, 73%) as a brown oil: IR ν_{max} (film) 3068, 2989, 2949, 2846, 1720, 1656 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.24−2.33 (m, 4H), 3.68 (s, 3H), 5.82 (ddd, *J* = 14.6, 1.3, 1.3 Hz, 1H), 6.14 (dq, *J* = 6.4 Hz, 1H,), 6.24 (d, *J* = 7.2 Hz, 1H), 6.29 (dt, *J* = 15.6, 6.6 Hz, 1H); ^{13}C NMR (75 MHz) δ 30.1, 32.8, 51.1, 83.7, 121.4, 139.0, 147.2, 166.3; HRMS (ESI) *m/z* [MH + Na]$^+$ calcd for $C_8H_{12}INaO_2$ 289.9785, found 289.9777.

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Table 1. Comparison of the ^{1}H and ^{13}C Spectra of Synthetic and Natural Deshydroxyajudazol A (3) in Methanol-d_4

atom	δ_H nat	δ_H syn	$\Delta\delta_H$	δ_C nat	δ_C syn	$\Delta\delta_C$
1					171.9	
2				*a*	*108.8*	
3				160.9	161.4	+0.5
4				126.0	125.9	−0.1
4-CH_3	2.22	2.21	−0.01	15.3	15.4	+0.1
5	7.33	7.34	+0.01	138.4	138.1	−0.3
6	6.72	6.73	+0.01	118.6	118.9	+0.3
7				*108.6*[a]	*138.8*	
8	3.01	3.02	+0.01	30.4	29.3	−0.9
9	4.5	4.51	+0.01	84.7	84.6	−0.1
10	2.33	2.33	0	*34.8*[b]	*37.7*	
10-CH_3	1.03	1.04	+0.01	15.2	15.3	+0.1
11	2.54/2.89	2.54/2.91	0/+0.03	34.0	33.1	−0.9
12				140.9	140.8	−0.1
13	7.64	7.65	+0.01	136.9	137.1	+0.2
14				163.7	163.4	−0.3
15				136.1	136.0	−0.1
15-CH_2	5.40/5.95	5.40/5.96	0/+0.01	118.6	118.5	−0.1
16	3.35	3.37	+0.02	31.2	30.5	−0.7
17	5.54	5.56	+0.02	128.9	128.4	−0.5
18	6.35	6.36	+0.01	126.9	126.3	−0.6
19	6.34	6.35	+0.01	124.9	124.9	0
20	5.48	5.48	+0.02	133.3	133.6	+0.3
21	2.28	2.29	+0.01	27.6	28.2	+0.6
22	2.03	2.17	+0.14	31.8	30.8	−1.0
23	5.33	5.61	+0.28	130.8	129.3	−1.5
24	5.39	5.50	+0.11	*c*	128.4/128.7	
25	3.92	3.94	+0.02	50.1	50.3/53.4	+0.2
NCH_3	2.66	2.90/2.97	+0.27	*38.0*[b]	*34.0/35.8*	
26				*c*	170.2/170.4	
27	5.26	5.28	+0.02	92.3	92.2	- 0.1
28				169.2	170.0	+0.8
29	2.10	2.11	+0.01	18.9	19.1	+0.2
28-OCH_3	3.53	3.62	+0.09	49.9	55.7	+5.8

[a]Signal misassigned to C7 in original report and should be for C2.[10] [b]Signal misassigned to C10 in original report and should be for NCH_3. [c]Peak not quoted for natural **3**.[10]

*(1E,5Z)-1-Iodohepta-1,5-dien-7-ol (**15**).* To a solution of the methyl ester **14** (150 mg, 0.563 mmol) in CH_2Cl_2 (5 mL) at 0 °C under Ar was added dropwise a solution of DIBAL-H in THF (1 M, 2.81 mL, 2.81 mmol), and the mixture was then warmed to rt and stirred for 2.5 h. Et_2O and 0.5 M potassium tartrate solution were added, and the mixture was allowed to stir for 30 min. The aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude product by flash chromatography eluting with 25% EtOAc/petroleum ether gave alcohol **15** (112 mg, 83%) as a colorless oil: IR ν_{max} (film) 3308, 2921, 2852, 1671, 1608, 1438 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.10−2.23 (m, 4H), 2.42 (s, 1H), 4.03 (s, 2H), 5.58−5.69 (m, 2H,), 6.12−6.19 (m, 2H); ^{13}C NMR (100 MHz) δ 30.2, 34.0, 63.1, 82.9, 129.7, 131.0, 140.1; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_7H_{11}INaO$ 260.9752, found 260.9747.

*(1E,5Z)-1-Iodo-N-methylhepta-1,5-dien-7-amine (**17**).* To a solution of the above allylic alcohol (30 mg, 0.126 mmol) in CH_2Cl_2 (6 mL) at 0 °C under Ar were added PPh_3 (319 mg, 1.21 mmol) and CBr_4 (242 mg, 0.730 mmol), and the resulting mixture was stirred for 1.5 h. The solvent was concentrated under reduced pressure, and purification of the crude product by flash chromatography eluting with 100% petroleum ether gave bromide **16** (172 mg, 93%) as a light yellow oil which was used immediately in the next reaction. To a solution of the allylic bromide **16** (800 mg, 2.65 mmol) in THF (15 mL) at 0 °C under Ar was added a solution of $MeNH_2$ in THF (2 M, 6.60 mL, 13.29 mmol), and the resulting solution was stirred for 2 h. The solvent and excess $MeNH_2$ was removed under reduced pressure. Purification by chromatography on alumina with a 1:1:0.1 mixture of CH_2Cl_2/petroleum ether/MeOH gave the secondary amine **17** (0.50 g, 75%) as an oil: IR ν_{max} (film) 3284, 2927, 2842, 2786, 1652, 1608, 1440 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.02−2.14 (m, 4H, H21−22), 2.29 (s, 3H), 3.04 (d, J = 4.4 Hz, 2H), 5.40−5.52 (m, 2H), 6.04−6.11 (m, 2H); ^{13}C NMR (100 MHz) δ 30.3, 34.0, 35.6, 53.2, 82.6, 128.9, 130.6, 140.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_8H_{15}IN$ 252.0249, found 252.0247.

*(E)-N-((2E,6Z)-7-Iodohepta-2,6-dien-1-yl)-3-methoxy-N-methylbut-2-enamide (**6**).* To a solution of the amine **17** (57.5 mg, 0.229 mmol) in CH_2Cl_2 (15 mL) were added the acid **17**[21] (29.2 mg, 0.252 mmol), EDC·MeI (122 mg, 0.412 mmol), and HOBt (6.2 mg, 0.046 mmol), and the mixture was stirred at rt for 18 h. The solvent was evaporated to give the crude product, which was purified by column chromatography eluting with 40% EtOAc/petroleum ether to give the amide **6** (63.5 mg, 79%) as a yellow oil: IR ν_{max} (film) 3462, 2920, 2846, 1647, 1604, 1438 cm^{-1}; ^{1}H NMR (400 MHz, 40 °C) δ 2.13−2.22 (m, 7H), 2.93 (br s, 3H), 3.58 (s, 3H), 3.87 (br s, 1H), 3.96 (br s, 1H), 5.15 (s, 1H), 5.42 (dt, J = 15.6, 6.0 Hz, 1H), 5.57 (dt, J = 15.6, 6.0 Hz, 1H), 6.14 (dt, J = 6.8, 6.8 Hz, 1H), 6.20 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 18.7, 30.4, 34.2, 35.5, 52.0, 54.8, 83.1, 91.1, 125.6, 126.2, 131.5, 132.0, 140.1, 168.5; HRMS (ESI) m/z [M + Na$^+$] calcd for $C_{13}H_{20}INNaO_2$ 372.0436, found 372.0434.

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*2-((tert-Butyldimethylsilyloxy)methyl)pent-4-yn-1-ol (**20**).* A solution of diol **19**[27] (1.08 g, 9.46 mmol) in THF (12 mL) was added at 0 °C to a suspension of NaH (228 mg, 7.00 mmol) in THF (20 mL). After 5 min, TBSCl (1.43 g, 9.49 mmol) was added slowly and the mixture stirred at 0 °C for 1 h before being allowed to warm to rt and stirred for a further 1.5 h. The mixture was diluted (Et_2O) and quenched (H_2O) before the usual workup into Et_2O gave the crude alcohol, which was purified by flash chromatography (10% EtOAc/petroleum ether) to afford alcohol **20** (1.39 g, 87%) as a colorless oil: IR ν_{max} (film) 3314, 2955, 2930, 2858, 2119, 1472, 1432, 1390, 1362, 1253, 1068, 1034, 939, 834, 775 cm^{-1}; ^1H NMR (500 MHz) δ 0.08 (s, 6H,), 0.90 (s, 9H), 1.93 (m, 1H), 1.98 (t, J = 2.7 Hz, 1H), 2.30 (m, 2H), 2.41 (t, J = 5.6 Hz, 1H), 3.72−3.87 (m, 4H); ^{13}C NMR (125 MHz) δ −5.44, −5.40, 17.6, 18.3, 26.0, 41.7, 65.1, 69.7, 82.6; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{25}O_2Si$ 229.16183, found 229.16180.

*2-((tert-Butyldimethylsilyloxy)methyl)pent-4-ynoic Acid (**8**).* To a solution of alcohol **20** (540.6 mg, 2.37 mmol) in CH_2Cl_2 (23 mL) at 0 °C was added Dess−Martin periodinane (1.30 g, 3.07 mmol) and the reaction stirred for 5 min before being allowed to warm to rt and stirred for a further 1 h. The mixture was diluted (Et_2O) and quenched (satd aq $NaHCO_3$, followed by 2 M $Na_2S_2O_3$) before the usual workup into Et_2O to provide the crude aldehyde (534.4 mg, 2.36 mmol, quant yield) which was used in the next step without further purification. The aldehyde was dissolved in ^{t}BuOH (59 mL) before 2-methyl-2-butene (9.8 mL) was added. A solution of $NaClO_4$ (843 mg, 9.32 mmol) and $NaH_2PO_4{\cdot}H_2O$ (1.29 g, 9.35 mmol) in H_2O (14 mL) was added dropwise and the resultant mixture stirred at rt overnight. Et_2O and H_2O were added, and the mixture was acidified to pH ∼2 with 1.2 M HCl before the usual workup into Et_2O yielded the desired acid **8** (510 mg, 89%) as a waxy solid: IR ν_{max} (film) 3314, 2957, 2932, 2857, 1715, 1472, 1430, 1258, 1117, 838, 779, 668 cm^{-1}; ^1H NMR (500 MHz) δ 0.09 (s, 6H), 0.89 (s, 9H), 2.00 (t, J = 2.6 Hz, 1H), 2.53 (ddd, J = 17.0, 8.2, 2.6 Hz, 1H), 2.62 (ddd, J = 17.0, 5.6, 2.6 Hz, 1H), 2.76 (m, 1H), 3.92 (dd, J = 10.0, 5.8 Hz, 1H), 3.98 (dd, J = 10.0, 5.2 Hz, 1H); ^{13}C NMR (125 MHz) δ 5.4, 17.2, 18.3, 25.9, 46.5, 62.2, 70.2, 81.2, 177.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{23}O_3Si$ 243.14110; Found 243.14108.

*(S)-((2R,S-4S)-2-Hydroxy-4-((R)-3-(4-methoxybenzyloxy)-4-methyl-1-oxoisochroman-9-yl)pentyl 2-((tert-Butyldimethylsilyloxy)methyl)pent-4-ynoate (**21**).* To a solution of diol **7** (76.4 mg, 0.191 mmol) and acid **8** (52.1 mg, 0.215 mmol) in CH_2Cl_2 (3.5 mL) at rt was added DMAP (3.9 mg, 31.9 μmol). The solution was subsequently cooled to −45 °C, and DIC (53 μL, 0.34 mmol) was added dropwise. The reaction was stirred at −45 °C for 40 min before being allowed to warm to rt and stirred for a further 3 h. The reaction was quenched (MeOH) before being concentrated under reduced pressure. The crude product was purified by flash chromatography (30% EtOAc/peroleum ether) to afford the desired ester **21** (94.9 mg, 80%) as a colorless oil: IR ν_{max} = 3486, 3294, 2949, 2930, 2856, 1726, 1613, 1515, 1464, 1425, 1389, 1249, 1171, 1120, 1036, 966, 837, 779 cm^{-1}; ^1H NMR (500 MHz) δ 0.06 (s, 6H), 0.87 (s, 9H), 1.12 (m, 3H), 1.36 (ddd, J = 12.7, 10.1, 2.5 Hz, 0.5H), 1.52 (m, 0.5H), 1.81 (m, 1H), 2.02 (m, 1H), 2.12 (m, 0.5H), 2.22 (m, 0.5H), 2.26 (s, 3H), 2.31 (d, J = 2.7 Hz, 0.25H), 2.37 (d, J = 3.8 Hz, 0.25H), 2.39 (d, J = 4.1 Hz, 0.25H), 2.44 (d, J = 3.1 Hz, 0.25H), 2.56 (m, 2H), 2.70−2.83 (m, 2H), 2.97 (m, 1H), 3.81 (s, 3H), 3.91 (m, 2H), 3.98−4.08 (m, 2H), 4.19−4.26 (m, 2H), 4.96 (m, 2H), 6.88−6.90 (m, 3H), 7.32 (dd, J = 7.7, 3.3 Hz, 1H), 7.44 (d, J = 8.6 Hz); ^{13}C NMR (125 MHz) δ −5.3, 15.39, 15.41, 16.3, 16.4, 16.5, 17.6, 17.7, 18.4, 23.7, 26.0, 31.3, 33.35, 33.36, 34.30, 34.32, 34.96, 35.03, 36.1, 47.20, 47.23, 47.3, 55.4, 62.68, 62.71, 62.8, 67.4, 67.5, 68.5, 68.6, 68.95, 69.02, 69.5, 69.6, 70.2, 75.7, 81.66, 81.68. 81.97, 82.02, 82.1, 113.93, 113.94, 118.7, 122.62, 122.64, 129.57, 129.59, 130.66, 130.69, 130.71, 132.4, 132.5, 136.00, 136.04, 139.1, 139.32, 139.33, 159.0, 159.7, 162.9, 163.1, 172.49, 172.52, 172.6; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{35}H_{48}NaO_8Si$ 647.30107, found 647.30109.

*(S)-((2R,S-4S)-2-Azido-4-((R)-8-(4-methoxybenzyloxy)-7-methyl-1-oxoisochroman-3-yl)pentyl 2-((tert-Butyldimethylsilyloxy)methyl)pent-4-ynoate (**22**).* To a solution of alcohol **21** (69.0 mg, 0.110 mmol) in toluene (2.0 mL) were added PPh_3 (89.0 mg, 0.339 mmol) and $Zn(N_3)_2{\cdot}2Py$[23] (50.1 mg, 0.163 mmol) at rt. The reaction was cooled to 0 °C, and DIAD (90 μL, 0.457 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for a further 4.5 h before being filtered through Celite (washing with EtOAc) and concentrated under reduced pressure. Flash chromatography (20% EtOAc/peroleum ether) afforded the desired azide **22** (49.6 mg, 69%) as a colorless oil: IR ν_{max} (film) 3288, 2954, 2930, 2857, 2113, 1729, 1613, 1515, 1464, 1375, 1249, 1170, 1119, 1036, 836, 778 cm^{-1}; ^1H NMR (500 MHz) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (m, 9H), 1.12 (m, 3H), 1.39 (m, 0.5H), 1.50 (m, 0.5H), 1.87 (m, 1H), 2.00 (m, 1H), 2.06 (m, 0.5H), 2.12 (m, 0.5H), 2.26 (s, 3H), 2.59 (m, 2H), 2.77−2.84 (m, 2H), 2.95 (m, 1H), 3.74 (m, 0.5H), 3.80 (m, 0.5H), 3.81 (s, 3H), 3.92 (m, 2H), 4.07 (m, 0.5H), 4.12−4.20 (m, 1.5H), 4.33 (m, 1H), 4.95 (m, 2H), 6.88−6.92 (m, 3H), 7.33 (dd, J = 7.6, 3.0 Hz, 1H), 7.44 (m, 2H). ^{13}C NMR (125 MHz) δ −5.40, −5.39, 15.0, 15.1, 15.3, 15.4, 16.25, 16.32, 16.5, 17.5, 18.3, 21.78, 21.82, 21.86, 21.91, 22.1, 22.3, 31.4, 31.6, 31.7, 32.78, 32.82, 33.36, 33.40, 33.5, 33.7, 33.8, 33.9, 34.0, 34.1, 34.5, 34.6, 47.06, 47.07, 47.11, 55.4, 58.6, 58.69, 58.74, 58.8, 59.6, 59.7, 62.20, 62.22, 62.3, 66.8, 67.0, 67.55, 67.64, 70.1, 70.2, 75.7, 81.28, 81.32, 81.34, 81.6, 81.8, 81.9, 82.0, 113.92, 113.92, 118.6, 122.59, 122.63, 129.5, 130.6, 130.67, 130.70, 132.6, 132.7, 136.10, 136.13, 136.2, 138.8, 138.9, 139.1, 139.2, 159.0, 159.1, 159.7, 162.6, 162.8, 172.1, 172.2; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{35}H_{47}N_3NaO_7Si$ 672.30755, found 672.30757.

*2-((tert-Butyldimethylsilyloxy)methyl)-N-((4S)-1-hydroxy-4-((R)-8-(4-methoxybenzyloxy)-7-methyl-1-oxoisochroman-3-yl)pentan-2-yl)pent-4-ynamide (**23**).* To a solution of azide **22** (41.2 mg, 63.4 μmol) in MeOH (1.5 mL) were added 1,3-propanedithiol (40 μL, 0.40 mmol) and NEt_3 (70 μL, 0.50 mmol). The mixture was heated at 55 °C for 24 h before being allowed to cool to rt and was subsequently diluted (EtOAc) and quenched (H_2O). The product was extracted (EtOAc), washed (H_2O, then brine), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to furnish the desired crude product, which was purified by flash chromatography (60% EtOAc/peroleum ether) providing **23** (34.5 mg, 87%) as a mixture of diastereomers as a clear oil: IR ν_{max} (film) 3305, 2932, 2855, 1723, 1653, 1515, 1464, 1249, 1171, 1114, 1038, 1030, 963, 837, 780 cm^{-1}; ^1H NMR (500 MHz) δ 0.10 (m, 6H), 0.90 (m, 9H), 1.09 (m, 3H), 1.32 (m, 0.5H), 1.44 (m, 0.5H), 1.91−2.06 (m, 3H), 2.25 (s, 1.5H), 2.26 (s, 1.5H), 2.42 (m, 1H), 2.68 (m, 2H), 2.62−2.73 (m, 0.5H), 2.76−2.84 (m, 1.5H), 2.92 (m, 1H), 3.56−3.64 (m, 1H), 3.69 (m, 1H), 3.81 (s, 3H), 3.85 (m, 2H), 4.07 (m, 1H), 4.19 (m, 1H), 4.95 (m, 2H), 6.34 (d, J = 8.7 Hz, 0.25H), 6.46 (d, J = 8.4 Hz, 0.25H), 6.63 (d, J = 8.0 Hz, 0.25H), 6.70 (d, J = 7.9 Hz, 0.25H), 6.87−6.90 (m, 3H), 7.32 (d, J = 7.6, Hz, 1H), 7.43 (m, 2H); ^{13}C NMR (125 MHz) δ −5.4, −5.3, 15.28, 15.31, 16.00, 16.02, 16.5, 18.1, 18.2, 18.3, 18.36, 18.40, 18.43, 22.1, 26.0, 31.20, 31.23, 31.7, 31.8, 33.78, 33.83, 33.9, 34.1, 34.4, 48.0, 48.1, 48.3, 48.4, 49.4, 49.5, 50.1, 50.2, 55.4, 63.1, 63.2, 63.3, 63.5, 64.8, 65.0, 66.7, 66.8, 70.26, 70.29, 70.31, 70.5, 75.7, 81.6, 81.77, 81.82, 81.9, 82.1, 82.2, 113.9, 118.55, 118.63, 118.7, 122.67, 122.71, 129.5, 129.6, 130.6, 130.7, 132.6, 136.1, 136.2, 139.1, 159.0, 159.1, 159.7, 162.9, 163.0, 173.2, 173.3, 173.66, 173.68; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{35}H_{50}NO_7Si$ 624.3351, found 624.3350.

*(3R)-3-((2S)-1-(2-(1-(tert-Butyldimethylsilyloxy)pent-4-yn-2-yl)-oxazol-4-yl)propan-2-yl)-8-(4-methoxybenzyloxy)-7-methylisochroman-1-one (**24**).* Amide alcohol **23** (33.9 mg, 54.3 μmol) was dissolved in a 1:1 mixture of DMSO (0.5 mL, 7.0 mmol) and CH_2Cl_2 (0.5 mL) before being cooled to 0 °C. NEt_3 (50 μL, 0.359 mmol) and $SO_3{\cdot}$pyridine (49.9 mg, 0.314 mmol) were added, and the resultant mixture was stirred at 0 °C for 90 min. The reaction was quenched (MeOH), the mixture was diluted (CH_2Cl_2), and the usual workup into CH_2Cl_2 afforded the crude aldehyde, which was used without further purification. The aldehyde was dissolved in CH_2Cl_2 (2.5 mL) and cooled to 0 °C. PPh_3 (45.0 mg, 0.172 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (61.1 mg, 0.298 mmol), and $(BrCl_2C)_2$ (55.9 mg, 0.172 mmol) were added, and the mixture was stirred at 0 °C for 5 min before being allowed to warm to rt and stirred for a further 90 min. *i*-Pr_2NEt (52 μL, 0.299 mmol) was added, and after 90 min the solvent was removed under reduced pressure. Flash chromatography

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(25% EtOAc/petroleum ether) yielded the desired oxazole **24** (21.4 mg, 65% from alcohol **23**) as a clear oil: IR ν_{max} (film) 3299, 2955, 2929, 2857, 1723, 1613, 1579, 1515, 1464, 1427, 1373, 1248, 1170, 1124, 1037, 962, 836, 778 cm^{-1}; ^1H NMR (500 MHz) δ −0.01 (m, 6H), 0.82 (s, 9H), 1.03 (d, J = 6.9 Hz, 3H), 1.88 (t, J = 2.7 Hz, 0.5H), 1.89 (t, J = 2.9 Hz, 0.5H), 2.26 (s, 3H), 2.29 (m, 1H), 2.51 (m, 1H), 2.69 (m, 2H), 2.81−2.89 (m, 2H), 2.97 (dd, J = 15.1, 12.7 Hz, 1H), 3.20 (m, 1H), 3.81 (s, 3H), 3.93 (ddd, J = 9.9, 6.5, 1.0 Hz, 1H), 3.96 (dd, J = 10.0, 5.5 Hz, 1H), 4.24 (ddd, J = 12.1, 6.1, 2.6 Hz, 1H), 4.94 (d, J = 10.1 Hz, 1H), 4.98 (d, J = 10.1 Hz, 1H), 6.87−6.90 (m, 3H), 7.32 (d, J = 7.6 Hz, 1H), 7.36 (s, 1H), 7.46 (m, 2H); ^{13}C NMR (125 MHz) δ −5.4, 14.1, 15.4, 16.5, 18.3, 19.0, 25.9, 28.5, 31.2, 36.5, 41.7, 55.4, 63.4, 69.9, 75.7, 81.3, 81.4, 81.47, 81.51, 113.9, 118.8, 122.6, 129.6, 130.7, 132.4, 135.0, 136.0, 138.6, 139.3, 159.0, 159.7, 163.1, 163.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{35}H_{46}NO_6Si$ 604.3089, found 604.3088.

*(3R)-3-((2S)-1-(2-(1-Hydroxypent-4-yn-2-yl)oxazol-4-yl)propan-2-yl)-8-(4-methoxybenzyloxy)-7-methylisochroman-1-one (**25**).* A solution of TBS ether **24** (17.9 mg, 29.6 μmol) in THF (2.0 mL) was added to a flask containing TBAF·$3H_2O$ (15.0 mg, 47.5 μmol). The resultant mixture was allowed to stir at rt for 6 h before being concentrated under reduced pressure to afford the crude product. Flash chromatography (50 − 60% EtOAc/petroleum ether) gave alcohol **25** (14.4 mg, quant) as a colorless oil: IR ν_{max} (film) 3305, 2926, 1720, 1612, 1564, 1515, 1481, 1463, 1424, 1371, 1301, 1249, 1171, 1129, 1037, 825 cm^{-1}; ^1H NMR (500 MHz) δ 1.04 (d, J = 6.9 Hz, 3H), 1.97 (t, J = 2.7 Hz, 0.5H), 1.99 (t, J = 2.7 Hz, 0.5H), 2.26−2.27 (m, 4H), 2.53 (dd, J = 14.6, 8.5 Hz, 1H), 2.68 (m, 2H), 2.83−2.90 (m, 2H), 2.97 (dd, J = 16.0, 11.9 Hz, 1H), 3.13 (m, 1H), 3.19 (m, 1H), 3.82 (s, 3H), 4.02 (m, 2H), 4.21 (m, 1H), 4.94 (d, J = 10.0 Hz, 1H), 4.98 (d, J = 10.1 Hz, 1H), 6.89−6.91 (m, 3H), 7.33 (d, J = 7.6 Hz, 1H), 7.40 (s, 1H), 7.46 (m, 2H); ^{13}C NMR (125 MHz) δ 15.6, 16.5, 19.4, 28.5, 29.9, 31.5, 36.5, 40.4, 55.4, 62.8, 70.59, 70.63, 75.7, 80.8, 81.37, 81.38, 113.9, 118.7, 122.7, 129.6, 130.7, 132.6, 135.3, 136.1, 138.6, 139.2, 159.0, 159.8, 163.0, 164.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{32}NO_6$ 490.2224, found 490.2223.

*(R)-8-(4-Methoxybenzyloxy)-7-methyl-3-((S)-1-(2-(pent-1-en-4-yn-2-yl)oxazol-4-yl)propan-2-yl)isochroman-1-one (**5**).* NEt_3 (5 μL, 36 μmol) and freshly distilled MsCl (5 μL, 65 μmol) were added to a solution of the alcohol **25** (14.4 mg, 29.4 μmol) in CH_2Cl_2 (1.0 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h before being allowed to warm to rt and stirred for an additional 1 h. The mixture was diluted (EtOAc) and quenched (H_2O) before the usual workup into EtOAc to provide the crude mesylate, which was used without further purification.

The crude mesylate was dissolved in a 1:1 mixture of MeOH (0.5 mL) and CH_2Cl_2 (0.5 mL) before being cooled to 0 °C. 10-CSA (8.5 mg, 36.6 μmol) was added, and after 5 min the mixture was allowed to warm to rt and stirred for a further 13 h. The reaction mixture was diluted (EtOAc) and quenched (H_2O) before the usual workup into EtOAc provided the crude phenol, which was purified by flash chromatography (40−100% EtOAc/peroleum ether) to give mesylate **26** (12.7 mg, 28.4 μmol, 97% from alcohol **25**) as a clear oil. This was used immediately in the elimination reaction.

DBU (13.0 μL, 86.9 μmol) was added to a solution of the mesylate **26** (12.7 mg, 28.4 μmol) in CH_2Cl_2 (1.0 mL) at 0 °C and the resultant mixture stirred for 50 min before being allowed to warm to rt and stirred for a further 2.5 h. The mixture was diluted with EtOAc and quenched (satd aq NH_4Cl) before the usual workup into EtOAc gave the crude product. Flash chromatography (20% EtOAc/peroleum ether) yielded alkene **5** (7.5 mg, 75%) as a colorless oil: $[\alpha]^{23}_D$ +38.7 (c 0.46, CH_2Cl_2); IR ν_{max} (film) 3299, 2968, 2923, 1671, 1622, 1592, 1532, 1508, 1459, 1427, 1383, 1293, 1253, 1174, 1136, 919, 805 cm^{-1}; ^1H NMR (600 MHz) δ 1.06 (d, J = 6.9 Hz, 3H), 2.20 (t, J = 2.6 Hz, 1H), 2.24 (s, 3H), 2.36 (m, 1H), 2.56 (dd, J = 14.5, 8.4 Hz, 1H), 2.83−2.91 (m, 2H), 3.00 (dd, J = 16.1, 12.2 Hz, 1H), 3.45 (s, 2H), 4.45 (ddd, J = 12.1, 6.4, 3.4 Hz, 1H), 5.82 (s, 1H), 6.10 (s, 1H), 6.62 (d, J = 7.3 Hz, 1H), 7.27 (d, J = 7.7 Hz, 1H), 7.39 (s, 1H), 11.21 (s, 1H); ^{13}C NMR (125 MHz) δ 15.3, 15.6, 22.3, 28.6, 29.8, 36.6, 72.0, 80.1, 82.9, 107.9, 117.5, 118.4, 125.4, 130.8, 135.4, 136.8, 137.0, 139.6, 160.7, 161.1, 170.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{22}NO_4$ 352.15433, found 352.15430.

*(9R,10S)-8-Deshydroxyajudazol A (**3**).* Enyne **5** (7.5 mg, 21.3 μmol) and vinyl iodide **6** (9.8 mg, 28.1 μmol) were dried azeotropically from toluene before being dissolved in CH_3CN (1.0 mL). $Pd(PPh_3)_2Cl_2$ (1.4 mg, 2.0 μmol) and CuI (1.0 mg, 5.3 μmol) were added, and the mixture was degassed with Ar before being cooled to 0 °C. NEt_3 (12 μL, 86.6 μmol) was added and the mixture stirred at 0 °C for 1 h before being allowed to warm to rt and stirred for a further 24 h. The mixture was diluted (EtOAc) and quenched (pH 7 buffer) before the usual workup into EtOAc to give the crude alkyne, which was flushed through a plug of silica and taken through to the next step without further purification. Zn dust (2.50 g, 38.2 mmol) was suspended in H_2O (15 mL) and the mixture degassed with Ar for 15 min. $Cu(OAc)_2·H_2O$ (0.25 g, 1.25 mmol) was added and the mixture stirred for 15 min before $AgNO_3$ (0.25 g, 1.47 mmol) was added and the mixture stirred for an additional 30 min. The solid was filtered and washed with H_2O, MeOH, acetone and Et_2O. The slightly Et_2O wet solid was transferred to a round-bottom flask and suspended in a 1:1 mixture of H_2O/MeOH (10 mL). 8 mL of the resultant mixture was added to a solution of the crude alkyne in MeOH (1 mL) and the mixture stirred at rt for 24 h. The mixture was filtered through Celite, eluting with MeOH, followed by EtOAc. The crude product was filtered through a plug of silica before purification by HPLC (5 μm silica semipreparative column: 10 × 250 mm, 60% EtOAc/petroleum ether eluent, flow rate: 2.00 mL/min, t_R 18.8 min) afforded pure deshydroxyajudazol A (**3**) (2.4 mg, 20% from alkyne **5**) as a clear oil: $[\alpha]^{26}_D$ +11.5 (c 0.14, CH_2Cl_2); IR ν_{max} (film) 3390, 2922, 2848, 1667, 1645, 1595, 1454, 1427, 1383, 1292, 1253, 1200, 1174, 1135, 1071, 972, 805, 742 cm^{-1}; ^1H NMR (500 MHz, d_4-methanol) δ 1.04 (d, J = 6.9 Hz, 3H, C10−CH_3), 2.11 (br s, 3H, *H29*), 2.14−2.21 (m, 5H, ArCH_3 and *H22*), 2.29 (dt, J = 7.3, 7.2 Hz, 2H, *H21*), 2.33 (m, 1H, *H10*), 2.54 (dd, J = 14.5, 8.9 Hz, 1H, *H11*), 2.89−2.93 (m, 2.5H, *H11* and NCH_3), 2.97 (br s, 1.5H, NCH_3), 3.02 (m, 2H, *H8*), 3.37 (d, J = 7.4 Hz, 2H, *H16*), 3.60 (br s, 1.5H, OCH_3), 3.64 (br s, 1.5H, OCH_3), 3.94 (m, 2H, *H25*), 4.51 (ddd, J = 9.1, 6.4, 6.2 Hz, 1H, *H9*), 5.27 (br s, 0.5H, *H27*), 5.30 (m, 0.5H, *H27*), 5.41 (d, J = 1.0 Hz, 1H, C15−CH_2), 5.46−5.65 (m, 4H, *H17*, *H20*, *H23* and *H24*), 5.96 (d, J = 0.8 Hz, 1H, C15−CH_2), 6.32−6.39 (m, 2H, *H18* and *H19*), 6.73 (d, J = 7.5 Hz, *H6*), 7.33 (d, J = 8.2 Hz, *H5*), 7.65 (s, 1H, *H13*); ^{13}C NMR (125 MHz) δ 15.3, 15.4, 19.0, 28.2, 29.3, 30.0, 30.5, 30.8, 31.3, 33.1, 33.2, 34.0, 35.8, 37.7, 53.4, 54.8, 55.7, 84.6, 92.3, 108.8, 118.5, 118.9, 124.9, 125.9, 126.3, 126.4, 126.6, 126.7, 128.4, 128.7, 129.3, 133.0, 133.7, 134.6, 136.0, 137.1, 138.1, 138.8, 140.8, 161.4, 163.4, 170.1, 170.2, 170.4, 170.9, 171.2, 171.9; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{34}H_{42}NaN_2O_6$ 597.29351, found 597.29349.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

†Dedicated to the memory of Professor Robert E. Ireland, a great scientist and mentor.

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(32) The original structures assigned to the ajudzols A (**1**) and B (**2**) in ref 5 have the C27 double bond in the *E*-configuration, i.e., OMe group is *trans* to the amide which was assigned based on NOE analysis. The structures depicted for compounds **1**–**4** in ref 10 have the 27*Z* geometry. We assume these are in error and the correct configuration for these compounds is 27*E*.
(33) **Note added in proof**: A total synthesis of (+)-ajudazol B (**2**) was reported following the acceptance of this manuscript which confirmed the absolute configurations of the ajudazols and deshydroxyajudazols as enantiomeric to those shown in Figure 1 see: Essig, S.; Bretzke, S.; Müller, R.; Menche, D. *J. Am. Chem. Soc.* **2012**, DOI: 10.1021/ja309685n.