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Synthesis of myxobacteria metabolites*

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Abstract: Myxobacteria are an excellent source of novel secondary metabolites with a range of biological activities. This review details the synthesis of several examples of these natural products. The total synthesis of all the members of the crocacin family is presented where the stereochemistry of the stereotetrad was set via a tin-mediated *syn*-aldol reaction followed by selective *anti*-reduction. The other key step in the route to crocacins A, B, and D was the introduction of the enamide functionality by acylation of an enecarbamate. A formal synthesis of apicularen A is also discussed, which involved a base-induced macrolactonization reaction and a transannular oxy-Michael cyclization to secure the tetrahydropyran ring. Finally, the total synthesis of deshydroxyajudazol B is summarized. This route details a modified approach to the 2,4-disubstituted oxazole, and a Diels–Alder reaction followed by aromatization was utilized to form the isochromanone moiety. A highly efficient Sonogashira coupling followed by partial reduction then gave deshydroxyajudazol B.

Keywords: natural products; organic synthesis; polyketides; total synthesis.

INTRODUCTION

Myxobacteria are Gram-positive bacteria that are at the interface between single and multicellular organisms [1]. They predominantly live in soil rich in organic matter and are found mostly in semiarid, warm areas. Thus far, some 7500 strains of myxobacteria have been identified, and these microorganisms can be distinguished readily from other bacteria in two main ways. Firstly, they move by gliding or creeping over a solid surface and can cover a culture plate completely in 6–8 days. The second unique difference is their astonishing life cycle. Upon starvation, these single-celled organisms congregate to produce fruiting bodies from 20 to 1000 μm in size with complex structures [1]. To date, there is no comprehensive explanation for this cooperative morphogenesis, and understanding this process is the subject of intense investigation in a number of laboratories. Myxobacteria are also a rich source of potentially useful secondary metabolites with more than 100 basic structural types with around 500 structural variants [2]. The vast majority of secondary metabolites isolated have been described by the Höfle and Reichenbach research groups in Germany, and many exhibit antifungal, antibacterial, cytostatic, and cytotoxic activity. Several examples of the diverse array of these metabolites are shown in Fig. 1. The species *Sorangium cellulosum* has the largest bacterial genome sequenced to date (~13 million base pairs) and produces the potent anticancer compound epothilone B (**1**) [3,4]. Ixabepelone, the less toxic synthetic macrolactam derivative of epothilone B (**1**), is currently used as a

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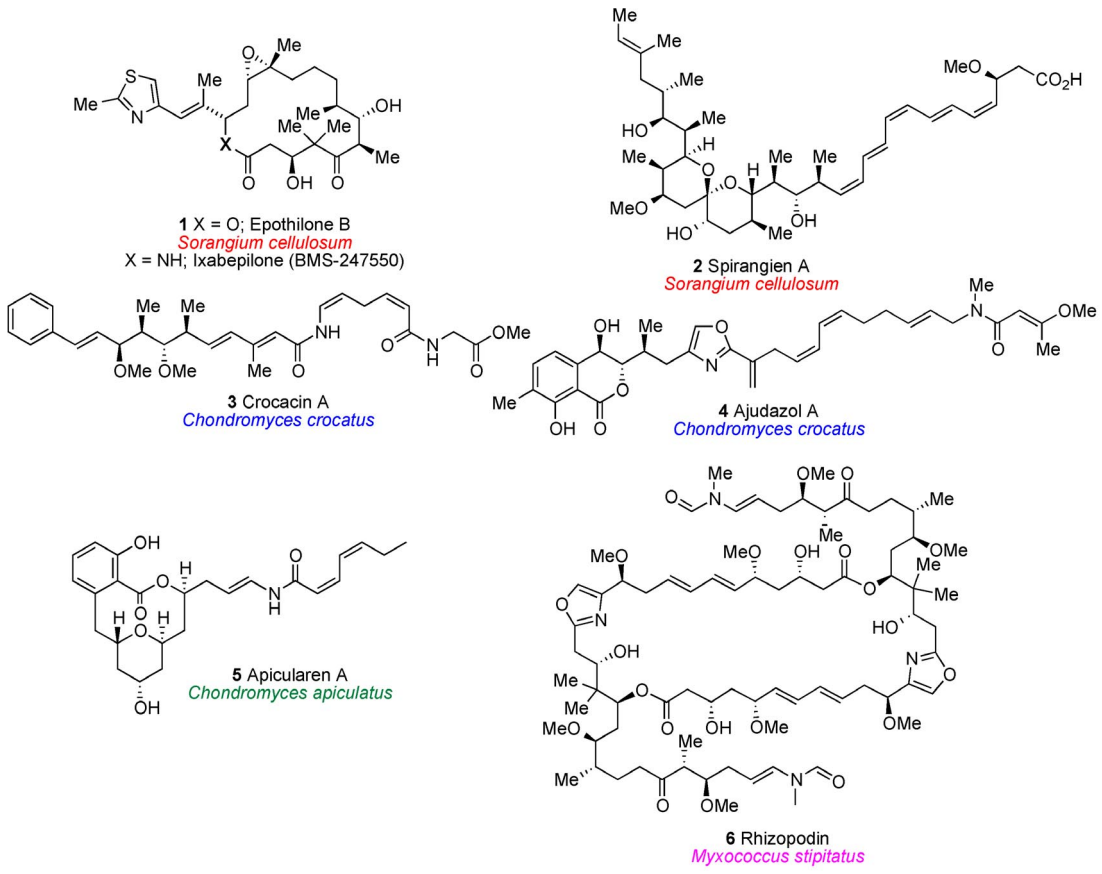


Fig. 1 Examples of myxobacteria metabolites.

chemotherapy agent for the treatment of metastatic breast cancer [5]. The complex polyketide spiroketal spirangien A (**2**), also isolated from *S. cellulosum*, shows activity against several yeasts and fungi and displayed very potent cytotoxicity against L929 mouse fibroblast cells with an IC_{50} = 0.7 ng mL^{-1} [6]. *Chondromyces crocatus* was found to produce the novel enamide containing compound crocacin A (**3**) [7] along with the isochromanone ajudazol A (**4**) [8]. Metabolite **4** also contains an oxazole moiety connected to a *Z*,*Z*,*E*-triene side chain that terminates in an *E*-3-methoxybutenamide. Ajudazol A (**4**) was identified as an inhibitor of the mitochondrial respiratory energy metabolism of beef heart sub-mitochondrial particles (IC_{50} = 22 nM) [9]. Apicularen A (**5**) [10] is a potent anticancer metabolite isolated from *Chondromyces apiculatus* and is structurally very similar to the marine metabolite salicylihalamide A [11]. Compound **5** shows highly effective growth inhibition of several human tumor cell lines originating from cervix (IC_{50} 0.4 ng mL^{-1}), kidney (IC_{50} 0.3 ng mL^{-1}), lung (IC_{50} 0.1 ng mL^{-1}), and prostate (IC_{50} 0.5 ng mL^{-1}) carcinomas. The final example is the dilactone rhizopodin from *Myxococcus stipitatus* [12]. Originally, the structure of **6** was assigned as a monomeric lactone that was later revised to the C_2-symmetric dimer shown [13]. Rhizopodin displays a number of biological properties including antifungal activity and potent nanomolar cytotoxicity against a range of tumor cell lines. The cytotoxicity of **6** has been attributed to its ability to disrupt the actin cytoskeleton [12]. In this brief review, we discuss the synthesis of some challenging targets such as the crocacins, apicularen A (**5**), and deshydroxyajudazol B.

Total synthesis of the crocacins A–D

An early series of targets within the group were the crocacins A (**3**), B (**7**), C (**8**), and D (**9**). As mentioned, this family of natural products was isolated from *C. crocatus* and show promise as lead compounds for agrochemicals [14]. The crocacins A (**3**), B (**7**), and D (**9**) all contain an interesting *Z*-enamide functionality and a common polyketide fragment represented in the simplest example, crocacin C (**8**). These compounds have attracted the interest of a number of synthetic groups [15], and our approach to this family of natural products [16] is exemplified by the retrosynthesis of crocacin D (**9**) as shown in Fig. 2. We envisaged that *Z*-enamide in **9** could be formed by acylation [17] of the anion derived from *N*-acylenamine or enecarbamate **11** with acid chloride **10**. A simple peptide coupling with glycine methyl ester would then afford the dipeptide and removal of the trimethylsilylethoxycarbonyl (TEOC) group would provide the target crocacin D (**9**). The *syn*, *anti*, *anti*-stereotetrad in acid chloride **10** would be secured by a *syn*-aldol reaction to form the C–C bond and stereoselective *anti* reduction whilst the *E*,*E*-diene could be introduced by a Stille cross-coupling reaction to forge the C–C bond. Enecarbamate **11** could be synthesized by Curtius rearrangement of a *N*-acylazide followed by treatment of the labile resultant isocyanate with triethylsilylethanol.

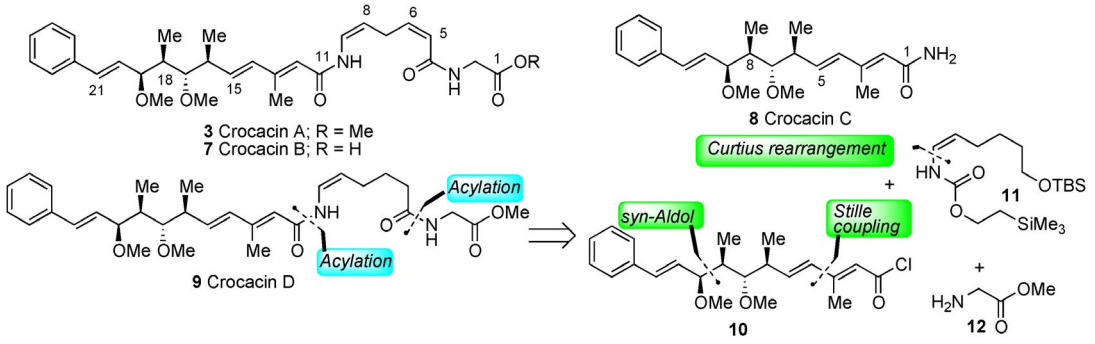
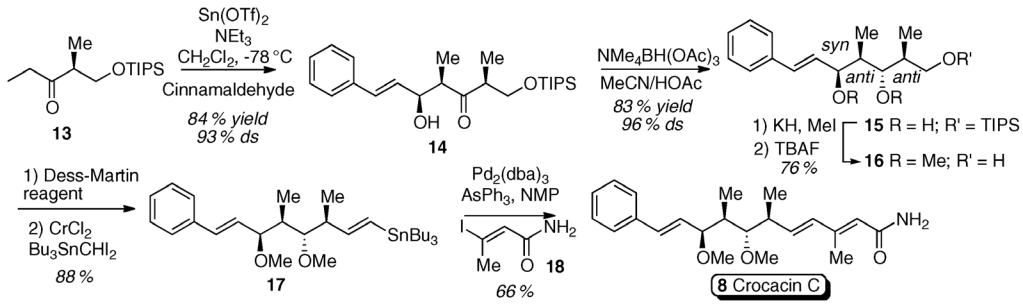


Fig. 2 The crocacins A–D and retrosynthetic analysis of crocacin D (**9**).

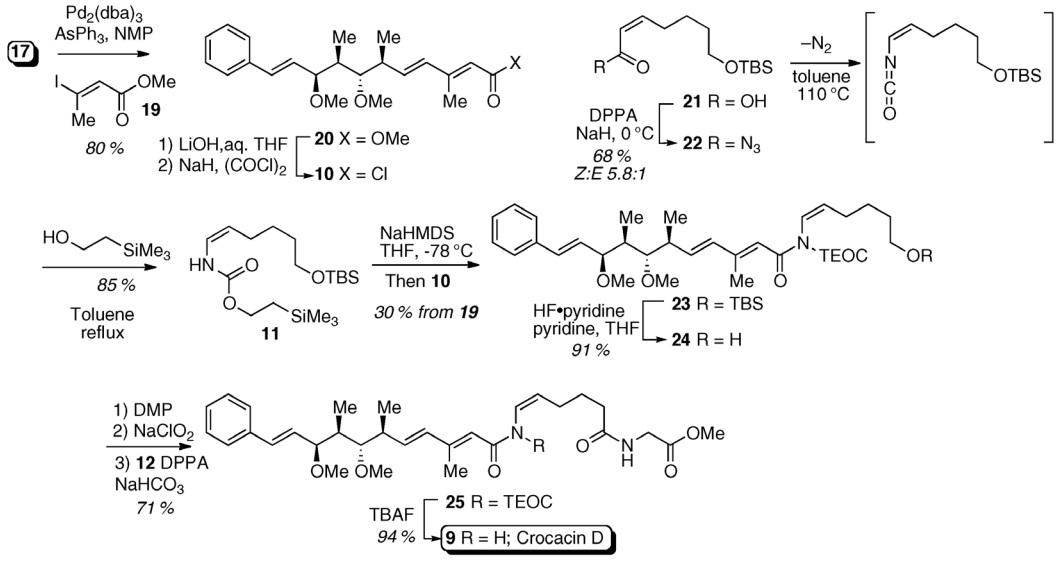
The total synthesis of the simplest example of these compounds, crocacin C (**8**), is shown in Scheme 1. This short route begins with a Paterson-type *syn*-aldol [18] reaction between the *Z*(O) tin enolate derived from ketone **13** and cinnamaldehyde. The *syn*-product **14** was formed in high yield and with good stereocontrol. Diastereoselective *anti* reduction of **14** produced the *syn*, *anti*, *anti*-stereotetrad diol which on methylation and removal of the silicon protecting group gave alcohol **16**. Oxidation followed by vinylstannylation [19] afforded the vinyl stannane **17** in excellent yield. Stille cross-coupling



Scheme 1 Total synthesis of crocacin C (**8**).

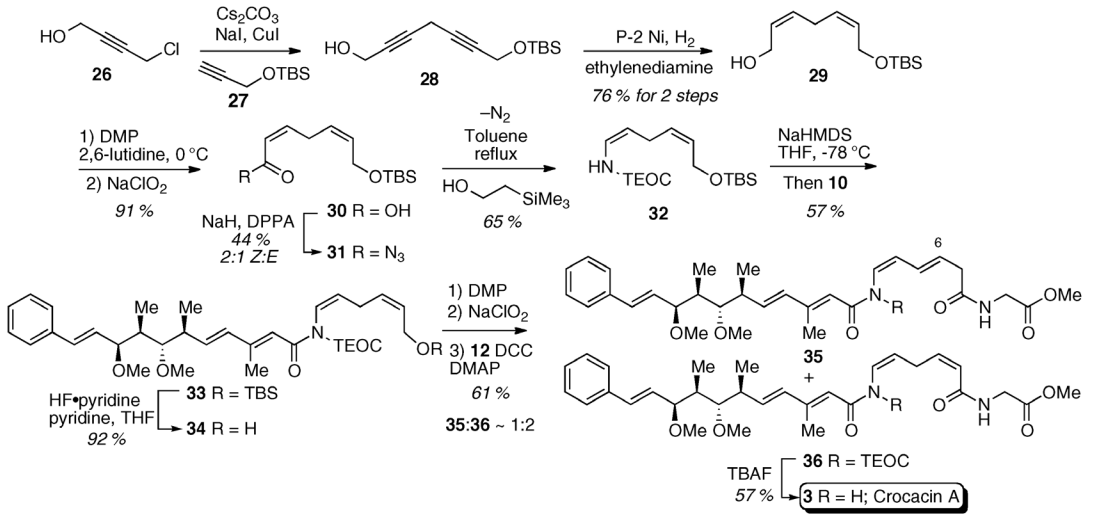
[20] with the iodide **18** then gave crocacin C (**8**) [21]. This first total synthesis confirmed the absolute configuration of this family of compounds.

The synthesis of crocacin D was then achieved as outlined in Scheme 2 and begins with the synthesis of the acid chloride **10**. Stille coupling between stannane **17** and iodide **19** afforded ester **20**. Hydrolysis followed by formation of the acid chloride via the sodium salt of the acid then gave **10**. The synthesis of the enecarbamate fragment **11** began with treatment of unsaturated acid **21** with diphenyl phosphoryl azide (DPPA) and NaH to give the *N*-acylazide **22** with minimal isomerization of *Z*-alkene. Heating **21** in toluene induced Curtius rearrangement to give the intermediate isocyanate, which was immediately treated with trimethylsilylethanol in boiling toluene to afford the required enecarbamate **11**. Treatment of **11** with base produced the anion, which was allowed to react with acid chloride **10** to give the protected enamide **23** in 30 % yield starting from ester **19**. Removal of the *tert*-butyldimethylsilyl (TBS) group in the presence of the TEOC protecting group was achieved with HF·pyridine buffered with pyridine to afford the alcohol **24** in excellent yield. Two-stage oxidation of the alcohol **24** to the corresponding acid was achieved with Dess–Martin periodinane followed by $NaClO_4$. Peptide coupling with glycine methyl ester (**12**) gave dipeptide **25**. Final removal of the TEOC group with tetrabutylammonium fluoride (TBAF) then afforded crocacin D (**9**).



Scheme 2 Total synthesis of crocacin D (**9**).

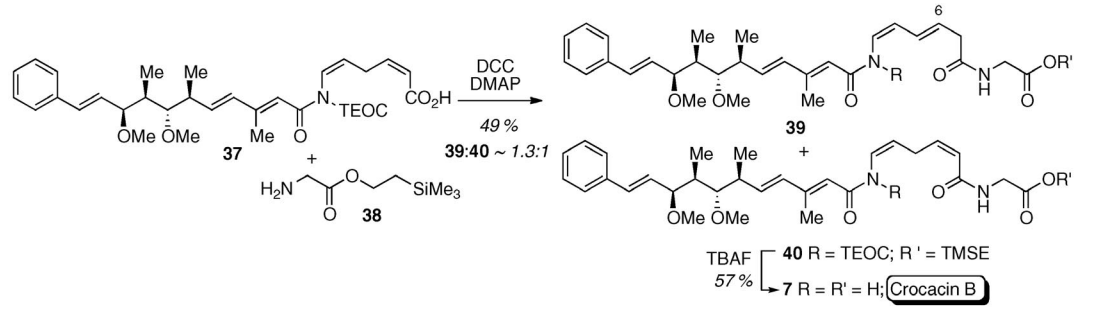
The total synthesis of crocacin A (**3**) followed a similar route to that described for crocacin D (**9**) (Scheme 3). Key to the approach was the effective synthesis of the skipped *Z*,*Z*-enamide system. This began with the copper-mediated coupling [22] of the terminal alkyne **27** and chloride **26** to afford sensitive diyne **28**, which was immediately converted into the diene **29** system by partial reduction of the diyne using hydrogen gas and P-2 nickel catalyst [23]. Other methods such as Lindlar reduction proved unreliable. Oxidation to the acid **30** followed by conversion to the azide **31** set the stage for Curtius rearrangement in boiling toluene followed by addition of trimethylsilylethanol to give dienecarbamate **32**. Deprotonation and acylation with acid chloride **10** gave the enamide **33**, which could be converted into alcohol **34** by treatment with HF·pyridine. Two-stage oxidation and peptide coupling with **12** yielded **36** along with some amount of the 6*E*-alkene isomer **35** produced by base-promoted isomerization. The unwanted isomer **35** could be separated from **36** by flash chromatography. Finally, expo-



Scheme 3 Total synthesis of crocacin A (**3**).

sure of **36** to TBAF allowed for removal of the TEOC group to provide crocacin A (**3**) in 57 % yield [24].

Attempted base hydrolysis of crocacin A (**3**) failed to provide crocacin B (**7**) so an ester protecting group was utilized (Scheme 4). Thus, treatment of acid **37** derived from alcohol **34** with the trimethylsilylethyl (TMSE) ester of glycine **38** and *N*,*N*′-dicyclohexylcarbodiimide/dimethylaminopyridine (DCC/DMAP) gave the dipeptide **40** and 6*E*-isomer **39** in a ratio now slightly favoring the undesired isomer **39**. Treatment of **40** with TBAF effected removal of the carbamate and ester protecting groups to afford crocacin B (**7**) for the first time.



Scheme 4 Total synthesis of crocacin B (**7**).

Formal total synthesis of apicularen A

The myxobacteria metabolite apicularen A (**5**) is very similar to marine sponge metabolite salicylihalamide A (Fig. 3). Thus, we were attracted to apicularen A (**5**) as a target [25,26] following our formal synthesis of salicylihalamide A [27,28]. We envisaged that a formal total synthesis of **5** could be achieved by the production of known intermediate **41** [29]. Compound **41** could be accessed from a salicylihalamide-type intermediate enone **42** or the 13*R* isomer **43** via a novel transannular oxy-Michael reaction which would secure the tetrahydropyranyl (THP) ring in intermediate **41**. The enones **42** and **43** could be both formed via a base-induced macrolactonization [28,30] of precursor alkenes **44** or **45**.

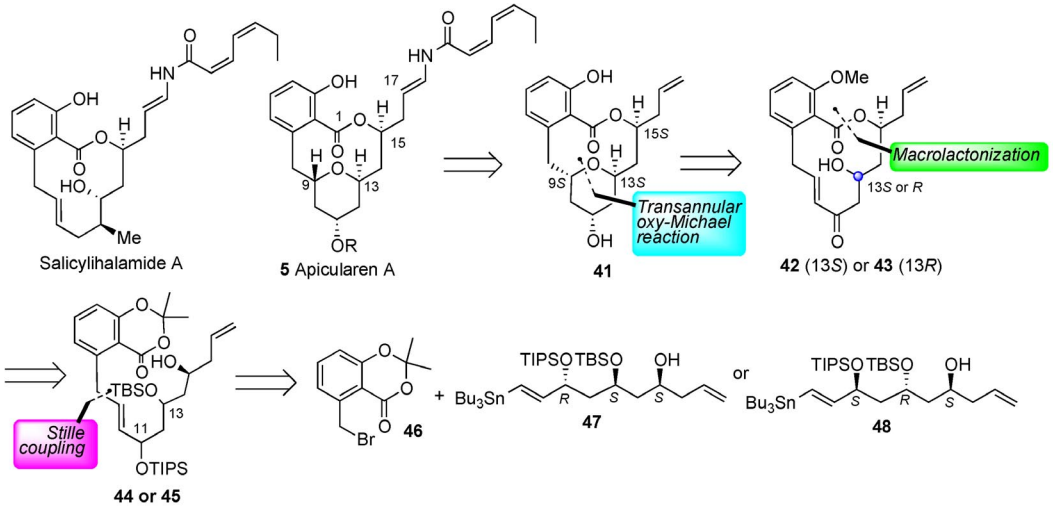


Fig. 3 Retrosynthetic analysis of apicularen A (**5**).

The macrolactonization reaction involves deprotonation of the 13-hydroxy group followed by attack at the carbonyl carbon of the 1,3-dioxanone with a loss of acetone. Methylation of the resultant phenolate anion followed by deprotection and allylic oxidation gives the macrolactones **42** or **43**. Again, the stereochemistry at the C11 stereocenter is not relevant since C11 is destroyed upon oxidation. The macrolactone precursor alkenes **44** or **45** could be then secured by a Stille cross-coupling between benzyl bromide **46** and either stannane diastereoisomer **47** or **48**.

If the cyclization of the enone **42** is conducted under conditions favoring thermodynamic control, then the stereoisomer that is lowest in energy should be preferred. Initial MM2 (PC Model) calculations (Fig. 4) showed that the desired 9,13-*trans*-13,15-*syn*-isomer **A** (twist boat conformer with a truncated enamide side chain) with the natural product stereochemistry was favored over the alternative isomers **B**, **C**, and **D**. These calculations suggested that isomer **A** would be favored in a ratio greater than 99:1 (average energy difference ~ 17.2 kJ mol^{-1}) ratio at 20 °C. In addition, the C13 and C9 stereocenters are set by an oxy-Michael retro-Michael sequence so that the stereochemistry at both these centers is controlled solely by the C15 stereocenter. Specifically, both enone diastereoisomers **42** and **43** can undergo epimerization at C13, which should ensure the required stereochemistry under equilibration conditions.

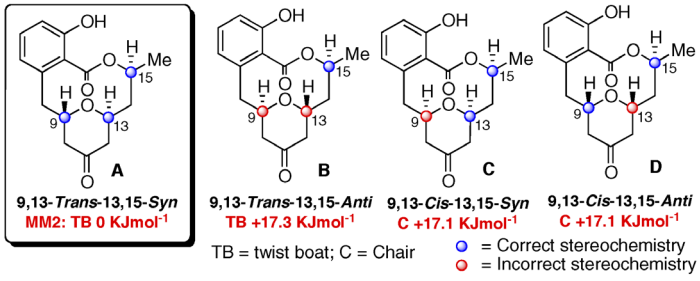
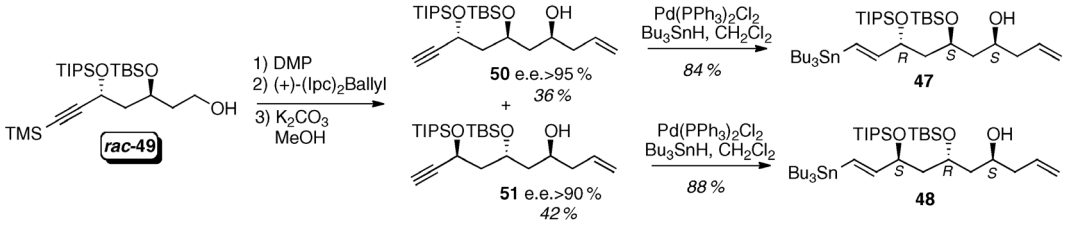


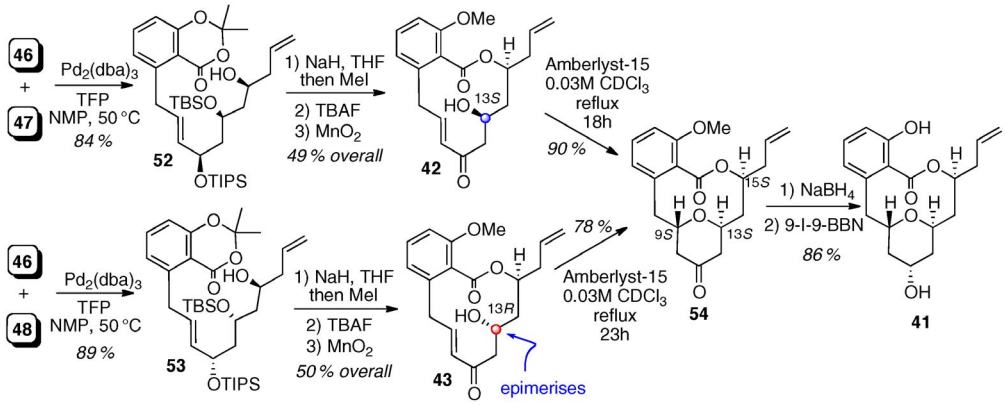
Fig. 4 MM2 calculations for pyranone isomers.

Based on the above proposal, we embarked on a formal synthesis of apicularen A (**5**) by targeting the known intermediate **41**. The approach began with the synthesis of the optically enriched stannanes **47** and **48** as shown in Scheme 5. Oxidation of racemic alcohol **49** followed by asymmetric allylation [31] of the resultant aldehyde stereoselectively introduced the new asymmetric center. Removal of the trimethylsilyl (TMS) group and flash chromatography afforded the *anti*, *syn*-alkyne **50** and *anti*, *anti*-isomer **51** in high enantiomeric excess (ee). Each of these now possessed the correct absolute configuration at what would eventually become the C15 stereocenter. Hydrostannylation of each isomer gave **47** and **48**, respectively.



Scheme 5 Synthesis of stannanes **47** and **48**.

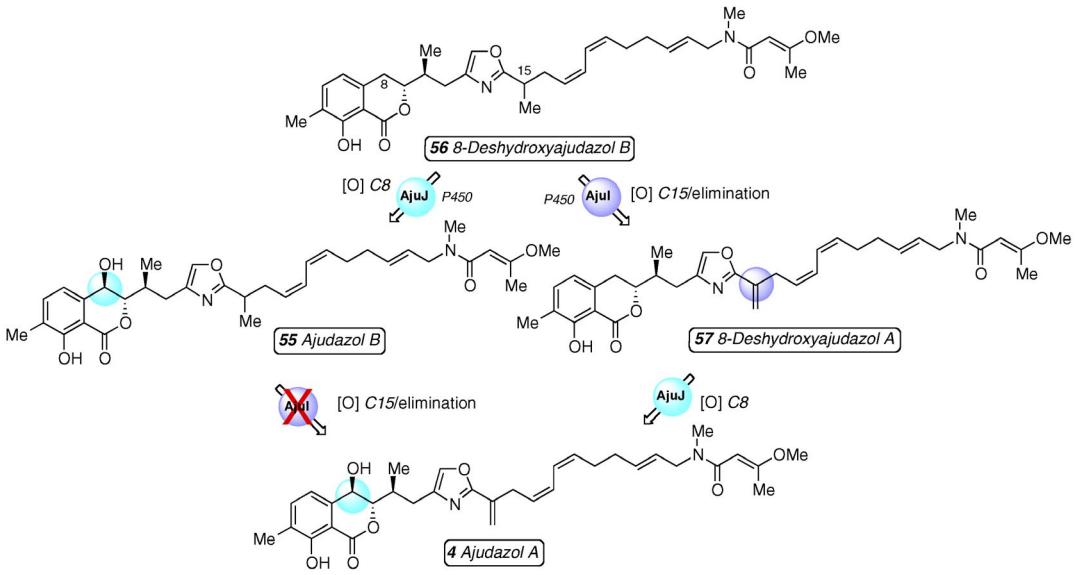
Stille coupling between stannane **47** and bromide **46** afforded alkene **52** in good yield (Scheme 6). Macrolactonization was effected by treatment of **52** with NaH, and methylation of the intermediate phenolate anion gave the methyl ether. Removal of the silicon protecting groups and selective allylic oxidation with MnO_2 gave the enone **42**. Transannular cyclization was then achieved using Amberlyst 15 acidic ion-exchange resin [32] to afford the pyranone **54** as a single stereoisomer. The structure of **54** was confirmed by X-ray crystallography and comparison to literature data. Reduction of the ketone was difficult to achieve stereoselectively but was effected in high yield with $NaBH_4$ (ratio 1:1). The incorrect isomer was converted into the desired one via Mitsunobu inversion [33]. Finally, demethylation with 9-iodo-9-BBN gave compound **41**, which had physical data identical to that reported [29,34,35]. This completed the formal total synthesis of apicularen A, which utilized a transannular oxy-Michael reactions as the key step [36].



Scheme 6 Formal total synthesis of apicularen A (**5**) by synthesis of known intermediate **41**.

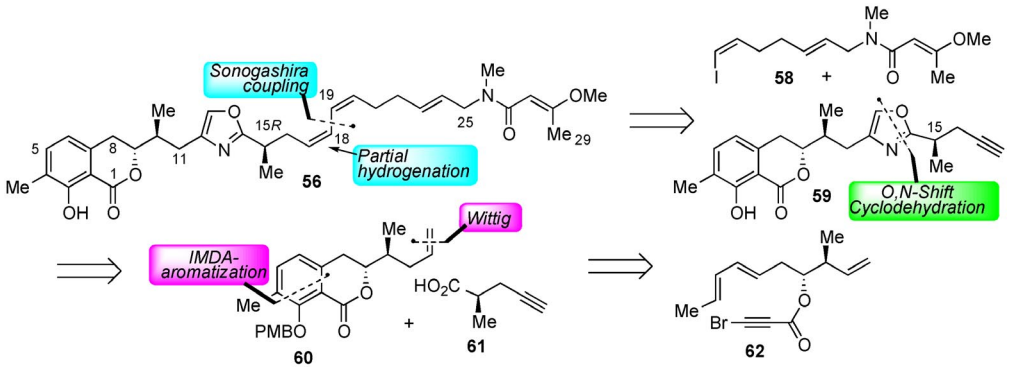
Total synthesis of deshydroxyajudazol A

The ajudazols A (**4**) and B (**55**) were isolated from the same myxobacterium *C. crocatus* that produces the crocacins and have an interesting biosynthesis (Scheme 7) [37]. The putative biosynthetic intermediate is proposed to be deshydroxyajudazol B (**56**). This intermdiate undergoes selective oxidation at C8 mediated by the cytochrome P450 enzyme AjuJ (encoded by the gene *ajuJ*) to produce ajudazol B (**55**). Alternatively, C15 oxidation and elimination by AjuI produces deshydroxyajudazol A (**57**), which is then finally oxidized by the enzyme AjuJ (encoded by the gene *ajuI*) to form ajudazol A (**4**), however, ajudazol B (**55**) is not a substrate for AjuI and is therefore not converted directly into **4**. Indeed, the deshydroxyajudazols A and B have been detected in trace amounts in extracts of *C. crocatus* and have been observed in larger amounts in extracts from mutants in which the genes *ajuI* and *ajuJ* were knocked out. We were intrigued by this biosynthesis and elected to synthesize the putative biosynthetic intermediate and trace natural product deshydroxyajudazol B (**56**) [38,39]. The relative *anti*, *anti*-stereochemistry for the C8–10 stereotriad was determined by ^{1}H NMR analysis, but the configuration at C15 is unknown and the absolute stereochemistry remains to be confirmed [8].



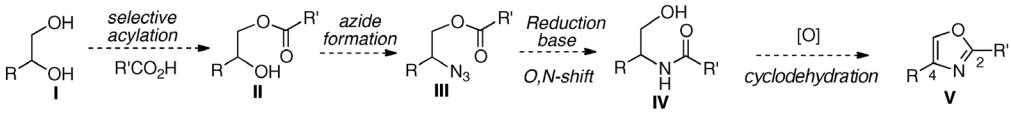
Scheme 7 The biosynthesis of the ajudazols.

Our retrosynthetic analysis of the 9*R*,10*S*,15*R*-stereoisomer of deshydroxyajudazol B (**56**) is shown in Scheme 8. The C18–C19 bond would be formed by a Sonogashira coupling [40] between eastern fragment vinyl iodide **58** [41] and western fragment alkyne **59**. The oxazole in **59** could be secured by a modified approach involving an acylation with acid **61** [42], an *O*,*N*-acyl shift to form an amide, and oxidation followed by subsequent cyclodehydration to give the 2,4-disubstituted oxazole (vide infra). The isochromanone in **60** could be formed by an intramolecular Diels–Alder reaction (IMDA) of the diene ester **62** followed by aromatization [34].



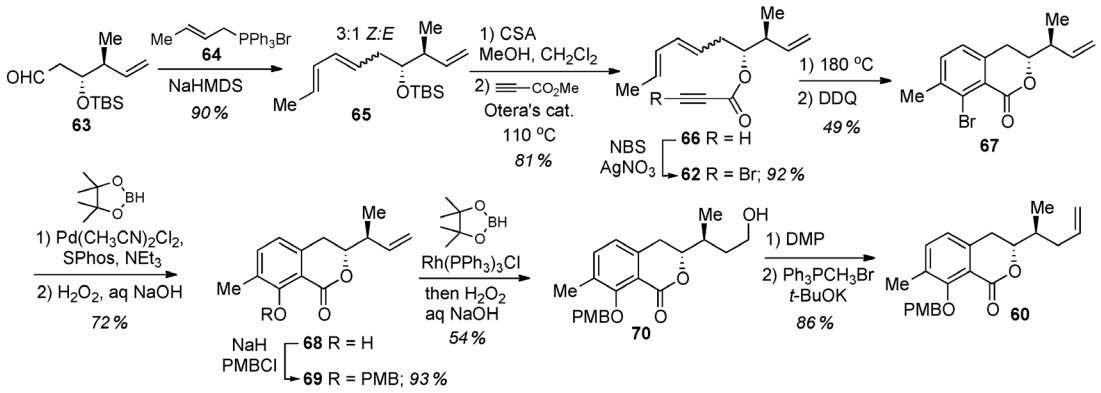
Scheme 8 Retrosynthetic analysis of deshydroxyajudazol B (**56**).

The detail of our modified approach to 2,4-disubstituted oxazoles is shown in Scheme 9. This begins with a vicinal diol **I** derived from a terminal alkene by dihydroxylation. Selective acylation of the primary alcohol with an acid gives ester **II**, which upon azide displacement affords secondary azide **III**. Azide reduction accompanied by base induced *O*,*N*-shift [43] yields the hydroxyamide **IV**. Oxidation of the alcohol **IV** to the aldehyde and cyclodehydration [44] then gives the 2,4-disubstituted oxazole **V**. In this manner, the use of an amino alcohol precursor is avoided and there is no need for protecting groups. In addition, this route provides access to a large variety of 2,4-substituents.



Scheme 9 Modified 2,4-disubstituted oxazole synthesis.

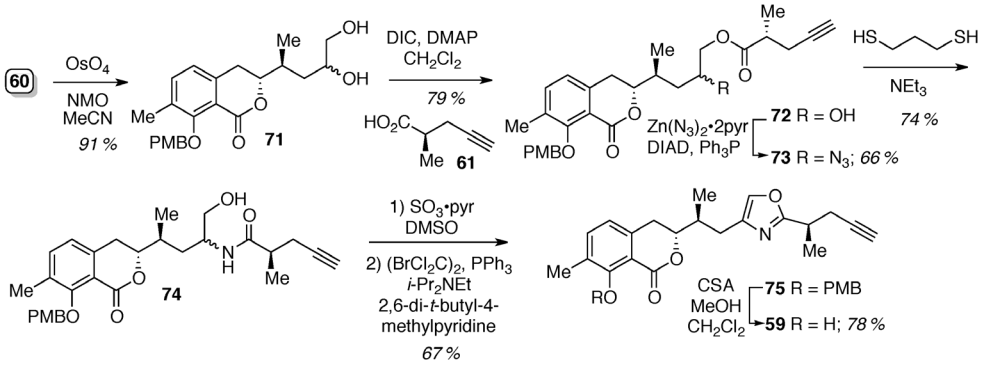
The synthesis of the isochromanone fragment begins with a Wittig reaction between known optically pure aldehyde **63** [45] and the ylide derived from phosphonium salt **64** [46], which gave the triene **65** in good yield as a *Z*:*E* mixture (3:1) (Scheme 10). Acid-induced TBS group removal and esterification with methyl propiolate mediated by Otera's catalyst [47] afforded ester **66**, and alkyne bromination [48] gave IMDA precursor. After some experimentation, the IMDA reaction of **62** could be induced by



Scheme 10 Synthesis of the isochromanone fragment **60**.

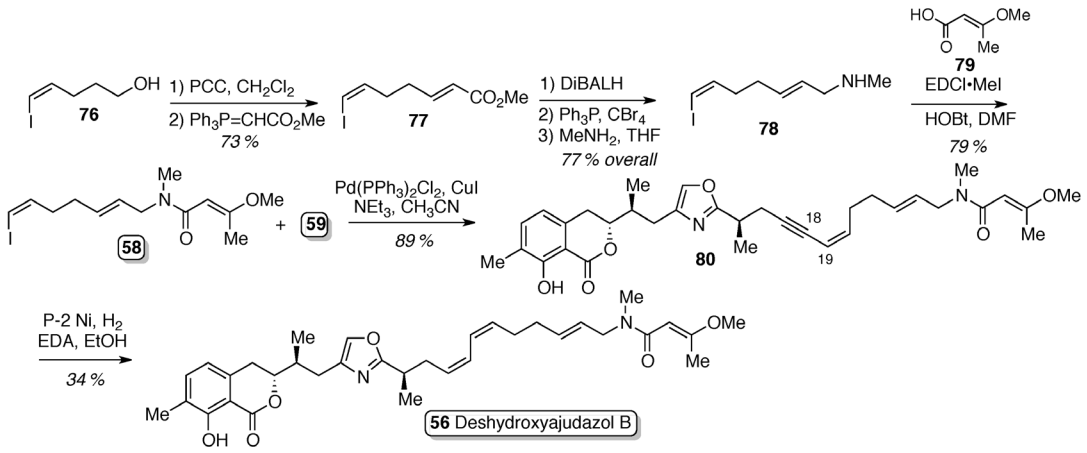
heating in toluene in a sealed tube at 180 °C. Aromatization was induced with dichlorodicyano-*p*-benzoquinone (DDQ) to afford bromide **67** [34]. Bromine oxygen exchange was best achieved via Pd-catalyzed cross-coupling with pinacolborane using Buchwald's SPhos ligand [49] followed by oxidation, and hydrolysis provided phenol **68**, which was protected as the *p*-methoxybenzyl (PMB) ether **69**. Hydroboration of the terminal alkene in **69** proved troublesome so we turned to the use of Wilkinson's catalyst and pinacolborane [50], which gave alcohol **70** in a reproducible manner. Oxidation and Wittig extension then gave the alkene **60**.

Dihydroxylation of **60** gave the diol **71** as a mixture of diastereoisomers in excellent yield (Scheme 11) [51]. We then applied the modified approach described above to secure the 2,4-disubstituted oxazole present in the ajudazols. Selective acylation of the primary alcohol in **71** with optically pure acid **61** [41] afforded the ester **72** in good yield. Azide displacement of the secondary alcohol was achieved using a Mitsunobu protocol using the stable crystalline $Zn(N_3)_2 \cdot 2$pyridine [52] as the azide source. Reduction of the resultant azide **73** was effected with 1,3-propanedithiol [53], and treatment with base induced the *O*,*N*-shift [43] to give the amide **74**. Parikh–Doering oxidation of the primary alcohol and cyclization was effected by treatment with 1,2-dibromotetrachloroethane and PPh_3 in the presence of hindered base 2,6-di-*tert*-butyl-4-methylpyridine [44b], and dehydrohalogenation with Hünigs base furnished the oxazole **75** in 67 % yield overall from the amido alcohol **76**. It should be noted that no racemization of the C15 stereocenter was observed in this process. Owing to problems with removal of the PMB at a latter stage of the synthesis, the free phenol was deprotected at this stage by treatment with CSA to give the western fragment **59.**



Scheme 11 Synthesis of the oxazole **59**.

The completion of the total synthesis of deshydroxyajudazol B (**56**) is shown in Scheme 12. The requisite eastern fragment vinyl iodide was synthesized from iodide **76** [40]. Oxidation and Wittig reaction using a stabilized ylide gave ester **77**. Reduction followed by formation of the bromide and substitution with methylamine gave secondary amine **78**. Peptide coupling with acid **79** yielded the eastern fragment **58**. Sonogashira coupling between iodide **58** and alkyne **59** was extremely efficient at forming the C18–C19 bond to give enyne **80** in high yield. The partial reduction of the alkyne in **80** proved somewhat difficult. We found that partial reduction could be achieved with P-2 Ni and H_2 gas in the presence of ethyl diazoacetate (EDA), however, some over-reduction was observed. High-performance liquid chromatography (HPLC) allowed for the separation of the desired product **56** from over-reduced compound and starting material. There was no physical data to compare directly with our synthetic deshydroxyajudazol B (**56**) however, this compound displayed NMR spectral data similar to that for the eastern half of ajudazol B (**55**) [8] and the western half of deshydroxyajudazol A (**57**) [37]. Due to the absence of any chiroptical data for **56**, the absolute configuration of this family of compounds remains to be determined.



Scheme 12 Total synthesis of deshydroxyajudzol B (**56**).

In this review, we have detailed the synthesis of some examples of myxobacteria metabolites. Ongoing research continues in our laboratories toward other targets from this life form, including the ajudazols A (**4**) and B (**55**), spirangien A (**2**), and rhizopodin (**6**).

ACKNOWLEDGMENTS

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