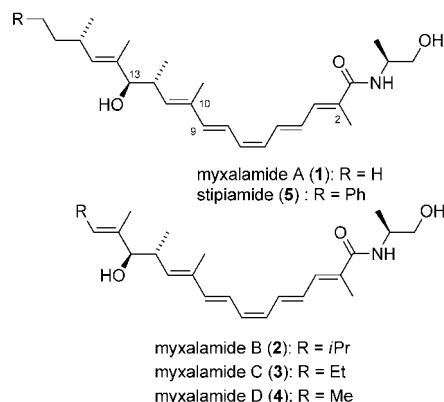


Concise Total Synthesis of (–)-Myxalamide A**

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Myxalamide A–D (**1–4**) were first isolated from the gliding bacterium *Myxococcus xanthus* by Jansen and co-workers in 1983 and were identified as polyene antibiotics^[1] (Scheme 1).

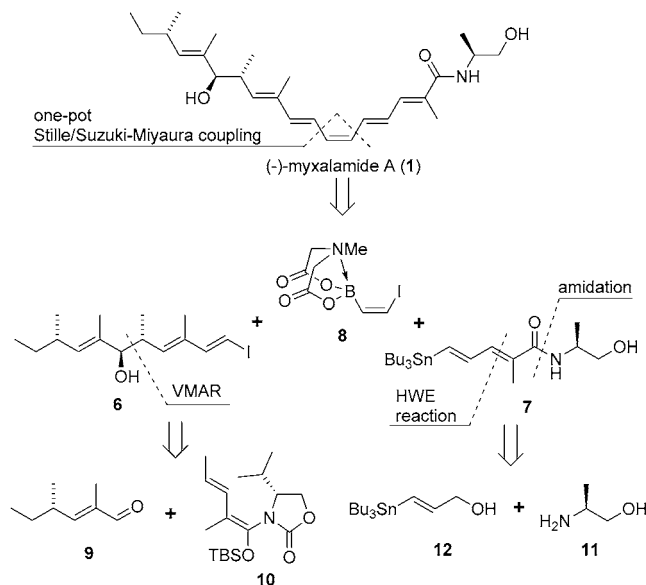


Scheme 1. Structure of (–)-myxalamide A and its analogues.

The characteristic structural feature of the myxalamides and an analogue, stipiamide^[2] (**5**), is the labile (*E,E,Z,E,E*)-pentaene motif, the synthesis of which has attracted considerable attention. Indeed, Mapp and Heathcock achieved an elegant total synthesis of **1** in 22 steps.^[3] Syntheses of other myxalamides and structurally related compounds have also been reported;^[4–6] for example, the 16-step synthesis of **5** by Andrus and Lepore^[4a] and the synthesis of 2'-O-methylmyxalamide D in 11 steps by Coleman et al.^[5]

We have previously reported a highly stereoselective vinylogous Mukaiyama aldol reaction (VMAR) involving vinylketene silyl N,O-acetals.^[7] This methodology can provide the *anti*- δ -hydroxy- α,γ -dimethyl- α,β -unsaturated carbonyl moiety, which is found in a number of naturally occurring polyketides. In fact, many groups have successfully utilized the VMAR in natural product syntheses.^[8,9] We envisaged that the C9–C13 segment of **1** could be constructed by using our methodology. Herein, we disclose a highly convergent, concise, and protecting-group-free synthesis of **1**.

Initially, our strategy was to construct the conjugated pentaene structure during the final step of the synthesis through a one-pot Stille/Suzuki–Miyaura cross-coupling reaction involving the three fragments, **6**, **7**, and (*Z*)-boronate **8**, the latter of which is derived from *N*-methyliminodiacetic acid (MIDA) (Scheme 2).^[10] This one-pot Stille/Suzuki–



Scheme 2. Convergent retrosynthetic strategy for **1**. TBS = *tert*-butyldimethylsilyl.

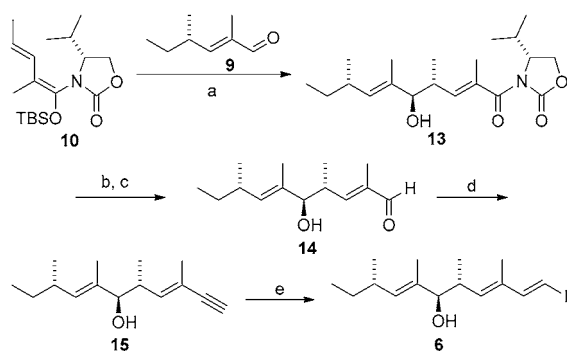
Miyaura cross-coupling reaction has the advantage of minimizing the handling of the labile *Z* olefin. The left-hand fragment **6** could be constructed by the VMAR involving aldehyde **9**, a reaction, which would lead to the formation of the C12–C13 bond with the required *anti* stereochemistry. The right-hand fragment **7** could be derived from a Horner–Wadsworth–Emmons reaction and an amidation reaction with the amine, (*S*)-alaninol (**11**).

Firstly, we synthesized the left-hand fragment **6** (Scheme 3). The enal **9** was prepared in four steps from commercially available (*S*)-2-methylbutanol.^[11] When **9** was subjected to the VMAR according to the protocol established in our laboratory, that is, the use of the TiCl_4 in CH_2Cl_2 and the employment of two equivalents of the aldehyde, the *anti* aldol adduct **13** was obtained in 86% yield with high diastereoselectivity (d.r. > 20:1). Furthermore, the addition of a catalytic amount of water (10 mol%) led to an accelerated VMAR that gave product with similar yield and diastereoselectivity.^[7d] Reductive removal of the chiral auxiliary with LiBH_4 , and oxidation of the resulting primary alcohol with MnO_2 provided aldehyde **14** in 91% yield (two steps).^[12]

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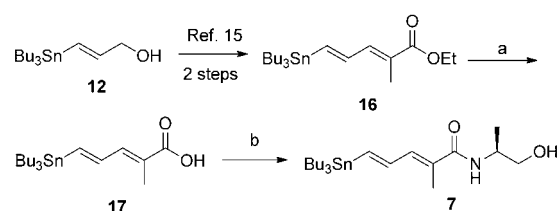


Scheme 3. Synthesis of left-hand fragment **6**. Reagents and conditions: a) TiCl_4 , **9**, CH_2Cl_2 , -78 to -50°C , 86 % (d.r. > 20:1); b) LiBH_4 , MeOH (cat), Et_2O , 0°C ; c) MnO_2 , CH_2Cl_2 , RT, 91 % (2 steps); d) $(\text{MeO})_2\text{P}(\text{O})\text{CHN}_2$, KOtBu , THF, -78°C to RT, 75 %; e) HZrCp_2Cl , THF, 0°C , then I_2 , -78°C , 58 % (E/Z > 20:1).

We next investigated the transformation of aldehyde **14** into vinyl iodide **6**. The use of the Takai–Utimoto olefination^[13] (CHI_3 and CrCl_2), as a means to achieve this transformation directly, was unsuitable because of low yield and low selectivity. Thus aldehyde **14** was first converted into the enyne **15** by using the Seyferth–Gilbert reagent.^[14] Hydrozirconation of enyne **15** by using the Schwartz reagent and treatment of the resulting vinyl zirconium species with iodine led to vinyl iodide **6** with high selectivity (E/Z > 20:1).

Next, we examined the synthesis of the right-hand fragment **7** (Scheme 4). Allyl alcohol **12** was converted into ester **16** in two steps.^[15] Hydrolysis of ester **16** with TMSOK gave carboxylic acid **17**. The crude carboxylic acid **17** was coupled with (*S*)-alaninol (**11**) by using PyBroP as the coupling reagent to give vinyl stannane **7** in 94 % yield (two steps).

Having all fragments, that is, **6**, **7**, and **8**,^[16] in hand, we next focused on the Stille coupling reaction of **7** and **8** (Table 1). Unfortunately, the use of standard Stille coupling reaction conditions^[17] resulted in the decomposition of (*Z*)-boronate **8** (Table 1, entry 1–4). When the reaction was conducted at low temperature and in the presence of

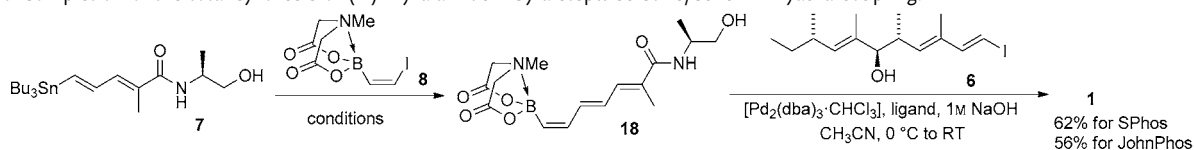


Scheme 4. Synthesis of right-hand fragment **7**. Reagents and conditions: a) TMSOK, THF, RT; b) **11**, PyBroP, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , 0°C to RT, 94 % (2 steps). THF = tetrahydrofuran, TMS = trimethylsilyl, PyBroP = bromotripyrrolidinophosphonium hexafluorophosphate.

$\text{P}(\text{2-furyl})_3$, the triene **18** was obtained, but the yield was moderate and variable (approximately 30–60%; Table 1, entry 5). Ethenyl boronate^[18] was observed as a degradation product, thus suggesting that the catalytic cycle was hampered after the oxidative addition reaction of (*Z*)-boronate **8** and the palladium catalyst, probably because of the instability of the resulting palladium complex. Thus we examined the reaction further by employing Buchwald's monodentate biaryldialkylphosphine ligands.^[19] To our delight, after extensive experimentation, we found that the desired triene **18** could be obtained in high yield when using JohnPhos as a monodentate ligand (Table 1, entries 7 and 8).

Next, we aimed to find suitable reaction conditions for achieving the Suzuki–Miyaura coupling reaction of **18** and vinyl iodide **6**. In doing so, the instability of the conjugated pentaene moiety had to be considered. The use of SPhos and JohnPhos in basic solution afforded (–)-myxalamide **1** in 62 % and 56 % yields, respectively.^[20] Although the coupling reaction proceeded smoothly the yield was moderate because of isomerization of the *Z* double bond of **1**. Several measures were adopted to minimize this isomerization. Manipulations were conducted in the dark and all solvents that were used for the reaction and for chromatography were thoroughly degassed prior to use. Unfortunately, isomerization of the *Z* double bond into the stable *E* double bond could not be completely suppressed (Figure 1).

Table 1: Completion of the total synthesis of (–)-myxalamide **1** by a stepwise Stille/Suzuki–Miyaura coupling.



Entry	Equiv. of 8	Catalyst (mol%)	Additive (mol%)	Solvent	T	Yield [%]
1	1.5	$[\text{Pd}(\text{PPh}_3)_4]$ (10)	CuI (150)	THF/DMF	RT	decomposed
2	1.5	$[\text{Pd}(\text{PPh}_3)_4]$ (10)	CuTC (150)	DMF	RT	trace
3	1.5	$[\text{PdCl}_2(\text{CH}_3\text{CN})_2]$ (10)	AsPh_3 (20)	THF/DMF	0°C to RT	decomposed
4	1.6	$[\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3]$ (10)	dppe (40)	THF/DMF	-20°C	trace
5	1.3	$[\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3]$ (20)	$\text{P}(\text{2-furyl})_3$ (50)	THF	-20°C	51
6	1.6	$[\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3]$ (10)	SPhos (40)	THF/DMF	-20°C	45
7	1.2	$[\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3]$ (5.0)	JohnPhos (20)	THF/DMF	-30°C	88
8	1.2	$[\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3]$ (5.0)	JohnPhos (20)	$\text{CH}_3\text{CN}/\text{DMF}$	-10°C	99

dba = dibenzylideneacetone, DMF = *N,N*-dimethylformamide, dppe = 1,2-bis(diphenylphosphino)ethane, JohnPhos = 2-(di-*tert*-butylphosphino) biphenyl, SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, TC = 2-thiophenecarboxylate.

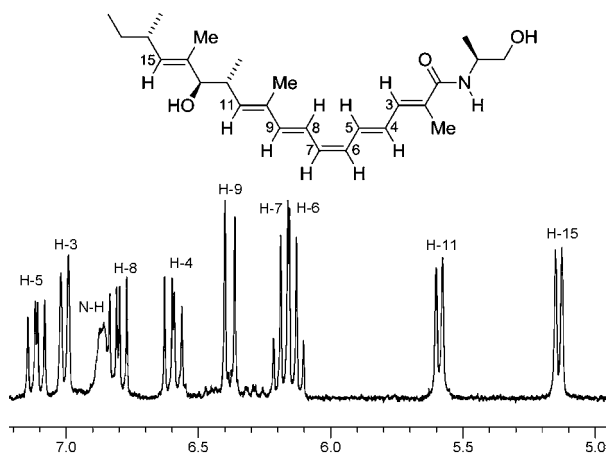
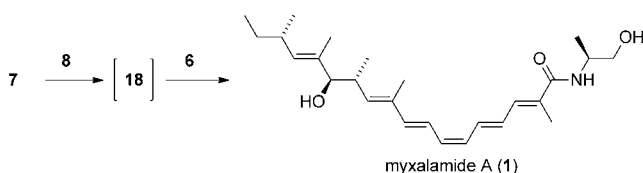


Figure 1. A downfield section of the ^1H NMR spectrum of our synthetic (–)-myxalamide A (5.0–7.2 ppm).

Having established the total synthesis of **1** by stepwise Stille and Suzuki–Miyaura coupling reactions, we then attempted a one-pot Stille/Suzuki–Miyaura coupling reaction (Scheme 5). Compound **8** (1.3 equivalents) and vinyl stan-



Scheme 5. Completion of the total synthesis of (–)-myxalamide A by a one-pot Stille/Suzuki–Miyaura coupling reaction. Reagents and conditions: **8**, $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$, JohnPhos, CH_3CN , DMF, -10°C , 24 h; then **6**, 1 M aq. NaOH, $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$, 0°C to RT, 22 h, 59%.

nane **7** (1.0 equivalent) in CH_3CN and DMF was treated with JohnPhos (20 mol %) and $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$ (5.0 mol %) and the resulting reaction mixture was allowed to stir at -10°C for 24 hours; subsequently, 1 M aqueous NaOH, vinyl iodide **6** (1.3 equivalents), and $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$ (5.0 mol %, to accelerate Suzuki–Miyaura coupling) were added and the reaction mixture was stirred at room temperature for 22 hours, thus affording (–)-myxalamide A in 59% yield. The ^1H -, ^{13}C NMR, IR, and HRMS spectra, as well the optical rotation of our synthetic (–)-**1** were identical to those of natural (–)-**1**.

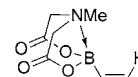
In summary, we have accomplished a protecting-group-free total synthesis of (–)-myxalamide A in six steps from N,O-acetal **10** (ten steps from commercially available (S)-2-methylbutanol). The characteristic features of the synthesis are: (i) a concise construction of the C9–C13 moiety using a vinylogous Mukaiyama aldol reaction; (ii) a one-pot Stille and Suzuki–Miyaura coupling reaction for connecting fragments **6** and **7** with (Z)-boronate **8**; and (iii) the first example of a natural product synthesis achieved by a research group other than that of Burke, wherein Burke's N-methyliminodiacetic acid (MIDA) boronates are employed. Our highly convergent synthetic strategy represents an efficient means for preparing a conjugated pentaene motif.

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