Total Synthesis of Myxalamide A

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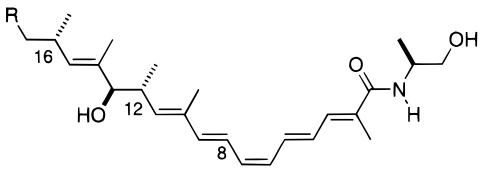
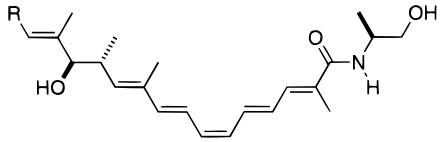
The polyene antibiotic myxalamide A (**1**) has been prepared by total synthesis. The synthesis illustrates a useful strategy for synthesis in which the high 1,2-stereocontrol achievable with the aldol reaction can be parlayed by other stereoselective processes so as to give compounds having two or more stereocenters with remote relationships. Application of the Evans asymmetric aldol reaction to aldehyde **13** gives the *β*-hydroxy imide **17**. Because the substrate is an α,*β*-unsaturated aldehyde, the alcohol is allylic. After suitable functional group manipulation, this allylic alcohol is subjected to enolate Claisen rearrangement (as propionate **22**) to give allylsulfide **23**, having three stereocenters with a 1,4,5-relationship. Further functional group manipulation and one-carbon homologation converts this intermediate into **26**, which is oxidized and subjected to Evans−Mislow allylsulfoxide rearrangement to obtain **27**, having three stereocenters with a 1,2,5-relationship. The synthesis of myxalamide A was completed by converting aldehyde **30** into dienyne **40**. Alkyne **40** was hydroborated with catechol borane, and the resulting *E*-vinylborane was subjected to Suzuki coupling with the *Z*-iodo triene **9** to provide myxalamide A (**1**).

As a result of a great amount of research in the 1970s and 1980s, the addition of preformed enolates to aldehydes to obtain α-substituted-*β*-hydroxy carbonyl compounds is a well-established synthetic procedure.[1] As part of our own work in this area, we showed that one can parlay the high 1,2-stereocontrol of the aldol reaction into relative control of more remote stereocenters. For example, by carrying out the aldol reaction on an α,*β*-unsaturated aldehyde and following with an Ireland ester enolate Claisen rearrangement, one can achieve 1,4- and 1,5-stereocontrol.[2] When the starting aldehyde is a *β*-alkylthio-α,*β*-unsaturated aldehyde, one can couple the stereocontrolled aldol reaction with an ester enolate Claisen rearrangement and an Evans−Mislow allylsulfoxide rearrangement to prepare compounds having three stereocenters with a 1,2,5-relationship.[3] In this article, we report a further application of this strategy for the total synthesis of myxalamide A (**1**).

Myxalamide A is one of a growing number of polyene antibiotics, which includes the phenalamides as well as the myxalamides. The four myxalamides were isolated from the gliding bacteria *Myxococcus xanthus*, and the most abundant of the group, myxalamide B (**3**), was found to be a potent electron-transport inhibitor and exhibited antibiotic and antifungal activity.[4] Myxalamide B was shown to inhibit NADH oxidation at complex I in beef heart submitochondrial particles with an IC_{50} of 170 pm/mg of protein. The phenalamides were isolated more recently from *Myxococcus stipiatus*.[5] Phenalamide A1 (stipiamide) (**2**) exhibits antifungal and antiviral properties as well as the ability to reverse P-glycoprotein-mediated multidrug resistance.[5,6]



1: R = Me **2**: R = CH_2Ph



3: R = *i*-Pr **4**: R = Et **5**: R = Me

The myxalamides and the phenalamides have attracted some synthetic attention. A partial synthesis of myxalamide D (**5**) was reported by Cox and Whiting in which an anti aldol reaction was used to set the C12/C13 stereochemistry.[7] In addition, a total synthesis of phenalamide A1 (**2**) was recently described.[6] In this approach, an asymmetric alkylation set the distal stereocenter (C16), while an asymmetric crotylboration created the anti stereorelationship at C12/C13. In

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(2) (a) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825. (b) Heathcock, C. H.; Jarvi, E. T.; Rosen, T. *Tetrahedron Lett.* **1984**, *25*, 243. (c) Heathcock, C. H.; Finkelstein, B. L. *J. Chem. Soc., Chem. Commun.* **1983**, 919. (d) Heathcock, C. H.; Finkelstein, B. L.; Aoki, T.; Poulter, C. D. *Science (Washington, D.C.)* **1985**, *229*, 862. (e) Heathcock, C. H.; Radel, P. A. *J. Org. Chem.* **1986**, *51*, 4323. (f) Heathcock, C. H.; Finklestein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1987**, *53*, 1922.

(3) Munchhof, M. J.; Heathcock, C. H. *J. Org. Chem.* **1994**, *59*, 7566.

(4) (a) Jansen, R.; Reifenstahl, G.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1983**, 1081. (b) Gerth, K.; Jansen, R.; Reifenstahl, G.; Höfle, G.; Irschik, H.; Kunze, B.; Reichenbach, H.; Thierbach. G. *J. Antibiot.* **1983**, *36*, 1150. (c) Jansen, R.; Sheldrick, W. S.; Höfle, G. *Liebigs Ann. Chem.* **1984**, 78.

(5) (a) Kim, Y. J.; Furihata, K.; Yamanaka, S.; Fudo, R.; Seto, H. *J. Antibiot.* **1991**, 553. (b) Trowitzsch-Kienast, W.; Forche, E.; Wray, V.; Riechenbach, H.; Junsmann, G.; Höfle, G. *Liebigs Ann. Chem.* **1992**, 659.

(6) (a) Andrus, M. B.; Lepore, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 2327. (b) Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 12159.

(7) (a) Cox, C. M.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. I* **1991**, 1901. (b) Cox, C. M.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. I*, **1991**, 1907. (c) Cox, C. M.; Whiting, D. A. *J. Chem. Soc., Perkin I*, **1991**, 660.

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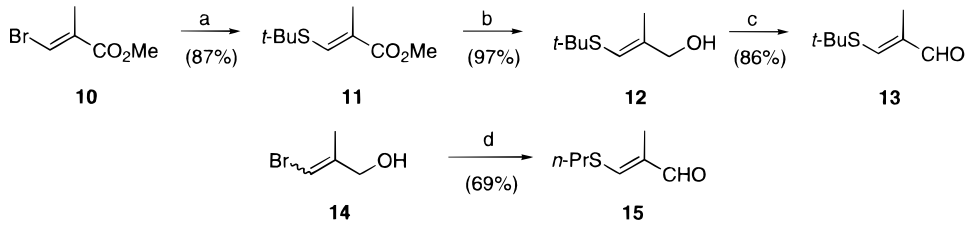
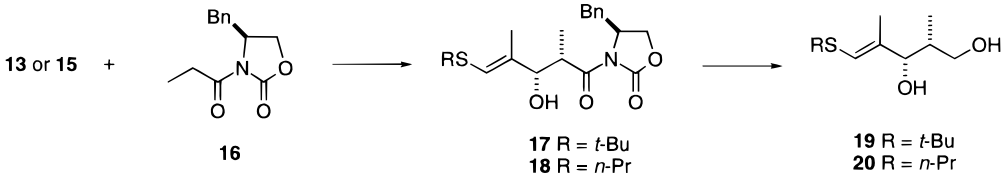
Scheme 1



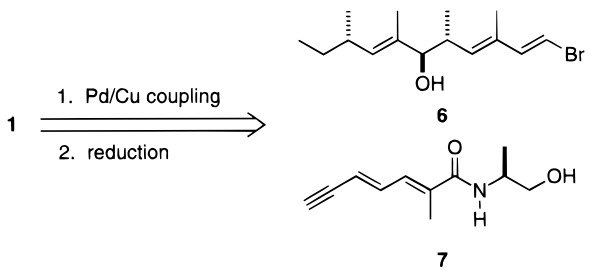
Conditions: (a) *t*-BuSH, NaH. (b) DIBALH, 0 °C. (c) MnO_2. (d) *i.* TPAP, NMO, CH_2Cl_2; *ii.* *n*-PrSH, Et_3N.



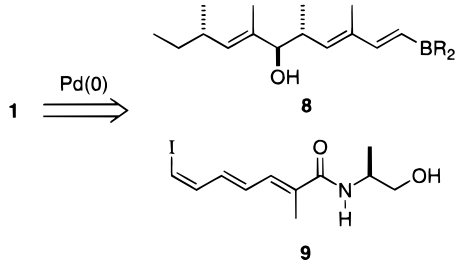
reaction conditions	results
Bu_2BOTf, Et_3N, -78 °C; pH 7 phosphate buffer workup	0% yield of **17** or **18**
Bu_2BOTf, Et_3N, -78 °C; $NaBO_3$, MeOH workup	56% yield of **18**
$TiCl_4$, DIPEA -78 °C; aq. $NaHCO_3$ workup	79% yield of **17**; 64% yield of **18**
Bu_2BOTf, Et_3N -78 °C; Amberlite™ IRA-743 resin	65% yield of **18**
i. Bu_2BOTf, Et_3N -78 °C; Amberlite™ IRA-743 resin *ii.* $LiBH_4$, ether/H_2O	90% of diol **19**; 89% yield of diol **20**

contrast to the other synthetic efforts, our approach to myxalamide A (**1**) would parlay a single asymmetric reaction early in the synthesis into the anti C12/C13 relationship as well as set the distal C16 stereocenter.

Retrosynthetically, formation of the pentaene late in the synthesis seemed desirable given the reported sensitivity of the natural product to light and oxygen.[4] Our early efforts utilized a Pd-mediated coupling of vinyl bromide **6** and dienyne **7** followed by partial reduction of the internal triple bond to install the sensitive pentaene system.



However, initial studies of this approach revealed that, while the coupling proceeded smoothly, the reduction of the alkyne was problematic.[8] Therefore, attention turned to the formation of the cis C6/C7 olefin prior to combining the two halves of the natural product. Given the recent report of Gênet and co-workers on the use of Suzuki couplings in aqueous media to produce stereodefined polyenes,[9] a Suzuki coupling appeared to be an excellent choice for the final step of the synthesis. Retrosynthetically, this led back to fragments **8** and **9**. Alcohol **8** would be prepared using the aldol−Claisen−Evans−Mislow strategy, while triene **9** was viewed as being accessible through a combination of metal-mediated couplings and Wittig reactions.



The initial syn 1,2-stereorelationship was to be set by an Evans asymmetric aldol reaction (Scheme 1).[10] Toward this end, aldehyde **13** was prepared from acrylate **10**[11] by treatment with *tert*-butyl thiolate to yield ester **11** followed by a reduction/oxidation sequence. Early attempts at the aldol reaction employed the conditions developed during the course of the ACRL Toxin IIIb synthesis for substrates containing readily oxidizable functional groups.[3] However, while this procedure had worked well for a less substituted aldehyde, only a complex mixture of products was isolated from the aldol reaction with aldehyde **13**. As a result, the less sterically encumbered aldehyde **15** was prepared,[12,13] but analogous results were obtained. Examination of the ^1H NMR spectra of the crude reaction mixtures from both aldol reactions revealed additional resonances in the alkyl region, thus suggesting that incomplete removal of dialkylboronates from the product aldols (**17** or **18**) at the conclusion of the reaction could be the culprit. Treatment of the crude reaction mixture with sodium perborate[14]

(8) For details of this approach, see: Mapp, A. K. Ph.D. Thesis, University of California, Berkeley, 1997.

(9) Genêt, J. P.; Linquist, A.; Blart, E.; Mouries, V.; Savignac, M. *Tetrahedron Lett.* **1995**, *36*, 1443.

(10) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83.

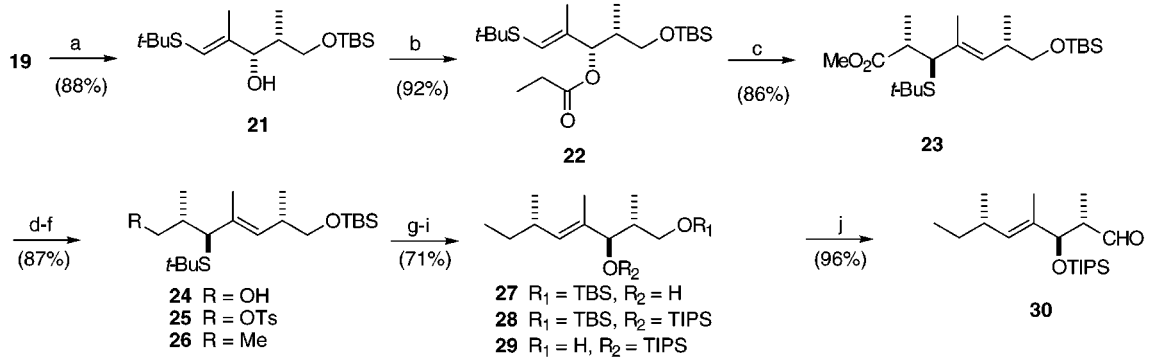
(11) (a) Ford, M. C.; Waters, W. A. *J. Chem. Soc.* **1951**, 1851. (b) Aberhart, D. J.; Tann, C.-H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 939.

(12) For preparation of bromide **14**, see: (a) Caubere, P. *Bull. Soc. Chim. Fr.* **1964**, *45*, 3584. (b) Brande, E. A.; Evans, E. A. *J. Chem. Soc.* **1955**, 3324. (c) Fischetti, W.; Mak, K. T.; Stakem, G.; Kim, J.-I.; Rheinhold, A. L.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 948.

(13) For oxidation of alcohol **14** using TPAP, see: Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(14) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

Scheme 2



conditions: (a) TBSCl, Et_3N, imid. (b) CH_3CH_2COCl, pyr. (c) *i.* LDA, THF -78 °C; *ii.* TBSCl, HMPA; *iii.* -78 °C → rt; *iv.* aq. K_2CO_3, THF; *v.* CH_2N_2. (d) $LiAlH_4$. (e) *p*-TsCl, Et_3N, DMAP. (f) $Me_2CuCNLi_2$, 0 °C. (g) *i. m*-CPBA; *ii.* $(MeO)_3P$, MeOH. (h) TIPSOTf, Et_3N. (i) 5% H_2SO_4, THF. (j) TPAP, NMO.

did remove the alkyl boronates, but the yields were variable due to oxidation of the vinyl sulfide moiety. However, the exchange resin IRA-743[15] cleanly and effectively removed all dialkyl boronates.[16,17] Because the product aldol was somewhat sensitive to silica gel chromatography, consistently higher yields were obtained when the crude reaction mixture was directly submitted to $LiBH_4$ reduction conditions.[18] This resulted in a 90% overall yield for the production of diol **19** from the two-step procedure. At this stage, the desired syn 1,2-stereorelationship had been obtained. Although either vinyl sulfide (*n*-propyl or *tert*-butyl) could be used in the subsequent chemistry, efforts focused on the *tert*-butyl sulfide due to its enhanced stability to varied reaction conditions.

In preparation for a Claisen rearrangement,[19] the primary alcohol of diol **19** was protected as the TBS ether and the secondary alcohol was then acylated using propionyl chloride to provide ester **22** (Scheme 2). Treatment of ester **22** with LDA followed by TBSCl produced the *E*-silyl ketene acetal, which upon warming to room temperature underwent the desired rearrangement. The crude silyl ester was hydrolyzed, and the resulting carboxylate was treated with diazomethane to yield methyl ester **23** with the appropriate 1,2- and 1,5-stereorelationships. In addition, the allylic thioether was positioned for the anticipated Evans−Mislow rearrangement to set the final 1,2-stereorelationship.

Prior to exploring the Evans−Mislow rearrangement, it was necessary to extend the carbon framework. Toward this end, methyl ester **23** was reduced to alcohol **24**, which was then treated with tosyl chloride. The displacement of the tosylate proved to be quite sensitive to reaction conditions. When methyllithium was added to a slurry of CuCN cooled to −78 °C followed by warming of the reaction mixture to room temperature and addition of tosylate **25**, 76% of the desired product was isolated along with significant amounts of alcohol **24**, presumably resulting from attack on the tosylate. After some experimentation with reaction conditions, it was found that when the cuprate was formed at a higher temperature (0 °C instead of −78 °C) the yield increased to 94% with little or no formation of alcohol **24**. The stage was then set for the Evans−Mislow rearrangement to produce the final anti 1,2-stereorelationship.[20] Oxidation of sulfide **26** with *m*-CPBA afforded a mixture of diastereomeric sulfoxides, which were then treated with the thiophile $P(OMe)_3$ to provide alcohol **27** in good overall yield. At this juncture, the necessary stereorelationships had been successfully created by the aldol−Claisen−Evans−Mislow strategy in 12 steps and 32% overall yield from acrylate **10**.

With the stereocenters in place, it only remained to elaborate the primary alcohol of **27** to an enyne. It seemed possible to install the enyne in one step using a phosphonate such as **31**. Related phosphonates have been used to produce disubstituted *E*-enynes in good yields and high selectivity.[21] In preparation for the transformation, the secondary alcohol in **27** was protected as a TIPS ether followed by selective cleavage of the TBS silyl ether under acidic conditions. Alcohol **29** was then oxidized using TPAP/NMO[22] in high yield. Aldehyde **30** was added to a solution of the lithium anion of phosphonate **31**,[23] and the reaction proceeded smoothly to produce a 1:1 mixture of *E*/*Z* enynes (Scheme 3). The use of a bulkier phosphonate (**32**) changed the selectivity slightly but in the undesired direction (1:1.5, *E*/*Z*).

Although formation of the enyne had not proven to be selective, it appeared likely that treatment of aldehyde **30** with a stabilized ylide or phosphonate would produce the trisubstituted C10−C11 bond with higher selectivity and subsequent functional group manipulations could

(15) Hicks, K. B.; Simpson, G. L.; Bradbury, A. G. W. *Carbohydr. Res.* **1986**, *147*, 39.

(16) Evans, D. A.; Ng, H. P.; Clark, S. J.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.

(17) Alternatively, reasonable yields of aldols **17** and **18** could be obtained by using $TiCl_4$ as the Lewis acid followed by a basic ($NaHCO_3$) workup, but careful chromatography of the crude product was necessary due to the presence of undesirable diastereomers. Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

(18) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Comm.* **1990**, *20*, 307.

(19) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Org. Chem.* **1976**, *41*, 986. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

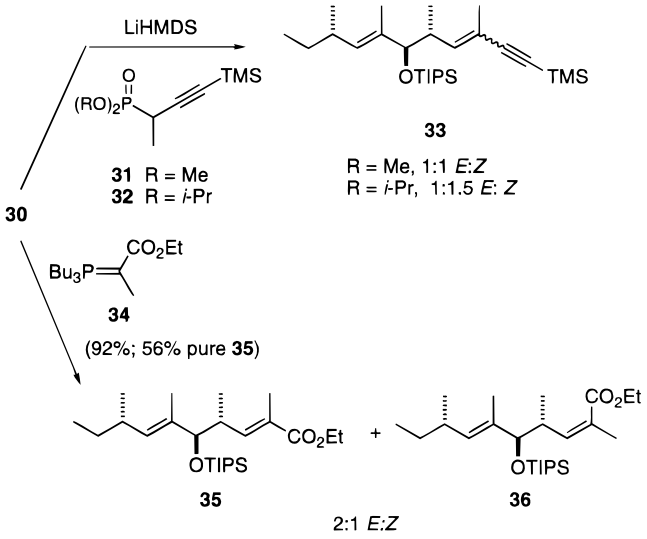
(20) (a) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100. (b) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956. (c) Evans, D. A.; Andrews, G. C. *J. Am. Chem. Soc.* **1972**, *94*, 3672.

(21) For example, see: (a) Nicolaou, K. C.; Veale, C. A.; Webber, S. E. *J. Am. Chem. Soc.* **1985**, *107*, 7515. (b) Gibson, A. W.; Humphrey, G. R.; Kennedy, D. J.; Wright, S. H. B. *Synthesis* **1991**, 414.

(22) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(23) Phosphonate **31** was prepared by heating trimethyl phosphite and 3-(trimethylsilyl)propynyl bromide followed by deprotonation with BuLi and subsequent treatment with MeI. Phosphonate **32** was prepared in analogous fashion starting with triisopropyl phosphite.

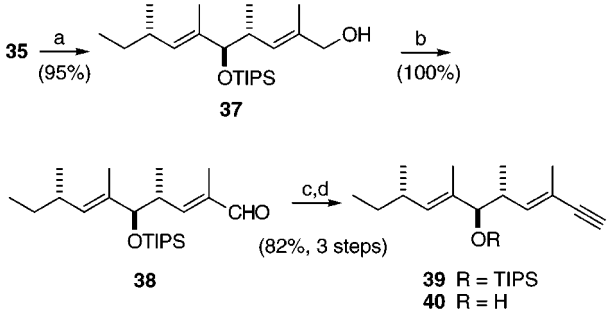
Scheme 3



then be used to install the triple bond. As anticipated, reaction of aldehyde **30** with tributylphosphonium ylide **34**[24] produced the unsaturated ester in an improved 2:1 (*E*/*Z*) ratio and good yield (56% of isomerically pure **35**). Similar results were obtained by using the anion of triethyl-2-phosphonopropionate. In an attempt to further increase selectivity, diisopropyl-2-phosphonopropionic acid ethyl ester was prepared following the procedure of Kishi[25] and the anion was added to aldehyde **30**. While the ratio did improve to 4:1 *E*/*Z*, the reaction was sluggish and proton transfer was a significant competing reaction. This is not surprising given the hindered nature of both the nucleophile and the electrophile. The unsaturated ester **35** was converted into enyne **39** by reduction with DIBALH to allylic alcohol **37**, oxidation to the aldehyde, and treatment with the Gilbert−Seyferth phosphonate.[26] Removal of the silyl protecting group was then achieved by treatment with TBAF in THF to yield **40** (Scheme 4).

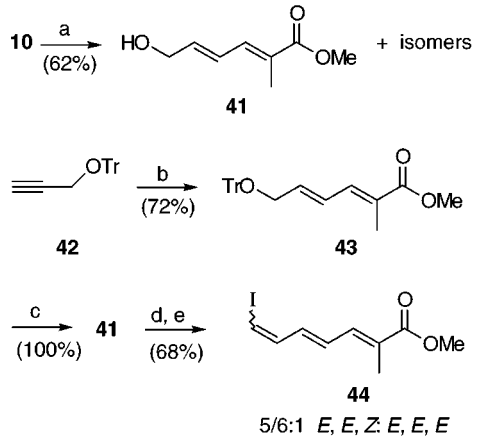
With enyne **40** in hand, attention turned to the synthesis of the requisite iodotriene **9**. Diene **41** appeared to be a good starting point for the synthesis, since oxidation of the allylic alcohol followed by a Wittig reaction would provide the desired cis vinyl iodide. Initially, we attempted to prepare diene **41** by a Heck reaction between allyl alcohol and bromide **10** as previously reported in the literature (Scheme 5);[27] however, we consistently isolated an inseparable mixture of isomers from the reaction. This was easily circumvented by hydroboration of propargyl ether **42**[28] followed by a Suzuki coupling with bromide **10** to produce the desired diene **43** as one stereoisomer. The trityl group was removed by treatment with Amberlyst-15. Oxidation of the allylic alcohol proceeded smoothly and the vinyl iodide was then installed by a Wittig reaction to provide **44** (5:1, E,E,Z/E,E,E) using the conditions of Stork.[29] While this was certainly an acceptable ratio, separation

Scheme 4



Conditions: (a) DIBALH. (b) TPAP, NMO. (c) $(MeO)_2P(O)CHN_2$, KO*t*-Bu. (d) TBAF.

Scheme 5



Conditions: (a) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, allyl alcohol. (b)*i.* catechol borane, *N, N*-diethylaniline *ii.* **10**,$Pd(OAc)_2$, TPPTS, *i*-Pr_2NH. (c) Amberlyst™-15. (d) Dess-Martin periodinane. (e) $(Ph_3P{=}CH_2I)I$, NaHMDS, HMPA.

of the isomers by a variety of purification methods (flash chromatography, HPLC, crystallization) proved difficult. For this reason, an alternate approach to iodotriene **9** was explored.

Our revised approach incorporated conversion of a cis vinyl stannane, readily available by reduction of the corresponding acetylenic stannane, to the vinyl iodide by treatment with iodine (Scheme 6). Silylation of 2-penten-4-yn-1-ol proceeded in a straightforward manner.[30] The alkyne was then deprotonated and treated with tributyltin chloride to furnish the alkynyl stannane. The crude product was treated with Cp_2ZrHCl followed by water[31] and then desilylated using TBAF to provide alcohol **47** in good overall yield.

Prior to installation of the trisubstituted olefin, allylic alcohol **47** was oxidized using MnO_2. Treatment with the anion of triethyl-2-phosphonopropionate provided the desired triene **48** in high yield. Following the procedure of Andrus,[6] the ester was hydrolyzed and the carboxylate was activated and treated with (*S*)-2-amino-1-propanol to produce amide **49** as one isomer. Upon treatment with iodine, tin−halogen exchange occurred to give a 2:1 mixture of isomers of triene **9**. This was unexpected but

(24) (a) Trippett, S.; Walker, D. M. *J. Am. Chem. Soc.* **1961**, *83*, 6. (b) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1987**, *52*, 2631.
(25) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
(26) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.
(27) Kao, L.-C.; Stakem, F. G.; Patel, B. A.; Heck, R. A. *J. Org. Chem.* **1982**, *47*, 1267.
(28) (a) Zeile, K.; Meyer, H. *Chem. Ber.* **1942**, *75*, 356. (b) Zhou, Z.-L.; Huang, Y.-Z.; Shi, L.-L.; Hu, J. *J. Org. Chem.* **1992**, *57*, 6598.
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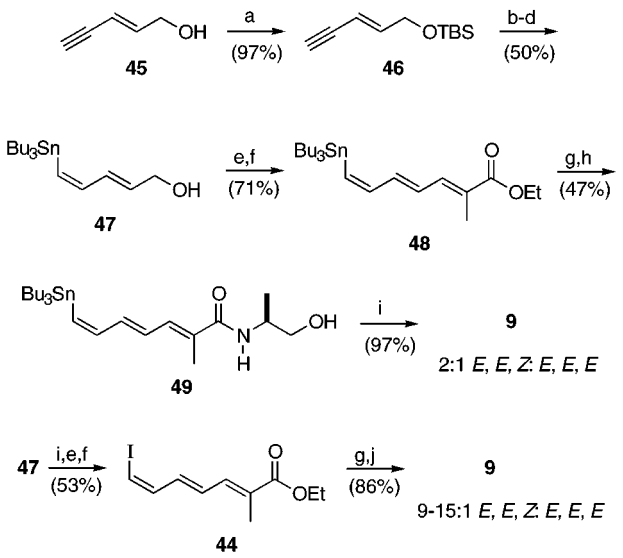
(31) Lipshutz, B. H.; Keil, R.; Barton, J. C. *Tetrahedron Lett.* **1992**, *33*, 5861.

Scheme 6



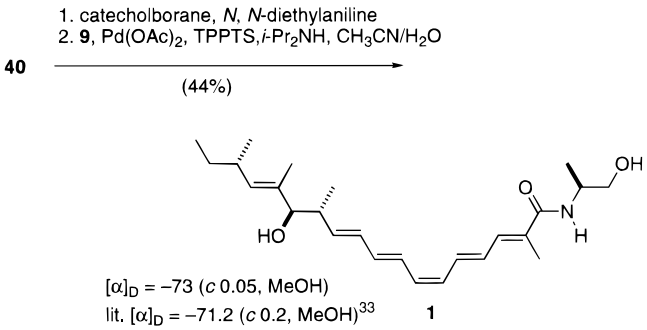
Conditions: (a) TBSCl, imid. (b) *i.* KHMDS *ii.* Bu_3SnCl. (c) *i.* Cp_2ZrHCl *ii.* H_3O^+. (d) TBAF. (e) MnO_2. (f) BuLi, triethyl-2-phosphonopropionate. (g) LiOH, *t*-BuOH, H_2O. (h) PyBroP, (*S*)-2-aminopropanol. (i) I_2. (j) pivaloyl chloride, Et_3N, (*S*)-2-amino-1-propanol.

in retrospect not surprising. If the mechanism of the reaction includes an intermediate with cationic character, the extended conjugation present in triene **49** could stabilize the intermediate long enough to allow isomerization. Thus, the reaction was repeated using ester **48** as a substrate, and indeed the isomeric ratio increased to 6:1. The course of the exchange reaction was monitored by ^1H NMR, and the results indicated that the isomerization occurred during the tin−halogen exchange as opposed to before or after the reaction, since the starting material remained as one isomer throughout the course of the reaction and the product ratio did not alter upon extended treatment with excess iodine. Furthermore, the treatment of diene **47** with iodine yielded a greater than 15:1 ratio of isomers as detectable by ^1H NMR.

A similar sequence of reactions was then used to prepare the target iodotriene. Diene **47** was transformed into iodotriene **44** by treatment with iodine, oxidation using MnO_2, and olefination. Hydrolysis of the ester then proceeded smoothly. The crude reaction mixture was filtered through a plug of silica gel, and the isolated material was treated with pivaloyl chloride followed by (*S*)-2-amino-1-propanol to yield the desired amide **9**. Although great care was taken to avoid light during handling of the compounds, some isomerization inevitably occurred. Therefore, the final iodotriene was generally isolated as a mixture of isomers (9:1 to 15:1), which was stored at low temperature and handled in the absence of light to prevent further isomerization.

In preparation for the final coupling reaction, enyne **40** was treated with 2 equiv of catecholborane[32] and, upon

Scheme 7



completion of the hydroboration, combined with iodotriene **9** and catalytic palladium acetate. After 6 h at room temperature, the reaction appeared to be complete. Analysis of the crude material by ^1H NMR spectroscopy revealed that it was a mixture of myxalamide A along with the all-trans isomer and triene **9**. There was some concern that the separation of myxalamide A from its all-trans isomer would be difficult given the inability of Andrus and co-workers to separate phenalamide A1 (**2**) from its all-trans isomer.[6] However, after flash chromatography on silica gel, the all-trans isomer of **1** had been removed, and further purification by HPLC removed the remaining impurities to yield myxalamide A in 44% yield for the two steps (hydroboration and coupling). The synthetic myxalamide A corresponded spectroscopically to the natural material (^1H, ^{13}C, IR, optical rotation, HRMS) (Scheme 7).[33]

In conclusion, the total synthesis of myxalamide A was accomplished in 22 steps (longest linear sequence) and 4.9% overall yield from bromide **10**. The completion of the synthesis not only expanded the utility of the aldol−Claisen−Evans−Mislow strategy but also emphasized the usefulness of the Suzuki coupling for the preparation of polyene-containing natural products. Given these results, the synthetic strategy would be useful for the preparation of other members of the polyene natural product family as well as related diastereoisomers for biological evaluation.

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Supporting Information Available: Full experimental details (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(32) Suseela, Y.; Prasad, A. S. B.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* **1990**, 446.

(33) One resonance in the ^{13}C NMR spectrum of synthetic **1** did not match that reported in the original isolation paper (ref 4a). However, this discrepancy proved to be the result of a typographical error in the isolation paper as confirmed by Dr. R. Jansen by personal communication.