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Total Synthesis of Amphirionin-4

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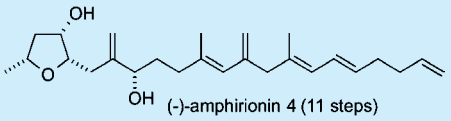
Supporting Information

ABSTRACT: The first total synthesis of amphirionin-4 has been achieved using a combination of cross-coupling strategies to access the polyene side chain and a chlorohydrin-based approach to construct the tetrahydrofuranol core. The remote C9-stereocenter was introduced through a Nozaki–Hiyama–Kishi coupling that proceeded with remote stereoinduction.



Amphidinium species of marine dinoflagellates have proven to be a rich source of structurally diverse polyketides,[1] many of which are characterized by cyclic ethers of various ring sizes and potent cytotoxic activity (e.g., amphidinolide B[2] and amphidinin A[3]). Recently, Tsuda and co-workers isolated a number of new cyclic ether-containing polyketides (e.g., **1**–**3**, Figure 1) from the KCA09051 strain of *Amphidinium* collected off the coast of Iriomote Island in the Okinawa archipelago.[4] Of particular interest is amphirionin-4 (**1**),[4a] which demonstrates selective and potent proliferation activity on murine bone marrow stromal ST-2 cells (+950% growth rate at 0.1 ng/mL).

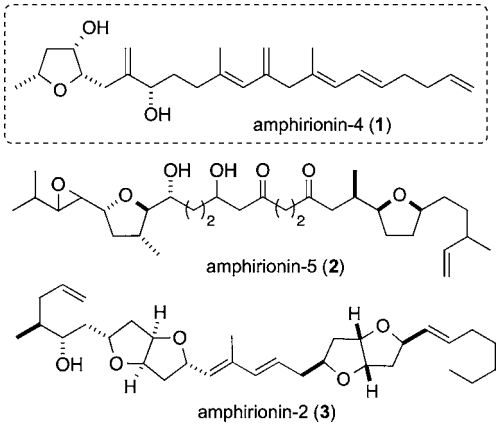
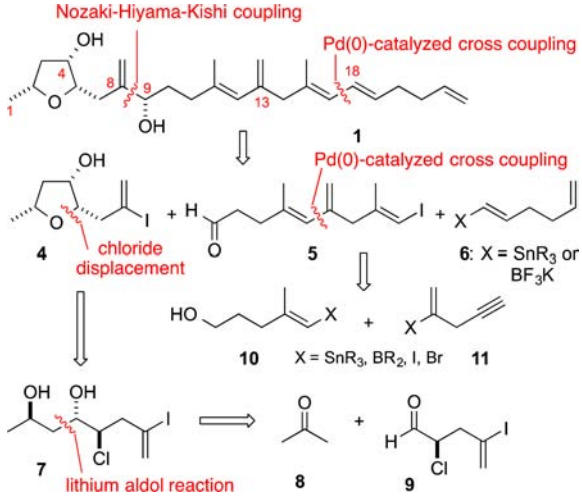


Figure 1. Structures of amphirionin-2, -4, and -5, isolated from a strain of *Amphidinium* KCA09051.

These cells promote the development of lymphocytes from bone marrow cells,[5] and consequently, amphirionin-4 (**1**) may have utility in enhancing immune response to disease and bone regeneration.[4a,6] Structurally, amphirionin-4 comprises an all-*syn*-tetrahydrofuranol core with both a remote allylic alcohol at C9 and skipped tetraene motif on the heptadecyl side chain. Considering its unique structure and potentially useful biological activity, we were interested in extending our chlorohydrin-based strategies for tetrahydrofuranol synthesis[7] to the preparation of this unusual *Amphidinium* polyketide.

With an ultimate goal of developing a modular synthesis of amphirionin-4 (**1**) that would provide access to analogues for medicinal chemistry purposes, we envisioned three key retrosynthetic disconnections (Scheme 1). Specifically, the

Scheme 1. Retrosynthetic Analysis for Amphirionin-4 (1)



remote allylic alcohol at C9 would be introduced through a Nozaki–Hiyama–Kishi (NHK)[8] reaction involving the vinyl iodide **4** and the aldehyde **5**, while assembling the polyene side chain would rely on iterative Pd-catalyzed cross-coupling reactions. Although we were apprehensive about the stereochemical outcome of the proposed NHK reaction, ultimately the undesired epimer could be inverted through a Mitsunobu reaction[9] or oxidation/reduction sequence if necessary. Synthesis of the tetrahydrofuranol **4** would then involve methodology previously developed by us[7] that exploits readily available and enantiomerically enriched α-chloroaldehydes[10] as building blocks for the stereoselective synthesis of heterocyclic natural products.[7] Thus, we anticipated that a lithium aldol reaction between a suitably functionalized α-chloroaldehyde (e.g., **9**) and acetone, followed by a diastereoselective ketone reduc-

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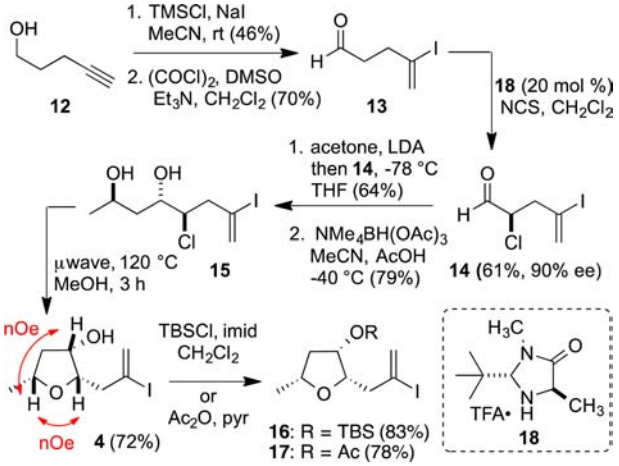
tion[11] and cyclization, would secure the all-*syn* tetrahydrofuranol **4** in an expedient manner.[7d]

The synthesis of the tetrahydrofuranol **4** is described in Scheme 2 and began with hydroiodination of the alkyne

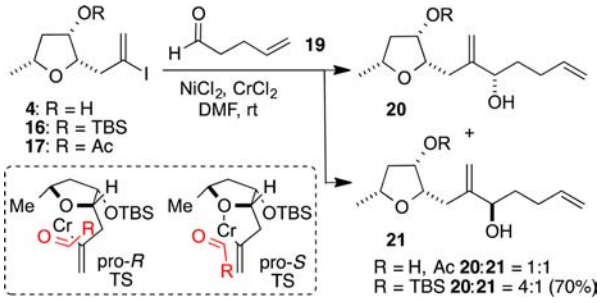
Scheme 2. Synthesis of Tetrahydrofuranol 4



function in 4-pentyn-1-ol (**12**)[12] followed by a Swern oxidation[13] to give aldehyde **13**. Notably, the modest yield for the hydroiodination of **12** (46%) reflects the necessary stoppage of this reaction at ∼60% conversion, which was required to prevent the generation of an inseparable byproduct produced after prolonged reaction times (yield >70% yield based on unreacted **12**). A subsequent asymmetric *α*-chlorination of **13** using MacMillan's catalyst **18**[10c] and NCS[14] gave the *α*-chloroaldehyde **14** in good enantiomeric excess (90% ee). We were pleased to find that reaction of this later material with the lithium enolate generated from acetone afforded the desired *β*-ketochlorohydrin (not shown) in good yield and diastereoselectivity (dr = 7:1), and a subsequent 1,3-*anti* selective reduction[11] of the resulting *β*-ketochlorohydrin provided diol **15**. This later material cyclized smoothly to the tetrahydrofuranol **4** when heated (120 °C) in MeOH in a microwave reactor.[7d] The relative stereochemistry of **4** was assigned by analysis of correlations in 1D NOESY spectra, while synthesis of the corresponding (*R*)- and (*S*)-MTPA esters and subsequent analysis using the modified Mosher's method[15] confirmed the absolute stereochemistry of **4** as shown.[16]

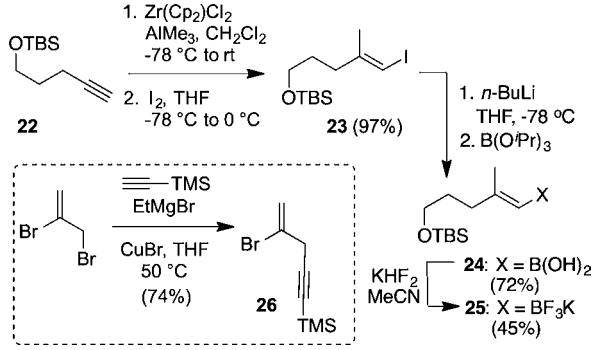
Having secured the correctly configured tetrahydrofuranol core of amphirionin-4, it was of interest to explore the planned NHK reaction. Toward this goal, we evaluated the reaction of vinyl iodide **4** with 4-pentenal (**19**) and were disappointed to find this reaction produced a 1:1 mixture of diastereomeric alcohols **20** and **21** as did the reaction of the corresponding acetate **17** (Scheme 3). Considering the competing coordination sites in **4** and **17** with the putative vinyl chromium intermediate, the C4 alcohol in **4** was also protected as a TBS ether to preclude coordination at this position and we were delighted to find that the diastereoselectivity of the subsequent NHK reaction improved to ∼4:1 in favor of the desired stereoisomer **20**. This unusual example of 1,4-stereoinduction may involve coordination of the vinyl chromium intermediate to the tetrahydrofuran oxygen,[17] with subsequent addition through the pro-*S* TS (see inset) to minimize steric interactions (cf. pro-*R* TS).

Scheme 3. 1,4-Stereoinduction in the NHK Reaction of Vinyl Iodide 4



Having established a means to control the stereochemical outcome of the key NHK coupling, we focused on preparing the requisite pentadecatetraenal **5**. Toward this goal, the vinyl bromide **26** was accessed from 2,3-dibromopropene following a copper(I) catalyzed reaction with the Grignard reagent derived from TMS-acetylene (Scheme 4).[18] A zirconium catalyzed

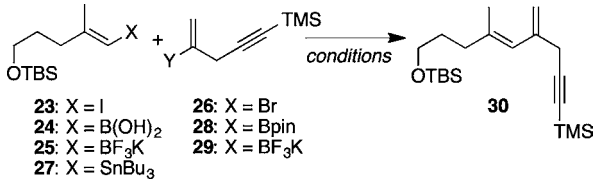
Scheme 4. Synthesis of the Vinyl Halides 23 and 26



carboalumination[19] of the alkyne **22** followed by reaction with I_2 afforded the vinyl iodide **24** in excellent yield. As described below, it was expected that the cross-coupling of the vinyl halides **23** and **26** could be effected following conversion of one of these compounds into the corresponding vinyl boronic acid (e.g., **23** → **24**).

Table 1 summarizes our efforts to effect a cross-coupling reaction between derivatives of the vinyl halides **23** and **26**,

Table 1. Cross-coupling Reactions to Access Diene 30



entry	reactants	temp	catalyst	additive	yield
1	**23**+**28**	50 °C	$Pd(PPh_3)_4$	$CsCO_3$[a]	∼10%
2	**23**+**28**	50 °C	$Pd(PPh_3)_4$	$Ba(OH)_2$[a]	<5%
3	**23**+**28**	50 °C	Pd(dtbpf)Cl_2	$Ba(OH)_2$[a]	<5%
4	**23**+**29**	50 °C	$Pd(PPh_3)_4$	$CsCO_3$[a]	<5%
5	**27**+**26**	50 °C	$Pd(PPh_3)_4$	CuI, CsF[b]	<5%
6	**24**+**26**	55 °C	$Pd(PPh_3)_4$	$CsCO_3$[c]	<5%
7	**25**+**26**	55 °C	$Pd(PPh_3)_4$	$CsCO_3$[a]	68%

[a]A 1:1 mixture of THF−H_2O was used as solvent. [b]DMF was used as solvent. [c]EtOH was used as solvent.

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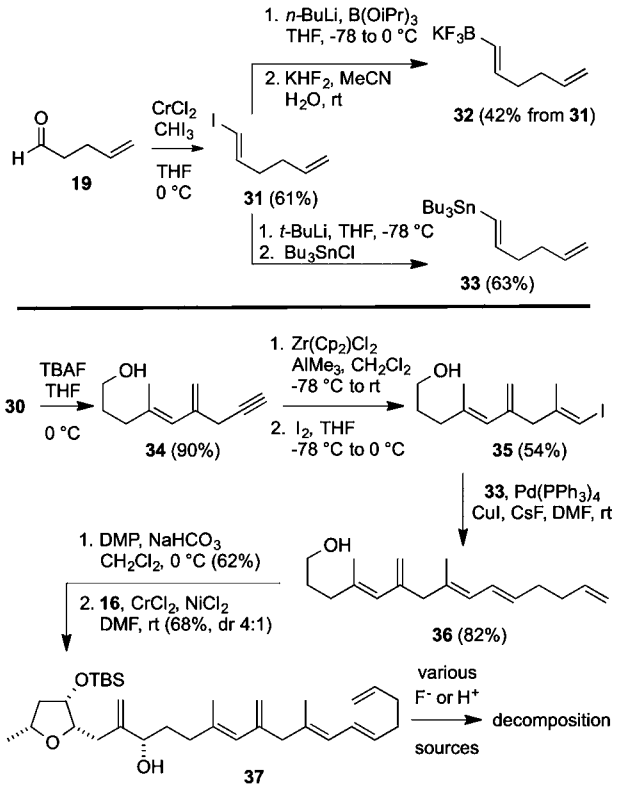
which proved challenging. As summarized in entries 1−4, coupling of the vinyl iodide **23** with either the Bpin or BF_3K salts derived from **26**[20,21] using various combinations of palladium catalyst, base, and solvent only afforded trace amounts of the desired diene **30** accompanied by degradation products derived from the vinyl boron species. Likewise, the cross-coupling of vinyl stannane **27** (entry 5) or boronic acid **24** (entry 6) with the vinyl bromide **26** were equally unsuccessful and only products of proteo-destannylation or deborylation were observed. Considering these results, we explored use of the corresponding vinyl trifluoroborate **25**, which reportedly offers improved stability in Suzuki−Miyaura couplings.[21] Gratifyingly, as indicated in entry 7, cross-coupling of the vinyl trifluoroborate **25** with the vinyl bromide **26** using Molander's conditions[21] afforded the desired diene **30** cleanly and in good yield (68%) on multigram scale.

Completion of the synthesis of the pentadecatetraenal is described in Scheme 5. Conversion of 4-pentenal into the *trans*-vinyl trifluoroborate **32** or tributylstannane **33** involved a Takai reaction[22] followed by lithium−iodide exchange and treatment with triisopropylborate followed by potassium hydrogenfluoride[21] or tributyl tin chloride. Sequential carboalumination of alcohol **34** and reaction with I_2[23] gave the vinyl iodide **35** in good overall yield. Our initial efforts to couple this sensitive vinyl iodide with vinyl trifluoroborate **32** were unsuccessful due to isomerization of the diene system in the former material at elevated temperatures in basic solution. However, a Stille coupling[24] between the vinyl stannane **33** and vinyl iodide **35** gave access to the polyene **36** in good yield. Subsequent oxidation[25] and NHK coupling with tetrahydrofuran **16** afforded the TBS-protected amphirionin-4 **37** in good yield and expected diastereoselectivity (*vide supra*). Unfortunately, all attempts to remove the TBS protecting group from this material resulted in decomposition. Considering the instability of the skipped tetraene function in **37**, we elected to modify the synthetic plan and thus incorporate the sensitive tetraene at the final stage in the synthesis.

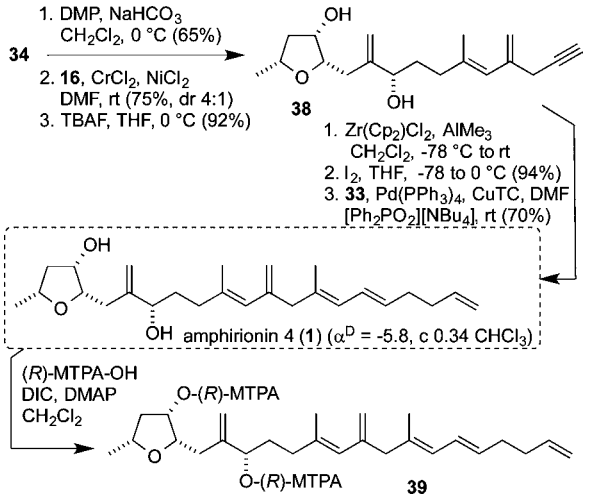
Scheme 5. Synthesis of TBS-Protected Amphirionin-4 37



A modified and ultimately successful synthetic approach to amphirionin-4 (**1**) is depicted in Scheme 6. Oxidation of the alcohol function in **34** followed by an NHK coupling and deprotection afforded the tetrahydrofuranol **38** cleanly and in excellent overall yield. The alkyne was subsequently converted into the requisite vinyl iodide following the sequence of reactions described above for the preparation of the related vinyl iodide **35** (Scheme 5). Disappointingly, efforts to effect the subsequent Stille cross-coupling with vinyl stannane **33** were unsuccessful using several standard reaction conditions including those that had provided the diene **30** (Table 1, entry 7) and resulted only in intractable mixtures of products. However, we were delighted to find that Fürstner's conditions,[26] which are ideal for sensitive substrates, proved effective and yielded access to amphirionin-4 (**1**) in excellent yield over these final two steps. The ^1H and ^{13}C NMR spectra recorded on synthetic amphirionin-4 were in agreement with that reported for the natural product;[4a] however, the specific rotation (−5.8, c 0.34, $CHCl_3$) differed in sign from that of natural amphirionin-4 (+6, *c* 0.29, $CHCl_3$).[4a] Considering that the absolute stereochemistry for **1** was originally assigned by analysis of bis(*R*)- and bis(*S*)-MTPA esters using the modified Mosher's method,[15] we also converted our synthetic amphirionin-4 into the corresponding bis(*R*)-MTPA ester **39**. The spectral data recorded on this derivative were in complete agreement with those reported by Tsuda[4a] for the bis(*R*)-MTPA ester derived from natural amphirionin-4 and differed significantly from the data reported for the corresponding bis(*S*)-MTPA ester of **1**.[4a] Considering these facts, the difference in specific rotation of synthetic and natural amphirionin-4 can then only result from its small absolute value and the consequent difficulty in accurately measuring specific rotation with small sample sizes.

In summary, we have completed the first total synthesis of amphirionin-4 through a linear 11-step sequence and confirmed both the relative and absolute stereochemistry of this unique

Scheme 6. Completion of the Synthesis of Amphirionin-4 (1)



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Amphidinium polyketide. The ultimately successful synthetic route highlights the efficiency of our chlorohydrin-based approach to access tetrahydrofuranols and relied on an unusual example of 1,4-stereoinduction to establish the correctly configured C9 allylic alcohol. Further investigation of remote stereoinduction of this kind for the purpose of analogue synthesis and potentially as a general method for the substrate-controlled synthesis of other tetrahydrofuran-containing natural products is currently being explored in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analysis data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01844.

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Notes

The authors declare no competing financial interest.

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