

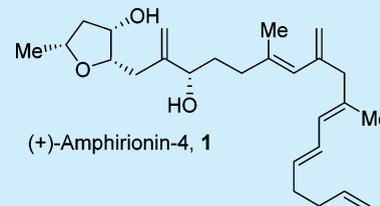
Enantioselective Total Synthesis of (+)-Amphirionin-4

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S Supporting Information

ABSTRACT: An enantioselective total synthesis of (+)-amphirionin-4 has been accomplished in a convergent manner. The synthesis features an efficient enzymatic lipase resolution to access the tetrahydrofuranol core in optically active form. The functionalized tetrahydrofuran derivative was synthesized via an oxocarbenium ion-mediated highly diastereoselective *syn*-allylation reaction. The polyene side chain was synthesized using Stille coupling reactions. Nozaki–Hiyama–Kishi coupling was utilized to construct the C-8 stereocenter and complete the synthesis of (+)-amphirionin-4.



Marine dinoflagellates of the genus *Amphidinium* species are rich sources of bioactive polyketide-like natural products with intriguing biological properties.^{1,2} Recently, Tsuda and co-workers isolated a number of polyketides, amphirionins-2, -4, and -5 from the dinoflagellate *Amphidinium* species.^{3–5} Among these, the linear polyketide (+)-amphirionin-4 (**1**, Figure 1) was isolated from the *Amphidinium* KCA09051 strain in the benthic sea sand collected off the Iriomote Island. This compound exhibited exceptionally potent proliferation-promoting activity (95% promotion) on murine bone marrow stromal ST-2 cells at 0.1 ng/mL concentration. Interestingly, it did not show

proliferation promotion when administered to MC3T3-E1 and NIH3TC cells.⁴

The structure of (+)-amphirionin-4 was elucidated by Tsuda and co-workers using extensive NMR analysis and the absolute configuration of the C4 and C8 hydroxyl groups was determined by Mosher ester analysis.⁴ Recently, Britton and co-workers have reported the first synthesis of amphirionin-4.⁶ However, the specific rotation of the synthetic compound was opposite to that reported for natural amphirionin-4.^{4,6} Considering the extreme proliferation-promoting activity of (+)-amphirionin-4 in ST-2 cells, its structural features, and its potential medicinal application, we sought to develop a convergent and concise enantioselective synthesis of (+)-amphirionin-4. Herein, we now report a route that proceeds in nine linear steps, starting from a readily available racemic butyrolactone.

Our retrosynthesis of (+)-amphirionin-4 is shown in Figure 1. We planned to utilize a Nozaki–Hiyama–Kishi (NHK)^{7,8} reaction similar to that reported by Britton and co-workers⁶ to assemble amphirionin-4 from vinyl iodide **2** and polyene aldehyde **3** at a late stage in the synthesis. The functionalized tetrahydrofuran ring **2** would be constructed from optically active γ -lactone **4** via a *cis*-selective allylation of the corresponding oxocarbenium ion derived from lactone **4**. Optically active lactone **4** would be readily synthesized via acid-catalyzed condensation of pyruvic acid and acetaldehyde, followed by hydrogenation and lipase-catalyzed optical resolution of racemic lactone. This will provide rapid access to both enantiomers for structure–activity relationship studies of amphirionin-4. The polyene side chain **3** would be constructed by Julia–Kocienski olefination of the aldehyde derived from allylic alcohol **5**.⁹ The requisite aldehyde precursor would be synthesized by iterative Stille cross-coupling reactions with appropriately protected vinyl iodide **6** and tributylstannanes **7** and **8**.

Our synthesis of functionalized tetrahydrofuran derivatives is shown in Scheme 1. Racemic lactone **4** was synthesized on gram scale by acid-catalyzed condensation of pyruvic acid **9** and

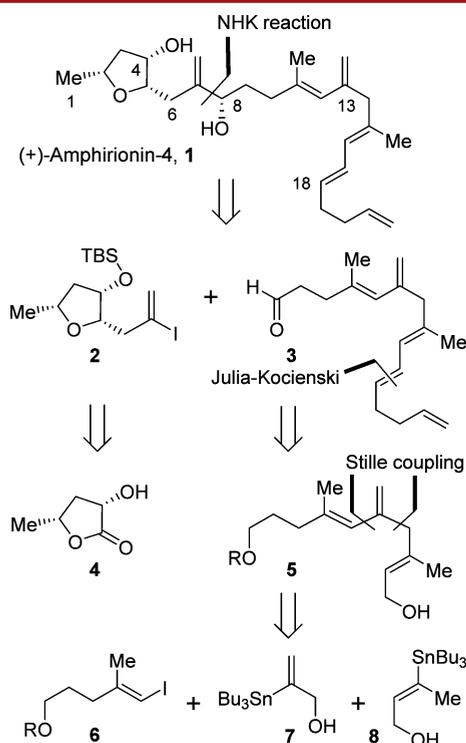
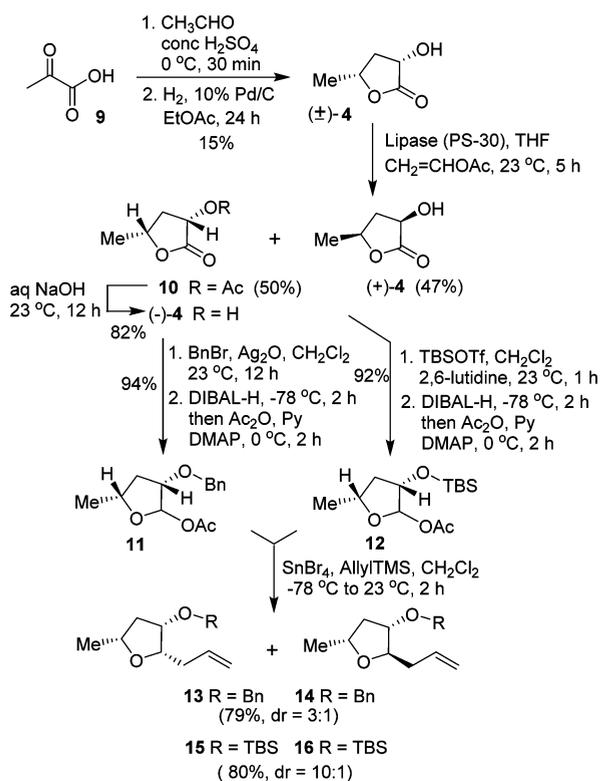


Figure 1. Retrosynthetic analysis of (+)-amphirionin-4.

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Scheme 1. Synthesis of Substituted Tetrahydrofurans



acetaldehyde, followed by hydrogenation of the resulting unsaturated lactone over 10% Pd–C in EtOAc.^{10,11} Racemic lactone 4 was then subjected to enzymatic resolution utilizing PS-30 in vinyl acetate at 23 °C for 5 h.^{12,13} While the racemic lactone was obtained in low yield, it can be readily prepared in gram quantity and the current resolution protocol provided optically active alcohol (+)-4 and acetate derivative 10 in 47% and 50% yields, respectively, with high optical purity. Acetate 10 was saponified with aqueous sodium hydroxide in methanol to provide optically active alcohol (–)-4 in 82% yield.¹⁴ The depicted absolute stereochemistry of lactones (+)-4 and (–)-4 was assigned based upon Kazlauskas' model¹⁵ and comparison with the reported specific rotations.¹⁶ Optically active lactone (–)-4 was protected as the benzyl ether (>90% ee by chiral HPLC analysis of this benzyl derivative). Dibal-H reduction of the protected lactone provided the corresponding lactol, which was treated with acetic anhydride and pyridine in the presence of DMAP to provide acetate 11 in excellent yield. The hydroxyl group of lactone (–)-4 was also protected as the TBS ether. Dibal-H reduction of that lactone provided a mixture of lactols, which were converted to the acetate 12. The reaction of acetate 11, bearing a C2 benzyl ether, with allyltrimethylsilane in the presence of SnBr₄ in CH₂Cl₂ at –78 to 23 °C provided the allyl derivatives 13 and 14 as a 3:1 mixture of diastereomers by ¹H NMR analysis. The corresponding reaction of acetate 12 containing a C2 silyl ether with allyltrimethylsilane under similar conditions furnished allylation products 15 and 16 in 80% yield. However, the diastereomeric ratio of 15 and 16 improved to 10:1 (by ¹H NMR analysis). The relative stereochemistry of alkenes 13, 14, and 15 was assigned by ¹H NMR NOESY analysis.

The observed *cis*-diastereoselectivity is consistent with a C2-benzyloxy substituted tetrahydrofuran substrate examined by Woerpel and co-workers.¹⁷ It appears that substituents at the C4-position, as in acetate 11, did not influence overall *cis*-

diastereoselectivity. The observed stereochemical outcome can be rationalized using similar steric and electronic arguments to those proposed by Woerpel and co-workers.¹⁷ Presumably, the oxocarbenium ion intermediate 17 is preferred over 18 due to pseudoequatorial orientation of the C-2 alkoxy group (Figure 2).

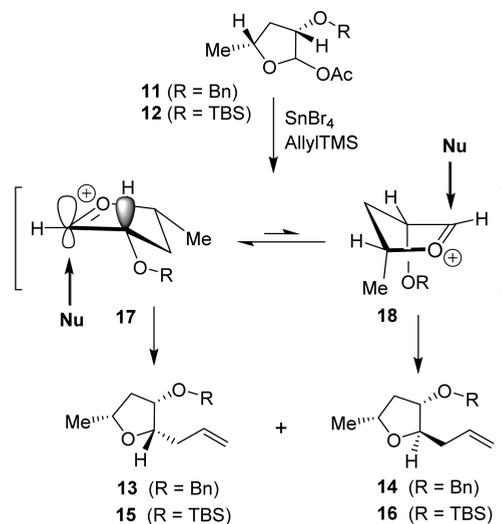
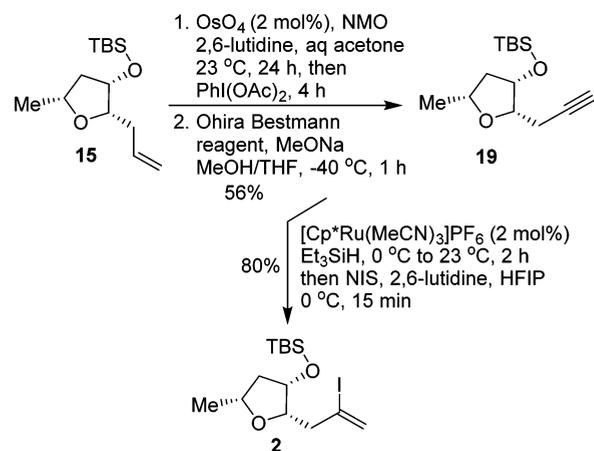


Figure 2. Stereochemical analysis for *cis*-allylation.

The σC–H orbital at C2 maximizes electron donation to the adjacent vacant orbital of the oxocarbenium ion. The bulky C2 silyloxy group further enhances the pseudoequatorial orientation, and therefore the overall *cis*-selectivity.

The desired allyl derivative 15 was converted to the corresponding vinyl iodide as shown in Scheme 2. Oxidative

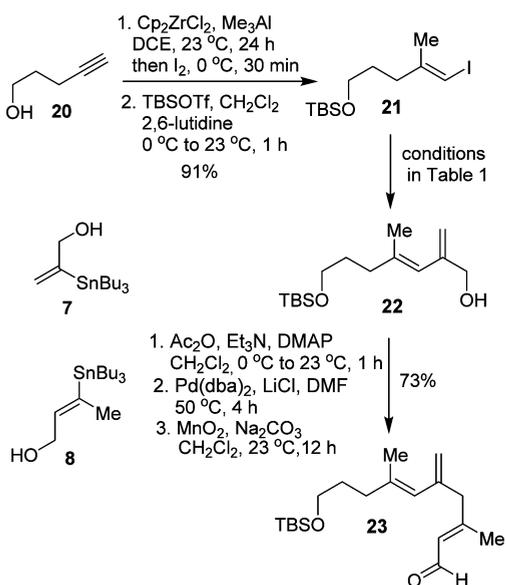
Scheme 2. Synthesis of Vinyl Iodide 2



cleavage of alkyne 15 using PhI(OAc)₂, NMO, and catalytic OsO₄ provided the corresponding aldehyde in 80% yield.¹⁸ Alkynylation of the resulting aldehyde with the Ohira–Bestmann reagent^{19,20} and MeONa in a mixture of MeOH and THF gave alkyne 19 in 70% yield. Hydrosilylation of the resulting alkyne 19 using Trost's procedure²¹ with ([Cp^{*}Ru(MeCN)₃]PF₆) and triethylsilane followed by iododesilylation²² with NIS and 2,6-lutidine in hexafluoroisopropanol (HFIP) furnished vinyl iodide 2 in 80% yield.

Synthesis of the amphirionin-4 side chain is shown in Scheme 3. A zirconium-catalyzed carboalumination of 4-pentyne-1-ol 20 followed by reaction with iodine provided the corresponding

Scheme 3. Synthesis of Aldehyde 23



vinyl iodide. TBS protection of the alcohol provided the vinyl iodide **21** in 91% yield.²³ We then investigated the Stille coupling of vinyl iodide **21** with the known²⁴ tributylstannane **7** under a variety of conditions. The results are summarized in Table 1.

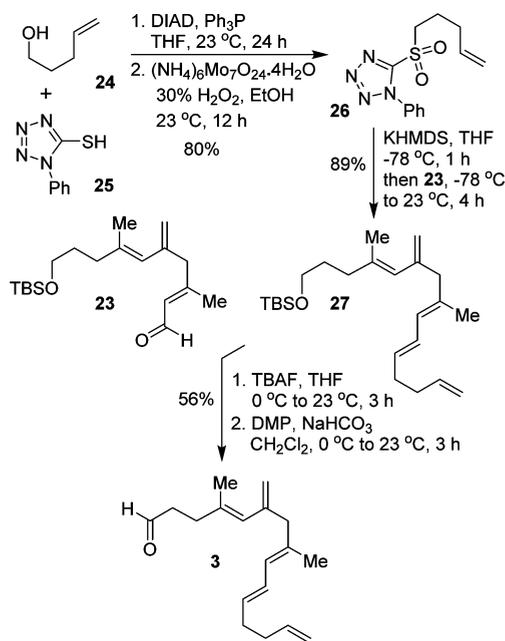
Table 1. Stille-Coupling Conditions to Access Diene 22

entry	catalyst and additive	mol (%)	solvent	time (h)	yield (%)
1	$\text{Pd}(\text{MeCN})_2\text{Cl}_2$	10	DMF	24	30
2	$\text{Pd}(\text{MeCN})_2\text{Cl}_2$	20	DMF	24	30
3	$\text{Pd}(\text{MeCN})_2\text{Cl}_2$	30	DMF	96	28
4	$\text{Pd}_2(\text{dba})_3$	30	DIPEA, NMP	24	25
5	$\text{Pd}(\text{PPh}_3)_4$, CuCl, LiCl	10	DMSO	2	90

Reactions with $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ (10 or 20 mol %) in DMF at 23 °C resulted in 30% yield (entries 1 and 2). Catalyst loading was then increased to 30 mol % and reaction temperature was increased to 50 °C for 96 h. This also resulted in low yield of coupling product **22** (entry 3). Coupling with $\text{Pd}_2(\text{dba})_3$ (30 mol %) at 23 °C in a mixture of DIPEA/NMP again resulted in low yield of product (25%, entry 4). We believe that these low yields can be attributed to the disubstituted vinylstannane due to a slow transmetalation step and a competing *cis* substitution.²⁵ In an attempt to enhance the transmetalation step, we decided to use cuprous chloride as a promoter in the Stille-coupling reactions as described by Corey and co-workers.²⁵ Modified Stille-coupling of vinyl iodide **21** and tributylstannane **7** in the presence of CuCl and LiCl at 23 °C for 2 h furnished the desired diene **22** in excellent (90%) yield. Acetylation of diene **22** furnished the corresponding allyl acetate in 95% yield. Stille-coupling²⁶ of the resulting allyl acetate with the known²⁷ hydroxystannane **8** using $\text{Pd}(\text{dba})_2$ and LiCl in DMF at 50 °C afforded the coupling product in 96% yield. MnO_2 oxidation of the resulting allylic alcohol furnished the aldehyde **23** in 80% yield.

Our synthesis of the polyene derivative **3** is shown in Scheme 4. Sulfone **26** was prepared in good yield by the reaction of 4-

Scheme 4. Synthesis of Aldehyde 3

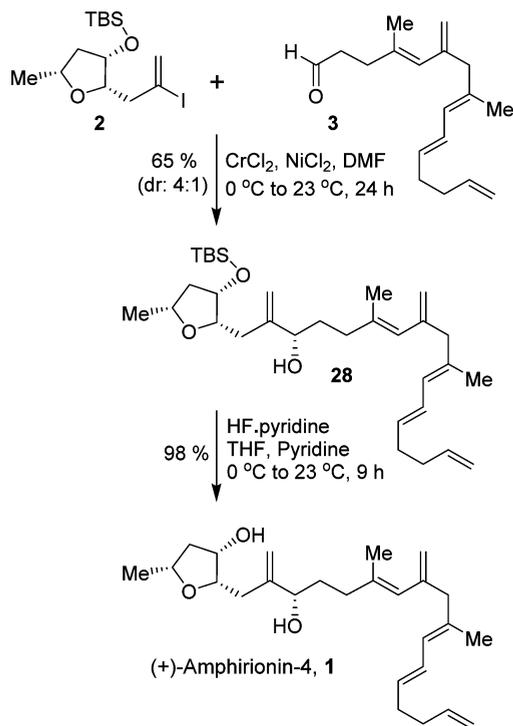


penten-1-ol **24** with 1-phenyl-1H-tetrazole-5-thiol **25**, followed by oxidation using catalytic ammonium molybdate and hydrogen peroxide. Julia–Kocienski olefination⁹ between aldehyde **23** and sulfone **26** gave the polyene **27** in 89% yield and only the *E*-isomer was formed (by ^1H NMR analysis). Removal of the TBS group followed by DMP oxidation of the resulting alcohol provided aldehyde **3** in good yield.

The final synthesis of (+)-amphirionin-4 is outlined in Scheme 5. NHK coupling⁶ between aldehyde **3** and vinyl iodide **2** was carried out in DMF at 0 °C to 23 °C for 24 h. This provided TBS-protected amphirionin-4 **28** as the major diastereomer (4:1) in 65% yield. The diastereomers were separated by silica gel chromatography. Deprotection of the TBS group using 70% HF, 30% pyridine in the presence of excess pyridine furnished synthetic (+)-amphirionin-4 (**1**) in 98% yield. The ^1H and ^{13}C NMR of our synthetic amphirionin-4 $\{[\alpha]_{\text{D}}^{23} + 6.4$ (*c* 0.08, CHCl_3) $\}$ are identical to the reported spectra for the natural (+)-amphirionin-4 $\{\text{lit}^4 [\alpha]_{\text{D}}^{20} + 6$ (*c* 0.29, CHCl_3) $\}$, thus confirming the absolute configuration of our synthetic material.

In summary, we have achieved an enantioselective synthesis of (+)-amphirionin-4 (**1**). The synthetic route is convergent and readily scalable. The longest linear path is nine steps from readily available racemic butyrolactone. The synthesis featured lipase resolution of a racemic lactone to give highly optically pure isomers. Other key reactions include a highly diastereoselective *syn*-allylation reaction, an efficient Stille coupling to construct the polyene side chain and a NHK coupling to establish the C8 allylic alcohol diastereoselectively. Our synthesis has provided rapid access to (+)-amphirionin-4 (**1**) and structural variants for biological studies. Further investigations of structural and biological studies are in progress.

Scheme 5. Synthesis of (+)-Amphirionin-4 (1)



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b00942](https://doi.org/10.1021/acs.orglett.6b00942).

Experimental procedures and ^1H - and ^{13}C - NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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