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Enantioselective Total Synthesis of (+)-Amphirionin-4

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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.

Graphical Abstract

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.^{3,4,5} 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

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Supporting Information

Experimental procedures and ¹H- and ¹³C- NMR spectra are available for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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 intense proliferation-promotion 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 9 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 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 °C 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. The $\sigma\text{C-H}$ 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 cleavage of alkene **15** using $\text{PhI}(\text{OAc})_2$, NMO and catalytic OsO_4 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 **20** in 70% yield. Hydrosilylation of the resulting alkyne **20** using Trost's procedure²¹ with $[(\text{CpRu}(\text{MeCN})_3)\text{PF}_6]$ and triethylsilane followed by iododesilylation²² with NIS and 2,6-lutidine in hexafluoroisopropanol furnished vinyl iodide **2** in 80% yield.

Synthesis of the side chain **5** is shown in Scheme 3. A zirconium-catalyzed carboalumination of 4-pentyne-1-ol **20** followed by reaction with iodine provided the corresponding 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. 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 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 also 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 transmetallation step and a competing *cine* substitution.²⁵ In an attempt to enhance the transmetallation 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-penten-1-ol **24** with 1-phenyl-1*H*-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 *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 [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 was 9 steps from readily available racemic butyrolactone. The synthesis featured a 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 will provide rapid access to (+)-amphirionin-4 (**1**) and structural variants for biological studies. Further investigations of structural and biological studies are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

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

Scheme 1.
Synthesis of substituted tetrahydrofurans.

Scheme 2.
Synthesis of vinyl iodide **2**.

Scheme 3.
Synthesis of aldehyde **23**.

Scheme 4.
Synthesis of aldehyde **3**.

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

Table 1

Stille-coupling reactions to access diene **22**.

entry	catalyst & additive	mol (%)	solvent	time (h)	yield (%)
1	Pd(MeCN) ₂ Cl ₂	10	DMF	24	30
2	Pd(MeCN) ₂ Cl ₂	20	DMF	24	30
3	Pd(MeCN) ₂ Cl ₂	30	DMF	96	28
4	Pd ₂ dba ₃	30	DIPEA, NMP	24	25
5	Pd(PPh ₃) ₄ CuCl, LiCl	10	DMSO	2	90