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Total Synthesis of Amphirionin-4

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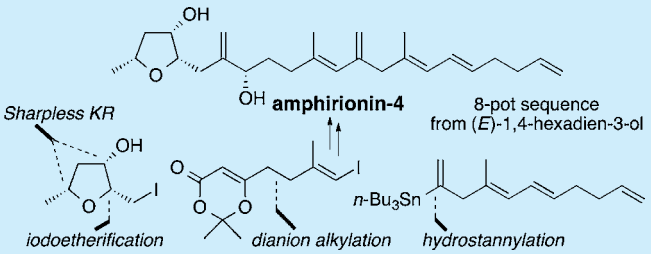
Supporting Information

ABSTRACT: An expeditious enantioselective total synthesis of amphirionin-4, a remarkably potent promoter of the proliferation of ST-2 cells, has been achieved from (±)-(*E*)-1,4-hexadien-3-ol by an 8-pot sequence that features the Sharpless kinetic resolution, iodoetherification, and the CBS reduction to install the stereocenters, utilization of four one-pot transformations to streamline the synthetic process, and the Stille coupling reaction at nearly the center of the target molecule to complete the total synthesis.



Marine dinoflagellates of the genus *Amphidinium* are known as a rich source of bioactive polyketides of high structural diversity such as potently cytotoxic macrolides with various ring sizes and long-chain linear molecules with a wide range of biological properties including antifungal, ichthyotoxic, and hemolytic activities.[1,2] Amphirionin-4 (**1**) is a tetrahydrofuran (THF) ring-containing polyketide natural product of medium chain length, isolated in minute amounts by Tsuda and co-workers from the marine benthic dinoflagellate *Amphidinium* sp. strain KCA09051 (Figure 1).[3] This strain of *Amphidinium* also produces the potent cytotoxin amphirionin-2, a linear polyketide featuring two hexahydrofuro[3,2-*b*]furan bicyclic ring motifs,[4] and another strain of *Amphidinium* (KCA09053) is a producer of amphirionin-5, a polyketide characterized by two THF units and an epoxide ring embedded in a linear 28-carbon chain.[5,6] While most macrolides and some linear polyketides isolated from *Amphidinium* spp. have been reported to exhibit significant inhibitory effects on cancer cell growth, as exemplified by the 26-membered macrolide amphidinolide N (IC_{50} 0.05 ng/mL and 0.06 ng/mL for L1210 and KB cell lines, respectively),[1,2,7] amphirionin-4 (**1**) and amphirionin-5 were, in contrast, revealed to strongly promote the proliferation of some normal cell lines (compound **1**: 950% promotion at 0.1 ng/mL for murine bone marrow stromal ST-2 cells; amphirionin-5: 282%, 320%, and 200% promotion at 10 ng/mL for ST-2, murine osteoblastic MC3T3-E1, and murine embryo fibroblastic NIH3T3 cells, respectively). The remarkable biological profiles of **1** and amphirionin-5, hopefully applicable to the treatment of several diseases (e.g., immune- and osteoporosis-related disorders),[3,5] as well as their attractive structural architectures and limited availability prompted synthetic studies on these marine natural products, which recently culminated in the first total synthesis of amphirionin-4 (**1**) by the Britton group and the stereochemical reassignment of amphirionin-5 by Kanto and Sasaki.[8,9] We describe herein a new enantioselective total synthesis of **1** from (*E*)-1,4-hexadien-3-ol by an eight-pot sequence that incorporates four one-pot transformations.

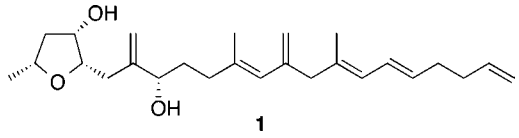


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Figure 1. Structure of amphirionin-4 (**1**).

Scheme 1 outlines our synthetic plan for **1**. The target molecule **1** was retrosynthetically disconnected into two segments, vinyl iodide **2** and vinyl stannane **3**, with the intention of assembling them into **1** by the Stille coupling reaction. The exomethylene-containing dihydroxy tetrahydrofuran segment **2** would be prepared by acylation of alcohol **4** with the dioxinone derivative **5** followed by intramolecular alkylation of the resulting keto ester and some additional steps involving an asymmetric reduction to install the C8 hydroxy group. Compound **5** should be obtainable by alkylation of a dianion derived from **6** with bromide **7** and subsequent dioxinone ring formation from the alkylation product. The other segment **3**, on the other hand, could be accessed via the Horner−Wadsworth−Emmons olefination between **8** and **9** followed by two-carbon elongation with TMS-acetylene and regioselective hydrostannylation to install the vinyl stannane moiety.

According to the synthetic plan, we began our synthesis of **1** with the preparation of the all-*cis* trisubstituted tetrahydrofuran derivative **4** (Scheme 2). Our literature search revealed that the antipode of **4** had previously been synthesized by Kim and Cha from (±)-**10** by basically the same sequence of reactions as depicted in Scheme 2, in which a highly diastereoselective iodoetherification (**12** → **4**) was employed as the key transformation.[10] Their paper was, however, devoid of physicochemical data for the product (including the enantio-

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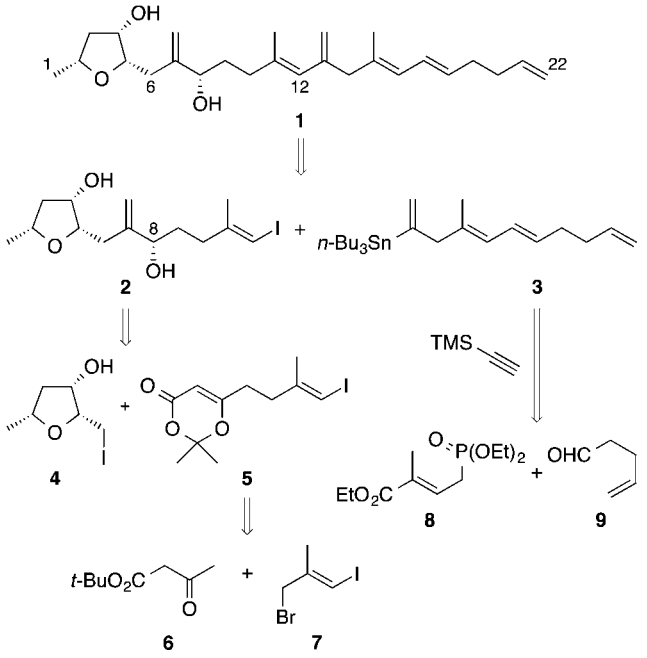
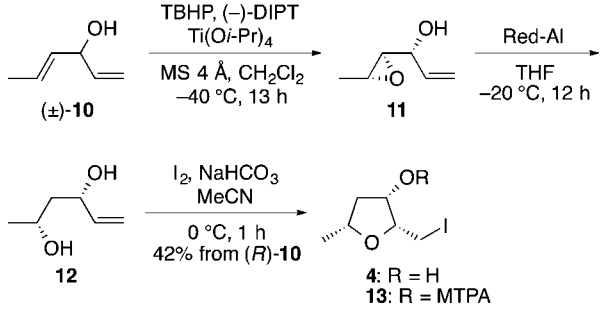
Scheme 1. Retrosynthetic Analysis of 1



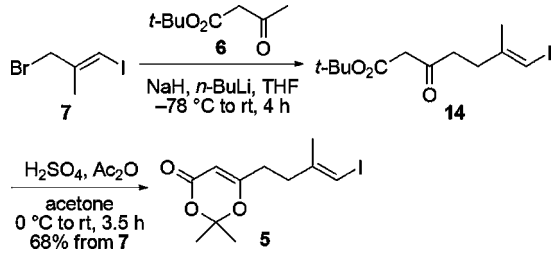
Scheme 2. 3-Step Preparation of All-*cis* Trisubstituted Tetrahydrofuran Moiety 4



meric excess and chemical yield) as well as detailed experimental procedures. Despite these ambiguities, we were attracted by the conciseness of this three-step sequence and thereby decided to examine the process in detail. Thus, (±)-**10** was first exposed to Sharpless kinetic resolution conditions to give epoxy alcohol **11** after chromatographic removal of unreacted (*S*)-**10**.[11] Regioselective epoxide ring-opening of **11** with Red-Al afforded diol **12**, which was then treated with iodine in MeCN in the presence of $NaHCO_3$ to provide the trisubstituted tetrahydrofuran **4** in a diastereomerically pure state after repeated chromatography of the reaction product to remove impurities originating mainly from incomplete diastereo- and regioselectivity in the kinetic resolution step.[12] Fortunately, this three-step process gave **4** in a satisfactory enantiomeric excess of 96%, which, along with its absolute configuration, was determined by NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters **13**.[13] Although the overall yield for the three steps was modest [42% based on (*R*)-**10** contained in the starting racemic alcohol], we believe that the succinctness of the sequence more than compensates for the modest overall yield.[14]

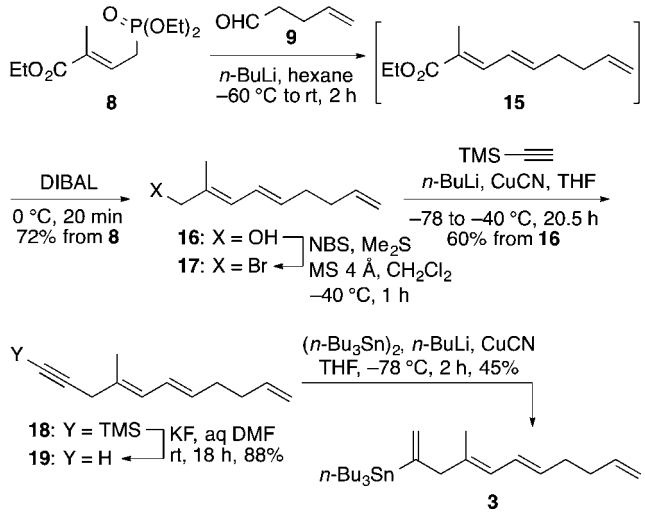
The preparation of the dioxinone derivative **5** was effected uneventfully in two steps, as shown in Scheme 3, by alkylation of a dianion generated from *t*-butyl acetoacetate **6** with known bromide **7** and subsequent treatment of the resulting product **14** with concn H_2SO_4 in acetone/Ac_2O.[15,16]

Scheme 3. Preparation of Iodo Alkene 5



The stannane segment **3** containing a skipped triene system was obtained in five operational steps as delineated in Scheme 4. The Horner–Wadsworth–Emmons olefination between **8** and **9** in THF (*n*-BuLi, −78 °C to rt, 2 h) gave a 11:1 mixture of desired triene ester **15** (4*E*-isomer) and its 4*Z*-isomer in yields of 45% and 4%, respectively. Quite interestingly, changing the reaction solvent from THF to hexane brought about a significant improvement in geometrical selectivity, providing the two isomers in a ratio of 40:1 favoring the 4*E*-iosmer **15**. Furthermore, by adding DIBAL directly to the reaction mixture containing **15** so formed, the corresponding alcohol **16** was obtained in one pot from **8** in a good yield of 72%. The alcohol was then converted into considerably unstable allylic bromide **17**, which, without purification, was subjected to a coupling reaction with TMS-acetylene to afford **18**.[17] Finally, removal of the TMS protecting group with KF in aq DMF followed by regioselective stannylcupration and protonation of the resulting terminal acetylene **19** delivered **3**.[18,19]

Scheme 4. Preparation of Vinyl Stannane Segment 3



With the three fragments **3**, **4**, and **5** in hand, we proceeded to the final stage of our total synthesis of **1**. As shown in Scheme 5, the conversion of the hydroxy tetrahydrofuran derivative **4** into lactone **22** was performed in a single operation comprising: (1) acylation of **4** with the dioxinone **5** in refluxing toluene to afford ester **20**; (2) intramolecular alkylation of **20** into α-acyl lactone **21** (as an equilibrium mixture with its tautomers) by treatment with NaH;[20] and (3) silyl enol

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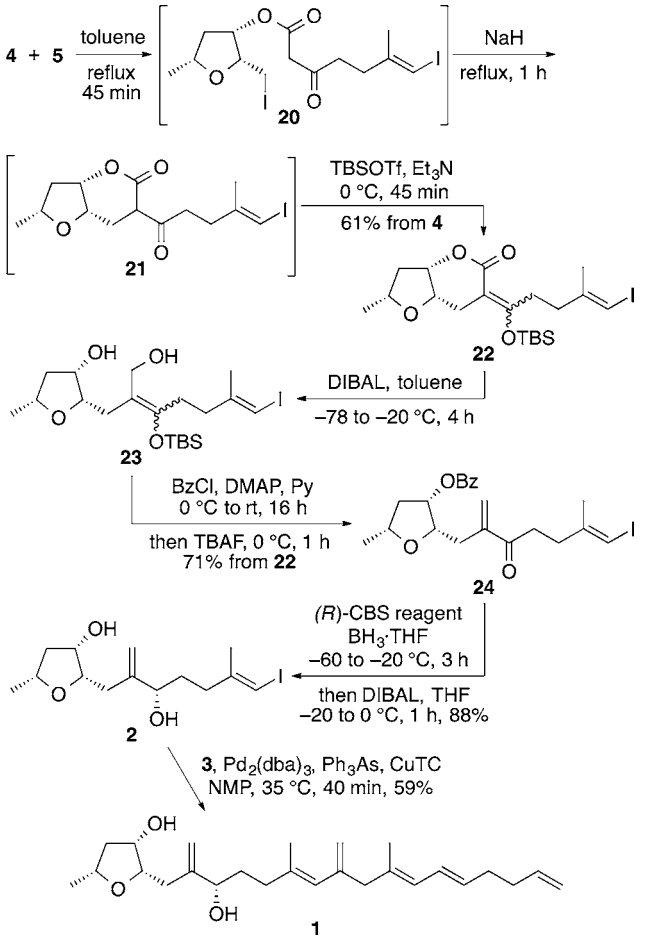
Scheme 5. Completion of the Total Synthesis of Amphirionin-4 (1)



etherification of the β-keto ester **21** with TBSOTf and Et_3N to give **22** as a single geometrical isomer (61% overall yield), although the geometry of the newly formed double bond was not assigned. It is worth mentioning that intermolecular alkylation between the TBS-protected form of **4** and β-keto esters [MeC(O)CHRCO$_2$R′: R = H or Me, R′ = Me, Et, or allyl] did not proceed at all probably due to severe steric congestion of the α-face of the all-*cis* configured tetrahydrofuran reactant. Reduction of **22** with DIBAL gave diol **23**, which, upon exposure to an excess amount of BzCl in pyridine in the presence of DMAP, afforded the corresponding dibenzoate intermediate. Direct treatment of the reaction mixture containing the intermediate with TBAF induced deprotection of the TBS group and subsequent elimination of a benzoate group to furnish conjugated enone **24** in 71% yield from **22**. The CBS reduction of the ketone group of **24** using (*R*)-2-methyl-CBS-oxazaborolidine and BH_3·THF followed by reductive removal of the benzoyl functionality with DIBAL gave a 25:1 mixture of diol **2** and its C8 epimer in one pot,[21] which, upon SiO_2 chromatographic purification, furnished **2** in a pure state in 88% yield. Finally, the Stille coupling of **2** with the right-hand stannane segment **3** completed our total synthesis of amphirionin-4 (**1**), the ^{1}H and ^{13}C NMR spectra of which showed good agreement with those reported in the literature.[3,8] The specific rotation value of **1**, $[\alpha]^{23}_D$ −13.8 (*c* 0.16, $CHCl_3$), was, however, significantly different from previously reported data, $[\alpha]^{20}_D$ +6 (*c* 0.29, $CHCl_3$) and $[\alpha]_D$ −5.8 (*c* 0.34, $CHCl_3$).[3,8] At present, we are unable to rationalize these discrepancies, but the samples employed for the measurement of specific rotation might have been contaminated with minute amounts of impurities with large optical rotation values.

In conclusion, an enantioselective total synthesis of amphirionin-4 (**1**) has been accomplished from (±)-1,4-hexadien-3-ol [(±)-**10**] in eight operational steps. The new expeditious synthesis of **1** featured the Sharpless kinetic resolution as a chirality-inducing step [(±)-**10** → **11**], exploitation of four one-pot transformations (**8** → **16**, **4** → **22**, **23** → **24**, and **24** → **2**) to streamline the synthetic process, highly efficient installation of the C8 asymmetric center by the CBS reduction (**24** → **2**), and the Stille coupling reaction to connect the two segments, **2** and **3**, to complete the total synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00883.

Experimental procedures, characterization data, and copies of NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

Structure 14 was corrected in Scheme 3 and the Supporting Information on May 2, 2016.

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